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[Continued on next page]

(54) Title: 14-MEMBERED KETOLIDES AND METHODS OF THEIR PREPARATION AND USE

(57) Abstract: Provided herein are methods of preparing new 14-membered ketolides via coupling of an eastern and western half moiety, followed by macrocyclization, and optional functionalization. Intermediates in the synthesis of these ketolides including the eastern and western halves are also provided. Pharmaceutical compositions and methods of treating infectious diseases and inflammatory conditions using these ketolides are also provided.

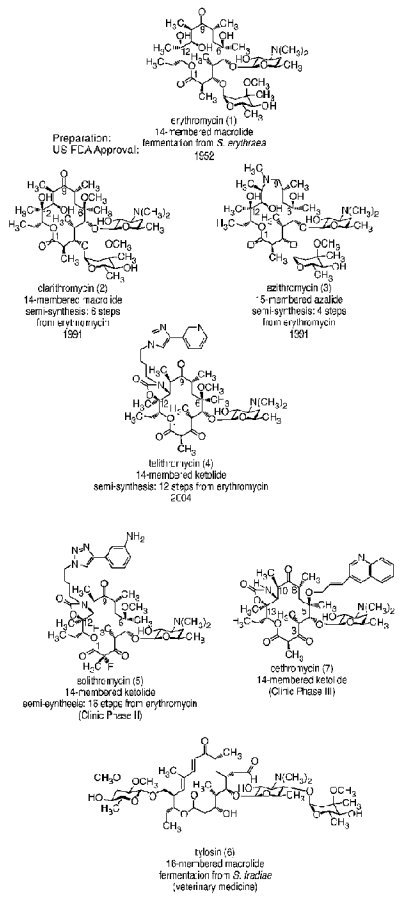

Figure 1

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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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14-MEMBERED KETOLIDES AND METHODS OF THEIR PREPARATION AND USE

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 62/061,571, filed October 8, 2014, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Emerging resistance to existing antibiotics is rapidly developing as a crisis of global proportions, especially for *Staphylococcus aureus, Streptococcus pyogenes*, and *Streptococcus pneumonia* infections. Pathogenic bacteria can transmit genes coding for antibiotic resistance both vertically (to their progeny) and horizontally (to neighboring bacteria of different lineages), and as a result antibiotic resistance can evolve quickly, particularly in nosocomial (hospital) settings. See, *e.g.*, Wright, *Chem. Commun.* (2011) 47:4055–4061. This year, >99,000 people will die in the U.S. from healthcare-associated infections, more than all casualties from car accidents, HIV, and breast cancer combined, creating an estimated burden of up to $45 billion in U.S. healthcare costs. See, *e.g.*, Klevens *et al.*, *Public Health Rep* (2007) *122*:160–166. The current crisis is exacerbated by the fact that most major pharmaceutical companies have essentially abandoned research in the development of new antibiotics. See, *e.g.*, Projan *Curr. Opin. Microbiol.* (2003) *6*: 427–430. The current rate of introduction of new antibiotics does not adequately address growing resistance, and with the ease of international travel and increasing population densities, the need for innovation in the field has never been higher.

[0003] The macrolides are one of the few major clinically important classes of antibiotics for which the only practical access has been through semi–synthesis, or chemical manipulation of structurally complex fermentation products, in routes as long as 16 steps. See, *e.g.*, Paterson, *Tetrahedron* (1985) *41*:3569–3624; Omura, Ed., *Macrolide Antibiotics: Chemistry, Biology, and Practice, Second Edition*; Academic Press, 2002. The macrolide class of antibiotics has proven safe and effective in the battle against pathogenic bacteria since the discovery of erythromycin over 60 years ago. See, *e.g.*, Wu *et al.*, *Curr. Med. Chem.* (2001) *8*, 1727–1758. Erythromycin displays a spectrum of antibacterial activity against Gram–positive bacteria similar to that of penicillin but has a lesser propensity to induce allergic interactions, and has been routinely prescribed for upper and lower respiratory tract infections

and urogenital infections. See, *e.g.*, Washington *et al.*, *Mayo. Clin. Proc.* (1985) *60*:189–203; Washington *et al.*, *Mayo. Clin. Proc.* (1985) *60*:271–278. However, erythromycin is known to undergo acid–promoted internal ketalization (cyclization of the C6 and C12 hydroxyl groups onto the C9 ketone) in the gut, which leads to adverse gastrointestinal events. See, *e.g.*, Kurath *et al.*, *Experientia* (1971) *27*:362. Second–generation macrolide antibiotics clarithromycin and azithromycin addressed issues of acid instability and were prepared semi–synthetically in 4–6 steps from erythromycin, which is readily available through large-scale fermentation. See, *e.g.*, Ma *et al.*, *Curr. Med. Chem.* (2011) *18*:1993–2015; Wu *et al.*, *Curr. Pharm. Des.* (2000) *6*:181–223; Ma *et al.*, *Mini–Rev. Med. Chem.* (2010) *10*:272–286; Asaka *et al.*, *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* (2003) *3*:961–989; Morimoto *et al.*, *J. Antibiot.* (1990) *43*:286–294; Morimoto *et al.*, *J. Antibiot.* (1984) *37*:187–189; Watanabe *et al.*, *J. Antibiot.* (1993) *46*: 1163–1167; Watanabe *et al.*, *J. Antibiot.* (1993) *46*:647–660; Bright *et al.*, *J. Antibiot.* (1988) *41*: 1029–1047; Djokic *et al.*, *J. Antibiot.* (1987) *40*:1006–1015; Mutak *et al.*, *J. Antibiot.* (2007) *60*: 85–122; and Retsema *et al.*, *Antimicrob. Agents Chemother.* (1987) *31*:1939–1947. Azithromycin has been shown to exhibit markedly improved efficacy against Gram–negative organisms, and has a longer half–life and higher tissue distribution than the other macrolide antibiotics, thought to correlate with its 15–membered ring containing a tertiary amine. See, *e.g.*, Ferwerda *et al.*, *J. Antimicrob. Chemother.* (2001) *47*:441–446; Girard *et al.*, *Antimicrob. Agents Chemother.* (1987) *31*:1948–1954. The natural product tylosin, a 16–membered macrolide used in veterinary medicine, has been shown by X–ray crystallography to occupy the same binding pocket as erythromycin and azithromycin, suggesting that there is a high tolerance for variability in ring size and composition of the macrocycle.

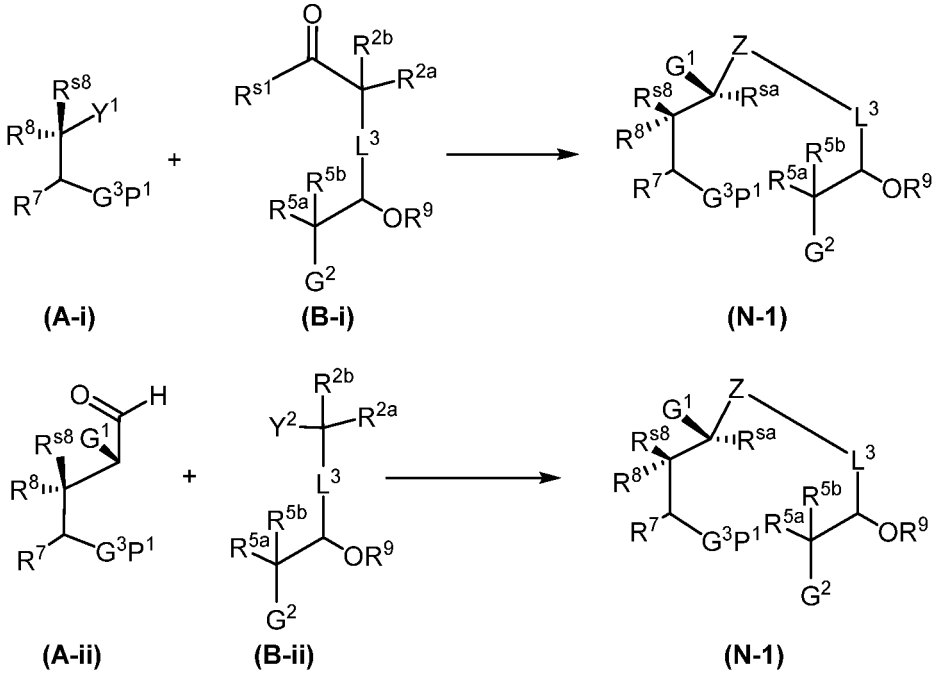
[0004] The three primary causes of resistance to macrolides in bacterial organisms are ribosome methylation encoded by *erm* genes, mutations in ribosomal RNA or peptides, and cell efflux mediated by *mef* and *msr* genes. See, *e.g.*, Leclercq *et al.*, *Antimicrob. Agents Chemother.* (1991) *35*:1273–1276; Leclercq *et al.*, *Antimicrob. Agents Chemother.* (1991) *35*:1267–1272; Weisblum, *Antimicrob. Agents Chemother.* (1995) *39*:577–585; Vester *et al.*, *Antimicrob. Agents Chemother.* (2001) *45*:1–12; Prunier *et al.*, *Antimicrob. Agents Chemother.* (2002) *46*:3054–3056; Li *et al.*, *J. Antimicrob. Chemother.* (2011) *66*:1983–1986; Sutcliffe *et al.*, *Antimicrob. Agents Chemother.* (1996) *40*:1817–1824; Wondrack *et al.*, *Antimicrob. Agents Chemother.* (1996) *40*: 992–998. Ketolides such as telithromycin and solithromycin defeat the efflux mechanism of resistance by replacement of the C3 cladinose sugar with a carbonyl group (hence the name "ketolides"), and are thought to exhibit greatly

increased binding by virtue of favorable interactions between the novel aryl–alkyl sidechain and the ribosome. See, *e.g.*, Ma *et al.*, *Curr. Med. Chem.* (2011) *18*:1993–2015; Ma *et al.*, *Mini–Rev. Med. Chem.* (2010) *10*:272–286. Despite greatly improved ribosomal binding, ketolides such as telithromycin and solithromycin have not addressed several of the newest forms of macrolide resistance that have evolved in nosocomial settings, especially ribosome methylation and RNA point mutations.

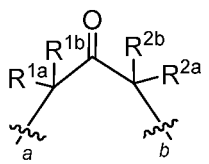
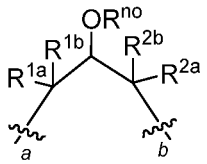
SUMMARY OF THE INVENTION

[0005] Described herein are methods and intermediates for making ketolides. This synthetic approach to macrolides, particularly 14-membered ketolides, includes the coupling of two components, a western half (A-i) or (A-ii) with an eastern half (B-i) or (B-ii), as depicted in *Scheme 1*, to provide a compound of Formula (N-1):

Scheme 1.

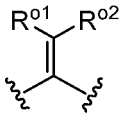


or salt thereof, wherein:

Z is of the formula  (z-i) or  (z-ii);

each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,

optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or



R^{2a} and R^{2b} are taken together to form ;

a indicates the point of attachment to the carbon substituted by G^1;

b indicates the point of attachment to L^3;

each of R^{o1} and R^{o2} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

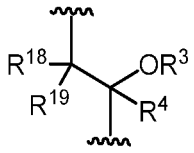
R^{no} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group;

R^{sa} is hydrogen, hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl;

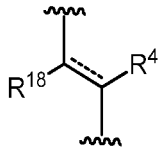
or R^{sa} and R^{1a} or R^{sa} and R^{1b} are taken together to form a bond;

R^{s8} is hydrogen or OR^{11};

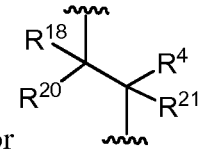
L^3 is a group of formula:



(**L^3-i**),



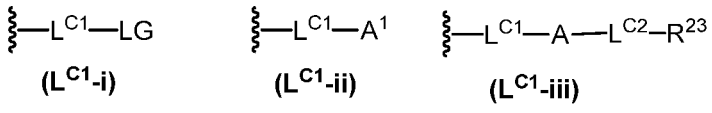
(**L^3-ii**),



or (**L^3-iii**);

====== represents a single or double bond;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:



(L^{C1}-i) (L^{C1}-ii) (L^{C1}-iii) ;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl;

each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring;

each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group;

R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

R^7 and R^8 are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

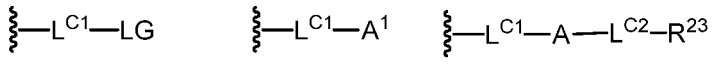
R^9 and R^{17} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate;

R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, and halogen;

G^3 is –O–, –S–, or $–N(R^{G1})–$, wherein R^{G1} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

G^1 is hydrogen, $–OR^{12}$ or $–NR^{13}R^{14}$;

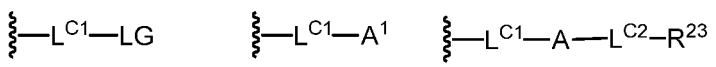
provided when G^1 is $–OR^{12}$, then R^{11} and R^{12} are joined as a group of formula –C(=O)- to provide a cyclic carbonate, or R^{11} and R^{12} are not joined, and R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, and R^{12} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group, or a group of formula:



(L^{C1}-i) (L^{C1}-ii) (L^{C1}-iii) ;

or provided when G^1 is $–NR^{13}R^{14}$, then R^{11} and R^{13} are joined as a group of formula –C(=O)- to provide a cyclic carbamate, or R^{11} and R^{13} are not joined, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, R^{13} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group, $-C(=O)R^{Z8}$, or $-C(=O)OR^{Z8}$, or a group of formula:

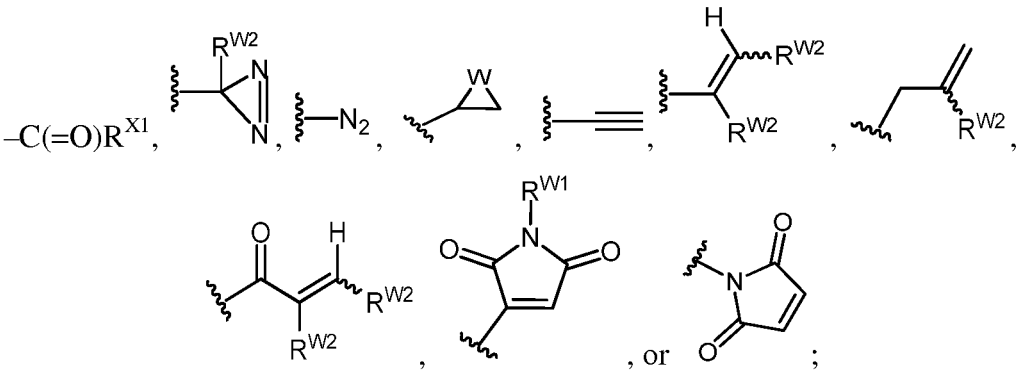


(L^{C1}-i) (L^{C1}-ii) (L^{C1}-iii)

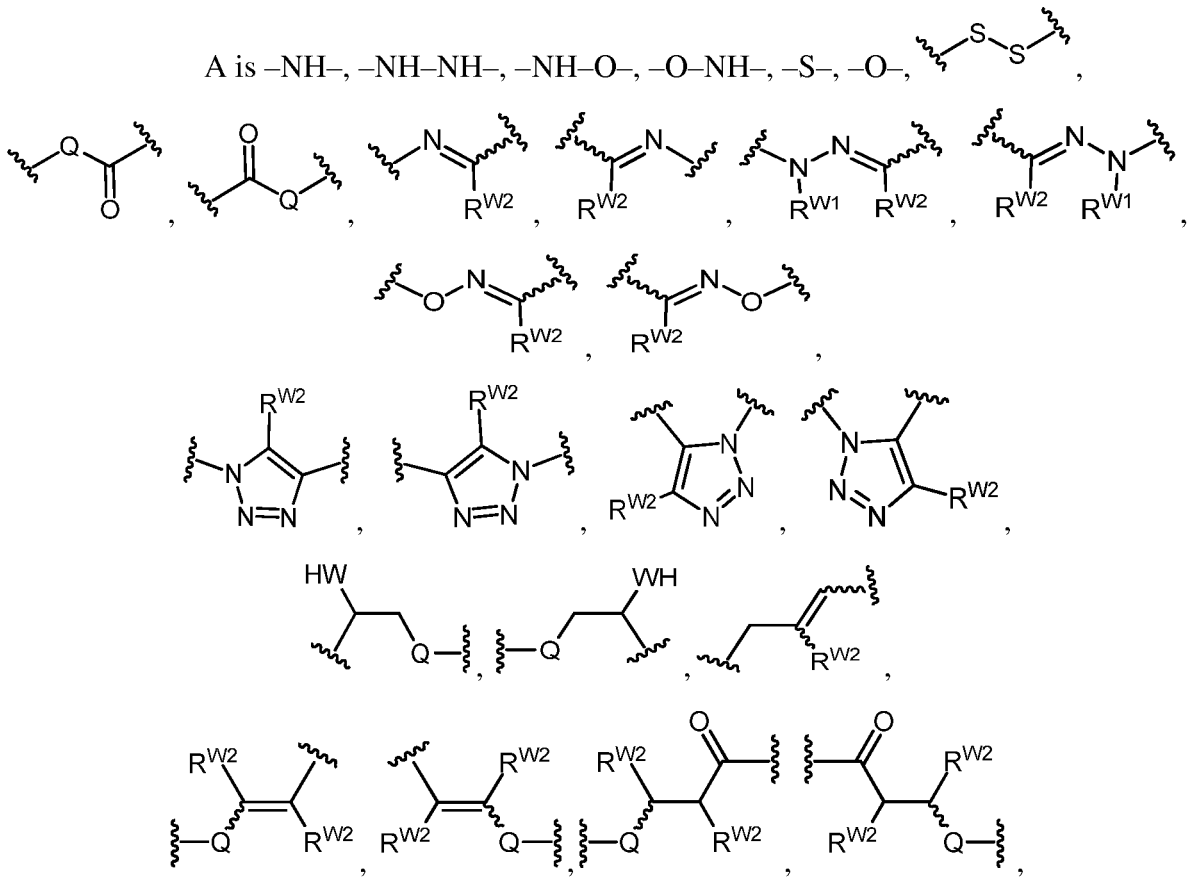
or R^{13} and R^{14} are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl;

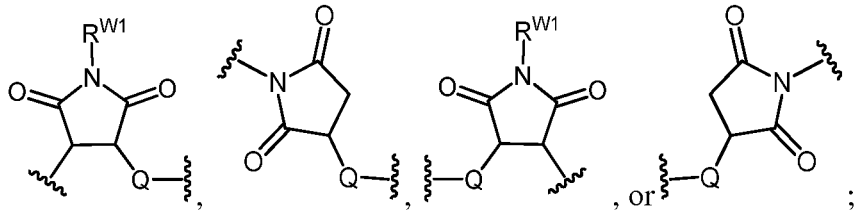
each instance of L^{C1} and L^{C2} is independently a bond, or a linking group selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof;

each instance of A^1 is independently a leaving group (LG), –SH, –OH, $–NH_2$, –NH–NH_2, $–N_3$, –O–NH_2,



A is –NH–, –NH–NH–, –NH–O–, –O–NH–, –S–, –O–,





Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or a nitrogen protecting group;

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety;

R^{X1} is hydrogen, halogen, or $–OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or an oxygen protecting group;

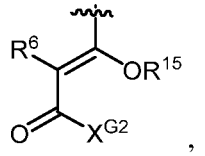
R^{23} is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl; and

each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

or A is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{s1} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

G^2 is a group of formula: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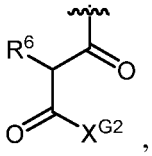
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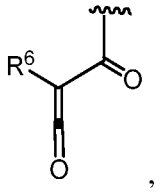
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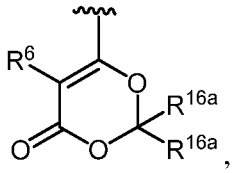
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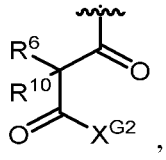
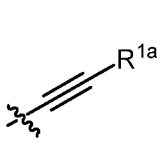
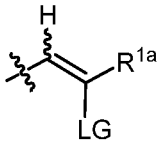
or

,

wherein R^6, R^{10}, R^{15}, R^{16a}, and X^{G2} are as defined herein;

P^1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group;

Y^1 is  or  ;

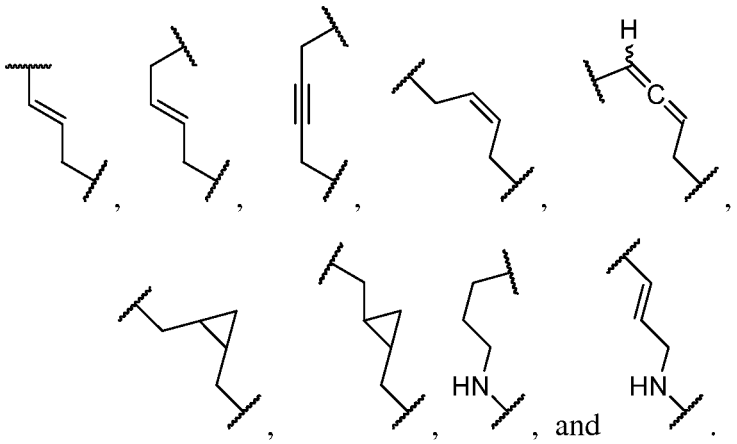
LG is a leaving group;

Y^2 is $–C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$ or $–C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$;

wherein the leaving group (LG), R^{P1}, R^{P2}, and R^{P3} are as defined herein, to provide various linkages of formula Z, as defined herein.

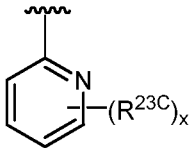
[0006] As demonstrated herein, macrolides which incorporate rigidifying motifs (*e.g.*, unsaturated or cyclic motifs) into the L^{C1} or L^{C2} linker show improved potencies compared with solithromycin (See, *e.g.*, Tables B1-B13). Therefore, in certain embodiments, one or both of L^{C1} and L^{C2} is a linker selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof, provided the linker comprises a optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted carbocyclylene group therein, thereby rigidifying the linker moiety. In certain embodiments, L^{C1} is a rigidified linker, as described herein, and L^{C2} is a bond.

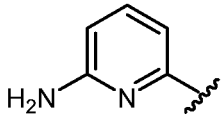
[0007] In certain embodiments, one or both of L^{C1} and L^{C2} is independently selected from one of the following formulae:



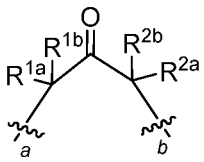
, and .

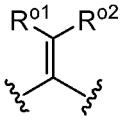
[0008] Furthermore, macrolides which comprising a non-hydrogen R^{1a} and/or R^{1b} group, such as a $-CH_3$ group, are found to be more potent than analogs without such substitution. The combination of a rigidified linker in addition to a non-hydrogen R^{1a} and/or R^{1b} group is thus envisioned as providing even more potent analogs.

[0009] Furthermore, as described herein, ketolides comprising heteroaryl R^{23} groups have been found to be more potent than solithromycin and analogs thereof. The combination of a rigidified L^{C1} and/or L^{C2} linker, a non-hydrogen R^{1a} and/or R^{1b} group, and a heteroaryl R^{23} group is thus envisioned as providing even more potent analogs. Therefore, in certain embodiments, R^{23} is of the formula: 

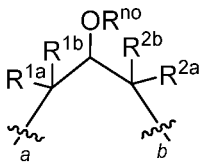
. In specific embodiments, R^{23} is of the formula: 

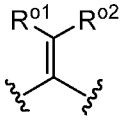
.

[0010] In certain embodiments, Z is 

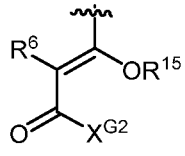
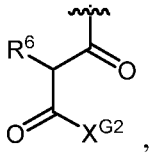
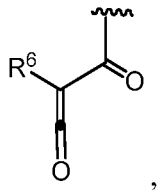
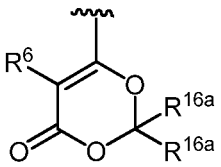
(z-i); and R^{1a}, R^{1b}, R^{2a}, and R^{2b} are as defined herein. In certain embodiments, R^{1a} and R^{1b} are hydrogen; and each of R^{2a} and R^{2b} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^{1a} is hydrogen; R^{1b} is optionally substituted alkyl; and each of R^{2a} and R^{2b} is independently hydrogen or optionally substituted alkyl. In some embodiments, R^{1a} and R^{1b} or R^{2a} and R^{2b} are taken together to form 

, wherein R^{o1} and R^{o2} are as defined herein. In certain embodiments, L^{C1} is a rigidified linker, as described herein, and L^{C2} is a bond.



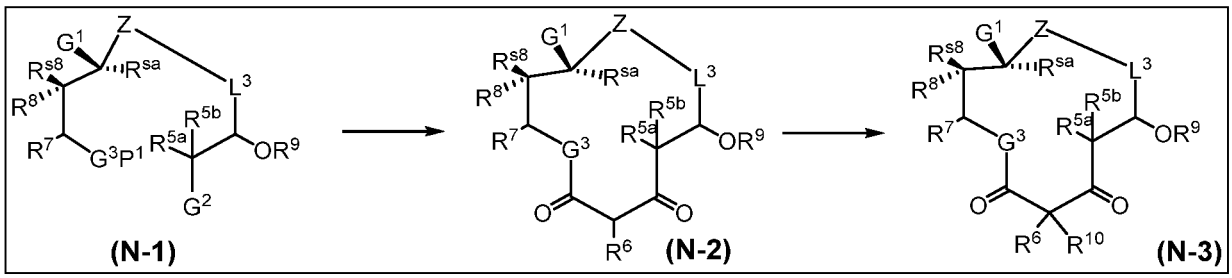
[0011] In certain embodiments, Z is (z-ii); R^{no} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group; and R^{1a}, R^{1b}, R^{2a}, and R^{2b} are as defined herein. In certain embodiments, R^{no}, R^{1a} and R^{1b} are hydrogen and each of R^{2a} and R^{2b} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^{no} and R^{1a} are hydrogen; R^{1b} is optionally substituted alkyl; and each of R^{2a} and R^{2b} is independently hydrogen or optionally substituted alkyl. In some embodiments, R^{1a} and R^{1b} or R^{2a} and R^{2b} are taken together to form  , wherein R^{o1} and R^{o2} are as defined herein. In certain embodiments, L^{C1} is a rigidified linker, as described herein, and L^{C2} is a bond.

[0012] Furthermore, various macrolides may be accessed from the coupled product of Formula (**N-i**), depending upon the nature of the group G^2, upon macrocyclization, *e.g.*, via thermally induced macrocylization. As depicted in *Scheme 2*, when G^2 is a group of formula:

 ,  ,  , or 

P^1 is hydrogen, and R^6 is a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**N-1**) provides a macrolide of Formula (**N-2**). Enolization of the macrolide of Formula (**N-2**) in the presence of a base, followed by addition of a non-hydrogen group R^{10}, provides a macrolide of Formula (**N-3**).

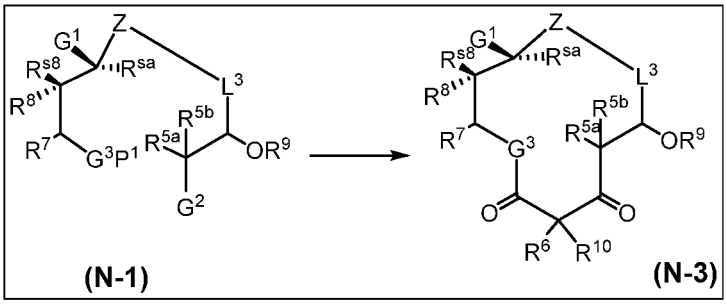
Scheme 2.



[0013] Alternatively, as depicted in *Scheme 3*, when G^2 is a group of formula:

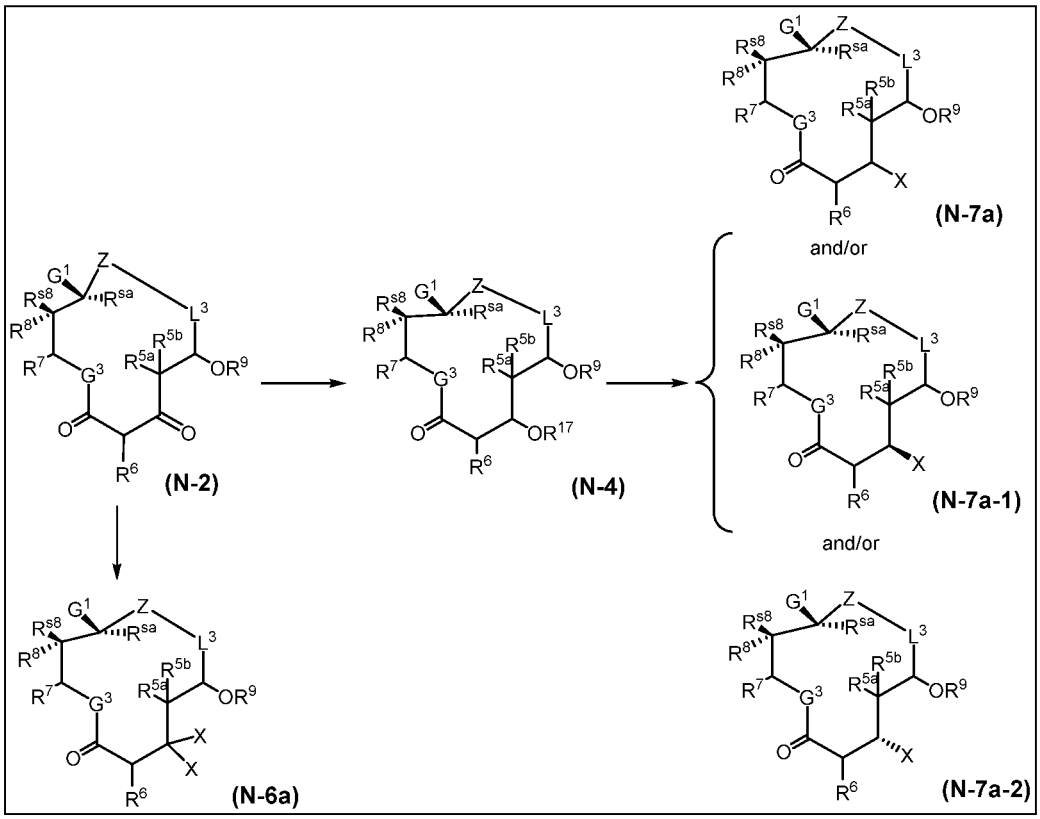
wherein P^1 is hydrogen, and each of R^6 and R^{10} is independently a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**N-1**) provides a macrolide of Formula (**N-3**).

Scheme 3.

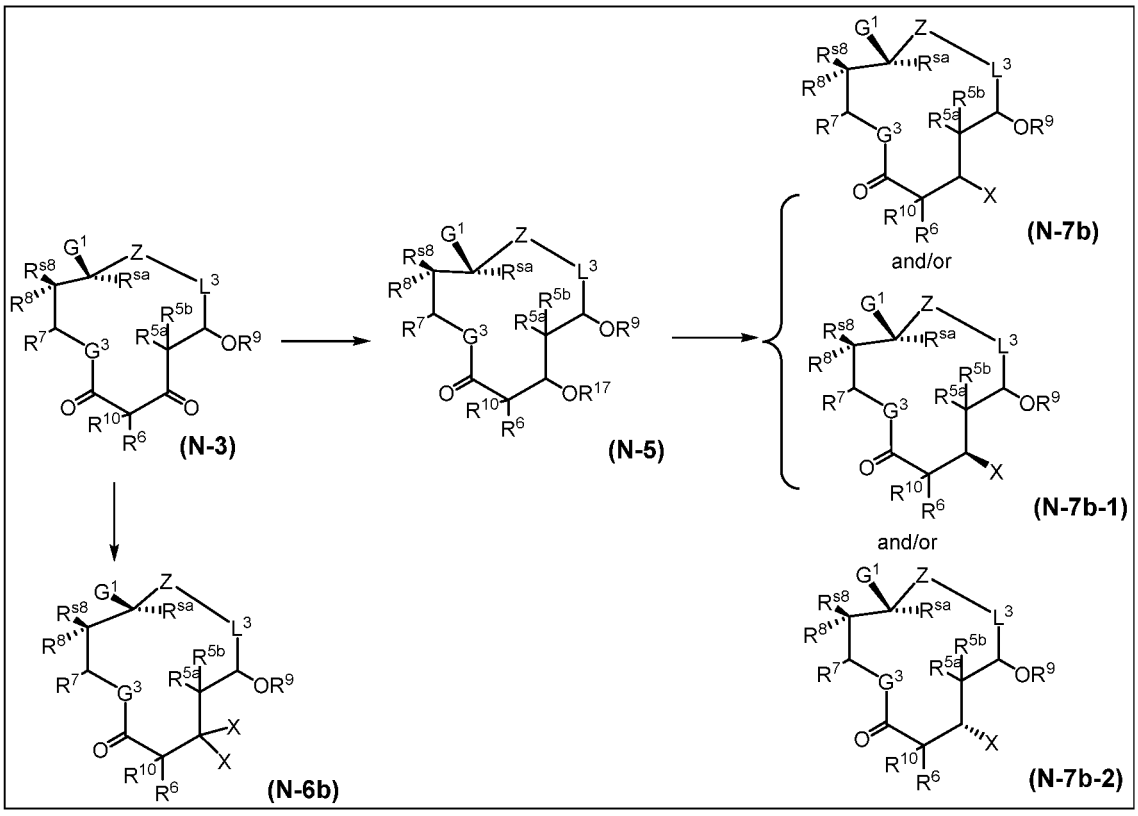


[0014] Additional functionalization of the macrolide is also contemplated. For example, as depicted in *Schemes 4* and *5*, reduction of the C3 ketone of macrolides (**N-2**) and (**N-3**) to a hydroxyl group, optionally followed by protection or other modification, provides macrolides (**N-4**) and (**N-5**), respectively, wherein R^{17} is as defined herein. Dihalogenation of the C3 ketone of macrolides (**N-2**) and (**N-3**), or monohalogenation of macrolides (**N-4**) and (**N-5**), providing the products, (**N6a/b**) and (**N7a/b**), is further contemplated, wherein X is halogen, *e.g.,* fluoro.

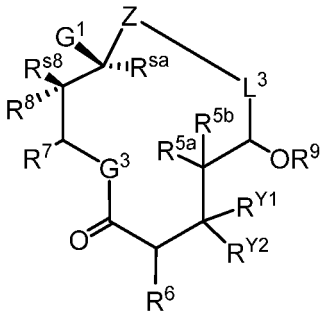
Scheme 4.



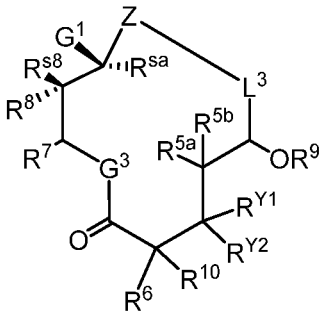
Scheme 5.



[0015] Formula (**N-6**) and subgenera thereof as described herein are intended to encompass compounds of Formulae (**N-2**), (**N-4**), (**N-6a**), and (**N-7a**) and subgenera thereof, wherein R^{Y1} is $-OR^{17}$, and R^{Y2} is hydrogen; or R^{Y1} is halogen, and R^{Y2} is hydrogen; or R^{Y1} is halogen, and R^{Y2} is halogen. Likewise, Formula (**N-7**) and subgenera thereof are intended to encompass compounds of Formula (**N-3**), (**N-5**), (**N-6b**), and (**N-7b**), wherein R^{Y1} is $-OR^{17}$, and R^{Y2} is hydrogen; or R^{Y1} is halogen and R^{Y2} is hydrogen; or R^{Y1} is halogen, and R^{Y2} is halogen; or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group.



(**N-6**)



(**N-7**)

[0016] Additional functionalization of the coupled product (**N-1**) and the macrolides (**N-2**), (**N-3**), (**N-4**), (**N-5**), (**N-6**), and (**N-7**), for example, by addition and synthetic manipulation of a tethered moiety on the eastern and/or western portion of the molecule, and construction of the eastern and western halves, is also described herein.

[0017] Is is generally understood that the synthetic methodologies described herein are both useful in the synthesis of known macrolides, such as those depicted in *Figure 1*, and in the synthesis and development of new macrolides (*e.g.*, 14-membered ketolides) as described herein. New macrolides synthesized using the inventive methodology, and pharmaceutical compositions thereof, are contemplated to be useful in the treatment of various conditions such as, for example, the treatment and/or prevention of infectious diseases, such as bacterial and parasitic infections, and the treatment and/or prevention of inflammatory conditions.

[0018] The details of certain embodiments of the invention are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the invention will be apparent from the Definitions, Examples, Figures, and Claims.

[0019]

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] *Figure 1* depicts exemplary 14–, 15–, and 16–membered macrolide antibiotics used in the United States.

DEFINITIONS

Chemical definitions

[0021] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0022] Compounds and macrolides described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds and macrolides described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds and macrolides as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0023] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0024] As used herein, "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group

has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is an unsubstituted C_{1-10} alkyl (*e.g.,* $–CH_3$). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl.

[0025] As used herein, "haloalkyl" is a substituted alkyl group as defined herein wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.,* fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In some embodiments, all of the haloalkyl hydrogen atoms are replaced with fluoro to provide a perfluoroalkyl group. In some embodiments, all of the haloalkyl hydrogen atoms are replaced with chloro to provide a "perchloroalkyl" group. Examples of haloalkyl groups include $–CF_3$, $–CF_2CF_3$, $–CF_2CF_2CF_3$, $–CCl_3$, $–CFCl_2$, $–CF_2Cl$, and the like.

[0026] As used herein, "heteroalkyl" refers to an alkyl group as defined herein which further includes at least one heteroatom (*e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a

heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl.

[0027] As used herein, "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon–carbon double bonds (*e.g.,* 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl

(C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{2-10} alkenyl.

[0028] As used herein, "heteroalkenyl" refers to an alkenyl group as defined herein which further includes at least one heteroatom (*e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0029] As used herein, "alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon–carbon triple bonds (*e.g.,* 1, 2, 3, or 4 triple bonds) ("$C_{2–10}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("$C_{2–9}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("$C_{2–8}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("$C_{2–7}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("$C_{2–6}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("$C_{2–5}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("$C_{2–4}$ alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("$C_{2–3}$ alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of $C_{2–4}$ alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of $C_{2–6}$ alkenyl groups include the aforementioned $C_{2–4}$ alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted $C_{2–10}$ alkynyl. In certain embodiments, the alkynyl group is a substituted $C_{2–10}$ alkynyl.

[0030] As used herein, "heteroalkynyl" refers to an alkynyl group as defined herein which further includes at least one heteroatom (*e.g.,* 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.,* inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–10}$ alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–9}$ alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–8}$ alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–7}$ alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("hetero$C_{2–6}$ alkynyl"). In some embodiments, a

heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[0031] As used herein, "carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 9 ring carbon atoms ("C_{3-9} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or

polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon–carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[0032] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 9 ring carbon atoms ("C_{3-9} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 7 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[0033] As used herein, "heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 14–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl

group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon–carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl.

[0034] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0035] Exemplary 3–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–

membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5–membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro–1,8–naphthyridinyl, octahydropyrrolo[3,2–b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H–benzo[e][1,4]diazepinyl, 1,4,5,7–tetrahydropyrano[3,4–b]pyrrolyl, 5,6–dihydro–4H–furo[3,2–b]pyrrolyl, 6,7–dihydro–5H–furo[3,2–b]pyranyl, 5,7–dihydro–4H–thieno[2,3–c]pyranyl, 2,3–dihydro–1H–pyrrolo[2,3–b]pyridinyl, 2,3–dihydrofuro[2,3–b]pyridinyl, 4,5,6,7–tetrahydro–1H–pyrrolo[2,3–b]pyridinyl, 4,5,6,7–tetrahydrofuro[3,2–c]pyridinyl, 4,5,6,7–tetrahydro-thieno[3,2–b]pyridinyl, 1,2,3,4–tetrahydro–1,6–naphthyridinyl, and the like.

[0036] As used herein, "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is

independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[0037] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group, as defined herein, substituted by an aryl group, as defined herein, wherein the point of attachment is on the alkyl moiety. An exemplary aralkyl group is $-CH_2$-phenyl (benzyl, Bz), wherein the phenyl moiety may be substituted or unsubstituted.

[0038] As used herein, "heteroaryl" refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.,* bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl).

[0039] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms

provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5–14 membered heteroaryl.

[0040] Exemplary 5–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl and phenazinyl.

[0041] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group, as defined herein, substituted by a heteroaryl group, as defined herein, wherein the point of attachment is on the alkyl moiety.

[0042] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.,* aryl or heteroaryl moieties) as herein defined.

[0043] As used herein, the term "saturated" refers to a ring moiety that does not contain a double or triple bond, *i.e.*, the ring contains all single bonds.

[0044] Affixing the suffix "–ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0045] As understood from the above, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are, in certain embodiments, optionally substituted. Optionally substituted refers to a group which may be substituted or unsubstituted (*e.g.,* "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent

as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0046] Exemplary carbon atom substituents include, but are not limited to, halogen, –CN, –NO_2, –N_3, –SO_2H, –SO_3H, –OH, –OR^{aa}, –$ON(R^{bb})_2$, –$N(R^{bb})_2$, –$N(R^{bb})_3^+X^-$, –$N(OR^{cc})R^{bb}$, –SH, –SR^{aa}, –SSR^{cc}, –$C(=O)R^{aa}$, –CO_2H, –CHO, –$C(OR^{cc})_2$, –CO_2R^{aa}, –$OC(=O)R^{aa}$, –OCO_2R^{aa}, –$C(=O)N(R^{bb})_2$, –$OC(=O)N(R^{bb})_2$, –$NR^{bb}C(=O)R^{aa}$, –$NR^{bb}CO_2R^{aa}$, –$NR^{bb}C(=O)N(R^{bb})_2$, –$C(=NR^{bb})R^{aa}$, –$C(=NR^{bb})OR^{aa}$, –$OC(=NR^{bb})R^{aa}$, –$OC(=NR^{bb})OR^{aa}$, –$C(=NR^{bb})N(R^{bb})_2$, –$OC(=NR^{bb})N(R^{bb})_2$, –$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, –$C(=O)NR^{bb}SO_2R^{aa}$, –$NR^{bb}SO_2R^{aa}$, –$SO_2N(R^{bb})_2$, –$SO_2R^{aa}$, –$SO_2OR^{aa}$, –$OSO_2R^{aa}$, –$S(=O)R^{aa}$, –$OS(=O)R^{aa}$, –$Si(R^{aa})_3$, –$OSi(R^{aa})_3$ –$C(=S)N(R^{bb})_2$, –$C(=O)SR^{aa}$, –$C(=S)SR^{aa}$, –$SC(=S)SR^{aa}$, –$SC(=O)SR^{aa}$, –$OC(=O)SR^{aa}$, –$SC(=O)OR^{aa}$, –$SC(=O)R^{aa}$, –$P(=O)_2R^{aa}$, –$OP(=O)_2R^{aa}$, –$P(=O)(R^{aa})_2$, –$OP(=O)(R^{aa})_2$, –$OP(=O)(OR^{cc})_2$, –$P(=O)(R^{aa})_2$, –$OP(=O)(R^{aa})_2$, –$OP(=O)(OR^{cc})_2$, –$NR^{bb}P(=O)(OR^{cc})_2$, –$P(R^{cc})_2$, –$OP(R^{cc})_2$, –$B(R^{aa})_2$, –$B(OR^{cc})_2$, –$BR^{aa}(OR^{cc})$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–14}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =$NN(R^{bb})_2$, =$NNR^{bb}C(=O)R^{aa}$, =$NNR^{bb}C(=O)OR^{aa}$, =$NNR^{bb}S(=O)_2R^{aa}$, =NR^{bb}, or =NOR^{cc};

each instance of R^{aa} is, independently, selected from $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, –OH, –OR^{aa}, –$N(R^{cc})_2$, –CN, –$C(=O)R^{aa}$, –$C(=O)N(R^{cc})_2$, –CO_2R^{aa}, –SO_2R^{aa}, –$C(=NR^{cc})OR^{aa}$, –$C(=NR^{cc})N(R^{cc})_2$, –$SO_2N(R^{cc})_2$, –SO_2R^{cc}, –SO_2OR^{cc}, –SOR^{aa}, –$C(=S)N(R^{cc})_2$, –$C(=O)SR^{cc}$, –$C(=S)SR^{cc}$, –$P(=O)_2R^{aa}$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl,

alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3^+X^-$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6}alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl,

heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^–$, $–NH(C_{1–6}$ alkyl$)_2^+X^–$, $–NH_2(C_{1–6}$ alkyl$)^+X^–$, $–NH_3^+X^–$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), –N(OH)$(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$ alkyl), $–OC(=O)(C_{1–6}$ alkyl), $–OCO_2(C_{1–6}$ alkyl), $–C(=O)NH_2$, $–C(=O)N(C_{1–6}$ alkyl$)_2$, –OC(=O)NH$(C_{1–6}$ alkyl), –NHC(=O)($C_{1–6}$ alkyl), $–N(C_{1–6}$ alkyl$)C(=O)($ $C_{1–6}$ alkyl), $–NHCO_2(C_{1–6}$ alkyl), $–NHC(=O)N(C_{1–6}$ alkyl$)_2$, –NHC(=O)NH$(C_{1–6}$ alkyl), $–NHC(=O)NH_2$, $–C(=NH)O(C_{1–6}$ alkyl),$–OC(=NH)(C_{1–6}$ alkyl), $–OC(=NH)OC_{1–6}$ alkyl, $–C(=NH)N(C_{1–6}$ alkyl$)_2$, –C(=NH)NH$(C_{1–6}$ alkyl), $–C(=NH)NH_2$, $–OC(=NH)N(C_{1–6}$ alkyl$)_2$, –OC(NH)NH$(C_{1–6}$ alkyl), $–OC(NH)NH_2$, $–NHC(NH)N(C_{1–6}$ alkyl$)_2$, $–NHC(=NH)NH_2$, $–NHSO_2(C_{1–6}$ alkyl), $–SO_2N(C_{1–6}$ alkyl$)_2$, $–SO_2NH(C_{1–6}$ alkyl), $–SO_2NH_2$,$–SO_2C_{1–6}$ alkyl, $–SO_2OC_{1–6}$ alkyl, $–OSO_2C_{1–6}$ alkyl, $–SOC_{1–6}$ alkyl, $–Si(C_{1–6}$ alkyl$)_3$, $–OSi(C_{1–6}$ alkyl$)_3$, $–C(=S)N(C_{1–6}$ alkyl$)_2$, -C(=S)NH$(C_{1–6}$ alkyl), $-C(=S)NH_2$, $–C(=O)S(C_{1–6}$ alkyl), $–C(=S)SC_{1–6}$ alkyl, $–SC(=S)SC_{1–6}$ alkyl, $–P(=O)_2(C_{1–6}$ alkyl), $–P(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(C_{1–6}$ alkyl$)_2$, $–OP(=O)(OC_{1–6}$ alkyl$)_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, hetero$C_{1–6}$ alkyl, hetero$C_{2–6}$ alkenyl, hetero$C_{2–6}$alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

[0047] In certain embodiments, the carbon substituents are selected from the group consisting of halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{aa}$, $–N(R^{bb})_2$–SH, $–SR^{aa}$, $–SSR^{cc}$, $–C(=O)R^{aa}$, $–CO_2H$, –CHO, $–C(OR^{cc})_2$, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $NR^{bb}SO_2R^{aa}$, $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, $–SO_2OR^{aa}$, $–OSO_2R^{aa}$, $–S(=O)R^{aa}$, $–OS(=O)R^{aa}$, $C_{1–10}$ alkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–14}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, or $=NR^{bb}$.

[0048] In certain embodiments, the carbon substituents are selected from the group consisting of halogen, –CN, $–NO_2$, –OH, $–OR^{aa}$, $–N(R^{bb})_2$, –SH, $–SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2H$, –CHO, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–6}$ carbocyclyl, 3–6 membered heterocyclyl, C_6 aryl, and 5–6 membered heteroaryl, wherein each alkyl, alkenyl,

alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

[0049] As used herein, the term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0050] As used herein, a "counterion" is a negatively charged group associated with a positively charged quarternary amine in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.,* acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0051] As used herein, the term "hydroxyl" or "hydroxy" refers to the group –OH. The term "substituted hydroxyl" or "substituted hydroxy," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $–OR^{aa}$, $–ON(R^{bb})_2$, $–OC(=O)SR^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–OC(=O)N(R^{bb})_2$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})N(R^{bb})_2$, $–OS(=O)R^{aa}$, $–OSO_2R^{aa}$, $–OSi(R^{aa})_3$, $–OP(R^{cc})_2$, $–OP(=O)(R^{aa})_2$, and $–OP(=O)(OR^{cc})_2$,wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0052] As used herein, the term "thiol" or "thio" refers to the group –SH. The term "substituted thiol" or "substituted thio," by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $–SR^{aa}$, $–S=SR^{cc}$, $–SC(=S)SR^{aa}$, $–SC(=O)SR^{aa}$, $–SC(=O)OR^{aa}$, and $–SC(=O)R^{aa}$, wherein R^{aa} and R^{cc} are as defined herein.

[0053] As used herein, the term, "amino" refers to the group $–NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino, as defined herein. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0054] As used herein, the term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $–NH(R^{bb})$, $–NHC(=O)R^{aa}$, $–NHCO_2R^{aa}$, $–NHC(=O)N(R^{bb})_2$, $–NHC(=NR^{bb})N(R^{bb})_2$, $–NHSO_2R^{aa}$, and $–NHP(=O)(OR^{cc})_2$, wherein R^{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $–NH(R^{bb})$ is not hydrogen.

[0055] As used herein, the term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $–N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $–NR^{bb}SO_2R^{aa}$, and $–NR^{bb}P(=O)(OR^{cc})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0056] As used herein, the term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $–N(R^{bb})_3$ and $–N(R^{bb})_3^+X^-$, wherein R^{bb} and X^- are as defined herein.

[0057] As used herein, the term "alkoxyalkyl" refers to an alkyl group as defined herein substituted by a group of formula $–OR^{aa}$ wherein R^{aa} is as defined herein, wherein the point of attachment is on the alkyl group.

[0058] As used herein, the term "aminoalkyl" refers to an alkyl group as defined herein substituted by an amino or substituted amino group, as defined herein, wherein the point of attachment is on the alkyl group.

[0059] As used herein, the term "sulfonyl" refers to a group selected from $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, and $–SO_2OR^{aa}$, wherein R^{aa} and R^{bb} are as defined herein.

[0060] As used herein, the term "sulfinyl" refers to the group $–S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0061] As used herein, the term "carbonyl" refers a group wherein the carbon directly attached to the parent molecule is sp^2 hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones ($–C(=O)R^{aa}$), carboxylic acids ($–CO_2H$), aldehydes (–CHO), esters ($–CO_2R^{aa}$, $–C(=O)SR^{aa}$, $–C(=S)SR^{aa}$), amides ($–C(=O)N(R^{bb})_2$, $–C(=O)NR^{bb}SO_2R^{aa}$, $–C(=S)N(R^{bb})_2$), and imines ($–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$), $–C(=NR^{bb})N(R^{bb})_2$), wherein R^{aa} and R^{bb} are as defined herein.

[0062] As used herein, the term "silyl" refers to the group $–Si(R^{aa})_3$, wherein R^{aa} is as defined herein.

[0063] As used herein, the term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0064] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, –

$C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0065] In certain embodiments, nitrogen substituents are selected from the group consisting of hydrogen, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0066] In certain embodiments, the substituent present on the nitrogen atom is an nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.,* aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0067] For example, nitrogen protecting groups such as amide groups *(e.g.,* $-C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)acetamide, 3–(*p*–hydroxyphenyl)propanamide, 3–(*o*–

nitrophenyl)propanamide, 2–methyl–2–(*o*–nitrophenoxy)propanamide, 2–methyl–2–(*o*–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, *o*–nitrocinnamide, *N*–acetylmethionine derivative, *o*–nitrobenzamide and *o*–(benzoyloxymethyl)benzamide.

[0068] Nitrogen protecting groups such as carbamate groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–*t*–butylphenyl)–1–methylethyl carbamate (*t*–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(*N,N*–dicyclohexylcarboxamido)ethyl carbamate, *t*–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, *N*–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), *m*–nitrophenyl carbamate, 3,5–dimethoxybenzyl carbamate, *o*–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(*o*–nitrophenyl)methyl carbamate, *t*–amyl carbamate, *S*–benzyl thiocarbamate, *p*–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*–decyloxybenzyl carbamate, 2,2–dimethoxyacylvinyl carbamate, *o*–(*N,N*–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(*N,N*–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–

furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*–(*p'*–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(*p*–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, *p*–(phenylazo)benzyl carbamate, 2,4,6–tri–*t*–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, and 2,4,6–trimethylbenzyl carbamate.

[0069] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $–S(=O)_2R^{aa}$) include, but are not limited to, *p*–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0070] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl–(10)–acyl derivative, *N'*–*p*–toluenesulfonylaminoacyl derivative, *N'*–phenylaminothioacyl derivative, *N*–benzoylphenylalanyl derivative, *N*–acetylmethionine derivative, 4,5–diphenyl–3–oxazolin–2–one, *N*–phthalimide, *N*–dithiasuccinimide (Dts), *N*–2,3–diphenylmaleimide, *N*–2,5–dimethylpyrrole, *N*–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, *N*–methylamine, *N*–allylamine, *N*–[2–(trimethylsilyl)ethoxy]methylamine (SEM), *N*–3–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N'*–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N',N'*–dimethylaminomethylene)amine, *N,N'*–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–

hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–[phenyl(pentaacylchromium– or tungsten)acyl]amine, *N*–copper chelate, *N*–zinc chelate, *N*–nitroamine, *N*–nitrosoamine, amine *N*–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3–nitropyridinesulfenamide (Npys).

[0071] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, and $-P(=O)(R^{aa})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0072] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–

methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, *p*–methoxyphenyldiphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4'–bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4′,4″–tris(levulinoyloxyphenyl)methyl, 4,4′,4″–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4′,4″–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1′–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodithiolan–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*–butyl carbonate (BOC), *p*–nitrophenyl carbonate, benzyl carbonate, *p*–methoxybenzyl carbonate, 3,4–dimethoxybenzyl carbonate, *o*–nitrobenzyl carbonate, *p*–nitrobenzyl carbonate, *S*–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, *o*–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)–2–methyl–2–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N',N'*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0073] In certain embodiments, the substituent present on an sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups

include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0074] As used herein, a "leaving group" (LG) is an art–understood term referring to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. As used herein, a leaving group can be an atom or a group capable of being displaced by a nucleophile. See, for example, Smith, March *Advanced Organic Chemistry* 6th ed. (501–502). Exemplary leaving groups include, but are not limited to, halo (*e.g.*, chloro, bromo, iodo), $-OR^{aa}$ (when the O atom is attached to a carbonyl group, wherein R^{aa} is as defined herein), $-O(C=O)R^{LG}$, or $-O(SO)_2R^{LG}$ (*e.g.*, tosyl, mesyl, besyl), wherein R^{LG} is optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl. In some cases, the leaving group is a halogen. In some embodiments, the leaving group is I.

[0075] As used herein, use of the phrase "at least one instance" refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[0076] A "non-hydrogen group" refers to any group that is defined for a particular variable that is not hydrogen.

[0077] A "carbohydrate group" or a "carbohydrate" refers to a monosaccharide or a polysaccharide (*e.g.*, a disaccharide or oligosaccharide). Exemplary monosaccharides include, but are not limited to, natural sugars, such as allose, altrose, glucose, mannose, gulose, idose, galactose, talose, ribose, arabinose, xylose, and lyxose. Disaccharides are two joined monosaccharides. Exemplary disaccharides include, but are not limited to, sucrose, maltose, cellobiose, and lactose. Typically, an oligosaccharide includes between three and ten monosaccharide units (*e.g.*, raffinose, stachyose). The carbohydrate group may be a natural sugar or a modified sugar. Exemplary modified sugars include, but are not limited to, sugars where the hydroxyl group is replaced with an amino group and/or alkyl group (*e.g.*, such as desosamine), 2´-deoxyribose wherein a hydroxyl group is removed, 2´-fluororibose wherein a hydroxyl group is replace with a fluorine, or N-acetylglucosamine, or a nitrogen-containing form of glucose (*e.g.*, 2´-fluororibose, deoxyribose, and hexose), and the like.

Various carbohydrates are further described below and herein. Carbohydrates may exist in many different forms, for example, conformers, cyclic forms, acyclic forms, stereoisomers, tautomers, anomers, and isomers.

[0078] As used herein, a nucleophile refers to a chemical species that donates an electron pair to an electrophile to form a chemical bond in relation to a reaction. All molecules or ions with a free pair of electrons or at least one pi bond can act as nucleophiles. The nucleophile can be a compound or an atom. In certain embodiments, a nucleophile is of formula X^{n1}-R^{23}, M-R^{23}, or $M_s(X^{n2})_t$, wherein M is a metal (*e.g.*, Li, Na, or K), or a metal complex (*e.g.* metal halide such as CuX^n, or MgX^{n2}); X^{n1} is -OR^{xn}, -SR^{xn}, or -$N(R^{xn})_2$; X^{n2} is a halogen, CN, N_3, -OR^{xn}, -SR^{xn}, -$N(R^{xn})_2$; each instance of R^{xn} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{23} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl; s is 1, 2, 3, or 4; and t is 1, 2, 3, or 4. As used herein, a metal complex refers to a metal chelated with ligands such as organic ompounds, anions such as halides, hydroxyls, or carboxylates. In certain embodiments, the nucleophile is X^{n1}-R^{23} (*e.g.* R^{23}-OH; R^{23}-SH, R^{23}-NH_2 (*e.g.,* NH_3)). In certain embodiments, nucleophile is M-R^{23} (*e.g.,* Li-alkyl). In certain embodiments, nucleophile is $M_s(X^{n2})_t$ (*e.g.* NaCN, NaN_3, $NaNH_2$, $LiOR^{xn}$, $NaOR^{xn}$).

[0079] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[0080] As used herein, the term "salt" refers to any and all salts, and encompasses pharmaceutically acceptable salts.

[0081] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the macrolides of this invention include those derived from suitable inorganic and organic

acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0082] The term "solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds as described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0083] The term "hydrate" refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x\ H_2O$, wherein R is the

compound, and x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5\ H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2\ H_2O$) and hexahydrates ($R \cdot 6\ H_2O$)).

[0084] As used herein, the term "tautomer" includes two or more interconvertable forms resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a double bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may be catalyzed by acid or base. Exemplary tautomerizations include keto–to–enol; amide–to–imide; lactam–to–lactim; enamine–to–imine; and enamine–to–(a different) enamine tautomerizations.

[0085] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[0086] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0087] The term "polymorphs" refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof) in a particular crystal packing arrangement. All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0088] The term "prodrugs" refer to compounds, including derivatives of the compounds of Formula (**I**), which have cleavable groups and become by solvolysis or under physiological conditions the compounds as described herein which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds as described herein may be preferred in certain instances.

[0089] The term "isotopes" refers to variants of a particular chemical element such that, while all isotopes of a given element share the same number of protons in each atom of the element, those isotopes differ in the number of neutrons.

[0090] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or other non–human animals, for example mammals [*e.g.*, primates (*e.g.,* cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs], birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), reptiles, amphibians, and fish. In certain embodiments, the non–human animal is a mammal. The non–human animal may be a male or female and at any stage of development. A non–human animal may be a transgenic animal.

[0091] "Disease," "disorder," and "condition" are used interchangeably herein.

[0092] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified infectious disease or inflammatory condition, which reduces the severity of the infectious disease or inflammatory condition, or retards or slows the progression of the infectious

disease or inflammatory condition ("therapeutic treatment"), and also contemplates an action that occurs before a subject begins to suffer from the specified infectious disease or inflammatory condition ("prophylactic treatment").

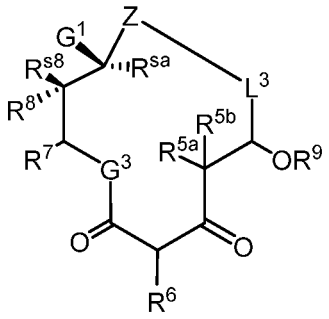
[0093] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0094] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of an infectious disease or inflammatory condition, or to delay or minimize one or more symptoms associated with the infectious disease or inflammatory condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the infectious disease or inflammatory condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of infectious disease or inflammatory condition, or enhances the therapeutic efficacy of another therapeutic agent.

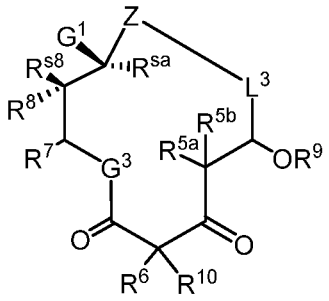
[0095] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent an infectious disease or inflammatory condition, or one or more symptoms associated with the infectious disease or inflammatory condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the infectious disease or inflammatory condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

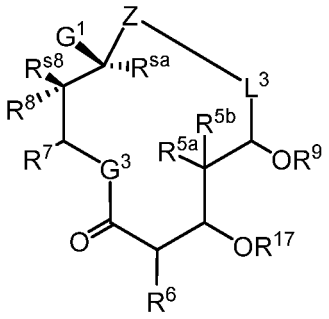
[0096] As generally understood from the present disclosure, the present invention is, in part, directed to ketolides of the formulae below, constructed from the coupling of an eastern half and a western half, followed by macrocyclization and optionally further synthetic manipulation:



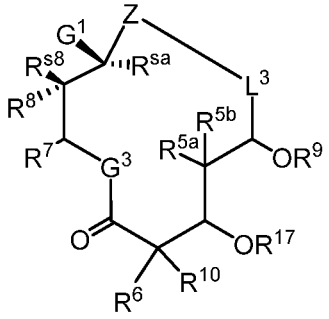
(**N-2**),



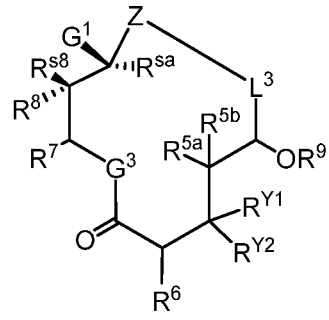
(**N-3**),



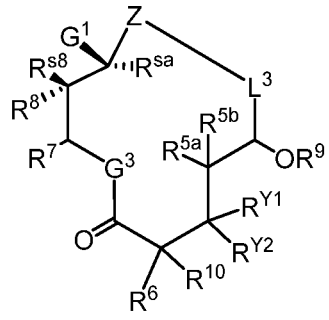
(**N-4**),



(**N-5**),

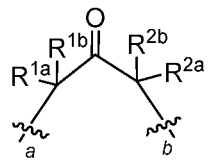


(**N-6**),

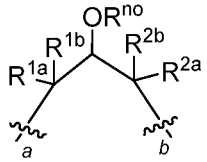


(**N-7**)

or a salt thereof,

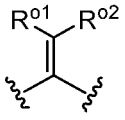


Z is of the formula (z-i) or



(z-ii);

each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or

R^{2a} and R^{2b} are taken together to form  ;

a indicates the point of attachment to the carbon substituted by G1;

b indicates the point of attachment to L^3;

each of R^{o1} and R^{o2} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

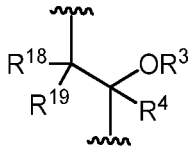
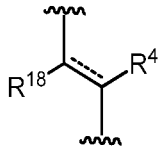
R^{no} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group;

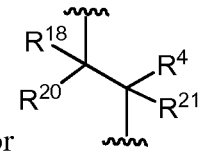
R^{sa} is hydrogen, hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl;

or R^{sa} and R^{1a} or R^{sa} and R^{1b} are taken together to form a bond;

R^{s8} is hydrogen or OR^{11};

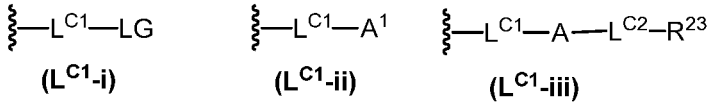
L^3 is a group of formula:

 (**L^3-i**),  (**L^3-ii**),

 or (**L^3-iii**);

====== represents a single or double bond;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:



(**L^{C1}-i**) (**L^{C1}-ii**) (**L^{C1}-iii**);

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl;

each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring;

each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group;

R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

R^7 and R^8 are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^9 and R^{17} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate;

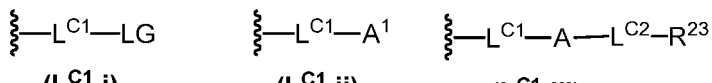
R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,

optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, and halogen;

G^3 is –O–, –S–, or $–N(R^{G1})–$, wherein R^{G1} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

G^1 is hydrogen, $–OR^{12}$ or $–NR^{13}R^{14}$;

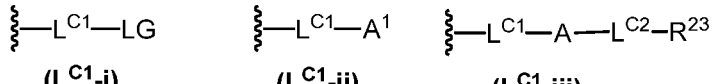
provided when G^1 is $–OR^{12}$, then R^{11} and R^{12} are joined as a group of formula –C(=O)- to provide a cyclic carbonate, or R^{11} and R^{12} are not joined, and R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, and R^{12} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group, or a group of formula:



$(L^{C1}\text{-i})$ $(L^{C1}\text{-ii})$ $(L^{C1}\text{-iii})$;

or provided when G^1 is $–NR^{13}R^{14}$, then R^{11} and R^{13} are joined as a group of formula –C(=O)- to provide a cyclic carbamate, or R^{11} and R^{13} are not joined, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, R^{13} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group, $-C(=O)R^{Z8}$, or $-C(=O)OR^{Z8}$, or a group of formula:



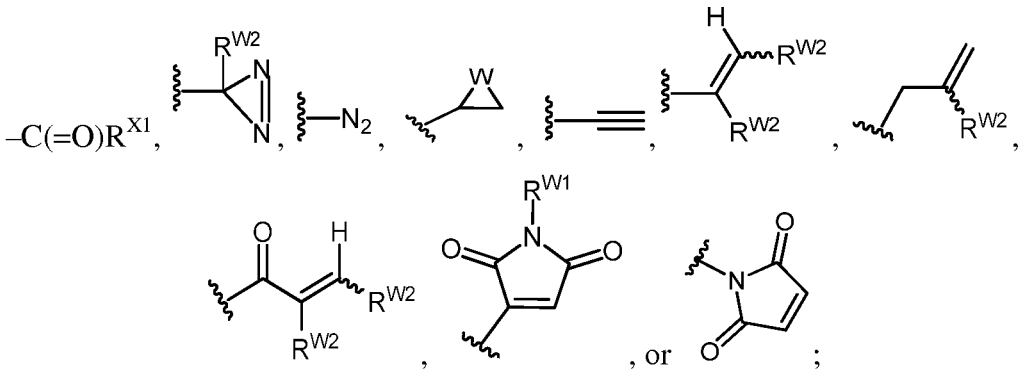
$(L^{C1}\text{-i})$ $(L^{C1}\text{-ii})$ $(L^{C1}\text{-iii})$

or R^{13} and R^{14} are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl;

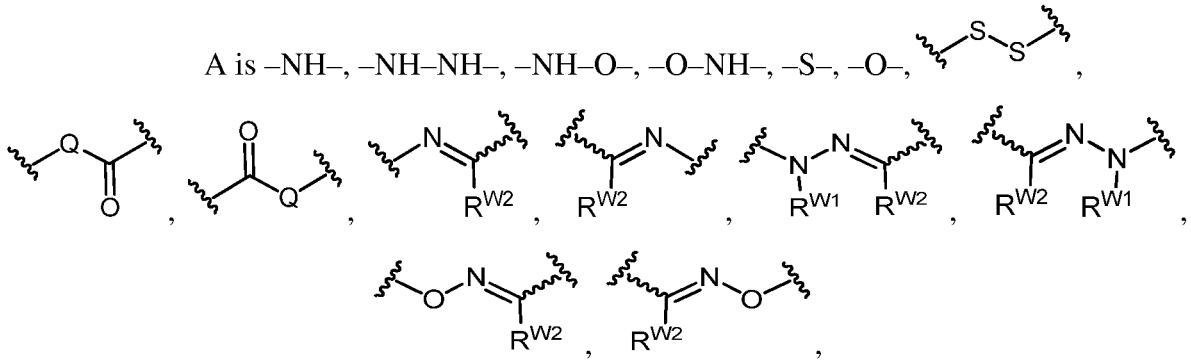
each instance of L^{C1} and L^{C2} is independently a bond, or a linking group selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene,

optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof;

each instance of A^1 is independently a leaving group (LG), –SH, –OH, $–NH_2$, –NH–NH_2, $–N_3$, –O–NH_2,



A is –NH–, –NH–NH–, –NH–O–, –O–NH–, –S–, –O–,



Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or a nitrogen protecting group;

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety;

R^{X1} is hydrogen, halogen, or $-OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or an oxygen protecting group;

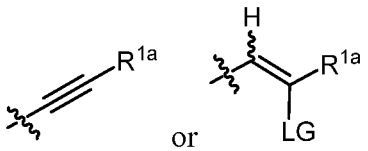
R^{23} is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl; and

each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

or A is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^{s1} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^{s1} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

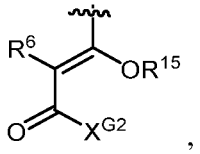
Y^1 is  ;

Y^2 is $-C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3})$ or $-C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})$;

each of R^{P1}, R^{P2}, and R^{P3} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

P^1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group; and

G^2 is a group of formula: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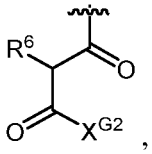
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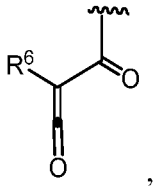
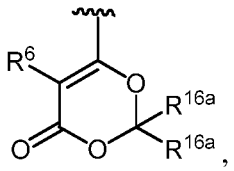

,

or ,

wherein:

each instance of X^{G2} is $-OR^{15}$, $-SR^{15}$, or $-N(R^{15})_2$;

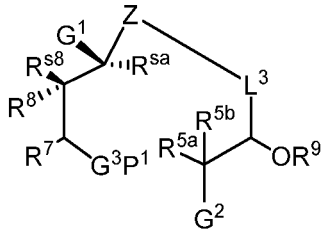
each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or two R^{15} groups are taken together to form an optionally substituted heteroaryl or heterocyclic ring; and

each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0097] Unless otherwise stated, any formulae as described herein are also meant to include a salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, and prodrug thereof. In certain embodiments, the provided macrolide is a salt of any of the formulae as described herein. In certain embodiments, the provided compound is a pharmaceutically acceptable salt of any of the formulae as described herein. In certain

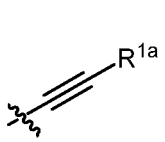
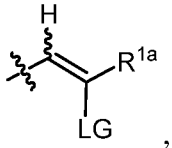
embodiments, the provided compound is a solvate of any of the formulae as described herein. In certain embodiments, the provided compound is a hydrate of any of the formulae as described herein. In certain embodiments, the provided compound is a polymorph of any of the formulae as described herein. In certain embodiments, the provided compound is a co-crystal of any of the formulae as described herein. In certain embodiments, the provided compound is a tautomer of any of the formulae as described herein. In certain embodiments, the provided compound is a stereoisomer of any of the formulae as described herein. In certain embodiments, the provided compound is of an isotopically labeled form of any of the formulae as described herein. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the disclosure. In certain embodiments, the provided compound is of a deuterated labeled form of any of the formulae as described herein. In certain embodiments, the provided compound is a prodrug of any of the formulae as described herein.

[0098] In certain embodiments, the macrolide is prepared from macrocyclization (*e.g.*, thermally induced macrocyclization) of the coupled precursor of the formula below, optionally followed by further synthetic manipulation, as described herein:



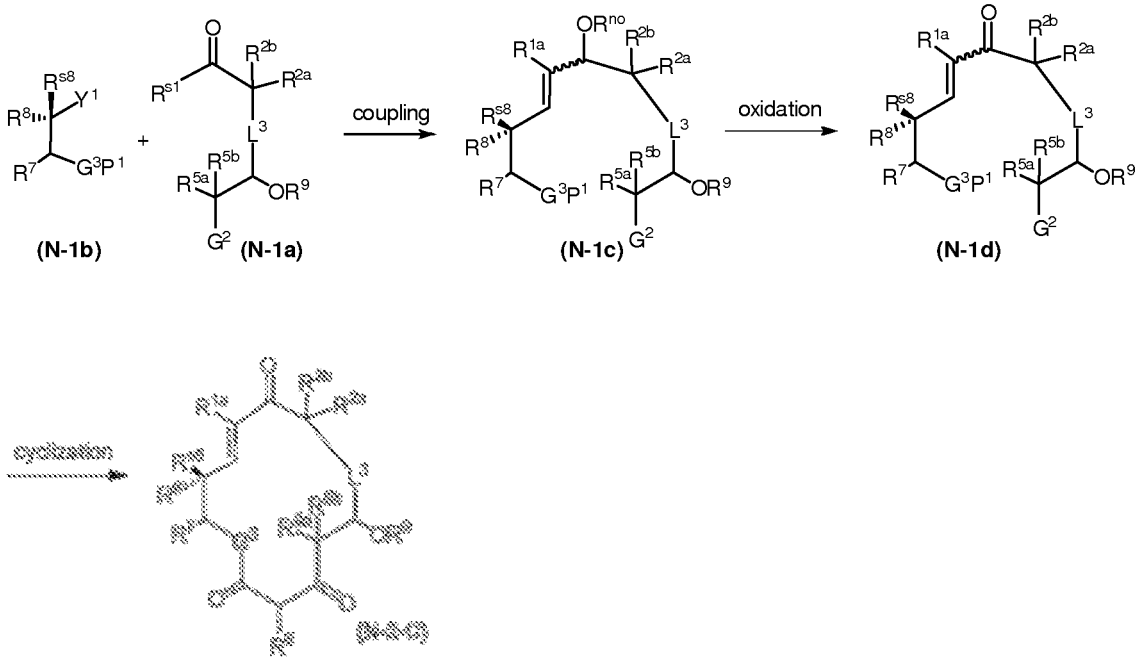
Coupling and Macrocyclization

[0099] As generally described herein, macrolides of the present invention are prepared by coupling of a western half (**A-i**) or (**A-ii**) with an eastern half (**B-i**) or (**B-ii**) to provide a compound of Formula (**N-1**), as depicted in *Scheme 1*. *Scheme 8a and 8b* depict certain specific embodiments of this coupling and macrocyclization steps to provide compounds falling with the scope of Formula (N-1).

[00100] As shown in *Scheme 8a*, when Y^1 is  or  , R^{1a} is as defined herein, R^{S1} is hydrogen, and LG is a leaving group; coupling of a compound of

Formula (**N-1b**) and Formula (**N-1a**) *via* hydromagnesiation provides a compound of Formula (**N-1c**).

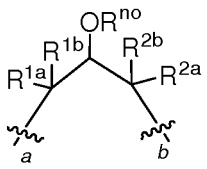
Scheme 8a.



[00101] In certain embodiments, the hydromagnesiation reaction is carried out in the presence of an organic base such as a Grignard reagent. In certain embodiments, more than one Grignard reagents are present. In certain embodiments, the Grignard reagent is of the formula R^{gr}-Mg-X^{gr}, wherein X^{gr} is halogen; and R^{gr} is optionally substituted alkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{gr} is optionally substituted alkyl or optionally substituted carbocyclyl. In certain embodiments, R^{gr} is optionally substituted alkyl. In certain embodiments, R^{gr} is branched alkyl (*e.g.*, iso-propyl, iso-butyl, or tert-butyl). In certain embodiments, R^{gr} is optionally substituted carbocyclyl (*e.g.*, cyclcopentyl). In certain embodiments, the Grignard reagent is iso-butyl-MgCl.

[00102] In certain embodimetns, the hydromagnesiation reaction is carried out in the presence of a catalyst. In certain embodiments, the catalyst is a Ti catalyst. In certain embodiments, the Ti catalyst is Cp_2TiCl_2.

[00103] In certain embodiments, the hydromagnesiation yields a compound of Formula (**N-1**), wherein Z is of the formula:



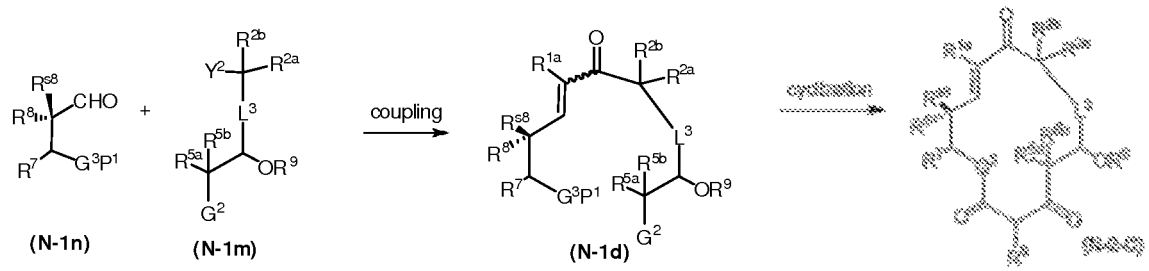
(**z-ii**)

wherein R^{sa} and R^{1a} or R^{sa} and R^{1b} are joined to form a bond; and R^{no}, R^{2b}, and R^{2a} are as defined herein.

[00104] As generally defined herein, LG is a leaving group capable of being displaced by a nucleophile as defined herein. In certain embodiments, the LG is a halide. In certain embodiments, the LG is I. In certain embodiments, the LG is a Br.

[00105] As shown in *Scheme 8b*, when Y^2 is –C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3}) or –C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3}), coupling of Formula (**N-1n**) and Formula (**N-1m**) *via* a Wittig or Horner-Emmons reaction forms the moiety –CH=CH-C(=O)–, and provides a compound of Formula (**N-1d**).

Scheme 8b.



[00106] As generally defined herein, R^{P1} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{P1} is optionally substituted alkyl. In certain embodiments, R^{P1} is unsubstituted alkyl.

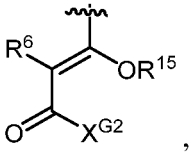
[00107] As generally defined herein, R^{P2} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{P2} is optionally substituted alkyl. In certain embodiments, R^{P2} is unsubstituted alkyl.

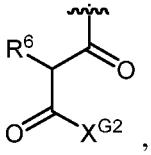
[00108] As generally defined herein, R^{P3} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted

carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{P3} is optionally substituted alkyl. In certain embodiments, R^{P3} is unsubstituted alkyl.

[00109] In certain embodiments, the double bond of the above recited formula such as Formula (**N-1-b**) is in the *cis*-configuration. In certain embodiments, the double bond of the above recited formula such as Formula (**N-1-b**) is in the *trans*-configuration.

[00110] Various macrolides may be accessed from these coupled products of Formula (**N-1**), depending upon the nature of the group G^2, upon macrocyclization. For example, as depicted in *Scheme 9*, when G^2 is a group of formula:



,


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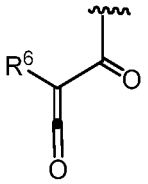
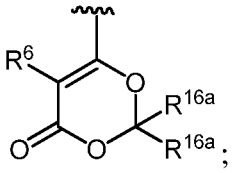
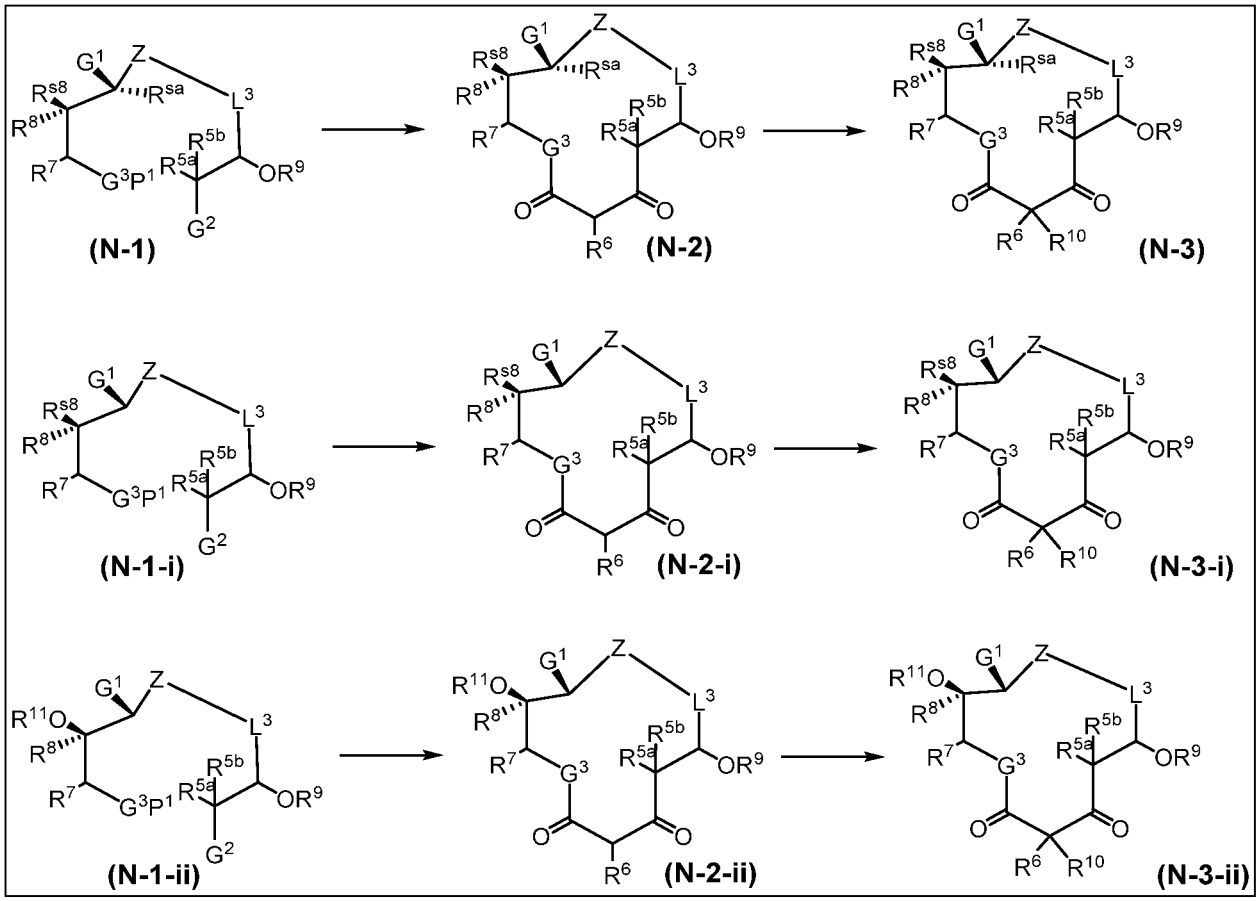


, or


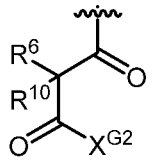
;

and R^6 is a hydrogen or non-hydrogen group, macrocyclization of the compound of Formula (**N-1**), *e.g.,* wherein P^1 is hydrogen, provides a macrolide of Formula (**N-2**). Enolization of the macrolide of Formula (**N-2**), followed by addition of a non-hydrogen group R^{10} (*e.g.,* with a base and an R^{10} alkylating agent, *e.g.*, R^{10}-LG, or with a halogenating agent if R^{10} is halogen), provides a macrolide of Formula (**N-3**).

Scheme 9.



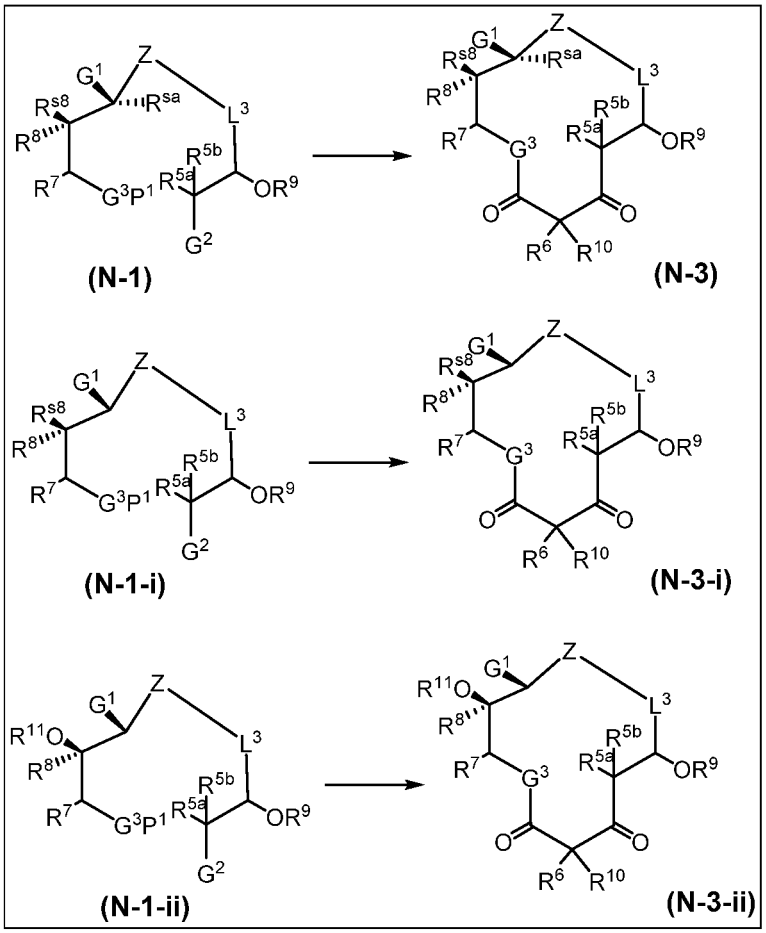
[00111] Alternatively, as depicted in *Scheme 10*, when G^2 is a group of formula:



;

wherein each of R^6 and R^{10} is hydrogen or a non-hydrogen group, macrocyclization of the compound of Formula (**N-1**), *e.g.,* wherein P^1 is hydrogen, provides a macrolide of Formula (**N-3**).

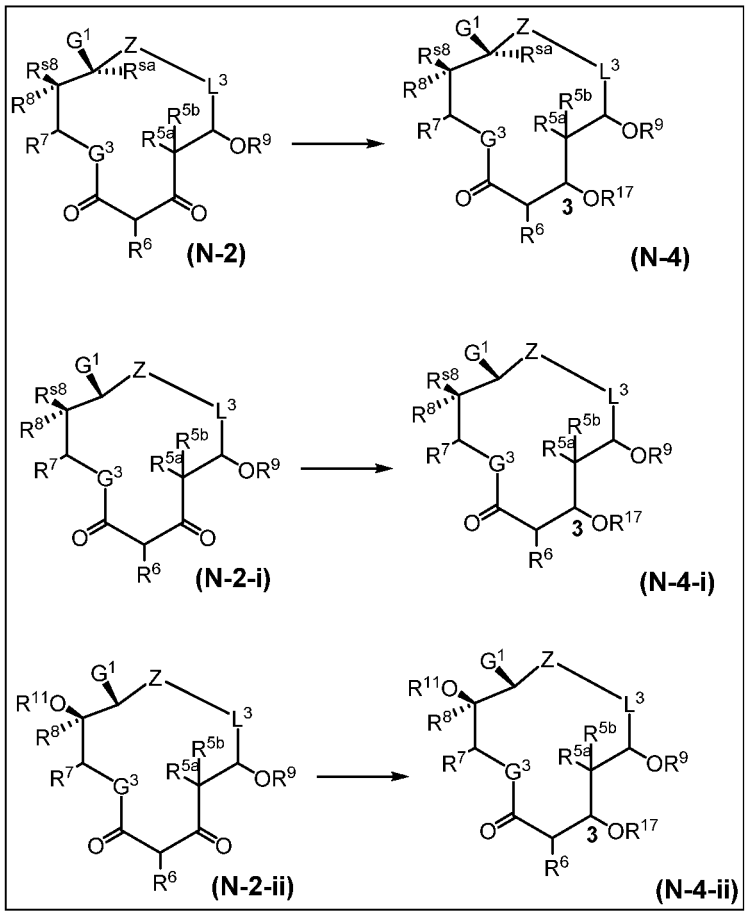
Scheme 10.



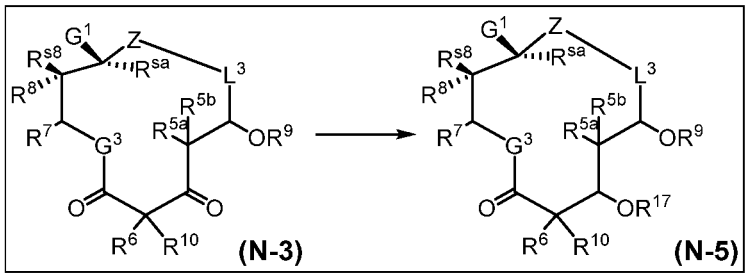
[00112] Further functionalization of the macrolide is also contemplated herein. For example, as depicted in Schemes 11 and 12, reduction of the C3 ketone of macrolides (**N-2**) and (**N-3**) to a hydroxyl group, optionally followed by protection, provides macrolides (**N-4**) and (**N-5**), respectively. Alternatively, the hydroxyl group at C3 can be modified through O-alkylation or acylation as depicted in *Schemes 13A-13B*, where LG is a leaving group as defined herein. In certain embodiments, R^{17} is $-C(=O)R^{Z8}$, wherein R^{Z8} is optionally substituted alkyl (*e.g.*, optionally substituted aralkyl or optionally substituted heteroaralkyl).

[00113] The ability to readily alter the oxidation state of the oxygen substituent at C3 enables the protection of this position as a carbonyl group while other free hydroxy groups are modified (*e.g.*, by O-alkylation). Therefore, oxidation or reduction of this position at various points along the specific synthetic sequence is contemplated herein.

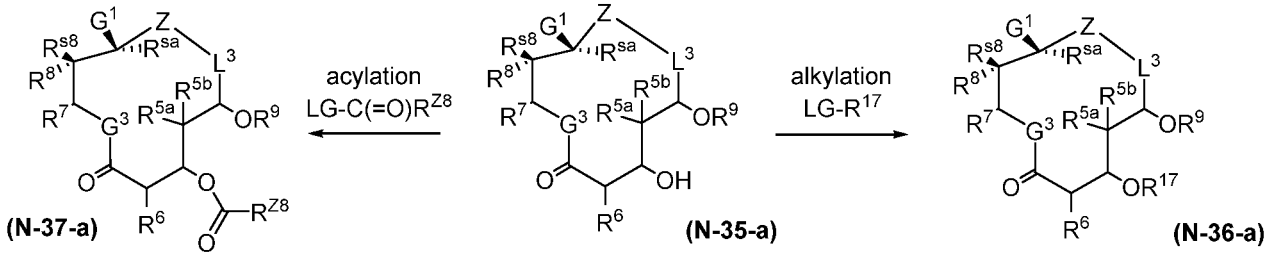
Scheme 11.



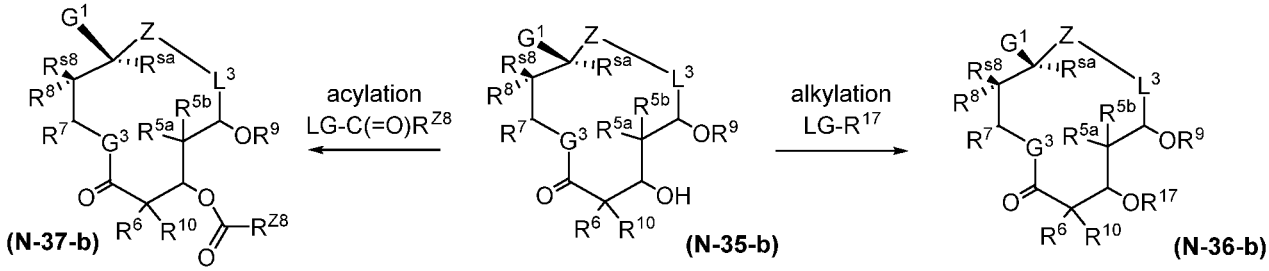
Scheme 12.



Scheme 13A.

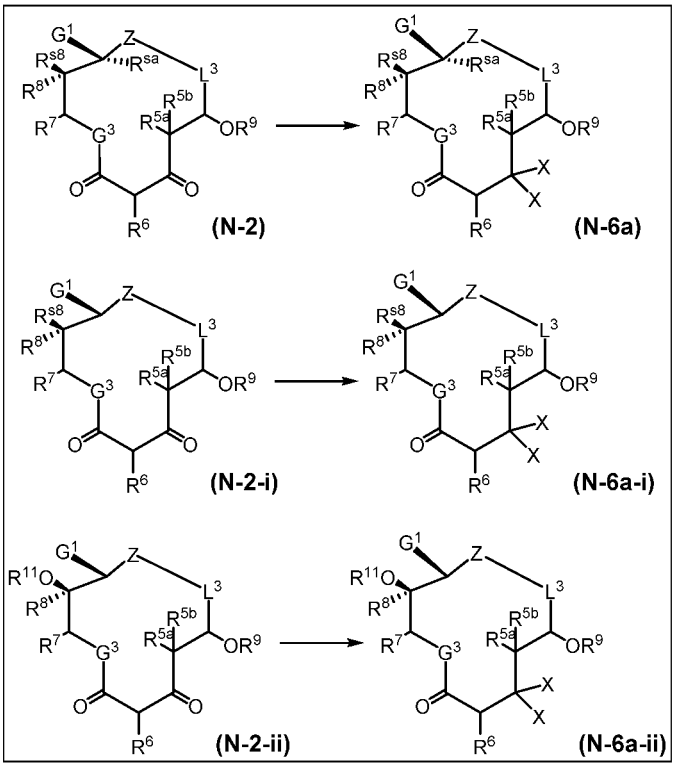


Scheme 13B.

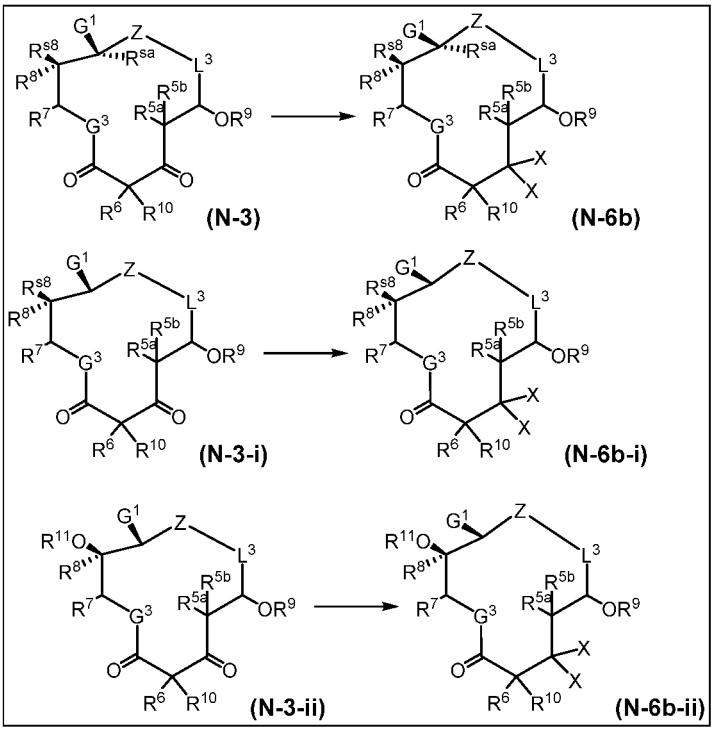


[00114] Further modification of the ketone or reduced macrolide is also contemplated herein. For example, as depicted in *Schemes 14A-14B* and *15A-15B*, the C3 ketone of Formula (**N-2**) or (**N-3**), or (**N-4**) or (**N-5**) (*e.g.,* hydroxyl at C3, wherein R^{17} is hydrogen), can be halogenated with an electrophilic halogenating agent (*e.g.*, Deoxo-Fluor) to give geminal dihalides such as Formula (**N-6**), or monohalides such as Formula (**N-7**), respectively, wherein each instance of X is independently a halogen (*e.g.*, fluorine, bromine, iodine).

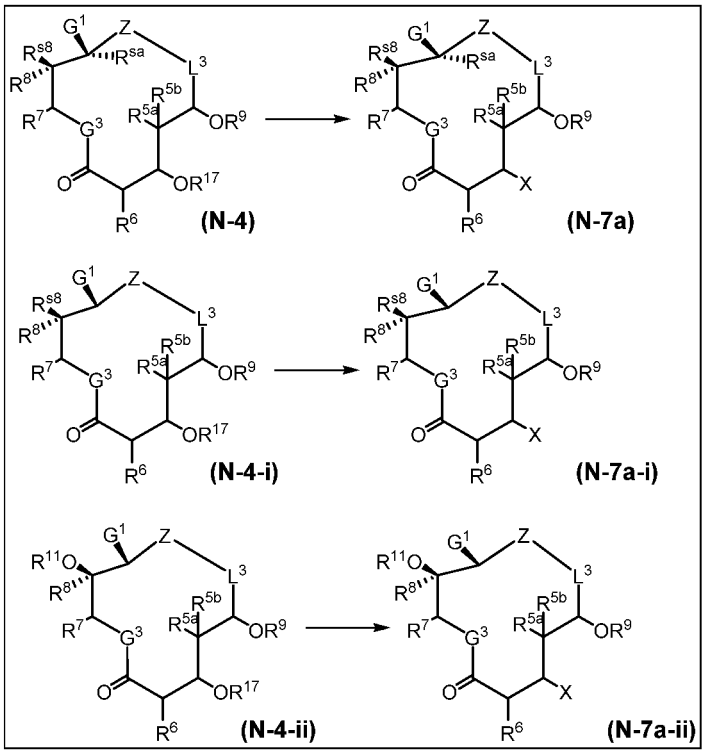
Scheme 14A.



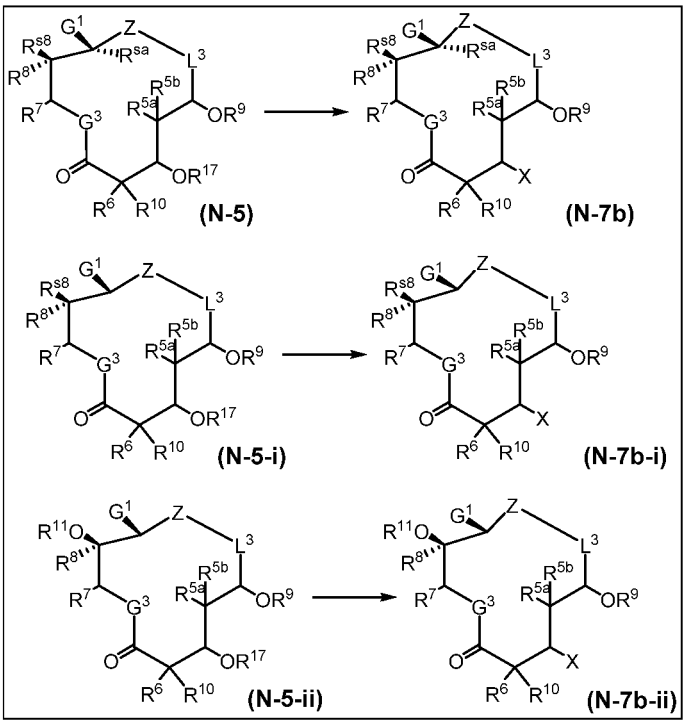
Scheme 14B.



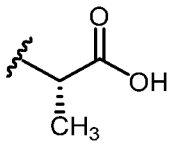
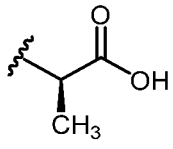
Scheme 15A.



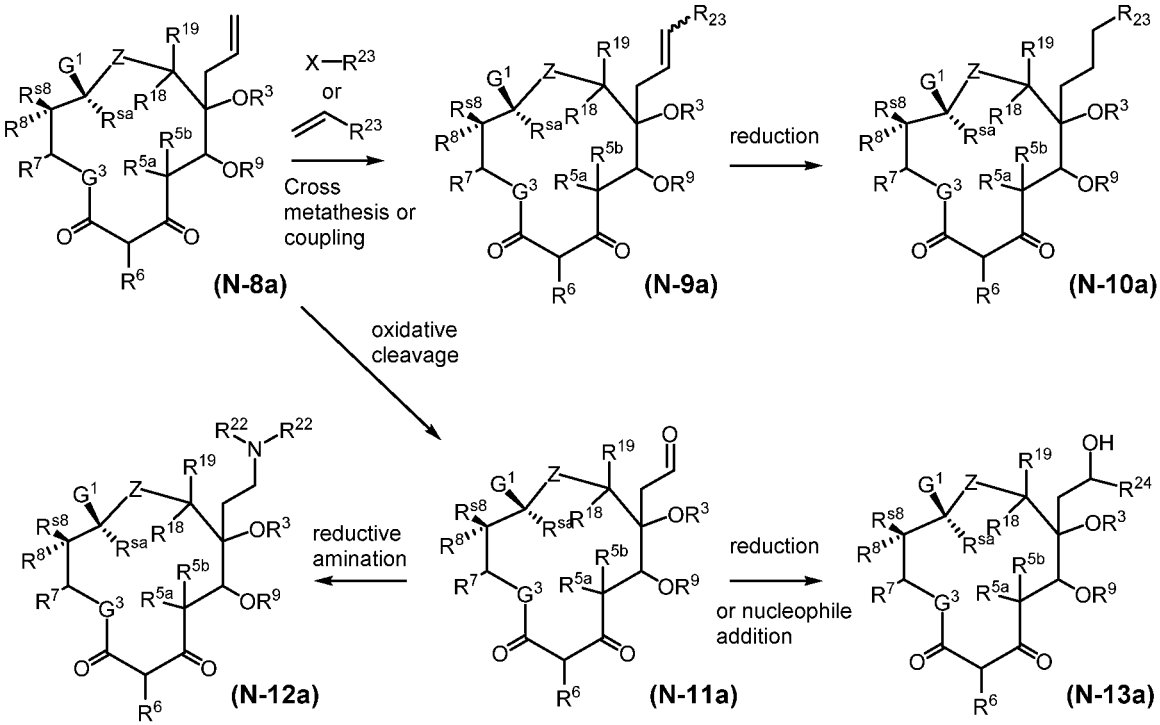
Scheme 15B.



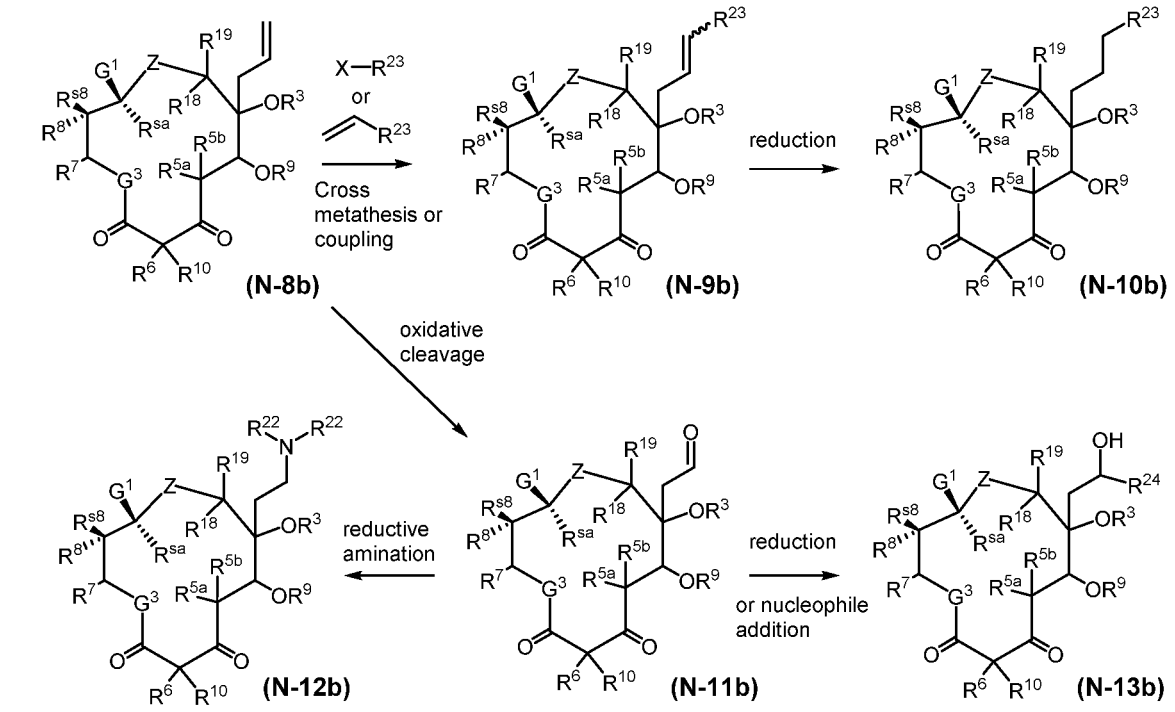
[00115] Instances wherein either R^3 or R^4 is allyl enable derivitization into novel macrolides as demonstrated in *Schemes 16A-16B* and *17A-17B*. A variety of groups, such as heteroaryl or aryl moieties, may be introduced through a transition metal catalyzed cross coupling (*e.g.*, Heck reaction) or through an olefin metathesis reaction (*e.g.*, cross methathesis using a Grubbs or Schrock metal carbene catalyst) leading to derivatives such as derivatives of

Formula (**N-9**) or (**N-15**). Subsequent manipulation of the olefin (*e.g.* hydrogenation) can be used to access further structural diversity (*e.g.* **N-10a-b**, **N-16a-b**). Alternatively, the olefin functionality can be oxidatively cleaved to produce a carbonyl functionality (**N-11a-b** or **N-17a-b**) that may be further modified by transformations such as reduction, nucleophilic additions (**N-13a-b** or **N-19a-b**), or reductive amination (**N-12a-b** or **N-18a-b**), wherein R^{23} is as defined herein; each instance of R^{22} is independently hydrogen or optionally substituted alkyl and R^{24} is hydrogen, optionally substituted alkyl, or optionally substituted aryl. In certain embodiments, R^{22} is $–CH_2C(=O)OH$. In certain embodiments, R^{22} is  . In certain embodiments, R^{22} is  .

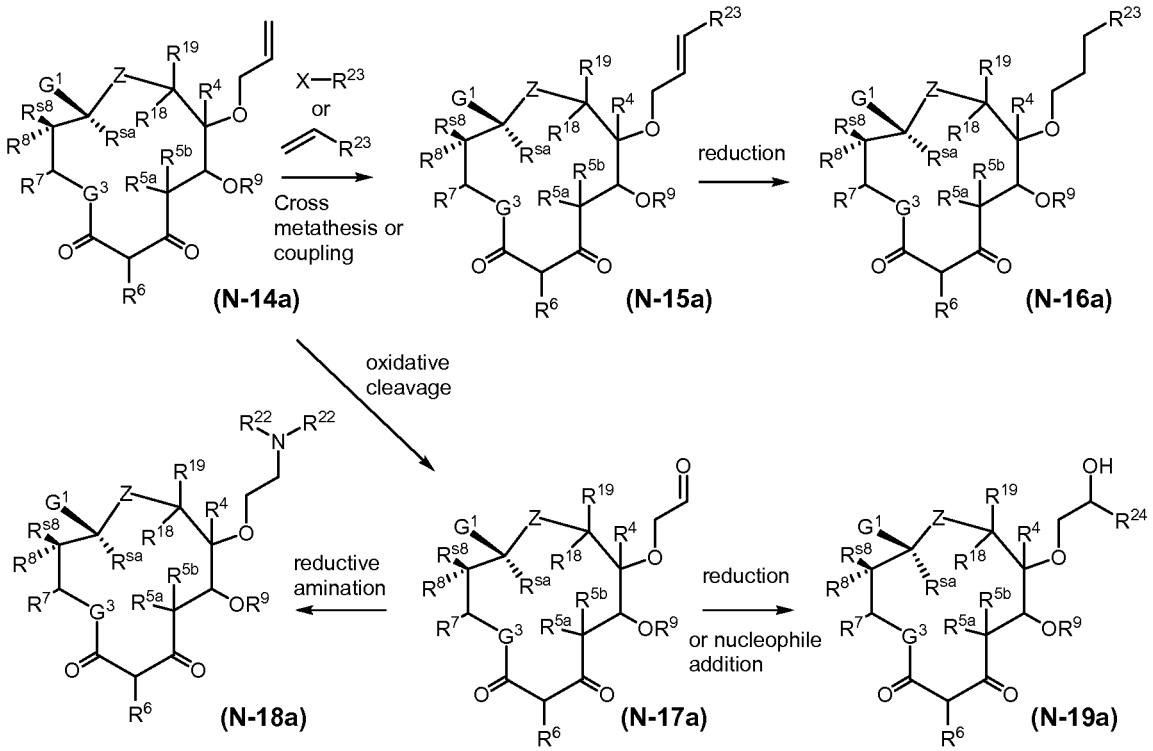
Scheme 16A.



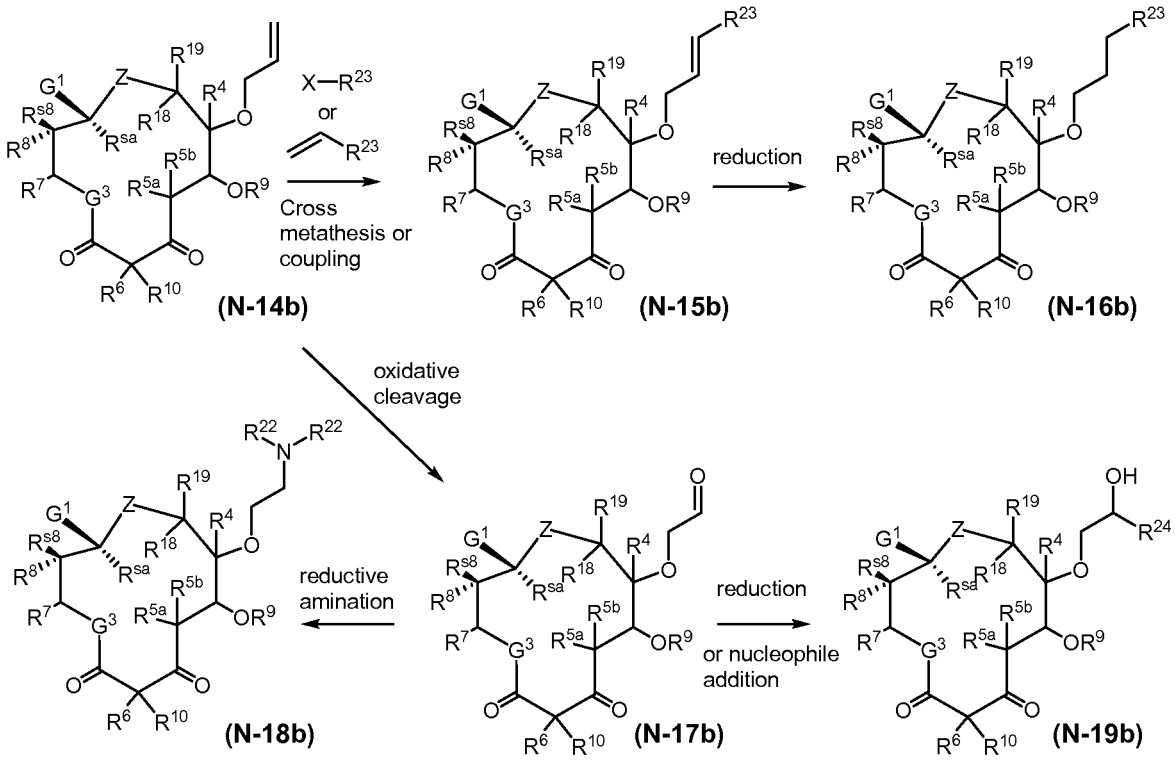
Scheme 16B.

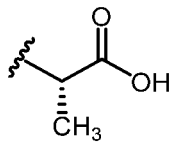
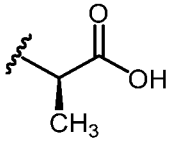


Scheme 17A.

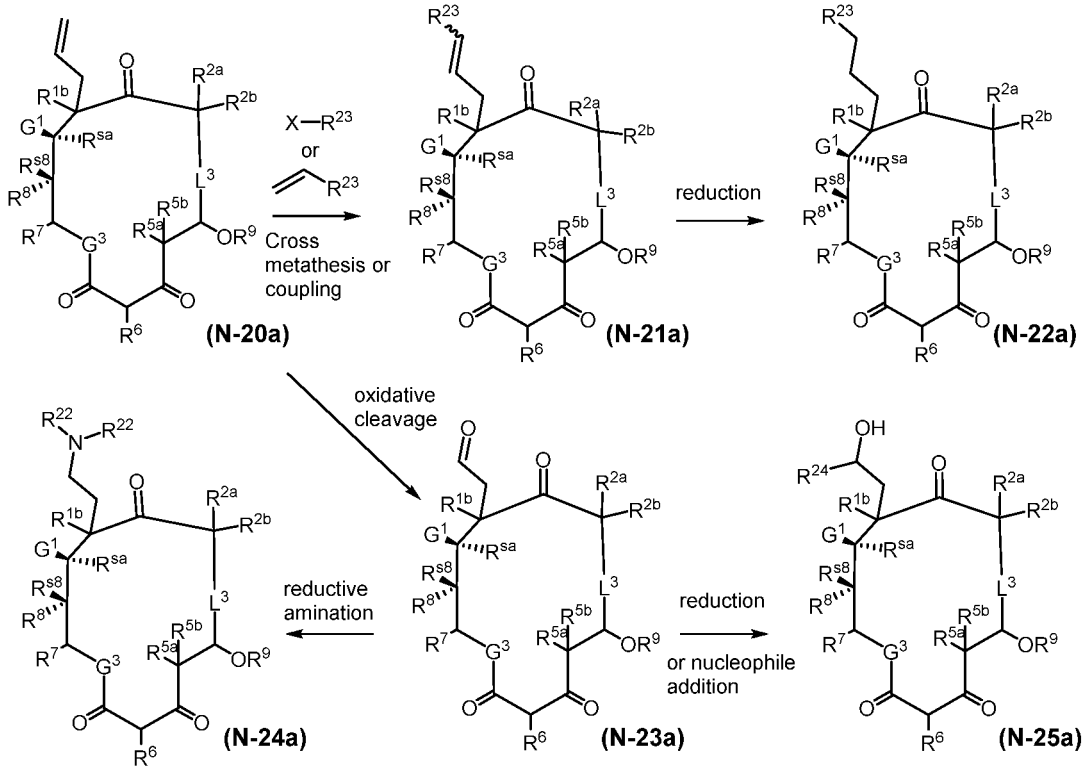


Scheme 17B.

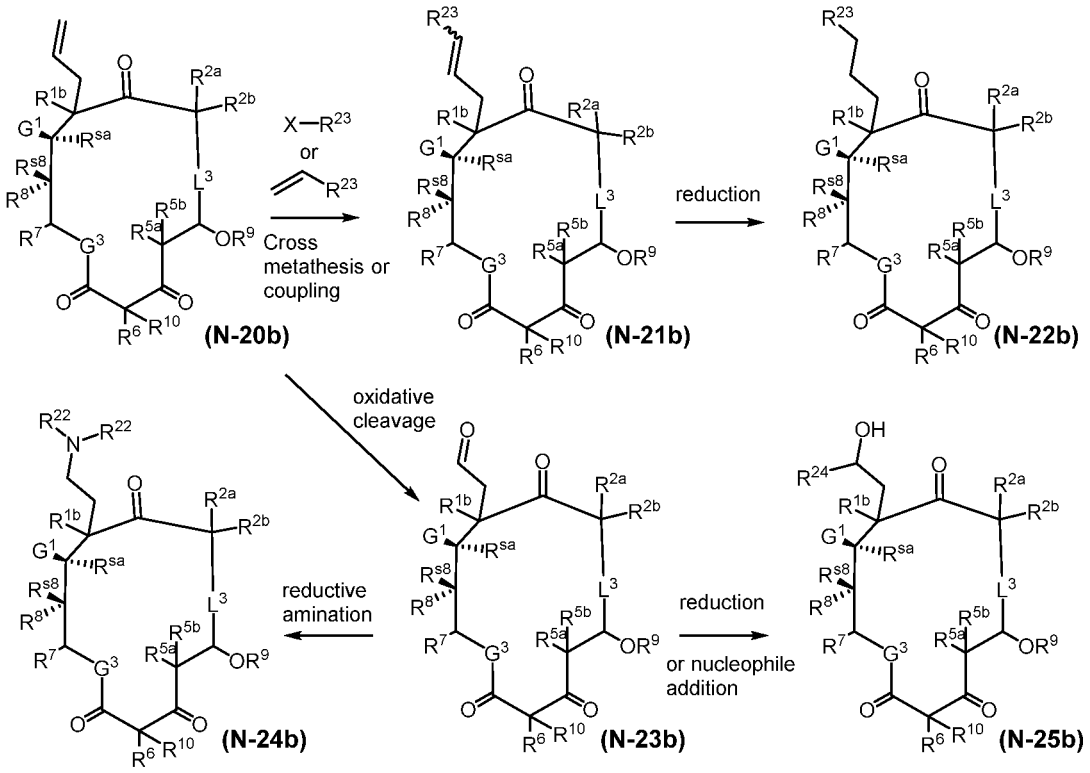


[00116] Further derivatization may be carried out using the transformations described herein pre- or post-macrocyclization wherein any of R^{1a}, R^{1b}, R^{2a}, or R^{2b} is allyl. While only depicted for macrocycles of Formulae (**N-20a**)-(**N-20b**) in *Scheme 18A-B*, such modifications are contemplated for any macrocycle, wherein at least one of R^{1a}, R^{1b}, R^{2a}, or R^{2b} is allyl. Derivitives wherein a -CH_2- moiety in the chain has been removed may be prepared using the precursor wherein any of R^{1a}, R^{1b}, R^{2a}, or R^{2b} is vinyl (*Scheme 19A-19B*). In certain embodiments, R^{22} is $-CH_2C(=O)OH$. In certain embodiments, R^{22} is  . In certain embodiments, R^{22} is  .

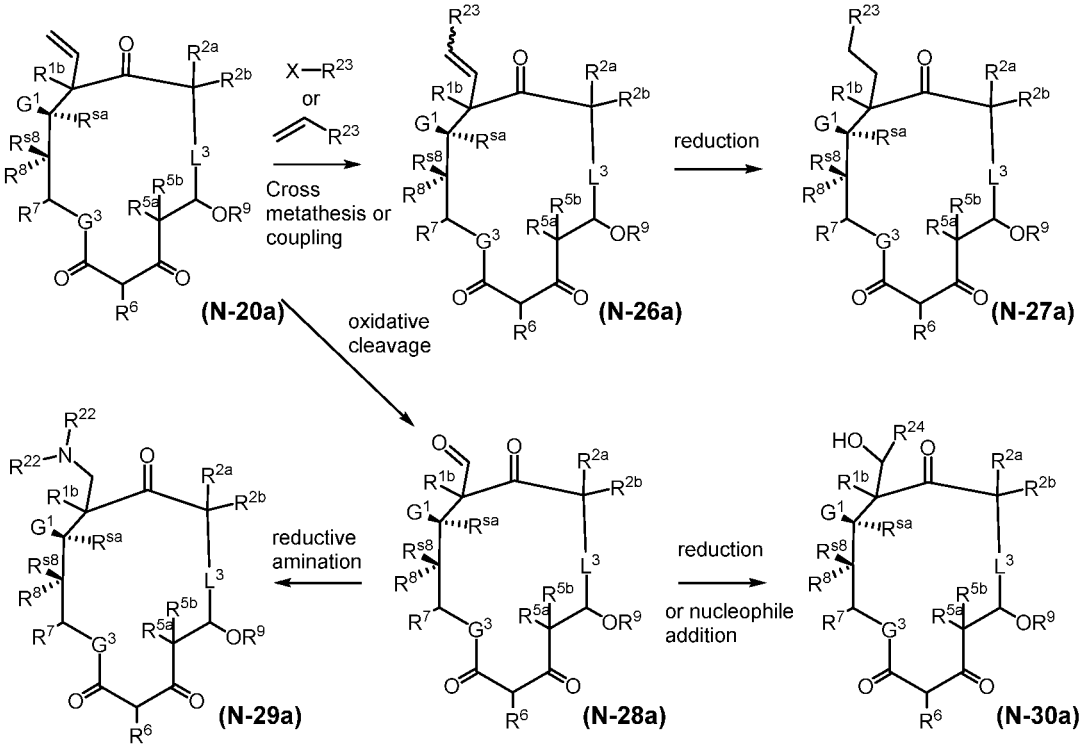
Scheme 18A.



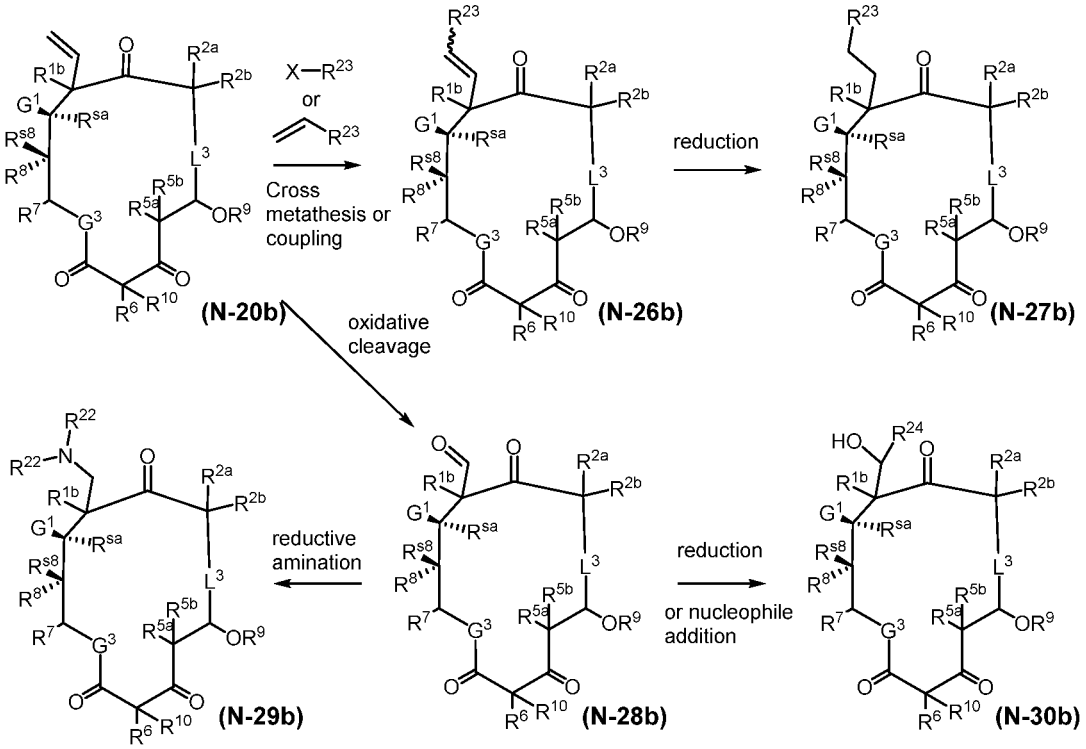
Scheme 18B.



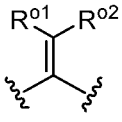
Scheme 19A.



Scheme 19B.

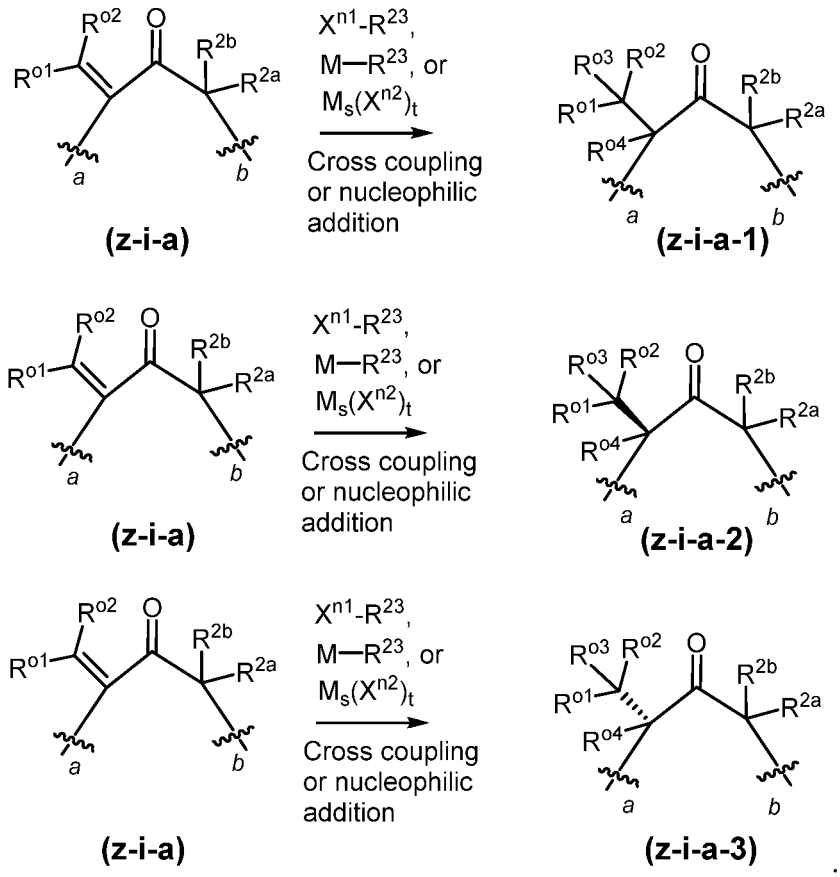


[00117] Further derivatization may be carried out using the transformations described herein pre- or post-macrocyclization when R^{1a} and R^{1b} or R^{2a} and R^{2b} are taken together to form



alpha to an oxo (=O) moiety, wherein R^{o1} and R^{o2} are as defined herein, and Z is of Formula (**z-i-a**). Exemplary transformations of Formula (**z-i-a**) include, but are not limited to, cross-coupling or nucleophilic addition (*e.g.* conjugated addition).

Scheme 20A.

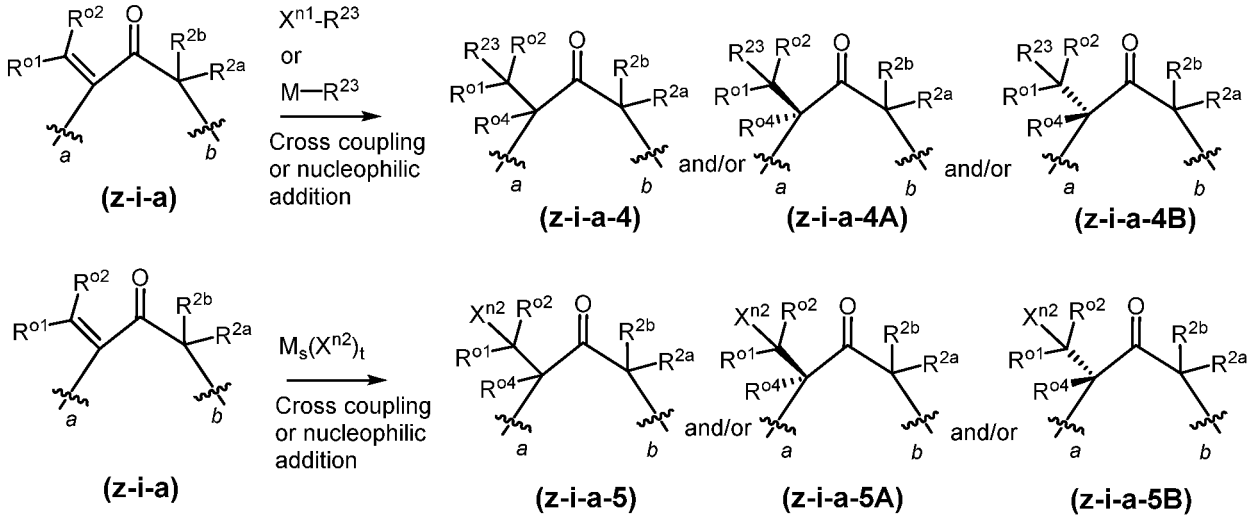


[00118] Conjugate addition reactions using a nucleophile such as an R^{23} species provide compounds of formula (**N-42a**) or (**N-42b**). As used herein, nucleophilic R^{23} species include, but are not limited to X^{n1}-R^{23}, M-R^{23}, or $M_s(X^{n2})_t$, wherein each instance of M is independently a metal (*e.g.*, Li, Na, K), or metal complex (*e.g.* CuX^{n2}, or MgX^{n2}); X^{n1} is -OR^{xn}, -SR^{xn}, or -$N(R^{xn})_2$; each instanc of X^{n2} is independently halogen, CN, N_3, -OR^{xn}, -SR^{xn}, -$N(R^{xn})_2$; each instance of R^{xn} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl; R^{23} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl; s is 1, 2, 3, or 4; and t is 1, 2, 3, or 4. As used herein, a metal complex refers to a

metal coordination complex having a central metal atom having one or more bound ligands (*e.g.* ion such as halide; or molecule (functional group) such as carboxylate) to form a coordination complex. The bonding between metal and ligand generally involves formal donation of one or more of the ligand's electron pairs. The nature of the metal-ligand bonding can range from covalent to ionic. Furthermore, the metal-ligand bond order can range from one to three. In certain embodiments, the nucleophile is X^{n1}-R^{23} (*e.g.* R^{23}-OH; R^{23}-SH, R^{23}-NH_2 (*e.g.* NH_3)). In certain embodiments, the nucleophile is M-R^{23} (*e.g.* Li-alkyl). In certain embodiments, the nucleophile is $M_s(X^{n2})_t$ (*e.g.* NaCN, NaN_3, $NaNH_2$, $LiOR^{xn}$, $NaOR^{xn}$).

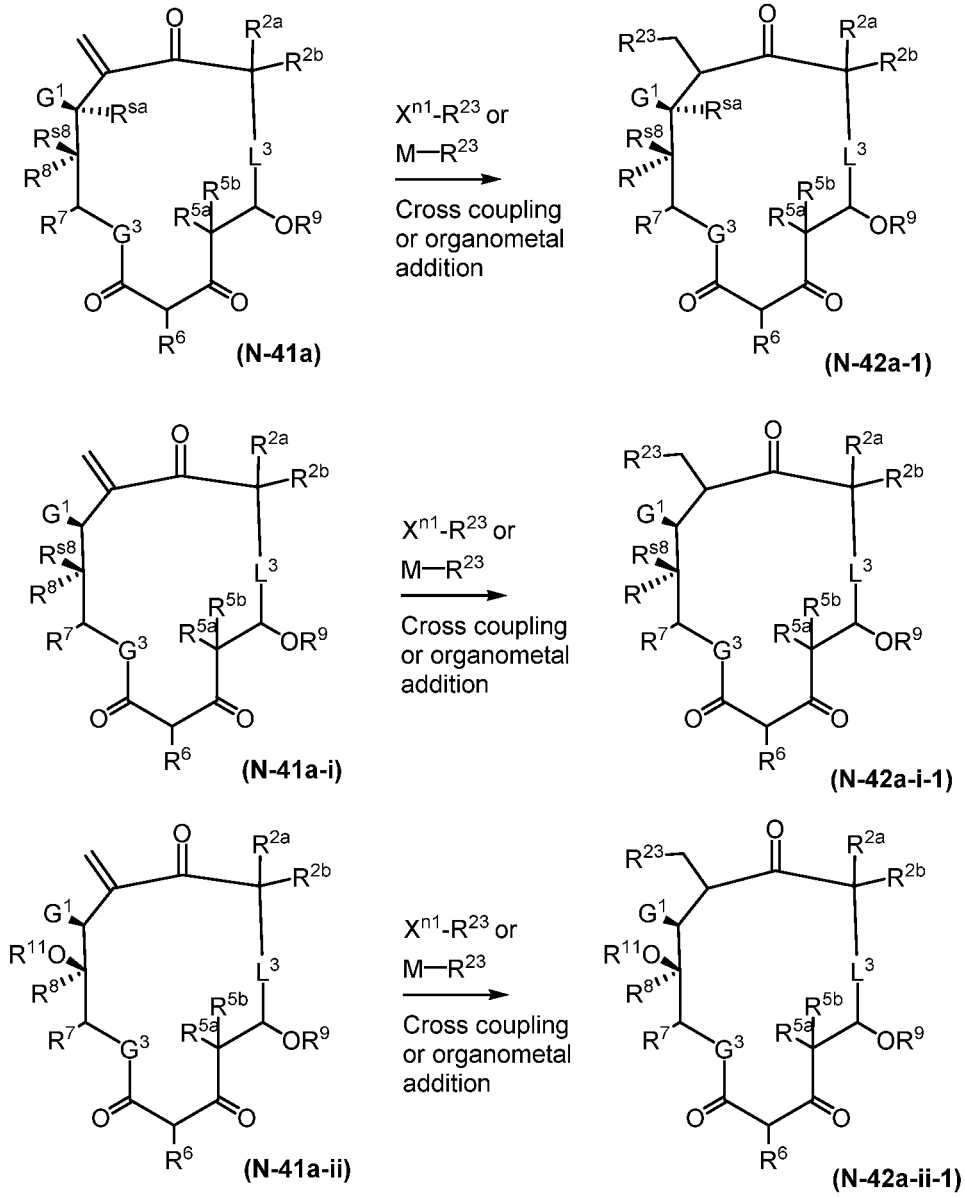
[00119] In certain embodiments, R^{o3} is R^{23}, wherein R^{23} is as defined herein. In certain embodiments, R^{o3} is X^{n2}, wherein X^{n2} is as defined herein.

Scheme 20B.

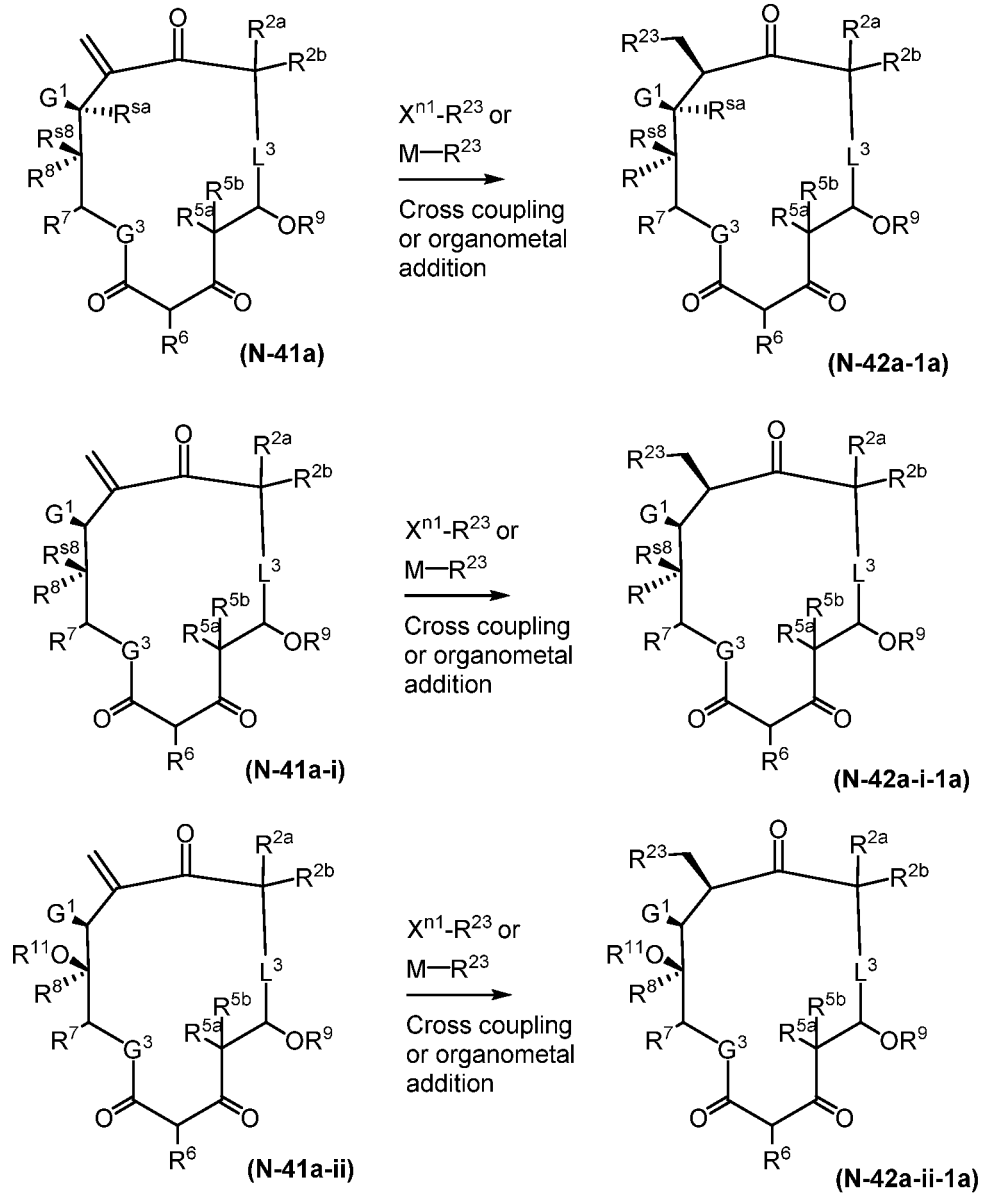


[00120] In certain embodiments, exemplified conjugated additions are carried out on Formulae (**N-41a**) and (**N-41b**) as shown in *Schemes 20C-N*.

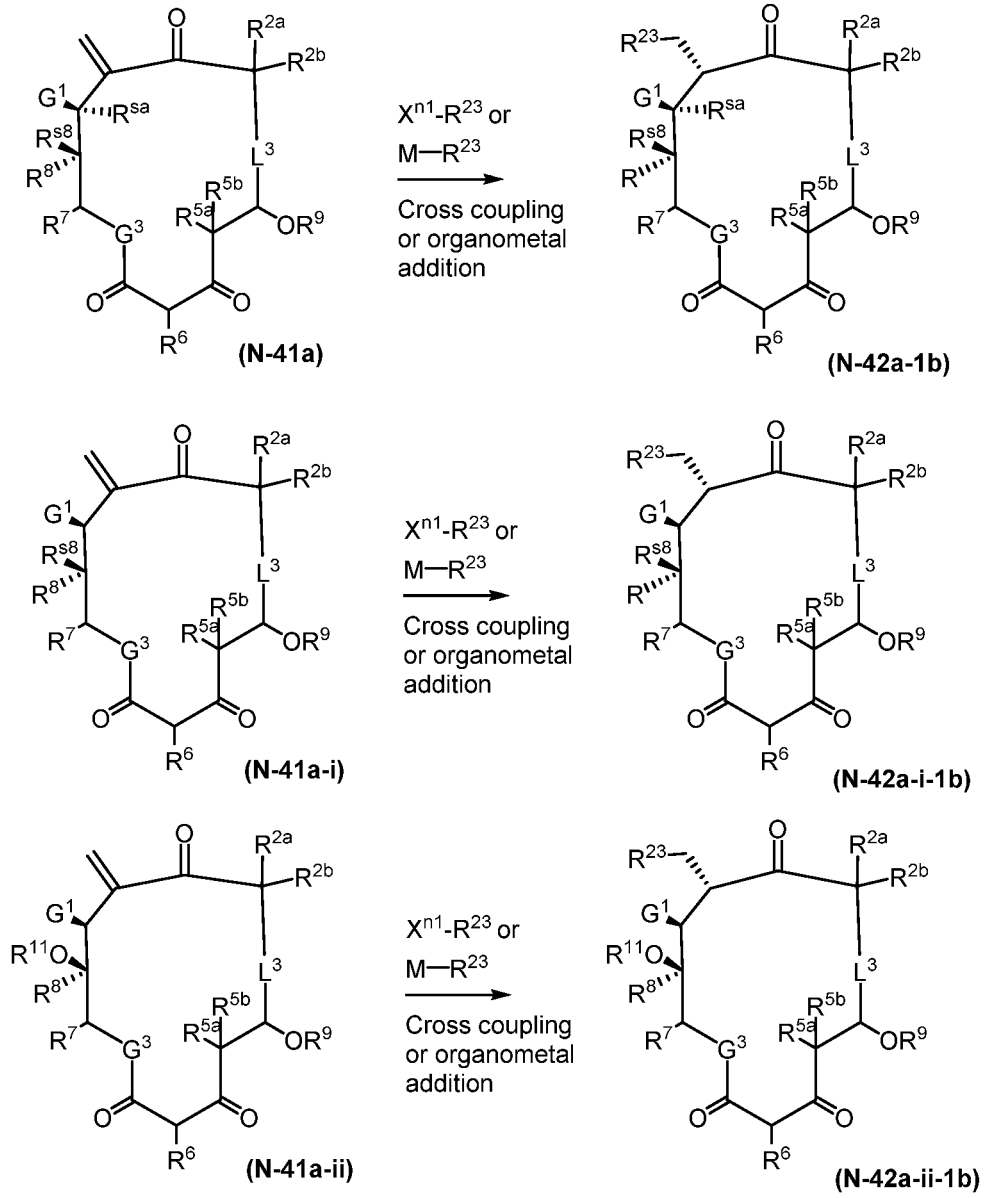
Scheme 20C.



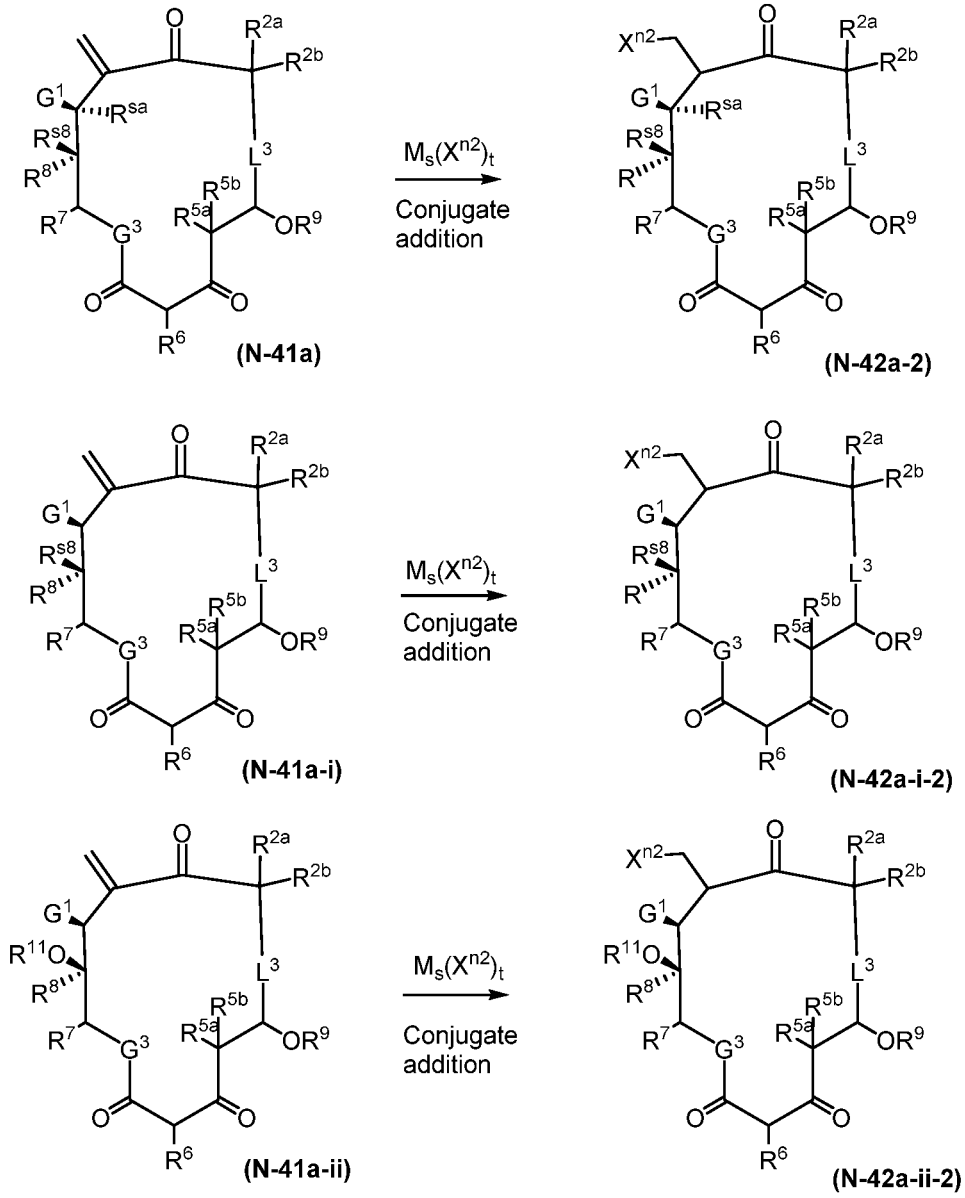
Scheme 20D.


(N-41a)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42a-1a)
(N-41a-i)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42a-i-1a)
(N-41a-ii)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42a-ii-1a)

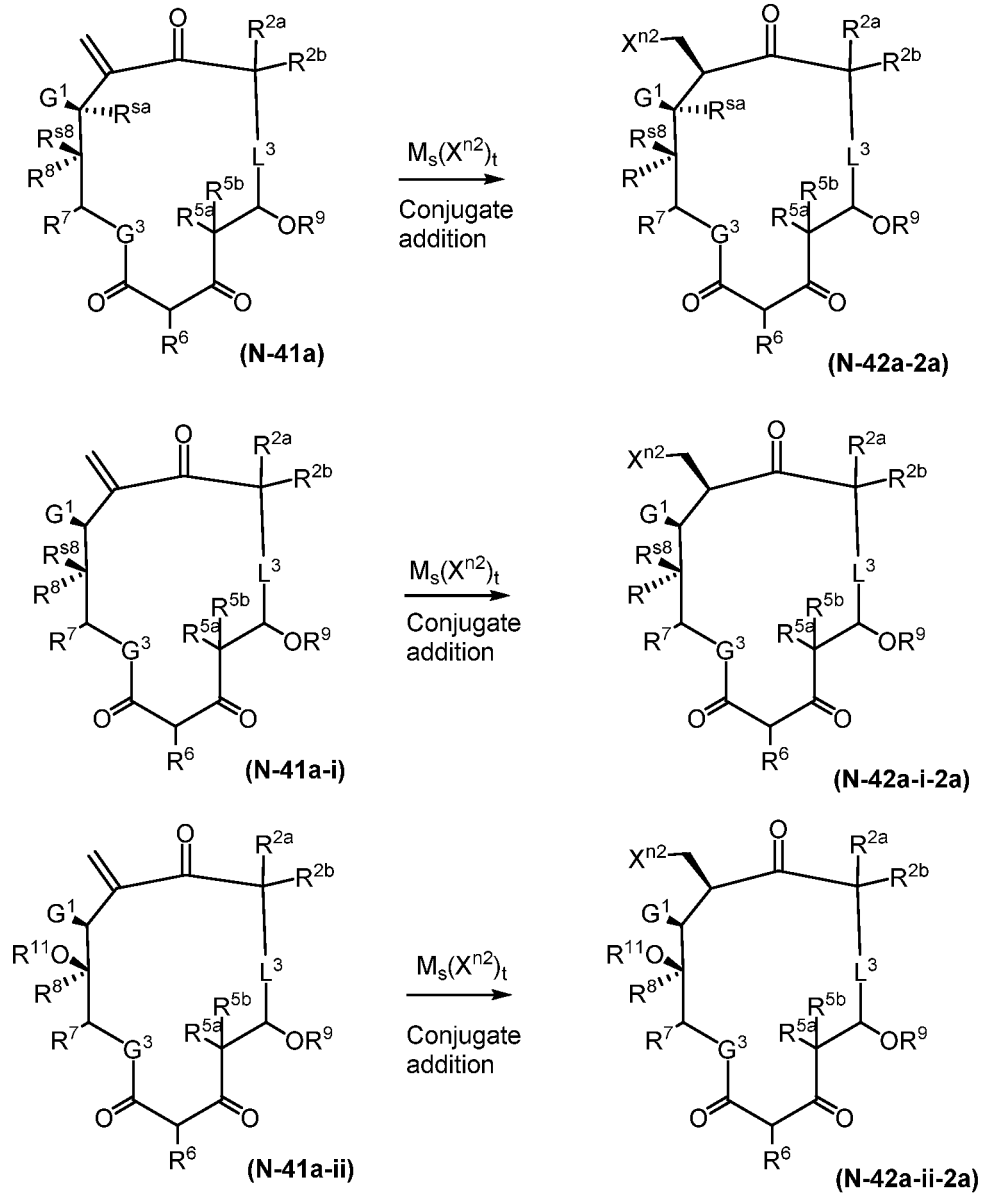
Scheme 20E.


(N-41a)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42a-1b)
(N-41a-i)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42a-i-1b)
(N-41a-ii)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42a-ii-1b)

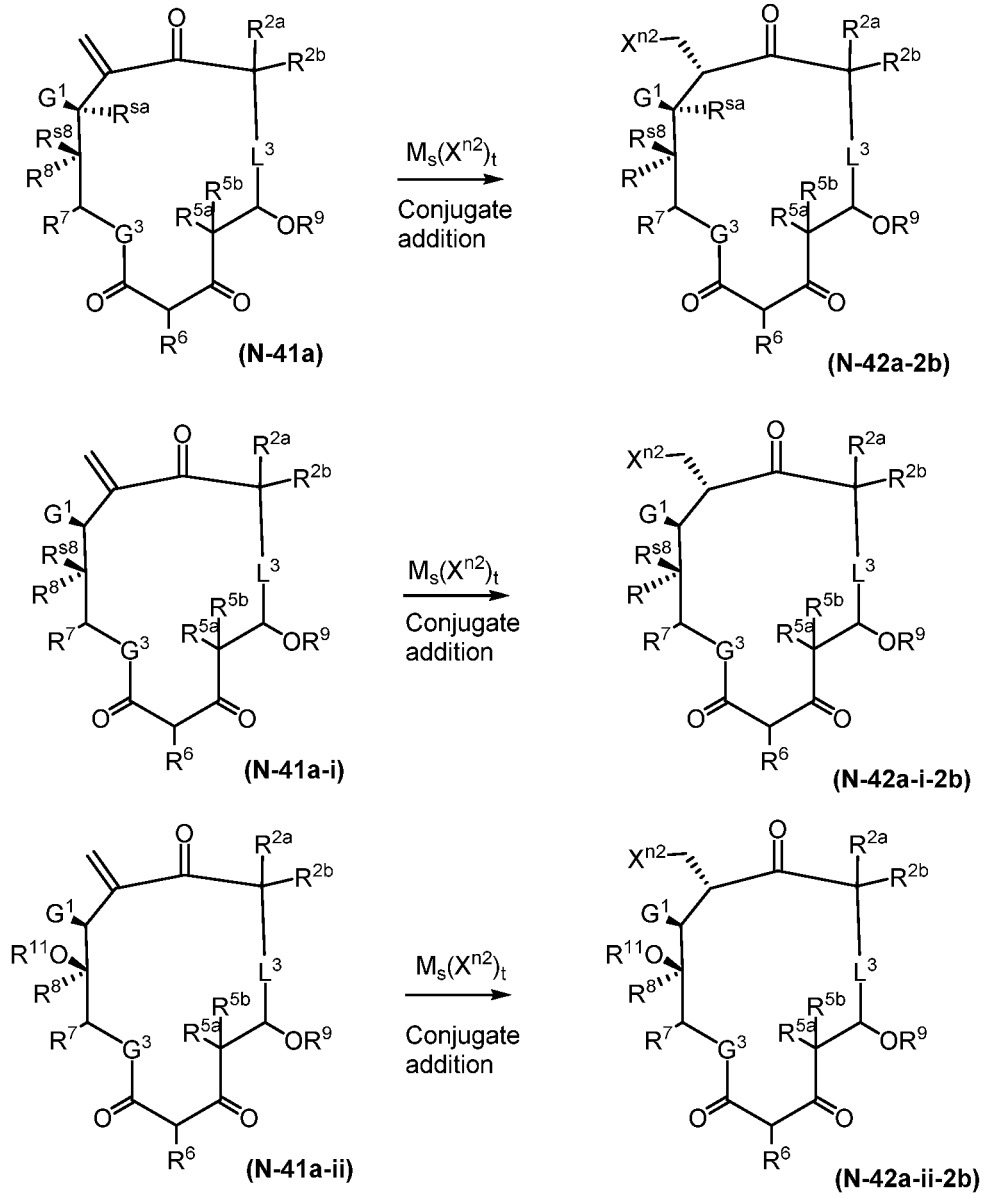
Scheme 20F.


(N-41a)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-2)
(N-41a-i)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-i-2)
(N-41a-ii)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-ii-2)

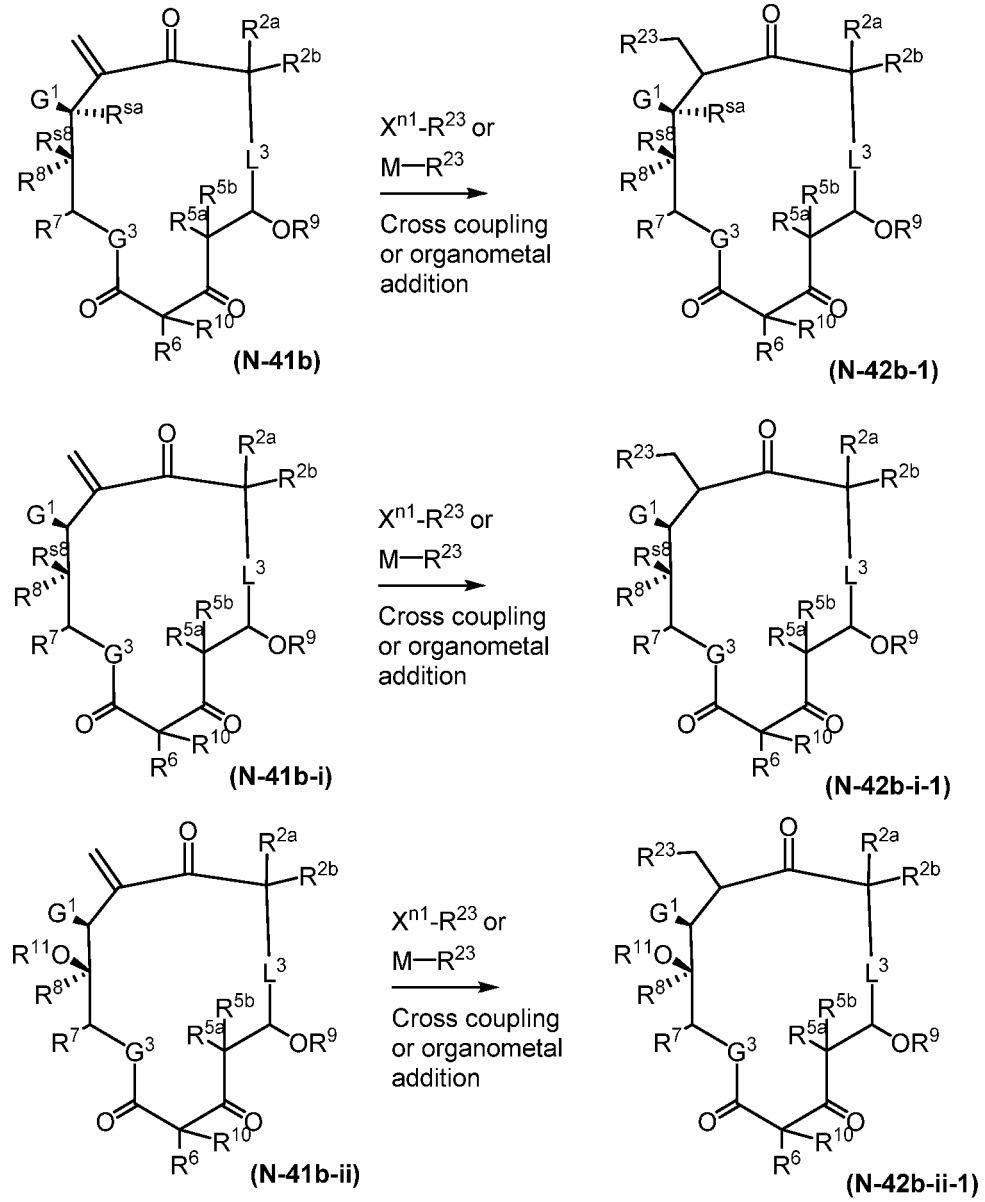
Scheme 20G.


(N-41a)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-2a)
(N-41a-i)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-i-2a)
(N-41a-ii)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-ii-2a)

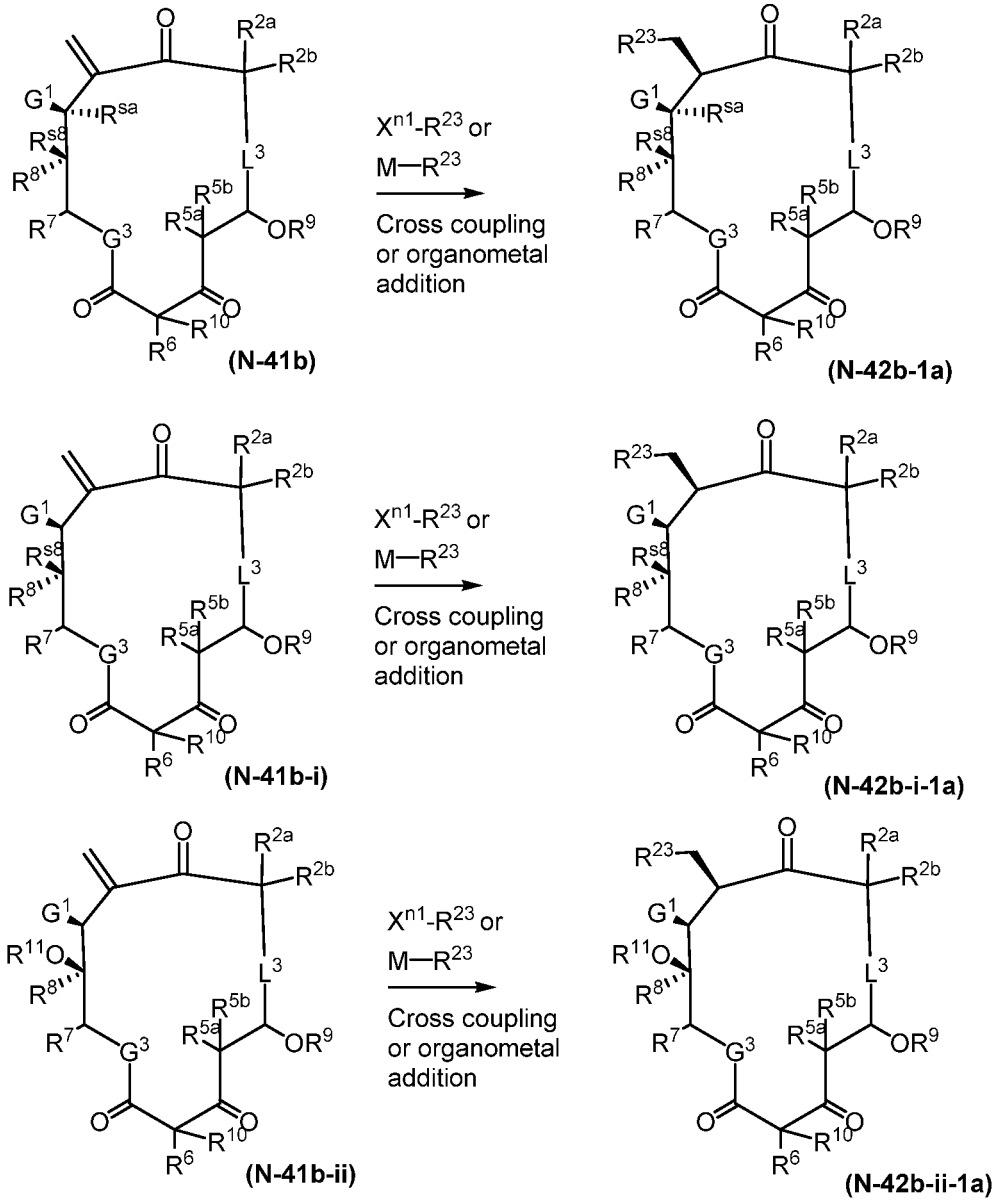
Scheme 20H.


(N-41a)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-2b)
(N-41a-i)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-i-2b)
(N-41a-ii)
$M_s(X^{n2})_t$
Conjugate addition
(N-42a-ii-2b)

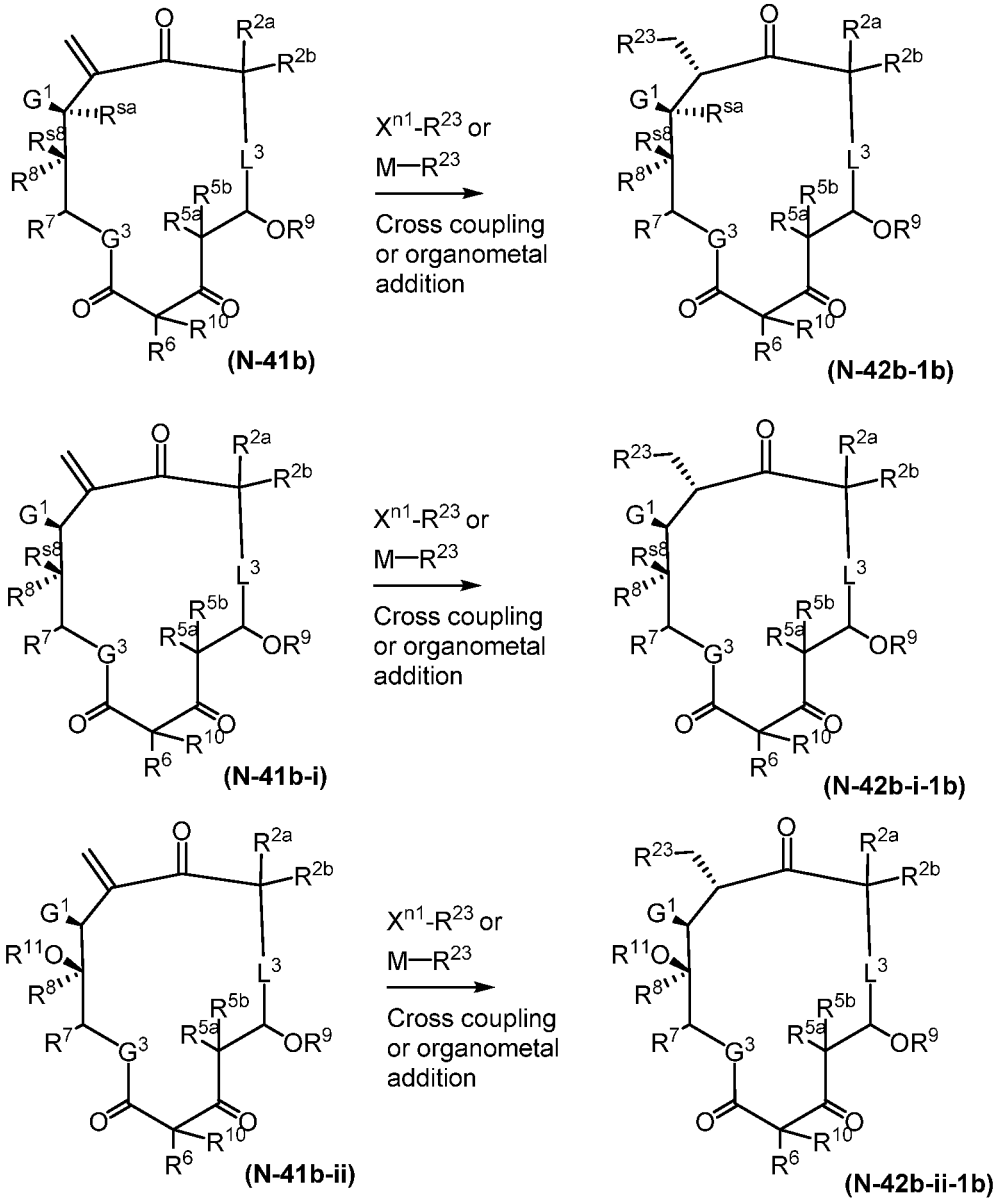
Scheme 20I.


(N-41b)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-1)
(N-41b-i)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-i-1)
(N-41b-ii)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-ii-1)

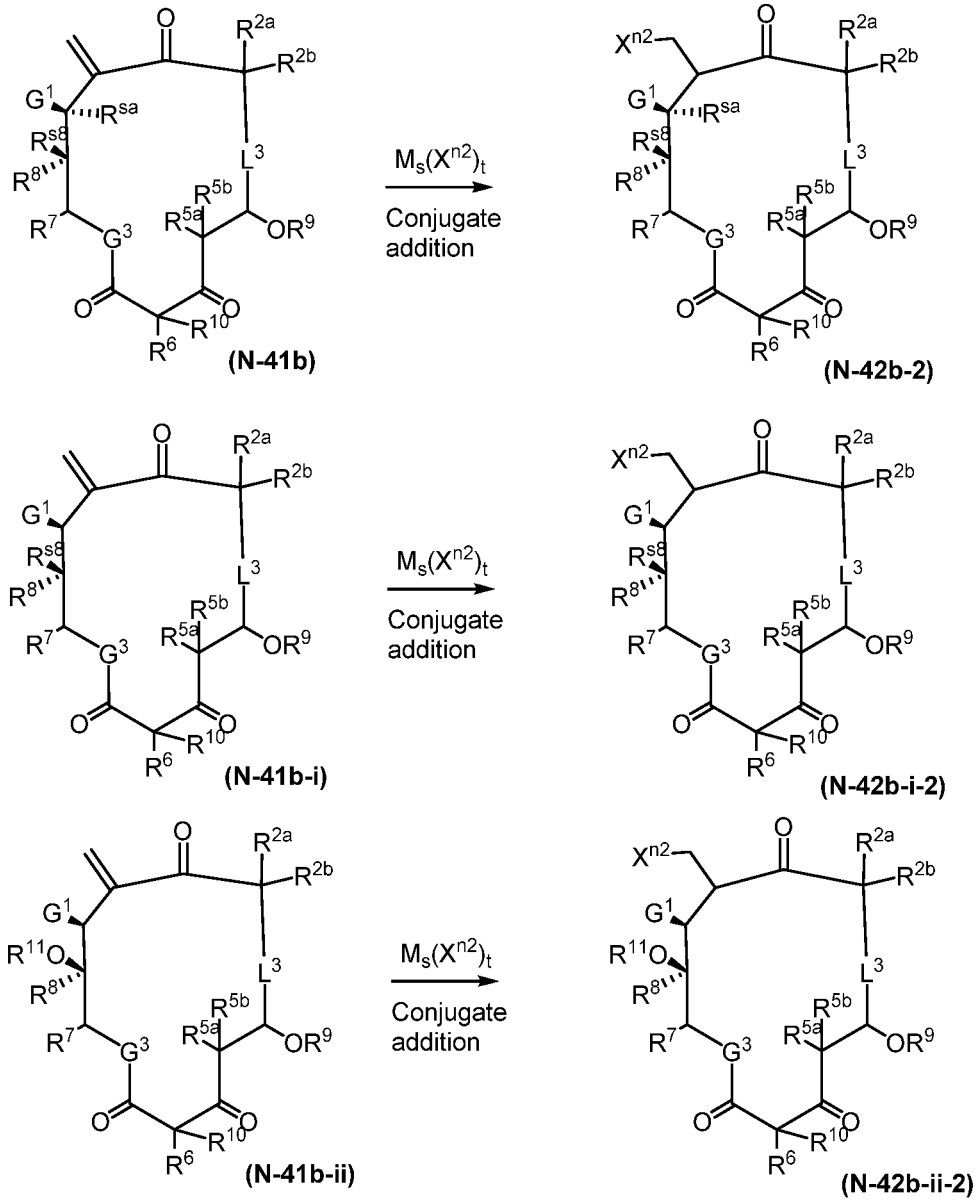
Scheme 20J.


(N-41b)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-1a)
(N-41b-i)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-i-1a)
(N-41b-ii)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-ii-1a)

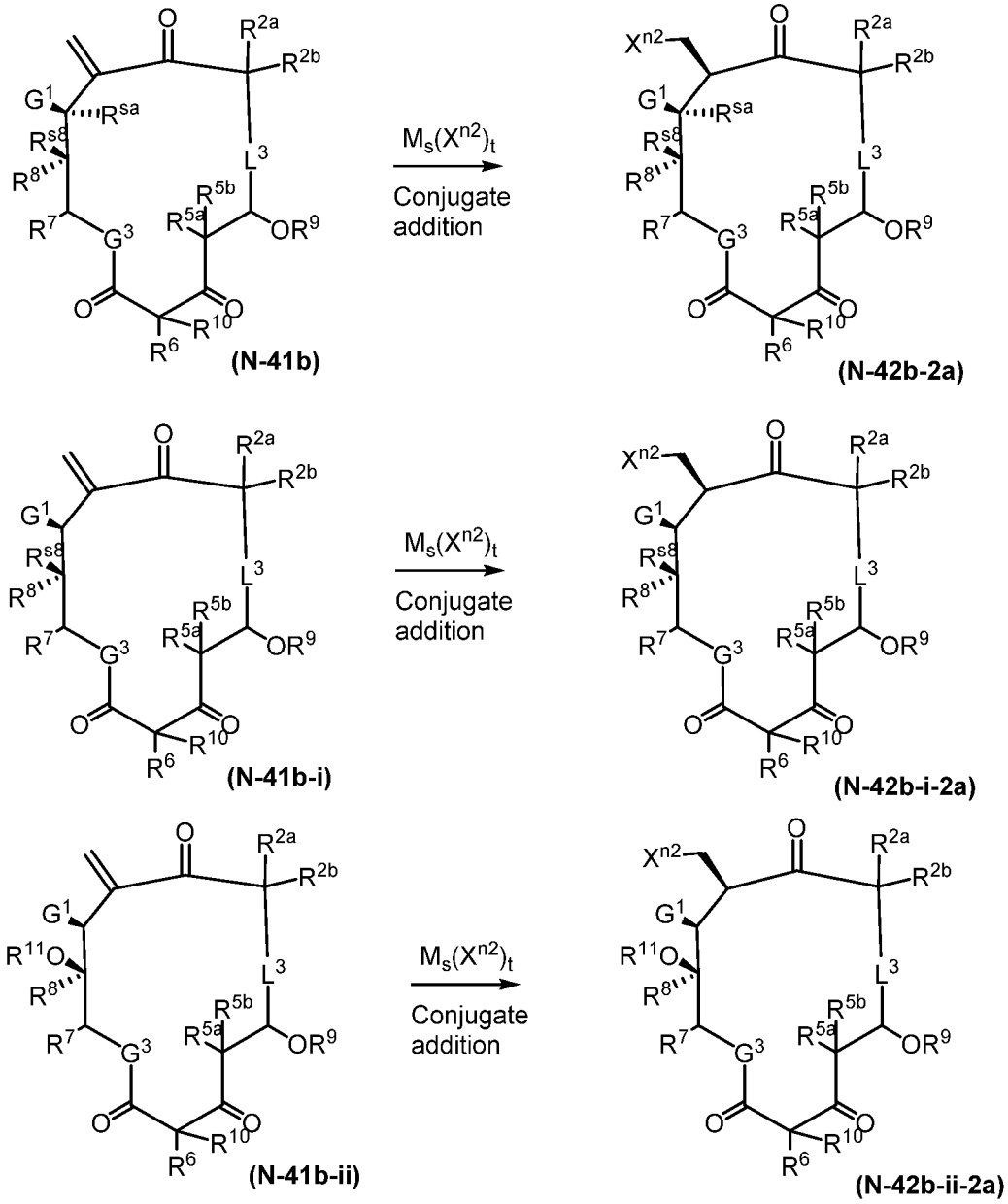
Scheme 20K.


(N-41b)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-1b)
(N-41b-i)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-i-1b)
(N-41b-ii)
X^{n1}-R^{23} or
M—R^{23}
Cross coupling or organometal addition
(N-42b-ii-1b)

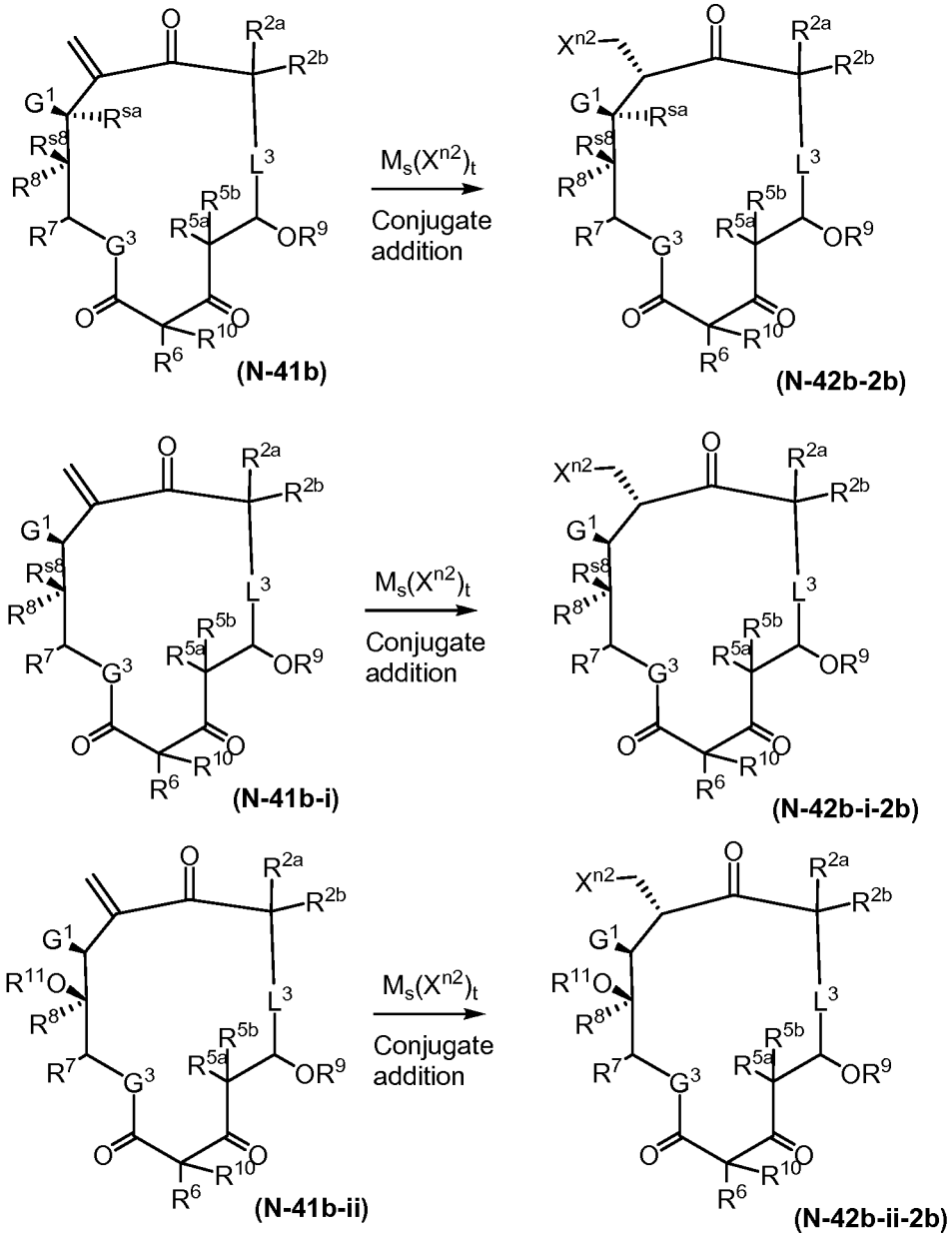
Scheme 20L.


(N-41b)
$M_s(X^{n2})_t$
Conjugate addition
(N-42b-2)
(N-41b-i)
$M_s(X^{n2})_t$
Conjugate addition
(N-42b-i-2)
(N-41b-ii)
$M_s(X^{n2})_t$
Conjugate addition
(N-42b-ii-2)

Scheme 20M.

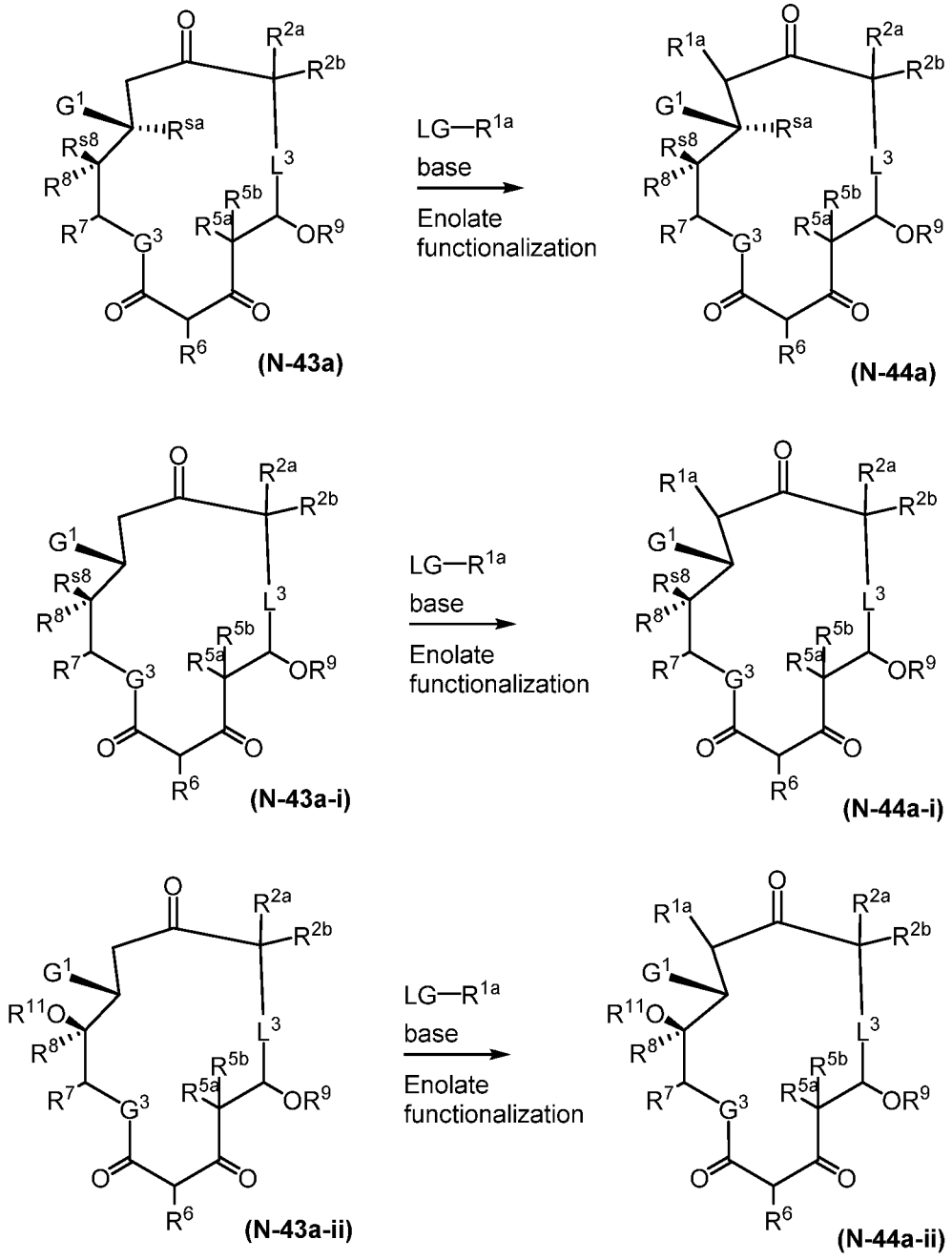

(N-41b)
$M_s(X^{n2})_t$
Conjugate addition
(N-42b-2a)
(N-41b-i)
$M_s(X^{n2})_t$
Conjugate addition
(N-42b-i-2a)
(N-41b-ii)
$M_s(X^{n2})_t$
Conjugate addition
(N-42b-ii-2a)

Scheme 20N.

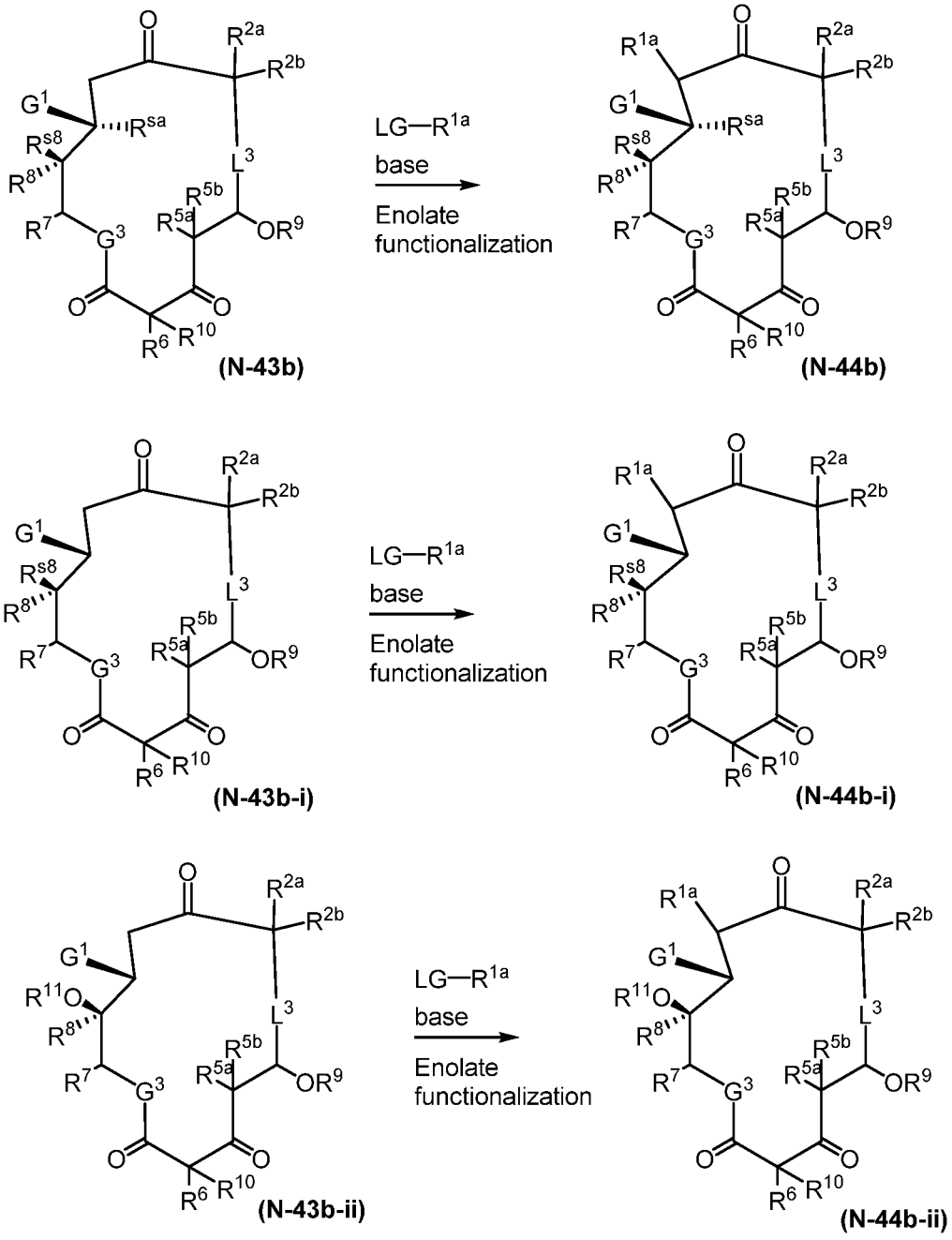


[00121] Further derivatization may be carried out using the transformations described herein pre- or post-macrocyclization when any of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is hydrogen, attached *alpha* to an oxo (=O) moiety. Base-mediated deprotonation and nucleophilic addition of the enolate to leaving group conjugates of R^{1a}, wherein LG is a leaving group as definied herein and R^{1a} is a non-hydrogen group, provide alpha-functionalized ketolides of Formula (**N-44a**) or Formula (**44-b**).

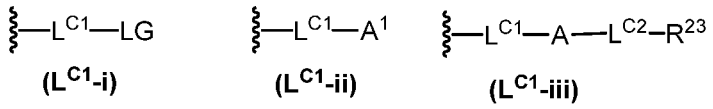
Scheme 21A.


LG—R1a
base
Enolate functionalization
(N-43a)
(N-44a)
(N-43a-i)
(N-44a-i)
(N-43a-ii)
(N-44a-ii)

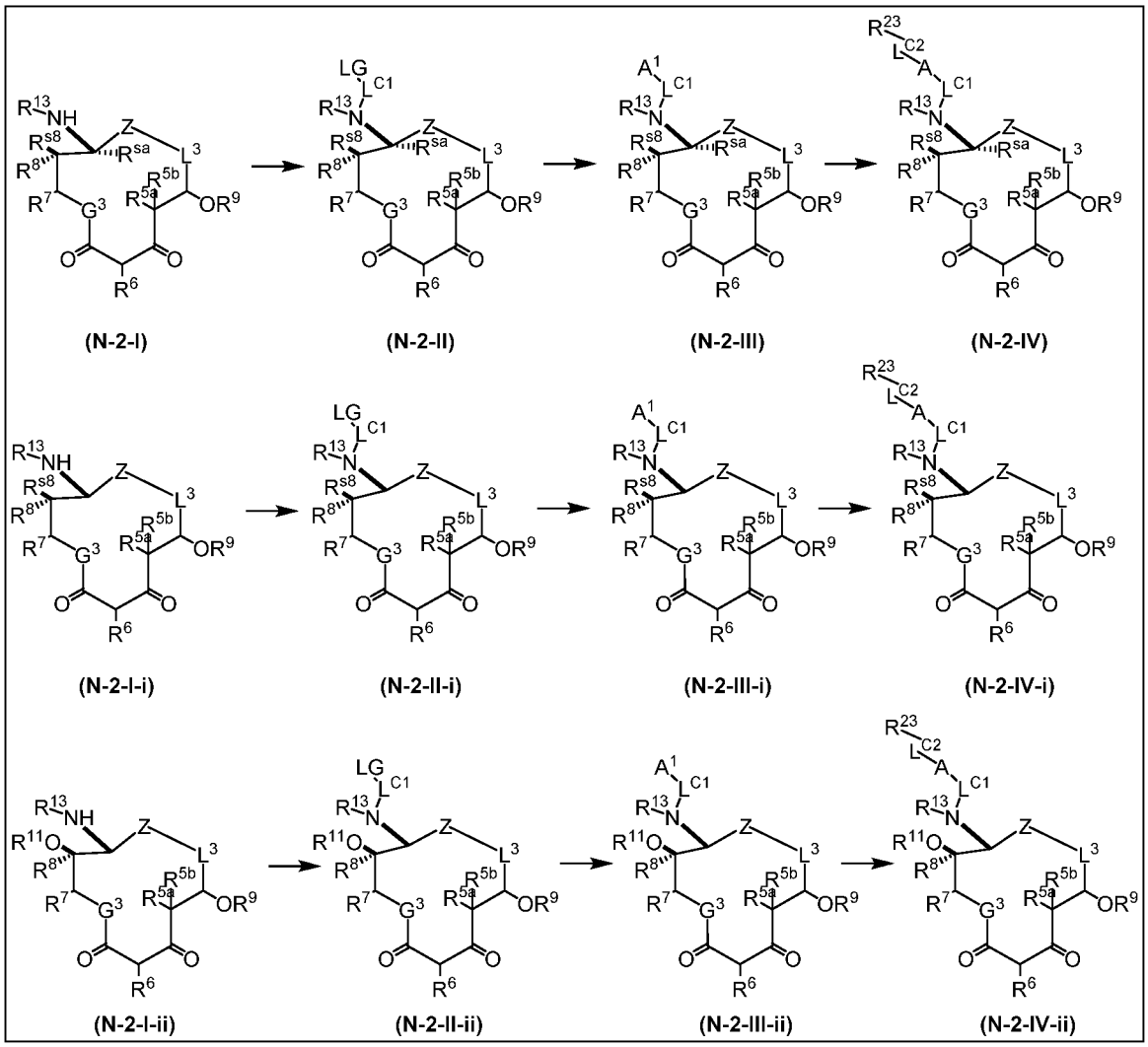
Scheme 21B.



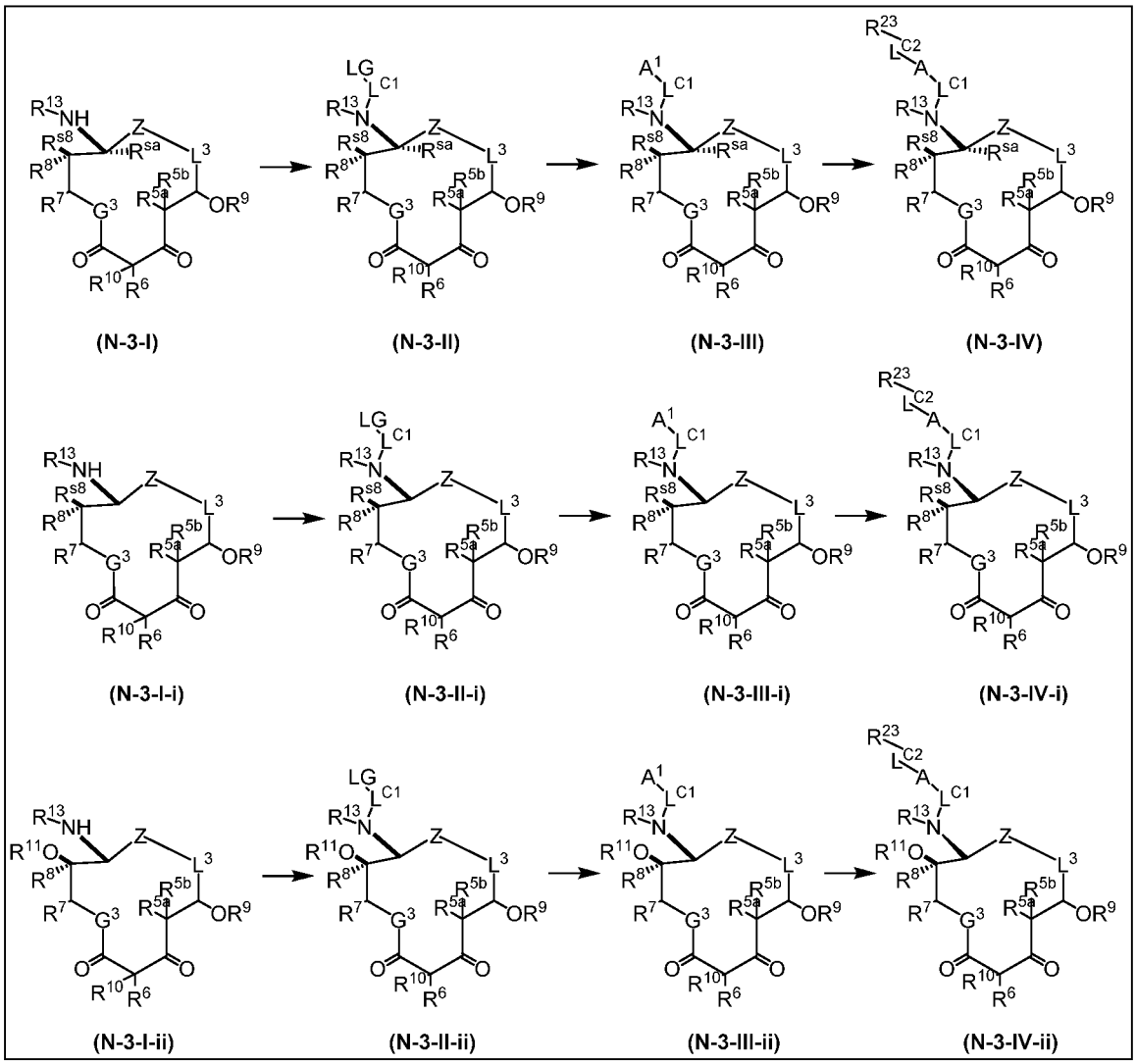
[00122] Furthermore, as depicted in Schemes 23-26, wherein G^1 is -NHR^{13}, installation of a group of Formula (**L^{C1}-i**) by reaction of the alcohol with a compound of formula LG-L^{C1}-LG, followed by displacement of the second leaving group with a nucleophilic group A^1 to provide a group of Formula (**L^{C1}-ii**), followed by reaction of the group A^1 and with a compound of formula A^2-L^{C2}-R^{23} to install a group of Formula (**L^{C1}-iii**), is contemplated herein.


—L^C1—LG
(L^C1-i)
—L^C1—A^1
(L^C1-ii)
—L^C1—A—L^C2—R^23
(L^C1-iii)

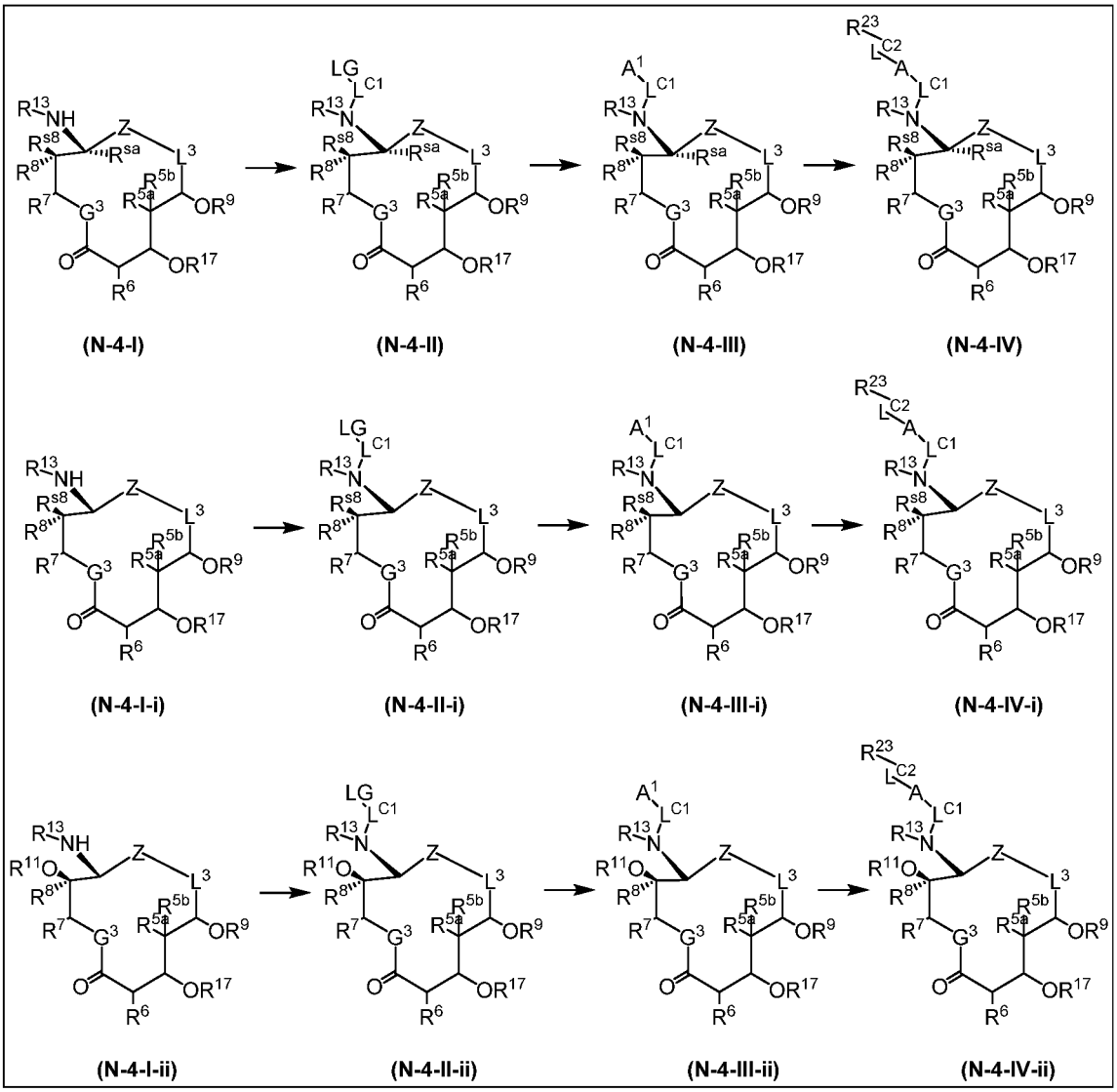
Scheme 23.


(N-2-I)
(N-2-II)
(N-2-III)
(N-2-IV)
(N-2-I-i)
(N-2-II-i)
(N-2-III-i)
(N-2-IV-i)
(N-2-I-ii)
(N-2-II-ii)
(N-2-III-ii)
(N-2-IV-ii)

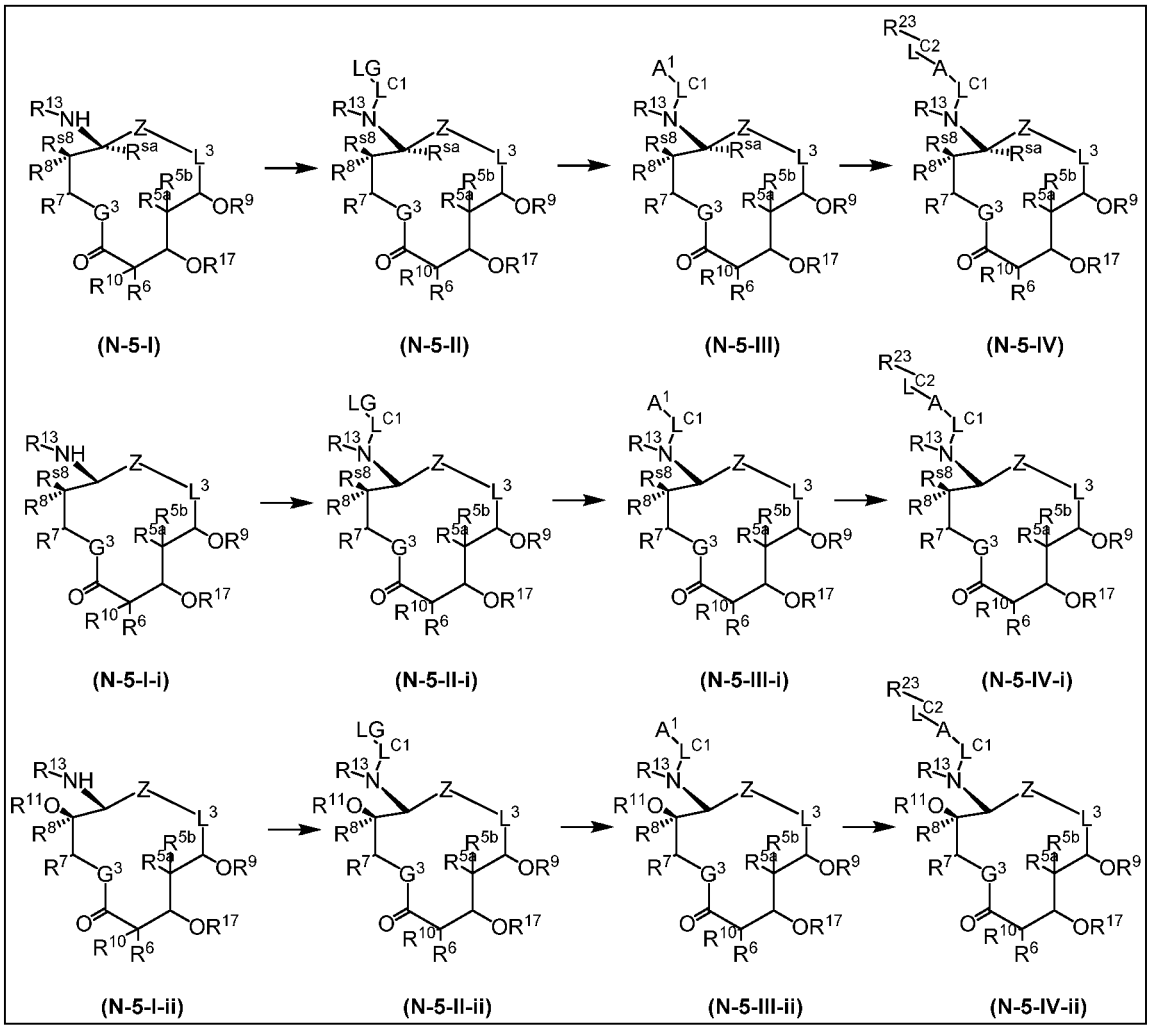
Scheme 24.


(N-3-I)
(N-3-II)
(N-3-III)
(N-3-IV)
(N-3-I-i)
(N-3-II-i)
(N-3-III-i)
(N-3-IV-i)
(N-3-I-ii)
(N-3-II-ii)
(N-3-III-ii)
(N-3-IV-ii)

Scheme 25.

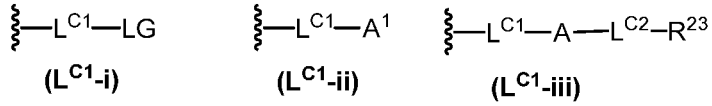

(N-4-I)
(N-4-II)
(N-4-III)
(N-4-IV)
(N-4-I-i)
(N-4-II-i)
(N-4-III-i)
(N-4-IV-i)
(N-4-I-ii)
(N-4-II-ii)
(N-4-III-ii)
(N-4-IV-ii)

Scheme 26.

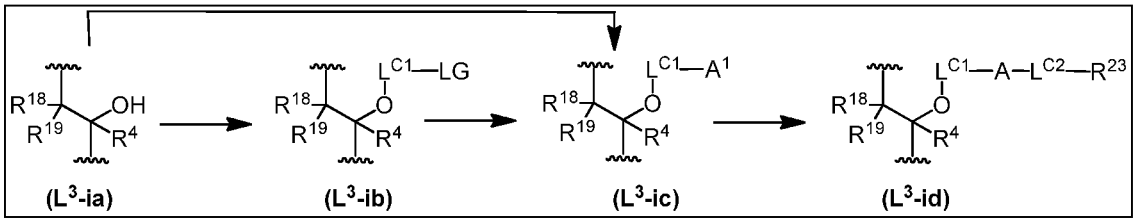


[00123] Alternatively, the group $-L^{C1}-A^1$ may be installed directly by reaction of the amine with a compound of formula $LG-L^{C1}-A^1$. Such reactions are also contemplated wherein G^1 is –OH.

[00124] Additionally, as depicted in Scheme 27, wherein L^3 is a group of formula (**L^3-i**), wherein R^3 is hydrogen (referred to as (**L^3-ia**)), installation of a group of formula (**L^{C1}-i**) by reaction of the alcohol with a compound of formula $LG-L^{C1}-LG$, followed by conversion of (*e.g.,* by nucleophilic displacement or other synthetic manipulation) of the second leaving group with a group A^1 to provide a group of formula (**L^{C1}-ii**), followed by reaction of the group A^1 and with a compound of formula $A^2-L^{C2}-R^{23}$ to install a group of formula (**L^{C1}-iii**), is also contemplated herein.



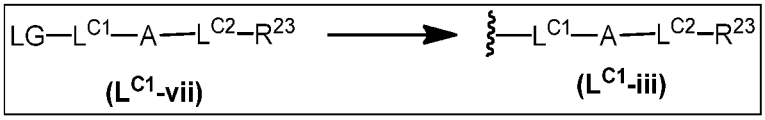
Scheme 27.



[00125] Alternatively, the group $-L^{C1}-A^1$ may be installed directly from (**L^3-ia**) to provide (**L^3-ic**) by reaction of the hydroxyl group with a compound of formula $LG-L^{C1}-A^1$.

[00126] Furthermore, there are many ways of adding a group of formula (**L^{C1}-iii**) which do not involve reaction of A^1 and A^2 to form A and thus A may be any group, *e.g.*, for example, a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl. For example, a group of formula (**L^{C1}-iii**) may be installed by reaction of the group $-OR^{12}$, $-NR^{13}R^{14}$, and/or $-OR^3$, wherein R^{12}, R^{14}, and/or R^3 are hydrogen, with a compound of formula (**L^{C1}-vii**), *e.g.,* by nucleophilic displacement, to provide a group wherein R^{12}, R^{14}, and/or R^3 is of formula (**L^{C1}-iii**). See, *e.g.*, Scheme 28.

Scheme 28.



[00127] Furthermore, as depicted in Scheme 28, wherein L^3 is a group of formula (**L^3-i**), elimination of the group $-OR^3$ provides an alkenyl moiety, which may be reduced (*e.g.*, by hydrogenation), or be further functionalized with groups R^{20} and R^{21}, as depicted in Scheme 29. Functionalization of double bonds to provide groups R^{20} and R^{21} are known in the art. See, *e.g.*, *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. Non-limiting examples of double bond fuctionalization include:

(i) reaction of the double bond with a cyclopropanting reagent to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl ring;

(ii) reaction of the double bond with an epoxidizing reagent to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are joined to form an oxiranyl ring;

(iii) reaction of the double bond with a dihydroxylation reagent (*e.g.*, OsO_4), optionally followed by protection of the hydroxyl groups, to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are each independently hydroxyl or substituted hydroxyl;

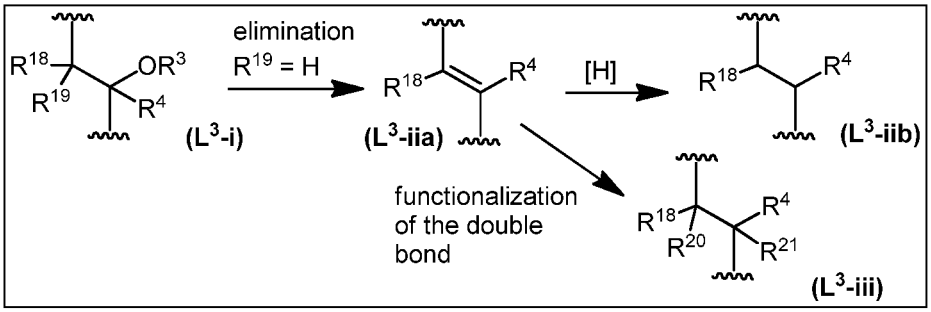
(iv) HX addition to the double bond, wherein X is a halogen or hydroxyl or substituted hydroxyl, to provide a group (**L^3-iii**) wherein one of R^{20} and R^{21} is halogen or hydroxyl or substituted hydroxyl, and one of R^{20} and R^{21} is hydrogen;

(v) X_2 addition to the double bond, wherein X is halogen, to provide a group (**L^3-iii**) wherein R^{20} and R^{21} are each independently halogen;

(vi) X_2/H_2O or X_2/alcohol addition to the double bond, wherein X is halogen, to provide a group (**L^3-iii**) wherein one of R^{20} and R^{21} is hydroxyl or substituted hydroxyl, and one of R^{20} and R^{21} is halogen; and

(viii) oxidative hydroboration of the double bond to provide a group (**L^3-iii**) wherein one of R^{20} and R^{21} is hydroxyl or substituted hydroxyl, and one of R^{20} and R^{21} is hydrogen.

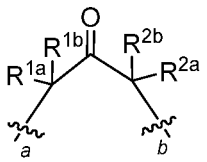
Scheme 29.



[00128] For all of the transformations pertaining to functionalization of the pre-formed macrocycle, incorporation of these groups through such general transformations at steps prior to ring formation is contemplated herein. Such reordering of steps as is appropriate to accomodate particular intermediates or functional groups is understood by those skilled in the art.

Synthesizing Ketolides via Wittig or Horner Emmons Reaction

[00129] As generally described herein, alternative methods of preparing the keto (oxo) product wherein Z is of formula:



(z-i)

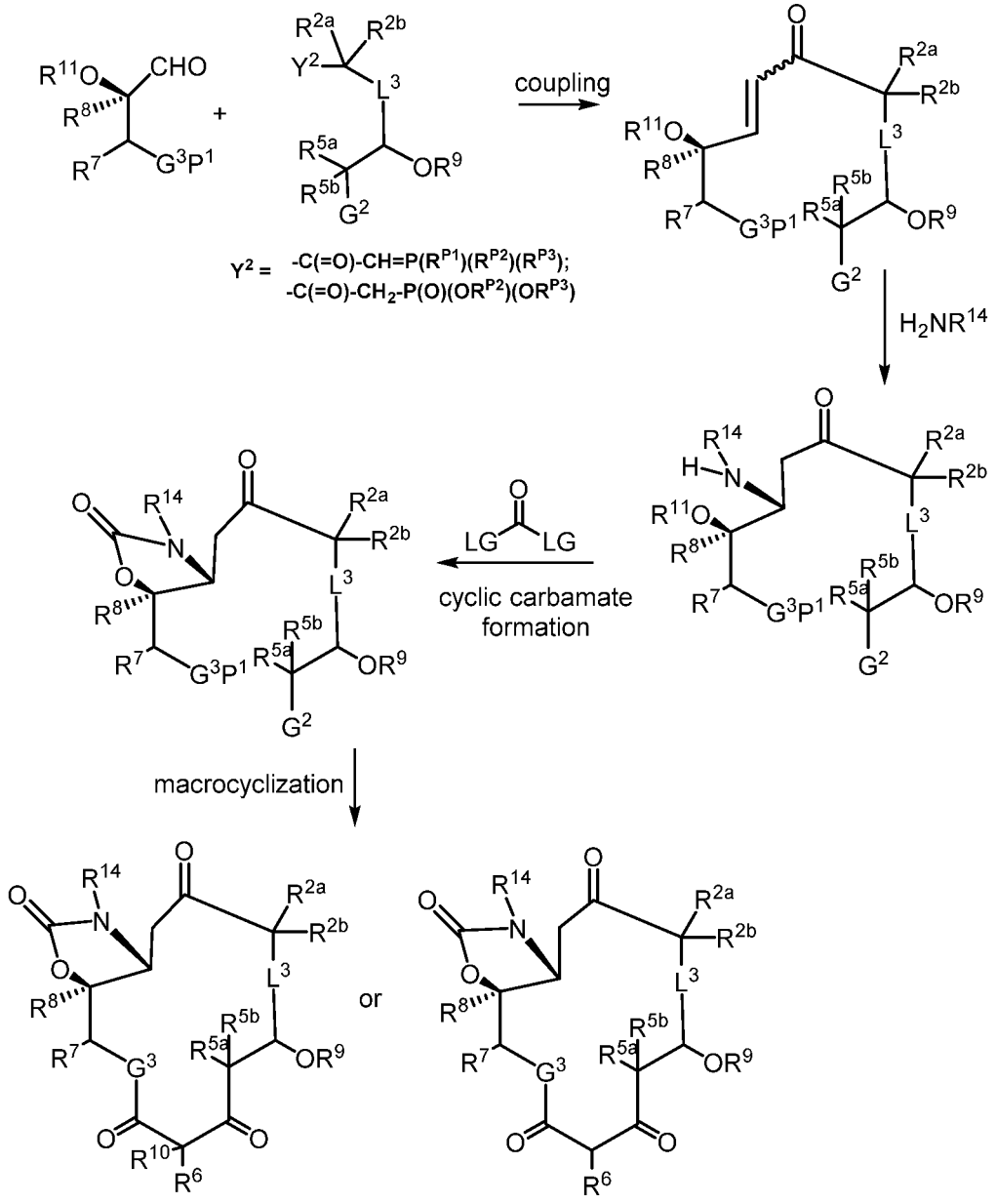
are further contemplated herein.

[00130] For example, the above recited Z linkage may be formed *via* Wittig or Horner Emmons reaction between an aldehyde and a ylide or phosphonate ester to form an α,β–unsaturated keto linked intermediate. See, *e.g.,* Schemes 30 and 31. In certain embodiments of s Schemes 30 and 31, the α,β-unsaturated ketone is of the trans-configuration. In certain embodiments of s Schemes 30 and 31, the α,β-unsaturated ketone is of the cis-configuration.

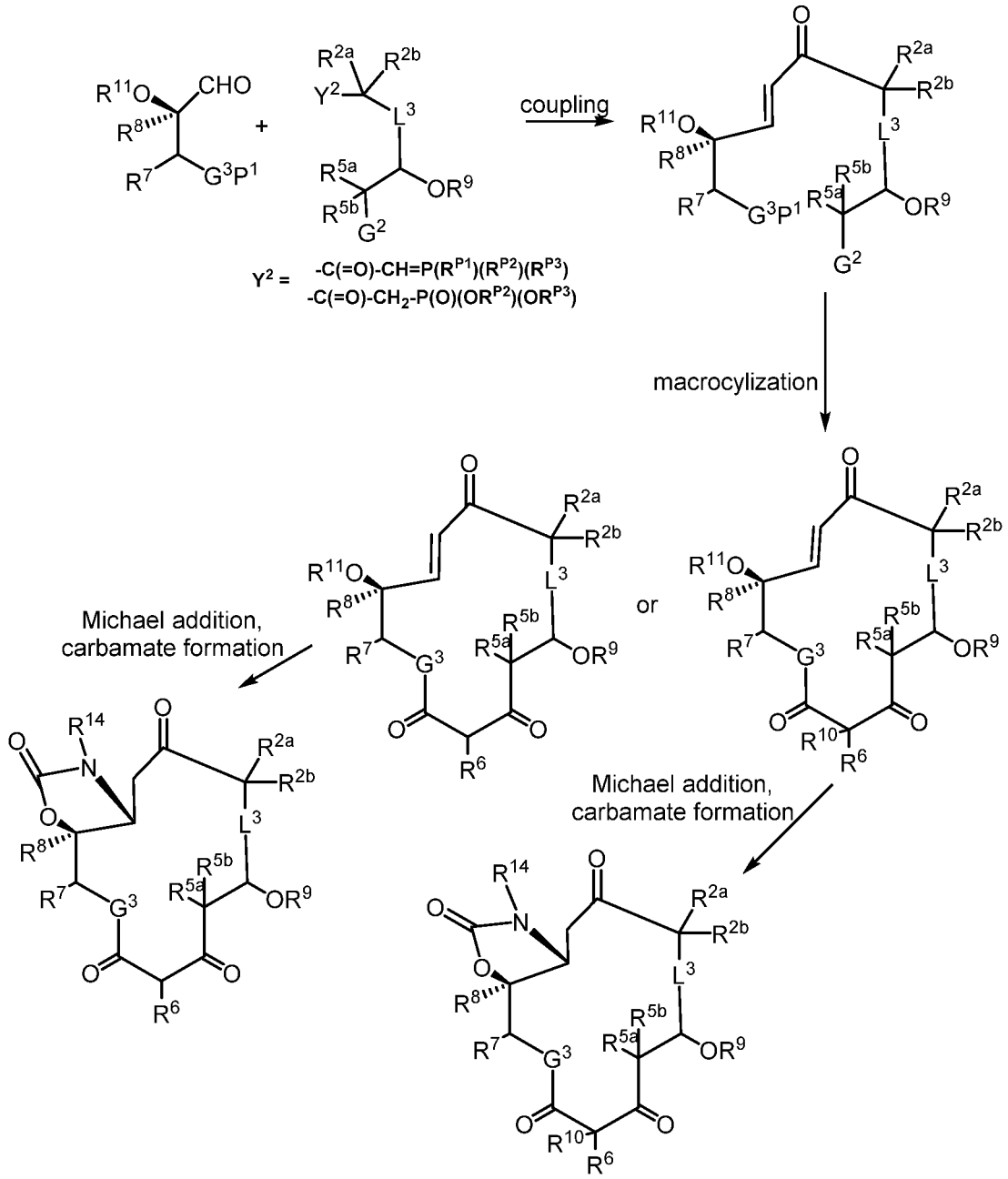
[00131] The cyclic carbamate, installed prior to macrocyclization (see, *e.g.,* Scheme 30) or after macrocylization (see, *e.g.,* Scheme 31), may be formed *via* Michael addition of the amine NH_2R^{14} to the α,β–unsaturated keto moiety, followed by reaction of the attached amino group -NHR^{14} and vicinal hydroxyl group (*i.e.,* R^{11} is hydrogen) with reagent LG-C(=O)-LG, wherein each LG is a leaving group as defined herein (*e.g.,* chloro), substituted hydroxyl (*e.g.,* to provide a carbonate ester), substituted thiol, substituted amino (*e.g.,* imidazolyl). In certain embodiments, the free hydroxyl group is first treated with reagent LG-C(=O)-LG, following which an amine of NH_2R^{14} is added, leading to initial formation of an acyclic carbamate prior to conjugate addition of the intermediate –NHR^{14} group to the unsaturated ketone.

[00132] Alternatively, the cyclic carbamate, installed prior to macrocyclization (see, *e.g.,* Scheme 30) or after macrocylization (see, *e.g.,* Scheme 31), may be formed *via* reaction of the free hydroxyl group (*i.e.*, R^{11} is hydrogen) with an isocyanate reagent O=C=N–R^{14}, followed by conjugate addition of the intermediate –NHR^{14} group to the unsaturated ketone. In certain embodiments, the isocyanate reacts with the free hydroxyl group and –NHR^{14} undergoes the conjugate addition reaction in a single step. In certain embodiments, the intermediate acyclic carbamate is isolated. In certain embodiments, base is added to the isolated acyclic carbamate to promote the conjugate addition reaction.

Scheme 30.

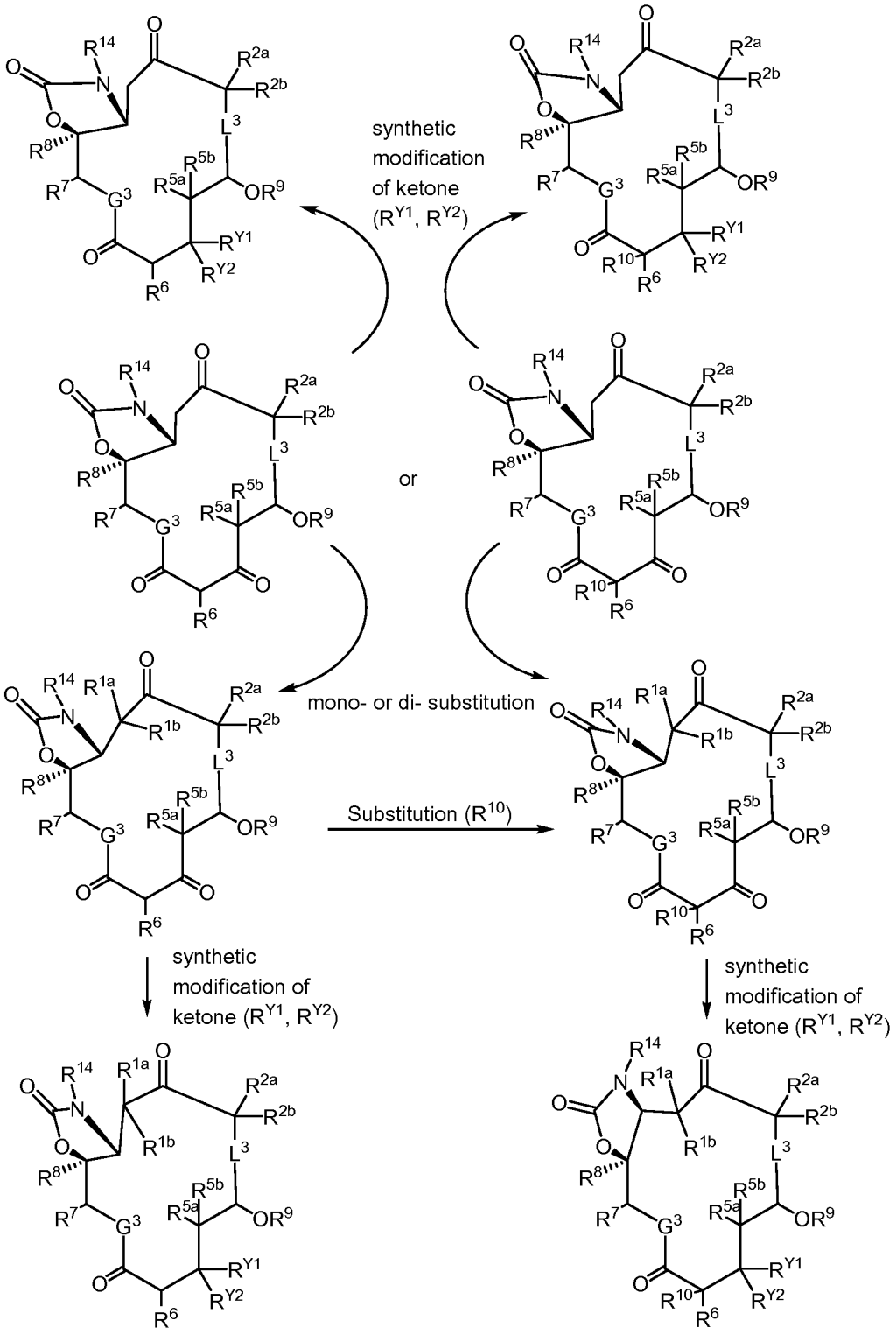

coupling
H_2NR^{14}
cyclic carbamate formation
macrocyclization
or
Y^2 = -C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3}); -C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3})

Scheme 31.



[00133] Scheme 32 depicts various synthetic modifications which are contemplated and further described in greater details elsewhere. For example, after formation of the cyclic carbamate, the carbon alpha to the ketone moiety so installed may be monosubstituted (*e.g.*, wherein R^{1a} is hydrogen and R^{1b} is a non-hydrogen) or di-substituted (*i.e.*, wherein both R^{1a} and R^{1b} are non-hydrogen groups). Synthetic modification of the C3 ketone by dihalogenation (*e.g.*, wherein each of R^{Y1} and R^{Y2} is halogen (*e.g.*, fluoro)), or by reduction to provide an alcohol wherein R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, followed by monohalogenation to provide a product wherein R^{Y1} is halogen (*e.g.*, fluoro) and R^{Y2} is hydrogen is further contemplated.

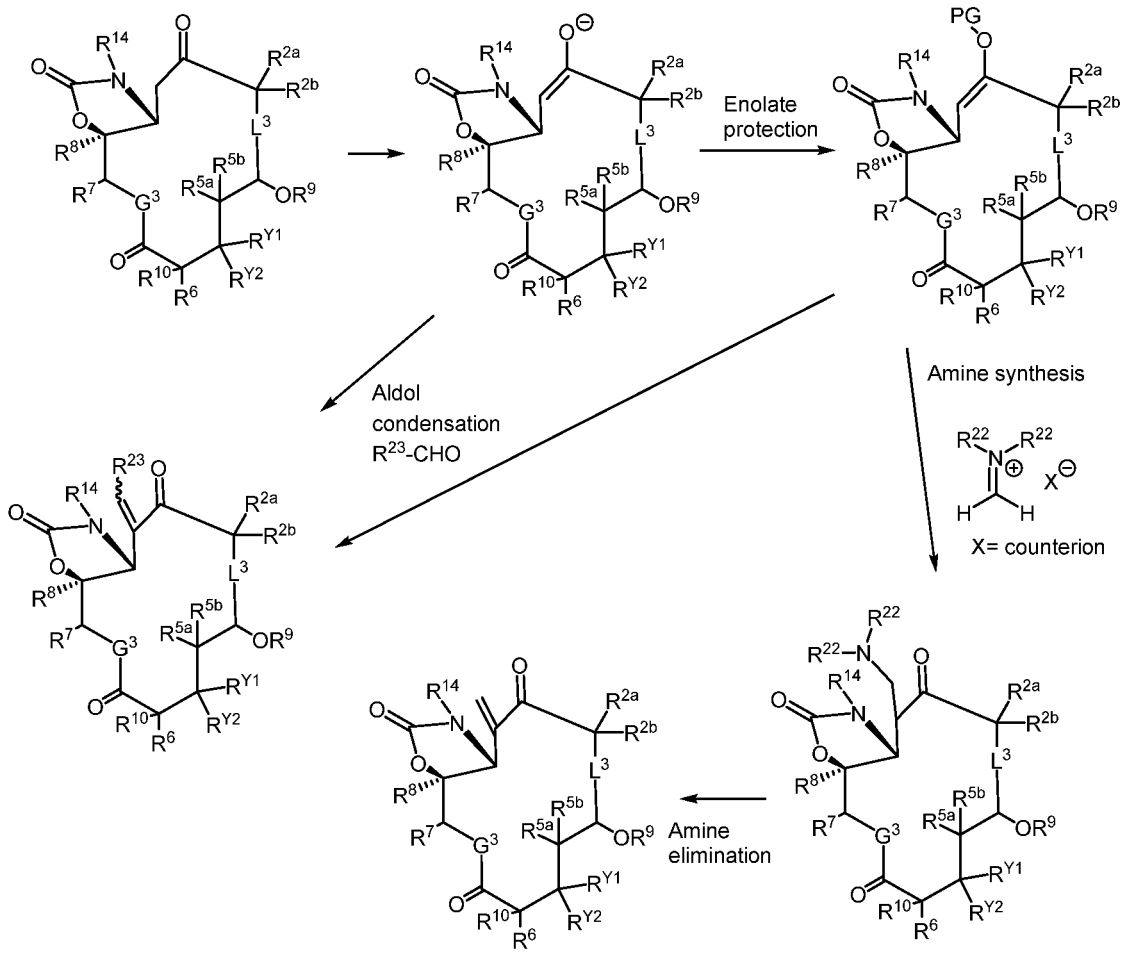
Scheme 32.



[00134] *Scheme 33a* depicts additional functionalization of ketolides prepared by the methods described herein via an enolate or trapped enolate, wherein PG is an oxygen protecting group as defined herein. In certain embodiments, the trapped enolate is trapped as a protected enol ether using a reagent of formula LG–PG wherein LG is leaving group and PG is protecting group as defined herein. In certain embodiments, either the protected enol

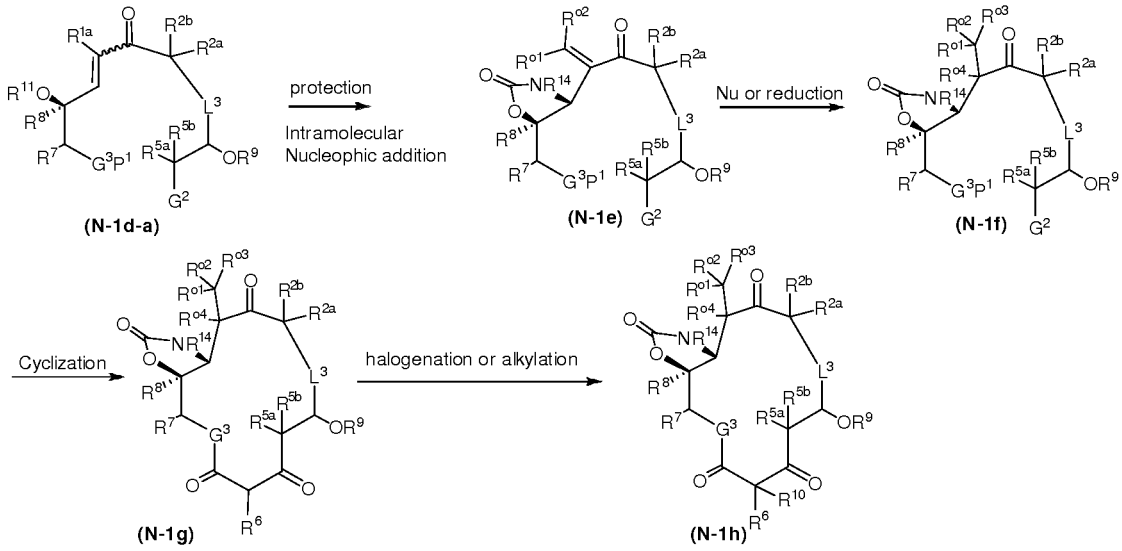
ether or the enolate can be utilized to carry out an aldol condensation reaction with aldehydes of formula R^{23}–CHO. Alternatively, the protected enol ether can be contacted with iminium salts under suitable conditions to afford amino substituted products. Amines produced *via* this method can be eliminated to provide exocyclic alkenes.

Scheme 33a.

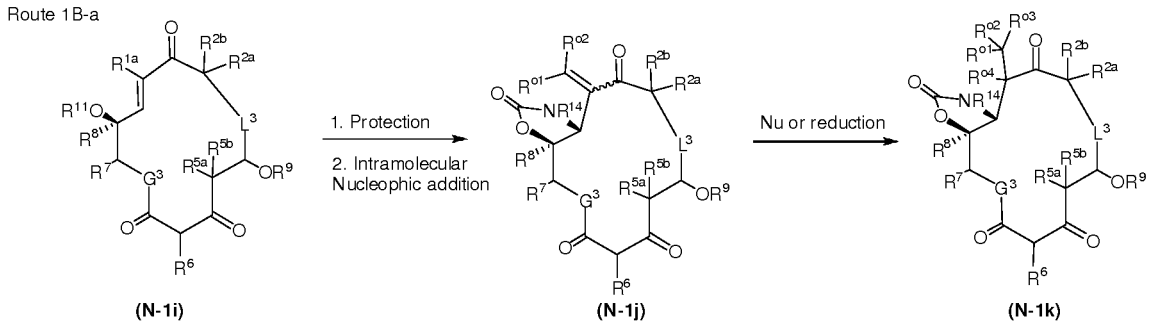


[00135] *Scheme 33b* depicts a scheme to synthesize compounds of Formula (**N-1d**). *Scheme 33c* depicts a scheme to synthesize macrolides from compounds of Formulae (**N-1d**) and (**N-1d-a**). As shown in *Scheme 33b*, macrocyclization can be performed after the formation of the cyclic carbamate of (**N-1e**) and subsequent elaboration at the C-10 positoon. Alternatively, as shown in *Scheme 33c*, formation of the cyclic carbamate and elaboration at C-10 can be performed after macrocyclization (*i.e.*, aftet the macrocyclic ring has been formed).

Scheme 33b



Scheme 33c



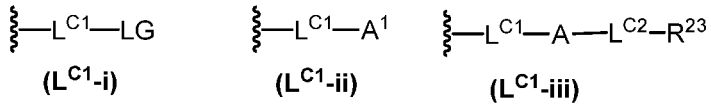
Group G^1 and R^{11}

[00136] As generally defined herein, G^1 is hydrogen, $-OR^{12}$ or $-NR^{13}R^{14}$.

[00137] In certain embodiments, G^1 is hydrogen.

[00138] In certain embodiments, G^1 is $-OR^{12}$, then R^{11} and R^{12} are joined as a group of formula –C(=O)- to provide a cyclic carbonate.

[00139] In certain embodiments, G^1 is $-OR^{12}$ and R^{11} and R^{12} are not joined to form a cyclic carbonate. In that instance, in certain embodiments, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, and R^{12} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group, or a group of formula:



$(L^{C1}\text{-i})$ $(L^{C1}\text{-ii})$ $(L^{C1}\text{-iii})$, as defined herein.

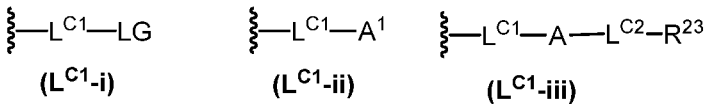
[00140] In certain embodiments, wherein R^{12} is not hydrogen, R^{12} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

[00141] In certain embodiments, G^1 is $-NR^{13}R^{14}$, and R^{11} and R^{13} are joined as a group of formula –C(=O)- to provide a cyclic carbamate.

[00142] In certain embodiments, G^1 is $-NR^{13}R^{14}$, and R^{11} and R^{13} are not joined to form a cyclic carbamate. In that instance, in certain embodiments, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, R^{13} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group.

[00143] In certain embodiments, wherein R^{13} is not hydrogen, R^{13} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

[00144] In certain embodiments, wherein G^1 is $-NR^{13}R^{14}$, R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group, $-C(=O)R^{Z8}$, or $-C(=O)OR^{Z8}$, or a group of formula:



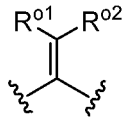
$(L^{C1}\text{-i})$ $(L^{C1}\text{-ii})$ $(L^{C1}\text{-iii})$, as defined herein.

[00145] In certain embodiments, wherein R^{14} is not hydrogen, R^{14} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

[00146] In certain embodiments, wherein G^1 is $-NR^{13}R^{14}$, R^{13} and R^{14} are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl. In certain embodiments, the heterocyclyl or heteroaryl ring system formed from the joining of R^{13} and R^{14} is optionally substituted with a non-hydrogen group of formula R^{23} as defined herein.

Groups R^{1a}, R^{1b}, R^{2a}, and R^{2b}

[00147] As generally defined herein, each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl,

optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or R^{2a} and R^{2b} are taken together to form  , wherein each of R^{o1} and R^{o2} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl .

[00148] In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (S)-configuration

[00149] In certain embodiments, at least one of R^{1a} and R^{1b} is hydrogen. In certain embodiments, both R^{1a} and R^{1b} are hydrogen.

[00150] In certain embodiments, at least one of R^{1a} and R^{1b} is halogen; *e.g.* –F, -Cl, -Br, or I. In certain embodiments, both R^{1a} and R^{1b} are halogen; *e.g.* –F, -Cl, -Br, or I.

[00151] In certain embodiments, at least one of R^{1a} and R^{1b} is carbonyl. In certain embodiments, at least one of R^{1a} and R^{1b} is a carboxylic acid. In certain embodiments, at least one of R^{1a} and R^{1b} is a ketone. In certain embodiments, at least one of R^{1a} and R^{1b} is an aldehyde (-CHO).

[00152] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is $–CH_3$. In certain embodiments, both instances of R^{1a} and R^{1b} are $–CH_3$. In certain embodiments, at least one instance of R^{1a} and R^{1b} is alkyl substituted with one or more halogen atoms, *e.g.,* optionally substituted haloalkyl; *e.g.*, $-CF_3$, $-CF_2CF_3$, or $-CF_2H$. In certain embodiments, at least one of R^{1a} and R^{1b} is $–CH_2CHO$.

[00153] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is vinyl, allyl, or prenyl.

[00154] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally

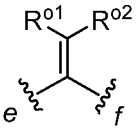
substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00155] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclopropyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is unsubstituted cyclopropyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclobutyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is unsubstituted cyclobutyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclopentyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is unsubstituted cyclopentyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted cyclohexyl. In certain embodiments, at least one instance of R^{1a} and R^{1b} is unsubstituted cyclohexyl.

[00156] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted heterocylyl, *e.g., e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

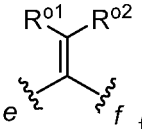
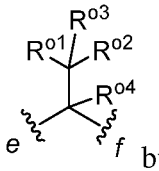
[00157] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

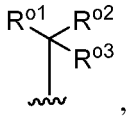
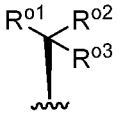
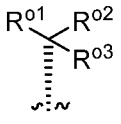
[00158] In certain embodiments, at least one instance of R^{1a} and R^{1b} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00159] In certain embodiments, R^{1a} and R^{1b} are taken together to form 

, wherein *e* indicates point of attachment to the carbon linked to G1, and *f* indicates the point of attachment to the C=O or the carbon substituted by OR^{no}; R^{o1} and R^{o2} are as defined herein. In certain embodiments, each of R^{o1} and R^{o2} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^{o1} and R^{o2} are hydrogen. In certain embodiments, R^{o1} is hydrogen and R^{o2} is optionally substituted alkyl. In certain embodiments, R^{o1} is hydrogen and R^{o2} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{o1} is hydrogen and R^{o2} is unsubstituted C_{1-6} alkyl (*e.g.* methyl or ethyl). In certain embodiments, R^{o1} is hydrogen and R^{o2} is substituted C_{1-6} alkyl (*e.g.* methyl or ethyl). In certain embodiments, R^{o2} is hydrogen and R^{o1} is optionally substituted alkyl. In certain embodiments, R^{o2} is hydrogen

and R^{o1} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{o2} is hydrogen and R^{o1} is unsubstituted C_{1-6} alkyl (*e.g.* methyl or ethyl). In certain embodiments, R^{o2} is hydrogen and R^{o1} is substituted C_{1-6} alkyl.

[00160] In certain embodiments, the moiety  formed by R^{1a} and R^{1b} can be converted to the formula  by a conjugated addition or reduction reaction, wherein R^{o1}-R^{o4} are as defined herein.

[00161] In certain embodiments, R^{1a} is optionally substituted alkyl. In certain embodiments, R^{1a} is optionally substituted alkyl of the formula  , wherein R^{o1}-R^{o3} are as defined herein. In certain embodiments, R^{1a} is optionally substituted alkyl of the formula  , wherein R^{o1}-R^{o3} are as defined herein. In certain embodiments, R^{1a} is optionally substituted alkyl of the formula  , wherein R^{o1}-R^{o3} are as defined herein. In certain embodiments, R^{1b} is R^{o4}, wherein R^{o4} is as defined herein.

[00162] As generally defined herein, R^{o1} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{o1} is hydrogen. In certain embodiments, R^{o1} is halogen (*e.g.* Br or I). In certain embodiments, R^{o1} is optionally substituted alkyl. In certain embodiments, R^{o1} is unsubstituted alkyl (*e.g.* methyl, ethyl, or n-propyl).

[00163] As generally defined herein, R^{o2} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{o2} is hydrogen. In certain embodiments, R^{o2} is halogen (*e.g.* Br or I). In certain embodiments, R^{o2} is optionally

substituted alkyl. In certain embodiments, R^{o2} is unsubstituted alkyl (*e.g.* methyl, ethyl, or n-propyl).

[00164] As generally defined herein, R^{o3} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl, $-OR^{n1}$, $-SR^{n1}$, or $-N(R^{n1})_2$; and each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen; or a sulfur protecting group when attached to a sulfur; or a nitrogen protecting group when attached to nitrogen. In certain embodiments, R^{o3} is hydrogen. In certain embodiments, R^{o3} is halogen (*e.g.* Br or I). In certain embodiments, R^{o3} is optionally substituted alkyl. In certain embodiments, R^{o1} is unsubstituted alkyl (*e.g.* methyl, ethyl, or n-propyl). In certain embodiments, R^{o3} is $-OR^{n1}$, wherein R^{n1} is as defined herein. In certain embodiments, R^{o3} is $-OR^{n1}$, wherein R^{n1} is hydrogen, optionally substituted alkyl, or an oxygen protecting group. In certain embodiments, R^{o3} is $-SR^{n1}$, wherein R^{n1} is hydrogen, optionally substituted alkyl, or an sulfur protecting group. In certain embodiments, R^{o3} is $–N(R^{n1})_2$, wherein each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

[00165] As generally defined herein, R^{o4} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, R^{o4} is hydrogen. In certain embodiments, R^{o4} is halogen (*e.g.* Br or I). In certain embodiments, R^{o4} is optionally substituted alkyl. In certain embodiments, R^{o4} is unsubstituted alkyl (*e.g.* methyl, ethyl, or n-propyl).

[00166] In certain embodiments, R^{o3} is hydrogen, halogen, or optionally substituted alkyl; and R^{o4} is hydrogen. In certain embodiments, R^{o3} and R^{o4} are hydrogen. In certain embodiments, R^{o3} is halogen or optionally substituted alkyl; and R^{o4} is hydrogen. In certain embodiments, R^{o3} is optionally substituted alkyl; and R^{o4} is hydrogen. In certain embodiments, R^{o3} is unsubstituted alkyl (*e.g.* methyl or ethyl); and R^{o4} is hydrogen.

[00167] In certain embodiments, R^{o3} is hydrogen, halogen, or optionally substituted alkyl; and R^{o4} is optionally substituted alkyl. In certain embodiments, R^{o3} is hydrogen and R^{o4} is optionally substituted alkyl. In certain embodiments, R^{o3} is halogen or optionally substituted alkyl; and R^{o4} is optionally substituted alkyl. In certain embodiments, R^{o3} is optionally

substituted alkyl; and R^{o4} is optionally substituted alkyl. In certain embodiments, R^{o3} is unsubstituted alkyl (*e.g.* methyl or ethyl); and R^{o4} is unsubstituted alkyl.

[00168] In certain embodiments, R^{o1} is hydrogen or optionally substituted alkyl; R^{o2} is hydrogen or optionally substituted alkyl; R^{o3} is hydrogen, halogen, or optionally substituted alkyl; and R^{o4} is hydrogen. In certain embodiments, R^{o1}, R^{o2}, R^{o3} and R^{o4} are hydrogen.

[00169] In certain embodiments, the carbon to which R^{2a} and R^{2b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{2a} and R^{2b} is attached is a stereocenter of the (S)-configuration.

[00170] In certain embodiments, at least one instance of R^{2a} and R^{2b} is hydrogen. In certain embodiments, both R^{2a} and R^{2b} are hydrogen.

[00171] In certain embodiments, at least one of R^{2a} and R^{2b} is halogen; *e.g.* –F, -Cl, -Br, or I. In certain embodiments, both R^{2a} and R^{2b} are halogen; *e.g.* –F, -Cl, -Br, or I.

[00172] In certain embodiments, at least one of R^{2a} and R^{2b} is carbonyl. In certain embodiments, at least one of R^{2a} and R^{2b} is a carboxylic acid. In certain embodiments, at least one of R^{2a} and R^{2b} is a ketone. In certain embodiments, at least one of R^{2a} and R^{2b} is an aldehyde (-CHO).

[00173] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, at least one instance of R^{2a} and R^{2b} is $–CH_3$. In certain embodiments, both instances of R^{2a} and R^{2b} are $–CH_3$. In certain embodiments, at least one instance of R^{2a} and R^{2b} is alkyl optionally substituted with one or more halogen atoms, *e.g.,* optionally substituted haloalkyl; *e.g.*, $-CF_3$, $-CF_2CF_3$, or $-CF_2H$. In certain embodiments, at least one of R^{2a} and R^{2b} is $–CH_2CHO$.

[00174] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, at least one instance of R^{2a} and R^{2b} is vinyl, allyl, or prenyl.

[00175] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

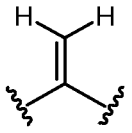
[00176] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-}

$_4$carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00177] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted heterocylyl, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

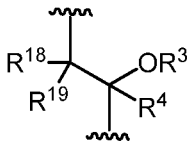
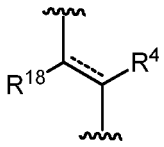
[00178] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

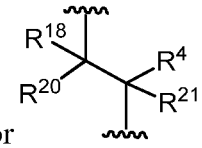
[00179] In certain embodiments, at least one instance of R^{2a} and R^{2b} is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00180] In certain embodiments, R^{2a} and R^{2b} are taken together to form  .

Group L^3 and Groups R^3, R^4, R^{18}, R^{19}, R^{20}, and R^{21}

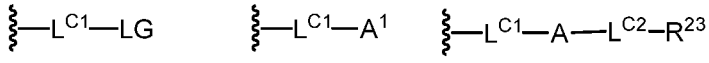
[00181] As generally defined herein, L^3 is a group of the formula:

 (**L^3-i**),  (**L^3-ii**),

 or (**L^3-iii**);

====== represents a single or double bond;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:


(**L^{C1}-i**) (**L^{C1}-ii**) (**L^{C1}-iii**) ;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl;

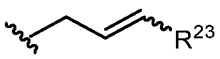
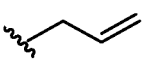
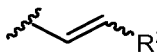
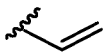
each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring.

[00182] In certain embodiments, the carbon to which R^3 is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^3 is attached is a stereocenter of the (S)-configuration.

[00183] In certain embodiments, R^3 is hydrogen.

[00184] In certain embodiments, R^3 is optionally substituted alkyl; *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or an optionally substituted C_{5-6}alkyl. In certain embodiments, R^3 is $–CH_3$. In certain embodiments, R^3 is $–CH_2CHO$. In certain embodiments, R^3 is $–CH_2N(R^{22})_2$ wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^3 is $–CH_2NH(R^{22})$. In certain embodiments, R^3 is $–CH_2NH_2$. In certain embodiments, R^3 is $–CH_2CH(OH)R^{24}$ wherein R^{24} is hydrogen, optionally substituted alkyl, or optionally substituted aryl. In certain embodiments, R^3 is $–CH_2CH_2OH$. In certain embodiments, R^3 is $–CH_2CH_2R^{23}$ wherein R^{23} is as defined herein.

[00185] In certain embodiments, R^3 is optionally substituted alkenyl; *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, R^3 is vinyl, allyl, or prenyl. In certain embodiments, R^3 is optionally substituted allyl, *e.g.,* substituted allyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted allyl  . In certain embodiments, R^3 is optionally substituted vinyl, *e.g.,* substituted vinyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted vinyl  .

[00186] In certain embodiments, R^3 is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00187] In certain embodiments, R^3 is optionally substituted carbocyclyl; *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

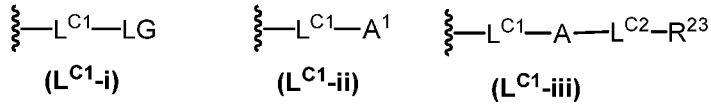
[00188] In certain embodiments, R^3 is optionally substituted heterocyclyl, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00189] In certain embodiments, R^3 is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00190] In certain embodiments, R^3 is optionally substituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl.

[00191] In certain embodiments, R^3 is $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, or an oxygen protecting group.

[00192] In certain embodiments, R^3 is or a group of formula:



(L^{C1}-i) **(L^{C1}-ii)** **(L^{C1}-iii)**

,

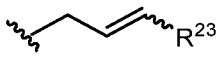
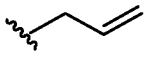
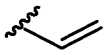
wherein L^{C1}, LG, A^1, A, L^{C2}, and R^{23} are as defined herein.

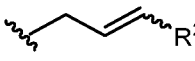
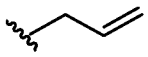
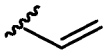
[00193] In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (S)-configuration.

[00194] In certain embodiments, R^4 is hydrogen.

[00195] In certain embodiments, R^4 is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, R^4 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CHO$. In certain embodiments, R^4 is $-CH_2N(R^{22})_2$ wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl. In certain embodiments, R^4 is $-CH_2NH(R^{22})$. In certain embodiments, R^4 is $-CH_2NH_2$. In certain embodiments, R^4 is $-CH_2CH(OH)R^{24}$ wherein R^{24} is hydrogen, optionally substituted alkyl, or optionally substituted aryl. In certain

embodiments, R^4 is $–CH_2CH_2OH$. In certain embodiments, R^4 is $–CH_2CH_2R^{23}$ wherein R^{23} is as defined herein.

[00196] In certain embodiments, R^4 is optionally substituted alkenyl, *e.g.*, optionally substituted $C_{2–6}$alkenyl, optionally substituted $C_{2–3}$alkenyl, optionally substituted $C_{3–4}$alkenyl, optionally substituted $C_{4–5}$alkenyl, or optionally substituted $C_{5–6}$alkenyl. In certain embodiments, R^4 is optionally substituted allyl, *e.g.,* substituted allyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted allyl  . In certain embodiments, R^4 is optionally substituted vinyl, *e.g.,* substituted vinyl, *e.g.,*  wherein R^{23} is as defined herein, or unsubstituted vinyl  .

[00197] Various combinations of R^4 and R^{21} are contemplated herein. For example, in certain embodiments, R^4 is optionally substituted $C_{1–3}$alkyl and R^{21} is hydrogen. In certain embodiments, R^3 is $–CH_2CHO$, $–CH_2N(R^{22})_2$, $–CH_2CH(OH)R^{24}$, or $–CH_2CH_2R^{23}$ and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted $C_{2–3}$alkenyl, and R^{21} is hydrogen. In certain embodiments, R^4 is  ,  ,  , or  and R^{21} is hydrogen.

[00198] In certain embodiments, R^4 is optionally substituted alkynyl, *e.g.*, optionally substituted $C_{2–6}$alkynyl, optionally substituted $C_{2–3}$alkynyl, optionally substituted $C_{3–4}$alkynyl, optionally substituted $C_{4–5}$alkynyl, or optionally substituted $C_{5–6}$alkynyl.

[00199] In certain embodiments, R^4 is optionally substituted carbocyclyl, *e.g.,* optionally substituted $C_{3–6}$carbocyclyl, optionally substituted $C_{3–4}$carbocyclyl, optionally substituted $C_{4–5}$ carbocyclyl, or optionally substituted $C_{5–6}$ carbocyclyl.

[00200] In certain embodiments, R^4 is optionally substituted heterocyclyl, *e.g.,* optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00201] In certain embodiments, R^4 is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

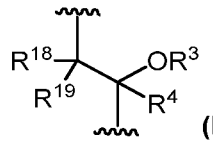
[00202] In certain embodiments, R^4 is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00203] In certain embodiments, each instance of R^{18} and R^{19} is independently hydrogen or optionally substituted alkyl, *e.g.,* hydrogen or $–CH_3$. In certain embodiments, the carbon to

which R^{18} and R^{19} are attached is a stereocenter in the (R) configuration. In certain embodiments, the carbon to which R^{18} and R^{19} are attached is a stereocenter in the (S) configuration.

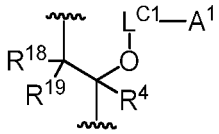
[00204] In certain embodiments, each instance of R^{20} and R^{21} is independently hydrogen, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring. In certain embodiments, R^{20} and R^{21} are syn to each other. In certain embodiments, R^{20} and R^{21} are anti to each other.

[00205] In certain embodiments, L^3 is:



(L^3-i).

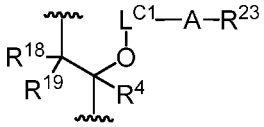
[00206] In certain embodiments, L^3 is:



(L^3-ic),

wherein L^{C1} and A^1 are as defined herein.

[00207] In certain embodiments, L^3 is of the formula:



(L^3-id),

wherein L^{C1}, A, L^{C2}, and R^{23} are as defined herein.

Groups R^{5a} and R^{5b}

[00208] As generally defined herein, each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl.

[00209] In certain embodiments, one instance of R^{5a} and R^{5b} is hydrogen, and the other of R^{5a} and R^{5b} is a non-hydrogen group. In certain embodiments, each instance of R^{5a} and R^{5b} is hydrogen. In certain embodiments, each instance of R^{5a} and R^{5b} is a non-hydrogen group, *e.g.,* halogen, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl.

[00210] In certain embodiments, the carbon to which R^{5a} and R^{5b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{5a} and R^{5b} is attached is a stereocenter of the (S)-configuration.

[00211] In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, at least one instance of R^{5a} and R^{5b} is $-CH_3$. In certain embodiments, both instances of R^{5a} and R^{5b} are $-CH_3$.

[00212] In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted carbocyclyl, *e.g.*, optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00213] In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00214] In certain embodiments, at least one instance of R^{5a} and R^{5b} is halogen, *e.g.,* bromo, iodo, chloro, or fluoro. In certain embodiments, at least one instance of R^{5a} and R^{5b} is fluoro. In certain embodiments, both instances of R^{5a} and R^{5b} are fluoro. In certain embodiments, one of R^{5a} and R^{5b} is hydrogen and the other of R^{5a} and R^{5b} is fluoro.

[00215] In certain embodiments, at least one instance of R^{5a} and R^{5b} is silyl.

Groups R^6 and R^{10}

[00216] As generally defined herein, R^6 and/or R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen.

[00217] In certain embodiments, R^6 and/or R^{10} is hydrogen. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^{10} is hydrogen. In certain embodiments, R^6 is hydrogen, and R^{10} is hydrogen. In certain embodiments, both of R^6 and R^{10} are non-hydrogen groups.

[00218] In certain embodiments, the carbon to which R^6 and R^{10} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^6 and R^{10} is attached is a stereocenter of the (S)-configuration.

[00219] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkyl; *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_3$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_3$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_2CN$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_2C(=O)OR^{32}$, wherein R^{32} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl. In certain embodiments, R^{32} is optionally substituted alkyl, *e.g.* C_{1-6} alkyl. In certain embodiments, R^{32} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{32} is methyl, ethyl, or propyl. In certain embodiments, R^{32} is substituted C_{1-6} alkyl. In certain embodiments, R^{32} is hydrogen.

[00220] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, at least one instance of R^6 and R^{10} is substituted or unsubstituted allyl. In certain embodiments, at least one instance of R^6 and R^{10} is substituted or unsubstituted vinyl. Such groups are contemplated after the macrocyclization step, converted, for example, from the enolate of the macrolide wherein R^6 and/or R^{10} is hydrogen.

[00221] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl. Such groups are contemplated after the macrocyclization step, converted, for example, from the enolate of the macrolide wherein R^6 and/or R^{10} is hydrogen.

[00222] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00223] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted

3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00224] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted aryl; *e.g.*, optionally substituted phenyl.

[00225] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted aralkyl; *e.g.*, optionally substituted benzyl.

[00226] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heteroaryl, *e.g.,* optionally substituted 5– to 6–membered heteroaryl.

[00227] In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heteroaralkyl; *e.g.*, optionally substituted pyrazolylalkyl, imidazolylalkyl, thiazolylalkyl, oxazolylalkyl, pyridinylalkyl, pyrimidinylalkyl, or pyrazinylalkyl.

[00228] In certain embodiments, at least one instance of R^6 and R^{10} is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, or substituted amino. Such groups are contemplated after the macrocyclization step, converted, for example, from wherein R^6 and/or R^{10} is a halogen.

[00229] In certain embodiments, at least one instance of R^6 and R^{10} is carbonyl, *e.g.,* acetyl.

[00230] In certain embodiments, at least one instance of R^6 and R^{10} is silyl. In certain embodiments, R^6 is silyl prior to macrocyclization, but is removed after the macrolide is formed and replaced with, for example, hydrogen.

[00231] In certain embodiments, at least one instance of R^6 and R^{10} is halogen, *e.g.,* fluoro, bromo, chloro, or iodo.

Groups R^7 and R^8

[00232] As generally defined herein, R^7 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00233] In certain embodiments, R^7 is hydrogen. However, in certain embodiments, R^7 is a non-hydrogen group, and the the carbon to which R^7 is attached is a stereocenter of the (R)-configuration. In certain embodiments, R^7 is a non-hydrogen group, and the the carbon to which R^7 is attached is a stereocenter of the (S)-configuration.

[00234] In certain embodiments, R^7 is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl,

optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, R^7 is $–CH_3$ or $–CH_2CH_3$.

[00235] In certain embodiments, R^7 is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, R^7 is vinyl, allyl, or prenyl.

[00236] In certain embodiments, R^7 is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00237] In certain embodiments, R^7 is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00238] In certain embodiments, R^7 is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00239] In certain embodiments, R^7 is optionally substituted aryl; *e.g.*, optionally substituted phenyl.

[00240] In certain embodiments, R^7 is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00241] As generally defined herein, R^8 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

[00242] In certain embodiments, R^8 is hydrogen.

[00243] In certain embodiments, R^8 is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. In certain embodiments, R^8 is $–CH_3$ or $–CH_2CH_3$.

[00244] In certain embodiments, R^8 is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl. In certain embodiments, R^8 is vinyl, allyl, or prenyl

[00245] In certain embodiments, R^8 is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00246] In certain embodiments, R^8 is optionally substituted carbocyclyl, *e.g.,* optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00247] In certain embodiments, R^8 is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00248] In certain embodiments, R^8 is optionally substituted aryl, *e.g.*, optionally substituted phenyl.

[00249] In certain embodiments, R^8 is optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

Groups R^9 and R^{17}, R^{Y1}, R^{Y2}

[00250] As generally defined herein, R^{Y1} is $–OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group.

[00251] In certain embodiments, R^{Y1} and R^{Y2} are joined to form an oxo (=O) group.

[00252] In certain embodiments, R^{Y1} is $–OR^{17}$ and R^{Y2} is hydrogen.

[00253] In certain embodments, R^{Y1} is halogen (*e.g.,* fluoro) and R^{Y2} is hydrogen.

[00254] In certain embodments, R^{Y1} is halogen (*e.g.,* fluoro) and R^{Y2} is halogen (*e.g.,* fluoro).

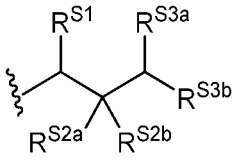
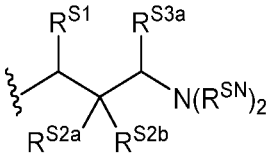
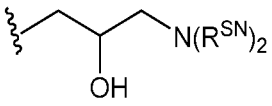
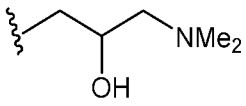
[00255] As generally defined herein, R^9 and/or R^{17} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $–C(=O)R^{Z8}$, $–C(=O)OR^{Z8}$, $–C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate, wherein each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring.

[00256] In certain embodiments, the carbon to which R^9 is attached is of the (R)-configuration. In certain embodiments, the carbon to which R^9 is attached is of the (S)-configuration.

[00257] In certain embodiments, the carbon to which R^{17} is attached is of the (R)-configuration. In certain embodiments, the carbon to which R^{17} is attached is of the (S)-configuration.

[00258] In certain embodiments, R^9 is hydrogen. In certain embodiments, R^{17} is hydrogen.

[00259] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl, *e.g.*, $-CH_3$.

[00260] In certain embodiments, R^9 is  , where R^{S1}, R^{S2a}, R^{S2b}, R^{S3a}, and R^{S3b} are defined herein. In certain embodiments, R^9 is  . In certain embodiments, R^9 is  . In certain embodiments, R^9 is  .

[00261] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted alkenyl, *e.g.*, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-3}alkenyl, substituted or unsubstituted C_{3-4}alkenyl, substituted or unsubstituted C_{4-5}alkenyl, or substituted or unsubstituted C_{5-6}alkenyl.

[00262] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted alkynyl, *e.g.*, substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-3}alkynyl, substituted or unsubstituted C_{3-4}alkynyl, substituted or unsubstituted C_{4-5}alkynyl, or substituted or unsubstituted C_{5-6}alkynyl.

[00263] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted carbocyclyl, *e.g.*, substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-4}carbocyclyl, substituted or unsubstituted C_{4-5} carbocyclyl, or substituted or unsubstituted C_{5-6} carbocyclyl.

[00264] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

[00265] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted aryl, *e.g.*, optionally substituted phenyl.

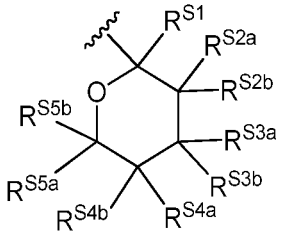
[00266] In certain embodiments, R^9 and/or R^{17} are each independently optionally substituted heteroaryl, *e.g.*, optionally substituted 5– to 6–membered heteroaryl.

[00267] In certain embodiments, R^9 and/or R^{17} are each independently $–C(=O)R^{Z8}$, $–C(=O)OR^{Z8}$, or $–C(=O)N(R^{Z8})_2$. For example, in certain embodiments, R^{17} is $–C(=O)R^{Z8}$, wherein R^{Z8} is optionally substituted aryl or optionally substituted heteroaryl. In certain embodiments, R^{17} is $–C(=O)R^{Z8}$, wherein R^{Z8} is optionally substituted aralkyl or optionally substituted heteroaralkyl.

[00268] In certain embodiments, R^9 and/or R^{17} are each independently an oxygen protecting group.

[00269] In certain embodiments, R^9 and/or R^{17} are each independently a carbohydrate.

[00270] In certain embodiments, R^9 and/or R^{17} is a group of Formula (**s - 1**), which encompasses carbohydrates, but also encompasses optionally substituted heterocylyl:



(s - 1)

wherein:

each of R^{S1}, R^{S2a}, R^{S2b}, R^{S3a}, R^{S3b}, R^{S4a}, R^{S4b}, R^{S5a}, and R^{S5b} is independently hydrogen, optionally substituted alkyl, $–OR^{SO}$, $–N(R^{SN})_2$, or wherein R^{S2a} or R^{S2b} may be taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring;

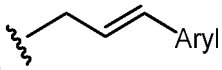
each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group; and

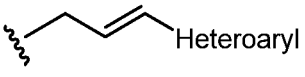
each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN} are taken with the intervening atoms to form a heterocyclic ring.

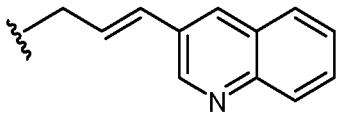
[00271] As generally defined herein, each instance of R^{S1} is independently hydrogen, optionally substituted alkyl, $–OR^{SO}$, or $–N(R^{SN})_2$.

[00272] In certain embodiments, R^{S1} is hydrogen.

[00273] In certain embodiments, R^{S1} is optionally substituted alkyl. In certain embodiments, R^{S1} is substituted $C_{1–6}$ alkyl. In certain embodiments, R^{S1} is unsubstituted $C_{1–6}$ alkyl. In certain embodiments, R^{S1} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, R^{S1} is isopropyl, isobutyl, or isoamyl. In certain embodiments, R^{S1} is isobutyl. In certain embodiments, R^{S1} is *tert*–butyl.

[00274] In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, R^{S1} is –OH. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, R^{S1} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, R^{S1} is optionally substituted –O–alkyl–aryl. In certain embodiments, R^{S1} is –O–Bz. In certain embodiments, R^{S1} is optionally substituted –O–alkyl–heteroaryl. In certain embodiments, R^{S1} is optionally substituted –O–alkenyl–aryl. In certain embodiments, R^{S1} is optionally substituted –O–alkenyl–heteroaryl. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, R^{S1} is $–OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00275] In certain embodiments, R^{S1} is $–N(R^{SN})_2$. In some embodiments, R^{S1} is $–N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, R^{S1} is $–N(R^{SN})_2$, wherein each R^{SN} is different.

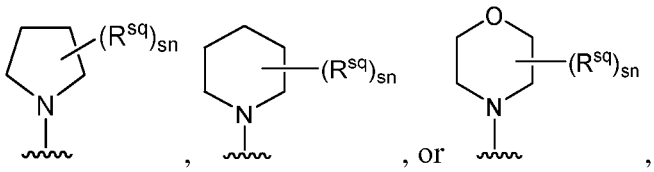
[00276] In certain embodiments, R^{S1} is $–NH_2$.

[00277] In certain embodiments, R^{S1} is $–NHR^{SN}$. In certain embodiments, R^{S1} is $–NHR^{SN}$, wherein R^{SN} is optionally substituted $C_{1–6}$ alkyl. In certain embodiments, R^{S1} is $–NHR^{SN}$, wherein R^{SN} is unsubstituted $C_{1–6}$ alkyl. In certain embodiments, R^{S1} is $–NHR^{SN}$, wherein R^{SN} is substituted $C_{1–6}$ alkyl. In certain embodiments, R^{S1} is –NH–benzyl.

[00278] In certain embodiments, R^{S1} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiments, R^{S1} is –NHFmoc. In certain embodiment, R^{S1} is –NHBoc.

[00279] In certain embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^{S1} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00280] In some embodiments, R^{S1} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, R^{S1} is of the formula:



, , or ,

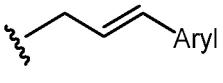
wherein R^{sq} is as defined herein, and sn is 0, 1, 2, or 3.

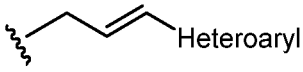
[00281] As generally defined above, each instance of R^{S2a} and R^{S2b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

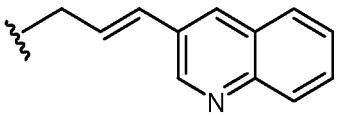
[00282] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is hydrogen.

[00283] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is isobutyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is *tert*–butyl.

[00284] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –OH. In certain embodiments, at least one instance of

R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –O–Bz. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –O–alkyl–heteroaryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted –O–alkenyl–aryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is optionally substituted –O–alkenyl–heteroaryl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is 

, wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00285] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

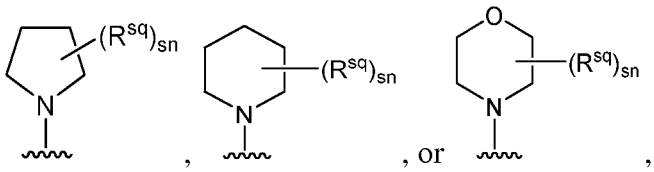
[00286] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NH_2$.

[00287] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is –NH–benzyl.

[00288] In certain embodiment, at least one instance of R^{S2a} and R^{S2b} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R^{S2a} and R^{S2b} is –NHFmoc. In certain embodiment, at least one instance of R^{S2a} and R^{S2b} is –NHBoc.

[00289] In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00290] In some embodiments, at least one instance of R^{S2a} and R^{S2b} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R^{S2a} and R^{S2b} is of the formula:



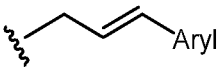
, , or ,

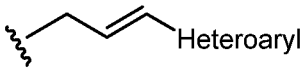
wherein R^{sq} is as defined herein, and sn is 0, 1, 2, or 3.

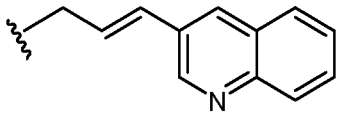
[00291] As generally defined above, each instance of R^{S3a} and R^{S3b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

[00292] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is hydrogen.

[00293] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is isobutyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is *tert*–butyl.

[00294] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –OH. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} –O–Bz. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –O–alkyl–heteroaryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is optionally substituted –O–alkenyl–aryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is optionally substituted –O–alkenyl–heteroaryl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S2a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00295] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S3a} and R^{S3b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00296] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NH_2$.

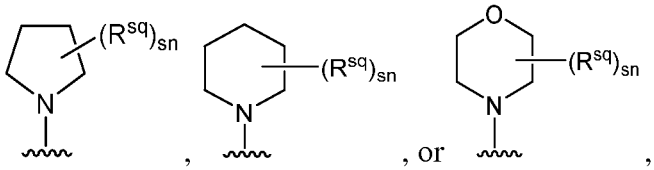
[00297] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance

of R^{S3a} and R^{S3b} is $–NHR^{SN}$, wherein R^{SN} is substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is –NH–benzyl.

[00298] In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is $–NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is –NHFmoc. In certain embodiment, at least one instance of R^{S3a} and R^{S3b} is –NHBoc.

[00299] In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $–N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted $C_{1–6}$ alkyl. In certain embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00300] In some embodiments, at least one instance of R^{S3a} and R^{S3b} is $–N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R^{S3a} and R^{S3b} is of the formula:



, , or ,

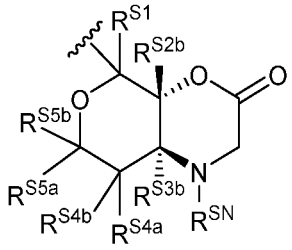
wherein R^{sq} is as defined herein, and sn is 0, 1, 2, or 3.

[00301] In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2a} is taken together with R^{S3a} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2b} is taken together with R^{S3b} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2a} is taken together with R^{S3b} to form an optionally substituted fused heterocyclic ring. In certain embodiments, R^{S2b} is taken together with R^{S3a} to form an optionally substituted fused heterocyclic ring.

[00302] In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused pyrrolidine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidinone. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazinone. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholine. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholinone.

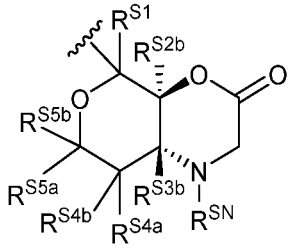
[00303] In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused pyrrolidine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperidinone; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused piperazinone; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholine; and R^{SN} is methyl. In certain embodiments, R^{S2a} or R^{S2b} is taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused morpholinone; and R^{SN} is methyl.

[00304] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



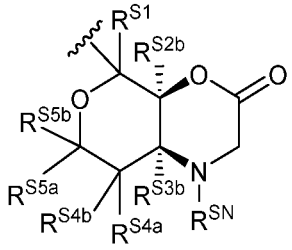
.

[00305] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



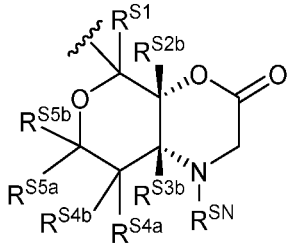
.

[00306] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



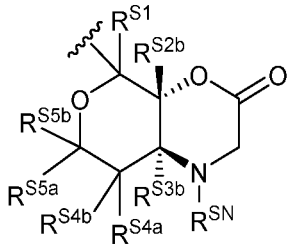
.

[00307] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



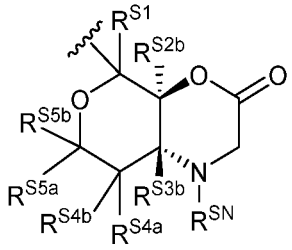
.

[00308] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



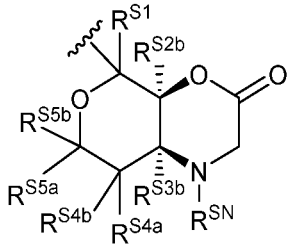
; and R^{SN} is methyl.

[00309] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



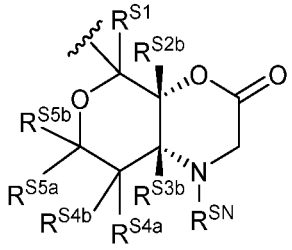
; and R^{SN} is methyl.

[00310] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form



; and R^{SN} is methyl.

[00311] In certain embodiments, R^{S2a} is taken together with R^{S3a} to form

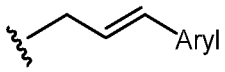


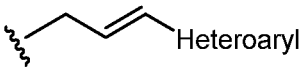
; and R^{SN} is methyl.

[00312] As generally defined above, each instance of R^{S4a} and R^{S4b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

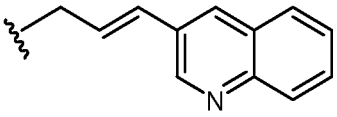
[00313] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is hydrogen.

[00314] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is isobutyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is *tert*–butyl.

[00315] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –OH. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –O–Bz. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is  wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is



wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is



. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00316] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00317] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NH_2$.

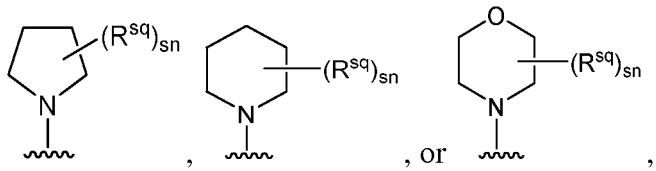
[00318] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is –NH–benzyl.

[00319] In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is –NHFmoc. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is –NHBoc.

[00320] In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(CH_2CH_3)R^{SN}$, wherein each

R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00321] In some embodiments, at least one instance of R^{S4a} and R^{S4b} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R^{S4a} and R^{S4b} is of the formula:



, , or ,

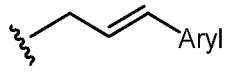
wherein R^{sq} is as defined herein, and sn is 0, 1, 2, or 3.

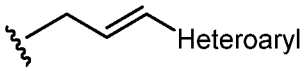
[00322] As generally defined above, each instance of R^{S5a} and R^{S5b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, or $-N(R^{SN})_2$.

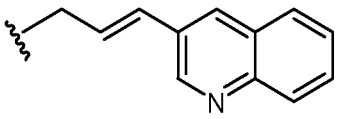
[00323] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is hydrogen.

[00324] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is methyl, ethyl, propyl, butyl, pentyl, or hexyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is isopropyl, isobutyl, or isoamyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is isobutyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is *tert*–butyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is alkoxyalkyl, *e.g.* $-CH_2OMe$, $-CH_2OEt$, or $-CH_2OBn$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2OH$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2OBz$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2OPG$, wherein PG is an oxygen protecting group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is aminoalkyl, *e.g.* $-CH_2NHMe$, $-CH_2NMe_2$, or $-CH_2NHBn$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2NH_2$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-CH_2NHPG$, wherein PG is an nitrogen protecting group.

[00325] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted heterocyclyl, or an oxygen protecting group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –OH. In certain

embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –O–methyl, –O–ethyl, or –O–propyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is optionally substituted –O–alkyl–aryl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –O–Bz. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Aryl is an optionally substituted aryl group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is 

wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is 

. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is an oxygen protecting group. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is carbonyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is acetyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-OR^{SO}$, wherein R^{SO} is optionally substituted heterocyclyl.

[00326] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$. In some embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is the same. In some embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is different.

[00327] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NH_2$.

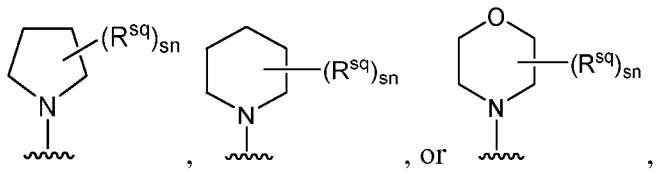
[00328] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is unsubstituted C_{1-6} alkyl. In certain embodiment, at least one instance R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is –NH–benzyl.

[00329] In certain embodiment, at least one instance of R^{S5a} and R^{S5b} is $-NHR^{SN}$, wherein R^{SN} is a nitrogen protecting group. In certain embodiment, at least one instance of R^{S4a} and R^{S4b} is –NHFmoc. In certain embodiment, at least one instance of R^{S5a} and R^{S5b} is –NHBoc.

[00330] In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least

one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(CH_2CH_3)R^{SN}$, wherein each R^{SN} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein each R^{SN} is independently selected from the group consisting of methyl, ethyl, isopropyl, isobutyl, isoamyl, and benzyl.

[00331] In some embodiments, at least one instance of R^{S5a} and R^{S5b} is $-N(R^{SN})_2$, wherein two R^{SN} groups are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. For example, in certain embodiments, at least one instance of R^{S5a} and R^{S5b} is of the formula:



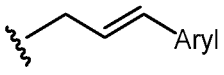
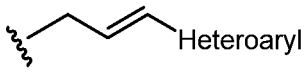
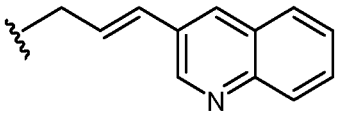
, , or ,

wherein R^{sq} is as defined herein, and sn is 0, 1, 2, or 3.

[00332] As used herein, each instance R^{sq} is independently halogen, optionally substituted alkyl, $-OR^{SO1}$, or $-N(R^{SN1})_2$, wherein R^{SO1} is independently hydrogen, optionally substituted alkyl, or an oxygen protecting group; and R^{SN1} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN1} are taken together with the intervening atoms to form an optionally substituted heterocyclic ring.

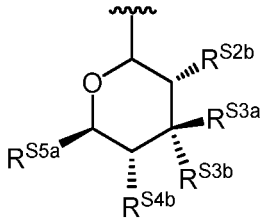
[00333] As generally defined herein, each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, carbonyl, optionally substituted heterocyclyl, or an oxygen protecting group.

[00334] In certain embodiments, R^{SO} is hydrogen. In certain embodiments, R^{SO} is optionally substituted alkyl. In certain embodiments, R^{SO} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{SO} is methyl, ethyl, or propyl. In certain embodiments, R^{SO} is optionally substituted aralkyl, *e.g.,* optionally substituted benzyl (Bn). In certain embodiments, R^{SO} is optionally substituted heterocyclyl. In certain embodiments, R^{SO} is carbonyl. In certain embodiments, R^{SO} is $-C(=O)CH_3$ (acetyl, Ac). In certain embodiments, R^{SO} is $-C(=O)Ph$

(benzoyl, Bz). In certain embodiments, R^{SO} is  wherein Aryl is an optionally substituted aryl group. In certain embodiments, R^{SO} is  wherein Heteroaryl is an optionally substituted heteroaryl group. In certain embodiments, R^{SO} is  . In certain embodiments, R^{SO} is an oxygen protecting group.

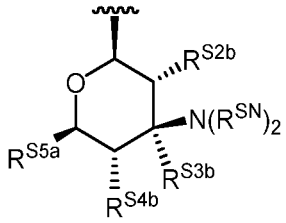
[00335] As generally defined herein, each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, optionally substituted heterocyclyl, or a nitrogen protecting group; or optionally two R^{SN} are taken together with the intervening atoms to form an optionally substituted heterocyclic ring. In certain embodiments, R^{SN} is hydrogen. In certain embodiments, R^{SN} is optionally substituted alkyl. In certain embodiments, R^{SN} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{SN} is methyl, ethyl, or propyl. In certain embodiments, R^{SN} is substituted aralkyl, *e.g.,* optionally substituted benzyl (Bn). In certain embodiments, R^{SN} is optionally substituted heterocyclyl. In certain embodiments, R^{SN} is carbonyl. In certain embodiments, R^{SN} is carbonyl. In certain embodiments, R^{SN} is $-C(=O)CH_3$ (acetyl, Ac). In certain embodiments, R^{SN} is –C(=O)Ph (benzoyl, Bz). In certain embodiments, R^{SN} is a nitrogen protecting group.

[00336] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 2**):



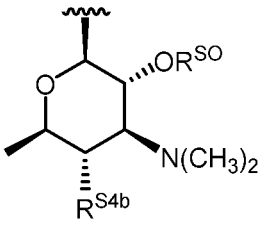
(**s - 2**).

[00337] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 2a**):

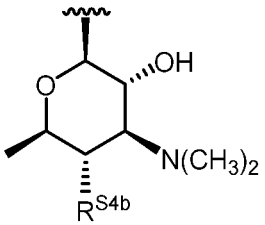


(**s - 2a**).

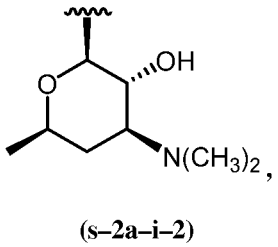
[00338] In certain embodiments, R^9 and/or R^{17} is of one of the following formulae:



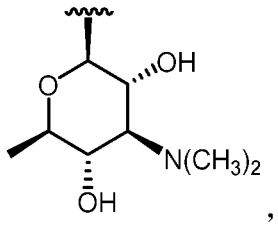
(s–2a–i),



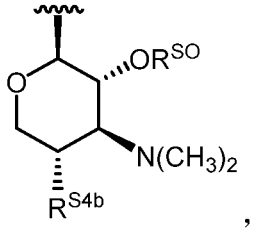
(s–2a–i–1),



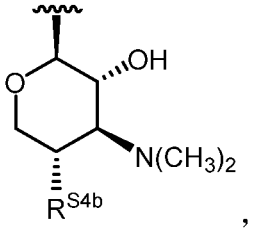
(s–2a–i–2),



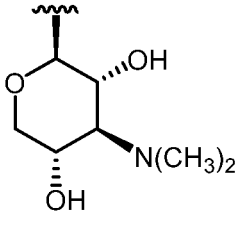
(s–2a–i–3),



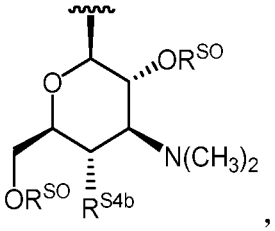
(s–2a–ii),



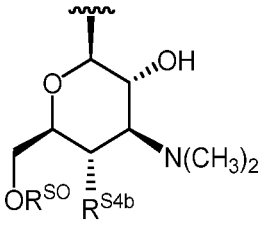
(s–2a–ii–1),



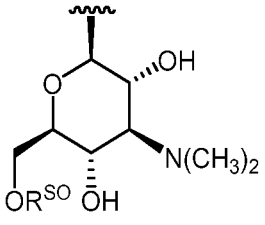
(s–2a–ii–2),



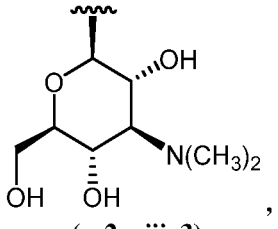
(s–2a–iii),



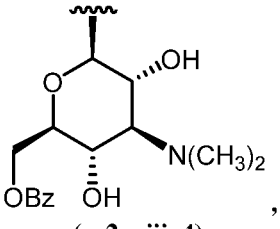
(s–2a–iii–1),



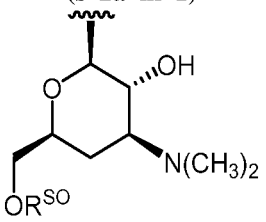
(s–2a–iii–2),



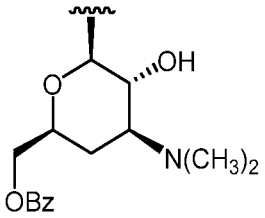
(s–2a–iii–3),



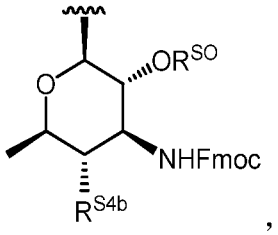
(s–2a–iii–4),



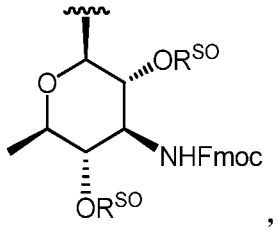
(s–2a–iii–5),



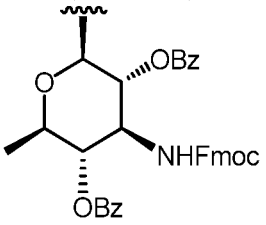
(s–2a–iii–6),



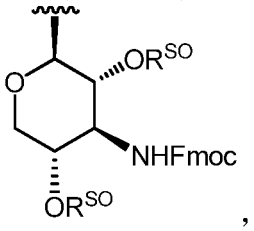
(s–2a–iv),



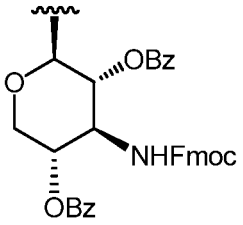
(s–2a–iv–1),



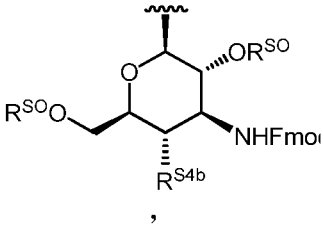
(s–2a–iv–2),



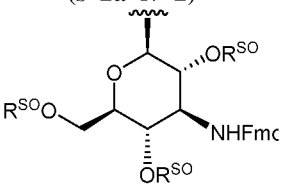
(s–2a–iv–3),



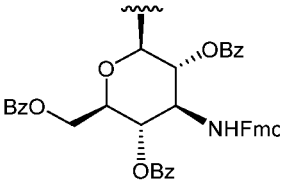
(s–2a–iv–4),



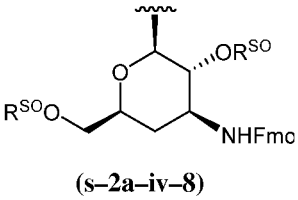
(s–2a–iv–5),



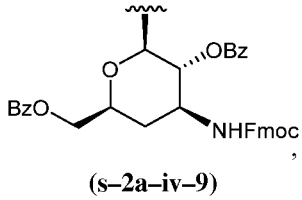
(s–2a–iv–6),



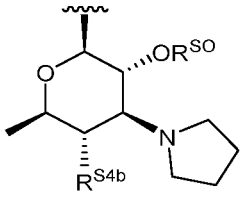
(s–2a–iv–7),



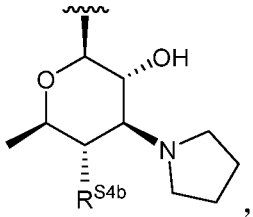
(s–2a–iv–8),



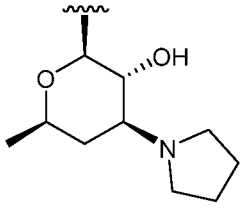
(s–2a–iv–9),



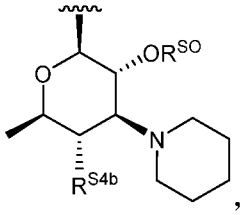
(s–2a–v),



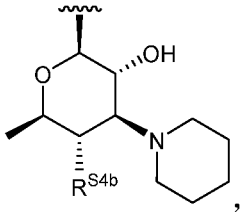
(s–2a–v–1),



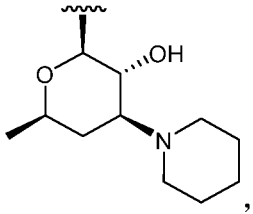
(s–2a–v–2),



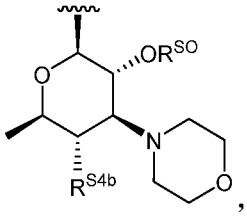
(s–2a–vi),



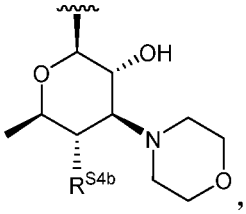
(s–2a–vi–1),



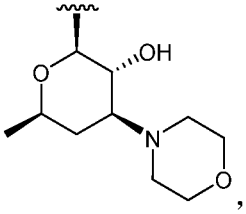
(s–2a–vi–2),



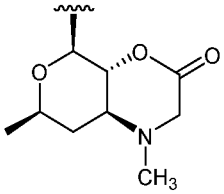
(s–2a–vii),



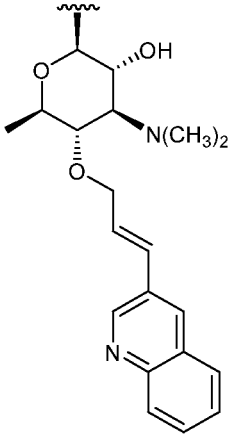
(s–2a–vii–1),



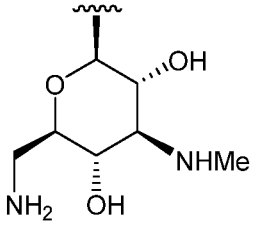
(s–2a–vii–2),



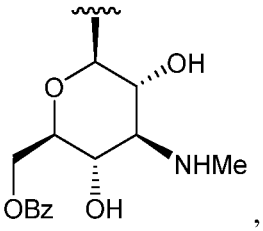
(s–2a–vii–3),



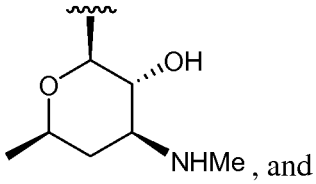
(s–2a–vii–4),



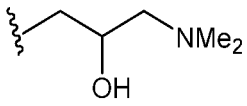
(s-2a-vii-5),



(s-2a-vii-5),



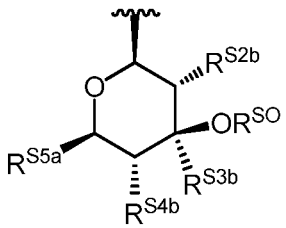
, and



(s-2a-vii-5)

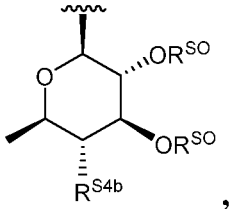
(s-2a-vii-5).

[00339] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 2b**):

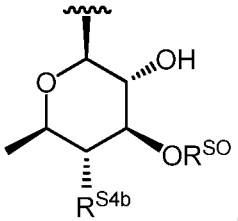


(**s - 2b**).

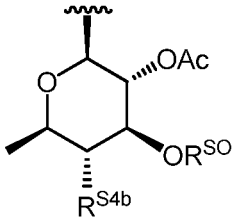
[00340] In certain embodiments, R^9 and/or R^{17} is of one of the following formulae:



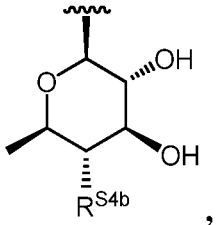
(s–2b–i),



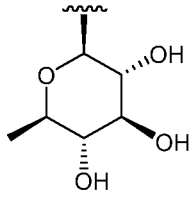
(s–2b–i-1),



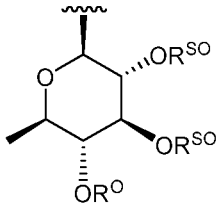
(s–2b–i-2),



(s–2b–i–3),

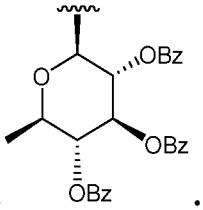


(s–2b–i–4),



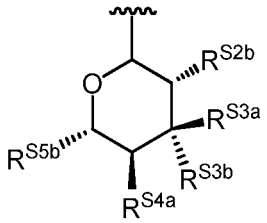
(s–2b–i–5),

and



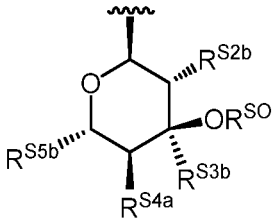
(s–2b–i–5).

[00341] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 3**):



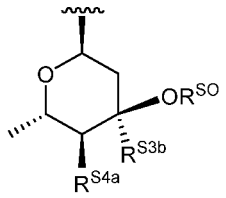
(**s - 3**).

[00342] In certain embodiments, R^9 and/or R^{17} is of Formula (**s - 3a**):

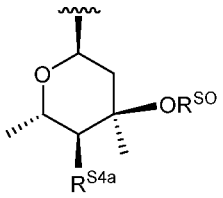


(**s - 3a**).

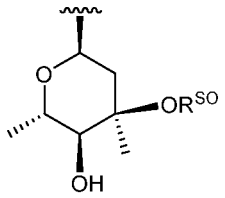
[00343] In certain embodiments, R^9 and/or R^{17} is one of the following formulae:



(s–3a–i),

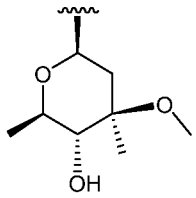


(s–3a–i–1),



and

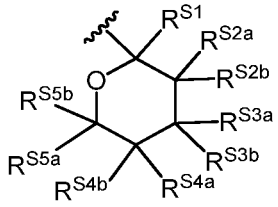
(s–3a–i–2),



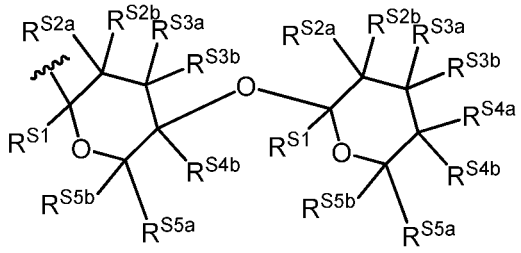
(s–3a–i–3).

[00344] In certain embodiments, R^{SO} is an optionally substituted heterocycyl.

[00345] For example, in certain embodiments, R^{SO} is of the formula:

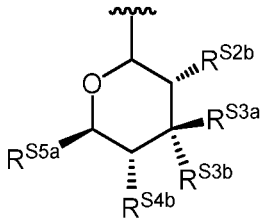


(**s-4**) or

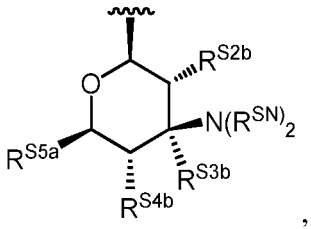
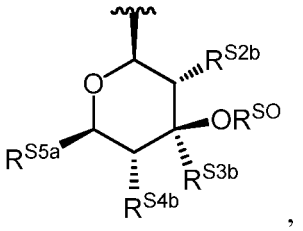
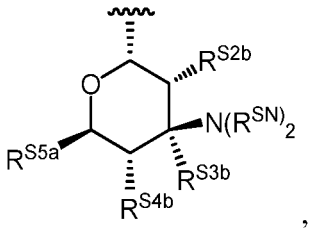
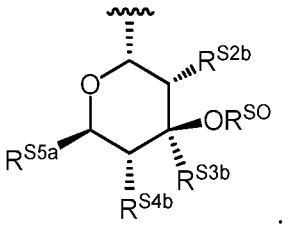


(**s-5**).

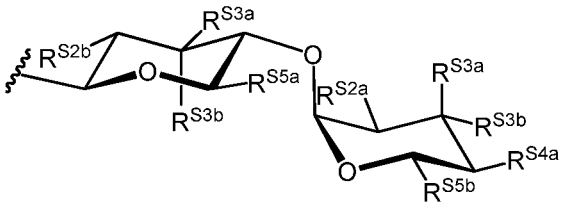
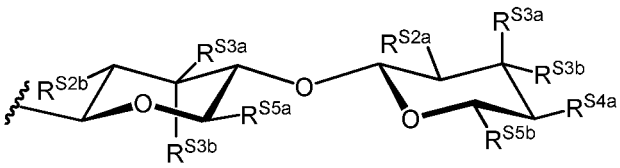
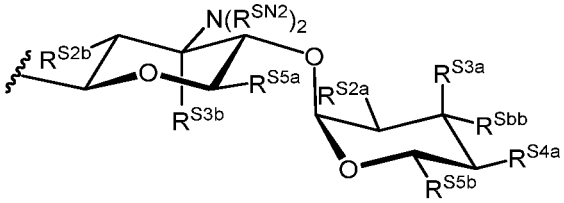
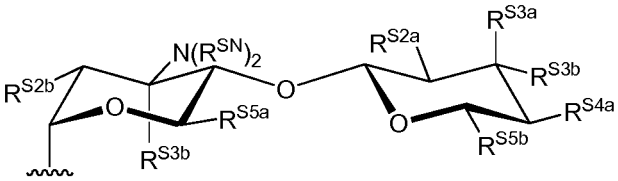
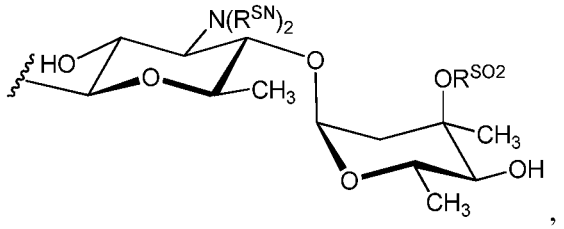
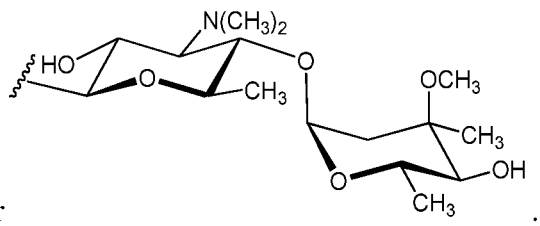
[00346] In certain embodiments, R^{SO} is of the formula:



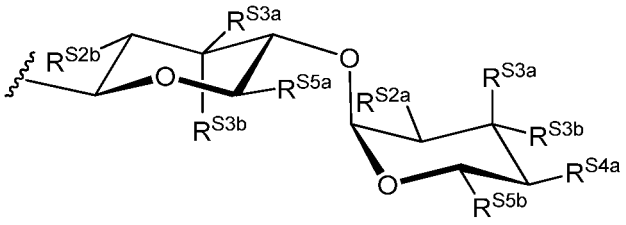
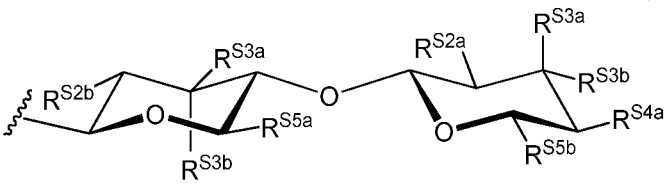
[00347] In certain embodiments, R^{SO} is of the formula:


,

,

, or

.

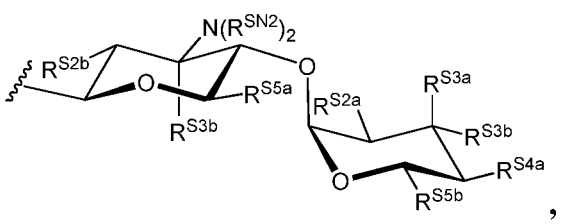
[00348] In certain embodiments, R^{SO} is of the formula:


,

,

,

,

, or

.

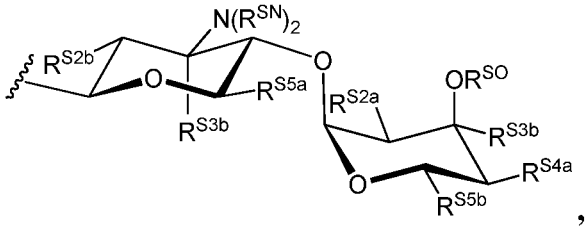
[00349] In certain embodiments, R^{9} and/or R^{17} is of the formula:


(**s - 2c**) or

(**s - 2d**).

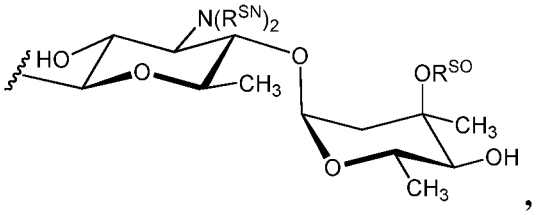
[00350] In certain embodiments, R^9 and/or R^{17} is one of the following formulae:



(s–2c–i)

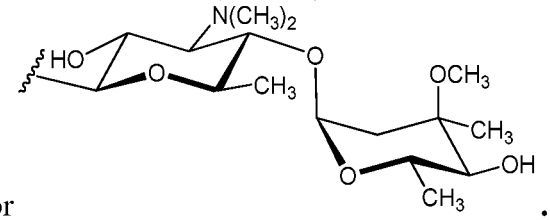


(s–2c–ii)



(s–2c–iii)

or

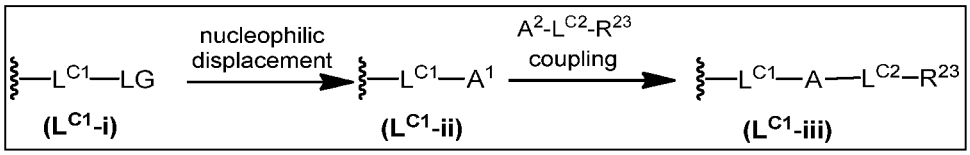


(s–2c–iv)

Groups A^1, A^2, and A

[00351] As is generally understood from the above disclosure, in certain embodiments, R^{12}, R^{14}, and/or R^3 is a group of Formula (**L^{C1}-i**), wherein LG is a leaving group as defined herein. In certain embodiments, nucleophilic displacement of the leaving group provides a group of Formula (**L^{C1}-ii**). See Scheme A1. It is generally understood that A^1 is a group which is reactive with A^2 of a compound of Formula A^2–L^{C2}–R^{23}, and reaction between the two halves provides a group of Formula (**L^{C1}-iii**). See, Scheme A1. These reactions, from (**L^{C1}-i**) to (**L^{C1}-ii**), and (**L^{C1}-ii**) to (**L^{C1}-iii**), are envisioned to take place at any stage of the synthesis, for example, during construction of the eastern or western halves, after coupling of the eastern or western halves, or after the macrocyclization step.

Scheme A1.

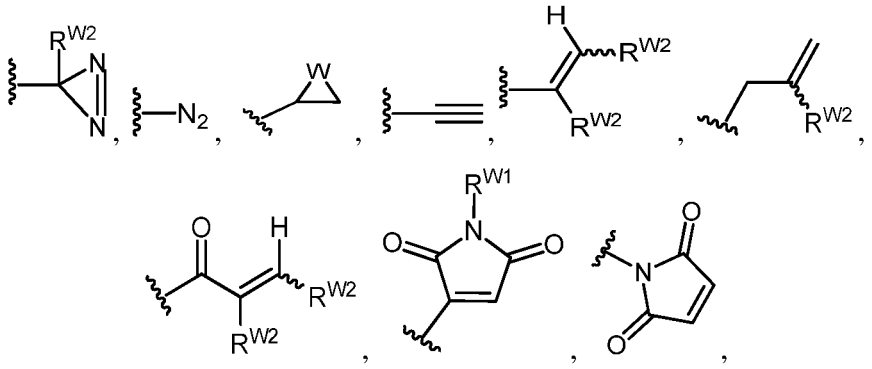


[00352] In certain embodiments, the coupling reaction from (**L^{C1}-ii**) to (**L^{C1}-iii**) comprises a reaction typically referred to as "click chemistry." Click chemistry is a chemical approach introduced by Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together. See, *e.g.*, Kolb, Finn and Sharpless *Angewandte Chemie International Edition* (2001) 40: 2004–2021; Evans, *Australian Journal of Chemistry* (2007) 60: 384–395). Exemplary coupling reactions (some of which may be classified as "Click chemistry") include, but are not limited to, formation of esters, thioesters, amides (*e.g.*, such as peptide coupling) from activated acids or acyl halides; nucleophilic displacement reactions (*e.g.*, such as nucleophilic displacement of a halide or ring opening of

strained ring systems); azide–alkyne Huisgon cycloaddition; thiol–yne addition; imine formation; and Michael additions (*e.g.,* maleimide addition).

[00353] In general, for the group (**L^{C1}-ii**), A^1 should be complimentary and reactive with the group A^2 in order to form the group (**L^{C1}-iii**). For example, if the group A^2 of A^2–L^{C2}–R^{23} is a nucleophilic group, the group A^1 must be a electrophilic group. Likewise, if the group A^2 of A^2–L^{C2}–R^{23} is an electrophilic group, the group A^1 must be a nucleophilic group. While A^1 and A^2 are defined the same in the present invention, it is thus understood that such groups are paired complements.

[00354] As genererally defined herein, A^1 and A^2 may be selected from the group consisting of a leaving group (LG), –SH, –OH, $–NH_2$, $–NH–NH_2$, $–N_3$, $–O–NH_2$, $–C(=O)R^{X1}$,



wherein:

R^{X1} is hydrogen, a leaving group, or $–OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; an oxygen protecting group;

Leaving group (LG) is –Br, –I, –Cl, $-O(C=O)R^{LG}$, or $-O(SO)_2R^{LG}$, wherein R^{LG} is optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or a nitrogen protecting group; and

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R^{W2} groups are joined to form a optionally substituted cyclic moiety.

[00355] In certain embodiments, A^2 is –SH. In certain embodiments, A^1 is –SH.

[00356] In certain embodiments, A^2 is –OH. In certain embodiments, A^1 is –OH.

[00357] In certain embodiments, A^2 is $–NH_2$. In certain embodiments, A^1 is $–NH_2$.

[00358] In certain embodiments, A^2 is $–NH–NH_2$. In certain embodiments, A^1 is $–NH–NH_2$.

[00359] In certain embodiments, A^2 is $–O–NH_2$. In certain embodiments, A^1 is $–O–NH_2$.

[00360] In certain embodiments, A^2 is $–N_3$. In certain embodiments, A^1 is $–N_3$.

[00361] In certain embodiments, A^2 is a leaving group, *e.g.*, –Cl, –Br, or –I. In certain embodiments, A^1 is a leaving group, *e.g.*, –Cl, –Br, or –I.

[00362] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is hydrogen, *i.e.,* to provide A^2 as an aldehyde –CHO. In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is hydrogen, *i.e.,* to provide A^1 as an aldehyde –CHO.

[00363] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is a leaving group (LG).

[00364] In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is a leaving group (LG).

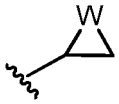
[00365] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is hydrogen, *i.e.,* to provide A^2 as a carboxylic acid –C(=O)OH.

[00366] In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is hydrogen, *i.e.,* to provide A^1 as a carboxylic acid –C(=O)OH.

[00367] In certain embodiments, A^2 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is a non-hydrogen group, *i.e.,* to provide A^2 as an ester $–C(=O)OR^{X2}$.

[00368] In certain embodiments, A^1 is $–C(=O)R^{X1}$, wherein R^{X1} is $–OR^{X2}$, and wherein R^{X2} is non-hydrogen group, *i.e.,* to provide A^1 as an ester $–C(=O)OR^{X2}$.

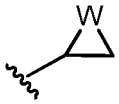
[00369] In certain embodiments, A^2 is an oxiranyl, thiorenyl, or azirdinyl group of formula:



,

wherein W is O, S, or NR^{W1}. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}.

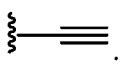
[00370] In certain embodiments, A^1 is an oxiranyl, thiorenyl, or azirdinyl group of formula:



,

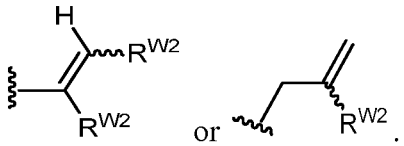
wherein W is O, S, or NR^{W1}. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}.

[00371] In certain embodiments, A^1 or A^2 is ethynyl:

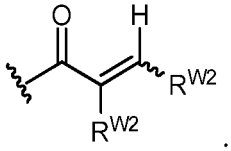


.

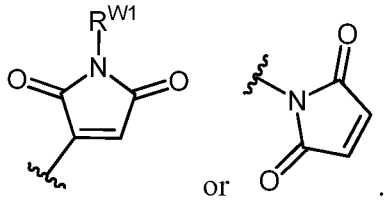
[00372] In certain embodiments, A^1 or A^2 is ethenyl or propenyl:



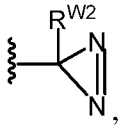
[00373] In certain embodiments, A^1 or A^2 is an α,β – unsaturated carbonyl:



[00374] In certain embodiments, A^1 or A^2 is a maleimide group:



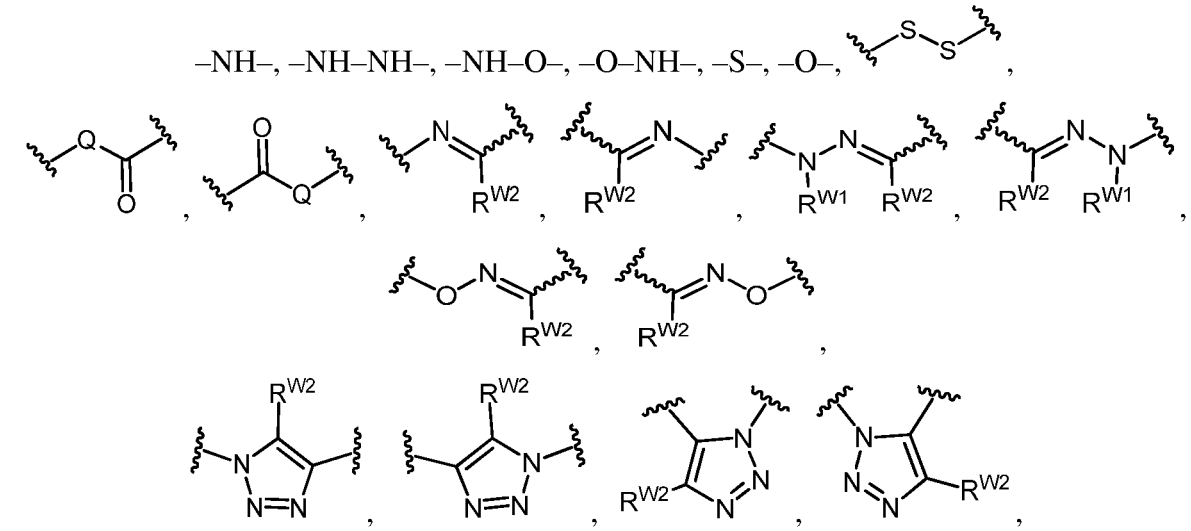
[00375] In certain embodiments, A^1 or A^2 is a group:

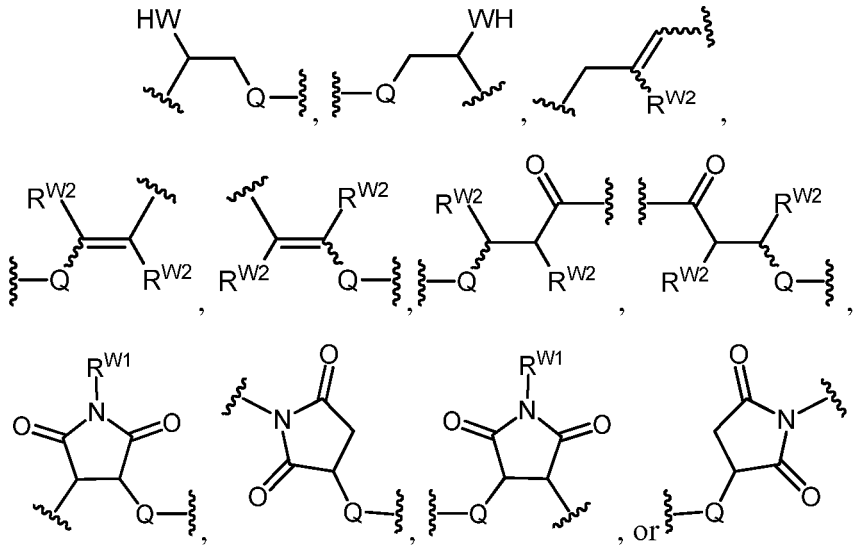


wherein R^{W2} is alkyl, *e.g.*, methyl.

[00376] In certain embodiments, A^1 or A^2 is a group:

[00377] Furthermore, as generally defined herein, A^1 or A^2 react together to form a group A, wherein A is a group of the formula:





wherein:

Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, or –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or a nitrogen protecting group; and

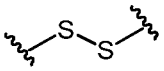
R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety.

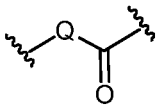
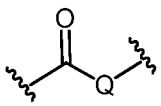
[00378] In certain embodiments, A is –NH–.

[00379] In certain embodiments, A is –NH–NH–.

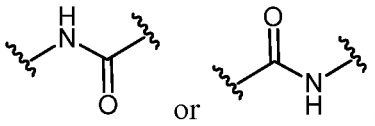
[00380] In certain embodiments, A is –S–.

[00381] In certain embodiments, A is –O–.

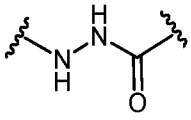
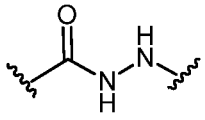
[00382] In certain embodiments, A is a disulfide group  .

[00383] In certain embodiments, A is  or  , wherein Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, –O–.

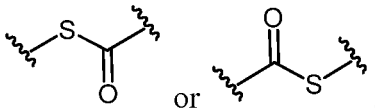
[00384] For example, in certain embodiments, wherein Q is –NH–, A is an amide group of the formula:

 or .

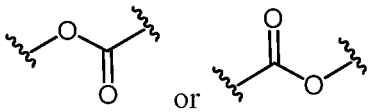
[00385] In certain embodiments, wherein Q is –NH–NH–, A is an amide hydrazide group of the formula:

 or  .

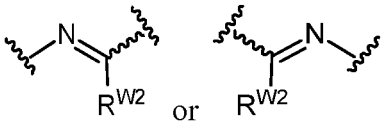
[00386] In certain embodiments, wherein Q is –S–, A is an thioester group of the formula:

 or .

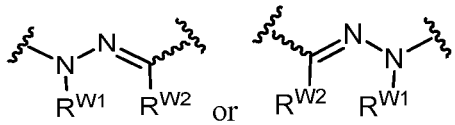
[00387] In certain embodiments, wherein Q is –O–, A is an ester group of the formula:

 or .

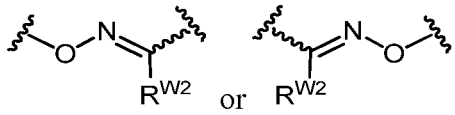
[00388] In certain embodiments, A is:

 or . In certain embodiments, R^{W2} is alkyl, *e.g.*, methyl.

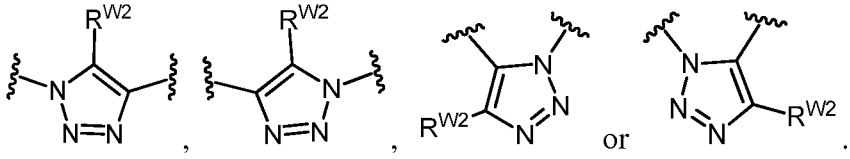
[00389] In certain embodiments, A is:

 or . In certain embodiments, R^{W2} is alkyl, *e.g.*, methyl. In certain embodiments, R^{W1} is hydrogen.

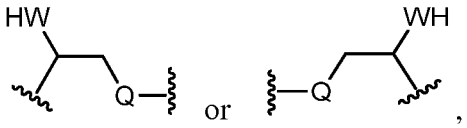
[00390] In certain embodiments, A is:

 or . In certain embodiments, R^{W2} is alkyl, *e.g.*, methyl.

[00391] In certain embodiments, A is:

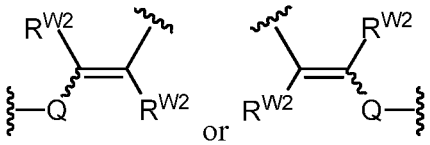
 .

[00392] In certain embodiments, A is:



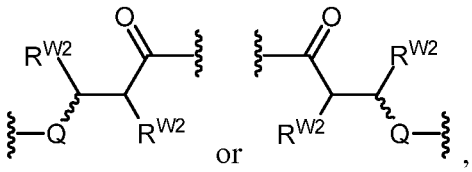
wherein W is O, S, or NR^{W1}, R^{W1} is hydrogen, optionally substituted alkyl, or an amino protecting group; and Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00393] In certain embodiments, A is:



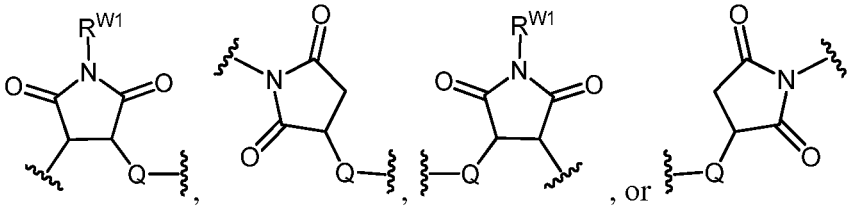
wherein Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00394] In certain embodiments, A is:



wherein Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00395] In certain embodiments, A is:



wherein Q is –NH–, –NH–NH–, –O–NH–, –NH–O–, –S–, or –O–. In certain embodiments, Q is –NH–. In certain embodiments, Q is –NH–NH–. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–.

[00396] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is –C(=O)R^{X1}, wherein

R^{X1} is a leaving group (LG) or $–OR^{X2}$, and the other of A^1 and A^2 is –SH, –OH, $–NH_2$, or $–NH–NH_2$ to provide a moiety A, wherein A is an amide, thioester, or ester group. See, for example, Scheme A2 and Table A1.

Scheme A2. Preparation via amide, thioester, and ester formation

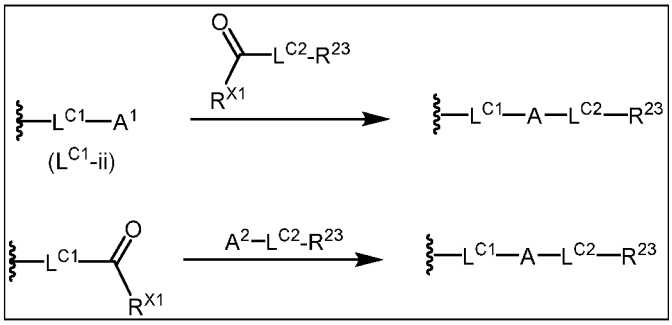


Table A1.			
R^{X1}	A^1	A^2	A –C(=O)Q–, –QC(=O)–
LG or $–OR^{X2}$	–SH	—	–C(=O)S–
	—	–SH	–SC(=O)–
	–OH	—	–C(=O)O–
	—	–OH	–OC(=O)–
	$–NH_2$	—	–C(=O)NH–
		$–NH_2$	–NHC(=O)–
	$–NH–NH_2$	—	–C(=O)NHNH–
	—	$–NH–NH_2$	–NHNHC(=O)–

[00397] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula $A^2–L^{C2}–R^{23}$, wherein one of A^1 and A^2 is a leaving group (LG), and the other of A^1 and A^2 is –SH, –OH, $–NH_2$, or $–NH–NH_2$ to provide a group of formula (**L^{C1}-iii**) wherein A is, respectively, –S–, –O–, –NH–, or –NH–NH–. See, for example, Scheme A3 and Table A2.

Scheme A3. Nucleophilic displacement of a halide or other leaving group

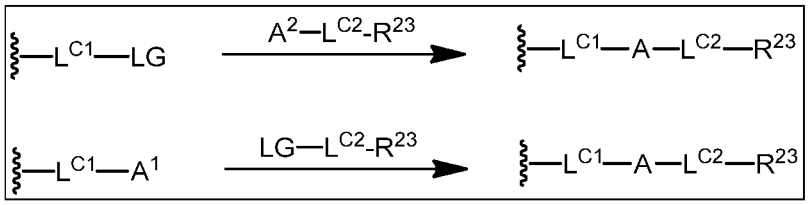


Table A2		
A^1	A^2	A
LG	–SH	–S–
	–OH	–O–
	$–NH_2$	–NH–
	$–NH–NH_2$	–NH–NH–

Table A2		
A^1	A^2	A
	$–O–NH_2$	$–O–NH–$
–SH	LG	–S–
–OH		–O–
$–NH_2$		–NH–
$–NH–NH_2$		$–NH–NH–$
$–O–NH_2$		$–NH–O–$

[00398] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula $A^2–L^{C2}–R^{23}$, wherein one of A^1 and A^2 is 

, and the other of A^1 and A^2 is –SH, –OH, $–NH_2$, or $–NH–NH_2$ to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A4 and Table A3.

Scheme A4. Nucleophilic addition to strained ring systems

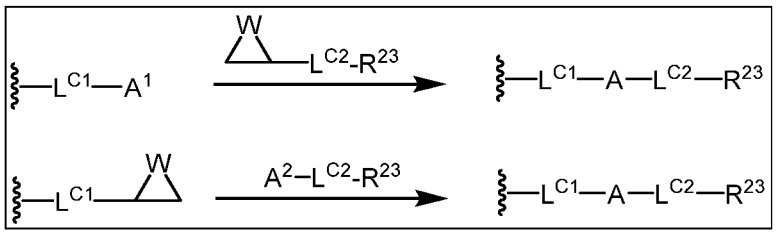


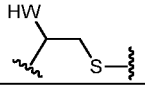
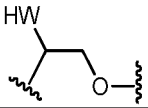
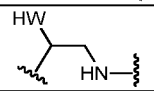
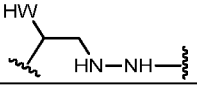
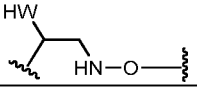
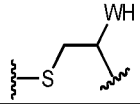
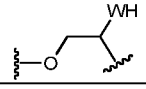
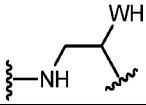
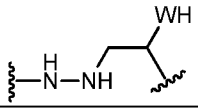
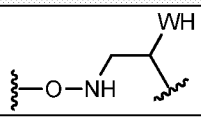
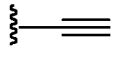
Table A3.			
W	A^2	A^1	A
O, S, NR^{W1}	–SH	—	
	–OH	—	
	$–NH_2$	—	
	$–NH–NH_2$	—	
	$–O–NH_2$	—	
O, S, NR^{W1}	—	–SH	
	—	–OH	
	—	$–NH_2$	
	—	$–NH–NH_2$	

Table A3.			
W	**A^2**	**A^1**	**A**
	—	–O–NH_2	

[00399] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is  , and the other of A^1 and A^2 is $–N_3$ to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A5 and Table A4.

Scheme A5. Azide–alkyne Huisgen cycloaddition

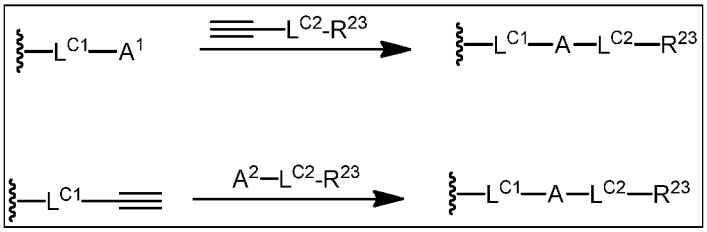
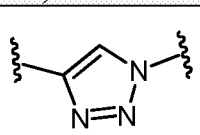
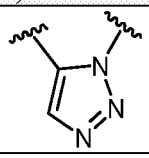
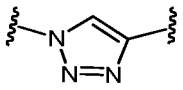
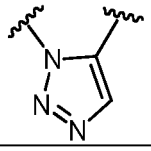
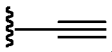


Table A4.			
A^1	A^2	A	
		1,4–adduct	*1,5–adduct*
—	$–N_3$		
$–N_3$	—		

[00400] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula $A^2–L^{C2}–R^{23}$, wherein one of A^1 and A^2 is  , and the other of A^1 and A^2 is –SH to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A6 and Table A5.

Scheme A6. Thiol–yne addition

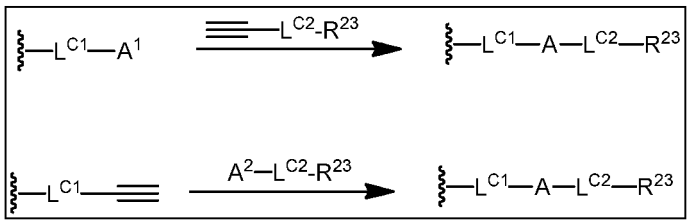
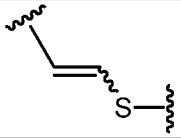
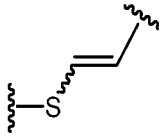


Table A5.		
A^1	A^2	A
—	–SH	
–SH	—	

[00401] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula $A^2–L^{C2}–R^{23}$, wherein one of A^1 and A^2 is an aldehyde –CHO or ketone, and the other of A^1 and A^2 is $–NH_2$, $–NH–NH_2$, or $–O–NH_2$ to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A7 and Table A6.

Scheme A7. Imine formation

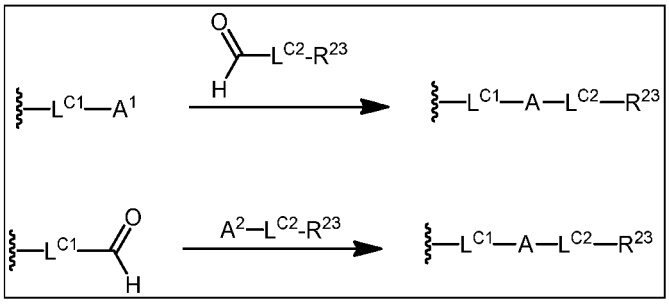
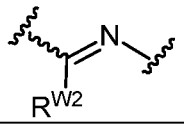
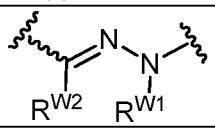
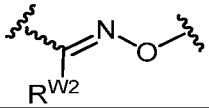
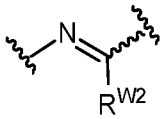
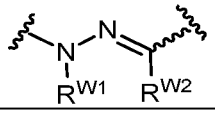
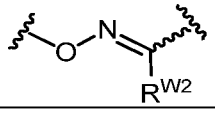


Table A6.

A^1	A^2	A
—	$–NH_2$	
—	$–NH–NH_2$	
—	$–O–NH_2$	
$–NH_2$	—	
$–NH–NH_2$	—	
$–O–NH_2$	—	

[00402] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is an α,β–unsaturated carbonyl, and the other of A^1 and A^2 is –OH, –SH, $–NH_2$, $–NHNH_2$, or $–O–NH_2$ to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A8 and Table A7.

Scheme A8. Michael addition

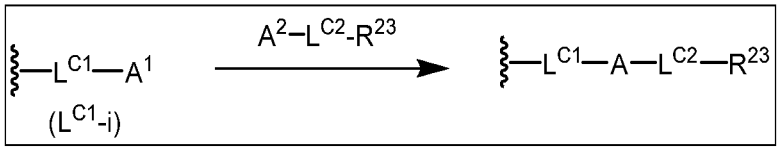
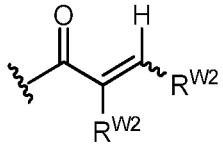
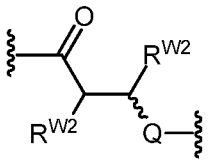
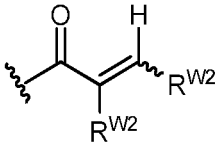
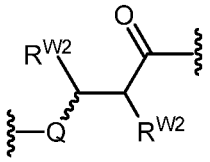


Table A7.		
A^1	**A^2**	**A**
	–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2	
–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2		

[00403] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula A^2–L^{C2}–R^{23}, wherein one of A^1 and A^2 is a maleimide group, and the other of A^1 and A^2 is –OH, –SH, –NH_2, –$NHNH_2$, or –O–NH_2 to provide a group of formula (**L^{C1}-iii**). See, for example, Scheme A9 and Table A8.

Scheme A9. Maleimide addition

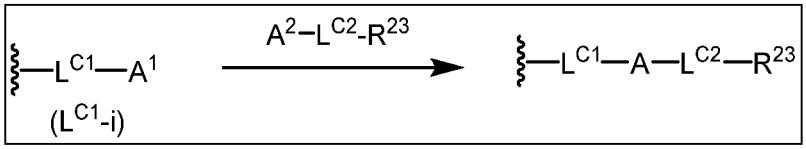


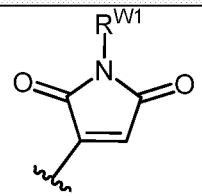
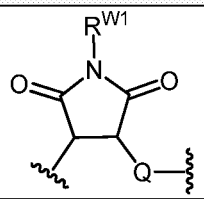
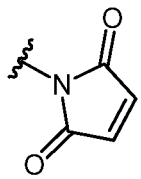
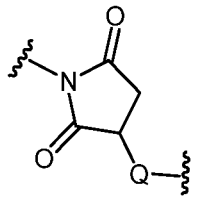
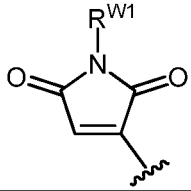
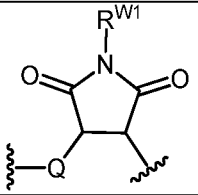
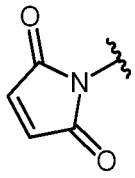
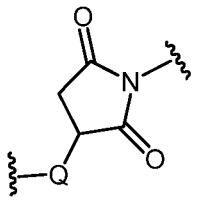
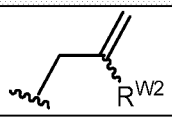
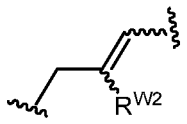
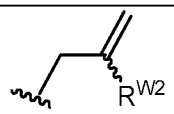
Table A8.		
A^1	**A^2**	**A**
	–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2	
	–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2	
–OH, –SH, –NH_2, –$NHNH_2$, –O–NH_2		

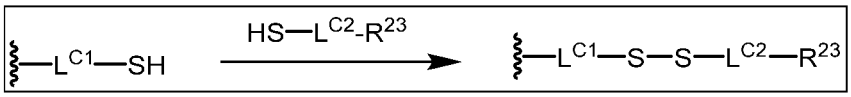
Table A8.		
A^1	A^2	A
–OH, –SH, $–NH_2$, $–NHNH_2$, $–O–NH_2$		

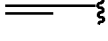
[00404] In certain embodiments, the method comprises coupling (*e.g.*, palladium catalyzed coupling) of a group of formula (**L^{C1}-ii**) with a compound of formula $A^2–L^{C2}–R^{23}$, wherein one of A^1 and A^2 is an propenyl group, and one of A^1 and A^2 is a leaving group, to provide a group of formula (**L^{C1}-iii**) upon treatment with a palladium catalyst. See, for example, Table A9.

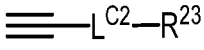
Table A9.		
A^1	A^2	A
	LG	
LG		

[00405] In certain embodiments, the method comprises coupling a group of formula (**L^{C1}-ii**) with a compound of formula $A^2–L^{C2}–R^{23}$, wherein one of A^1 and A^2 is –SH to provide, upon treatment with an oxidant, a group of formula (**L^{C1}-iii**), wherein A is a disulfide bond. See, for example, Scheme A8.

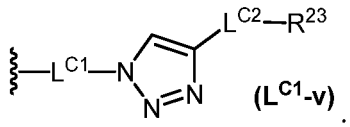
Scheme A8. Disulfide formation



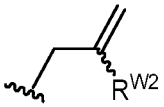
[00406] In certain preferred embodiments, A^1 is $–N_3$ and A^2 is  , such that the compound of formula $A^2–L^{C2}–R^{23}$ is of the formula:

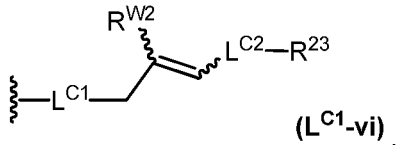


and A^1 and A^2–L^{C2}–R^{23} react together to provide a group of formula:



(L^{C1}-v)

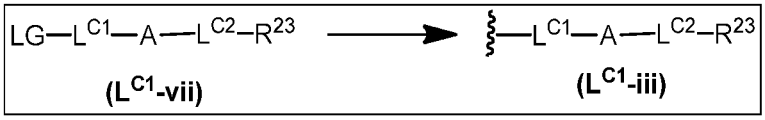
[00407] In certain preferred embodiments, A^1 is  and A^2 is a leaving group, and A^1 and A^2–L^{C2}–R^{23} react together (*e.g.*, via palladium catalysis) to provide a group of formula:



(L^{C1}-vi)

[00408] Furthermore, as described herein, there are many ways of adding a group of formula (**L^{C1}-iii**) which do not involve reaction of A^1 and A^2 to form A. For example, a group of formula (**L^{C1}-iii**) may be installed by reaction of the group -OR^{12}, -$NR^{13}R^{14}$, and/or -OR^3, wherein R^{12}, R^{14}, and/or R^3 are hydrogen, with a compound of formula (**L^{C1}-vii**), *e.g.*, by nucleophilic displacement, to provide a group wherein R^{12}, R^{14}, and/or R^3 is of formula (**L^{C1}-iii**). See, *e.g.*, Scheme A9.

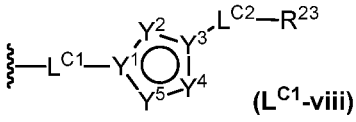
Scheme A9.



[00409] Thus, in certain embodiments, A may be any group as defined above, and further may be any cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl.

[00410] In certain embodiments, A is an optionally substituted heteroaryl, *e.g.*, a 5- to 6-membered optionally substituted heteroaryl.

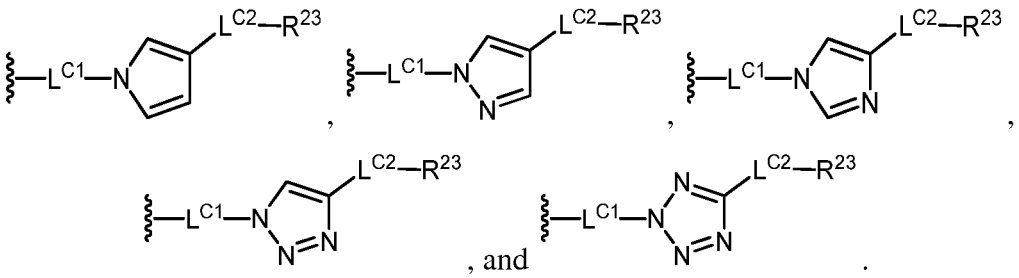
[00411] In certain embodiments, wherein A is a 5-membered optionally substituted heteroaryl, the group of formula (**L^{C1}-iii**) is of the formula (**L^{C1}-v**):



(L^{C1}-viii)

wherein each instance of Y^1, Y^2, Y^3, Y^4, and Y^5 is independently CR^Y, O, S, N, or NR^Y, wherein R^Y is hydrogen or optionally substituted alkyl.

[00412] In certain embodiments wherein A is a 5-membered heteroaryl, the group of formula (**L^{C1}-iii**) is selected from:



L^{C1}, L^{C2} and Group R^{23}

[00413] As generally defined above, each instance of L^{C1} and L^{C2} is independently a bond, or a linking group selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof.

[00414] In certain embodiments, L^{C1} is a bond. It is generally understood that if L^{C1} is a bond, then the group -LG, $-A^1$, or $–A-L^{C2}-R^{23}$, as described herein, is directly attached to the parent moiety, *e.g.,* the macrolide or intermediate compounds. Furthermore, in certain embodiments, L^{C2} is a bond. It is generally understood that if L^{C2} is a bond, then the group R^{23} is directly attached to A, as described herein.

[00415] Alternatively, in certain embodiments, L^{C1} is a linking group. In certain embodiments, L^{C2} is a linking group.

[00416] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of optionally substituted alkylene, *e.g.,* substituted or unsubstituted $C_{1–6}$alkylene, substituted or unsubstituted $C_{2–6}$alkylene, substituted or unsubstituted $C_{3–6}$alkylene, substituted or unsubstituted $C_{4–6}$alkylene, substituted or unsubstituted $C_{5–6}$alkylene, substituted or unsubstituted $C_{2–5}$alkylene, substituted or unsubstituted $C_{2–4}$alkylene, substituted or unsubstituted $C_{2–3}$alkylene, substituted or unsubstituted C_1alkylene, substituted or unsubstituted C_2alkylene, substituted or unsubstituted C_3alkylene, substituted or unsubstituted C_4alkylene, substituted or unsubstituted C_5alkylene, or substituted or unsubstituted C_6alkylene. In certain embodiments, L^{C1} and L^{C2} are each optionally and independently an alkylene linking group of the formula $–(CH_2)_n–$, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00417] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted alkenylene, *e.g.*, substituted or unsubstituted C_{2-6}alkenylene, substituted or unsubstituted C_{3-6}alkenylene, substituted or unsubstituted C_{4-6}alkenylene, substituted or unsubstituted C_{5-6}alkenylene, substituted or unsubstituted C_{2-5}alkenylene, substituted or unsubstituted C_{2-4}alkenylene, substituted or unsubstituted C_{2-3}alkenylene, substituted or unsubstituted C_2alkenylene, substituted or unsubstituted C_3alkenylene, substituted or unsubstituted C_4alkenylene, substituted or unsubstituted C_5alkenylene, or substituted or unsubstituted C_6alkenylene.

[00418] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising substituted or unsubstituted alkenylene, wherein L^{C1} and L^{C2} are each optionally and independently linking groups comprising an allene moiety. In certain embodiments, L^{C1} is a linking group comprising an allene moiety. In certain embodiments, L^{C2} is a linking group comprising an allene moiety.

[00419] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted alkynylene, *e.g.*, substituted or unsubstituted C_{2-6}alkynylene, substituted or unsubstituted C_{3-6}alkynylene, substituted or unsubstituted C_{4-6}alkynylene, substituted or unsubstituted C_{5-6}alkynylene, substituted or unsubstituted C_{2-5}alkynylene, substituted or unsubstituted C_{2-4}alkynylene, substituted or unsubstituted C_{2-3}alkynylene, substituted or unsubstituted C_2alkynylene, substituted or unsubstituted C_3alkynylene, substituted or unsubstituted C_4alkynylene, substituted or unsubstituted C_5alkynylene, or substituted or unsubstituted C_6alkynylene.

[00420] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heteroalkylene, *e.g.*, substituted or unsubstituted heteroC_{1-6}alkylene, substituted or unsubstituted heteroC_{2-6}alkylene, substituted or unsubstituted heteroC_{3-6}alkylene, substituted or unsubstituted heteroC_{4-6}alkylene, substituted or unsubstituted heteroC_{5-6}alkylene, substituted or unsubstituted heteroC_{2-5}alkylene, substituted or unsubstituted heteroC_{2-4}alkylene, substituted or unsubstituted heteroC_{2-3}alkylene, substituted or unsubstituted heteroC_1alkylene, substituted or unsubstituted heteroC_2alkylene, substituted or unsubstituted heteroC_3alkylene, substituted or unsubstituted heteroC_4alkylene, substituted or unsubstituted heteroC_5alkylene, or substituted or unsubstituted heteroC_6alkylene.

[00421] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heteroalkenylene, *e.g.*, substituted or unsubstituted heteroC_{2-6}alkenylene, substituted or unsubstituted heteroC_{3-}

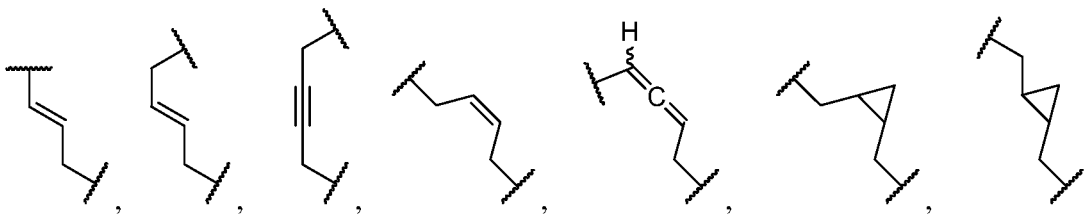
$_6$alkenylene, substituted or unsubstituted heteroC_{4-6}alkenylene, substituted or unsubstituted heteroC_{5-6}alkenylene, substituted or unsubstituted heteroC_{2-5}alkenylene, substituted or unsubstituted heteroC_{2-4}alkenylene, substituted or unsubstituted heteroC_{2-3}alkenylene, substituted or unsubstituted heteroC_2alkenylene, substituted or unsubstituted heteroC_3alkenylene, substituted or unsubstituted heteroC_4alkenylene, substituted or unsubstituted heteroC_5alkenylene, or substituted or unsubstituted heteroC_6alkenylene.

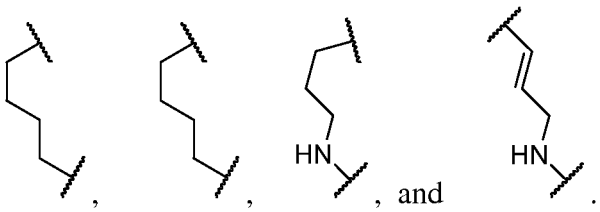
[00422] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heteroalkynylene, *e.g.,* substituted or unsubstituted heteroC_{2-6}alkynylene, substituted or unsubstituted heteroC_{3-6}alkynylene, substituted or unsubstituted heteroC_{4-6}alkynylene, substituted or unsubstituted heteroC_{5-6}alkynylene, substituted or unsubstituted heteroC_{2-5}alkynylene, substituted or unsubstituted heteroC_{2-4}alkynylene, substituted or unsubstituted heteroC_{2-3}alkynylene, substituted or unsubstituted heteroC_2alkynylene, substituted or unsubstituted heteroC_3alkynylene, substituted or unsubstituted heteroC_4alkynylene, substituted or unsubstituted heteroC_5alkynylene, or substituted or unsubstituted heteroC_6alkynylene.

[00423] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted carbocyclylene, *e.g.,* substituted or unsubstituted C_{3-6}carbocyclylene, substituted or unsubstituted C_{4-6}carbocyclylene, substituted or unsubstituted C_{5-6}carbocyclylene, substituted or unsubstituted C_{3-5}carbocyclylene, substituted or unsubstituted C_{4-5}carbocyclylene, or substituted or unsubstituted C_{3-4}carbocyclylene.

[00424] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups comprising at least one instance of substituted or unsubstituted heterocyclylene, *e.g.,* substituted or unsubstituted C_{3-6}heterocyclylene, substituted or unsubstituted C_{4-6}heterocyclylene, substituted or unsubstituted C_{5-6}heterocyclylene, substituted or unsubstituted C_{3-5}heterocyclylene, substituted or unsubstituted C_{4-5}heterocyclylene, or substituted or unsubstituted C_{3-4}heterocyclylene.

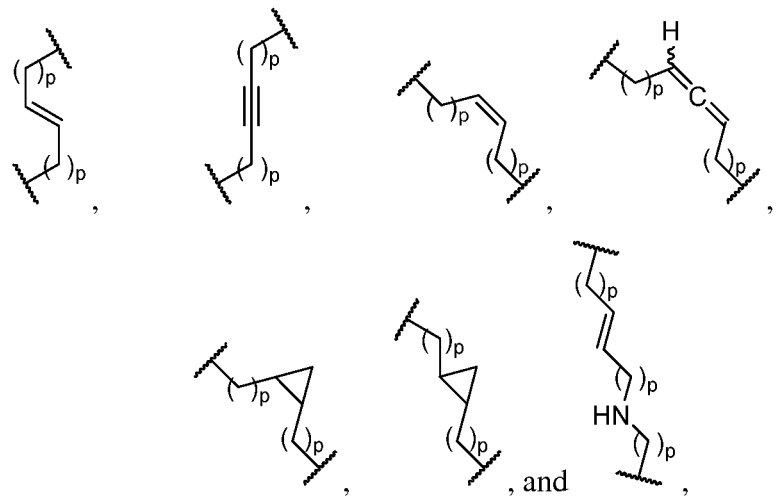
[00425] In certain embodiments, L^{C1} and L^{C2} are each optionally and independently linking groups of one of the following formulae:





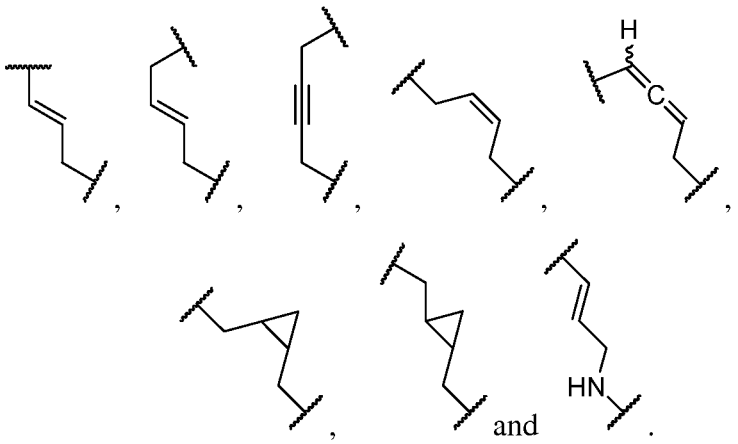
[00426] As demonstrated herein, macrolides which incorporate rigidifying motifs (*e.g.*, unsaturated or cyclic motifs) into the L^{C1} or L^{C2} linker show improved potencies compared with solithromycin (See, *e.g.*, Tables B1-B13). Therefore, in certain embodiments, one or both of L^{C1} and L^{C2} is a linker selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof, provided the linker comprises a optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted carbocyclylene group therein, thereby rigidifying the linker moiety. In certain embodiments, L^{C1} is a rigidified linker, as described herein, and L^{C2} is a bond. In certain embodiments of L^{C1} and/or L^{C2}, specific combinations contemplated herein include optionally substituted C_{1-3}alkyl-C_{2-4}alkenyl-C_{1-3}alkyl, optionally substituted C_{1-3}alkyl-C_{2-4}alkenyl-heteroC_{1-3}alkyl, optionally substituted heteroC_{1-3}alkyl-C_{2-4}alkenyl-C_{1-3}alkyl, optionally substituted heteroC_{1-3}alkyl-C_{2-4}alkenyl-heteroC_{1-3}alkyl, C_{1-3}alkyl- C_{1-2}alkynyl- C_{1-3}alkyl, and C_{1-3}alkyl- C_{3-6}carbocyclyl-C_{1-3}alkyl.

[00427] In certain embodiments, one or both of L^{C1} and L^{C2} is of one of the following formulae:

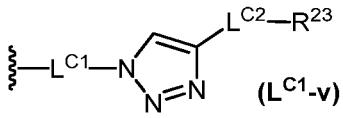


wherein each instance of p is independently 0, 1, or 2.

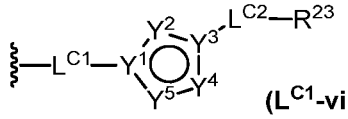
[00428] In certain embodiments of the present invention, each of L^{C1} and L^{C2} is independently selected from one of the following formulae:



[00429] In certain embodiments, L^{C1} is an optionally substituted alkylene, and L^{C2} is a bond, *e.g.*, L^{C1} is an optionally substituted alkylene of the formula $-(CH_2)_n-$, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and L^{C2} is a bond in groups of formula (**L^{C1}-v**) or (**L^{C1}-viii**) as described herein.

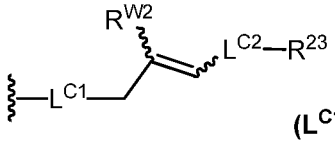


(**L^{C1}-v**)



(**L^{C1}-viii**)

[00430] In other embodiments, both of L^{C1} and L^{C2} are bonds, *e.g.*, both of L^{C1} and L^{C2} are bonds in the group of formula (**L^{C1}-vi**) as described herein.



(**L^{C1}-vi**)

[00431] Furthermore, it is also generally understood that R^{23} may be an acyclic moiety or a cyclic moiety selected from the group consisting of optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; and optionally substituted heteroaryl.

[00432] For example, in certain embodiments, R^{23} is an acyclic moiety selected from the group consisting of optionally substituted alkyl; optionally substituted alkenyl; and optionally substituted alkynyl.

[0001] In certain embodiments, R^{23} is optionally substituted alkyl, *e.g.*, optionally substituted C_{1-6}alkyl, substituted or unsubstituted C_{1-2}alkyl, optionally substituted C_{2-3}alkyl, optionally substituted C_{3-4}alkyl, optionally substituted C_{4-5}alkyl, or optionally substituted C_{5-6}alkyl. Exemplary R^{23} C_{1-6} alkyl groups include, but are not limited to,

optionally substituted methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6).

[00433] In certain embodiments, R^{23} is optionally substituted alkenyl, *e.g.*, optionally substituted C_{2-6}alkenyl, optionally substituted C_{2-3}alkenyl, optionally substituted C_{3-4}alkenyl, optionally substituted C_{4-5}alkenyl, or optionally substituted C_{5-6}alkenyl.

[00434] In certain embodiments, R^{23} is optionally substituted alkynyl, *e.g.*, optionally substituted C_{2-6}alkynyl, optionally substituted C_{2-3}alkynyl, optionally substituted C_{3-4}alkynyl, optionally substituted C_{4-5}alkynyl, or optionally substituted C_{5-6}alkynyl.

[00435] In certain embodiments, R^{23} is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; and optionally substituted heteroaryl.

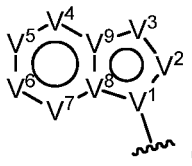
[00436] In certain embodiments, R^{23} is optionally substituted carbocyclyl, *e.g.*, optionally substituted C_{3-6}carbocyclyl, optionally substituted C_{3-4}carbocyclyl, optionally substituted C_{4-5} carbocyclyl, or optionally substituted C_{5-6} carbocyclyl.

[00437] In certain embodiments, R^{23} is optionally substituted heterocyclyl, *e.g.*, optionally substituted 3–6 membered heterocyclyl, optionally substituted 3–4 membered heterocyclyl, optionally substituted 4–5 membered heterocyclyl, or optionally substituted 5–6 membered heterocyclyl.

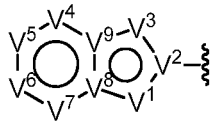
[00438] In certain embodiments, R^{23} is optionally substituted aryl, *e.g.*, optionally substituted monocyclic aryl, optionally substituted 5,6-fused bicyclic aryl, or optionally substituted 6,6-fused aryl. In certain embodiments, R^{23} is optionally substituted phenyl. In certain embodiments, R^{23} is optionally substituted napthyl.

[00439] In certain embodiments, R^{23} is optionally substituted heteroaryl, *e.g.*, optionally substituted monocyclic heteoaryl or optionally substituted bicyclic heteroaryl, *e.g.,* optionally substituted 5–6 membered heteroaryl, optionally substituted 5,6 fused-bicyclic heteroaryl, or optionally substituted 6,6 fused-bicyclic heteroaryl.

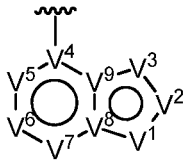
[00440] Specific aryl and heteroaryl R^{23} groups are further contemplated herein. For example, in certain embodiments, R^{23} is an aryl or heteroaryl ring system of formula:

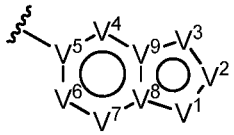


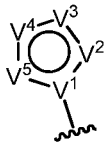
(e–1)

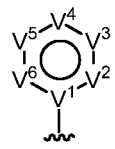


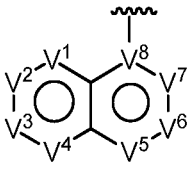
(e–2)

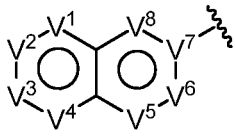

(e–3)

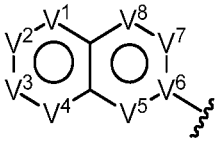

(e–4)


(e–5),


(e–6),


(e-7),


(e-8), or


(e-9),

wherein:

each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 may independently be O, S, N, NR^{23N}, C, or CR^{23C}, as valency permits;

R^{23N} is independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or a nitrogen protecting group; and

R^{23C} is hydrogen, halogen, –CN, $–NO_2$, $–N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, or carbonyl.

[00441] In certain embodiments, V^1 is O, S, N or NR^{23N}. In certain embodiments, V^1 is N or NR^{23N}. In certain embodiments, V^1 is O. In certain embodiments, V^1 is S.

[00442] In certain embodiments, V^2 is O, S, N or NR^{23N}. In certain embodiments, V^2 is N or NR^{23N}. In certain embodiments, V^2 is O. In certain embodiments, V^2 is S.

[00443] In certain embodiments, V^3 is O, S, N or NR^{23N}. In certain embodiments, V^3 is N or NR^{23N}. In certain embodiments, V^3 is O. In certain embodiments, V^3 is S.

[00444] In certain embodiments, V^4 is O, S, N or NR^{23N}. In certain embodiments, V^4 is N or NR^{23N}. In certain embodiments, V^4 is O. In certain embodiments, V^4 is S.

[00445] In certain embodiments, V^5 is O, S, N or NR^{23N}. In certain embodiments, V^5 is N or NR^{23N}. In certain embodiments, V^5 is O. In certain embodiments, V^5 is S.

[00446] In certain embodiments, V^6 is O, S, N or NR^{23N}. In certain embodiments, V^6 is N or NR^{23N}. In certain embodiments, V^6 is O. In certain embodiments, V^6 is S.

[00447] In certain embodiments, V^7 is O, S, N or NR^{23N}. In certain embodiments, V^7 is N or NR^{23N}. In certain embodiments, V^7 is O. In certain embodiments, V^7 is S.

[00448] In certain embodiments, V^8 is O, S, N or NR^{23N}. In certain embodiments, V^8 is N or NR^{23N}. In certain embodiments, V^8 is O. In certain embodiments, V^8 is S.

[00449] In certain embodiments, V^9 is O, S, N or NR^{23N}. In certain embodiments, V^9 is N or NR^{23N}. In certain embodiments, V^9 is O. In certain embodiments, V^9 is S.

[00450] In certain embodiments, only one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is selected from the group consisting of N and NR^{23N}. In certain embodiments, only one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is O. In certain embodiments, only one of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 is S. In any of the above instances, in certain embodiments, the rest of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are independently C or CR^{23C} as valency permits.

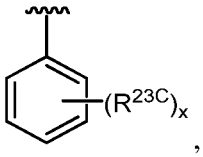
[00451] In certain embodiments, only two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of N and NR^{23N}. In certain embodiments, only two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of O, N and NR^{23N}. In certain embodiments, only two of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are each independently selected from the group consisting of S, N and NR^{23N}. In any of the above instances, in certain embodiments, the rest of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are independently C or CR^{23C} as valency permits.

[00452] In certain embodiments, all V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 are independently C or CR^{23C} as valency permits.

[00453] In certain embodiments, R^{23C} is hydrogen, halogen, –CN, hydroxyl, substituted hydroxyl, amino, or substituted amino.

[00454] In certain embodiments, R^{23N} is independently hydrogen or optionally substituted alkyl (*e.g.*, $-CH_3$).

[00455] In certain embodiments, R^{23} is selected from any one of the following aryl or heteroaryl ring systems:



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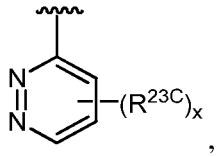

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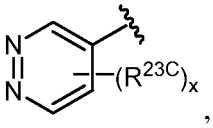

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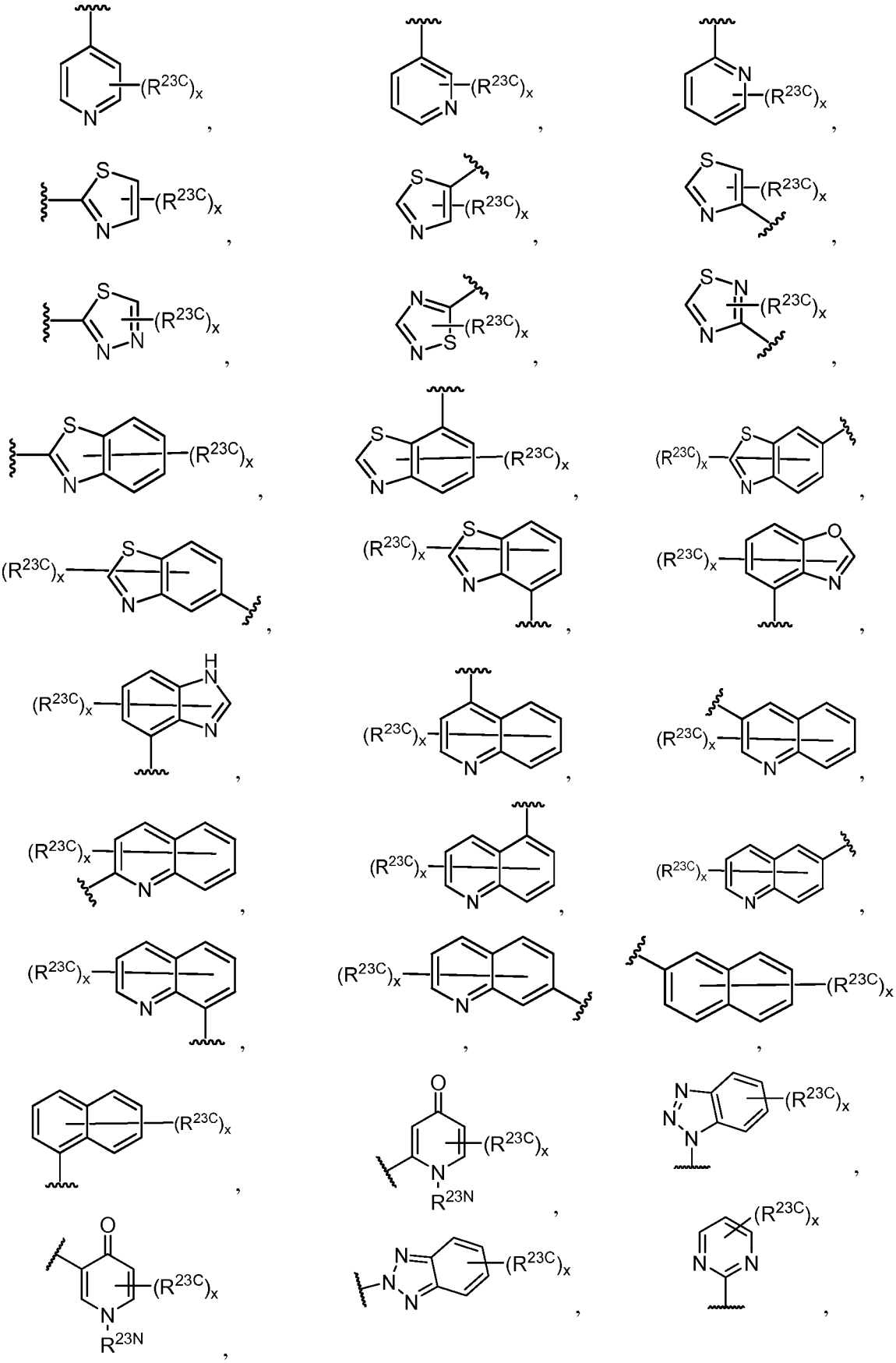
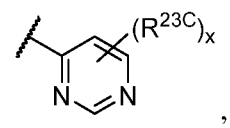
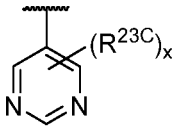
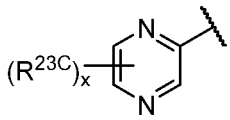
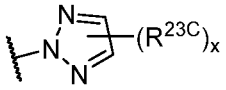
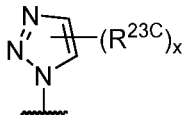
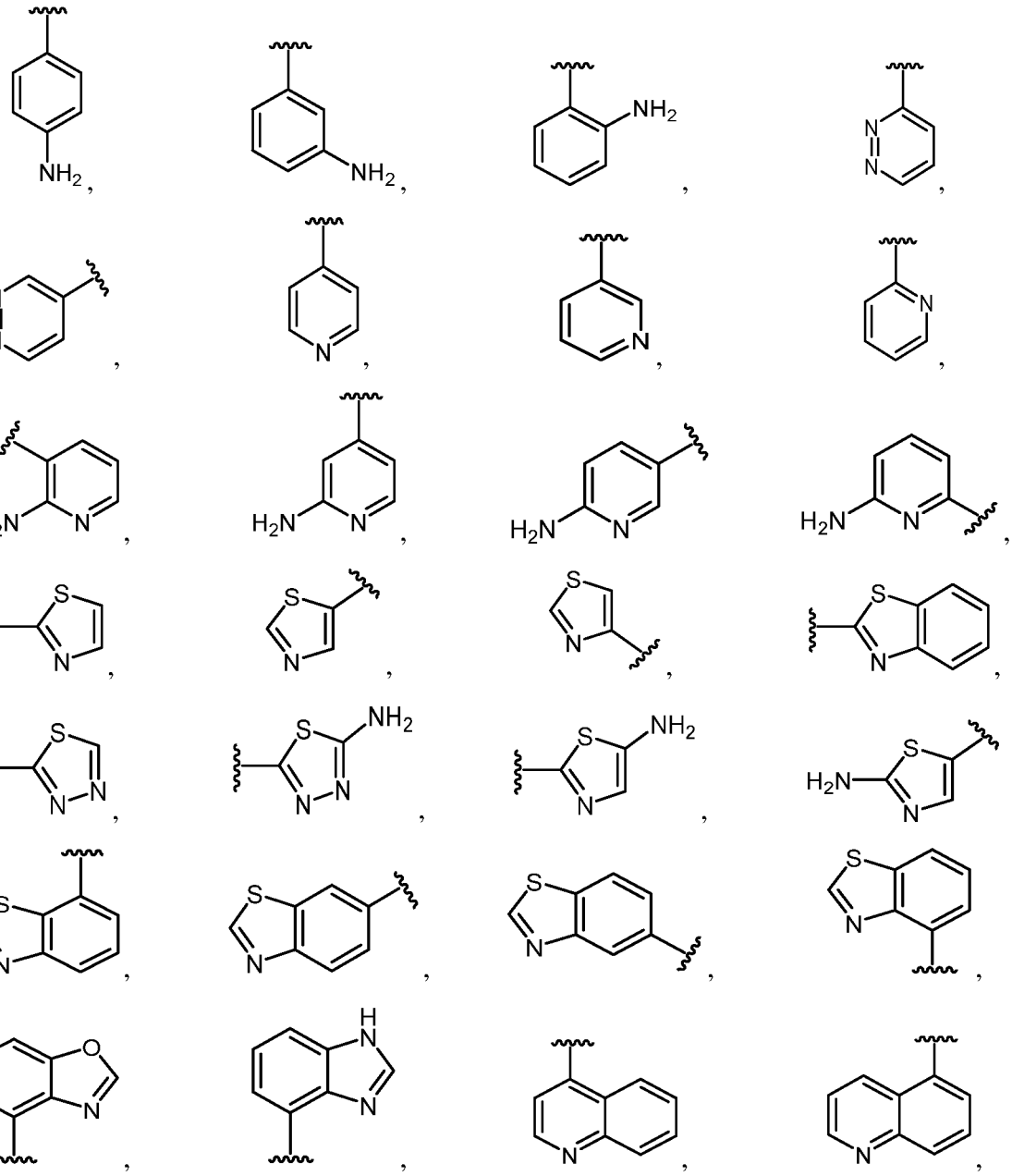
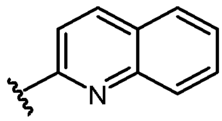
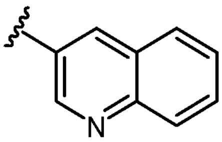
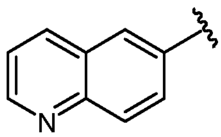
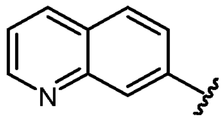


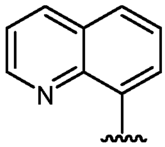
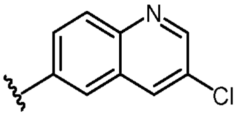
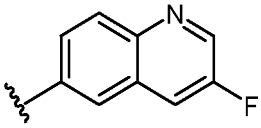
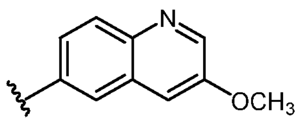





, and

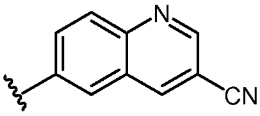
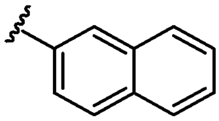
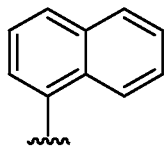
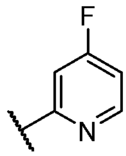

wherein R^{23C} is as defined herein, and x is 0, 1, or 2.

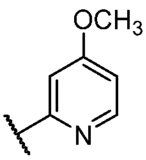
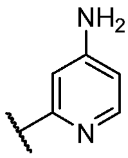
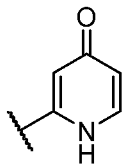
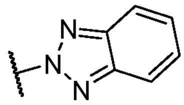
[00456] In certain embodiments, R^{23} is selected from any one of the following aryl or heteroaryl ring systems:

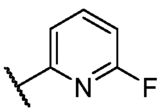
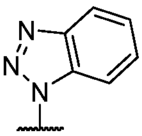
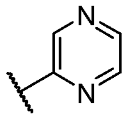
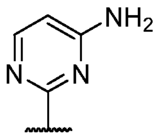


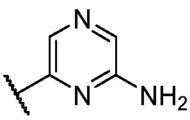
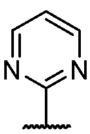
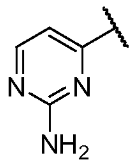
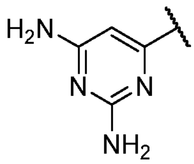
 ,  ,  ,  ,

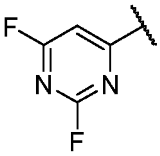
 ,  ,  ,  ,

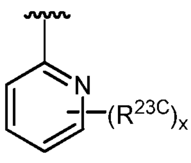
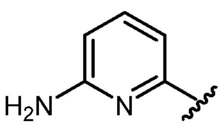
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

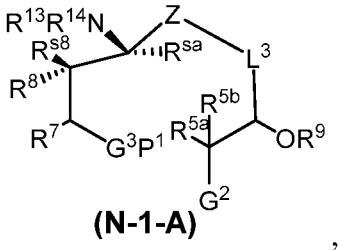
 ,  ,  ,  ,

and  .

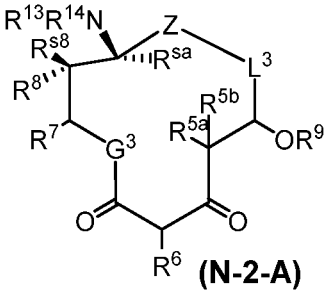
[00457] As described herein, ketolides comprising a heteroaryl R^{23} group show improved potency over solithromycin and analogs thereof. Therefore, in certain embodiments, R^{23} is of the formula:  . In specific embodiments, R^{23} is of the formula:  .

Further Embodiments of the Invention

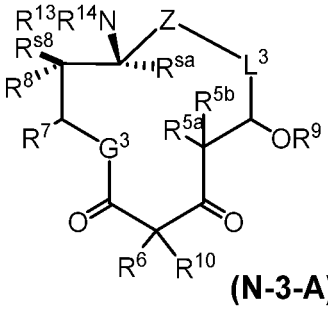
[00458] Various combinations of the above described embodiments are further contemplated herein. For example, in certain embodiments, G^1 is $-NR^{13}NR^{14}$, to provide a compound or ketolide of formula:



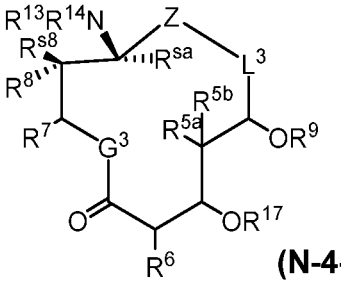
(N-1-A),



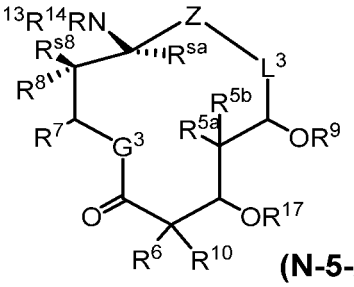
(N-2-A)



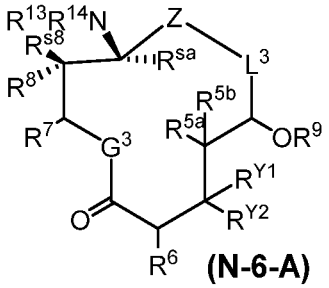
(N-3-A),



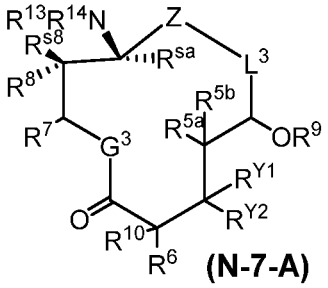
(N-4-A),



(N-5-A),



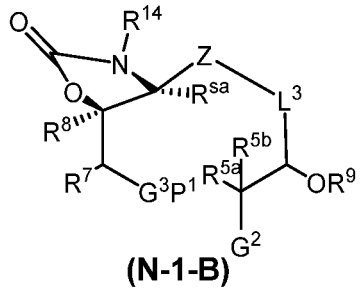
(N-6-A)



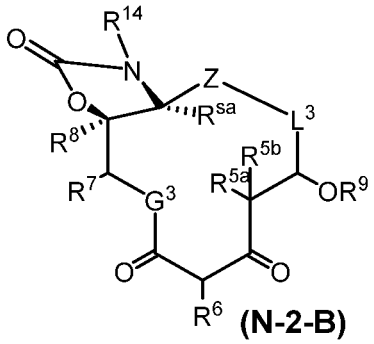
(N-7-A)

or a salt thereof.

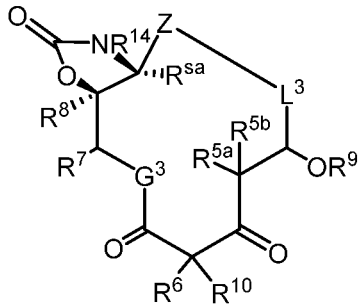
[00459] In certain embodiments, G^1 is $-NR^{13}NR^{14}$, and R^{13} and R^{11} are joined to form a carbamate group to provide a compound or ketolide of formula:



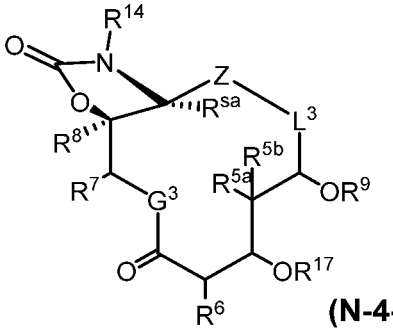
(N-1-B),



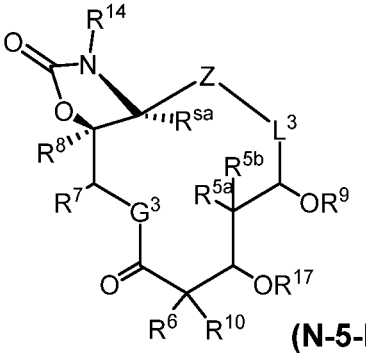
(N-2-B)



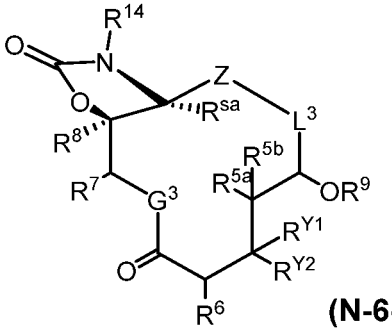
(N-3-B),



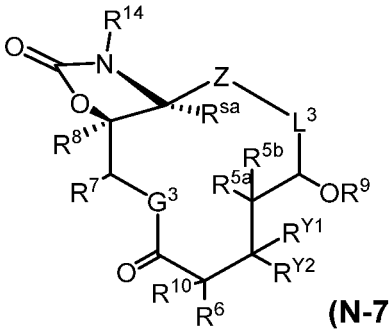
(N-4-B),



(N-5-B),



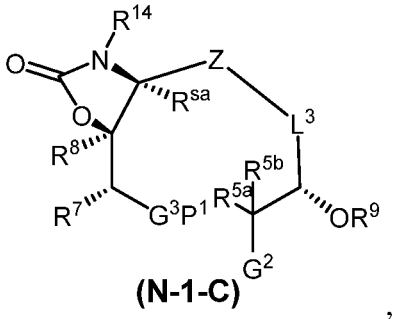
(N-6-B),



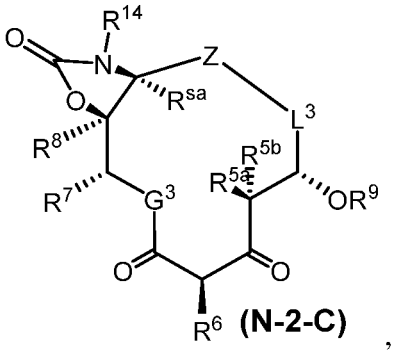
(N-7-B)

or a salt thereof.

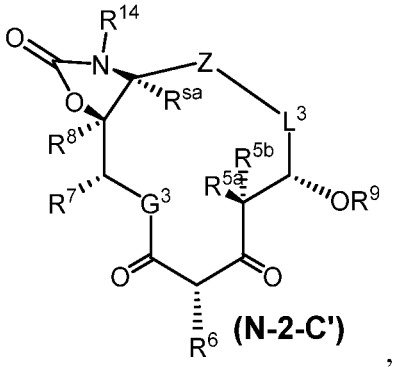
[00460] In certain embodiments, G^1 is $-NR^{13}NR^{14}$, and R^{13} and R^{11} are joined to form a carbamate group to provide a compound or ketolide having the following stereochemistry:



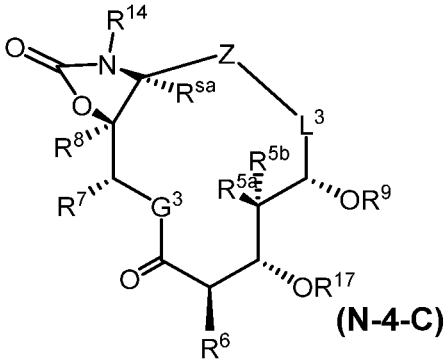
(N-1-C),



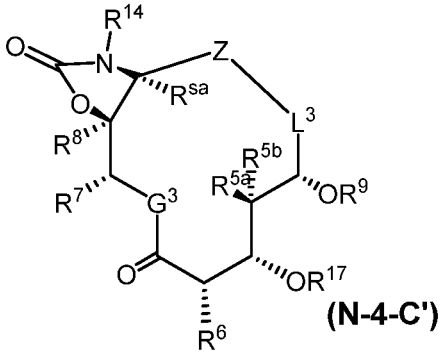
(N-2-C),



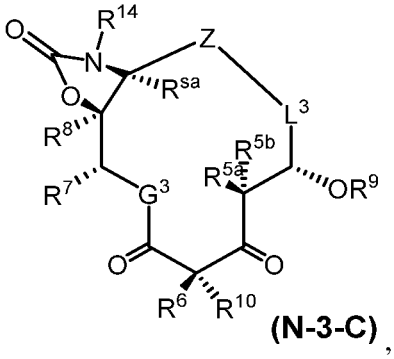
(N-2-C'),



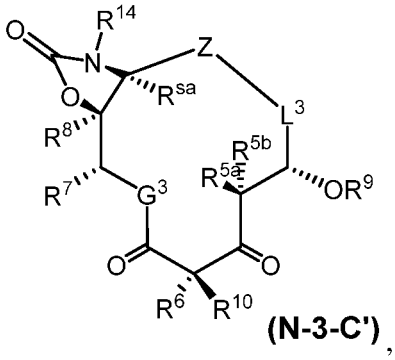
(N-4-C),



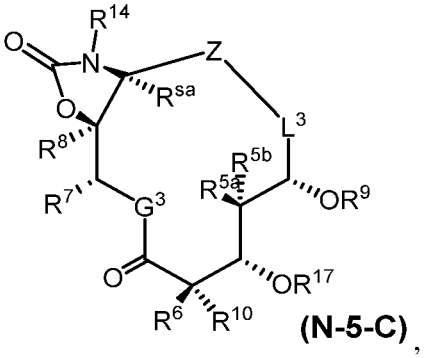
(N-4-C'),



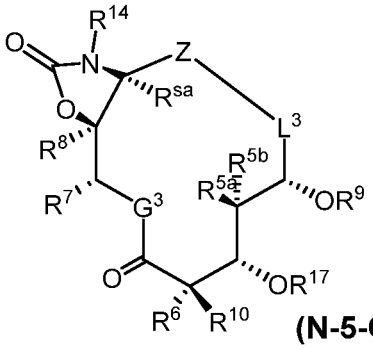
(N-3-C),



(N-3-C'),



(N-5-C),

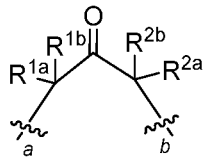


or (N-5-C')

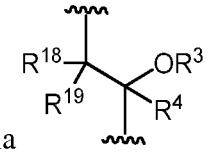
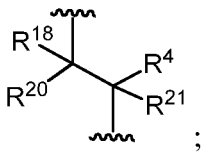
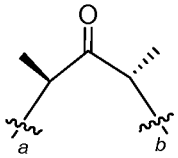
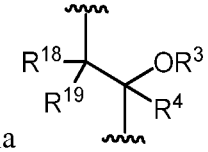
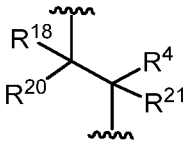
or salts thereof.

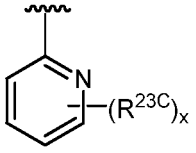
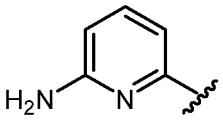
[00461] Various embodiments are further contemplated in combination with any formulae depicted herein, *e.g.,* for example, any of the above depicted formulae (**N-1-A**) to (**N-5-C'**).

[00462] For example, in certain embodiments of any of the above formulae, Z is of formula:

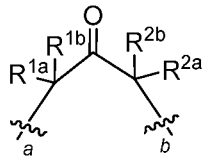


(z-i),

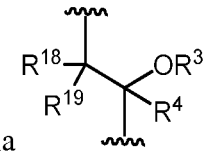
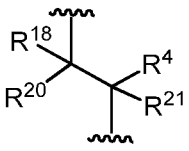
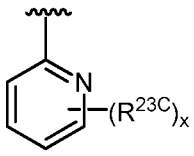
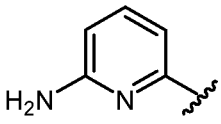
wherein R^{1a} is $-CH_3$; R^{1b} is hydrogen; R^{2a} is $-CH_3$; and R^{2b} is hydrogen; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$; G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is hydrogen; R^{5b} is $-CH_3$; and R^{18} is hydrogen. For example, in certain embodiments of any of the above formulae, Z is of formula:  ; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$; G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is hydrogen; R^{5b} is $-CH_3$; and R^{18} is hydrogen. In certain embodiments of any of the above formulae, the L^{C1} is a rigidified linker as described herein, *e.g.,* selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof, provided the linker comprises a optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted

carbocyclylene group therein, thereby rigidifying the linker moiety, and L^{C2} is a bond. In certain embodiments of any of the above formulae, R^{23} is of the formula:  . In specific embodiments, R^{23} is of the formula:  .

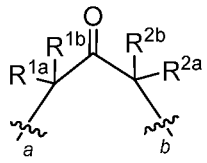
[00463] In certain embodiments of any of the above formulae, Z is of formula:



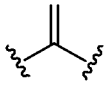
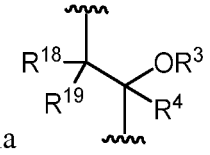
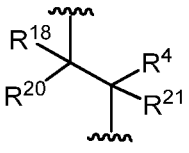
(z-i);

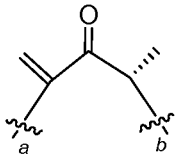
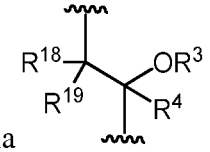
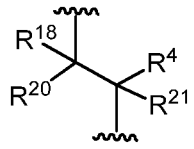
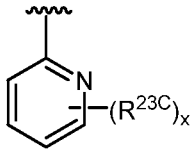
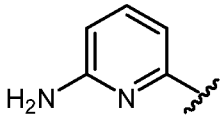
R^{1a} is hydrogen; R^{1b} is hydrogen; R^{2a} is $-CH_3$; and R^{2b} is hydrogen; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$; G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is hydrogen; R^{5b} is $-CH_3$; and R^{18} is hydrogen. In certain embodiments of any of the above formulae, L^{C1} is a rigidified linker as described herein; and L^{C2} is a bond. In certain embodiments of any of the above formulae, R^{23} is of the formula:  . In specific embodiments, R^{23} is of the formula:  .

[00464] In certain embodiments of any of the above formulae, Z is of formula:

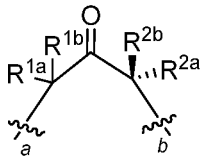


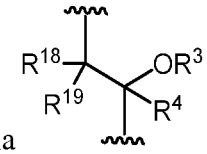
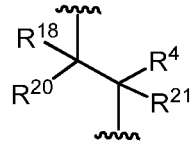
(z-i);

R^{1a} and R^{1b} are joined to form  ; R^{2a} is $-CH_3$; and R^{2b} is hydrogen; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$;G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is

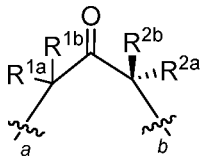
hydrogen; R^{5b} is $-CH_3$; and R^{18} is hydrogen. In certain embodiments of any of the above formulae, Z is of formula:  ; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$; G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is hydrogen; R^{5b} is $-CH_3$; R^{18} is hydrogen; L^{C1} is a rigidified linker as described herein; and L^{C2} is a bond. As described herein, in certain embodiments, R^{23} is of the formula:  . In specific embodiments, R^{23} is of the formula:  .

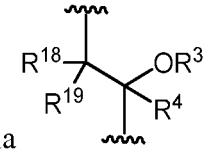
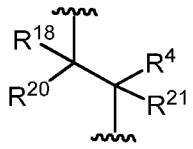
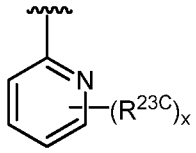
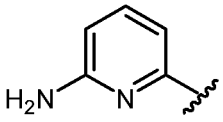
[00465] In certain embodiments of any of the above formulae, Z is of formula:



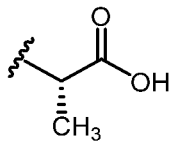
R^{1a} is $-CH_3$; R^{1b} and R^{sa} are joined to form a bond; R^{2a} is $-CH_3$; and R^{2b} is hydrogen; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$;G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is hydrogen; R^{5b} is $-CH_3$; R^{18} is hydrogen; L^{C1} is a rigidified linker as described herein; and L^{C2} is a bond.

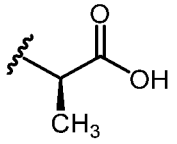
[00466] In certain embodiments of any of the above formulae, Z is of formula:



R^{1a} is hydrogen; R^{1b} and R^{sa} are joined to form a bond; R^{2a} is $-CH_3$; and R^{2b} is hydrogen; R^7 is $-CH_2CH_3$; R^8 is $-CH_3$;G^3 is –O–; L^3 is a group of formula  or  ; R^{5a} is hydrogen; R^{5b} is $-CH_3$; andR^{18} is hydrogen. In certain embodiments of any of the above formulae, L^{C1} is a rigidified linker as described herein; and L^{C2} is a bond. In certain embodiments of any of the above formulae, R^{23} is of the formula:  . In specific embodiments, R^{23} is of the formula:  .

[00467] In certain aspects of the formulae depicted herein, *e.g.,* for example, any of the above depicted formulae (**N-1-A**) to (**N-5-C'**), further specific combinations are contemplated, as provided below.

[00468] In certain embodiments, at least one of R^{1a} and R^{1b} is hydrogen. In certain embodiments, both R^{1a} and R^{1b} are hydrogen. In certain embodiments, neither R^{1a} nor R^{1b} are hydrogen. In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{1a} and R^{1b} is attached is a stereocenter of the (S)-configuration. In certain embodiments, R^{1a} is optionally substituted C_{1-6}alkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted C_{1-2}alkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_3$; and R^{1b} is hydrogen. In certain embodiments, both R^{1a} and R^{1b} are $-CH_3$. In certain embodiments, R^{1a} is optionally substituted haloalkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is -CF_3; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2OH$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2N(R^{22})_2$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2N(R^{22})_2$; R^{22} is $-CH_3$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2NHR^{22}$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2NHR^{22}$; R^{22} is $-CH_2C(=O)OH$; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is $-CH_2CH_2NHR^{22}$; R^{22} is  ; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is –



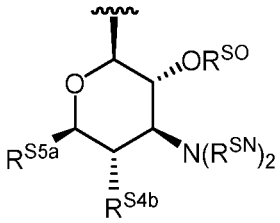
$CH_2CH_2NHR^{22}$; R^{22} is ; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted aralkyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is substituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is monosubstituted benzyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is benzyl substituted by one instance of halogen; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted C_{2-6}alkenyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted vinyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted vinyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted allyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted allyl; and R^{1b} is hydrogen. In certain embodiments R^{1a} is optionally substituted carbocyclyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted C_{3-6}carbocyclyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is optionally substituted cyclopropyl; and R^{1b} is hydrogen. In certain embodiments, R^{1a} is unsubstituted cyclopropyl; and R^{1b} is hydrogen.

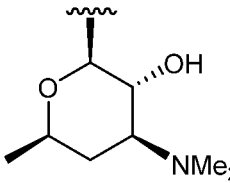
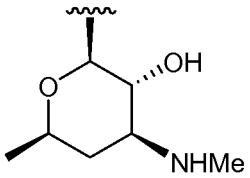
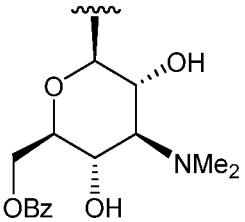
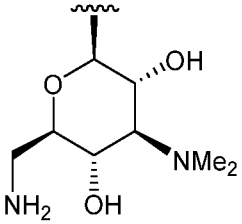
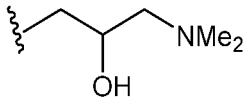
[00469] In certain embodiments, at least one of R^{2a} and R^{2b} is hydrogen. In certain embodiments, both R^{2a} and R^{2b} are hydrogen. In certain embodiments, neither R^{2a} nor R^{2b} are hydrogen. In certain embodiments, R^{2a} is optionally substituted C_{1-6}alkyl; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is optionally substituted C_{1-2}alkyl; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is $-CH_3$; and R^{2b} is hydrogen. In certain embodiments, both R^{2a} and R^{2b} are $-CH_3$. In certain embodiments, R^{2a} is optionally substituted haloalkyl; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is $-CF_3$; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is halogen; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is –F; and R^{2b} is hydrogen. In certain embodiments, R^{2a} is halogen; and R^{2b} is C_{1-6}alkyl. In certain embodiments, R^{2a} is –F; and R^{2b} is C_{1-6}alkyl. In certain embodiments, R^{2a} is halogen; and R^{2b} is $-CH_3$. In certain embodiments, R^{2a} is –F; and R^{2b} is $-CH_3$.

[00470] In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^4 is attached is a stereocenter of the (S)-configuration. In certain embodiments, R^3 is hydrogen; and R^4 is not hydrogen. In certain embodiments, neither R^3 nor R^4 are hydrogen. In certain embodiments, R^3 is hydrogen. In certain embodiments, R^3 is optionally substituted C_{1-6}alkyl. In certain

embodiments, R^3 is optionally substituted C_{1-2}alkyl. In certain embodiments, R^3 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{2-6}alkenyl. In certain embodiments, R^3 is optionally substituted allyl. In certain embodiments, R^3 is unsubstituted allyl. In certain embodiments, R^3 is allyl substituted with one optionally substituted heteroaryl ring. In certain embodiments, R^3 is allyl substituted with one optionally substituted quinoline ring. In certain embodiments, R^3 is hydrogen; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{1-6}alkyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{1-2}alkyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is $-CH_3$; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted C_{2-6}alkenyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is optionally substituted allyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is unsubstituted allyl; and R^4 is $-CH_3$. In certain embodiments, R^3 is allyl substituted with one optionally substituted heteroaryl ring; and R^4 is $-CH_3$. In certain embodiments, R^3 is allyl substituted with one optionally substituted quinoline ring; and R^4 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{1-6}alkyl. In certain embodiments, R^4 is optionally substituted C_{1-2}alkyl. In certain embodiments, R^4 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl. In certain embodiments, R^4 is optionally substituted allyl. In certain embodiments, R^4 is unsubstituted allyl. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring. In certain embodiments, R^4 is $-CH_2CH_2OH$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; and R^{22} is $-CH_3$. In certain embodiments, R^4 is $-CH_2CHO$. In certain embodiments, R^4 is optionally substituted C_{1-6}alkyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{1-2}alkyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally substituted allyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is unsubstituted allyl; and R^3 is $-CH_3$. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring; and R^3 is $-CH_3$. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CH_2OH$; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CH_2N(R^{22})_2$; R^{22} is $-CH_3$; and R^3 is $-CH_3$. In certain embodiments, R^4 is $-CH_2CHO$; and R^3 is $-CH_3$. In certain embodiments, R^4 is optionally substituted C_{1-6}alkyl; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted C_{1-2}alkyl; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted C_{2-6}alkenyl; and R^3 is hydrogen. In certain embodiments, R^4 is optionally

substituted allyl; and R^3 is hydrogen. In certain embodiments, R^4 is unsubstituted allyl; and R^3 is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring; and R^3 is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring; and R^3 is hydrogen. In certain embodiments, R^4 is $–CH_2CH_2OH$; and R^3 is hydrogen. In certain embodiments, R^4 is $–CH_2CH_2N(R^{22})_2$; and R^3 is hydrogen. In certain embodiments, R^4 is $–CH_2CH_2N(R^{22})_2$; R^{22} is $–CH_3$; and R^3 is hydrogen. In certain embodiments, R^4 is $–CH_2CHO$; and R^3 is hydrogen. In certain embodiments, R^4 is optionally substituted $C_{1–6}$alkyl; and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted $C_{1–2}$alkyl; and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted $C_{2–6}$alkenyl; and R^{21} is hydrogen. In certain embodiments, R^4 is optionally substituted allyl; and R^{21} is hydrogen. In certain embodiments, R^4 is unsubstituted allyl; and R^{21} is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted heteroaryl ring; and R^{21} is hydrogen. In certain embodiments, R^4 is allyl substituted with one optionally substituted quinoline ring; and R^{21} is hydrogen. In certain embodiments, R^4 is $–CH_2CH_2OH$; and R^{21} is hydrogen. In certain embodiments, R^4 is $–CH_2CH_2N(R^{22})_2$; and R^{21} is hydrogen. In certain embodiments, R^4 is $–CH_2CH_2N(R^{22})_2$; R^{22} is $–CH_3$; and R^{21} is hydrogen. In certain embodiments, R^4 is $–CH_2CHO$; and R^{21} is hydrogen.

[00471] In certain embodiments, R^9 is hydrogen. In certain embodiments, R^9 is not hydrogen. In certain embodiments, R^9 is an oxygen protecting group. In certain embodiments, R^9 is  . In certain embodiments, R^{SO} is hydrogen. In certain embodiments, R^{SO} is an oxygen protecting group. In certain embodiments, R^9 is methyl carbonate. In certain embodiments, at least one R^{SN} is hydrogen. In certain embodiments, at least one R^{SN} is $–CH_3$. In certain embodiments, one R^{SN} is $–CH_3$; and the second R^{SN} is hydrogen. In certain embodiments, both R^{SN} groups are $–CH_3$. In certain embodiments, R^{S4b} is hydrogen. In certain embodiments, R^{S4b} is not hydrogen. In certain embodiments, R^{S4b} is $–OR^{SO}$; and R^{SO} is hydrogen. In certain embodiments, R^{S4b} is $–OR^{SO}$; and R^{SO} is an oxygen protecting group. In certain embodiments, R^{S5a} is optionally substituted alkyl. In certain embodiments, R^{S5a} is alkoxyalkyl. In certain embodiments, R^{S5a} is $–CH_2OH$. In certain embodiments, R^{S5a} is $–CH_2OBz$. In certain embodiments, R^{S5a} is aminoalkyl. In certain

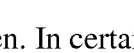
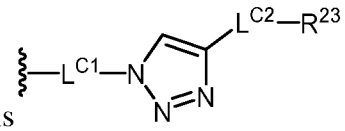
embodiments, R^{S5a} is $-CH_2NH_2$. In certain embodiments, R^9 is  . In certain embodiments, R^9 is  . In certain embodiments, R^9 is  . In certain embodiments, R^9 is  . In certain embodiments, R^9 is  .

[00472] In certain embodiments, the carbon to which R^{5a} and R^{5b} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^{5a} and R^{5b} is attached is a stereocenter of the (S)-configuration. In certain embodiments, at least one of R^{5a} and R^{5b} is hydrogen. In certain embodiments, both R^{5a} and R^{5b} are hydrogen. In certain embodiments, neither R^{5a} nor R^{5b} are hydrogen. In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted alkyl. In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted C_{1-6}alkyl. In certain embodiments, at least one instance of R^{5a} and R^{5b} is optionally substituted C_{1-2}alkyl. In certain embodiments, at least one instance of R^{5a} and R^{5b} is unsubstituted C_{1-2}alkyl. In certain embodiments, at least one instance of R^{5a} and R^{5b} is $-CH_3$. In certain embodiments, R^{5a} is optionally substituted alkyl; and R^{5b} is hydrogen. In certain embodiments, R^{5a} is optionally substituted C_{1-6}alkyl; and R^{5b} is hydrogen. In certain embodiments, R^{5a} is optionally substituted C_{1-2}alkyl; and R^{5b} is hydrogen. In certain embodiments, R^{5a} is unsubstituted C_{1-2}alkyl; and R^{5b} is hydrogen. In certain embodiments, R^{5a} is $-CH_3$; and R^{5b} is hydrogen. In certain embodiments, both instances of R^{5a} and R^{5b} are $-CH_3$. In certain embodiments, neither R^{5a} nor R^{5b} is $-CH_3$.

[00473] In certain embodiments, R^{17} is hydrogen. In certain embodiments, R^{17} is not hydrogen. In certain embodiments, R^{17} is an oxygen protecting group. In certain embodiments, R^{17} is $-C(=O)R^{Z8}$.

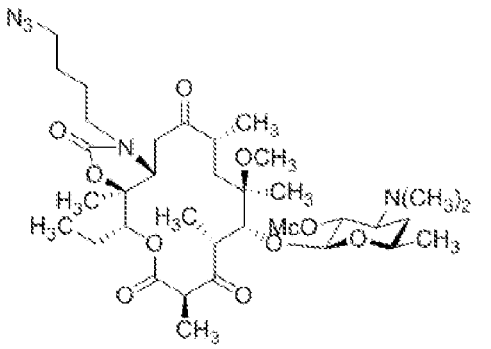
[00474] In certain embodiments, the carbon to which R^6 and R^{10} is attached is a stereocenter of the (R)-configuration. In certain embodiments, the carbon to which R^6 and R^{10} is attached is a stereocenter of the (S)-configuration. In certain embodiments, at least one of R^6 and R^{10} is hydrogen. In certain embodiments, both R^6 and R^{10} are hydrogen. In certain embodiments, neither R^6 nor R^{10} are hydrogen. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted C_{1-6}alkyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted C_{1-2}alkyl. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_3$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_2CN$. In certain embodiments, at least one instance of R^6 and R^{10} is $–CH_2C(=O)OR^{32}$; and R^{32} is optionally substituted alkyl or hydrogen. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted heteroaralkyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted pyrazolylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is imidazolylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is thiazolylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is oxazolylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is pyridinylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is pyrimidinylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is pyrazinylalkyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted alkenyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted allyl. In certain embodiments, at least one instance of R^6 and R^{10} is unsubstituted allyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted aralkyl. In certain embodiments, at least one instance of R^6 and R^{10} is optionally substituted benzyl. In certain embodiments, at least one instance of R^6 and R^{10} is unsubstituted benzyl. In certain embodiments, R^6 is optionally substituted alkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted C_{1-6}alkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted C_{1-2}alkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is $–CH_3$; and R^{10} is hydrogen. In certain embodiments, R^6 is $–CH_2CN$; and R^{10} is hydrogen. In certain embodiments, R^6 is $–CH_2C(=O)OR^{32}$; R^{32} is optionally substituted alkyl or hydrogen; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted heteroaralkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted pyrazolylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is imidazolylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is thiazolylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is oxazolylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is pyridinylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is

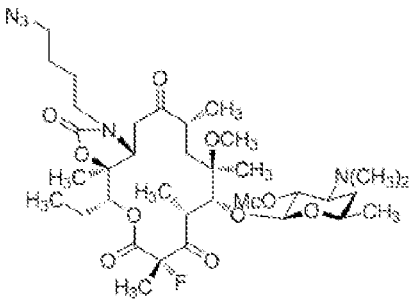
pyrimidinylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is pyrazinylalkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted alkenyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted allyl; and R^{10} is hydrogen. In certain embodiments, R^6 is unsubstituted allyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted aralkyl; and R^{10} is hydrogen. In certain embodiments, R^6 is optionally substituted benzyl; and R^{10} is hydrogen. In certain embodiments, R^6 is unsubstituted benzyl; and R^{10} is hydrogen. In certain embodiments, at least one instance of R^6 and R^{10} is halogen. In certain embodiments, at least one instance of R^6 and R^{10} is fluorine. In certain embodiments, both R^6 and R^{10} are halogen. In certain embodiments, both R^6 and R^{10} are fluorine. In certain embodiments, R^6 is optionally substituted alkyl; and R^{10} is halogen. In certain embodiments, R^6 is optionally substituted C_{1-6}alkyl; and R^{10} is halogen. In certain embodiments, R^6 is optionally substituted C_{1-2}alkyl; and R^{10} is halogen. In certain embodiments, R^6 is $-CH_3$; and R^{10} is halogen. In certain embodiments, R^6 is optionally substituted alkyl; and R^{10} is fluorine. In certain embodiments, R^6 is optionally substituted C_{1-6}alkyl; and R^{10} is fluorine. In certain embodiments, R^6 is optionally substituted C_{1-2}alkyl; and R^{10} is fluorine. In certain embodiments, R^6 is $-CH_3$; and R^{10} is fluorine.

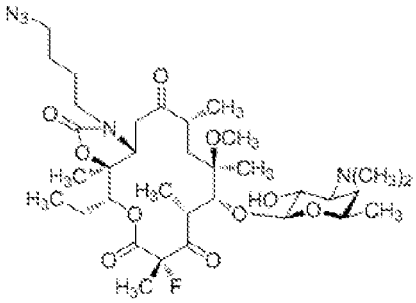
[00475] In certain embodiments, R^{14} is hydrogen. In certain embodiments, R^{14} is not hydrogen. In certain embodiments, R^{14} is  ; and A^1 is $-N_3$. In certain embodiments, R^{14} is  ; and L^{C2} is a bond. In certain embodiments, L^{C1} is a linking group comprising at least one instance of optionally substituted alkylene. In certain embodiments, L^{C1} is a linking group comprising at least one instance of substituted or unsubstituted C_{3-6}alkylene. In certain embodiments, L^{C1} is an alkylene linking group of the formula $-(CH_2)_n-$, wherein n is 3, 4, or 5. In certain embodiments, L^{C1} is a linking group comprising at least one instance of optionally substituted alkenylene. In certain embodiments, L^{C1} is a linking group comprising at least one instance of substituted or unsubstituted C_{3-6}alkenylene. In certain embodiments, L^{C1} is a linking group comprising at least one instance of optionally substituted alkynylene. In certain embodiments, L^{C1} is a linking group comprising at least one instance of substituted or unsubstituted C_{3-6}alkynylene. In certain embodiments, R^{23} is optionally substituted aryl. In certain embodiments, R^{23} is optionally substituted phenyl. In certain embodiments, R^{23} is optionally substituted 5–6 membered heteroaryl. In certain embodiments, R^{23} is optionally substituted aniline. In certain

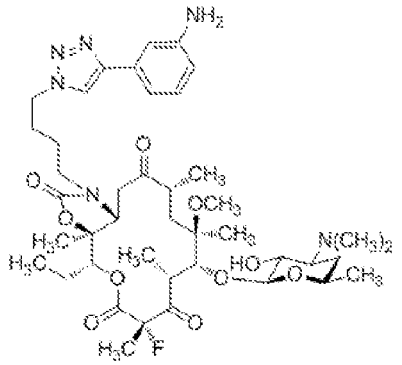
embodiments, R^{23} is optionally substituted pyridizine. In certain embodiments, R^{23} is optionally substituted pyridine. In certain embodiments, R^{23} is optionally substituted aminopyridine. In certain embodiments, R^{23} is optionally substituted thiazole. In certain embodiments, R^{23} is optionally substituted aminothiazole. In certain embodiments, R^{23} is optionally substituted thiadiazole. In certain embodiments, R^{23} is optionally substituted aminothiadiazole. In certain embodiments, R^{23} is optionally substituted 5,6 fused-bicyclic heteroaryl. In certain embodiments, R^{23} is optionally substituted benzothiazole.

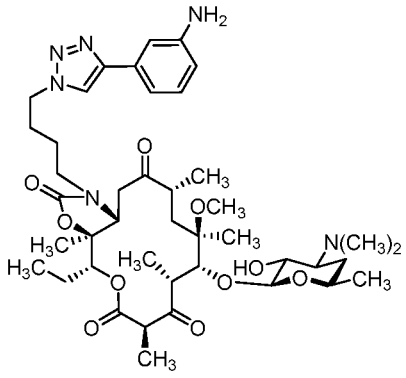
[00476] In certain embodiments, known ketolides, such as the ketolides disclosed in Figure 1, are specifically excluded. In certain embodiments, ketolides as disclosed in International Patent Application No. PCT/US2014/033025, filed April 4, 2014, are specifically excluded. In certain embodiments, ketolides:











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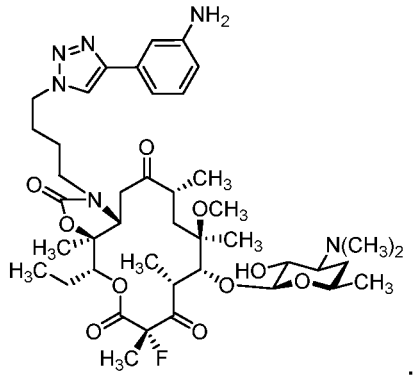

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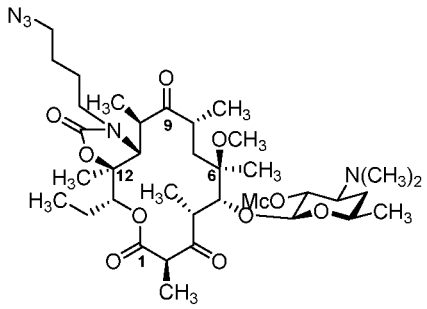
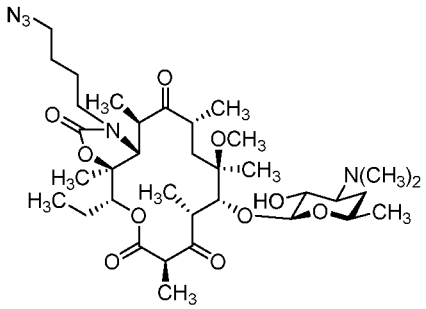
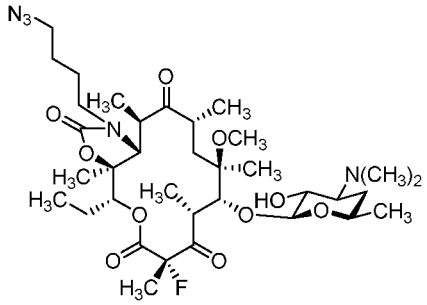
and salts thereof, are specifically excluded.

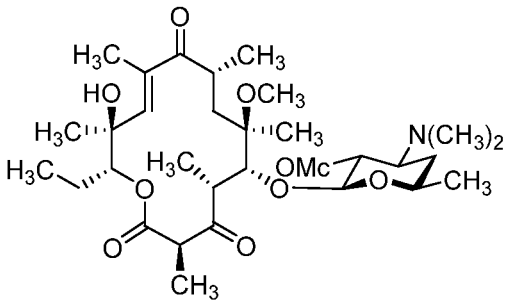
[00477] Exemplary novel ketolides of the present invention include, but are not limited to the compounds and salts thereof in Table 1.

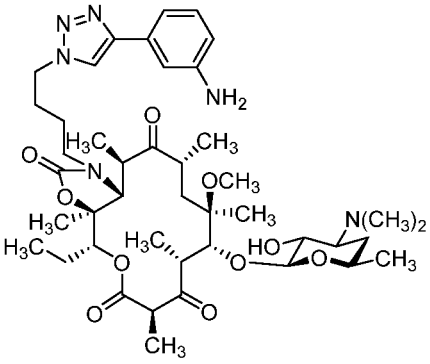
Table 1. Exemplary Ketolides











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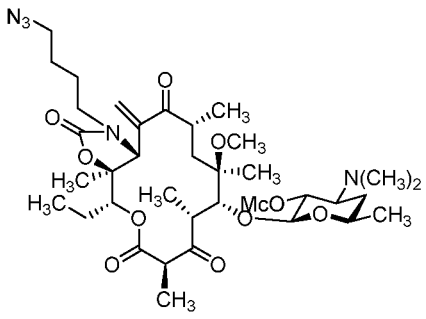
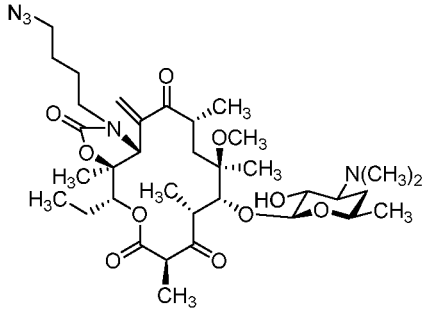
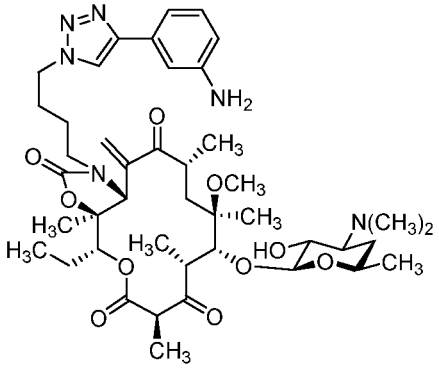
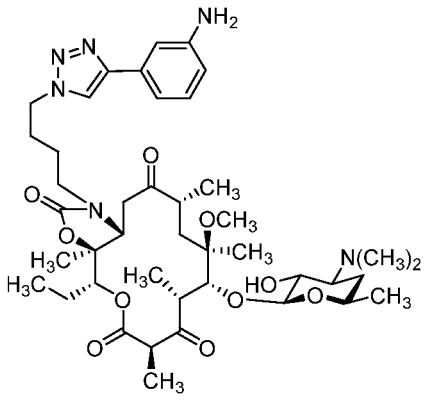




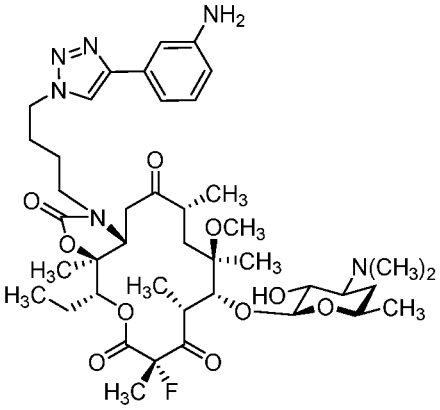


FSM-21828

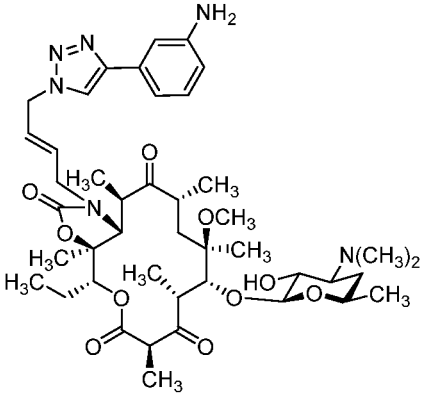
Table 1. Exemplary Ketolides



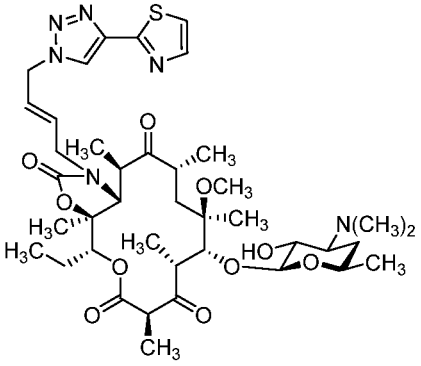
FSM-21535



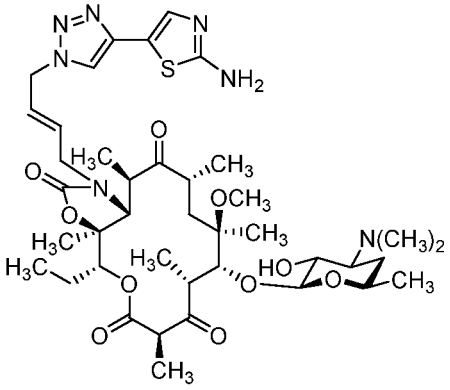
FSM-21598



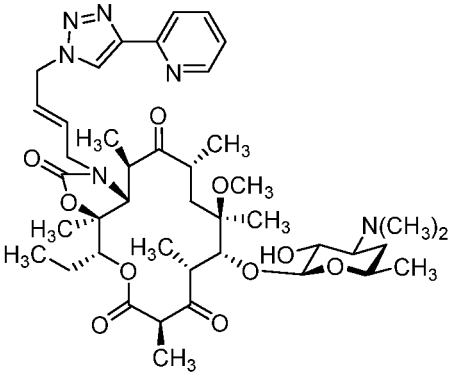
FSM-11561



FSM-11559

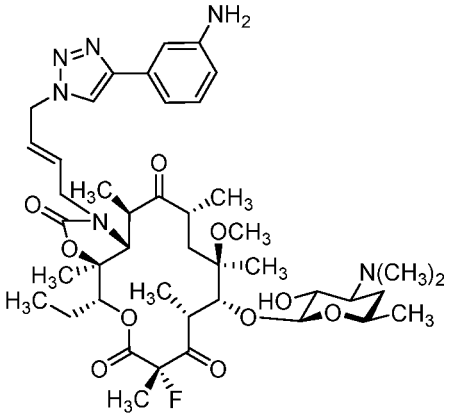


FSM-100237

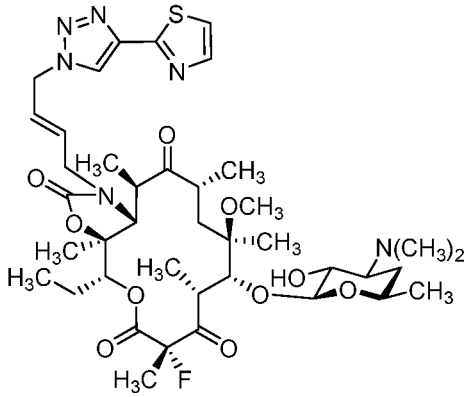


FSM-100341

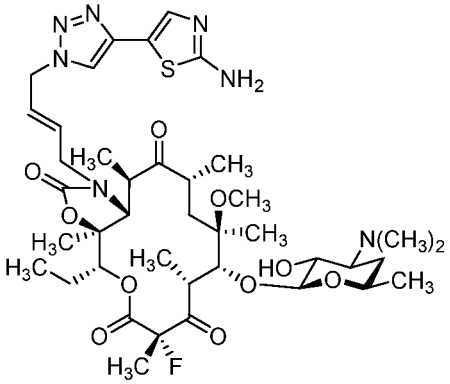
Table 1. Exemplary Ketolides



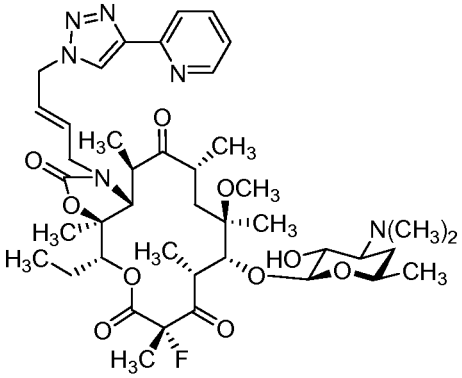
FSM-11563



FSM-11562



FSM-100240



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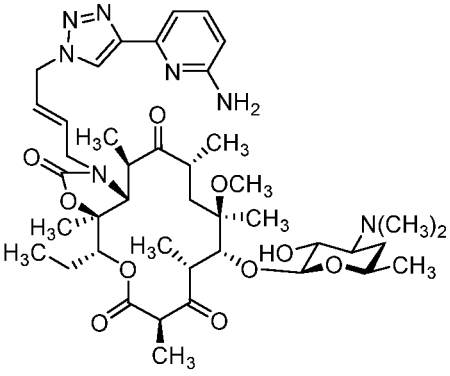
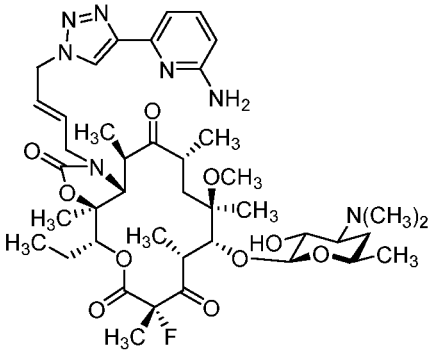
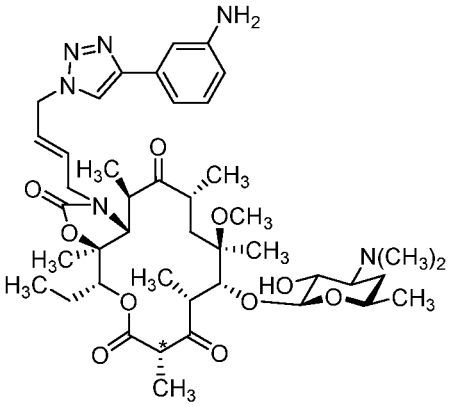


FSM-100364

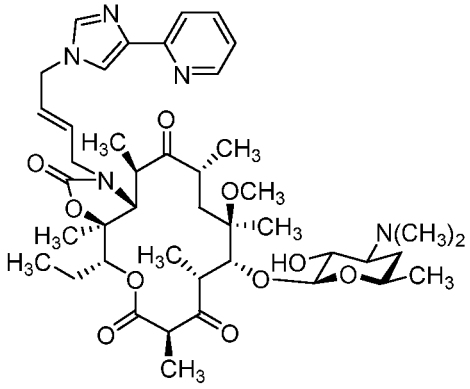


FSM-100407

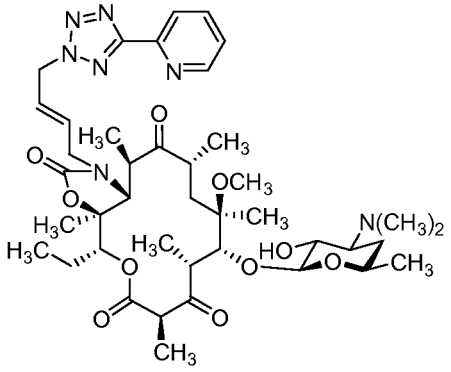
Table 1. Exemplary Ketolides



FSM-100432



FSM-100421



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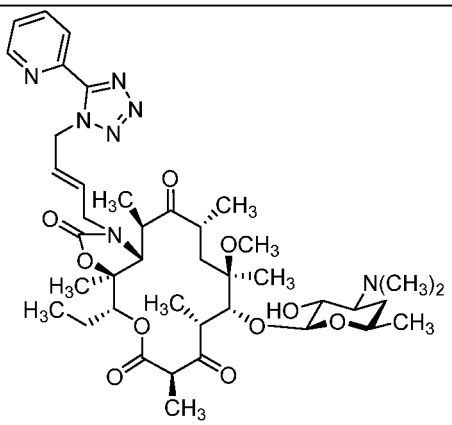

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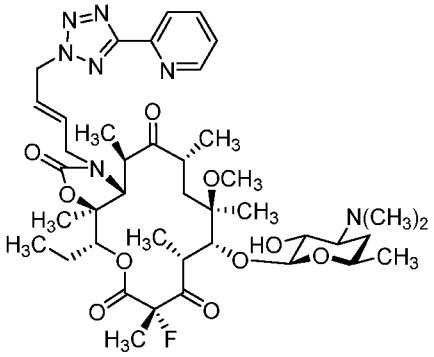
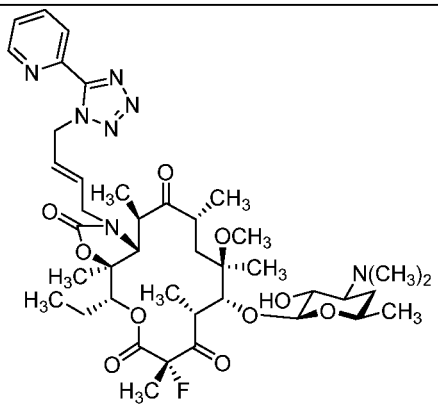
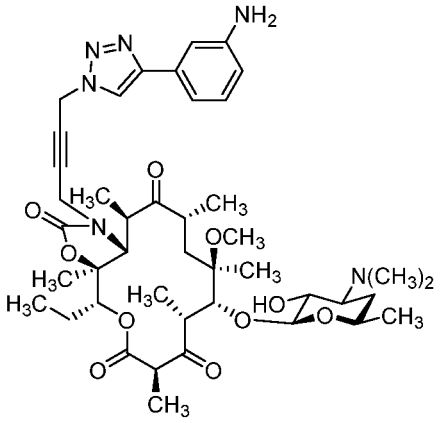


FSM-100389

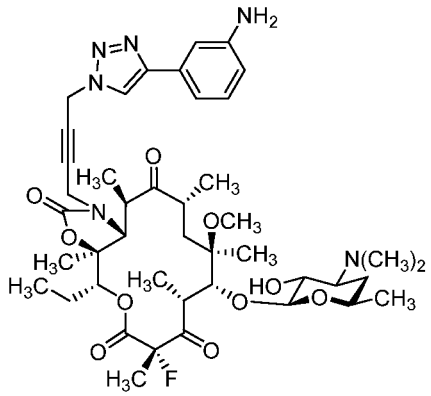


FSM-100386

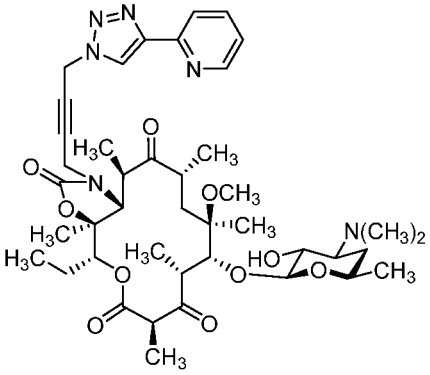
Table 1. Exemplary Ketolides



FSM-100239



FSM-100426



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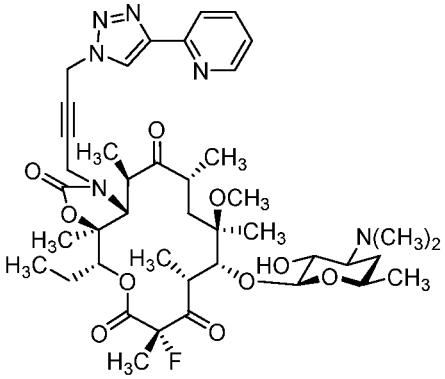
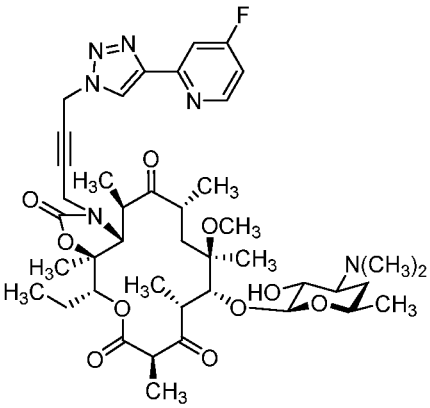
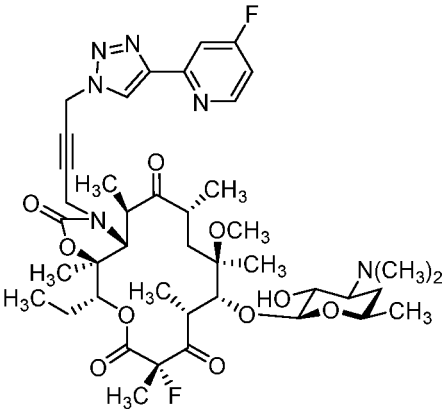


FSM-100490

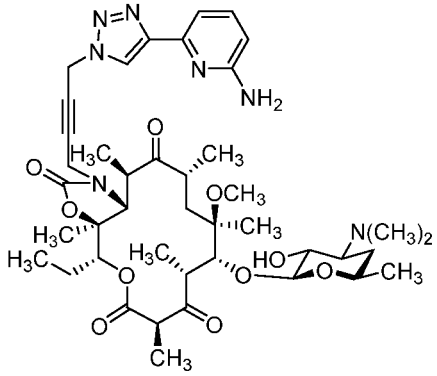


FSM-100566

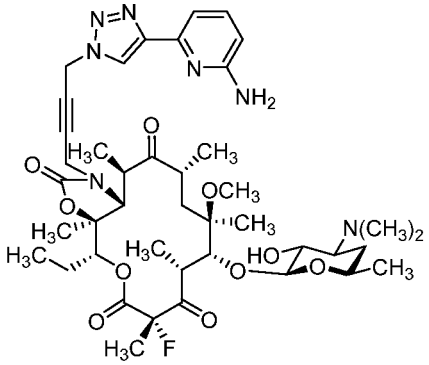


FSM-100563

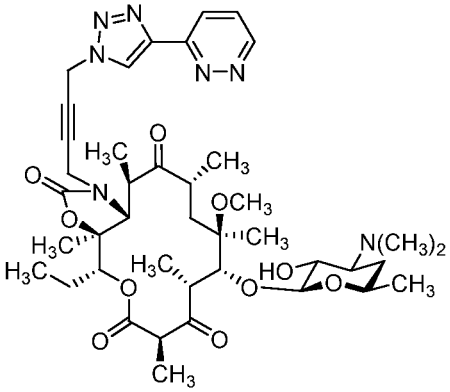
Table 1. Exemplary Ketolides



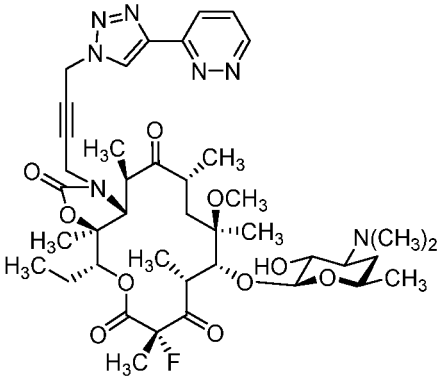
FSM-100551



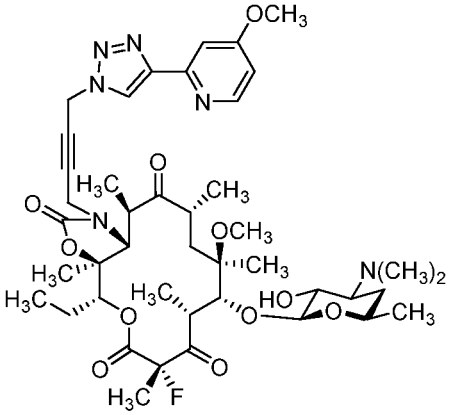
FSM-100573



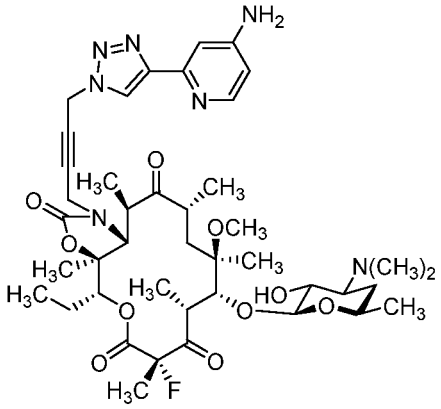
FSM-130216



FSM-130217

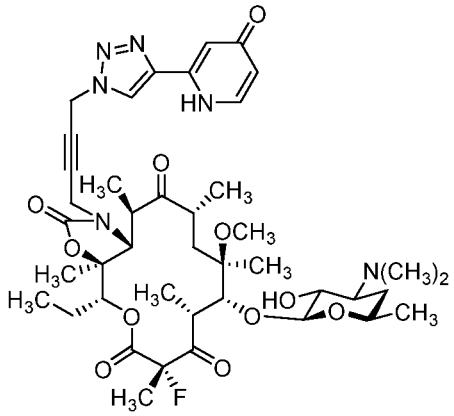


FSM-100576

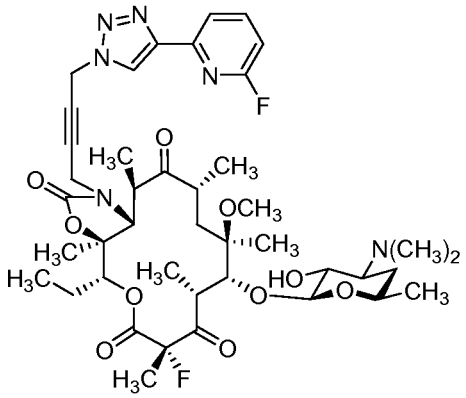


FSM-100593

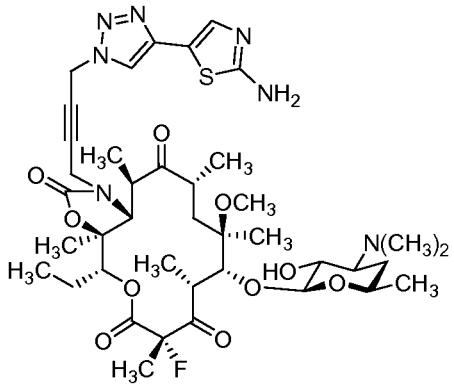
Table 1. Exemplary Ketolides



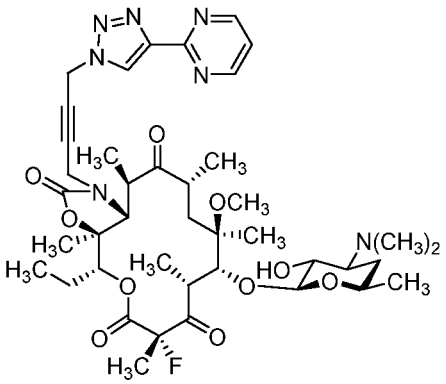
FSM-100597



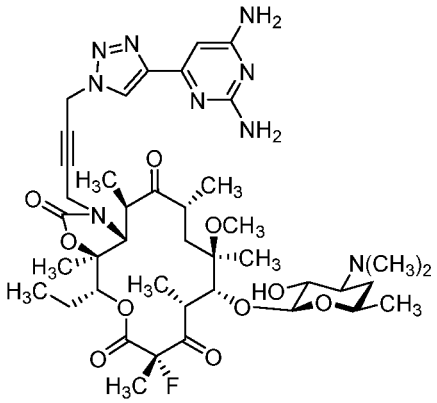
FSM-100627



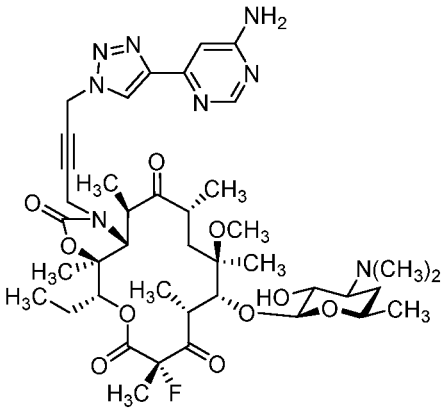
FSM-100633



FSM-22741

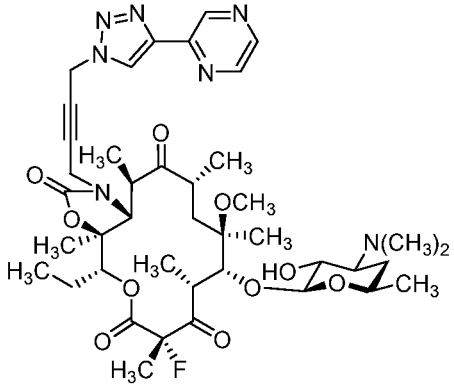


FSM-22742

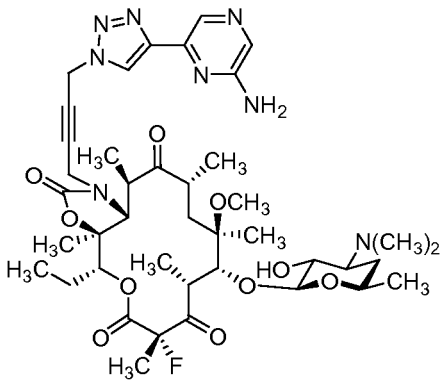


FSM-22745

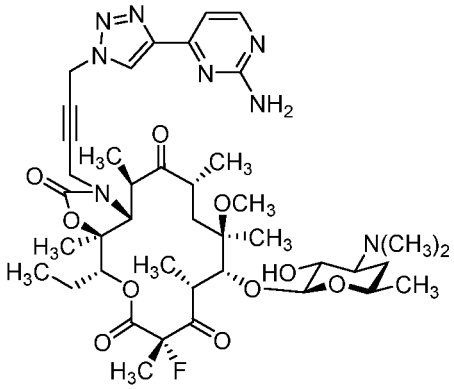
Table 1. Exemplary Ketolides



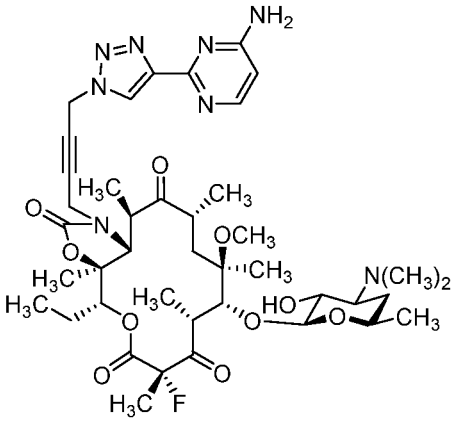
FSM-22746



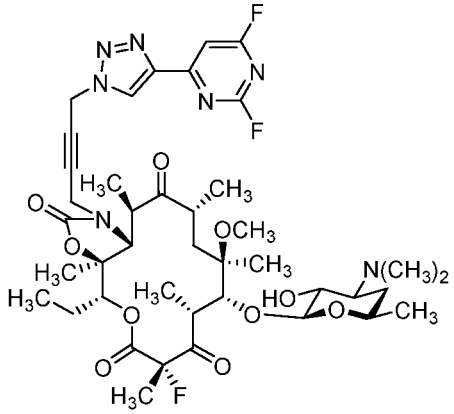
FSM-22747



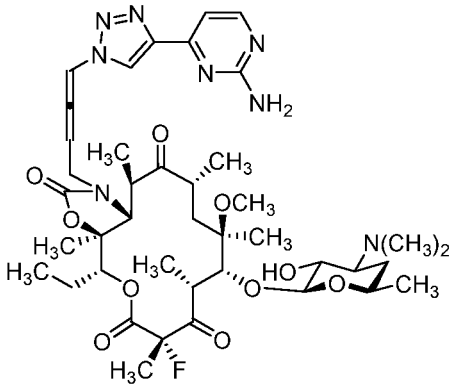
FSM-22748



FSM-22749

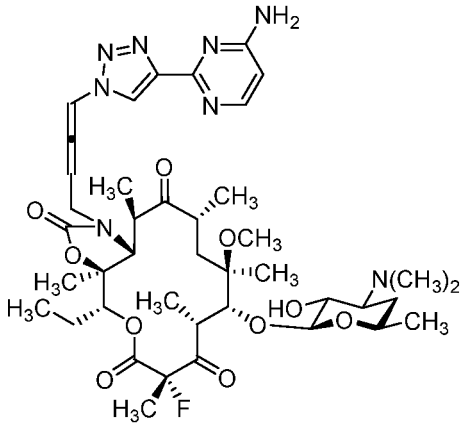


FSM-22750

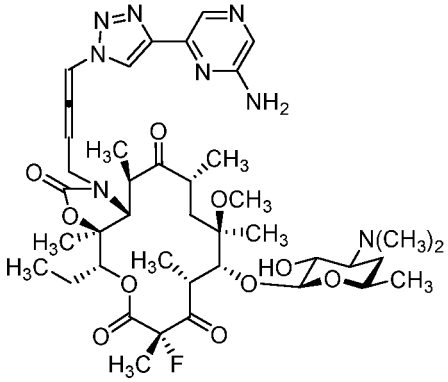


FSM-22737

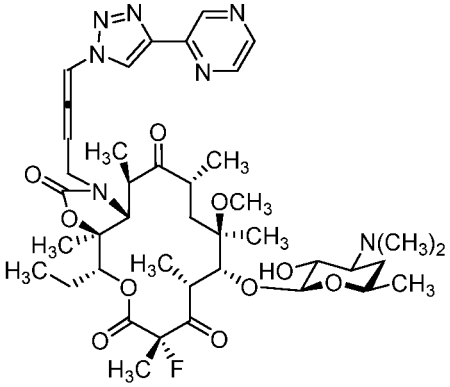
Table 1. Exemplary Ketolides



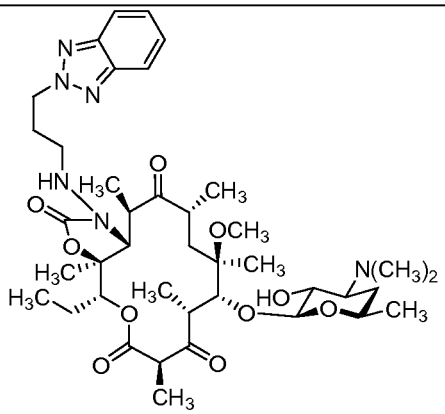
FSM-22738



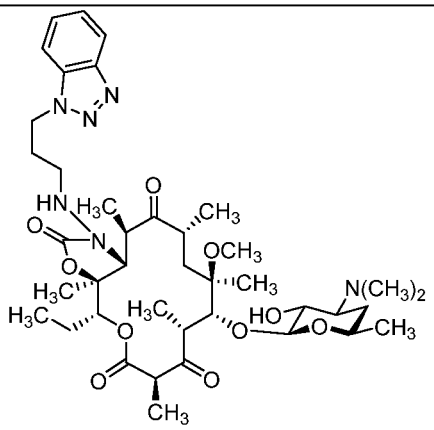
FSM-22739



FSM-22740



FSM-140132



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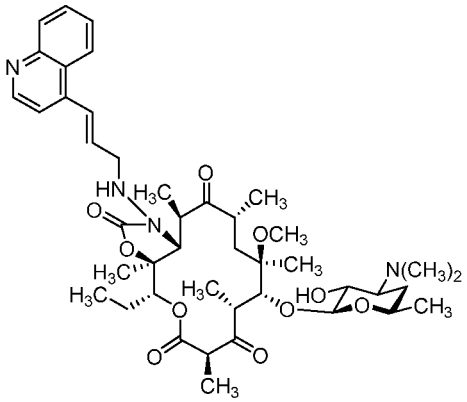
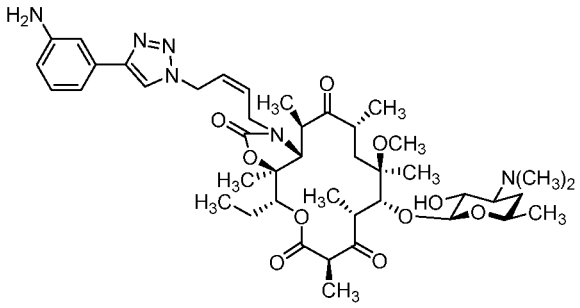
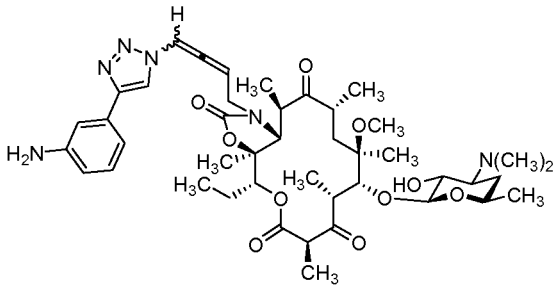


FSM-140135

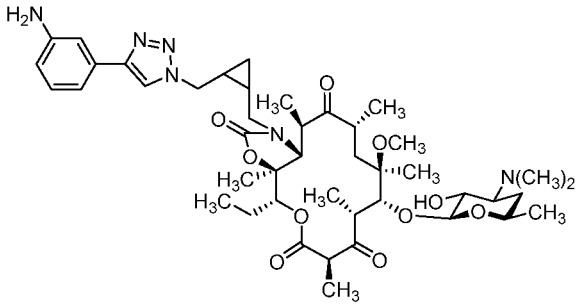
Table 1. Exemplary Ketolides



FSM-100423



FSM-100427 Diastereomer 1
FSM-100433 Diastereomer 2



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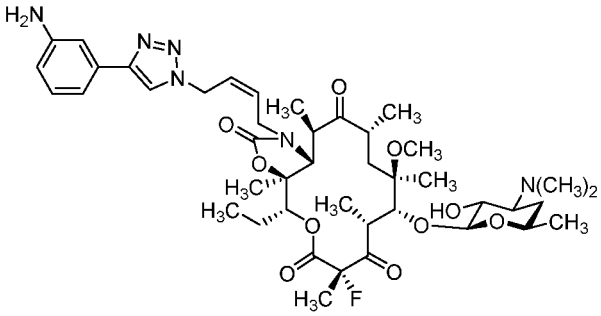

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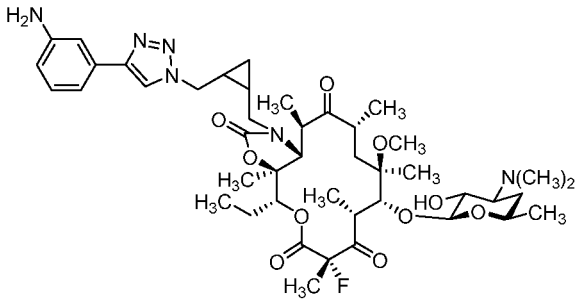
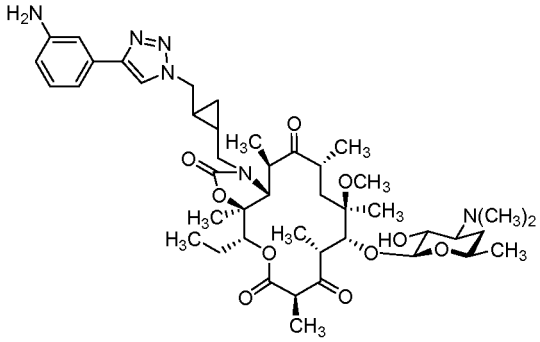


FSM-100439 Diastereomer 1
FSM-100441 Diastereomer 2



FSM100428 Diastereomer 1
FSM100434 Diastereomer 2

Pharmaceutical Compositions and Administration

[00478] The present invention provides pharmaceutical compositions comprising a ketolide as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00479] Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as

suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00480] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the ketolide of the present invention into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single– or multi–dose unit.

[00481] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the ketolide of the present invention. The amount of the ketolide is generally equal to the dosage of the ketolide which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one–half or one–third of such a dosage.

[00482] Relative amounts of the ketolide, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) ketolide.

[00483] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00484] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00485] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium

carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00486] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* Cremophor), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether [Brij 30]), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00487] Exemplary binding agents include starch (*e.g.* cornstarch and starch paste), gelatin, sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene

oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00488] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00489] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00490] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00491] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00492] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00493] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00494] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00495] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00496] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00497] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00498] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the ketolides, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol,

polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00499] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00500] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00501] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00502] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non–irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the ketolide.

[00503] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the ketolide is mixed with at least one inert,

pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00504] Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the ketolide(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00505] The ketolide can be in micro–encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the ketolide can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the ketolide(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00506] Dosage forms for topical and/or transdermal administration of a ketolide of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the ketolide is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an ketolide to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the ketolide in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the ketolide in a polymer matrix and/or gel.

[00507] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00508] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) ketolide, although the concentration of the ketolide can be as high as the solubility limit of the ketolide in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00509] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a

formulation may comprise dry particles which comprise the ketolide and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the ketolide dissolved and/or suspended in a low–boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00510] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the ketolide may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non–ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the ketolide).

[00511] Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the ketolide in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the ketolide, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00512] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the ketolide and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered.

by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00513] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the ketolide, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) ketolide, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the ketolide. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00514] A pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the ketolide in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically–administrable formulations which are useful include those which comprise the ketolide in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[00515] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00516] Ketolides provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily amount of the ketolide will be decided by the attending physician within the scope of sound

medical judgment. The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific ketolide employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific ketolide employed; the duration of the treatment; drugs used in combination or coincidental with the specific ketolide employed; and like factors well known in the medical arts.

[00517] The ketolides and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra–arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent, the therapeutic regimen, and/or the condition of the subject. Oral administration is the preferred mode of administration. However, in certain embodiments, the subject may not be in a condition to tolerate oral administration, and thus intravenous, intramuscular, and/or rectal administration are also preferred altermative modes of adminsitration.

[00518] The exact amount of a ketolide required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular ketolide(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00519] In certain embodiments, an effective amount of a ketolide for administration one or more times a day to a 70 kg adult human may comprise about 0.1 mg to about 3000 mg, about 0.1 mg to about 2000 mg, about 0.1 mg to about 1000 mg, about 0.1 mg to about 100 mg, about 1 mg to about 100 mg, or about 10 mg to about 100 mg, of a ketolide per unit dosage form.

[00520] In certain embodiments, the ketolides of the present invention may be administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 100 mg/kg, from about 0.1 mg/kg to about 100 mg/kg, from about 0.5 mg/kg to about 100 mg/kg, from about 10 mg/kg to about 100 mg/kg, from about 20 mg/kg to about 100 mg/kg, and from about 25 mg/kg to about 100 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00521] It will be also appreciated that a ketolide or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. The ketolide or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of the inventive ketolide with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00522] In any of the above described methods, one or more additional therapeutic agents (also referred to as the "agent") may be administered concurrently with, prior to, or subsequent to, administration of the ketolide of the present invention, as described herein. The agent may be added at the same time as the ketolide of the present invention (simultaneous administration), before or after administration of the ketolide of the present invention (sequential administration), or any combination thereof. For example, in certain embodiments, the agent is administered first, followed by simultaneous administration of the agent and the ketolide of the present invention. In certain embodiments, the ketolide of the present invention is administered first, followed by simultaneous administration of the agent and the ketolide of the present invention. In any of the above embodiments, either the agent or the ketolide of the present invention may be further administered alone after the simultaneous administration.

[00523] Exemplary additional therapeutically active agents include, but are not limited to, antibiotics, anti–viral agents, anesthetics, anti–coagulants, inhibitors of an enzyme, steroidal agents, steroidal or non–steroidal anti–inflammatory agents, antihistamine,

immunosuppressant agents, antigens, vaccines, antibodies, decongestant, sedatives, opioids, pain–relieving agents, analgesics, anti–pyretics, hormones, and prostaglandins. Therapeutically active agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the US Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[00524] In certain embodiments, the additional therapeutically agent is an antibiotic. Exemplary antibiotics include, but are not limited to, penicillins (*e.g.*, penicillin, amoxicillin), cephalosporins (*e.g.*, cephalexin), macrolides (*e.g.*, erythromycin, clarithormycin, azithromycin, troleandomycin), fluoroquinolones (*e.g.*, ciprofloxacin, levofloxacin, ofloxacin), sulfonamides (*e.g.*, co–trimoxazole, trimethoprim), tetracyclines (*e.g.*, tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, doxycline, aureomycin, terramycin, minocycline, 6–deoxytetracycline, lymecycline, meclocycline, methacycline, rolitetracycline, and glycylcycline antibiotics (*e.g.*, tigecycline)), aminoglycosides (*e.g.*, gentamicin, tobramycin, paromomycin), aminocyclitol (*e.g.*, spectinomycin), chloramphenicol, sparsomycin, and quinupristin/dalfoprisin (Syndercid™).

[00525] Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise an inventive pharmaceutical composition or ketolide and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or ketolide. In some embodiments, the inventive pharmaceutical composition or ketolide provided in the container and the second container are combined to form one unit dosage form.

Method of Treatment

[00526] The present invention contemplates using ketolides of the present invention for the treatment of infectious diseases, for example, fungal, bacterial, viral, or parasitic infections, and for the treatment of inflammatory conditions. Ketolides are known to exhibit anti–bacterial activity as well as anti–parasitic activity. See, for example, Clark *et al., Bioorganic & Medicinal Chemistry* Letters (2000) 10:815–819 (anti–bacterial activity); and Lee *et al., J.*

Med. Chem. (2011) 54:2792–2804 (anti–bacterial and anti–parasitic activity). Ketolides are also known to exhibit an anti–inflammatory effect. See, for example, Amsden, *Journal of Antimicrobial Chemotherapy* (2005) 55:10–21 (chronic pulmonary inflammatory syndromes).

[00527] Thus, as generally described herein, provided is a method of treating a infectious disease comprising administering an effective amount of a ketolide of the present invention, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. Such a method can be conducted *in vivo* (*i.e.*, by administration to a subject) or *in vitro* (*e.g.*, upon contact with the pathogen, tissue, or cell culture). Treating, as used herein, encompasses therapeutic treatment and prophylactic treatment.

[00528] In certain embodiments, the effective amount is a therapeutically effective amount. For example, in certain embodiments, the method slows the progress of an infectious disease in the subject. In certain embodiments, the method improves the condition of the subject suffering from an infectious disease. In certain embodiments, the subject has a suspected or confirmed infectious disease.

[00529] In certain embodiments, the effective amount is a prophylatically effective amount. For example, in certain embodiments, the method prevents or reduces the likelihood of an infectious disease, *e.g.*, in certain embodiments, the method comprises administering a ketolide of the present invention to a subject in need thereof in an amount sufficient to prevent or reduce the likelihood of an infectious disease. In certain embodiments, the subject is at risk of an infectious disease (*e.g.,* has been exposed to another subject who has a suspected or confirmed infectious disease or has been exposed or thought to be exposed to a pathogen).

[00530] In another aspect, provided is an *in vitro* method of inhibiting pathogenic growth comprising contacting an effective amount of the ketolide of the present invention with a pathogen (*e.g.,* a bacteria, virus, fungus, or parasite) in a cell culture.

[00531] As used herein, "infectious disease" and "microbial infection" are used interchangeably, and refer to an infection with a pathogen, such as a fungus, bacteria, virus, or a parasite. In certain embodiments, the infectious disease is caused by a pathogen resistant to other treatments. In certain embodiments, the infectious disease is caused by a pathogen that is multi–drug tolerant or resistant, *e.g.,* the infectious disease is caused by a pathogen that neither grows nor dies in the presence of or as a result of other treatments.

[00532] In certain embodiments, the infectious disease is a bacterial infection. For example, in certain embodiments, provided is a method of treating a bacterial infection comprising

administering an effective amount of a ketolide of the present invention, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[00533] In certain embodiments, the ketolide has a mean inhibitory concentration (MIC), with respect to a particular bacteria, of less than 50 μg/mL, less than 25 μg/mL, less than 20 μg/mL, less than 10 μg/mL, less than 5 μg/mL, or less than 1 μg/mL.

[00534] In certain embodiments, the bacteria is susceptible (*e.g.,* responds to) or resistant to known commercial macrolides, such as azithromycin, clindamycin, telithromycin, erythromycin, spiramycin, and the like. See also Figure 1 for a listing of known macrolides. In certain embodiments, the bactera is resistant to a known macrolide. For example, in certain embodiments, the bacteria is erythromycin resistant (ER).

[00535] In certain embodiments, the bacterial infection is resistant to other antibiotics (*e.g.,* non–macrolide) therapy. For example, in certain embodiments, the pathogen is vancomycin resistant (VR). In certain embodiments, the pathogen is a methicillin–resistant (MR), *e.g.*, in certain embodiments, the bacterial infection is an methicillin–resistant *S. aureus* infection (a MRSA infection).

[00536] In certain embodiments, the bacteria has an efflux (*e.g.,* mef, msr) genotype. In certain embodiments, the bacteria has a methylase (*e.g.,* erm) genotype. In certain embodiments, the bacteria has a constitutive genotype. In certain embodiments, the bacteria has an inducible genotype.

[00537] Exemplary bacterial infections include, but are not limited to, infections with a Gram positive bacteria (*e.g.*, of the phylum *Actinobacteria,* phylum *Firmicutes*, or phylum *Tenericutes*); Gram negative bacteria (*e.g.*, of the phylum *Aquificae*, phylum *Deinococcus–Thermus*, phylum *Fibrobacteres/Chlorobi/Bacteroidetes* (FCB), phylum *Fusobacteria*, phylum *Gemmatimonadest*, phylum *Ntrospirae*, phylum *Planctomycetes/Verrucomicrobia/Chlamydiae* (PVC), phylum *Proteobacteria*, phylum *Spirochaetes*, or phylum *Synergistetes*); or other bacteria (*e.g.*, of the phylum *Acidobacteria*, phylum *Chlroflexi*, phylum *Chrystiogenetes*, phylum *Cyanobacteria*, phylum *Deferrubacteres*, phylum *Dictyoglomi*, phylum *Thermodesulfobacteria*, or phylum *Thermotogae*).

[00538] In certain embodiments, the bacterial infection is an infection with a Gram positive bacteria.

[00539] In certain embodiments, the Gram positive bacteria is a bacteria of the phylum *Firmicutes*.

[00540] In certain embodiments, the bacteria is a member of the phylum *Firmicutes* and the genus *Enterococcus*, *i.e.*, the bacterial infection is an *Enterococcus* infection. Exemplary *Enterococci* bacteria include, but are not limited to, *E. avium*, *E. durans*, *E. faecalis*, *E. faecium*, *E. gallinarum*, *E. solitarius*, *E. casseliflavus*, and *E. raffinosus*.

[00541] In certain embodiments, the bacteria is a member of the phylum *Firmicutes* and the genus *Staphylococcus*, *i.e.*, the bacterial infection is a *Staphylococcus* infection. Exemplary *Staphylococci* bacteria include, but are not limited to, *S. arlettae, S. aureus, S. auricularis, S. capitis, S. caprae, S. carnous, S. chromogenes, S. cohii, S. condimenti, S. croceolyticus, S. delphini, S. devriesei, S. epidermis, S. equorum, S. felis, S. fluroettii, S. gallinarum, S. haemolyticus, S. hominis, S. hyicus, S. intermedius, S. kloosii, S. leei, S. lenus, S. lugdunesis, S. lutrae, S. lyticans, S. massiliensis, S. microti, S. muscae, S. nepalensis, S. pasteuri, S. penttenkoferi, S. piscifermentans, S. psuedointermedius, S. psudolugdensis, S. pulvereri, S. rostri, S. saccharolyticus, S. saprophyticus, S. schleiferi, S. sciuri, S. simiae, S. simulans, S. stepanovicii, S. succinus, S. vitulinus, S. warneri,* and *S. xylosus*. In certain embodiments, the *Staphylococcus* infection is an *S. aureus* infection. In certain embodiments, the *S. aureus* has an efflux (*e.g.,* mef, msr) genotype. In certain embodiments, the *S. aureus* has a methylase (*e.g.,* erm) genotype.

[00542] In certain embodiments, the bacteria is a member of the phylum *Firmicutes* and the genus *Bacillus*, *i.e.*, the bacterial infection is a *Bacillus* infection. Exemplary *Bacillus* bacteria include, but are not limited to, *B. alcalophilus*, *B. alvei*, *B. aminovorans*, *B. amyloliquefaciens*, *B. aneurinolyticus*, *B. anthracis*, *B. aquaemaris*, *B. atrophaeus*, *B. boroniphilus*, *B. brevis*, *B. caldolyticus*, *B. centrosporus*, *B. cereus*, *B. circulans*, *B. coagulans*, *B. firmus*, *B. flavothermus*, *B. fusiformis*, *B. globigii*, *B. infernus*, *B. larvae*, *B. laterosporus*, *B. lentus*, *B. licheniformis*, *B. megaterium*, *B. mesentericus*, *B. mucilaginosus*, *B. mycoides*, *B. natto*, *B. pantothenticus*, *B. polymyxa*, *B. pseudoanthracis*, *B. pumilus*, *B. schlegelii*, *B. sphaericus*, *B. sporothermodurans*, *B. stearothermophilus*, *B. subtilis*, *B. thermoglucosidasius*, *B. thuringiensis*, *B. vulgatis*, and *B. weihenstephanensis.* In certain embodiments, the *Bacillus* infection is a *B. subtilis* infection. In certain embodiments, the *B. subtilis* has an efflux (*e.g.,* mef, msr) genotype. In certain embodiments, the *B. subtilis* has a methylase (*e.g.,* erm) genotype.

[00543] In certain embodiments, the bacteria is a member of the phylum *Firmicutes* and the genus *Strepococcus*, *i.e.*, the bacterial infection is a *Strepococcus* infection. Exemplary *Strepococcus* bacteria include, but are not limited to, *S. agalactiae*, *S. anginosus*, *S. bovis*, *S. canis*, *S. constellatus*, *S. dysgalactiae*, *S. equinus*, *S. iniae*, *S. intermedius*, *S. mitis*, *S. mutans*,

S. oralis, *S. parasanguinis*, *S. peroris*, *S. pneumoniae*, *S. pyogenes*, *S. ratti*, *S. salivarius*, *S. thermophilus*, *S. sanguinis*, *S. sobrinus*, *S. suis*, *S. uberis*, *S. vestibularis*, *S. viridans*, and *S. zooepidemicus.* In certain embodiments, the *Strepococcus* infection is an *S. pyogenes* infection. In certain embodiments, the *Strepococcus* infection is an *S. pneumoniae* infection. In certain embodiments, the *S. pneumoniae* has an efflux (*e.g.,* mef, msr) genotype. In certain embodiments, the *S. pneumoniae* has a methylase (*e.g.,* erm) genotype.

[00544] In certain embodiments, the bacterial infection is an infection with a Gram negative bacteria.

[00545] In certain embodiments, the Gram negtive bacteria is a bacteria of the phylum *Proteobacteria* and the genus *Escherichia. i.e.,* the bacterial infection is an *Escherichia* infection. Exemplary *Escherichia* bacteria include, but are not limited to, *E. albertii*, *E. blattae*, *E. coli*, *E. fergusonii*, *E. hermannii*, and *E. vulneris.* In certain embodiments, the *Escherichia* infection is an *E. coli* infection.

[00546] In certain embodiments, the Gram negtive bacteria is a bacteria of the phylum *Proteobacteria* and the genus *Haemophilus. i.e.,* the bacterial infection is an *Haemophilus* infection. Exemplary *Haemophilus* bacteria include, but are not limited to, *H. aegyptius*, *H. aphrophilus*, *H. avium*, *H. ducreyi*, *H. felis*, *H. haemolyticus*, *H. influenzae*, *H. parainfluenzae*, *H. paracuniculus*, *H. parahaemolyticus*, *H. pittmaniae*, *Haemophilus segnis*, and *H. somnus.* In certain embodiments, the *Escherichia* infection is an *H. influenzae* infection.

[00547] In certain embodiments, the infectious disease is an infection with a parasitic infection. Thus, in certain embodiments, provided is a method of treating a parasitic infection comprising administering an effective amount of a ketolide of the present invention, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[00548] In certain embodiments, the ketolide has a IC_{50} (uM) with respect to a particular parasite, of less than 50 uM, less than 25 uM, less than 20 uM, less than 10 uM, less than 5 uM, or less than 1 uM.

[00549] Exemplary parasites include, but are not limited to, *Trypanosoma spp.* (*e.g.*, *Trypanosoma cruzi*, *Trypansosoma brucei*), *Leishmania spp.*, *Giardia spp.*, *Trichomonas spp.*, *Entamoeba spp.*, *Naegleria spp.*, *Acanthamoeba spp.*, *Schistosoma spp.*, *Plasmodium spp.* (*e.g., P. flaciparum*), *Crytosporidium spp.*, *Isospora spp.*, *Balantidium spp.*, *Loa Loa*, *Ascaris lumbricoides*, *Dirofilaria immitis*, and *Toxoplasma ssp.* (*e.g. T. gondii*).

[00550] As generally described herein, the present invention further a method of treating an inflammatory condition comprising administering an effective amount of a ketolide of the

present invention, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. Such a method can be conducted *in vivo* (*i.e.*, by administration to a subject) or *in vitro* (*e.g.*, upon contact with the pathogen, tissue, or cell culture). Treating, as used herein, encompasses therapeutic treatment and prophylactic treatment.

[00551] In certain embodiments, the effective amount is a therapeutically effective amount. For example, in certain embodiments, the method slows the progress of an inflammatory condition in the subject. In certain embodiments, the method improves the condition of the subject suffering from an inflammatory condition. In certain embodiments, the subject has a suspected or confirmed inflammatory condition.

[00552] In certain embodiments, the effective amount is a prophylatically effective amount. For example, in certain embodiments, the method prevents or reduces the likelihood of an inflammatory condition, *e.g.*, in certain embodiments, the method comprises administering a ketolide of the present invention to a subject in need thereof in an amount sufficient to prevent or reduce the likelihood of an inflammatory condition. In certain embodiments, the subject is at risk to an inflammatory condition.

[00553] In another aspect, provided is an *in vitro* method of treating an inflammatory condition comprising contacting an effective amount of the ketolide of the present invention with an inflammatory cell culture.

[00554] The term "inflammatory condition" refers to those diseases, disorders, or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent). Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[00555] Exemplary inflammatory conditions include, but are not limited to, inflammation associated with acne, anemia (*e.g.,* aplastic anemia, haemolytic autoimmune anaemia), chronic pulmonary inflammatory syndromes (*e.g.*, diffuse panbronchiolitis, cystic fibrosis, asthma, bronchiectasis, chronic obstructive pulmonary disease), arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis,

osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, cermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain–Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), a gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo, and Wegener's granulomatosis.

[00556] In certain embodiments, the inflammatory condition is an acute inflammatory condition (*e.g.*, for example, inflammation resulting from an infection). In certain embodiments, the inflammatory condition is a chronic inflammatory condition. In certain embodiments, the inflammatory condition is inflammation associated with cancer.

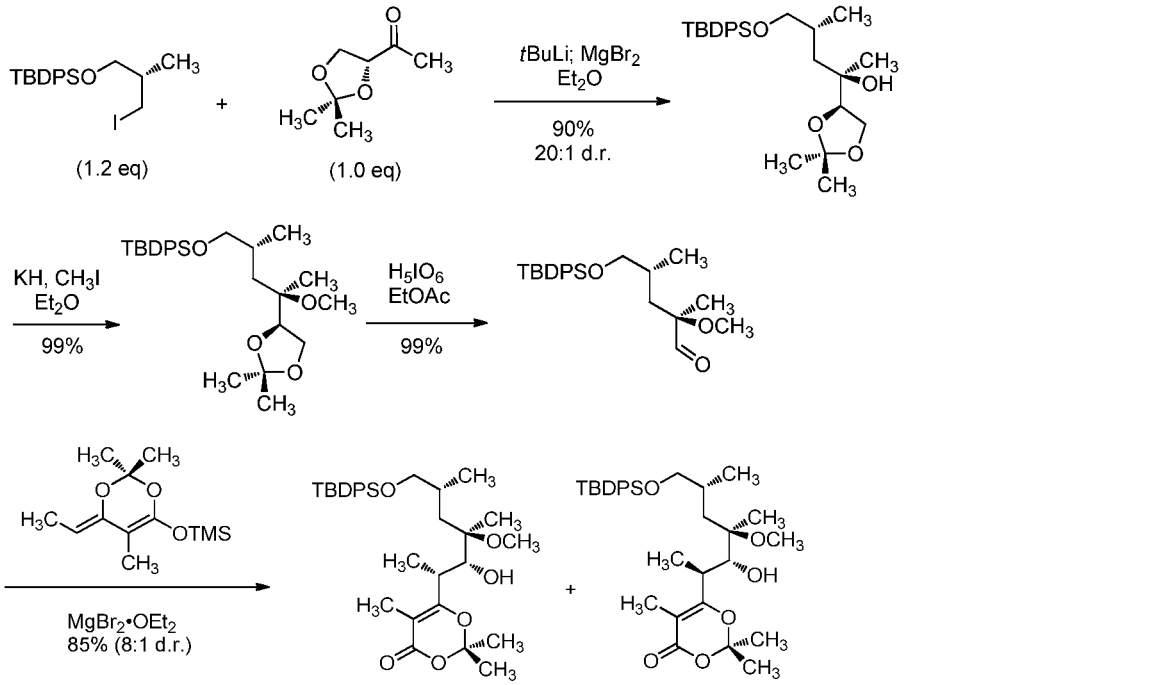
EXAMPLES

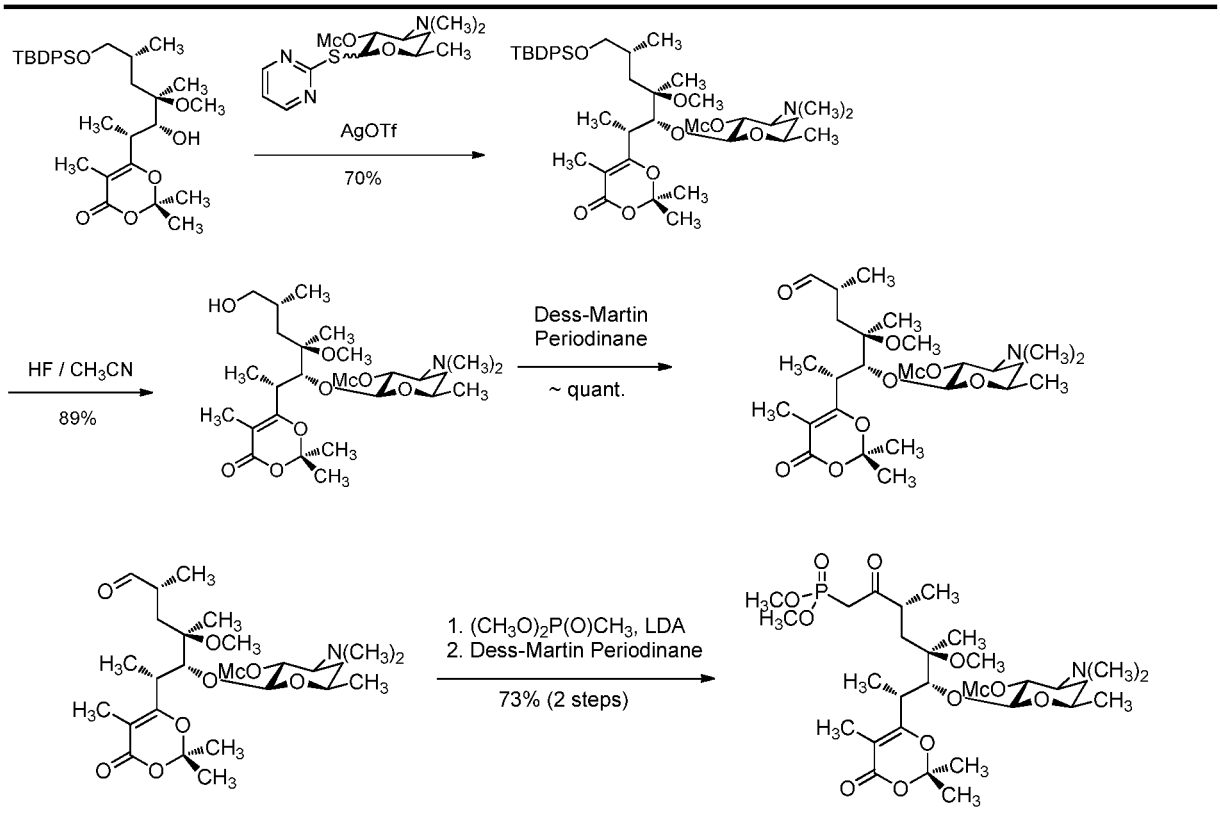
[00557] These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

International Application No. PCT/US2014/033025 is incorporated herein by reference in its entirety.

EXEMPLARY EASTERN HALF SYNTHETIC PROCEDURES

Example 1A. Preparation of Aldehyde and Phosphonate Eastern Halves





Step 1:

[00558] To a solution of (*S*)-*tert*-butyl(3-iodo-2-methylpropoxy)diphenylsilane (74.1 g, 169 mmol) in ether (512 mL) was added *t*-BuLi (1.52 M, 222 mL, 338 mmol) dropwise at –78 °C. The resulting slightly cloudy suspension was stirred for 30min. At this point, TLC(100% hexanes) indicated complete halogen-lithium exchange. A 1.5 M solution of $MgBr_2$ in 3:1 ether:benzene (123 mL, 184 mmol) (Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112,* 5583-5601.) was added dropwise. The resulting suspension was stirred for 30 min at –78 °C and briefly warmed to 0 °C (5 min) to give a clear solution. After cooling back to –78 °C, a solution of (*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (22.15 g, 154 mmol) (Leyes, A. E.; Poulter, C. D. *Org. Lett.* **1999**, *1*, 1067-1070.) in ether (50 mL) was added dropwise to Grignard solution above *via* cannula. The resulting white mixture was stirred for 2 h at –78 °C. TLC (30% ethyl acetate-hexanes) showed complete conversion. The reaction was quenched with half-saturated NH_4Cl solution (300 mL). The layers were partitioned, and the aqueous layer was extracted with ether (3 x 300 mL). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (10-15% ether in hexanes) to give the product as a colorless oil (63.0 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4H), 7.48 – 7.36 (m, 6H), 4.03 – 3.86 (m, 3H), 3.55 (dd, J = 9.8, 5.3 Hz, 1H), 3.44 (dd, J = 9.8, 7.7 Hz, 1H), 3.09 (s, 1H), 2.07 – 1.96 (m, 1H), 1.86 (dd, J = 14.5, 6.3 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.33 (dd, J = 14.4, 4.5 Hz, 1H), 1.14 (s, 3H), 1.08 (s, 9H), 0.91 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.66, 135.61, 133.31, 133.27, 129.68, 127.68, 127.65, 109.17, 82.02, 71.46, 70.08, 65.12, 43.02, 30.83, 26.87, 26.36, 25.39, 22.49, 19.45, 19.16. FTIR (neat), cm^{-1}: 3450 (br), 2957(m), 1369 (s), 1211 (s), 1111 (s), 1066 (s), 823 (s), 738 (s), 702 (s); HRMS (ESI): Calcd for $(C_{27}H_{40}O_4Si + H)^+$: 457.2769; Found: 457.2775.

Step 2:

[00559] To a suspension of KH (35% dispersion in mineral oil, 6.67 g, 49.9 mmol) in ether (83 mL) was added an ether solution (83 mL) of (2*R*,4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpentan-2-ol (19 g, 41.6 mmol) dropwise at 0 °C. The transfer was quantitated with ether (2 x 5 mL). The resulting suspension was stirred for 1h. Methyl iodide (freshly passed through basic alumina, 26.0 mL, 416 mmol) was added and the mixture was warmed to rt. After 2 h, TLC indicated complete reaction. The reaction mixture was slowly poured into 100 mL half-saturated NH_4Cl solution, and diluted with 100 mL ether. The layers were separated, and the aqueous layer was extracted with ether (2 x 50

mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (12% to 20% ether in hexanes) to give the product as a colorless oil. (19.5 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 4H), 7.45 – 7.34 (m, 6H), 4.15 (t, *J* = 7.2 Hz, 1H), 3.91 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.64 (t, *J* = 7.9 Hz, 1H), 3.46 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.40 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.19 (s, 3H), 1.90 – 1.82 (m, 1H), 1.58 (dd, *J* = 14.9, 4.0 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.23 (dd, *J* = 15.0, 7.8 Hz, 1H), 1.11 (s, 3H), 1.06 (d, *J* = 2.8 Hz, 9H), 1.02 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.63, 135.59, 133.87, 129.56, 129.54, 127.59, 109.21, 80.14, 77.12, 69.60, 65.51, 49.92, 36.84, 31.28, 26.90, 26.23, 25.02, 19.26, 18.92, 18.50. FTIR (neat), cm^{-1}: 2957(m), 1471 (s), 1369 (s), 1211 (s), 1155 (s), 1107 (s), 1066 (s), 823 (s), 738 (s), 700 (s); HRMS (ESI): Calcd for $(C_{28}H_{43}O_4Si + H)^+$: 471.2925; Found: 471.2944.

Step 3:

[00560] *tert*-butyl(((2*R*,4*R*)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methoxy-2-methylpentyl)oxy)diphenylsilane (19.5 g, 41.4 mmol) was dissolved in ethyl acetate (138 mL), and then periodic acid (18.89 g, 83 mmol) was added in one portion. The mixture was vigorously stirred for 1 h. The reaction was diluted with hexanes (138 mL). The suspension was passed through a short pad of silica, eluting with 50% ethyl acetate/hexanes (300 mL). The filtrate was concentrated to give the product as a colorless oil (16.8 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.67 (dd, *J* = 7.9, 1.5 Hz, 4H), 7.47 – 7.35 (m, 6H), 3.48 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.41 (dd, *J* = 9.8, 6.2 Hz, 1H), 3.24 (s, 3H), 1.90 – 1.77 (m, 2H), 1.42 (dd, *J* = 14.1, 6.6 Hz, 1H), 1.22 (s, 3H), 1.07 (s, 9H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.68, 135.62, 135.60, 133.80, 133.79, 129.55, 127.59, 82.41, 68.97, 51.51, 37.91, 31.31, 26.88, 19.28, 18.58, 17.69. FTIR (neat), cm^{-1}: 2958(m), 1735 (s), 1427 (s), 1105 (s), 1080 (s), 823 (s), 738 (s), 700 (s); HRMS (ESI): Calcd for $(C_{24}H_{34}O_3Si + H)^+$: 399.2350; Found: 399.2360.

Step 4:

[00561] A solution of (2*R*, 4*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-2-methoxy-2,4-dimethylpentanal (10.5 g, 26.3 mmol) in CH_2Cl_2 (105 mL) was cooled to –10 °C and treated with magnesium bromide diethyl etherate (20.41 g, 79 mmol). The mixture was stirred at this temperature for 10 min, and cooled to –78 °C. (Z)-((4-ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy)trimethylsilane (13.44 mL, 52.7 mmol) was added dropwise to the solution above. The mixture was stirred at –78 °C for 12 h, at which point TLC analysis (30% ethyl acetate / hexanes) indicated full conversion. The reaction was quenched by addition of ether (200 mL) and 1N HCl (100 mL). The layers were separated, and the aqueous layer was

extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL) and dried over $MgSO_4$. The solution was filtered and concentrated *in vacuo*. Two columns were necessary to obtain pure *syn* diastereomer. The first column, eluting with 15:15:70 ether/ethyl acetate/hexanes gave product as an 8:1 diasteromeric mixture. The second column, eluting with 1-3% acetone in dichloromethane, gave the *syn* diastereomer (11.5 g, 77%), followed by *anti* diastereomer (1.2 g, 8%). Major isomer (*syn*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.62 (m, 4H), 7.48 – 7.34 (m, 6H), 3.72 (t, *J* = 5.6 Hz, 1H), 3.47 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.43 (dd, *J* = 9.8, 6.5 Hz, 1H), 2.96 (p, *J* = 6.9 Hz, 1H), 2.42 (d, *J* = 5.7 Hz, 1H), 1.85 (s, 3H), 1.83 – 1.77 (m, 1H), 1.74 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.33 (dd, *J* = 14.2, 7.0 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 168.22, 162.87, 135.59, 135.55, 133.76, 133.72, 129.60, 129.58, 127.61, 104.80, 99.04, 79.57, 73.86, 69.44, 49.08, 36.89, 35.98, 31.44, 26.87, 26.41, 23.62, 19.33, 19.26, 18.90, 14.14, 9.88. FTIR (neat), cm^{-1}: 3500 (br), 2931 (m), 1722 (s), 1637 (s), 1388 (s), 1356 (s), 1111 (s), 1072 (s), 702 (s), 613 (s); HRMS (ESI): Calcd for $(C_{33}H_{45}O_6Si + H)^+$: 569.3293; Found: 569.3304. Minor isomer (*anti*): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.5 Hz, 4H), 7.50 – 7.35 (m, 6H), 3.55 – 3.47 (m, 2H), 3.44 (dd, *J* = 9.8, 6.6 Hz, 1H), 3.10 (s, 3H), 2.94 – 2.88 (m, 1H), 2.59 (d, *J* = 7.5 Hz, 1H), 1.84 (s, 3H), 1.82 – 1.72 (m, 1H), 1.72 – 1.67 (m, 1H), 1.68 (s, 3H), 1.65 (s, 3H), 1.44 (dd, *J* = 14.2, 7.1 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.10 (s, 3H), 1.07 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 168.23, 162.88, 135.60, 135.57, 133.78, 133.74, 129.62, 129.59, 127.62, 104.82, 99.06, 79.58, 73.88, 69.45, 49.09, 36.90, 35.99, 31.46, 26.88, 26.43, 23.63, 19.34, 19.28, 18.91, 14.15, 9.89. FTIR (neat), cm^{-1}: 3483 (br), 2955 (m), 1720 (s), 1639 (s), 1466 (s), 1388 (s), 1359 (s), 1111 (s), 1074 (s), 702 (s), 615 (s); HRMS (ESI): Calcd for $(C_{33}H_{45}O_6Si + H)^+$: 569.3293; Found: 569.3292.

Step 5:

[00562] To a dry 200-mL flask was charged powdered dry 4Å molecular sieves (10.0 g), toluene (41.8 mL) and CH_2Cl_2 (41.8 mL). In a separate flask, a mixture of 6-((2*R*,3*R*,4*R*,6*R*)-7-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-4-methoxy-4,6-dimethylheptan-2-yl)-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (9.5 g, 16.70 mmol) and (2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-6-methyl-2-(pyrimidin-2-ylthio)tetrahydro-2*H*-pyran-3-yl methyl carbonate (16.40 g, 50.1 mmol) (Velvadapu, V.; Andrade, R. B.; Carbohydr. Res. **2008**, *343,* 145-150.) were azeotropically dried from benzene for 3 times. Then the residue was dissolved in CH_2Cl_2 (30 mL). This solution was added to the molecular sieves suspension above *via* cannula. The suspension was cooled to 0 °C, and silver(I) trifluoromethanesulfonate (21.46 g, 84 mmol)

was added in one portion. The mixture was stirred for 1 h at 0 °C. At this point, TLC analysis (50% ethyl acetate in hexanes) indicated full consumption of starting material. The reaction was quenched with saturated aqueous NH_4Cl (10.0 mL), stirred for 5 min, and saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was filtered through a pad of Celite, rinsing with CH_2Cl_2 (100 mL), and the filtrate was washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography (70% ethyl acetate in hexanes) to give the product as a white foam (9.0 g, 70%). ^{1}H NMR (500 MHz, Benzene) δ 7.86 – 7.79 (m, 4H), 7.26 – 7.17 (m, 6H), 4.70 (dd, *J* = 10.4, 7.5 Hz, 1H), 4.65 (d, *J* = 7.5 Hz, 1H), 4.19 (t, *J* = 8.0 Hz, 1H), 3.89 (dt, *J* = 10.5, 5.3 Hz, 1H), 3.59 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.40 (s, 3H), 3.25 – 3.19 (m, 1H), 3.19 – 3.11 (m, 1H), 2.93 (s, 3H), 2.52 (td, *J* = 12.1, 4.5 Hz, 1H), 2.09 (d, *J* = 12.9 Hz, 6H), 2.03 (s, 3H), 1.85 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.62 (dt, *J* = 18.6, 6.1 Hz, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.22 (d, *J* = 8.5 Hz, 3H), 1.20 (s, 9H), 1.18 (d, *J* = 8.5 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.94, 163.00, 155.17, 135.62, 134.26, 134.21, 129.38, 129.36, 127.47, 104.40, 99.83, 99.61, 79.02, 75.52, 69.16, 69.12, 63.11, 54.64, 49.40, 40.70, 36.40, 33.94, 31.12, 30.86, 26.87, 25.68, 24.38, 20.98, 20.20, 19.79, 19.34, 12.86, 9.77. FTIR (neat), cm^{-1}: 2935(m), 1755 (s), 1724 (s), 1641 (s), 1456 (s), 1377 (s), 1265 (s), 1106 (s), 1053 (s), 704 (s), 613 (s); HRMS (ESI): Calcd for $(C_{43}H_{65}NO_{10}Si + H)^+$: 784.4451; Found: 784.4467.

Step 6:

[00563] In a plastic vial, TBDPS-OCH_3-EH (9.0 g, 11.48 mmol) was dissolved in CH_3CN (57.4 mL), and hydrofluoric acid (48% aq, 9.90 mL, 574 mmol) was added with a plastic syringe. The mixture was then stirred at room temperature for 12 h, at which point TLC analysis (10% methanol in ethyl acetate) indicated full consumption of starting material. The reaction solution was slowly added to an Erlenmyer containing saturated aqueous $NaHCO_3$ solution (300 mL). After gas evolution subsided, the mixture was extracted with ether (3 x 100 mL). The organic layers were combined, and extracted with 1 N HCl (3 x 25 mL). The ether layer was discarded. The acid layers were combined, to which solid $NaHCO_3$ was slowly added to adjust pH to 8. This aqueous solution was extracted with CH_2Cl_2 (3 x 100 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered and concentrated to give the product as a white foam (5.58 g, 89%). ^{1}H NMR (500 MHz, Benzene) δ 4.85 (dd, *J* = 10.5, 7.7 Hz, 1H), 4.69 (d, *J* = 7.6 Hz, 1H), 3.96 (d, *J* = 2.9 Hz, 1H), 3.61 (ddd, *J* = 11.3, 7.2, 4.4 Hz, 1H), 3.49 – 3.36 (m, 2H), 3.33 (s, 3H), 3.15 – 3.01 (m, 1H), 2.97 (t, *J* = 6.4 Hz, 1H), 2.73 (s, 3H), 2.56 (td, *J* = 12.0, 4.3 Hz, 1H), 2.11 (s, 6H), 1.87 (s, 3H), 1.86 – 1.81 (m, 1H),

1.74 (dd, J = 14.5, 3.1 Hz, 1H), 1.57 (dd, J = 14.4, 9.1 Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.26 (dd, J = 12.8, 2.9 Hz, 1H), 1.16 (d, J = 7.3 Hz, 3H), 1.11 – 1.04 (m, 1H), 1.02 (d, J = 6.1 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.34, 162.79, 155.25, 104.54, 99.84, 79.79, 76.37, 75.48, 69.27, 68.42, 63.05, 54.71, 49.56, 40.69, 38.69, 33.83, 31.07, 30.83, 25.89, 24.19, 20.99, 19.92, 19.86, 13.00, 9.89. FTIR (neat), cm^{-1}: 3437 (br), 2939 (m), 1753 (s), 1724 (s), 1641 (s), 1454 (s), 1379 (s), 1267 (s), 1109 (s), 1053 (s), 732 (s); HRMS (ESI): Calcd for $(C_{27}H_{47}NO_{10} + H)^+$: 546.3272; Found: 546.3280.

Step 7:

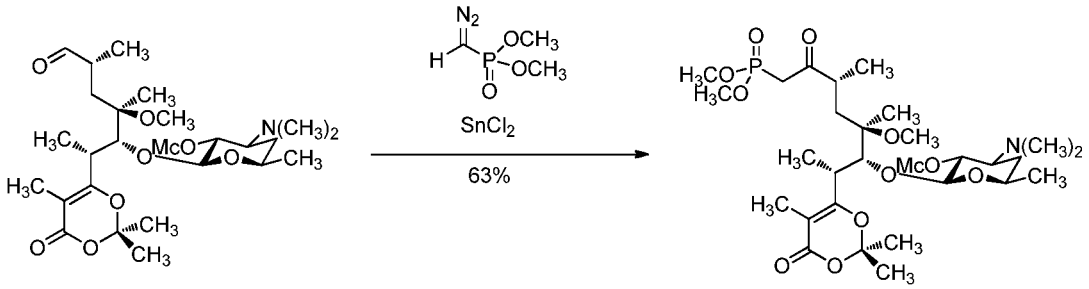
[00564] To a solution of the alcohol (2.1 g, 3.85 mmol) in CH_2Cl_2 (3.85 mL) was added Dess-Martin Periodinane (2.448 g, 5.77 mmol) and water (7.7 μL, 2 μL/mL CH_2Cl_2). The resulting milky suspension was stirred for 0.5 h at rt. The reaction was diluted with ether (50 mL), saturated aqueous $Na_2S_2O_3$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The resulting mixture was vigorously stirred for 30 min, and the layers were separated. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to give the product as a white foam (2.1 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (d, J = 4.7 Hz, 1H), 4.62 – 4.51 (m, 2H), 3.86 (d, J = 3.3 Hz, 1H), 3.78 (s, 3H), 3.51 – 3.40 (m, 1H), 3.37 (qd, J = 7.3, 3.4 Hz, 1H), 2.97 (s, 3H), 2.81 – 2.69 (m, 1H), 2.47 (ddd, J = 10.9, 7.7, 3.9 Hz, 1H), 2.31 (s, 6H), 1.86 (s, 3H), 1.81 (dd, J = 14.0, 11.1 Hz, 1H), 1.77 – 1.73 (m, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 1.58 (dd, J = 14.1, 3.0 Hz, 1H), 1.43 – 1.30 (m, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.25 (s, 3H), 1.07 (d, J = 3.0 Hz, 3H), 1.06 (d, J = 2.6 Hz, 3H). ^{13}C NMR (126 MHz, Benzene) δ 202.57, 166.45, 161.71, 155.83, 104.17, 100.60, 100.46, 78.64, 78.26, 75.43, 69.23, 63.64, 54.18, 49.19, 42.02, 40.51, 37.52, 34.08, 30.22, 25.66, 24.02, 20.84, 20.33, 15.42, 13.14, 10.03. FTIR (neat), cm^{-1}: 2937 (m), 1753 (s), 1724 (s), 1643 (s), 1442 (s), 1377 (s), 1265 (s), 1109 (s), 1053 (s); HRMS (ESI): Calcd for $(C_{27}H_{45}NO_{10} + H)^+$: 544.3116; Found: 544.3139.

Step 8a: Phosphonate preparation

[00565] Lithium diisopropylamide (1.0 M solution in THF, freshly prepared from diisopropylamine and *n*BuLi, 2.415 mL, 2.415 mmol) was charged into a flamed-dried flask. THF (6.9 mL) was added to supplement the volume to 9.3 mL, and the solution was cooled to –78 °C. A solution of dimethyl methylphosphonate (0.262 mL, 2.415 mmol) in THF (1 mL) was added dropwise. The resulting solution was stirred at –78 °C for 15 min. A solution of the aldehyde (1.01g, 1.858 mmol) in THF (9.3 mL) was added dropwise *via* cannula, and the reaction was stirred for 30 min at –78 °C. At this point, TLC (10% methanol in ethyl acetate) indicated full consumption of the aldehyde. The reaction was quenched by addition of

saturated aqueous NH_4Cl solution (10 mL) at –78 °C and diluted with ethyl acetate (10 mL). The mixture was warmed to rt, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude material was dissolved in CH_2Cl_2 (5 mL), and Dess-Martin Periodinane (1.18 g, 2.79 mmol) was added in one batch, followed by water (10 μL, 2 μL/mL CH_2Cl_2). The reaction was stirred at rt for 1 h. At this point, TLC (10% methanol in ethyl acetate) indicated complete conversion to a less polar compound. To the reaction mixture was added Et_2O (20 mL), saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). The mixture was vigorously for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (2-3% methanol in CH_2Cl_2 + 0.2% saturated NH_4OH) to give the product as a white foam (0.90 g, 73%). ^1H NMR (600 MHz, $CDCl_3$) δ 4.57 – 4.46 (m, 2H), 3.84 (d, J = 3.3 Hz, 1H), 3.76 (t, J = 3.7 Hz, 3H), 3.74 (d, J = 2.7 Hz, 3H), 3.74 (s, 3H), 3.42 (dtd, J = 11.9, 5.9, 4.3 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.16 (dd, J = 22.0, 14.7 Hz, 1H), 3.04 (dd, J = 21.0, 14.7 Hz, 1H), 2.94 (s, 3H), 2.84 – 2.76 (m, 1H), 2.76 – 2.66 (m, 1H), 2.27 (s, 6H), 1.92 (dd, J = 14.1, 10.5 Hz, 1H), 1.78 (s, 3H), 1.77 – 1.69 (m, 1H), 1.64 (d, J = 12.4 Hz, 3H), 1.62 (s, 3H), 1.47 – 1.40 (m, 1H), 1.38 – 1.28 (m, 1H), 1.23 (s, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.81 (d, J = 6.2 Hz), 167.20, 162.75, 155.17, 104.39, 99.91, 99.84, 78.41, 76.52, 75.40, 69.23, 62.97, 54.66, 52.75, 52.74, 49.47, 42.19, 42.17, 40.62, 40.37, 39.31, 33.92, 30.75, 25.79, 24.17, 20.92, 19.78, 18.43, 13.04, 9.64. FTIR (neat), cm^{-1}: 2937 (m), 1753 (s), 1716 (s), 1643 (s), 1456 (s), 1377 (s), 1265 (s), 1109 (s), 1053 (s), 731 (s); HRMS (ESI): Calcd for $(C_{30}H_{52}NO_{13}P + H)^+$: 666.3249; Found: 666.3266.

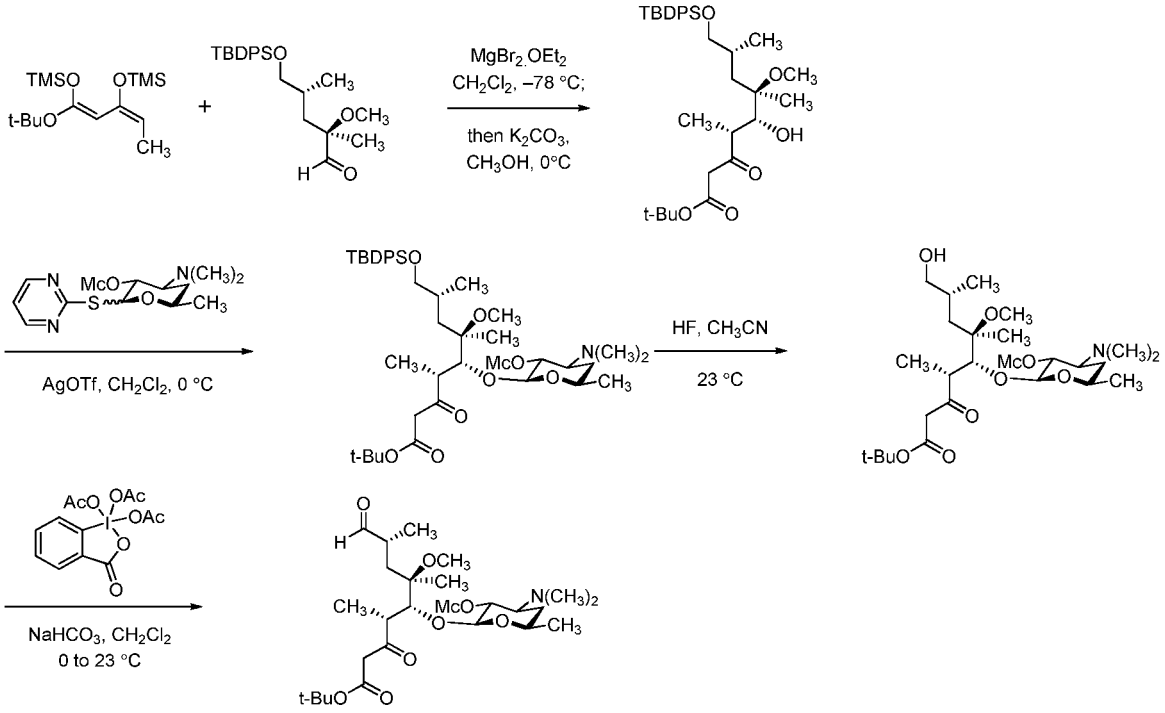
Step 8b: Alternative phosphonate preparation:



[00566] The aldehyde (100 mg, 0.184 mmol) was dissolved in CH_2Cl_2 (2.62 mL), and tin(II) chloride (6.98 mg, 0.037 mmol) was added. The solution was stirred at rt for 5 min, before dimethyl (diazomethyl)phosphonate (55.2 mg, 0.368 mmol) was added *via* syringe. The

reaction was then warmed to 40 °C. After 12 h, TLC (10% methanol in ethyl acetate) indicated full consumption of the aldehyde. The reaction was diluted with ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) and vigorously stirred. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (2-3% methanol in CH_2Cl_2 + 0.2% saturated NH_4OH) to give the product as a white foam (75 mg, 63%).

Example 1B. Eastern Half *without* C2 Methyl via β-keto-t-Butyl Ester



Step 1:

[00567] The aldehyde (575 mg, 1.443 mmol, 1 equiv) was dried by azeotropic distillation (benzene) and then dissolved in dichloromethane (11 mL). Magnesium bromide ethyl etherate (1.86 g, 7.21 mmol, 5.0 equiv) was added in one portion to this solution and the resulting mixture was cooled to –78 °C. A solution of 1,3-bistrimethylsilyl dienol ether (1.37 g, 4.33 mmol, 3.0 equiv, for preparation see: Takai, K.; Nawate, Y.; Okabayashi, T.; Nakatsuji, H.; Iida, A.; Tanabe, Y. *Tetrahedron* **2009**, *65*, 5596–5607) in dichloromethane (1.5 mL) was added dropwise via syringe over 5 min to the aldehyde mixture at –78 °C. The reaction mixture was stirred at this temperature for 3 h, then saturated aqueous ammonium chloride solution (12 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. Water (40 mL) and dichloromethane (50 mL) were added and

the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 50 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude aldol mixture was then dissolved in methanol (12 mL) and the resulting solution was cooled to 0 °C. Potassium carbonate (20 mg, 0.1 equiv) was added in one portion to the crude product solution. After stirring at 0 °C for 6 min, aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 25 mL) was added to the reaction solution. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. Water (25 mL) and dichloromethane (60 mL) were added and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 60 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The product was purified by flash-column chromatography (10% ethyl acetate–hexanes, grading to 12%), providing the aldol product in diastereomerically pure form (490 mg, 60%). A minor aldol diastereomer was isolated separately in diastereomerically pure form (97 mg, 12%). NB – clearly distinguishable peaks corresponding to the enol tautomer of aldol product (<10%) are reported with non-integer integrals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, 4H, J = 7.8, 1.5 Hz), 7.42-7.36 (m, 6H), 4.96 (s, 0.07H), 3.86 (d, 1H, J = 6.3 Hz), 3.53 (dd, 1H, J = 9.8, 5.9 Hz), 3.41 (AB quartet, 2H), 3.40 (dd, 1H, J = 9.8, 5.9 Hz), 3.12 (s, 0.21H), 3.00 (s, 3H), 2.86 (m, 1H), 2.24 (brs, 1H), 1.84-1.78 (m, 1H), 1.63 (dd, 1H, J = 14.2, 4.9 Hz), 1.45 (s, 9H), 1.36 (dd, 1H, J = 14.2, 6.3 Hz), 1.17 (d, 3H, J = 7.3 Hz), 1.09 (s, 3H), 1.06 (s, 9H), 1.02 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 166.6, 135.6, 135.6, 133.9, 129.5, 127.6, 81.5, 79.1, 75.1, 69.4, 49.9, 49.1, 47.0, 36.9, 31.5, 27.9, 26.9, 19.9, 19.2, 19.0, 12.9; FTIR (neat film), 3487 (w), 2932 (w), 1732 (m), 1707 (m), 1107 (s), 1071 (s), 700 (s) cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calcd for $C_{33}H_{50}O_6SiNa$, 593.3269; found, 593.3278.

Step 2:

[00568] A mixture of the aldol product (1.55 g, 2.72 mmol, 1 equiv) and the 2-pyrimidinylthio glycoside (1.78 g, 5.43 mmol, 2.0 equiv) was dried by azeotropic distillation (benzene, 2 x 20 mL). The dried mixture was dissolved in dichloromethane (4.0 mL) and transferred via syringe to a flask containing a mixture of toluene (6.5 mL), dichloromethane (3.0 mL) and activated 4Å molecular sieves (1.5 g). An additional portion of dichloromethane (1.0 mL) was used to ensure complete transfer into the reaction flask. The resulting mixture was stirred at 23 °C for 15 min, then was cooled to 0 °C. Silver (I) trifluoromethanesulfonate (4.19 g, 16.3 mmol, 6.0 equiv) was added in one portion to the ice-cold, stirring reaction

mixture. After stirring at 0 °C for 90 min, the reaction mixture was diluted with dichloromethane (10 mL) and then quenched by sequential dropwise addition of saturated aqueous ammonium chloride solution (1.5 mL) and saturated aqueous sodium bicarbonate solution (2.5 mL). The resulting mixture was allowed to warm to 23 °C, then was filtered through a thick pad of Celite. The Celite pad was washed with dichloromethane (100 mL) and the resulting filtrate was concentrated, providing an orange-brown foam. The crude product was purified by flash-column chromatography (40% ethyl acetate–hexanes, grading to 70%), affording the glycosylated product ** as a white foam (1.09 g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 4H, J = 6.3 Hz), 7.42-7.34 (m, 6H), 4.52 (dd, 1H, J = 10.2, 7.8 Hz), 4.40 (d, 1H, J = 7.8 Hz), 3.95 (d, 1H, J = 7.8 Hz), 3.75 (s, 3H), 3.67 (dd, 1H, J = 9.8, 4.4 Hz), 3.52-3.46 (m, 1H), 3.35-3.32 (m, 1H), 3.34 (AB quartet, 2H), 3.03-2.97 (m, 1H), 2.78 (s, 3H), 2.78-2.71 (m, 1H), 2.28 (s, 6H), 1.89-1.82 (m, 1H), 1.74 (brd, 1H), 1.43 (s, 9H), 1.35-1.30 (m, 2H), 1.26-1.23 (m, 1H), 1.22 (d, 3H, J = 6.3 Hz), 1.14 (s, 3H), 1.12 (d, 3H, J = 7.3 Hz), 1.06 (s, 9H), 1.04 (d, 3H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 166.7, 155.1, 135.6, 134.2, 134.2, 129.4, 127.5, 101.2, 81.3, 80.8, 78.8, 75.5, 69.3, 69.0, 63.1, 54.7, 50.6, 49.4, 46.2, 40.7, 37.4, 31.4, 30.6, 28.0, 26.9, 20.9, 20.0, 19.6, 19.3, 13.7; FTIR (neat film), 2932 (w), 1755 (m), 1709 (w), 1263 (s), 1055 (s), 702 (s) cm^{-1}; HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_{43}H_{68}NO_{10}Si$, 786.4607; found, 786.4619.

Step 3:

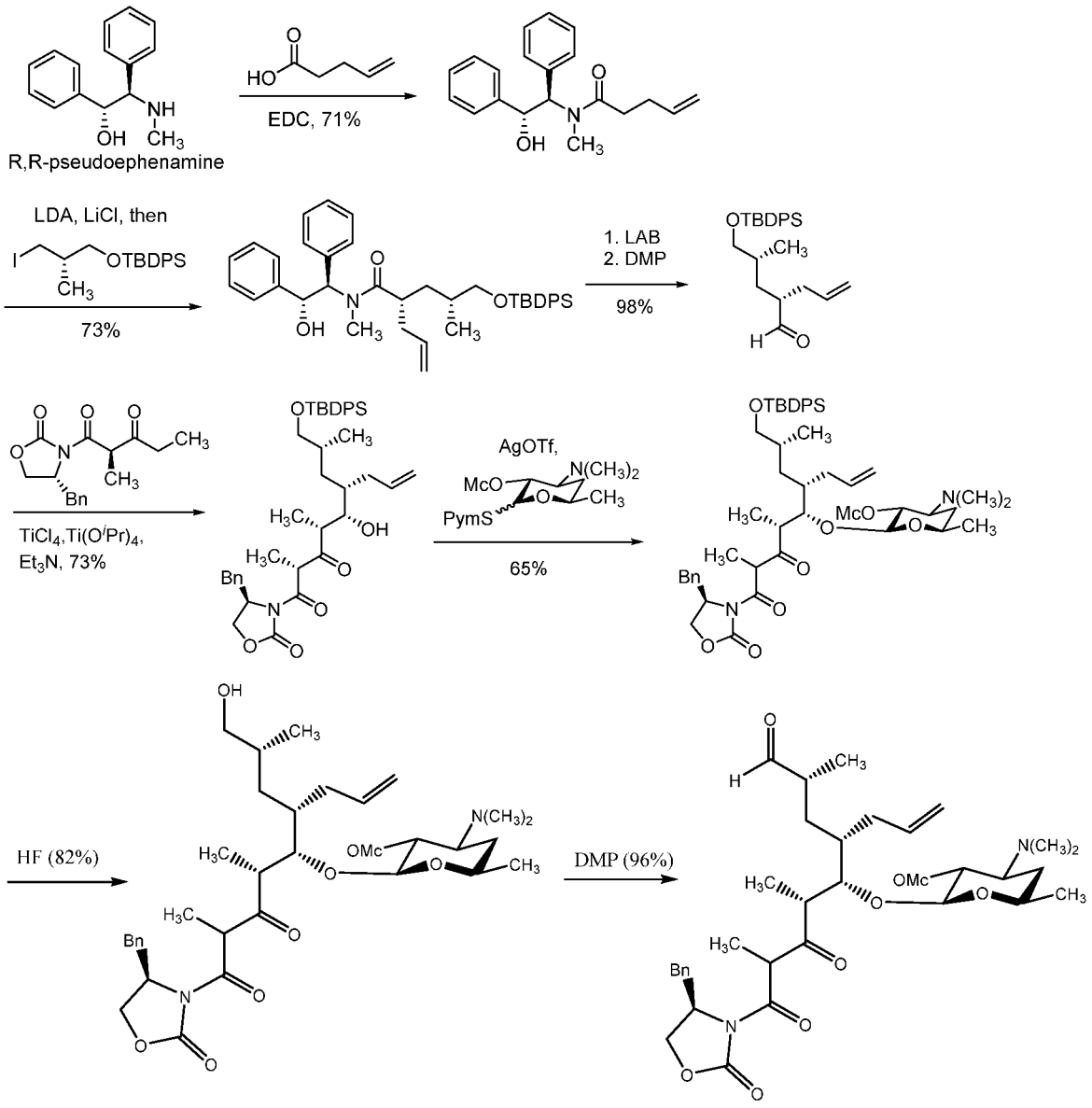
[00569] Concentrated aqueous hydrofluoric acid solution (48%, 2.00 mL, 50.9 mmol, 40 equiv) was added dropwise via syringe to a solution of the glycosylated product (1.00 g, 1.27 mmol, 1 equiv) in acetonitrile (12 mL) in a polypropylene reaction vessel at 23 °C. The reaction solution was stirred vigorously at 23 °C for 15 h, then was added dropwise via plastic pipette to an ice-cold solution of saturated aqueous sodium bicarbonate (60 mL). The resulting mixture was extracted with ethyl acetate (3 x 60 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The crude product was purified by flash column chromatography (65% ethyl acetate–hexanes, grading to 75%), affording the deprotection product as a white foam (435 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (dd, 1H, J = 10.7, 7.8 Hz), 4.42 (d, 1H, J = 7.8 Hz), 4.09 (d, 1H, J = 7.8 Hz), 3.76 (s, 3H), 3.57-3.48 (m, 2H), 3.43 (s, 2H), 3.29-3.23 (m, 2H), 3.10-3.05 (m, 1H), 2.98 (s, 3H), 2.75-2.70 (m, 1H), 2.26 (s, 6H), 1.85-1.80 (brm, 1H), 1.73 (dd, 1H, J = 12.7, 2.4 Hz), 1.55-1.45 (m, 2H), 1.45 (s, 9H), 1.35-1.28 (m, 1H), 1.27 (s, 3H), 1.22 (d, 3H, J = 5.9 Hz), 1.14 (d, 3H, J = 7.3 Hz), 0.92 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 166.5, 155.2,

101.2, 81.6, 79.7, 79.5, 75.5, 69.1, 68.2, 62.9, 54.7, 50.4, 49.7, 46.1, 40.6, 38.7, 31.1, 30.6, 27.9, 20.9, 20.0, 19.7, 13.8; FTIR (neat film), 2936 (w), 1751 (m), 1709 (m), 1263 (s), 1051 (s) cm^{-1}; HRMS–ESI (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{50}NO_{10}$, 548.3429; found, 548.3435.

Step 4:

[00570] Sodium bicarbonate (557 mg, 6.63 mmol, 10 equiv) and Dess–Martin periodinane (618 mg, 1.46 mmol, 2.2 equiv) were added sequentially to a stirring solution of the alcohol (363 mg, 0.663 mmol, 1 equiv) in dichloromethane (10 mL) and water (20 μL) at 0 °C. The resulting mixture was allowed to warm to 23 °C. After stirring at this temperature for 1 h, the reaction mixture was diluted with diethyl ether (30 mL). Saturated aqueous sodium thiosulfate solution (15 mL), saturated aqueous sodium bicarbonate solution (7 mL) and saturated aqueous sodium chloride solution (7 ml) were added in sequence, and the resulting mixture was stirred vigorously for 10 min. The phases were then separated and the aqueous phase was extracted with diethyl ethyl (3 x 30 mL). The organic extracts were combined and the combined solution was washed sequentially with saturated aqueous sodium thiosulfate solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The resulting organic solution was then dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The resulting yellow solid was used directly in the next step (reductive amination) without further purification (crude aldehyde >90% pure by ^1H NMR analysis). ^1H NMR (500 MHz, $CDCl_3$) δ 9.33 (d, 1H, J = 4.9 Hz), 4.52 (dd, 1H, J = 10.7, 7.8 Hz), 4.43 (d, 1H, J = 7.8 Hz), 4.01 (d, 1H, J = 8.8 Hz), 3.78 (s, 3H), 3.52-3.46 (m, 1H), 3.41 (AB quartet, 2H), 3.10-3.05 (m, 1H), 2.83 (s, 3H), 2.77-2.71 (m, 1H), 2.48-2.43 (m, 1H), 2.30-2.27 (m, 1H), 2.27 (s, 6H), 1.91 (dd, 1H, J = 14.6, 11.2 Hz), 1.76-1.72 (m, 1H), 1.60 (dd, 1H, J = 14.6, 3.4 Hz), 1.47 (s, 9H), 1.37-1.28 (m, 2H), 1.25 (s, 3H), 1.22 (d, 3H, J = 5.9 Hz), 1.16 (d, 3H, J = 7.3 Hz), 1.06 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 204.1, 166.6, 155.2, 101.3, 81.5, 81.1, 78.3, 75.4, 69.1, 63.0, 54.7, 50.6, 49.5, 46.0, 41.9, 40.5, 38.0, 30.5, 27.9, 20.8, 19.9, 15.5, 13.8; FTIR (neat film), 2974 (w), 1753 (m), 1724 (m), 1711 (m), 1263 (s), 1053 (m) cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calcd for $C_{27}H_{47}NNaO_{10}$, 568.3092; found, 568.3094.

Example 1C. Synthesis of C6 Allyl Derivatives



Step 1:

[00571] To a solution of Hunig's Base (10.48 ml, 60.0 mmol) in DMF (22 mL) cooled in an ice-water bath was added pent-4-enoic acid (2.041 ml, 20.00 mmol), HOBT (3.06 g, 20.00 mmol), and EDC (4.22 g, 22.00 mmol) sequentially. The solution was stirred at 0 °C for 5 minutes, and remains a light orange slurry throughout this time. (*R*,*R*)-pseudoephenamine (5g, 22.00 mmol) (freshly crushed) was added in one portion, and the vessel was allowed to warm to 23 °C. After 5 minutes, some product was visible by TLC (10% MeOH/DCM, +1% NH4OH). After 20 minutes, the solution was completely homogeneous. After 1 h, conversion was >50%. At 19 h, progress had not changed. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 x 75 mL). The organic layers were combined and the

resulting light yellow solution was washed with water (2 x 100 mL), sat aq NaCl (1 x 75 mL), dried through a pad of sodium sulfate, and concentrated. The product was purified by flash chromatography (30% to 50% ethyl acetate to hexane) affording *N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpent-4-enamide (5.32g, 17.19 mmol, 86 % yield).

Step 2:

[00572] Lithium chloride (3.29 g, 78 mmol) was added to a 200-mL round-bottom flask equipped with a stir bar, and the whole was exposed to a gentle flame under vacuum (0.1 mmHg) for 2 minutes. The vessel and its contents were allowed to cool to 23 °C, and THF (25 mL) and diisopropylamine (4.16 ml, 29.2 mmol) were added. The vessel was cooled to –78 °C, and BuLi (12.06 ml, 28.6 mmol) was added dropwise. The solution was allowed to warm to 0 °C, was stirred for 5 minutes at this temperature, and was re-cooled to –78 °C. A solution of (*R*,*R*)-pseudoephenamine pent-4-enamide (4g, 12.93 mmol) in tetrahydrofuran (20 mL + 5 mL wash) was added dropwise *via* cannula, and the mixture was stirred for 30 min at –78 °C, was allowed to warm to 23 °C and was stirred for 5 minutes at this temperature. A solution of (*S*)-*tert*-butyl(3-iodo-2-methylpropoxy)diphenylsilane (6.80 g, 15.51 mmol) in THF (10 mL) was added, and the transfer was quantitated with THF (2 x 2.5 mL). After 3 h, conversion was <50% . After 41 h,

half-sat. aq. ammonium chloride (200 mL) was added, and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried through a pad of sodium sulfate, and concentrated. The product was purified by column chromatography (20% to 25% ethyl acetate to hexanes) affording (*S*)-2-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpent-4-enamide (5.86 g, 9.45 mmol, 73.1 % yield).

Step 3:

[00573] BuLi (12.61 ml, 29.9 mmol) was added by syringe to a stirring solution of diisopropylamine (4.59 ml, 32.2 mmol) in THF (32 mL) at –78 °C. The vessel was transferred to an ice-water bath and was allowed to warm to 0 °C. Borane-ammonia complex (1.051 g, 30.6 mmol) was added as a single portion, and a vigorous evolution of gas was observed. The mixture was stirred for 3 minutes at 0 °C, and was then allowed to warm to 23 °C, and was stirred for 15 minutes at this temperature. The vessel was re-cooled to 0 °C, and a solution of (*S*)-2-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpent-4-enamide (4.75 g, 7.66 mmol) in THF (32 mL + 5 mL wash) was added by cannula. The reaction vessel was then allowed to warm to 23 °C (11:50 AM). After 3 h, the starting material had been completely consumed. The vessel was cooled in an

ice-water bath, and 3 M hydrochloric acid (90 mL) was added carefully with vigorous stirring. The mixture was stirred at 0-10 °C for 30 minutes, and was then extracted with ether (4 x 100 mL). The combined ether extracts were washed with 3 M HCl (100 mL), 2 M NaOH (100 mL), sat aq NaCl (100 mL). The washed organic solution was dried over sodium sulfate and filtered, and the filtrate was concentrated. The first acidic, aqueous layer was treated with 2 M NaOH (~200 mL) until pH 14, and the resulting suspension was extracted with dichloromethane (2 x 150 mL) to recover pseudoephenamine ((1*R*,2*R*)-2-(methylamino)-1,2-diphenylethanol (1.61 g, 7.08 mmol, 92 % yield). The crude product was purifed by column chromatography (25% ether to hexanes) affording (*S*)-2-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)pent-4-en-1-ol (2.99g, 7.54 mmol, 98 % yield).

[00574] To a solution of (*S*)-2-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)pent-4-en-1-ol (1 g, 2.52 mmol) in dichloromethane (25 mL, 0.1 M) was added water (0.045 ml, 2.52 mmol), and the mixture was stirred vigorously. The vessel was immersed in a 23 °C water bath, and DMP (2.139 g, 5.04 mmol) was added. After 10 minutes, sat. aq. sodium bicarbonate (15 mL) and sat. aq. sodium thiosulfate (15 mL) were added to the reaction mixture, and the resulting biphasic, cloudy solution was stirred rapidly until each layer was homogeneous (~30 minutes). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were filtered through sodium sulfate, and the filtrate was concentrated. The crude product was purified by column chromatography (5% ether to hexanes) affording the product (~850 mg).

Step 4:

[00575] Dichloromethane (3.5 mL, starting concentration of keto-imide 0.2 M, final concentration 0.1 M) was added to a flame-dried 25-mL round-bottom flask equipped with a magnetic stir bar. The vessel was cooled to 0 °C, and $TiCl_4$ (535 µl, 0.535 mmol) (DCM solution) was added, followed by titanium (IV) tetraisopropoxide (52.1 µl, 0.178 mmol). The mixture was stirred for 15 minutes at this temperature, at which time a solution of (*R*)-1-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-2-methylpentane-1,3-dione (200mg, 0.691 mmol) in DCM (1.2 mL + 0.6 mL wash) was added. To the resulting yellow solution was added triethylamine (103 µl, 0.737 mmol), resulting in a dark red solution. Stirring was continued at 0 °C for 1 h, at which point the vessel was cooled in a dry ice/acetone bath to –78 °C, and a solution of (*S*)-2-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)pent-4-enal (182 mg, 0.461 mmol) in DCM (1.2 mL + 0.6 mL wash) was added dropwise. After 2 h, sat. aq. ammonium chloride was added (10 mL), and the mixture was allowed to warm to ambient temp with vigorous stirring. The layers were separated and the aqueous layer was extracted with DCM (2 x 10

mL). The organic layers were combined and the resulting solution was filtered through a pad of sodium sulfate, and the creamy filtrate was concentrated. The crude product was purified by column chromatography (33% to 40% ether to hexanes first column, DCM then 5% ether to DCM second column) affording the product (2*R*,4*R*,5*S*,6*S*)-1-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-6-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)-5-hydroxy-2,4-dimethylnon-8-ene-1,3-dione (229mg, >10:1 dr, 0.335 mmol, 72.7 % yield).

Step 5:

[00576] A solution of (2*R*,4*R*,5*S*,6*S*)-1-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-6-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)-5-hydroxy-2,4-dimethylnon-8-ene-1,3-dione (50mg, 0.073 mmol) in benzene (2.5 mL) was added to a 10-mL round-bottom flask containing activated desosmaine (47.9 mg, 0.146 mmol), and the resulting solution was evaporated under reduced pressure. The residue was exposed to high vacuum (0.1 Torr) for 10 minutes, and the vessel was back-filled with argon, equipped with a stir bar and a septum. 4Å molecular sieves were added, followed by toluene (244 µl) and CH_2Cl_2 (244 µl). The solution was cooled to 0 °C, and silver(I) trifluoromethanesulfonate (65.7 mg, 0.256 mmol) was added as a single portion. The resulting suspension changes visibly from a grainy precipitate to a fine powdery precipitate within the first 5 minutes. After 1.5 h, dichloromethane (2 mL) was added, followed by sat. aq. NH_4Cl (2 mL). The layers were mixed vigorously for 5 minutes, and sat. aq. sodium bicarbonate (5 mL) was added, and the layers were mixed vigorously. The resulting emulsion was filtered through a sintered-glass funnel, and the resulting biphasic mixture was mixed vigorously and separated. The aqueous layer was extracted with dichloromethane (5 mL), and the organic phases were combined, and the resulting solution was dried through a pad of sodium sulfate. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (100% ethyl acetate) to afford the product (2*S*,3*R*,4*S*,6*R*)-2-(((4*S*,5*S*,6*R*,8*R*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)-6,8-dimethyl-7,9-dioxonon-1-en-5-yl)oxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl methyl carbonate (43mg, 0.048 mmol, 65.4 % yield).

Step 6:

[00577] HF (80 µl, 2.224 mmol) (48% aqueous) was added to a solution of (2*S*,3*R*,4*S*,6*R*)-2-(((4*S*,5*S*,6*R*,8*R*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4-((*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropyl)-6,8-dimethyl-7,9-dioxonon-1-en-5-yl)oxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl methyl carbonate (40mg, 0.044 mmol) in acetonitrile (445 µl) in a teflon tube at room temperature. After 20 h, the mixture was

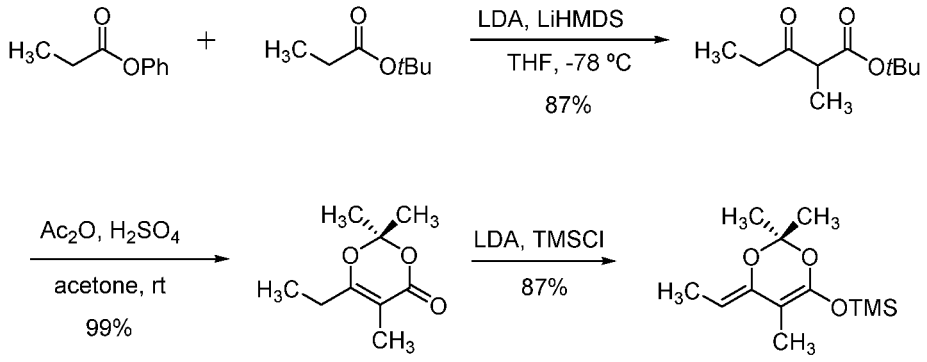
quenched carefully with sat. aq. sodium bicarbonate (3 mL), and was stirred vigorously until all bubbling ceased. The suspension was extracted with ether (3 x 2 mL). The organic layers were combined, and the resulting organic solution was extracted with 1 M HCl (2 x 1 mL). The acidic aqueous layer was basified with sat. aq. sodium bicarbonate (~5 mL), and the resulting suspension was extracted with dichloromethane (3 x 2 mL). The dichloromethane extracts were combined and the resulting clear, colorless solution was filtered through a pad of sodium sulfate. The filtrate was concentrated under reduced pressure to provide the product (2*S*,3*R*,4*S*,6*R*)-2-(((4*S*,5*S*,6*R*,8*R*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4-((*R*)-3-hydroxy-2-methylpropyl)-6,8-dimethyl-7,9-dioxonon-1-en-5-yl)oxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl methyl carbonate as a colorless oil (24mg, 0.036 mmol, 82 % yield).

Step 7:

[00578] DMP (32.1 mg, 0.076 mmol) was added to a solution of (2*S*,3*R*,4*S*,6*R*)-2-(((4*S*,5*S*,6*R*,8*R*)-9-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-4-((*R*)-3-hydroxy-2-methylpropyl)-6,8-dimethyl-7,9-dioxonon-1-en-5-yl)oxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl methyl carbonate (25 mg, 0.038 mmol) in water-saturated dichloromethane (0.5 mL) in a 5-mL round-bottom flask that was immersed in a room-temperature water bath. After 15 minutes, LCMS indicated complete conversion to a peak of the desired mass. DCM (1 mL), sat aq sodium bicarbonate (1 mL), and sat sodium thiosulfate (1 mL) were added, and the solution was stirred vigorously for 10 minutes. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 1 mL). The organic layers were combined and the resulting solution was filtered through a pad of sodium sulfate. The filtrate was concentrated to provide C6-allyl Evans Right Half aldehyde (24mg, 0.036 mmol, 96 % yield).

Example 1D. Synthesis of Eastern Half Building Blocks

(*Z*)-((4-ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy)trimethylsilane:



Step 1: Phenyl propionate

[00579] Phenol (25 g, 266 mmol) and propionyl chloride (70 mL, 797 mmol) were added to a solution of trifluoromethanesulfonic acid (5.88 mL, 66.4 mmol) in acetonitrile (1 L) at 0 °C. The resulting mixture was stirred at rt for 2 h. An ice water (1 L) and diethyl ether (500 mL) were added to the mixture. The organic layer was separated and the organic layer was washed with 1 M hydrogen chloride (1 L), saturated sodium bicarbonate aqueous solution (1 L), brine (1 L), dried over sodium sulfate and concentrated under reduced pressure. The residue was passed through a column of silica (*n*-pentane/diethyl ether, 10:1) to provide phenyl propionate (35.9 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.38 (t, 2H, J = 7.8 Hz, CH of Ph), 7.22 (t, 1H, J = 7.8 Hz, CH of Ph), 7.08 (d, 2H, J = 7.8 Hz, CH of Ph), 2.60 (q, 2H, J = 7.6 Hz, CH_2), 1.27 (t, 3H, J = 7.6 Hz, CH_3).

Step 2: *tert*-Butyl 2-methyl-3-oxopentanoate

[00580] A 2.58 M solution of *n*-butyllithium in hexane (71.0 mL, 183 mmol) and a 2.41 M solution of *n*-butyllithium in hexane (33.2 mL, 80 mmol) was added dropwise to a solution of hexamethyldisilazane (58.4 mL, 275 mmol) in THF (160 mL) at 0 °C and the mixture was stirred at 0 °C for 45 min to prepare lithium hexamethyldisilazide (as a hexane and THF solution). A 2.42 M solution of *n*-butyllithium in hexane (69.0 mL, 167 mmol) and a 2.41 M solution of *n*-butyllithium in hexane (37.8 mL, 91 mmol) were added dropwise to a solution of diisopropylamine (36.3 mL, 258 mmol) in THF (160 mL) at –78 °C. The resulting mixture was warmed to 0 °C, stirred for 10 min and recooled to –78 °C. A solution of *tert*-butyl propionate (32.5 g, 250 mmol) in THF (90 mL + 35 mL × 2 wash) was added to the above lithiumdiisopropylamide solution. The resulting mixture was stirred at –78 °C for 15 min. A freshly prepared solution of lithium hexamethyldisilazide in hexane and THF (323 mL, 30 mL × 2 wash with THF) was added and then after 5 min a solution of phenyl propionate (39.4 g, 263 mmol) in THF (50 mL + 25 mL × 2 wash) was added to the reaction mixture at –78 °C.

The resulting mixture was stirred at –78 °C. After 1 h, saturated ammonium chloride aqueous solution (150 mL) at –78 °C. Diethyl ether (300 mL) and water (600 mL) were added to the mixture at rt. The organic layer was separated and washed with saturated sodium bicarbonate aqueous solution (2 × 300 mL), brine (300 mL) and dried over sodium sulfate. The aqueous layer was extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with a saturated $NaHCO_3$ aqueous solution (2 × 300 mL), brine (300 mL) and dried over sodium sulfate. The organic extracts were concentrated under reduced pressure. The residue was passed through a column of silica (*n*-pentane/diethyl ether, 40:1 ~ 2:1) to provide a mixture of phenyl propionate, *tert*-butyl 2-methyl-3-oxopentanoate and phenol. 1 M sodium hydroxide aqueous solution (500 mL) was added to a solution of the mixture in diethyl ether (250 mL) and the resulting solution was stirred at rt for 1.5 h. The organic layer was separated and washed with 1 M sodium hydroxide aqueous solution (250 mL), water (250 mL), brine (250 mL) and dried over sodium sulfate. The organic extract was concentrated under reduced pressure to provide *tert*-butyl 2-methyl-3-oxopentanoate (40.4 g, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 3.42 (q, 2H, *J* = 7.3 Hz, CH_2 of Et), 2.64–2.46 (m, 1H, CH), 1.45 (s, 9H, $(CH_3)_3$), 1.29 (d, *J* = 6.6 Hz, CH_3 of Me), 1.08 (t, 3H, *J* = 7.3 Hz, CH_3 of Et).

Step 3: 6-Ethyl-2,2,5-trimethyl-4H-1,3-dioxin-4-one

[00581] Acetic anhydride (55.3 mL, 586 mmol) and sulfuric acid (10.4 mL, 195 mmol) were added to a mixture of *tert*-butyl 2-methyl-3-oxopentanoate (36.4 g, 195 mmol) and acetone (28.7 mL, 391 mmol) at 0 °C and the resulting mixture was stirred at rt for 5 h. The reaction mixture was diluted in diethyl ether (1 L) and saturated sodium bicarbonate aqueous solution (1.6 L). The mixture was stirred at rt for 2 h. The organic layer was separated and washed with saturated sodium bicarbonate aqueous solution (1 L × 2), brine (1 L) and dried over sodium sulfate and concentrated under reduced pressure to provide 6-ethyl-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (32.8 g, 99%) as a colorless oil. The product was purified by distillation under reduced pressure (70 °C, 520 mTorr). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.30 (q, 2H, *J* = 7.6 Hz, CH_2 of Et), 1.82 (s, 3H, CH_3 of 5-Me), 1.65 (s, 6H, $(CH_3)_2$ of 2-Me), 1.12 (t, 3H, *J* = 7.6 Hz, CH_3 of Et).

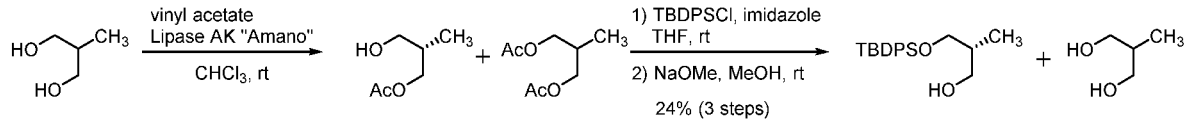
Step 4: (*Z*)-((4-ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy)trimethylsilane:

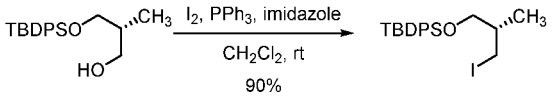
[00582] To a solution of diisopropylamine(25.1 mL, 176 mmol) in THF (210 mL) at –78 °C was added *n*BuLi (76 mL, 2.32 M in hexanes, 176 mmol) dropwise. The resulting solution was warmed to 0 °C and stirred for 15 min. The solution was cooled to –78 °C, and a solution of 6-ethyl-2,2,5-trimethyl-4H-1,3-dioxin-4-one in THF (50 mL + 6 mL-rinse) was added

dropwise *via* cannula. After stirring for 1 h at –78 °C, freshly distilled TMSCl was added dropwise and the mixture was stirred for 3 h at –78 °C. The mixture was warmed to r.t. and the solvent was removed under reduced pressure. The residue was diluted with dry pentane (100 mL) and filtered. The filtrate was concentrated. Crude material was purified by vacuum distillation. (~200mTorr, 63-67 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (q, J = 6.9 Hz, 1H), 1.66 (d, J = 6.9 Hz, 3H), 1.63 (s, 3H), 1.52 (s, 6H), 0.24 (s, 9H).

Example 1E. Synthesis of Eastern Half Building Blocks

(S)-*tert*-Butyldiphenylsiloxy-3-iodo-2-methylpropane:





Step 1: (*R*)-3-*tert*-Butyldiphenylsiloxy-2-methylpropan-1-ol

[00583] Vinyl acetate (286 mL, 3.11 mol) and lipase-AK "Amano" (17.1 g) were added to a solution of 2-methyl-1,3-propanediol (70 g, 777 mmol) in chloroform (1.5 L). The resulting mixture was stirred at rt for 20 h. The lipase was removed by filtration and washed with ethyl acetate. Then the filtrate was concentrated to provide a mixture of (*S*)-3-hydroxy-2-methylpropyl acetate (>99% ee) and 1,3-diacetoxy-2-methylpropane. The mixture was used in the next reaction step without separation. *tert*-Butyldiphenylsilylchloride (79 mL, 303 mmol) was added dropwise to a mixture of (*S*)-3-hydroxy-2-methylpropyl acetate and 1,3-diacetoxy-2-methylpropane (140 g, crude) and imidazole (41.3 g) in THF (620 mL). The resulting mixture was stirred at rt for 21 h. The reaction mixture was diluted with diethyl ether (1 L) and washed water (2 × 1 L) and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. A 25% solution of sodium methoxide in methanol (61 mL) was added to a solution of a mixture of (*R*)-3-*tert*-butyldiphenylsiloxy-2-methylpropyl acetate and 1,3-diacetoxy-2-methylpropane (194 mg, crude) in methanol (1 L) at 0 °C. The resulting mixture was stirred at rt for 24 h. The reaction mixture was diluted with diethyl ether (1 L) and *n*-pentane (1 L), washed with saturated ammonium chloride aqueous solution (1 L), water (2 × 1 L) and brine (1 L). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was passed through a column of silica (*n*-hexane/diethyl ether, 40:1 ~ 20:1 ~ 4:1) to provide (*R*)-3-*tert*-butyldiphenylsiloxy-2-methylpropan-1-ol (60.9 g) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.69–7.67 (m,

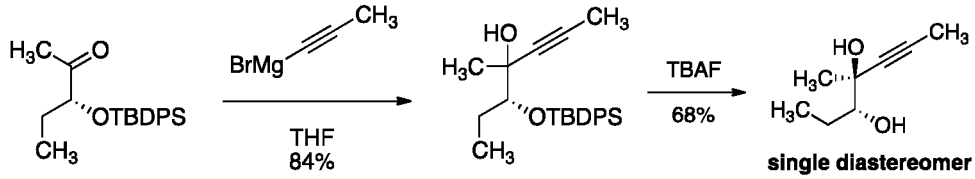
4H, CH of Ph), 7.46–7.38 (m, 6H, CH of Ph), 3.75–3.57 (m, 4H, $CH_2OTBDPS$, CH_2OH), 2.03–1.96 (m, 1H, $CH_2CH(CH_3)CH_2$), 1.06 (s, 9H, $(CH_3)_3$), 0.83 (d, 3H, J = 10.8 Hz, $CH_2CH(CH_3)CH_2$)

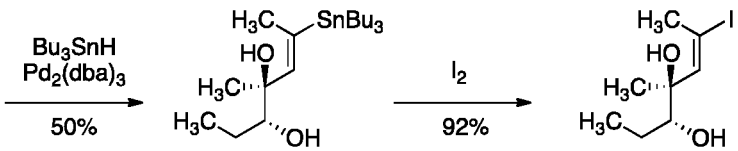
Step 2: (S)-*tert*-Butyldiphenylsiloxy-3-iodo-2-methylpropane

[00584] Imidazole (12.4 g, 183 mmol, 2 equiv) and iodine (23.2 g, 91 mmol, 1 equiv) were added to a stirred solution of triphenylphosphine (24.0 g, 91 mmol, 1 equiv) in dichloromethane (180 mL). A solution of (*R*)-3-*tert*-butyldiphenylsiloxy-2-methylpropan-1-ol (30.0 g, 91 mmol) in dicholomethane (60 mL) was added to the reaction mixture at 0 °C. The resulting mixture was stirred at rt for 5 h. A small amount of iodine was added to "titrate" triphenylphosphine, until the color of the reaction mixture is slightly yellow. The solvent was removed under reduced pressure. Siliga gel (75 g) and hexane (300 mL) were added to the residue. The suspension was stirred for 20 min to absorb triphenylphosphine oxide and salts on silica. Then the mixture was filtered through a short pad of silica (*n*-hexane/diethyl ether, 95:5) to provide (S)-*tert*-butyldiphenylsiloxy-3-iodo-2-methylpropane (35.9 g, 90%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.69–7.65 (m, 4H, CH of Ph), 7.46–7.36 (m, 6H, CH of Ph), 3.61–3.31 (m, 4H, CH_2O, CH_2I), 1.78–1.68 (m, 1H, $CH_2CH(CH_3)CH_2$), 1.06 (s, 9H, $(CH_3)_3$), 0.96 (d, 3H, J = 10.2 Hz, $CH_2CH(CH_3)CH_2$).

EXEMPLARY WESTERN HALF SYNTHETIC PROCEDURES

Example 2A. Preparation of Western Half Building Blocks





Step 1:

[00585] 1-propynylmagnesium bromide (Sigma) (21.14 ml, 10.57 mmol) (0.5 M) was added dropwise over 6 minutes to a solution of (R)-3-((tert-butyldiphenylsilyl)oxy)pentan-2-one (2.4 g, 7.05 mmol) in Tetrahydrofuran (28.2 ml) at 0 °C. Five minutes after the addition, TLC (eluted in 10% ether/hexanes) indicated ~30% conversion to a more polar spot. After 1 h, conversion was ~60%. After 4 h, the mixture was poured into half-saturated aqueous NH4Cl

(50 mL), and the layers were mixed vigorously and separated. The aqueous layer was extracted with hexanes (2 x 25 mL), and the combined organic layers were washed with water (50 mL) and brine (25 mL). The washed organic solution was gravity-filtered through a pad of sodium sulfate, and the filtrate was concentrated under reduced pressure. d.r.: 3:1. Column: 5% ether in hexanes.(5R)-5-((tert-butyldiphenylsilyl)oxy)-4-methylhept-2-yn-4-ol (2.25 g, 5.91 mmol, 84 % yield) emerged as a 3:1 mixture of diastereomers, as a yellow oil.

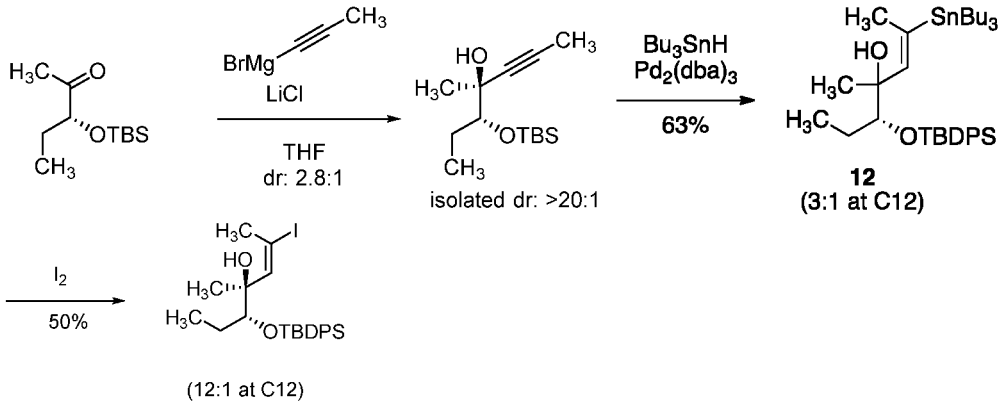
Step 2:

[00586] TBAF (1971 µl, 1.971 mmol) was added dropwise to a solution of (5R)-5-((tert-butyldiphenylsilyl)oxy)-4-methylhept-2-yn-4-ol (500 mg, 1.314 mmol) in Tetrahydrofuran (6569 µl) at 0 °C. The mixture was allowed to warm to 23 °C. After 2 h, TLC (10% ether in hexanes) the mixture was concentrated under reduced pressure. The residue was purified with column chromatography (50% EtOAc in Hexanes). The purified product mixture was subjected to high vacuum for 5 minutes, at which point it began to crystallize. The vessel (200-mL round-bottom flask) was removed from high vacuum until crystallization was complete on the sides of the flask, and was re-exposed to high vacuum for 1 h. NMR at this point showed still >20% minor diastereomer left. The NMR sample was re-combined with the remaining crystals in the flask and the mixture was evaporated (from DCM/hexanes). The flask was equipped with a reflux condensor with cool water running through it, and exposed to high vacuum overnight. The product was very pure (minor diastereomer was almost undetectable, having evaporated overnight). No sublimation on the sides of the reflux condensor were observed. (3R,4S)-4-methylhept-5-yne-3,4-diol (127mg, 0.893 mmol, 68.0 % yield) was a white, crystalline solid. This matched the spectra from the following references: J. Org Chem. 2011, 76, 7516, and ACS *Med. Chem. Lett.* **2012**, *3*, 1013.

Steps 3 and 4:

[00587] These procedures were carried out identically to the following references: This matched the spectra from the following references: *J. Org Chem.* **2011**, *76*, 7516, and *ACS Med. Chem. Lett.* **2012**, *3*, 1013.

Example 2B. Preparation of Western Half Building Blocks



Step 1:

[00588] 1-propynylmagnesium bromide (Sigma) (12.02 ml, 6.01 mmol) (0.5 M in THF) was added dropwise over 6 minutes to a solution of (R)-3-((tert-butyldimethylsilyl)oxy)pentan-2-one (1g, 4.62 mmol) in THF (9.24 ml) at -20 °C. After 1 hour, TLC (25% ether/hexanes) indicated ~90% conversion to a more polar spot. After 90 min, the starting material had been completely consumed. Half-sat aq NH4Cl (25 mL) was added, and the mixture was stirred vigorously for 5 minutes. The resulting biphasic solution was extracted with ether (2 x 25 mL), the organic layers were combined and washed with brine (10 mL), and the washed organic solution was gravity-filtered through a pad of sodium sulfate. The filtrate was concentrated. Crude dr: 2.8:1; Column: 4% ether in hexanes, once minor diast. is off, flush with 6% to remove rest of major. Second column: same conditions. The major diastereomer was isolated in 21:1 dr as a light yellow oil (614mg, 2.394 mmol, 51.8 % yield).

Step 2:

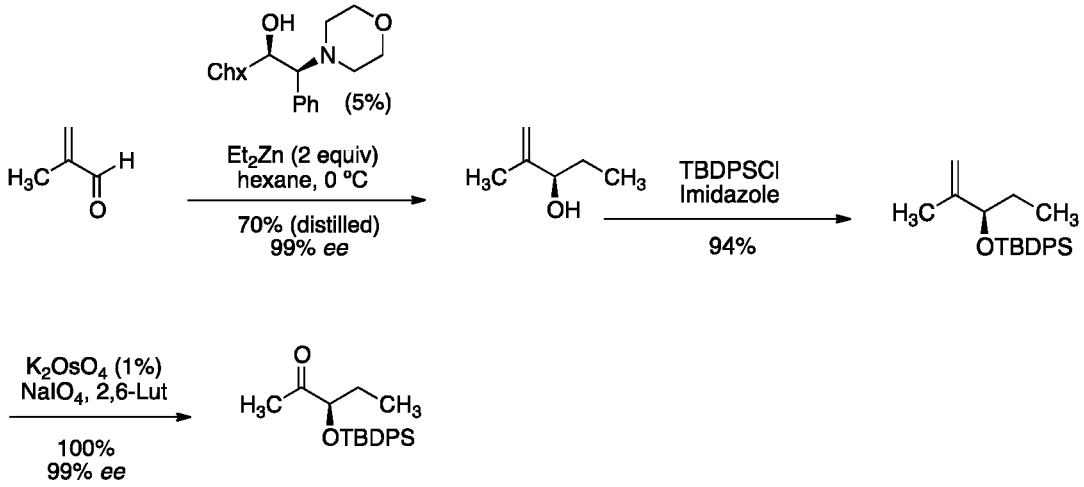
[00589] $PdCl_2(PPh_3)_2$ (1.844 mg, 2.63 µmol) was added to a solution of (5R)-5-((tert-butyldiphenylsilyl)oxy)-4-methylhept-2-yn-4-ol (50 mg, 0.131 mmol) (single diastereomer) in tetrahydrofuran (657 µl). tributylstannane (53.6 µl, 0.197 mmol) was added dropwise over 2 minutes. Visible gas elution occurred. After 2 minutes, TLC revealed very low conversion to a less polar spot (10% ether/hexanes). After 10 minutes, this had not changed. The solution had turned deep golden/brown. After 1 h, this had still not changed. Another portion of tributylstannane (53.6 µl, 0.197 mmol) was added, and TLC (2 min after addition) showed further (~20%?) conversion to the less polar spot. Another 3 equiv of Bu3SnH was added, resulting in more bubbling, and ~50% conversion after 5 minutes. The mixture was allowed to stir for 16 h, and the conversion did not change at all. Another 6 equiv of Bu3SnH was added over 30 min (portionwise, 6 portions), and TLC after 2 minutes indicated complete conversion to a less polar spot (which appeared to be two very very close spots in several

solvent systems. After 24 h, the THF was removed under a stream of argon, and the crude mixture was direclty loaded onto a silica gel column and eluted with 20% DCM/hexanes to provide (5R,E)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-(tributylstannyl)hept-2-en-4-ol (56mg, 0.083 mmol, 63.5 % yield) as a yellow oil.

Step 3:

[00590] A solution of iodine (26.5 mg, 0.104 mmol) in dichloromethane (834 µl). To a solution of (5R,E)-5-((tert-butyldiphenylsilyl)oxy)-4-methyl-2-(tributylstannyl)hept-2-en-4-ol (56 mg, 0.083 mmol) in Dichloromethane (834 µl) at 0 °C. During the addition, the iodine color vanished until the end point, at which point the reaction was done. Sodium thiosulfate (sat aq, 3 mL) was added, and the mixture was stirred vigorously. The organic phase was separated, and the aqueous layer was further extracted with DCM (2 x 3 mL). The organic layers were filtered through a pad of sodium sulfate, and the filtrate was concentrated under reduced pressure. NMR revealed a pure mixture of two isomers (~3.5:1). Column: long silica gel column with 5% ether in hexanes. Some overlapping fractions, and products emerge fairly quickly. The major product that was isolated was 12:1 dr as a light yellow oil: (4S,5R,E)-5-((tert-butyldiphenylsilyl)oxy)-2-iodo-4-methylhept-2-en-4-ol (21mg, 0.041 mmol, 49.5 % yield).

Example 2C. Preparation of Western Half Building Blocks



Step 1:

[00591] To a suspension of (1R,2S)-1-cyclohexyl-2-morpholino-2-phenylethanol (2.065 g, 7.13 mmol, prepared according to the procedure published by W. A. Nugent: *Org. Lett.* **2002**, *4*, 2133-2136) in n-hexane (100 mL) in a 1-L round-bottom flask under argon cooled with an ice water bath was added diethylzinc (285 ml, 285 mmol, Aldrich 1.0 M solution in hexanes)

via cannula by applying a mild vacuum to the receiving flask. Large amounts of white smoke are present in the receiving flask during the transfer. The solution was allowed to stir for 30 minutes at this temperature, then methacrolein (11.81 ml, 143 mmol, freshly distilled prior to use to remove polymers and stabilizers) was added dropwise over 15 minutes, resulting in a pale-yellow, homogeneous solution. TLC (20% EA/H, compare to product, stain with KMnO4) five minutes after the addition showed only the desired product and catalyst - however, it should be noted that methacrolein boils at 69 °C, and monitoring for its disappearance is very difficult. After 15 minutes, the color had faded and the solution was clear and colorless. After 3 hours, 2 M HCl was added carefully, and a white precipitate crashes out, but re-dissolves as the solution reaches pH 1 (~500 mL HCl). The biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was further extracted with diethyl ether (2 x 250 mL), and the combined organic layers were washed with brine (300 mL) dried over sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure (~40 Torr) at 0 °C. The resulting clear oil was transferred to a 100-mL round-bottom flask, and the transfer was quantitated with ether (2 x 5 mL). The solvent was distilled off at atmospheric pressure through a short-path distillation head using a 90 °C oil bath. The vessel was cooled and the pressure was reduced to ~40 Torr. Once bubbling has stopped, the system was backfilled with air, the receiving flask was exchanged for a new one, and the pressure was once again reduced to 40 Torr. The receiving flask was immersed in a 0 °C ice bath, and the distillation was resumed using a 90 °C oil bath. The product distills as a clear liquid with a steady boiling point of 67 °C at ~40 Torr. Yield: 10.04 g (70%). The ee was not determined at this stage, but was measured for a later intermediate. The ^{1}H-NMR and 13C-NMR data matched literature values: Paterson, I.; Perkins, M. V.Tetrahedron **1996**, *52*, 1811–1834; Cossy, J.; Bauer, D.; Bellosta, V. Tetrahedron **2002**, *58*, 5909–5922. The acidic aqueous layers from the extraction were combined and the resulting solution was basified with 2 M NaOH until the pH was 14, and a white solid precipitated. The resulting suspension was extracted with dichloromethane (3 x 100 mL). The organic layer was dried over sodium sulfate and concentrated. The residue was recrystallized from hexane to provide (1R,2S)-1-cyclohexyl-2-morpholino-2-phenylethanol (1.44g, 4.98 mmol, 69.7 % recovery).

Step 2:

[00592] To a solution of (R)-2-methylpent-1-en-3-ol (8 g, 80 mmol) in DMF (160 mL) was added imidazole (10.88 g, 160 mmol) followed by TBDPS-Cl (26.7 ml, 104 mmol) dropwise. The reaction solution was stirred at 23 °C for 18 hours, after which time TLC (20% EA/H)

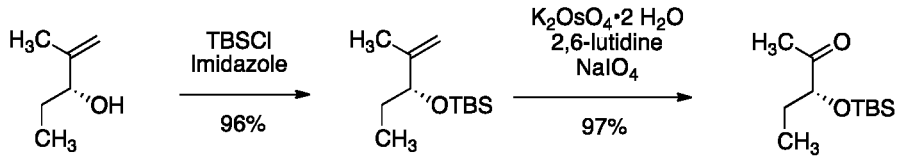
indicated that the starting material was consumed. The reaction solution was partitioned between hexanes (200 mL) and water (750 mL), and after vigorous mixing, the layers were separated. The aqueous layer was further extracted with hexanes (2 x 200 mL), and the combined organic layers were washed with water (2 x 300 mL). The washed solution was loaded onto a silica gel pad (4" diameter, 5" length) which was slurry-packed with hexanes. The pad was eluted in 500 mL fractions with hexanes (4000 mL total), and the fractions containing product (5-8) were combined and concentrated under reduced pressure, providing (R)-tert-butyl((2-methylpent-1-en-3-yl)oxy)diphenylsilane (25.33 g, 74.8 mmol, 94% yield) as a colorless oil. TLC (hexanes): R_f = 0.24 (UV, $KMnO_4$), ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.73 – 7.65 (m, 4H), 7.46 – 7.33 (m, 6H), 4.78 – 4.74 (m, 2H), 4.06 (dd, *J* = 6.8, 5.6 Hz, 1H), 1.69 (s, 3H), 1.53 – 1.45 (m, 2H), 1.09 (s, 9H), 0.68 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 146.0, 136.0, 135.9, 134.8, 134.2, 129.4, 129.4, 127.4, 127.3, 111.6, 78.4, 28.0, 27.0, 19.4, 17.2, 9.0. FTIR (neat), cm^{-1}: 2963, 2932, 1728, 1427, 1109, 1063, 714. HRMS could not be acquired due to poor ionization on ESI-TOF.

Step 3:

[00593] (R)-tert-butyl((2-methylpent-1-en-3-yl)oxy)diphenylsilane (13.65g, 40.3 mmol) was suspended in THF (112 mL) and water (56 mL), resulting in a white slurry. 2,6-Lutidine (9.39 ml, 81 mmol) was added, followed by sodium periodate (34.5 g, 161 mmol) and potassium osmate dihydrate (0.149 g, 0.403 mmol), and the solution was vigorously stirred. After 26 h, the thick white slurry was diluted with water (400 mL) and extracted with hexanes (3 x 125 mL). The combined organic layers were washed with sodium thiosulfate (2 x 250 mL) and saturated copper sulfate (2 x 250 mL), and the washed solution was filtered through a pad of sodium sulfate. The filtrate was concentrated to provide (R)-3-((tert-butyldiphenylsilyl)oxy)pentan-2-one as a colorless oil (13.75 g, 100%). TLC (5% ether in hexanes): R_f = 0.16 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.67 – 7.60 (m, 4H), 7.48 – 7.41 (m, 2H), 7.41 – 7.34 (m, 4H), 4.09 (dd, *J* = 6.5, 5.2 Hz, 1H), 2.08 (s, 3H), 1.71 – 1.52 (m, 2H), 1.13 (s, 9H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 211.3, 135.8, 135.8, 133.5, 133.1, 129.9, 129.9, 127.7, 127.6, 80.2, 27.7, 27.00, 25.8, 19.3, 8.7. FTIR (neat), cm^{-1}: 2965, 2934, 2859, 1717, 1427, 1111, 1018, 713. HRMS (ESI): Calculated for $(C_{21}H_{28}O_2Si + Na)^+$: 363.1751; found: 363.1763.

[00594] The ee of the product was determined to be 99% by analysis on a chiral stationary phase OD-H column using pure hexanes as eluent with detection at 168-218 nm at a flow rate of 1.0 mL/min.

Example 2D. Preparation of Western Half Building Blocks



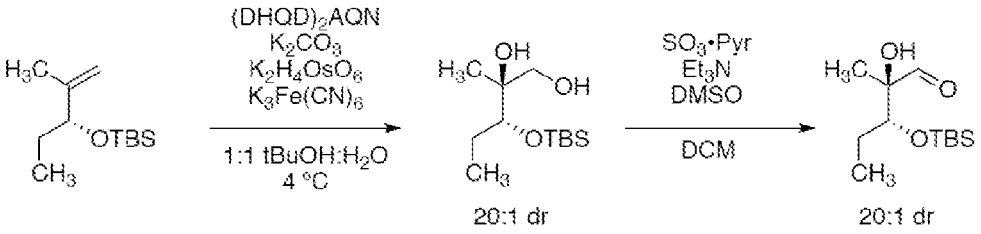
Step 1:

[00595] To a solution of (R)-2-methylpent-1-en-3-ol (3.4 g, 33.9 mmol) (pure from MLC-IV-050) in DMF (33 mL) was added imidazole (4.62 g, 67.9 mmol) followed by TBS-Cl (6.65 g, 44.1 mmol) . The reaction solution was stirred at room temperature. After 24 h, the reaction solution was partitioned between hexanes (60 mL) and water (225 mL), and after vigorous mixing, the layers were separated. The aqueous layer was further extracted with hexanes (2 X 60 mL), and the combined organic layers were washed with water (2 x 90 mL), and loaded onto a silica gel pad (2" diameter, 9" length) which was slurry-packed with hexanes. The pad was eluted into 150 mL fractions with hexanes (1200 mL), and the fractions containing product were combined and concentrated under reduced pressure, providing (R)-tert-butyldimethyl((2-methylpent-1-en-3-yl)oxy)silane (7.00 g, 32.6 mmol, 96 % yield) as a colorless liquid.

Step 2:

[00596] (R)-tert-butyldimethyl((2-methylpent-1-en-3-yl)oxy)silane (2.75 g, 12.83 mmol) was dissolved in THF:H_2O (42.8 ml) (2:1), resulting in a slurry. 2,6-lutidine (2.99 ml, 25.7 mmol) was added, followed by sodium periodate (10.97 g, 51.3 mmol) and potassium osmate dehydrate (0.095 g, 0.257 mmol), and the solution was vigorously stirred (9:45 AM). After 3 hours, the starting material was completely consumed as indicated by TLC (10% ether in hexanes). The thick white slurry was diluted with water (75 mL) and the resulting slurry was extracted with hexanes (2 x 50 mL). The combined organic layers were washed with sodium thiosulfate (2 x 100 mL, vigorous mixing) and saturated copper sulfate (2 x 50 mL). The washed organic solution was gravity-filtered through a pad of sodium sulfate, and the filtrate was concentrated (*no high vacuum*) to provide (R)-3-((tert-butyldimethylsilyl)oxy)pentan-2-one (2.7g, 12.48 mmol, 97 % yield) as a yellow oil.

Example 2E.

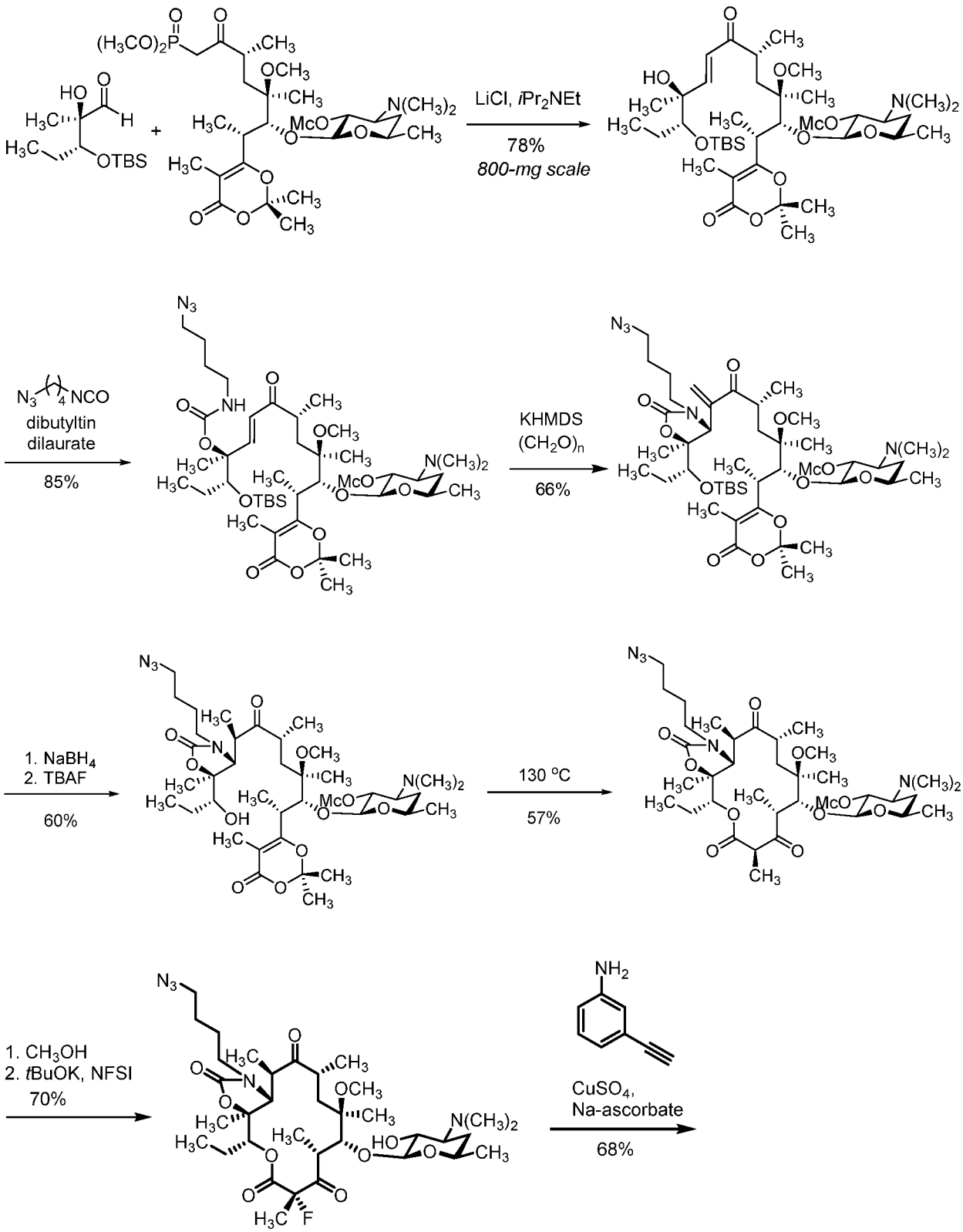


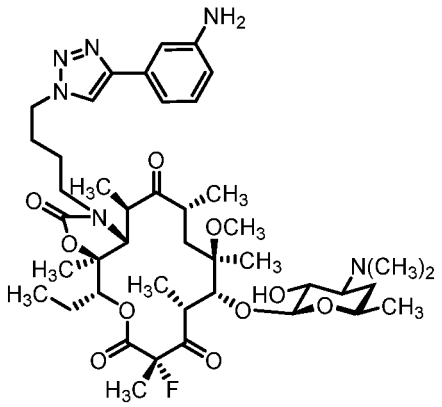
[00597] $(DHQD)_2AQN$ (0.280 g, 0.326 mmol), $K_3Fe(CN)_6$ (32.2 g, 98 mmol), K_2CO_3 (13.54 g, 98 mmol), and Potassium Osmate Dihydrate (0.024 g, 0.065 mmol) were dissolved in 1:1 tBuOH:H_2O (330 mL) and was cooled to 0 °C with vigorous stirring. (R)-tert-butyldimethyl((2-methylpent-1-en-3-yl)oxy)silane (7 g, 32.6 mmol) was added neat via syringe. The mixture was stirred for 72 h at 4 °C. Solid sodium sulfite was added and the mixture was stirred vigorously for 30 min. Then, ether (300 mL) and water (100 mL) were added and the layers were separated. The aqueous layer was further extracted with ether (2 x 150 mL) and the combined organics were washed with water and dried through a pad of sodium sulfate. The filtrate was concentrated under reduced pressure. The yellow residue was purified by flash chromatography (50% ether/hexanes). (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentane-1,2-diol was afforded as a 15:1 - 20:1 mixture of diastereomers in favor of the depicted one: 7.6 g, 94% yield.

[00598] To a solution of (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-methylpentane-1,2-diol (1.2 g, 4.83 mmol) (16:1 ratio of isomers) in dichloromethane (20 mL) was added triethylamine (3.37 ml, 24.15 mmol) and DMSO (3.43 ml, 48.3 mmol). The mixture was cooled to 0 °C, and SO_3•Pyridine (3.08 g, 19.32 mmol) was added as a solid. After 1.5 h at 0 °C, conversion was about 50%, so the vessel was removed from the ice water bath. After 4 h total, the starting material was completely consumed. The mixture was diluted with ether (30 mL) and washed with water (2 x 30 mL), sat aq copper sulfate (20 mL), sat aq NaCl (20 mL), and was dried through a pad of sodium sulfate and concentrated (no high vacuum) to provide the aldehyde product in a yield of 1.10 g (92%) as a crude yellow oil.

EXEMPLARY COUPLING OF EASTERN AND WESTERN HALVES

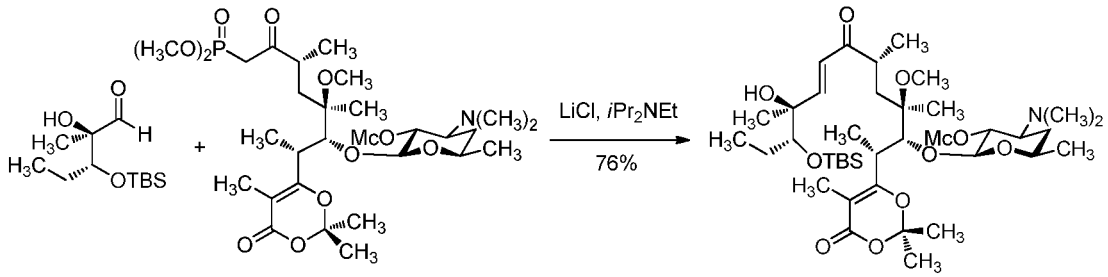
Example 3A. Synthesis of Solithromycin via Horner-Emmons Coupling





solithromycin, fully synthetic
17 steps

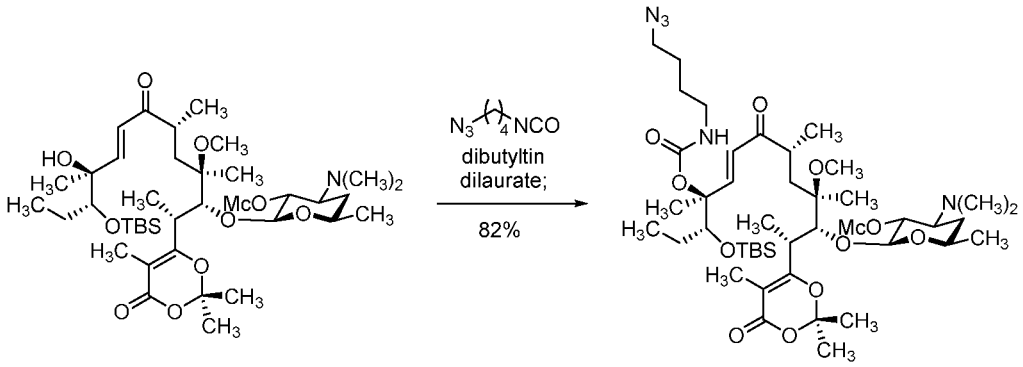
Step 1:



[00599] A 25-mL flask equipped with a stir bar was charged with anhydrous LiCl (0.153 g, 3.61 mmol). The vessel was heated with a gentle flame under vacuum (0.1 mmHg) for 2 min. The phosphonate (2.0 g, 3.00 mmol) was added as a solution in acetonitrile (15.02 mL), followed by diisopropylethylamine (0.630 mL, 3.61 mmol). The suspension was stirred at rt for 5 min. (2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methylpentanal (0.740 g, 3.00 mmol) was added neat dropwise. The resulting suspension was then stirred at 30 °C. After 12 h, TLC (10% methanol in ethyl acetate) indicated full consumption of the phosphonate. The reaction mixture was diluted with CH_2Cl_2 (30 mL), saturated aqueous $NaHCO_3$ (15 mL) and vigorously stirred. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (2-3% methanol in CH_2Cl_2 + 0.2% saturated NH_4OH) to give the product as a white foam (1.80 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 15.6 Hz, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 4.63 – 4.48 (m, 2H), 3.82 (d, *J* = 3.4 Hz, 1H), 3.78 (s, 3H), 3.52 (dd, *J* = 5.8, 4.6 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.38 – 3.30 (m, 1H), 2.93 (s, 3H), 2.80 – 2.71 (m, 1H), 2.59 (s, 1H), 2.31 (s, 6H), 2.12 (dd, *J* = 14.1, 10.2 Hz, 1H), 1.82 (s, 3H), 1.80 – 1.74 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.64 – 1.57 (m, 1H), 1.49 – 1.41 (m, 2H), 1.41 – 1.31 (m, 1H), 1.27 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 4H), 1.21 (s, 3H), 1.07 (d, *J* = 3.5 Hz, 3H), 1.06 (d, *J* = 3.0 Hz, 3H), 0.92 (s, 9H), 0.90 (t, *J* = 2.8 Hz, 3H), 0.10 (d, *J* = 1.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

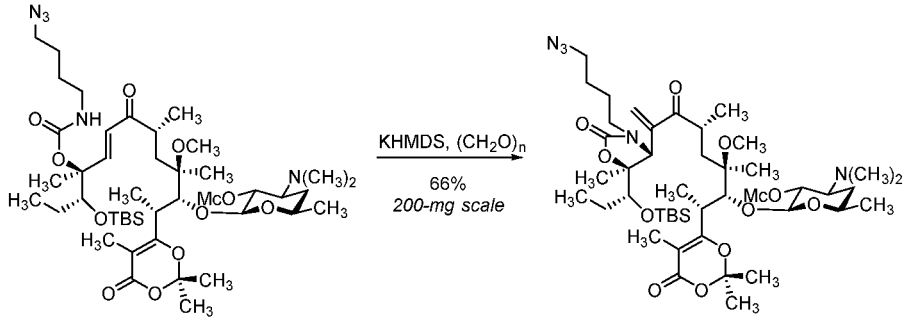
203.61, 167.58, 162.99, 155.24, 147.02, 125.97, 104.34, 99.94, 99.78, 79.32, 78.24, 77.40, 75.63, 75.49, 69.22, 63.04, 54.69, 49.40, 40.67, 39.82, 37.99, 34.12, 30.85, 26.16, 25.95, 25.89, 25.73, 24.32, 20.95, 20.09, 18.93, 18.20, 13.00, 10.75, 9.69, -3.88, -4.43. FTIR (neat), cm^{-1}: 3470(br), 2937 (m), 1751 (s), 1716(s), 1639 (s), 1267 (s), 1055 (s), 910 (s); HRMS (ESI): Calcd for $(C_{40}H_{71}NO_{12}Si + H)^+$: 786.4818; Found: 786.4824.

Step 2:



[00600] HWE Product (600 mg, 0.763 mmol) was dissolved in Dichloroethane (7633 µl). 1-azido-4-isocyanatobutane (105 µl, 0.840 mmol) was added, followed by dibutyltin dilaurate (455 µl, 0.763 mmol). The reaction was heated to reflux (80°C). After 18h, LC-MS indicated complete conversion. The reaction mixture was directly concentrated purified by column chromatography (10-25% Acetone in Hexanes + 0.5% Et3N) to give the product as a white foam (580mg, 82%). ^{1}H NMR (500 MHz, cdcl$_3$) δ 6.95 (d, J = 16.2 Hz, 1H), 6.19 (d, J = 16.2 Hz, 1H), 4.78 (s, 1H), 4.59 (dt, J = 13.9, 7.6 Hz, 2H), 3.98 (d, J = 4.6 Hz, 1H), 3.85 (d, J = 3.3 Hz, 1H), 3.80 (s, 3H), 3.47 (dd, J = 10.1, 5.2 Hz, 1H), 3.42 – 3.24 (m, 3H), 3.17 (q, J = 6.4 Hz, 1H), 3.05 – 2.98 (m, 1H), 2.95 (s, 3H), 2.81 – 2.70 (m, 1H), 2.32 (s, 6H), 2.20 (dd, J = 14.1, 9.9 Hz, 1H), 1.83 (s, 3H), 1.81 – 1.73 (m, 1H), 1.67 (s, 3H), 1.67 (s, 3H), 1.65 – 1.58 (m, 5H), 1.57 (s, 3H), 1.46 – 1.32 (m, 4H), 1.27 (d, J = 6.1 Hz, 3H), 1.23 (s, 3H), 1.09 (d, J = 3.4 Hz, 3H), 1.08 (d, J = 3.0 Hz, 3H), 0.98 – 0.92 (m, 3H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 203.4, 167.6, 163.0, 155.3, 154.8, 146.1, 128.0, 104.3, 99.9, 99.8, 84.3, 78.4, 78.2, 77.1, 75.5, 69.2, 63.0, 54.7, 51.0, 49.5, 40.7, 40.1, 38.3, 37.8, 34.1, 30.9, 27.3, 26.1, 26.0, 25.7, 25.5, 24.3, 20.9, 20.19, 20.14, 19.2, 13.0, 11.3, 9.70, -3.94. FTIR (neat), cm^{-1}: 3381(br), 2951 (s), 2096 (s), 1720 (s), 1267 (s), 1053 (s), 731 (s); HRMS (ESI): Calcd for $(C_{45}H_{79}N_5O_{13}Si + H)^+$: 926.5516; Found: 926.5533.

Step 3:

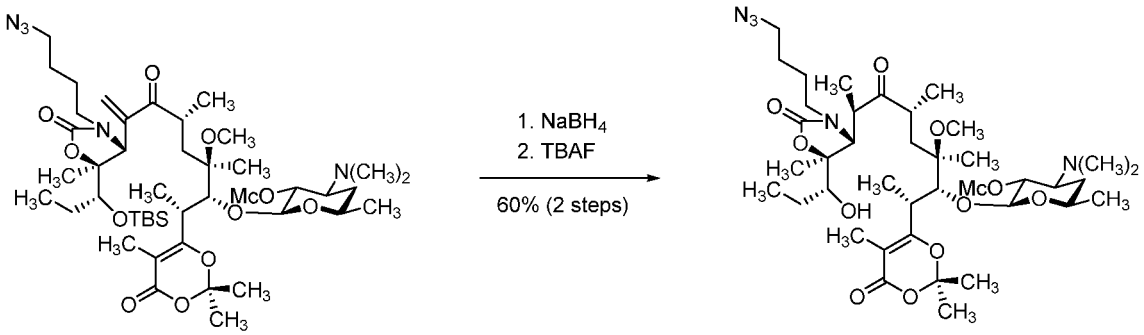


[00601] Paraformaldehyde (324 mg, 10.8 mmol, 50.0 equiv) was added to a solution of open carbamate (200 mg, 0.216 mmol, 1 equiv) in THF (1.0 mL) at 23 °C. The suspension was cooled to –78 °C (dry ice–acetone bath). A solution of KHMDS in THF (0.50 M, 0.950 mL, 0.475 mmol, 2.20 equiv) was added dropwise via syringe at –78 °C over 10 min. The resulting solution was allowed to warm to 0 °C over 1 h and was held at that temperature for 1 h. Saturated aqueous sodium bicarbonate solution (10 mL) was added at 0 °C. After warming to 23 °C, the mixture was extracted with ether (3 x 10 mL). The combined ether layers were washed with brine and dried over magnesium sulfate. The dried solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (10→25% acetone–hexanes + 0.5% triethylamine) to afford the product as a white foam (134 mg, 66%).

^{1}H NMR (500 MHz, cdcl$_3$) δ 6.62 (br s, J = 33.7 Hz, 1H), 5.84 (br s, J = 31.9 Hz, 1H), 4.96 (br s, 1H), 4.62 – 4.52 (m, 2H), 3.84 (d, J = 3.3 Hz, 1H), 3.79 (s, 3H), 3.68 – 3.60 (m, 1H), 3.59 – 3.38 (m, 3H), 3.38 – 3.23 (m, 3H), 2.92 (s, 3H), 2.82 – 2.73 (m, 1H), 2.73 – 2.61 (m, 1H), 2.31 (s, 6H), 1.80 (s, 3H), 1.79 – 1.75 (m, 1H), 1.66 (s, 3H), 1.66 (s, 3H), 1.62 – 1.47 (m, 7H), 1.47 – 1.29 (m, 2H), 1.25 (d, J = 6.1 Hz, 3H), 1.20 (s, 3H), 1.09 (d, J = 7.4 Hz, 3H), 1.06 (s, 2H), 1.05 (d, J = 7.0 Hz, 3H), 1.00 (t, J = 7.5 Hz, 3H), 0.93 (s, 10H), 0.13 (d, J = 12.8 Hz, 6H).

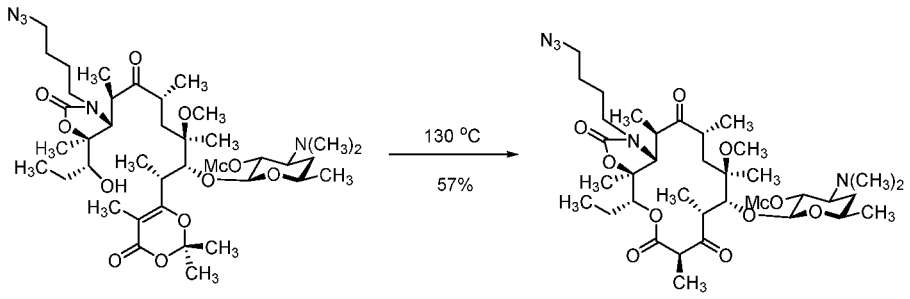
^{13}C NMR (126 MHz, cdcl$_3$) δ 167.35, 162.78, 157.64, 155.31, 142.69, 104.42, 100.13, 99.79, 78.80, 78.27, 77.70, 75.46, 69.27, 63.00, 54.73, 51.12, 50.88, 49.53, 42.00, 40.65, 37.51, 34.83, 34.25, 30.85, 26.34, 26.07, 25.94, 25.48, 24.70, 24.14, 20.99, 20.27, 18.25, 13.04, 11.73, 9.62, -3.92, -4.23. Note: The carbon spectrum of this compound is complicated by severe line broadening. Only clearly discernible peaks are reported. FTIR (neat), cm^{-1}: 2937 (m), 2096 (s), 1749 (s), 1724 (s), 1267 (s), 1112 (s), 1053 (s), 729 (s). HRMS (ESI): Calcd for ($C_{46}H_{79}N_5O_{13}Si$ + H)$^+$: 938.5516; Found: 938.5550.

Step 4:



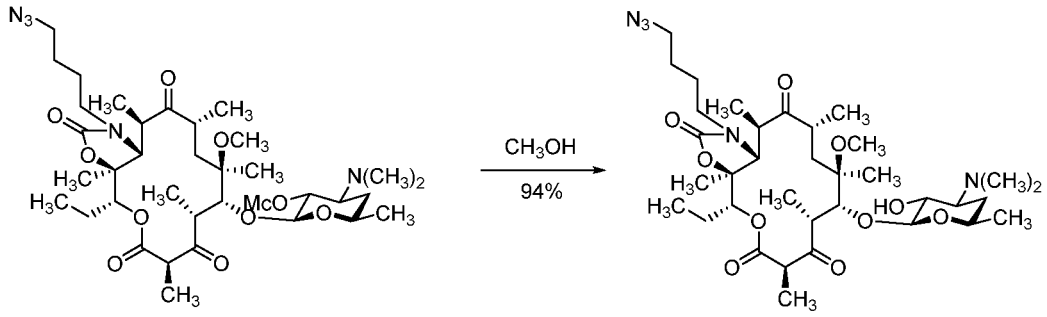
[00602] Sodium borohydride (2.2 mg, 0.059 mmol, 1.0 equiv) was added to a solution of open chain exomethylene (55 mg, 0.059 mmol, 1 equiv) in methanol (0.2 mL) at –15 °C. After 30 min, the reaction mixture was allowed to warm to 23 °C and concentrated under reduced pressure. The residue was partitioned between ether (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The aqueous layer was extracted with ether (2 x 5 mL). The combined ether layers were dried over magnesium sulfate and the dried solution was concentrated under reduced pressure. The residue was dissolved in THF (0.2 mL), and a solution of TBAF in THF (0.12 mL, 0.12 mmol, 2.0 equiv) was added at 23 °C. After 1 h, the solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (10→25% acetone–hexanes + 0.5% triethylamine) to afford the product as a white foam (31 mg, 60%). ^{1}H NMR (500 MHz, cdcl$_3$) δ 4.59 – 4.48 (m, 2H), 4.27 (s, 1H), 3.86 (d, J = 3.1 Hz, 1H), 3.75 (s, 3H), 3.53 – 3.36 (m, 3H), 3.35 – 3.22 (m, 3H), 2.96 – 2.91 (m, 1H), 2.93 (s, 3H), 2.88 – 2.79 (m, 1H), 2.79 – 2.67 (m, 1H), 2.41 (br s, 1H), 2.28 (s, 6H), 2.10 (dd, J = 14.2, 10.0 Hz, 1H), 1.78 (s, 3H), 1.77 – 1.73 (m, 1H), 1.70 – 1.66 (m, 2H), 1.65 (s, 3H), 1.64 (s, 3H), 1.62 – 1.51 (m, 6H), 1.41 – 1.37 (m, 1H), 1.34 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H), 1.23 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 7.4 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 215.21, 167.20, 162.72, 157.51, 155.27, 104.46, 99.94, 99.84, 83.34, 78.53, 77.80, 76.56, 75.44, 69.26, 62.93, 57.06, 54.69, 51.00, 49.41, 46.10, 42.10, 40.63, 38.51, 33.89, 30.84, 26.02, 25.90, 24.27, 24.16, 23.63, 20.95, 20.11, 15.67, 13.03, 10.85, 10.57, 9.68. FTIR (neat), cm^{-1}: 3462 (br), 2939 (m), 2098 (s), 1753 (s), 1724 (s), 1267 (s), 1112 (s), 1053 (s), 999 (s). HRMS (ESI): Calcd for ($C_{40}H_{67}N_5O_{13}$ + H)$^+$: 826.4808; Found: 826.4820.

Step 5:



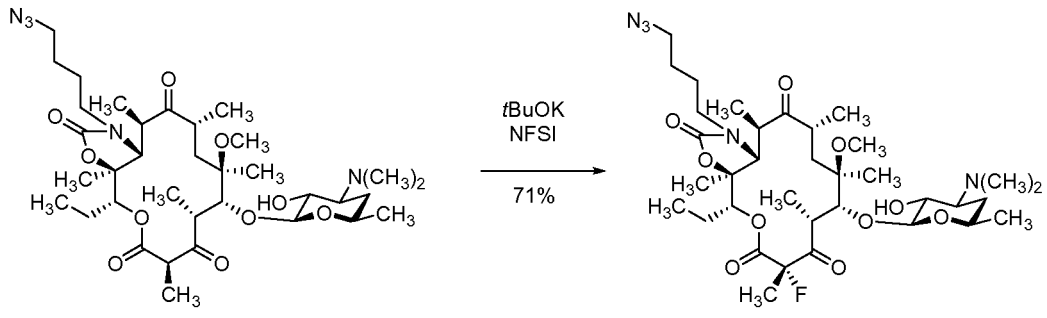
[00603] C10-methylmacrocyclization_precursor (31 mg, 0.038 mmol) was dissolved in chlorobenzene (38 mL) in a 50-mL flask. The flask was fitted with a dry reflux condensor. Dry argon was bubbled through the solution via a 19-gauge needle for 10 min. The flask was then immersed in an oil bath preheated to 150 °C to allow a gentle reflux of the reaction solution. After 16 h, the heating bath was removed and the solution was allowed to cool to 23 °C. The cooled solution was concentrated under reduced pressure (rotary evaporation, ~10 mmHg, 40 °C water bath) and the residue was purified by flash column chromatography (25% acetone–hexanes + 0.5% triethylamine) to afford the product as a white foam (15 mg, 52%). ^{1}H NMR (3:1 diastereomeric mixture at C2, major isomer is reported, 500 MHz, cdcl$_3$) ^{1}H NMR (500 MHz, cdcl$_3$) δ 4.95 (dd, *J* = 10.6, 2.4 Hz, 1H), 4.53 (dd, *J* = 10.5, 7.6 Hz, 1H), 4.40 (d, *J* = 7.6 Hz, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 3.83 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.64 (m, 1H), 3.60 (s, 1H), 3.59 – 3.53 (m, 1H), 3.40 – 3.22 (m, 3H), 3.15 – 3.08 (m, 1H), 3.08 – 3.02 (m, 1H), 2.78 – 2.69 (m, 1H), 2.66 (s, 3H), 2.64 – 2.52 (m, 1H), 2.28 (s, 6H), 2.03 – 1.89 (m, 1H), 1.81 – 1.59 (m, 8H), 1.49 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.34 (s, 3H), 1.28 – 1.25 (m, 4H), 1.20 – 1.14 (m, 6H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). Note: peaks for the minor isomer are not clearly discernible. ^{13}C NMR (3:1 diastereomeric mixture at C2, major isomer is reported, 126 MHz, cdcl$_3$) δ 215.98, 203.72, 169.53, 157.15, 155.19, 101.36, 82.10, 78.56, 78.11, 77.42, 75.55, 69.19, 63.27, 60.48, 54.78, 51.17, 50.96, 49.65, 46.99, 44.87, 42.95, 40.62, 39.12, 39.01, 30.23, 26.24, 24.34, 22.30, 20.95, 20.92, 19.69, 18.36, 15.49, 14.71, 13.94, 13.91, 10.39. FTIR (neat), cm^{-1}: 2941 (m), 2096 (s), 1753 (s), 1712 (s), 1267 (s), 1109 (s), 1055 (s), 999 (s). HRMS (ESI): Calcd for $(C_{37}H_{61}N_5O_{12} + H)^+$: 768.4389; Found: 768.4395.

Step 6:



[00604] A solution of C10-methyl-macrocycle (15 mg, 0.020 mmol) in methanol (1 mL) was allowed to stand at 23 °C for 24 h. The solution was then concentrated to afford the product as a colorless film (13 mg, 94%). ^{1}H NMR (500 MHz, cdcl$_3$) δ 4.94 (dd, *J* = 10.6, 2.4 Hz, 1H), 4.29 (d, *J* = 7.3 Hz, 1H), 4.25 (d, *J* = 8.8 Hz, 1H), 3.85 (q, *J* = 6.8 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.65 – 3.59 (m, 1H), 3.58 (s, 1H), 3.57 – 3.48 (m, 1H), 3.38 – 3.23 (m, 2H), 3.19 (dd, *J* = 10.2, 7.3 Hz, 1H), 3.15 – 3.11 (m, 1H), 3.11 – 3.04 (m, 1H), 2.67 (s, 3H), 2.65 – 2.57 (m, 1H), 2.45 (ddd, *J* = 12.3, 10.4, 3.9 Hz, 1H), 2.27 (s, 6H), 2.00 – 1.88 (m, 1H), 1.83 (dd, *J* = 14.5, 2.4 Hz, 1H), 1.78 – 1.51 (m, 7H), 1.47 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 3H), 1.31 (d, *J* = 7.5 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.24 – 1.21 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, CDCl3) δ 216.09, 203.76, 169.54, 157.17, 103.92, 82.11, 79.54, 78.14, 77.30, 70.33, 69.60, 65.85, 60.39, 51.21, 50.97, 49.75, 47.57, 44.90, 42.92, 40.20, 39.53, 39.01, 29.66, 28.14, 26.26, 24.32, 22.25, 21.16, 19.72, 18.36, 15.76, 14.63, 14.34, 13.88, 10.38. FTIR (neat), cm^{-1}: 3477 (br), 2937 (m), 2096 (s), 1753 (s), 1712 (s), 1456 (s), 1165 (s), 1109 (s), 1076 (s), 1051 (s), 991 (s). HRMS (ESI): Calcd for ($C_{35}H_{59}N_5O_{10}$ + H)$^+$: 710.4335; Found: 710.4343.

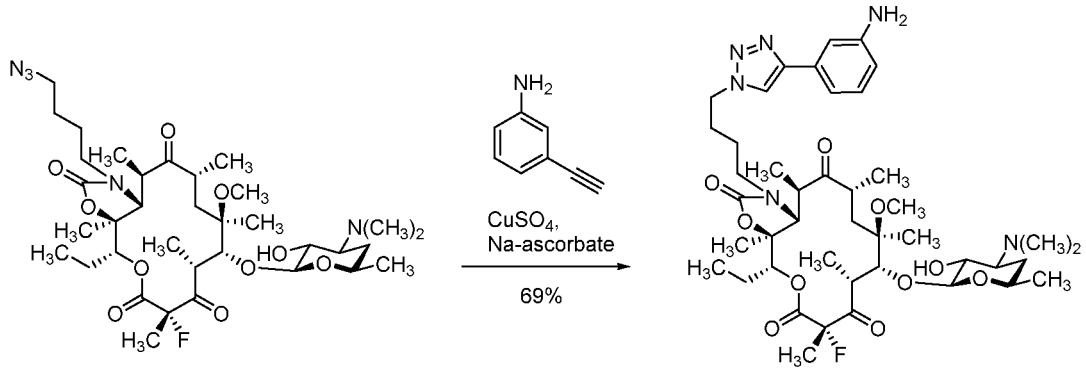
Step 7:



[00605] A solution of potassium *tert*-butoxide in THF (1.0 M, 18 µL, 18 µmol, 1.0 equiv) was added dropwise to a solution of C10-methylmacrocycle (13 mg, 18 µmol, 1 equiv) in THF (0.2 mL) at –78 °C. The solution was stirred for 5 min, and a solution of *N*-fluorobenzenesulfonimide (5.8 mg, 18 µmol, 1.0 equiv) in THF (0.1 mL) was added

dropwise via syringe at –78 °C. The mixture was stirred at –78 °C for 1 h. Saturated aqueous sodium thiosulfate solution (0.5 mL) and saturated aqueous sodium bicarbonate solution (0.5 mL) were added at –78 °C. The mixture was allowed to warm to 23 °C, and was extracted with dichloromethane (3 x 1 mL). The combined organic layers were dried over sodium sulfate and the dried solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (3% methanol–dichloromethane + 0.3% saturated ammonium hydroxide solution) to afford the C2 fluorination product as a colorless film (9.4 mg, 71%). This product is an 8:1 mixture of C2 diastereomers.

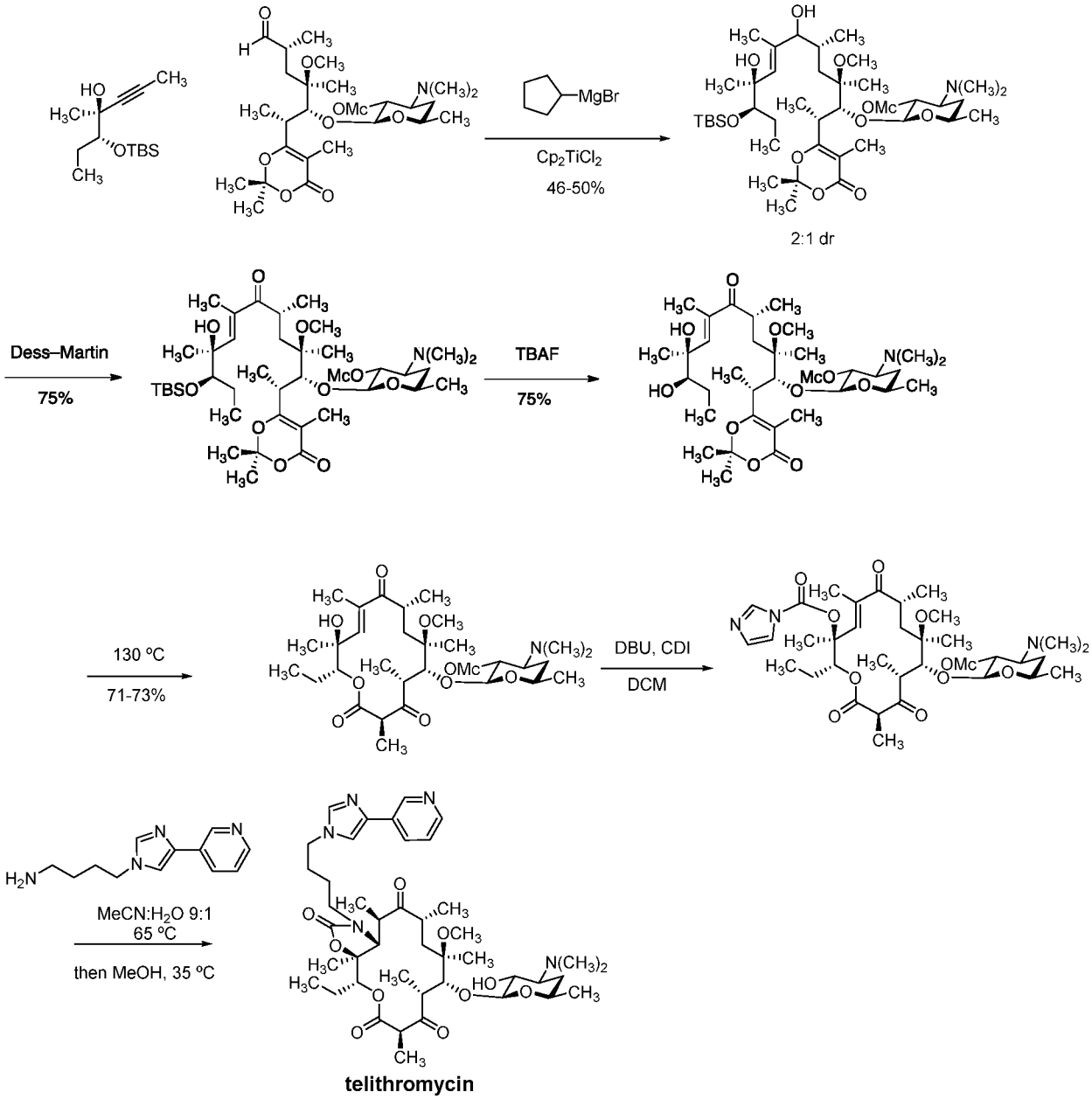
Step 8:



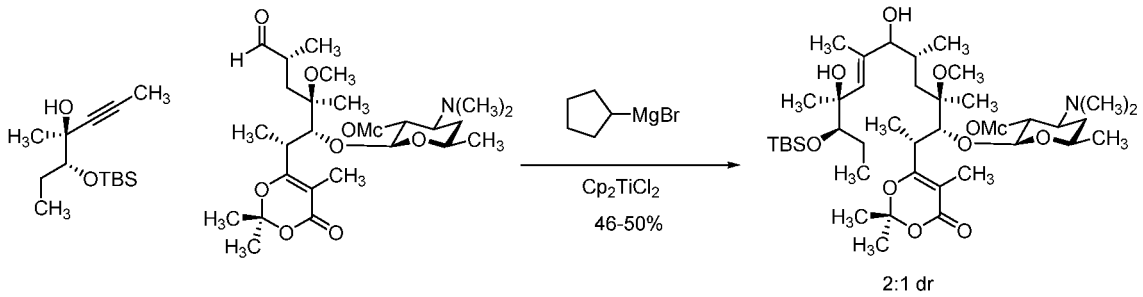
[00606] 3-ethynylaniline (4.5 mg, 0.039 mmol, 3.0 equiv), an aqueous solution of sodium ascorbate (0.10 M, 26 µL, 2.6 µmol, 0.20 equiv) and an aqueous solution of copper(II) sulfate (0.10 M, 6.5 µL, 0.65 µmol, 0.050 equiv) were added sequentially to a stirred solution of C2-fluoromacrocycle (9.4 mg, 0.013 mmol, 1 equiv) 1:1 *t*-butanol:water (0.2 mL). After 16 h, the reaction mixture was partitioned between dichloromethane (1 mL) and saturated aqueous sodium bicarbonate solution (1 mL). The aqueous layer was extracted with dichloromethane (2 x 1 mL). The combined organic layers were dried over sodium sulfate and the dried solution was concentrated under reduced pressure. The residue was purified by preparatory thin layer chromatography (10% methanol–dichloromethane + 1% saturated ammonium hydroxide solution) to afford solithromycin as a white solid (7.5 mg, 69%). ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.82 (s, 1H), 7.31 – 7.29 (m, 1H), 7.23 – 7.15 (m, 2H), 6.66 (dt, *J* = 7.2, 2.1 Hz, 1H), 4.89 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.43 (td, *J* = 7.1, 1.5 Hz, 2H), 4.32 (d, *J* = 7.3 Hz, 1H), 4.08 (d, *J* = 10.6 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.68 – 3.60 (m, 1H), 3.60 – 3.49 (m, 2H), 3.45 (s, 1H), 3.20 (dd, *J* = 10.2, 7.3 Hz, 1H), 3.13 (q, *J* = 6.9 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.57 (s, 3H), 2.51 – 2.42 (m, 1H), 2.29 (s, 6H), 2.05 – 1.93 (m, 3H), 1.90 (dd, *J* = 14.5, 2.7 Hz, 1H), 1.79 (d, *J* = 21.4 Hz, 3H), 1.75 – 1.60 (m, 4H), 1.55 (d, *J* = 13.0 Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.28 – 1.24 (m, 1H), 1.26 (d, *J* =

6.1 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 216.52, 202.79 (d, J = 28.0 Hz), 166.44 (d, J = 22.9 Hz), 157.19, 147.82, 146.82, 131.72, 129.63, 119.66, 116.14, 114.71, 112.36, 104.24, 97.78 (d, J = 206.2 Hz), 82.11, 80.72, 78.59, 78.54, 70.35, 69.64, 65.82, 61.05, 49.72, 49.22, 44.58, 42.77, 40.86, 40.22, 39.57, 39.20, 28.13, 27.59, 25.20 (d, J = 22.4 Hz) 24.28, 22.14, 21.15, 19.76, 17.90, 15.04, 14.70, 13.76, 10.47. ^{19}F NMR (471 MHz, cdcl$_3$) δ -163.24 (q, J = 11.2 Hz). FTIR (neat), cm^{-1}: 3362 (br), 2976 (m), 1753 (s), 1460 (s), 1263 (s), 1078 (s), 1051 (s), 991 (s). HRMS (ESI): Calcd for $(C_{43}H_{65}FN_6O_{10} + H)^+$: 845.4819; Found: 845.4841.

Example 3B. Synthesis of Solithromycin Intermediate via Hydromagnesiation

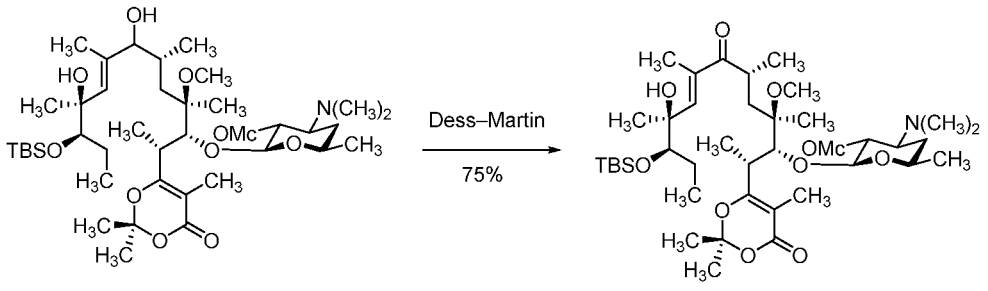


Step 1:



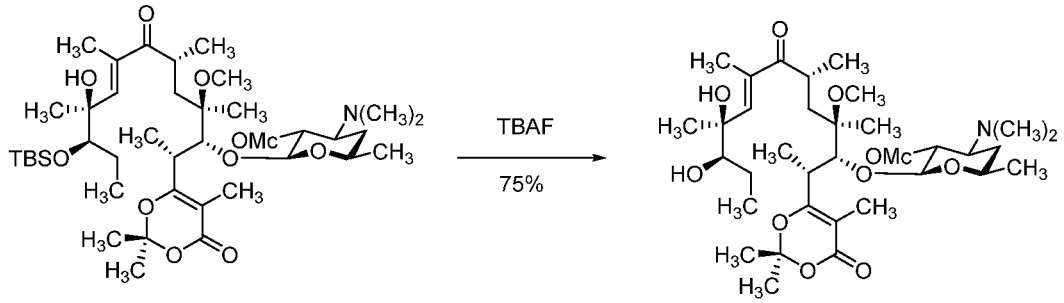
[00607] A flame-dried, 5-mL flask was charged with Cp_2TiCl_2 (47.6 mg, 0.191 mmol). The vessel was evacuated and refilled with dry argon (this process was repeated three times), and was then equipped with a rubber septum and a positive pressure of argon through a needle. Ethyl ether (5790 µl) was added and the red suspension was cooled to 0 °C in an ice water bath. cyclopentylmagnesium bromide (2548 µl, 5.10 mmol) (2 M solution in ether) was added, and the purple/gray solution was stirred for 5 minutes at this temperature. A solution of (4S,5R)-5-((tert-butyldimethylsilyl)oxy)-4-methylhept-2-yn-4-ol (490mg, 1.911 mmol) in ether (2 mL) was added dropwise (the transfer was quantitated with 2 x 0.5 mL ether). After 5 min, the mixture was allowed to warm to 23 °C. After 2 h, the mixture was cooled to -20 °C, and a solution of Right Half Aldehyde (630 mg, 1.158 mmol) in ether (2 mL) was added. The mixture was allowed to warm to 23 °C, and THF (5 mL) was added, and most of the solids went into solution. TLC revealed high conversion to a less polar spot, with some "starting material" and some more polar contaminant. After 30 minutes at 23 °C, sat aq NH4Cl (20 mL) was added, and the layers were mixed vigorously and were separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL), and the organic layers were combined and washed with water (20 mL) and brine (20 mL). The washed organic solution was gravity-filtered through a pad of sodium sulfate and the filtrate was concentrated. The resulting residue was purified by column chromatography (15% to 20% acetone in hexanes + 0.5% Et_3N). The byproducts were flushed off with 30% acetone/hexanes. The coupled allylic alcohol (425 mg, 0.530 mmol, 45.8 % yield) emerged in >85% purity as a 2.5:1 mixture of diastereomers as yellow foam.

Step 2:



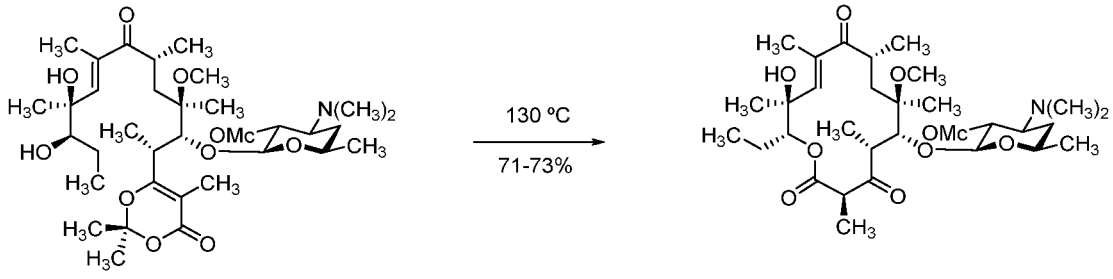
[00608] Dess-Martin Periodinane (439 mg, 1.035 mmol) (DMP) was added to a solution of coupled allylic diol (415 mg, 0.517 mmol) in squirt bottle DCM (5174 µl) at 23 °C. Monitored by TLC (30% acetone/hexanes +0.5% Et3N). After 30 minutes added another portion of DMP (26 mg, 1.0 equiv). After another 15 minutes the TLC had not changed, so sat aq $NaHCO_3$ (3 mL), sat aq $Na_2S_2O_4$ (3 mL), and DCM (3 mL) were added. The layers were stirred vigorously until each layer was clear (~5 minutes). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organic layers were filtered through a pad of sodium sulfate, and the filtrate was concentrated under reduced pressure. Silica gel chromatography (10% to 16% acetone/hexanes + 0.5% Et_3N) provided the desired enone (310mg, 0.387 mmol, 74.9 % yield) as a white foam.

Step 3:



[00609] TBAF (750 µl, 0.750 mmol) (1.0 M solution in THF) was added to a solution of enone TBS ether (300 mg, 0.375 mmol) in THF (3750 µl) at 0 °C (11:40 AM). After 30 minutes, the starting material was no longer present by TLC (33% acetone in hexanes + 0.5% Et_3N). The THF was evaporated under a stream of argon, and the crude residue was directly purified by silica gel chromatography (20% to 30% acetone/hexanes +0.5% Et3N). This effectively removed the impurities (less polar, all). The product emerged in high purity: enone diol (210mg, 0.306 mmol, 82 % yield)

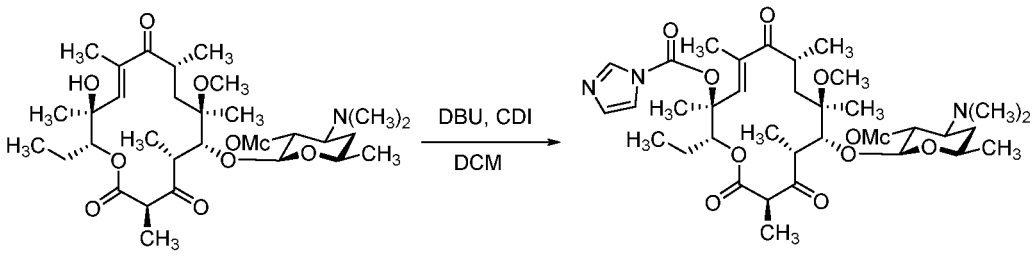
Step 4:



[00610] A stream of argon was passed through a solution of enone macrocycle precursor (210 mg, 0.306 mmol) and in chlorobenzene (300 mL) in a 50-mL round-bottom flask by means of a needle through a rubber septum while the vessel was exposed to sonication. After 10 minutes, the vessel was removed from sonication and was equipped with a straight-path

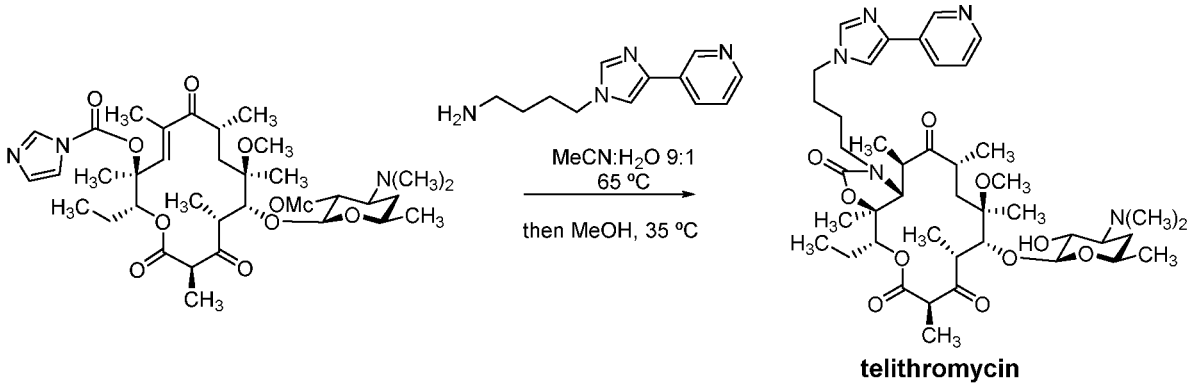
reflux condensor. The system was evacuated and backfilled with argon (this process was repeated three times), and was then heated in a 150 °C oil bath. After 1 h, LCMS showed very low conversion to the desired mass (confirmed by TLC in 30% acetone in hexanes, +1% Et_3N). After 18 h, LCMS indicated consumption starting material. The mixture was cooled to 23 °C and was concentrated under reduced pressure. By crude ^{1}H-NMR: 2:1 mixture of C2 epimers. Purification by silica gel chromatography (15% to 20% acetone/hexanes + 0.5% Et3N) provided enone macrocycle (136mg, 0.217 mmol, 70.8 % yield) as a white foam. Post-column NMR: 16:1 ratio of C2 epimers, equilibrated on column.

Step 5:



[00611] CDI (3.87 mg, 0.024 mmol) (solution in DCM) was added to a solution of macrocyclic enone (5 mg, 7.96 µmol) in DCM (0.3 mL) at -15 °C. DBU (4.80 µl, 0.032 mmol) was added and the solution was allowed to stir at this temperature. After 90 min, sat aq NH4Cl (1 mL) was added, and the mixture was stirred vigorously for 1 min and then extracted with DCM (2 x 1 mL). the organic layers were dried through a pad of sodium sulfate and the filtrate was concentrated to provide the acyl imidazole as a white foam, which was of sufficient purity to carry forward.

Step 6:

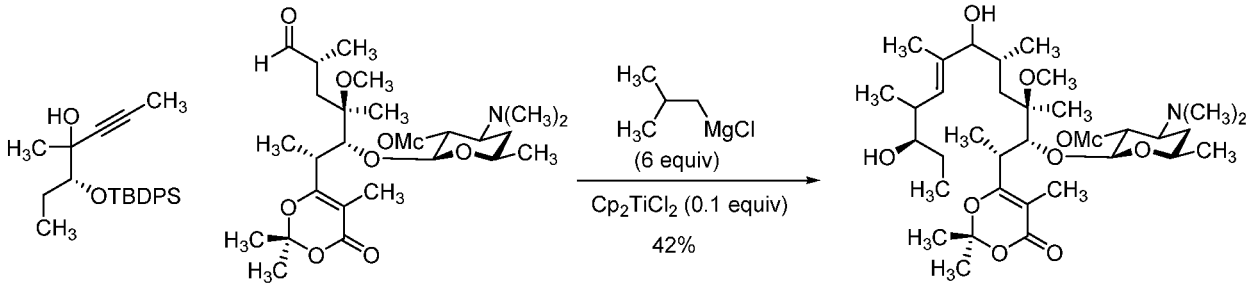


telithromycin

[00612] 4-(4-(pyridin-3-yl)-1H-imidazol-1-yl)butan-1-amine (7.49 mg, 0.035 mmol) was added to a solution of Acyl Imidazole (5mg, 6.93 µmol) in Acetonitrile:H2O (0.5 ml). The solution was heated to 65 °C for 36 h, and the mixture was concentrated. The residue was dissolved in methanol (0.5 mL) and the mixture was heated to 35 °C. After 2 h, the mixture

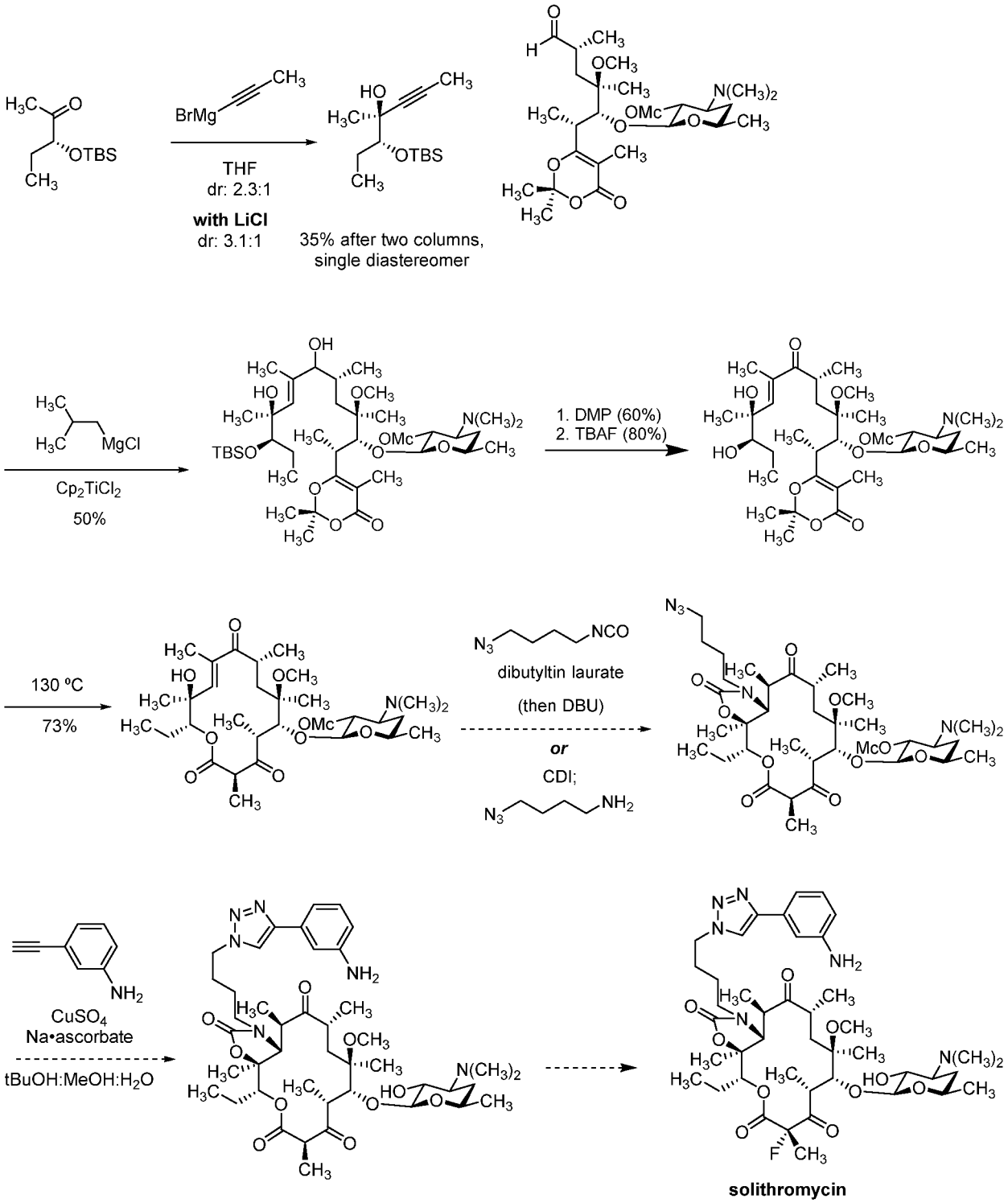
was allowed to cool to 23 °C and was concentrated. The crude residue was purified by column chromatography on silica gel (5% methanol in DCM, 0.5% NH_4OH) to provide telithromycin as a white foam. The produdct was confirmed to be telithromycin by H-NMR and LCMS matching spectra published by Bioorg. Med. Chem. 2006, 14, 5592.

Example 3C. Synthesis of C12-desoxy Analogs by Hydromagnesiation

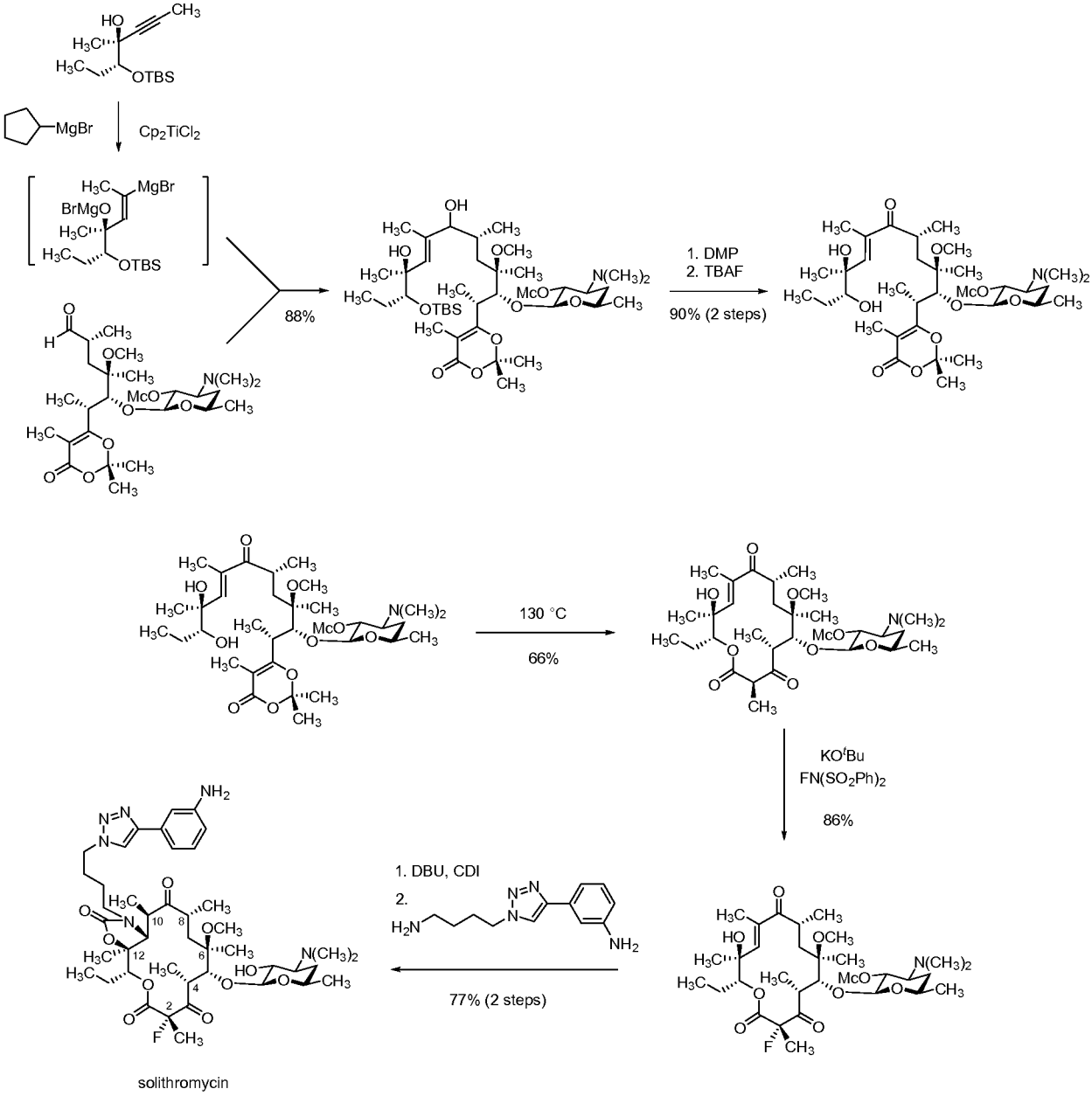


[00613] To a suspension of Cp_2TiCl_2 (3.27 mg, 0.013 mmol) in ethyl ether (525 µl) at 0 °C was added cyclopentyl magnesium chloride (394 µl, 0.788 mmol). The deep grey mixture was stirred for 5 min at this temperature, and a solution of (5R)-5-((tert-butyldiphenylsilyl)oxy)-4-methylhept-2-yn-4-ol (100 mg, 0.263 mmol) in ethyl ether (525 µl) was added. The mixture was allowed to warm to 23 °C (10:30 AM). After 2.5 h, conversion was >90% to a more polar spot that stains pink in anisaldehyde (15% ethyl ether/hexanes). The mixture was cooled to -78 °C (solid crashed out), and (2S,3R,4S,6R)-4-(dimethylamino)-2-(((2R,3R,4R,6R)-4-methoxy-4,6-dimethyl-7-oxo-2-(2,2,5-trimethyl-4-oxo-4H-1,3-dioxin-6-yl)heptan-3-yl)oxy)-6-methyltetrahydro-2H-pyran-3-yl methyl carbonate (71.4 mg, 0.131 mmol) was added as a solution in ether (0.3 mL + 0.2 mL wash). An emulsion formed, which was warmed to 23 °C. The emulsion did not get better, so THF (0.5 mL) was added, and helped a little. TLC showed high conversion to a more polar spot. After 1 h, the mixture was quenched by the addition of sat aq ammonium chloride (1 mL), and the layers were mixed vigorously and separated. THe aqueous layer was extracted with ether (2 x 1 mL), and the combined organic layers were filtered through a pad of sodium sulfate. The filtrate was concentrated, and crude NMR indicated one major product from the eastern half. Column: 25% to 30% acetone in hexanes with +0.5% Et3N). The structure was confirmed by 1D and 2D NMR, along with HRMS as the C12-deoxygenated product (37 mg, 0.055 mmol, 41.9 % yield).

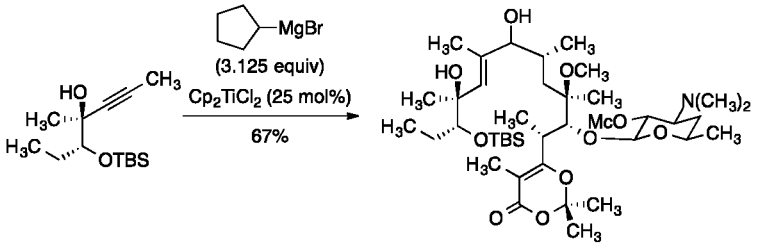
Example 3D. Synthesis of Solithromycin via Hydromagnesiation



Example 3D-1. Synthesis of Solithromycin via Hydromagnesiation (Alternative Route)



Step 1:

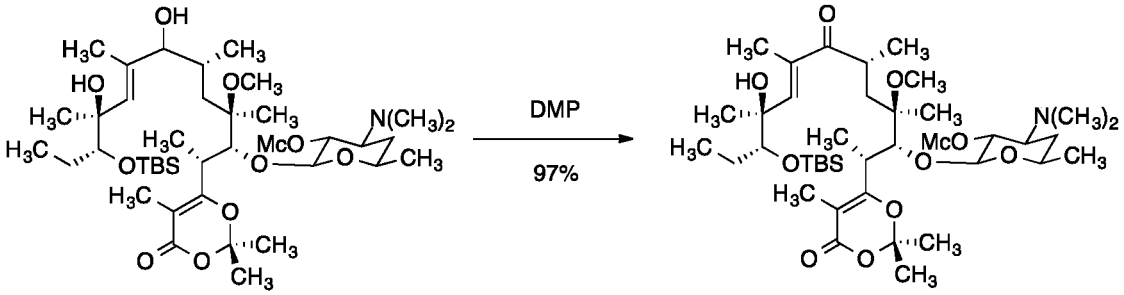


[00614] A flame-dried, 200-mL round-bottom flask was charged with ethyl ether (18.39 ml). The vessel was cooled to 0 °C in an ice–water bath and cyclopentylmagnesium bromide (2.0 M solution in ether, 8.62 ml, 17.24 mmol, 3.13 equiv) was added. Cp_2TiCl_2

(343 mg, 1.38 mmol, 0.25 equiv) was added in a single portion, and the black solution was stirred for 30 minutes at this temperature. A solution of (4S,5R)-5-((tert-butyldimethylsilyl)oxy)-4-methylhept-2-yn-4-ol (1.77 g, 6.90 mmol, 1.25 equiv) in ether (7.5 mL) was added dropwise over the course of 5 minutes. The transfer was quantitated with ether (2 x 1 mL). Stirring was continued at 4 °C for 20 h, after which time a green/gray solid had precipitated from the dark gray solution. Analysis by TLC analysis indicated complete consumption of the starting material and appearance of a less polar spot (85:15 hexanes:ether; visualization: UV and then anisaldehyde stain). The mixture was diluted with THF (18 mL), and the precipitate dissolved. A solution of right half aldehyde (3.00 g, 5.52 mmol, 1 equiv) in THF (7.0 mL) was added dropwise over 5 minutes. The transfer was quantitated with THF (2 x 1 mL). The mixture was stirred at 0 °C for 30 min, at which point TLC indicated complete consumption of starting material (eluent: 50:50:1 acetone:hexanes:triethylamine; visualization: UV and anisaldehyde). Saturated aqueous ammonium chloride (100 mL) was added in a single portion. The resulting biphasic mixture was allowed to warm to 23 °C and was rapidly stirred for 8 h. The mixture was filtered through a sintered glass funnel, and the filtrate was transferred to a 500-mL separatory funnel. The layers were separated, and the aqueous layer was extracted with ethyl ether (3 x 50 mL). The organic layers were combined and the resulting solution was washed with water (100 mL) and brine (100 mL). The washed organic solution was dried with sodium sulfate, filtered, and the filtrate was concentrated. The crude residue was purified by column chromatography on silica gel (20% acetone in hexanes as eluent). The overlapping fractions were re-purified in the same solvent system to provide the allylic alcohol as a 2:1 mixture if diastereomers as a white foam (2.95 g, 3.68 mmol, 67 % yield). Spectrum indicates a 2:1 mixture of diastereomers; reported as seen. TLC (50:50:1 hexanes:acetone:triethylamine): R_f = 0.65 (UV, anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.47 (s, 1.0 H), 5.37 (s, 0.53 H), 4.63 – 4.55 (m, 3.41 H), 4.09 (br s, 0.98 H), 3.96 (d, J = 2.8 Hz, 0.5 H), 3.89 (d, J = 3.1 Hz, 0.97 H), 3.77 (s, 1.43 H), 3.77 (s, 2.65 H), 3.53 – 3.37 (m, 3.21 H), 3.16 (s, 1.43 H), 3.10 (s, 2.82 H), 3.01 (br s, 0.85 H), 2.79 – 2.72 (m, 2.65 H), 2.36 (s, 1.44 H), 2.31 (ap s, 8.89 H), 2.03 – 1.94 (m, 0.89 H), 1.86 (s, 1.51 H), 1.85 (s, 2.50 H), 2.32 – 2.30 (m, 5.79 H), 1.69 – 1.64 (m, 9.90 H), 1.57 – 1.49 (m, 3.72 H), 1.43 – 1.33 (m, 1.82 H), 1.32 (s, 3.25 H), 1.32 (s, 1.65 H), 1.29 (s, 2.55 H), 1.29 – 1.26 (m, 5.27 H), 1.05 (d, J = 7.4 Hz, 3.62 H), 0.97 – 0.91 (m, 16.35 H), 0.81 (d, J = 7.0 Hz, 1.36 H), 0.76 (d, J = 6.8 Hz, 2.66 H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 167.48, 167.10, 162.80, 162.70, 155.20, 137.53, 136.24, 131.05, 126.63, 104.50, 104.47, 100.03, 99.88, 99.79, 99.65, 85.74, 80.39, 80.32, 79.83, 79.73, 77.20, 76.50, 76.48, 76.10, 76.02, 75.66, 75.45, 75.42, 69.28, 69.22,

63.06, 63.00, 54.68, 49.86, 49.49, 40.66, 39.33, 36.08, 33.83, 31.87, 31.48, 30.84, 30.82, 27.39, 26.83, 26.04, 25.91, 25.89, 25.83, 25.80, 24.26, 24.13, 20.97, 20.71, 19.74, 19.18, 18.26, 15.50, 14.97, 12.98, 12.92, 11.46, 11.19, 9.87, 9.79, -3.71, -3.76, -4.22, -4.25. FTIR (neat), cm^{-1}: 3485, 2936, 2858, 2251, 1755, 1720, 1641, 1456, 1377, 1267. HRMS (ESI): Calculated for $(C_{41}H_{75}NO_{12}Si + H)^+$: 802.5131; found: 802.5149.

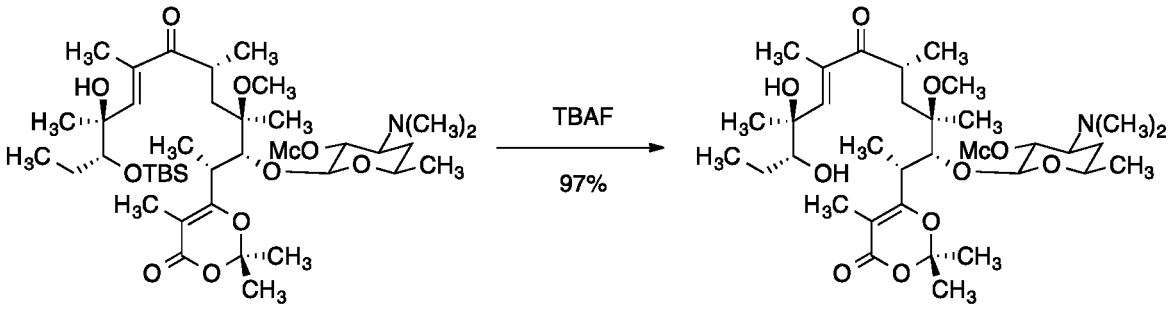
Step 2:



[00615] Dess–Martin periodinane (1.533 g, 3.62 mmol, 1.0 equiv) was added to a solution of Coupled Allylic Alochol (2.9 g, 3.62 mmol, 1 equiv) in water-saturated DCM (36 ml) in a 200-mL round-bottom flask that was immersed in a 22 °C water bath. After 5 minutes, a second portion of Dess–Martin periodinane (1.533 g, 3.62 mmol, 1 equiv) was added. After 90 min, the mixture was diluted with 10% aqueous sodium biarbonate (50 mL) and ether (50 mL). The mixture was stirred vigorously for 3 min, at which time saturated aqueous sodium thiosulfate (50 mL) was added. The resulting cloudy mixture was stirred vigorously for 20 min, and the layers were separated. The aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined, and the resulting solution was washed with 1:1 10% aqueous sodium bicarb:saturated aqueous sodium thiosulfate (50 mL) and brine (50 mL). The washed organic solution was dried with sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the resulting residue was purified by chromatography on silica gel (short column, 160:40:1 hexanes:acetone:triethylamine as eluent) to provide the acyclic TBS protected enone (2.8 g, 3.50 mmol, 97 % yield) as a white foam. TLC (50:50:1 acetone:hexanes:triethylamine): R_f = 0.42 (UV, anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.58 (s, 1H), 4.57 (dd, *J* = 10.3, 7.6 Hz, 1H), 4.52 (d, *J* = 7.6 Hz, 1H), 3.82 (d, *J* = 3.2 Hz, 1H), 3.77 (s, 3H), 3.67 (dd, *J* = 5.9, 4.1 Hz, 1H), 3.49 – 3.40 (m, 1H), 3.40 – 3.29 (m, 2H), 2.89 (s, 3H), 2.75 (ddd, *J* = 12.3, 10.5, 4.4 Hz, 1H), 2.57 (s, 1H), 2.30 (s, 6H), 2.21 (dd, *J* = 14.0, 10.1 Hz, 1H), 1.96 (s, 3H), 1.80 (s, 3H), 1.76 (ddd, *J* = 13.0, 4.2, 1.6 Hz, 1H), 1.69 – 1.66 (m, 1H), 1.64 (s, 6H), 1.57 – 1.49 (m, 1H), 1.43 – 1.38 (m, 1H), 1.36 (s, 3H), 1.35 – 1.31 (m, 1H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.18 (s, 3H), 1.07 (d, *J* = 7.4 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.12 (t, *J* = 4.1 Hz, 6H). ^{13}C

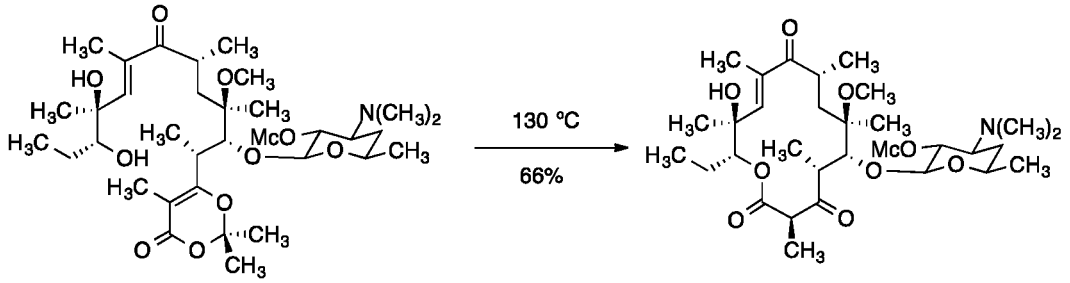
NMR (125 MHz, $CDCl_3$), δ: 206.81, 167.57, 162.98, 155.26, 141.13, 137.14, 104.33, 100.00, 99.98, 79.49, 78.28, 77.20, 77.09, 76.56, 75.50, 69.24, 63.02, 54.71, 49.45, 40.71, 38.95, 34.17, 34.11, 30.98, 26.32, 26.25, 25.96, 25.83, 24.28, 20.98, 20.28, 20.09, 18.22, 13.08, 10.90, 9.66, -3.77, -4.32. FTIR (neat), cm^{-1}: 3565 (br), 2935, 2858, 2251, 1755, 1720, 1641, 1454, 1377, 1267. HRMS (ESI): Calculated for $(C_{41}H_{73}NO_{12}Si + Na)^+$: 822.4794; found: 822.4776.

Step 3:



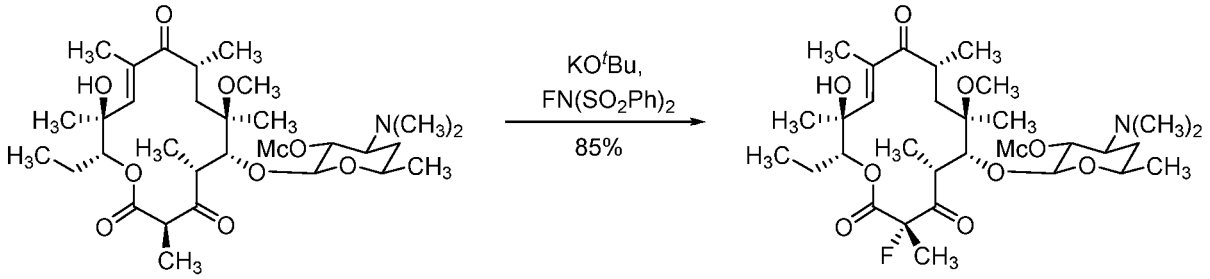
[00616] Tetrabutylammonium fluoride (1.0 M solution in THF, 4.20 ml, 4.20 mmol, 1.2 equiv) was added dropwise to a solution of TBS-protected enone (2.8 g, 3.50 mmol, 1 equiv) in THF (17.50 ml) at 0 °C. The mixture was allowed to warm to 23 °C, and was stirred at this temperature for 90 min, and then was concentrated. The resulting brown oil was purified by column chromatography on silica gel (25-30-40% acetone in hexanes with +0.5% triethylamine additive throughout) to provide the macrocycle precursor as a white foam (2.28 g, 3.32 mmol, 95 % yield). TLC (50:50:1 acetone:hexanes:triethylamine): R_f = 0.51 (UV, anisaldehyde). ^1H NMR (500 MHz, $CDCl_3$), δ: 6.58 (d, J = 1.1 Hz, 1H), 4.57 (dd, J = 10.4, 7.6 Hz, 1H), 4.52 (d, J = 7.6 Hz, 1H), 3.79 (d, J = 3.3 Hz, 1H), 3.77 (s, 3H), 3.49 (dd, J = 10.4, 2.1 Hz, 1H), 3.48 – 3.35 (m, 2H), 3.35 – 3.27 (m, 1H), 2.93 (s, 3H), 2.75 (ddd, J = 12.2, 10.6, 4.3 Hz, 1H), 2.50 (s, 1H), 2.30 (s, 6H), 2.23 (dd, J = 14.1, 10.0 Hz, 1H), 1.98 (d, J = 1.0 Hz, 3H), 1.80 (s, 3H), 1.80 – 1.72 (m, 1H), 1.64 (s, 3H), 1.64 (s, 3H), 1.63 – 1.58 (m, 1H), 1.44 (s, 3H), 1.44 – 1.31 (m, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.15 (s, 3H), 1.06 (d, J = 7.4 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 206.87, 167.56, 163.03, 155.37, 141.01, 137.87, 104.36, 100.00, 99.94, 79.58, 78.21, 77.76, 77.20, 76.22, 75.56, 69.28, 63.03, 54.78, 49.41, 40.73, 38.51, 34.31, 34.21, 30.97, 25.84, 25.11, 24.85, 24.25, 20.96, 20.42, 20.02, 13.03, 12.97, 11.10, 9.66. FTIR (neat), cm^{-1}: 3487 (br), 2974, 2935, 2875, 2833, 2785, 2251, 1753, 1717, 1641. HRMS (ESI): Calculated for $(C_{35}H_{59}NO_{12} + Na)^+$: 708.3929 found: 708.3907.

Step 4:



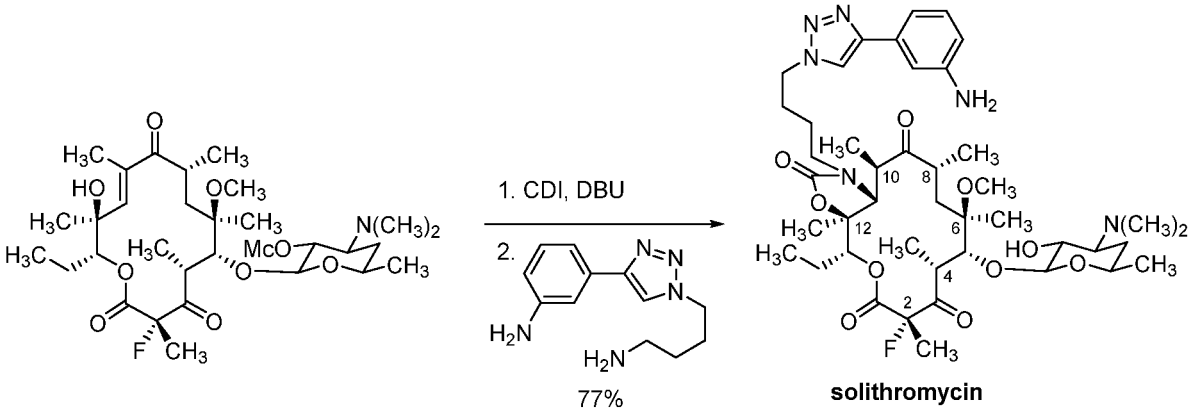
[00617] A solution of Macrocycle precursor (1.70 g, 2.48 mmol, 1 equiv) in chlorobenzene (4.0 mL) in a 5-L round-bottom flask was degassed by means of a stream of argon for 1 h. The vessel was equipped with a dry reflux condensor, and the system was evacuated to 1 Torr and refilled with argon (this process was repeated three times). The vessel and its contents were then heated by means of an oil bath. The solution was maintained at reflux for 16 h, after which time it was allowed to cool to 23 °C and was concentrated. The crude residue was purified by column chromatography (2% methanol in dichloromethane with +0.2% NH4OH). TLC (50:50:1 hexanes:acetone:triethylamine): Compound was a ~5:1 mixture of diastereomers (presumed to be C2 epimers based on equilibration in subsequent steps); spectral data is only reported for the major diastereomer. R_f = 0.60 (UV, anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.58 (s, 1H), 4.94 (dd, *J* = 9.8, 2.9 Hz, 1H), 4.44 (dd, *J* = 10.5, 7.6 Hz, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.10 (d, *J* = 8.6 Hz, 1H), 3.71 (s, 3H), 3.69 (t, *J* = 6.9 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.16 – 3.08 (m, 1H), 3.04 – 2.95 (m, 2H), 2.81 (s, 3H), 2.70 – 2.59 (m, 1H), 2.49 (s, 1H), 2.21 (s, 6H), 1.96 (d, *J* = 1.1 Hz, 3H), 1.95 – 1.86 (m, 1H), 1.79 (dd, *J* = 14.5, 6.1 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.56 – 1.44 (m, 2H), 1.42 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.27 (s, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). FTIR (neat), cm^{-1}: 3493 (br), 2972, 2939, 2879, 2787, 2255, 1745, 1708, 1668, 1456, 1443, 1377, 1265. HRMS (ESI): Calculated for $(C_{32}H_{53}NO_{11} + H)^+$: 628.3691; found: 628.3713.

Step 5:



[00618] A solution of potassium *tert*-butoxide in THF (1.0 M, 89 µL, 0.089 mmol, 1.4 equiv) was added dropwise to a solution of Macrocyclic enone (40 mg, 0.064 mmol, 1 equiv) in THF (0.64 mL) at –78 °C. The mixture was stirred at 78 °C for 5 minutes, and a solution of *N*-fluorobenzenesulfonimide (24 mg, 0.076 mmol, 1.2 equiv) in THF (100 mg/mL) was added. After 5 min, the solution was allowed to warm to 23 °C. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL), saturated aqueous sodium thiosulfate solution (1 mL) and dichloromethane (1 mL) were added sequentially, and the mixture was stirred rapidly for 1 min. The layers took ~5 minutes to resolve, at which point they were separated. The aqueous layer was extracted with dichloromethane (2 x 1 mL). The organic layers were filtered through a pad of sodium sulfate, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (15–20% acetone in hexanes) to afford the fluoromacrocyclic enone as a white foam (35 mg, 85%). TLC (50:50:1 hexanes:acetone:triethylamine): R_f = 0.65 (UV, anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.50 (s, 1H), 5.00 (dd, *J* = 9.4, 2.9 Hz, 1H), 4.51 (dd, *J* = 10.3, 7.6 Hz, 1H), 4.41 (d, *J* = 7.5 Hz, 1H), 4.01 (d, *J* = 10.0 Hz, 1H), 3.81 (s, 3H), 3.57 – 3.42 (m, 2H), 3.04 – 2.94 (m, 1H), 2.77 – 2.68 (m, 1H), 2.66 (s, 3H), 2.27 (s, 6H), 2.11 – 1.99 (m, 2H), 1.97 (s, 3H), 1.85 (dd, *J* = 14.0, 9.2 Hz, 1H), 1.76 (d, *J* = 21.6 Hz, 3H), 1.71 – 1.56 (m, 2H), 1.51 (s, 3H), 1.41 – 1.30 (m, 2H), 1.28 – 1.21 (m, 9H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). FTIR (neat), cm^{-1}: 3497 (br), 2974, 1753, 1654, 1442, 1263, 1053, 997. HRMS (ESI): Calculated for $(C_{32}H_{52}FNO_{11} + Na)^+$: 668.3417; found: 668.3407.

Step 6:

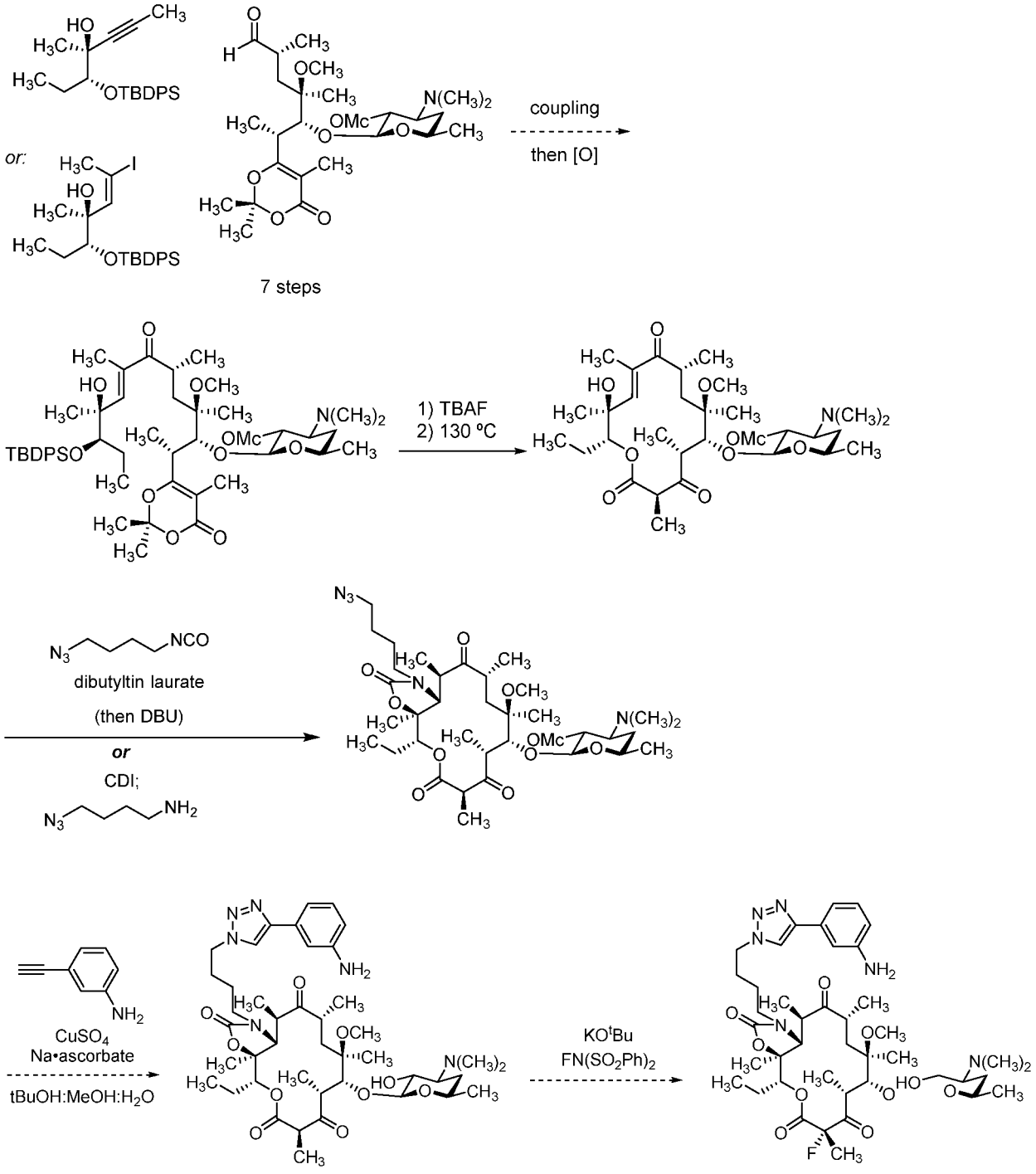


[00619] DBU (55 µL, 0.37 mmol, 3.0 equiv) was added to a solution of Fluoro Macrocyclic Enone (79 mg, 0.122 mmol, 1 equiv) in DCM (1.22 mL) at –10 °C (ice/acetone bath). A solution of carbonyl diimidazole (60 mg, 0.37 mmol, 3.0 equiv) in dichloromethane (0.23 mL) was added dropwise via syringe. After 30 min, TLC in 50:50:1

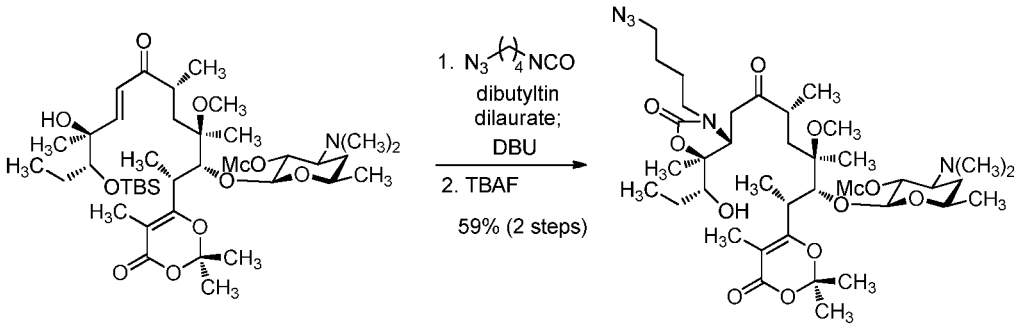
acetone:hexanes:triethylamine indicated complete conversion to a more polar spot. After 1.5 h total, saturated aqueous ammonium chloride solution (3 mL) was added. The mixture was extracted with ether (3 x 2 mL). The organic layers were combined and the resulting solution was washed with water (2 mL) and brine (2 mL). The dried organic solution was gravity-filtered through a pad of sodium sulfate. The filtrate was concentrated to provide the crude acyl imidazolide intermediate as a white foam. NMR analysis of the residue showed the desired product in high purity. The foam was dried under vacuum (0.1 mmHg) at 23 °C for 12 h. 3-(1-(4-aminobutyl)-1H-1,2,3-triazol-4-yl)aniline (84 mg, 0.37 mmol, 3.0 equiv), acetonitrile (0.30 mL) and DBU (18 μL, 0.12 mmol, 1.0 equiv) were added sequentially. The resulting solution was warmed to 45 °C. In 2 h, TLC analysis (50% acetone–hexanes) indicated full consumption of starting material. The reaction mixture was allowed to cool to 23 °C. Methanol (5 mL) was added, and the solution was allowed to stand at 23 °C. After 24 h, the reaction solution was concentrated under reduced pressure. The residue was partitioned between water (5 mL) and dichloromethane (5 mL). The aqueous layer was separated and further extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (3% methanol–dichloromethane + 0.3% saturated aqueous ammonium hydroxide) to provide solithromycin (79 mg, 77%) as a white powder. TLC (90:10:1 dichloromethane:methanol:saturated aqueous ammonium hydroxide): R_f = 0.48 (UV, anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.31 – 7.29 (m, 1H), 7.23 – 7.15 (m, 2H), 6.66 (dt, *J* = 7.2, 2.1 Hz, 1H), 4.89 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.43 (td, *J* = 7.1, 1.5 Hz, 2H), 4.32 (d, *J* = 7.3 Hz, 1H), 4.08 (d, *J* = 10.6 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.68 – 3.60 (m, 1H), 3.60 – 3.49 (m, 2H), 3.45 (s, 1H), 3.20 (dd, *J* = 10.2, 7.3 Hz, 1H), 3.13 (q, *J* = 6.9 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.57 (s, 3H), 2.51 – 2.42 (m, 1H), 2.29 (s, 6H), 2.05 – 1.93 (m, 3H), 1.90 (dd, *J* = 14.5, 2.7 Hz, 1H), 1.79 (d, *J* = 21.4 Hz, 3H), 1.75 – 1.60 (m, 4H), 1.55 (d, *J* = 13.0 Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.28 – 1.24 (m, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.52, 202.79 (d, *J* = 28.0 Hz), 166.44 (d, *J* = 22.9 Hz), 157.19, 147.82, 146.82, 131.72, 129.63, 119.66, 116.14, 114.71, 112.36, 104.24, 97.78 (d, *J* = 206.2 Hz), 82.11, 80.72, 78.59, 78.54, 70.35, 69.64, 65.82, 61.05, 49.72, 49.22, 44.58, 42.77, 40.86, 40.22, 39.57, 39.20, 28.13, 27.59, 25.20 (d, *J* = 22.4 Hz).
24.28, 22.14, 21.15, 19.76, 17.90, 15.04, 14.70, 13.76, 10.47. ^{19}F NMR (471 MHz, $CDCl_3$) δ –163.24 (q, *J* = 11.2 Hz). FTIR (neat), cm^{-1}: 3362 (br), 2976 (m), 1753 (s), 1460 (s), 1263 (s),

1078 (s), 1051 (s), 991 (s). HRMS (ESI): Calcd for $(C_{43}H_{65}FN_6O_{10} + H)^+$: 845.4819; Found: 845.4841.

Example 3E. Synthesis of Solithromycin via Hydroacylation

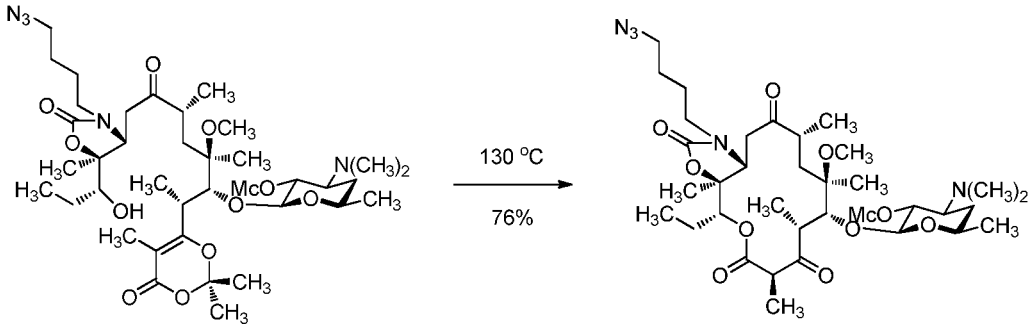


Example 3F. Synthesis of Exemplary 10-Desmethyl Ketolides

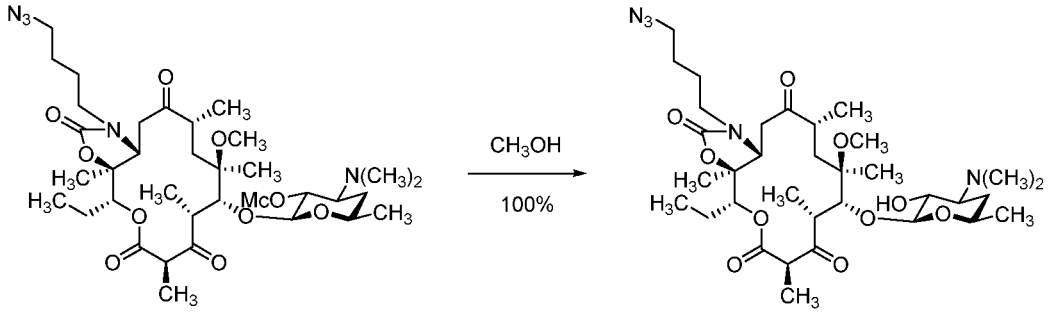


[00620] 1-Azido-4-isocyanatobutane (176 mg, 1.26 mmol, 5.00 equiv) and dibutyltin dilaurate (150 μL, 0.252 mmol, 1.00 equiv) were added to a solution of HWE_Product (198 mg, 0.252 mmol, 1 equiv) in dichloromethane (2.5 mL) at 23 °C. The solution was warmed to 80 °C and held at that temperature for 6 h, at which point LC-MS indicated full consumption of starting material. The solution was concentrated under reduced pressure and the residue was dissolved in DMF (2 mL). DBU (38.0 μL, 0.252 mmol, 1.00 equiv) was added at 23 °C. After 1 h, the reaction mixture was partitioned between ether (10 mL) and water (5 mL). The aqueous layer was extracted with ether (2 x 5 mL). The combined ether layers were washed with saturated sodium chloride solution and dried over magnesium sulfate. The dried solution was concentrated under reduced pressure and the residue was dissolved in THF (2 mL). A solution of TBAF in THF (1.0 M, 0.378 mL, 0.378 mmol, 1.50 equiv) was added via syringe at 23 °C. After 20 min, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product as a white foam (120 mg, 59%). ^{1}H NMR (10:1 ratio of C11 epimers, major epimer is reported, 500 MHz, $CDCl_3$) δ 4.60 – 4.50 (m, 2H), 4.27 (t, J = 5.9 Hz, 1H), 3.87 (d, J = 3.5 Hz, 1H), 3.77 (s, 3H), 3.51 (d, J = 10.5 Hz, 1H), 3.49 – 3.41 (m, 2H), 3.32 (t, J = 6.5 Hz, 2H), 3.25 (qd, J = 7.2, 3.4 Hz, 1H), 2.96 (s, 3H), 2.91 – 2.87 (m, 1H), 2.87 – 2.80 (m, 1H), 2.80 – 2.71(m, 2H), 2.29 (s, 6H), 2.02 (dd, J = 14.1, 10.7 Hz, 1H), 1.81 (s, 3H), 1.79 – 1.74 (m, 1H), 1.67 (d, J = 6.3 Hz, 3H), 1.65 (s, 3H), 1.63 – 1.51 (m, 5H), 1.45 (dd, J = 14.2, 1.9 Hz, 1H), 1.42 – 1.33 (m, 3H), 1.33 – 1.27 (m, 1H), 1.25 (d, J = 6.0 Hz, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.4 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.38, 167.16, 162.69, 156.89, 155.22, 104.51, 100.00, 99.58, 83.44, 78.67, 78.25, 75.41, 69.27, 62.94, 54.67, 54.45, 50.89, 49.62, 41.48, 41.29, 40.68, 40.61, 38.35, 34.02, 30.75, 25.94, 24.12, 23.99, 23.44, 20.92, 20.01, 19.06, 16.50, 13.08, 10.79, 9.72. FTIR (neat), cm^{-1}:

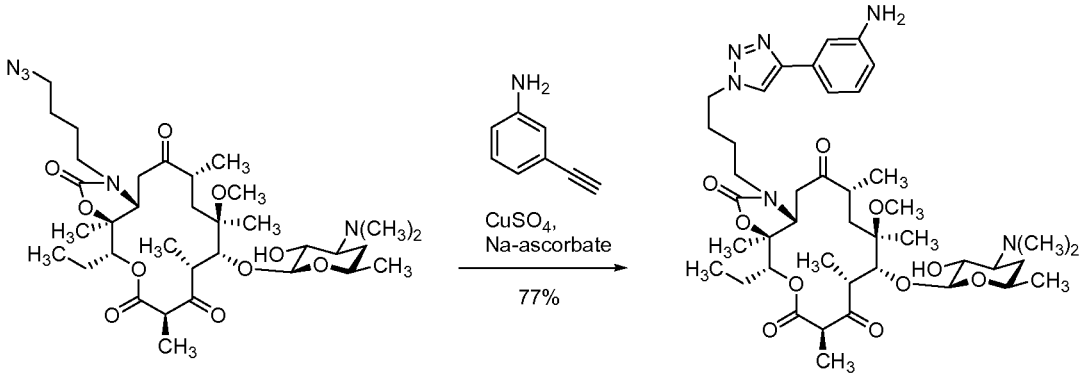
3443(br), 2939 (m), 2096 (s), 1747 (s), 1720 (s), 1641 (s), 1265 (s), 1053 (s), 731 (s); HRMS (ESI): Calcd for $(C_{39}H_{65}N_5O_{13} + H)^+$: 812.4652; Found: 812.4666.



[00621] Cyclic carbamate (110 mg, 0.135 mmol) was dried by azeotropic distillation (benzene) and was dissolved in chlorobenzene (13.5 mL) in a 50-mL flask. The flask was fitted with a dry reflux condenser, and dry argon was bubbled through the solution via a 19-gauge needle for 10 min. The flask was then immersed in a 150-°C oil bath to maintain a gentle reflux of the reaction solution. After 16 h, the reaction solution was cooled to 23 °C and concentrated under reduced pressure (rotary evaporation, 10 mmHg, 40 °C water bath). The residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product as a white foam (78 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (dd, J = 9.1, 3.1 Hz, 1H), 4.49 (dd, J = 10.4, 7.6 Hz, 1H), 4.39 (d, J = 7.3 Hz, 1H), 3.97 (d, J = 10.1 Hz, 1H), 3.84 – 3.81 (m, 1H), 3.79 (s, 3H), 3.71 (q, J = 7.1 Hz, 1H), 3.55 – 3.42 (m, 2H), 3.37 – 3.25 (m, 2H), 3.10 – 3.00 (m, 1H), 3.00 – 2.89 (m, 2H), 2.76 – 2.66 (m, 1H), 2.66 – 2.57 (m, 1H), 2.53 (s, 3H), 2.39 (dd, J = 18.0, 9.3 Hz, 1H), 2.26 (s, 6H), 2.01 – 1.88 (m, 1H), 1.78 – 1.66 (m, 4H), 1.66 – 1.47 (m, 4H), 1.43 (d, J = 6.8 Hz, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.28 – 1.24 (m, 1H), 1.22 (d, J = 5.7 Hz, 3H), 1.16 (d, J = 7.0 Hz, 6H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.98, 203.32, 168.76, 156.80, 155.18, 101.78, 81.62, 81.09, 79.65, 78.57, 75.56, 69.18, 63.24, 59.95, 54.80, 51.52, 51.02, 49.70, 48.45, 43.69, 42.92, 40.72, 40.61, 36.60, 30.17, 26.09, 25.22, 23.52, 20.85, 19.15, 18.20, 18.00, 15.35, 14.83, 10.47. FTIR (neat), cm^{-1}: 2939 (m), 2096 (s), 1751 (s), 1712 (s), 1265 (s), 1053 (s), 993 (s), 731 (s); HRMS (ESI): Calcd for $(C_{36}H_{59}N_5O_{12} + H)^+$: 754.4233; Found: 754.4257.



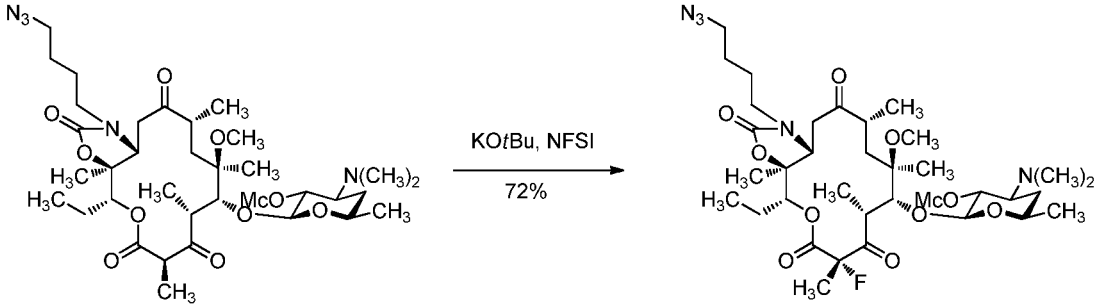
[00622] A solution of C10-desmethyl-macrocycle (29 mg, 0.038 mmol) in methanol (1 mL) was allowed to stand at 23 °C for 24 h. The solution was then concentrated under reduced pressure to afford the product as a white foam (27 mg, 100%). ^{1}H NMR (8:1 diastereomeric mixture at C2, major isomer is reported, 500 MHz, cdcl$_3$) δ 4.96 (dd, *J* = 9.1, 3.2 Hz, 1H), 4.31 (d, *J* = 7.3 Hz, 1H), 4.00 (d, *J* = 10.3 Hz, 1H), 3.86 (d, *J* = 8.7 Hz, 1H), 3.74 (q, *J* = 7.0 Hz, 1H), 3.61 – 3.38 (m, 3H), 3.38 – 3.24 (m, 2H), 3.17 (dd, *J* = 10.2, 7.3 Hz, 1H), 3.11 – 2.95 (m, 2H), 2.68 – 2.59 (m, 1H), 2.56 (s, 3H), 2.49 – 2.43 (m, 1H), 2.40 (dd, *J* = 18.2, 9.6 Hz, 1H), 2.27 (s, 6H), 2.03 – 1.91 (m, 1H), 1.87 (dd, *J* = 14.4, 3.8 Hz, 1H), 1.84 – 1.70 (m, 2H), 1.70 – 1.64 (m, 1H), 1.64 – 1.50 (m, 4H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.22 – 1.20 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.97, 203.53, 168.77, 156.89, 104.29, 82.46, 81.11, 79.71, 78.58, 70.32, 69.60, 65.78, 59.99, 51.62, 51.05, 49.70, 48.74, 43.78, 42.96, 41.20, 40.19, 36.54, 28.09, 26.12, 25.23, 23.56, 21.11, 19.13, 18.22, 17.98, 15.34, 15.28, 10.48. FTIR (neat), cm^{-1}: 3444 (br), 2970 (m), 2096 (s), 1747 (s), 1712 (m), 1070 (s), 908 (s), 731 (s); HRMS (ESI): Calcd for $(C_{34}H_{57}N_5O_{10} + H)^+$: 696.4178; Found: 696.4194.



FSM-21535

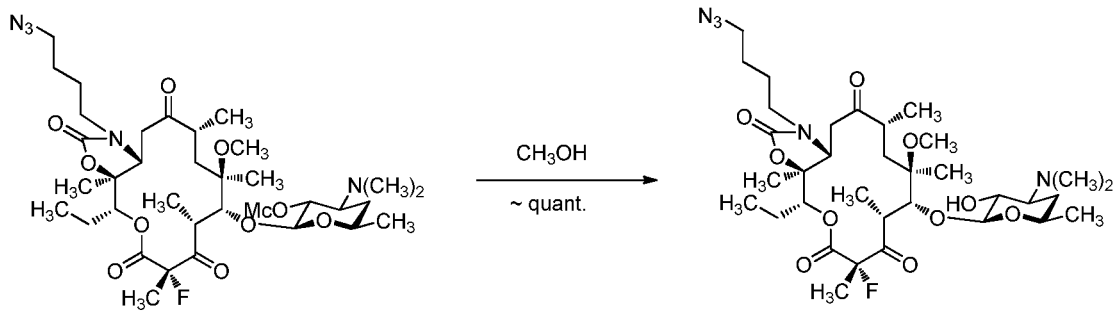
[00623] 3-ethynylaniline (13.6 mg, 0.116 mmol, 3.00 equiv), an aqueous solution of sodium ascorbate (0.10 M, 78 μL, 7.7 μmol, 0.20 equiv) and an aqueous solution of copper (II) sulfate (0.10 M, 19 μL, 1.9 μmol, 0.050 equiv) were added sequentially to a solution of

C10-desmethyl-ketolide-2'OH (27 mg, 39 μmol) in 1:1 *t*-butanol:water (0.8 mL) at 23 °C. After 16 h, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (1 mL) and dichloromethane (1 mL). The aqueous layer was separated and further extracted with dichloromethane (2 x 1 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product as a pale yellow solid (24.3 mg, 77%). TLC (10% methanol–dichloromethane + 1% saturated aqueous ammonium hydroxide solution): R_f = 0.60 (UV, *p*-anisaldehyde). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.24 – 7.09 (m, 3H), 6.66 (d, *J* = 6.2 Hz, 1H), 4.97 (d, *J* = 9.0 Hz, 1H), 4.45 (t, *J* = 6.7 Hz, 2H), 4.32 (d, *J* = 7.2 Hz, 1H), 3.98 (d, *J* = 10.3 Hz, 1H), 3.85 (d, *J* = 9.3 Hz, 1H), 3.73 (q, *J* = 6.9 Hz, 1H), 3.62 – 3.49 (m, 2H), 3.24 – 3.14 (m, 1H), 3.14 – 2.89 (m, 3H), 2.67 – 2.55 (m, 1H), 2.52 (s, 3H), 2.49 – 2.43 (m, 1H), 2.37 (dd, *J* = 18.6, 9.2 Hz, 1H), 2.30 (s, 6H), 2.06 – 1.91 (m, 2H), 1.89 – 1.63 (m, 7H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.28 (d, *J* = 10.9 Hz, 3H), 1.25 (d, *J* = 5.6 Hz, 3H), 1.23 – 1.20 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 210.15, 203.51, 168.76, 157.01, 147.76, 146.83, 131.60, 129.64, 119.71, 115.99, 114.75, 112.20, 104.26, 82.48, 81.22, 79.69, 78.58, 70.30, 69.57, 65.75, 60.05, 51.61, 49.73, 49.65, 48.72, 43.74, 42.59, 41.20, 40.18, 36.45, 28.08, 27.45, 24.97, 23.57, 21.10, 19.07, 18.25, 17.98, 15.33, 15.29, 10.46. FTIR (neat), cm^{-1}: 3365 (br), 2939 (m), 1747 (s), 1708 (m), 1163 (s), 1074 (s), 1049 (s), 995 (s), 731 (s); HRMS (ESI): Calcd for $(C_{42}H_{64}N_6O_{10} + H)^+$: 813.4757; Found: 813.4764.

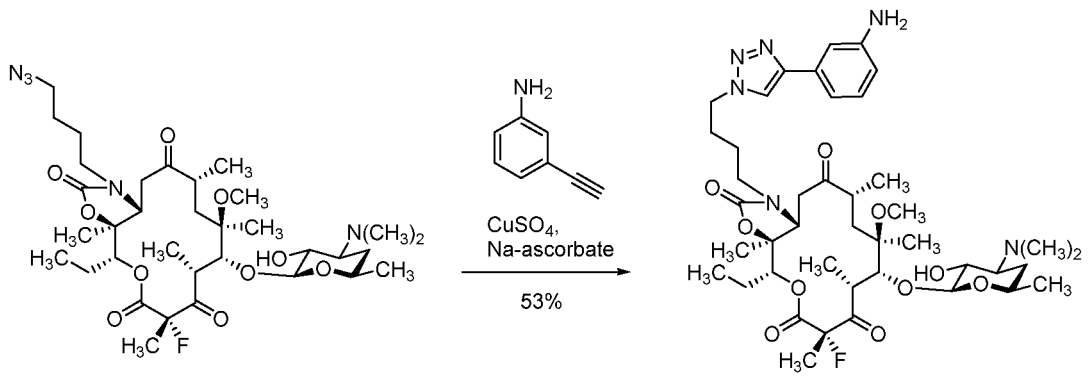


[00624] A solution of potassium *tert*-butoxide in THF (1.0 M, 0.044 mL, 0.044 mmol, 1.1 equiv) was added dropwise via syringe to a solution of C10-desmethylmarcrocycle (30 mg, 0.040 mmol, 1 equiv) in THF (0.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 30 min and warmed to –20 °C. After 5 min, the solution was cooled to –78 °C, and a solution of *N*-fluorobenzenesulfonimide (13 mg, 0.040 mmol, 1.0 equiv) in THF (0.5 mL) was added via syringe. After 20 min, saturated aqueous sodium bicarbonate solution (1 mL)

and ethyl acetate (5 mL) were added., and the mixture was allowed to warm to 23 °C. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with saturated sodium chloride solution and dried over sodium sulfate. The dried solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product (22 mg, 72%) as a white foam. ^{1}H NMR (500 MHz, cdcl$_3$) δ 4.94 (dd, *J* = 8.2, 3.7 Hz, 1H), 4.50 (dd, *J* = 10.5, 7.6 Hz, 1H), 4.42 (d, *J* = 7.6 Hz, 1H), 3.85 (d, *J* = 10.4 Hz, 1H), 3.81 (s, 3H), 3.83 – 3.79 (m, 1H), 3.62 – 3.57 (m, 1H), 3.55 – 3.37 (m, 2H), 3.36 – 3.24 (m, 2H), 3.06 (d, *J* = 18.4 Hz, 1H), 2.76 – 2.67 (m, 2H), 2.65 – 2.56 (m, 1H), 2.43 (s, 3H), 2.42 – 2.33 (m, 1H), 2.26 (s, 6H), 2.06 – 1.90 (m, 2H), 1.75 (d, *J* = 21.4 Hz, 3H), 1.70 – 1.48 (m, 7H), 1.38 (s, 3H), 1.28 (s, 3H), 1.27 – 1.24 (m, 1H), 1.22 (d, *J* = 6.1 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 6H), 0.95 (t, *J* = 7.5 Hz, 3H). HRMS (ESI): Calcd for ($C_{36}H_{58}FN_5O_{12}$ + H)$^+$: 772.4139; Found: 772.4155.

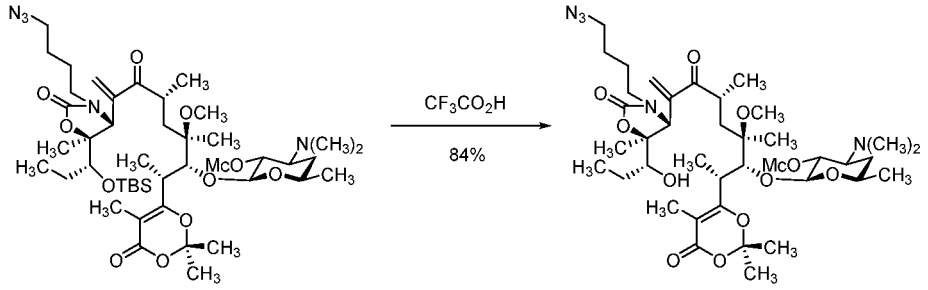


[00625] A solution of C10-desmethyl-C2-fluoro-macrocycle (8.0 mg, 10 μmol) in methanol (1 mL) was allowed to stand at 23 °C for 24 h. The solution was then concentrated under reduced pressure to afford the product as a white foam (7.4 mg, ~100%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.94 (dd, *J* = 8.1, 3.8 Hz, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 3.87 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.7 Hz, 1H), 3.75 – 3.66 (m, 1H), 3.56 – 3.49 (m, 1H), 3.49 – 3.40 (m, 1H), 3.37 – 3.23 (m, 2H), 3.24 – 3.14 (m, 1H), 3.09 (d, *J* = 18.8 Hz, 1H), 3.04 (dd, *J* = 12.6, 4.1 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.52 – 2.47 (m, 1H), 2.45 (s, 3H), 2.39 (dd, *J* = 18.7, 9.9 Hz, 1H), 2.28 (s, 6H), 2.05 – 1.93 (m, 2H), 1.93 – 1.81 (m, 2H), 1.75 (d, *J* = 21.4 Hz, 3H), 1.72 – 1.46 (m, 5H), 1.39 (s, 3H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 1.27 – 1.25 (m, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H).
HRMS (ESI): Calcd for ($C_{34}H_{56}FN_5O_{10}$ + H)$^+$: 714.4084; Found: 714.4101.



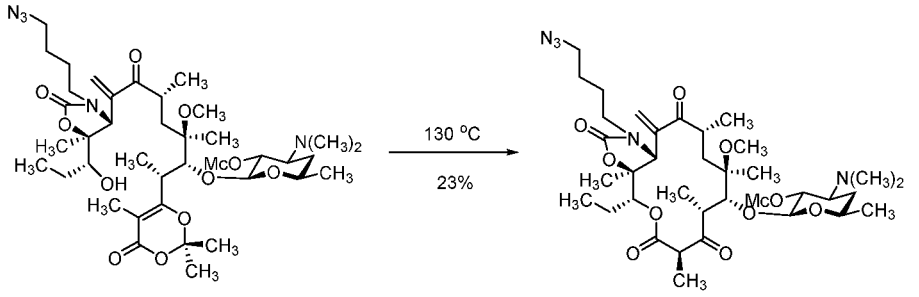
FSM-21598

[00626] 3-ethynylaniline (3.5 mg, 0.030 mmol, 3.0 equiv), an aqueous solution of sodium ascorbate (0.1 M, 19 µL, 1.9 µmol, 0.20 equiv) and an aqueous solution of copper (II) sulfate (0.1 M, 4.9 µL, 0.49 µmol, 0.050 equiv) were added sequentially to a solution of C10-desmethyl-C2-fluoro-ketolide-2'OH (7.4 mg, 10 µmol) in 1:1 *t*-butanol:water (0.2 mL) at 23 °C. After 16 h, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (1 mL) and dichloromethane (1 mL). The aqueous layer was separated and further extracted with dichloromethane (2 x 1 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product as a pale yellow solid (4.3 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.26 – 7.13 (m, 3H), 6.68 – 6.61 (m, 1H), 4.96 (dd, *J* = 8.1, 3.8 Hz, 1H), 4.45 (dd, *J* = 7.4, 6.2 Hz, 2H), 4.36 (d, *J* = 7.3 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.81 (d, *J* = 9.7 Hz, 1H), 3.76 – 3.63 (m, 1H), 3.59 – 3.48 (m, 2H), 3.20 (dd, *J* = 10.2, 7.3 Hz, 1H), 3.09 (d, *J* = 18.7 Hz, 1H), 3.06 – 2.99 (m, 1H), 2.63 – 2.55 (m, 1H), 2.55 – 2.45 (m, 1H), 2.42 (s, 3H), 2.34 (dd, *J* = 18.7, 9.9 Hz, 1H), 2.29 (s, 6H), 2.09 – 1.81 (m, 4H), 1.77 (d, *J* = 21.4 Hz, 3H), 1.74 – 1.54 (m, 5H), 1.40 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.29 (s, 3H), 1.28 – 1.26 (m, 1H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.78, 202.42 (d, *J* = 29.1 Hz), 165.28 (d, *J* = 23.4 Hz), 157.08, 147.79, 146.83, 131.61, 129.66, 119.72, 116.03, 114.78, 112.21, 104.30, 96.39 (d, *J* = 207.0 Hz),83.06, 81.30, 81.18, 79.02, 70.29, 69.55, 65.81, 60.66, 49.75, 48.90, 43.63, 42.68, 40.64, 40.22, 39.20, 36.22, 28.24, 27.48, 25.96 (d, *J* = 23.2 Hz), 25.04, 23.87, 21.12, 18.79, 17.87, 16.10, 15.25, 10.67. FTIR (neat), cm^{-1}: 3381 (br), 2974 (s), 2098 (s), 1753 (s), 1712 (s), 1267 (s), 1053 (s), 731 (s); HRMS (ESI): Calcd for $(C_{42}H_{63}FN_6O_{10} + H)^+$: 831.4662; Found: 831.4668.



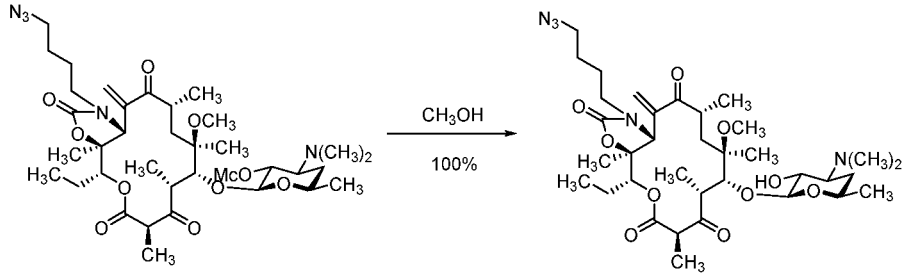
[00627] Trifluoroacetic acid (0.30 mL, 3.9 mmol, 56 equiv) was added to a solution of Open chain exomethylene (65 mg, 0.069 mmol, 1 equiv) in 9:1 dichloromethane:water (1.0 mL) at 0 °C. The solution was allowed to warm to 23 °C and was stirred at that temperature for 20 h. Saturated aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over sodium sulfate and the dried solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product as a white foam (48 mg, 84%). ^{1}H NMR (500 MHz, cdcl$_3$) δ 6.68 (br s, 1H), 5.91 (br s, 1H), 4.82 (br s, 1H), 4.60 – 4.49 (m, 2H), 3.84 (d, *J* = 3.8 Hz, 1H), 3.80 (s, 3H), 3.62 – 3.41 (m, 4H), 3.38 – 3.23 (m, 3H), 2.91 (s, 3H), 2.77 (ddd, *J* = 12.3, 10.2, 4.4 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.32 (s, 6H), 1.82 (s, 3H), 1.81 – 1.74 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.70 – 1.52 (m, 6H), 1.45 (d, *J* = 13.1 Hz, 1H), 1.35 (dd, *J* = 23.8, 12.6 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.21 (s, 3H), 1.13 – 1.04 (m, 12H).

^{13}C NMR (126 MHz, cdcl$_3$) δ 205.60, 167.23, 162.76, 157.55, 155.27, 141.72, 127.44, 104.41, 100.18, 99.71, 84.33, 78.89, 78.22, 77.57, 75.41, 69.24, 62.93, 58.17, 50.76, 49.63, 41.67, 40.60, 38.05, 34.58, 34.34, 30.82, 25.98, 25.94, 23.99, 23.97, 23.44, 20.95, 20.25, 17.48, 13.08, 10.91, 9.58. HRMS (ESI): Calcd for $(C_{40}H_{65}N_5O_{13} + H)^+$: 824.4652; Found: 824.4672.



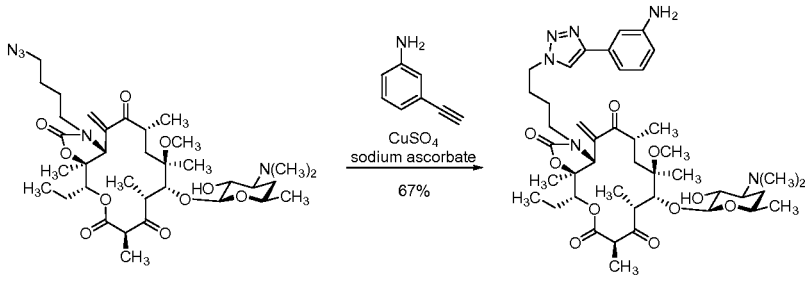
[00628] C10-methyl macrocyclization precursor (70 mg, 0.085 mmol) was dissolved in chlorobenzene (85 mL) in a 200-mL flask. The flask was fitted with a dry reflux condensor. Dry argon was bubbled through the solution via a 19-gauge needle for 10 min. The flask was

then immersed in an oil bath preheated to 150 °C to allow a gentle reflux of the reaction solution. After 16 h, the heating bath was removed and the solution was allowed to cool to 23 °C. The cooled solution was concentrated under reduced pressure (rotary evaporation, ~10 mmHg, 40 °C water bath) and the residue was purified by flash column chromatography (2→3% methanol–dichloromethane + 0.2→0.3% saturated aqueous ammonium hydroxide solution) to afford the product as a white foam (15 mg, 23%). ^{1}H NMR (17:1 diastereomeric mixture at C2, major isomer is reported, 500 MHz, cdcl$_3$) δ 6.03 (s, 1H), 5.53 (s, 1H), 4.93 (dd, J = 11.0, 1.9 Hz, 1H), 4.52 (dd, J = 10.6, 7.5 Hz, 1H), 4.37 (d, J = 7.5 Hz, 1H), 4.19 (d, J = 8.8 Hz, 1H), 4.01 (q, J = 7.0 Hz, 1H), 3.95 (s, 1H), 3.81 (s, 3H), 3.60 – 3.44 (m, 2H), 3.41 – 3.17 (m, 3H), 2.97 – 2.86 (m, 1H), 2.75 (s, 3H), 2.75 – 2.60 (m, 1H), 2.42 – 2.31 (m, 1H), 2.29 (s, 6H), 1.96 – 1.86 (m, 1H), 1.86 – 1.51 (m, 8H), 1.47 (d, J = 7.1 Hz, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 1.25 (d, J = 6.1 Hz, 3H), 1.23 – 1.21 (m, 1H), 1.18 (d, J = 6.9 Hz, 6H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (17:1 diastereomeric mixture at C2, major isomer is reported, 126 MHz, cdcl$_3$) δ 206.87, 205.57, 171.25, 156.81, 155.22, 145.01, 120.69, 101.66, 83.33, 77.79, 77.59, 75.65, 69.06, 63.26, 63.08, 54.83, 51.09, 50.81, 50.42, 49.04, 42.74, 41.46, 40.62, 38.97, 30.47, 26.13, 25.05, 21.55, 21.49, 20.91, 20.14, 18.52, 16.20, 13.96, 10.33. FTIR (neat), cm^{-1}: 2974 (m), 2098 (m), 1753 (s), 1456 (m), 1267 (s), 1057 (s). HRMS (ESI): Calcd for $(C_{37}H_{59}N_5O_{13} + H)^+$: 782.4182; Found: 782.4186.



[00629] A solution of Exomethylene-macrocycle (15 mg, 0.020 mmol) in methanol (1 mL) was allowed to stand at 23 °C for 24 h. The solution was then concentrated under reduced pressure to afford the product as a white foam (14 mg, 100%). ^{1}H NMR (500 MHz, cdcl$_3$) δ 6.02 (s, 1H), 5.52 (s, 1H), 4.94 (dd, J = 10.9, 1.7 Hz, 1H), 4.28 (d, J = 7.3 Hz, 1H), 4.20 (d, J = 9.0 Hz, 1H), 4.04 (q, J = 7.0 Hz, 1H), 3.97 (s, 1H), 3.62 – 3.47 (m, 2H), 3.47 – 3.38 (m, 1H), 3.38 – 3.23 (m, 2H), 3.18 (dd, J = 10.2, 7.3 Hz, 1H), 3.00 – 2.86 (m, 1H), 2.76 (s, 3H), 2.73 – 2.61 (m, 1H), 2.57 – 2.42 (m, 2H), 2.28 (s, 6H), 1.95 – 1.85 (m, 1H), 1.85 – 1.75 (m, 1H), 1.75 – 1.51 (m, 7H), 1.48 (d, J = 7.1 Hz, 3H), 1.40 (s, 3H), 1.33 (d, J = 7.5 Hz, 3H), 1.30 (s, 3H), 1.28 – 1.25 (m, 1H), 1.24 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H),

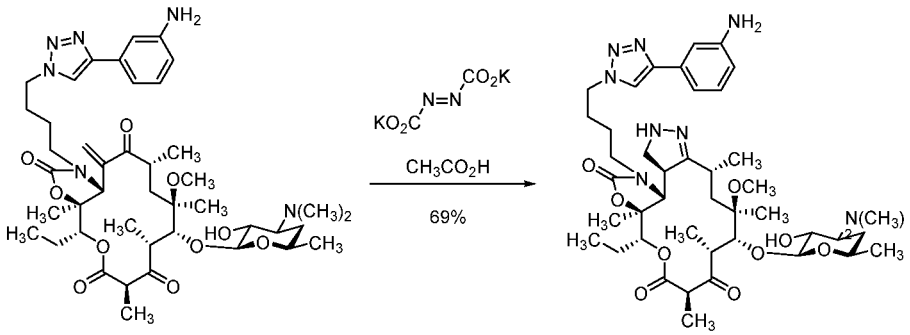
0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 206.40, 205.92, 171.31, 156.84, 145.10, 120.54, 104.20, 83.34, 78.44, 77.82, 77.17, 70.43, 69.44, 65.73, 63.23, 51.03, 50.81, 50.47, 49.24, 42.75, 41.69, 40.22, 39.01, 30.30, 29.67, 28.29, 26.14, 25.01, 21.55, 21.47, 21.16, 20.15, 18.66, 16.25, 14.45, 10.32. FTIR (neat), cm^{-1}: 3454 (br), 2937 (m), 2098 (m), 1753 (s), 1458 (m), 1161 (s), 1053 (s). HRMS (ESI): Calcd for ($C_{35}H_{57}N_5O_{10}$ + H)$^+$: 708.4178; Found: 708.4195.



FSM-21828

[00630] 3-ethynylaniline (7.0 mg, 0.059 mmol, 3.0 equiv), an aqueous solution of sodium ascorbate (0.10 M, 40 µL, 4.0 µmol, 0.20 equiv) and an aqueous solution of copper(II) sulfate (0.10 M, 10 µL, 1.0 µmol, 0.050 equiv) were added sequentially to a stirred solution of C10-methylenemacrocycle (14 mg, 0.020 mmol, 1 equiv) 1:1 *t*-butanol:water (0.2 mL). After 16 h, the reaction mixture was partitioned between dichloromethane (1 mL) and saturated aqueous sodium bicarbonate solution (1 mL). The aqueous layer was extracted with dichloromethane (2 x 1 mL). The combined organic layers were dried over sodium sulfate and the dried solution was concentrated under reduced pressure. The residue was purified by preparatory thin layer chromatography (10% methanol–dichloromethane + 1% saturated ammonium hydroxide solution) to afford FSM-21828 as a white solid (11 mg, 67%). ^{1}H NMR (10:1 diastereomeric mixture at C2, major isomer is reported, 500 MHz, cdcl$_3$) δ 7.80 (s, 1H), 7.32 – 7.29 (m, 1H), 7.24 – 7.19 (m, 2H), 6.71 – 6.62 (m, 1H), 6.02 (s, 1H), 5.51 (s, 1H), 4.94 (dd, J = 10.9, 1.7 Hz, 1H), 4.51 – 4.33 (m, 2H), 4.28 (d, J = 7.3 Hz, 1H), 4.18 (d, J = 9.0 Hz, 1H), 4.06 (q, J = 7.1 Hz, 1H), 3.98 (s, 1H), 3.80 (br s, 2H), 3.60 – 3.48 (m, 2H), 3.48 – 3.37 (m, 1H), 3.18 (dd, J = 10.2, 7.3 Hz, 1H), 3.00 – 2.86 (m, 1H), 2.74 (s, 3H), 2.74 – 2.68 (m, 1H), 2.55 – 2.41 (m, 2H), 2.28 (s, 6H), 2.03 – 1.56 (m, 9H), 1.49 (d, J = 7.1 Hz, 3H), 1.41 (s, 3H), 1.33 (d, J = 7.5 Hz, 3H), 1.28 (s, 3H), 1.27 – 1.25 (m, 1H), 1.23 (d, J = 6.1 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR (10:1 diastereomeric mixture at C2, major isomer is reported, 126 MHz, cdcl$_3$) δ 206.32, 205.97, 171.49, 157.00, 147.84, 146.88, 144.85, 131.59, 129.67, 120.70, 119.78, 116.04, 114.76, 112.31, 104.26, 83.50, 78.46, 77.84, 70.43, 69.47, 65.75, 63.22, 51.13, 50.50, 49.54, 49.27, 42.19, 41.68,

40.23, 38.93, 28.27, 27.40, 24.88, 21.55, 21.48, 21.17, 20.13, 18.71, 16.25, 14.44, 10.38. FTIR (neat), cm^{-1}: 3360 (br), 2972 (m), 1753 (s), 1458 (m), 1109 (s), 1049 (s), 734 (s). HRMS (ESI): Calcd for $(C_{43}H_{64}N_6O_{10} + H)^+$: 825.4757; Found: 825.4764.



FSM-21992

[00631] Potassium azodicarboxylate (2.3 mg, 0.012 mmol, 5.0 equiv) was added to a solution of FSM-21828 (2.0 mg, 2.4 µmol, 1 equiv) in methanol (0.1 mL) at 23 °C. Acetic acid (0.6 µL, 10 µmol, 4.0 equiv) was added dropwise as a solution in methanol (0.1 mL) at 23 °C. After 2 h, the reaction solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (5% methanol–dichloromethane + 0.5% saturated aqueous ammonium hydroxide solution) to afford the product as a colorless film (1.4 mg, 69%).

^{1}H NMR (500 MHz, cdcl$_3$) δ 7.80 (s, 1H), 7.22 – 7.12 (m, 3H), 6.67 (d, *J* = 6.4 Hz, 1H), 5.36 (br s, 1H), 4.99 (dd, *J* = 9.7, 2.8 Hz, 1H), 4.47 (t, *J* = 7.1 Hz, 2H), 4.32 – 4.24 (m, 2H), 4.11 (s, 1H), 3.85 (q, *J* = 6.7 Hz, 1H), 3.77 (br s, 2H), 3.70 – 3.48 (m, 3H), 3.29 – 3.21 (m, 1H), 3.18 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.14 – 2.98 (m, 2H), 2.94 (s, 3H), 2.82 (dt, *J* = 10.7, 5.7 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.50 – 2.41 (m, 1H), 2.28 (s, 6H), 2.08 – 1.90 (m, 1H), 1.77 – 1.49 (m, 8H), 1.47 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.32 (d, *J* = 7.4 Hz, 3H), 1.30 – 1.28 (m, 1H), 1.27 (s, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). HRMS (ESI): Calcd for $(C_{43}H_{66}N_8O_9 + H)^+$: 839.5026; Found: 839.5030.

Biological Screening

[00632] MIC data was collected for the novel macrolides that this platform has produced against over 21 unique strains of *B. subtilis, E. coli, S. aureus, S. pneumoniae,* and *H.* influenzae, including several multidrug–resistant strains, with a special focus on macrolide resistant mechanisms (*vide supra*). Azithromycin (Azithro) and Solithromycin (Solithro) were included as a control macrolides in many cases. CLSI standard procedures for broth

dilution MIC determination were used. Data for exemplary macrolides of the present invention are shown in Tables B1–B13. Certain analogs show greater activity than azithromycin in all strains of bacteria, especially against *S. aureus* and *S. pneumoniae* with efflux (*mef*, *msr*) and methylase (*erm*) genotypes, which are the two most prevalent forms of resistance to macrolides in the United States and Europe (*ermA/B* = ribosomal methylation, *mefA, msrA* = macrolide efflux). These genotypes can be constitutive or inducible.

[00633] In the future, all fully synthetic macrolides will be evaluated in a two–tier system, involving an initial in house screen against macrolide susceptible strains of *S. aureus* and *S. pneumoniae*. Macrolides found to possess threshold activity (MICs of 4 μg/mL or lower) against these bacterial strains will then be submitted for second–tier analysis against a full panel (16 strains, Gram–positive and Gram–negative organisms, including macrolide–resistant strains). After further rounds of optimization (synthesis, MIC determination), macrolides showing highly promising anti–microbial activity, especially against resistant strains, may be subject to further evaluation in rodent models of infection.

Table B1.

	Species	Strain or Genotype	Azithro	Solithro	FSM-11561	FSM-11563	FSM-11559	FSM-11562
Gram-positive	*S. aureus*	ATCC 29213	1	0.125	0.0625	0.0625	0.125	0.0625
	S. aureus	MRSA: USA300	32	1	0.5	0.125	4	1
	S. aureus	MRSA: USA100	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	USA600, GISA	> 32	> 32	> 32	> 32	> 32	> 32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125
	S. pneumoniae	mef A genotype	0.25	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125
	S. pneumoniae	mef A genotype	4	0.125	0.0625	≤ 0.03125	0.125	0.0625
	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125
	S. pneumoniae	erm B + mef A genotype	> 32	0.25	0.125	≤ 0.03125	1	0.25
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125
	S. pyogenes	Macrolide-resistant	2	0.0625	0.0625	≤ 0.03125	0.125	0.125
	E. faecalis	ATCC 29212	4	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125
	E. faecalis	Vancomycin-resistant	> 32	32	32	4	> 32	> 32

Gram-negative	*E. coli*	ATCC 25922	4	32	16	16	> 32	16
	E. coli	NDM-1	> 32	> 32	> 32	> 32	> 32	> 32
	E. coli	TEM-1	1	32	8	16	32	16
	E. coli	CTX-M-14	> 32	> 32	> 32	> 32	> 32	> 32
	A. baumannii	ATCC 19606	16	8	4	4	16	8
	A. baumannii	imipenem-resistant	8	4	2	4	32	8
	A. baumannii	chromosomal class C	32	8	4	2	16	8
	A. baumannii	IMP-4	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	ATCC 10031	4	8	2	4	4	4
	K. pneumoniae	KPC-2	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	TEM-10	8	> 32	32	32	> 32	32
	K. pneumoniae	SHV-12	16	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	> 32	32	32	> 32	> 32
	P. aeruginosa	HPA101-1477	> 32	> 32	> 32	> 32	> 32	> 32
	H. influenzae	Erythro >4, Azithro 1	0.125	2	2	4	4	2
	H. influenzae	ATCC49247	0.5	4	2	2	4	4

Table B2.

	Species	**Strain or Genotype**	**FSM-100364**	**FSM-100407**	**FSM-100239**	**FSM-100240**	**FSM-100341**	**FSM-100383**
Gram-positive	*S. aureus*	ATCC 29213	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. aureus	MRSA: USA300	2	0.5	0.25	1	2	0.5
	S. aureus	MRSA: USA100	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	USA600, GISA	> 32	> 32	> 32	> 32	> 32	> 32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	0.25	< 0.03125	≤ 0.03125	0.25	< 0.03125	< 0.03125
	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	erm B + mef A genotype	0.125	< 0.03125	0.0625	0.125	0.25	< 0.03125
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pyogenes	Macrolide-resistant	< 0.03125	< 0.03125	≤ 0.03125	0.25	< 0.03125	< 0.03125
	E. faecalis	ATCC 29212	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	E. faecalis	Vancomycin-resistant	> 32	16	16	8	> 32	> 32
negati	*E. coli*	ATCC 25922	16	16	16	> 32	> 32	8

	E. coli	NDM-1	> 32	> 32	> 32	> 32	> 32	32
	E. coli	TEM-1	> 32	> 32	16	32	32	16
	E. coli	CTX-M-14	> 32	> 32	> 32	> 32	> 32	> 32
	A. baumannii	ATCC 19606	8	8	8	32	16	4
	A. baumannii	imipenem-resistant	4	8	4	32	16	8
	A. baumannii	chromosomal class C	8	8	2	16	32	8
	A. baumannii	IMP-4	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	ATCC 10031	8	4	4	4	8	2
	K. pneumoniae	KPC-2	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	TEM-10	32	32	32	32	32	16
	K. pneumoniae	SHV-12	> 32	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	32	> 32	> 32	> 32	> 32
	P. aeruginosa	HPA101-1477	> 32	> 32	> 32	> 32	> 32	> 32
	H. influenzae	Erythro >4, Azithro 1	0.5	1	1	1	1	0.5
	H. influenzae	ATCC49247	2	1	1	1	1	0.5

Table B3.

	Species	**Strain or Genotype**	**Azithro**	**Solithro**	**FSM-11561**	**FSM-11563**	**FSM-100371**	**FSM-100389**	**FSM-100376**	**FSM-100386**	**FSM-100421**
Gram-positive	*S. aureus*	ATCC 29213	1	0.125	0.0625	0.0625	< 0.03125	< 0.03125	< 0.03125	< 0.03125	0.0625
	S. aureus	MRSA: USA300	32	1	0.5	0.125	4	2	8	4	2
	S. aureus	MRSA: USA100	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	USA600, GISA	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	0.25	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	4	0.125	0.0625	≤ 0.03125	0.125	< 0.03125	< 0.03125	0.0625	0.0625

	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	erm B + mef A genotype	> 32	0.25	0.125	≤ 0.03125	0.25	0.0625	0.25	0.25	< 0.03125
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pyogenes	Macrolide-resistant	2	0.0625	0.0625	≤ 0.03125	0.0625	< 0.03125	< 0.03125	0.0625	< 0.03125
	E. faecalis	ATCC 29212	4	< 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	E. faecalis	Vancomycin-resistant	> 32	32	32	4	> 32	> 32	> 32	> 32	32
Gram-negative	*E. coli*	ATCC 25922	4	32	16	16	> 32	32	8	16	32
	E. coli	NDM-1	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	E. coli	TEM-1	1	32	8	16	> 32	32	16	16	32
	E. coli	CTX-M-14	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	A. baumannii	ATCC 19606	16	8	4	4	16	16	16	32	16
	A. baumannii	imipenem-resistant	8	4	2	4	> 32	16	32	> 32	16
	A. baumannii	chromosomal class C	32	8	4	2	32	32	16	32	32
	A. baumannii	IMP-4	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	ATCC 10031	4	8	2	4	8	4	8	8	4
	K. pneumoniae	KPC-2	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	TEM-10	8	> 32	32	32	> 32	> 32	32	> 32	32
	K. pneumoniae	SHV-12	16	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	> 32	32	32	> 32	> 32	32	> 32	> 32
	P. aeruginos	HPA101-1477	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32

	a										
	H. influenza e	Erythro >4, Azithro 1	0.125	2	2	4	2	1	1	2	1
	H. influenza e	ATCC49247	0.5	4	2	2	2	1	1	4	2

Table B4.

	Species	**Strain or Genotype**	**Azithro**	**Solithro**	**FSM-100239**	**FSM-100426**	**FSM-100423**
Gram-positive	*S. aureus*	ATCC 29213	1	0.125	≤ 0.03125	0.0625	0.125
	S. aureus	MRSA: USA300	32	1	0.25	0.5	> 32
	S. aureus	MRSA: USA100	> 32	> 32	> 32	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32	> 32	> 32	> 32
	S. aureus	USA600, GISA	> 32	> 32	> 32	32	> 32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	0.25	< 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	4	0.125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	erm B + mef A genotype	> 32	0.25	0.0625	< 0.03125	0.0625
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	S. pyogenes	Macrolide-resistant	2	0.0625	≤ 0.03125	< 0.03125	< 0.03125
	E. faecalis	ATCC 29212	4	< 0.03125	≤ 0.03125	< 0.03125	< 0.03125
	E. faecalis	Vancomycin-resistant	> 32	32	16	8	> 32
Gram-negative	*E. coli*	ATCC 25922	4	32	16	32	> 32
	E. coli	NDM-1	> 32	> 32	> 32	> 32	> 32
	E. coli	TEM-1	1	32	16	> 32	> 32
	E. coli	CTX-M-14	> 32	> 32	> 32	> 32	> 32
	A. baumannii	ATCC 19606	16	8	8	16	32
	A. baumannii	imipenem-resistant	8	4	4	8	32
	A. baumannii	chromosomal class C	32	8	2	32	32
	A. baumannii	IMP-4	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	ATCC 10031	4	8	4	8	16
	K. pneumoniae	KPC-2	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	TEM-10	8	> 32	32	> 32	> 32
	K. pneumoniae	SHV-12	16	> 32	> 32	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	HPA101-1477	> 32	> 32	> 32	> 32	> 32
	H. influenzae	Erythro >4, Azithro 1	0.125	2	1	4	4
	H. influenzae	ATCC49247	0.5	4	1	4	2

Table B5.

	Species	Strain or Genotype	FSM-100431	FSM-100427	FSM-100433	FSM-100429	FSM-100428	FSM-100434
Gram-positive	*S. aureus*	ATCC 29213	0.125	< 0.03125	0.5	0.125	< 0.03125	0.25
	S. aureus	MRSA: USA300	> 32	0.5	> 32	> 32	4	> 32
	S. aureus	MRSA: USA100	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	USA600, GISA	> 32	32	> 32	> 32	> 32	> 32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	< 0.03125	< 0.03125	< 0.03125	0.0625	< 0.03125	0.125
	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pneumoniae	erm B + mef A genotype	8	< 0.03125	2	> 32	0.0625	1
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	S. pyogenes	Macrolide-resistant	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125	< 0.03125
	E. faecalis	ATCC 29212	< 0.03125	< 0.03125	0.0625	< 0.03125	< 0.03125	< 0.03125
	E. faecalis	Vancomycin-resistant	> 32	8	> 32	> 32	> 32	> 32
Gram-negative	*E. coli*	ATCC 25922	> 32	32	> 32	> 32	32	> 32
	E. coli	NDM-1	> 32	> 32	> 32	> 32	> 32	> 32
	E. coli	TEM-1	> 32	32	> 32	> 32	32	> 32
	E. coli	CTX-M-14	> 32	> 32	> 32	> 32	> 32	> 32
	A. baumannii	ATCC 19606	16	16	> 32	> 32	16	16
	A. baumannii	imipenem-resistant	16	8	> 32	32	16	16
	A. baumannii	chromosomal class C	8	16	> 32	32	16	16
	A. baumannii	IMP-4	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	ATCC 10031	32	4	> 32	32	16	32
	K. pneumoniae	KPC-2	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	TEM-10	> 32	32	> 32	> 32	32	> 32
	K. pneumoniae	SHV-12	> 32	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	HPA101-1477	> 32	> 32	> 32	> 32	> 32	> 32
	H. influenzae	Erythro >4, Azithro 1	> 32	2	> 32	> 32	2	> 32

	H. influenzae	ATCC49247	> 32	2	> 32	> 32	4	> 32

Table B6.

	Species	Strain or Genotype	Azithro	Solithro	FSM-21535	FSM-21598	FSM-21828	FSM-100432
Gram-positive	*S. aureus*	ATCC 29213	1	0.125	16	32	4	1
	S. aureus	MRSA: USA300	32	1	32	32	> 32	> 32
	S. aureus	MRSA: USA100	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32	> 32	> 32	> 32	> 32
	S. aureus	USA600, GISA	> 32	> 32	> 32	> 32	> 32	> 32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	0.25	< 0.03125	0.0625	≤ 0.03125	0.0625	0.125
	S. pneumoniae	mef A genotype	4	0.125	0.5	0.25	0.5	0.5
	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125
	S. pneumoniae	erm B + mef A genotype	> 32	0.25	8	8	32	2
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125	≤ 0.03125	≤ 0.03125	≤ 0.03125	< 0.03125
	S. pyogenes	Macrolide-resistant	2	0.0625	0.5	0.25	0.5	0.0625
	E. faecalis	ATCC 29212	4	< 0.03125	≤ 0.03125	≤ 0.03125	1	0.125
	E. faecalis	Vancomycin-resistant	> 32	32	> 32	> 32	> 32	> 32
Gram-negative	*E. coli*	ATCC 25922	4	32	> 32	> 32	> 32	> 32
	E. coli	NDM-1	> 32	> 32	> 32	> 32	> 32	> 32
	E. coli	TEM-1	1	32	> 32	> 32	> 32	> 32
	E. coli	CTX-M-14	> 32	> 32	> 32	> 32	> 32	> 32
	A. baumannii	ATCC 19606	16	8	> 32	> 32	> 32	> 32
	A. baumannii	imipenem-resistant	8	4	> 32	> 32	> 32	> 32
	A. baumannii	chromosomal class C	32	8	> 32	32	> 32	> 32
	A. baumannii	IMP-4	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	ATCC 10031	4	8	4	8	16	32
	K. pneumoniae	KPC-2	> 32	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	TEM-10	8	> 32	> 32	> 32	> 32	> 32
	K. pneumoniae	SHV-12	16	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	> 32	> 32	> 32	> 32	> 32
	P. aeruginosa	HPA101-1477	> 32	> 32	> 32	> 32	> 32	> 32
	H. influenzae	Erythro >4, Azithro 1	0.125	2	8	8	16	8
	H. influenzae	ATCC49247	0.5	4	4	4	16	8

Table B7.

	Species	Strain No.	Genotype	FSM-100563	FSM-100566	FSM-100551	FSM-100573
Gram-positive	*S. aureus*	MP-12	ATCC29213	0.06	0.06	0.06	0.06
	S. aureus (MRSA)	MP-549	USA300	0.125	0.125	0.125	0.06

	S. aureus (MRSA)	MP-618 UNT-096	USA100	32	>64	>64	16
	S. aureus (MRSA)	MP-620 UNT-146	ermA phenotype	16	>64	>64	16
	S. aureus (MRSA)	MP-619 UNT-120	GISA USA600	16	64	64	16
	S. pneumoniae	MP-21	ATCC49619	<0.03	<0.03	<0.03	<0.03
	S. pneumoniae	MP-626 UNT-038	mefA	<0.03	<0.03	<0.03	<0.03
	S. pneumoniae	MP-627 UNT-039	mefA	<0.03	<0.03	<0.03	<0.03
	S. pyogenes	MP-19	ATCC19615	<0.03	<0.03	<0.03	<0.03
	S. pyogenes	MP-625 UNT-014	mac resistant	<0.03	<0.03	0.06	<0.03
	E. faecalis	MP-24	ATCC29212	<0.03	<0.03	<0.03	<0.03
	E. faecalis	UNT-039	van resistant	2	8	4	1
	A. baumannii	MP-15	ATCC19606	8	16	4	2
	K. pneumoniae	MP-14	ATCC10031	8	8	8	2
	P. aeruginosa	MP-3	ATCC27853	32	64	16	16
	E. coli	MP-4	ATCC25922	16	32	8	8
New Strains	*E. coli*	MP-9	ATCC25922:tolC	2	2	2	2
	P. aeruginosa	MP-7	PAO1	64	>64	32	32
	P. aeruginosa	MP-8	PAO1:mex	8	8	4	4
	S. aureus	MP-17	ATCCBAA-977	0.06	0.06	0.06	0.06
	S. aureus (MRSA)	MP-513	ST-228 cErm	16	>64	>64	16
	E. coli	MP541	clinical	16	32	16	16
	E. coli	MP532	clinical - cErm	>64	>64	>64	64
	K. pneumoniae	MP548	clinical	64	64	32	32
	K. pneumoniae	MP546	clinical	>64	>64	>64	64
	A. baumannii	MP577	clinical	32	64	16	16
	A. baumannii	MP576	clinical	>64	>64	>64	64

Table B8.

	Species	**Description**	**Strain No.**	**FSM-100576**	**FSM-100593**	**FSM-100597**	**FSM-140132**
Gram-positive	*S. aureus*	ATCC29213	MP-12	0.125	0.125	1	0.25
	S. aureus	BAA 977 iErm	MP-17	0.125	0.125	1	0.25
	S. aureus	Clinical- cErm	MP-513	>32	64	>64	>64
	S. aureus	USA300 - msr(a)	MP-549	0.25	0.25	2	0.5
Gram-negative	*E. coli*	ATCC25922	MP-4	32	4	64	16
	E. coli	tolC	MP-9	2	0.5	4	2
	E. coli	Clinical	MP-541	32	8	32	32
	E. coli	clinical-cErmB	MP-532	>32	>64	>64	>64
	K. pneumoniae	ATCC 10031	MP-14	4	1	8	4
	K. pneumoniae	Clinical	MP-548	>32	16	>64	64
	K. pneumoniae	Clinical - MDR	MP-546	>32	32	>64	>64
	P. aeruginosa	ATCC27853	MP-3	>32	32	>64	>64
	P. aeruginosa	mex-oprM-deletion	MP-8	8	2	16	8

	P. aeruginosa	PAO1	MP-7	>32	32	>64	>64
	A. baumannii	ATCC 19606	MP-15	16	8	64	32
	A. baumannii	Clinical - AZT low	MP-577	>32	8	>64	32
	A. baumannii	Clinical - MDR	MP-576	>32	>64	>64	>64

Table B9.

	Species	Description	Strain No.	FSM-100627	FSM-100633	FSM-130216	FSM-130217	FSM-140133
Gram-positive	*S. aureus*	ATCC29213	MP-12	0.06	0.125	0.25	0.25	0.25
	S. aureus	BAA 977 iErm	MP-17	0.06	0.125	0.25	0.25	0.25
	S. aureus	Clinical- cErm	MP-513	32	64	>64	>64	>64
	S. aureus	USA300 - msr(a)	MP-549	0.125	0.125	0.5	0.25	0.5
Gram-negative	*E. coli*	ATCC25922	MP-4	16	8	32	32	16
	E. coli	tolC	MP-9	1	1	4	4	4
	E. coli	Clinical	MP-541	8	8	64	32	16
	E. coli	clinical-cErmB	MP-532	>64	>64	>64	>64	>64
	K. pneumoniae	ATCC 10031	MP-14	2	2	4	8	4
	K. pneumoniae	Clinical	MP-548	32	32	>64	>64	64
	K. pneumoniae	Clinical - MDR	MP-546	64	64	>64	>64	>64
	P. aeruginosa	ATCC27853	MP-3	64	32	>64	>64	64
	P. aeruginosa	mex-oprM-deletion	MP-8	4	4	16	16	8
	P. aeruginosa	PAO1	MP-7	64	32	>64	>64	64
	A. baumannii	ATCC 19606	MP-15	8	4	16	16	8
	A. baumannii	Clinical - AZT low	MP-577	32	16	64	32	64
	A. baumannii	Clinical - MDR	MP-576	>64	>64	>64	>64	>64

Table B10.

	Species	Description	Strain No.	FSM-140135	FSM-22737	FSM-22738	FSM-22739	FSM-22740
Gram-positive	*S. aureus*	ATCC29213	MP-12	2	0.25	0.25	0.25	0.25
	S. aureus	BAA 977 iErm	MP-17	2	0.25	0.25	0.25	0.25
	S. aureus	Clinical- cErm	MP-513	>64	>64	32	64	64
	S. aureus	USA300 - msr(a)	MP-549	2	0.25	0.25	0.25	0.25
Gram-negative	*E. coli*	ATCC25922	MP-4	>64	16	8	16	16
	E. coli	tolC	MP-9	16	2	1	4	2
	E. coli	Clinical	MP-541	>64	16	16	16	16

	E. coli	clinical-cErmB	MP-532	>64	>64	>64	>64	>64
	K. pneumoniae	ATCC 10031	MP-14	8	8	4	8	8
	K. pneumoniae	Clinical	MP-548	>64	64	64	64	>64
	K. pneumoniae	Clinical - MDR	MP-546	>64	>64	>64	>64	>64
	P. aeruginosa	ATCC27853	MP-3	>64	>64	64	>64	>64
	P. aeruginosa	mex-oprM-deletion	MP-8	32	16	8	16	16
	P. aeruginosa	PAO1	MP-7	>64	>64	64	>64	>64
	A. baumannii	ATCC 19606	MP-15	>64	16	8	16	16
	A. baumannii	Clinical - AZT low	MP-577	>64	32	32	32	64
	A. baumannii	Clinical - MDR	MP-576	>64	>64	>64	>64	>64

Table B11.

	Species	Description	Strain No.	FSM-22741	FSM-22742	FSM-22745	FSM-22746	FSM-22747	FSM-22748	FSM-22749	FSM-22750
Gram-positive	*S. aureus*	ATCC29213	MP-12	0.125	0.5	0.5	0.25	0.25	0.25	2	4
	S. aureus	BAA 977 iErm	MP-17	0.125	1	1	0.25	0.25	0.25	2	8
	S. aureus	Clinical-cErm	MP-513	>64	>64	>64	>64	>64	>64	>64	>64
	S. aureus	USA300 - msr(a)	MP-549	0.25	1	1	0.5	0.5	0.25	2	8
Gram-negative	*E. coli*	ATCC25922	MP-4	16	16	32	32	32	16	64	>64
	E. coli	tolC	MP-9	4	2	4	4	4	4	8	>64
	E. coli	Clinical	MP-541	32	16	32	64	32	16	64	>64
	E. coli	clinical-cErmB	MP-532	>64	>64	>64	>64	>64	>64	>64	>64
	K. pneumoniae	ATCC 10031	MP-14	4	4	8	8	8	8	16	>64
	K. pneumoniae	Clinical	MP-548	64	64	>64	>64	>64	64	>64	>64
	K. pneumoniae	Clinical - MDR	MP-546	>64	>64	>64	>64	>64	>64	>64	>64
	P. aeruginosa	ATCC27853	MP-3	>64	64	>64	>64	>64	64	>64	>64
	P. aeruginosa	mex-oprM-deletion	MP-8	8	8	16	16	16	16	16	>64
	P. aeruginosa	PAO1	MP-7	>64	64	>64	>64	>64	64	>64	>64
	A. baumannii	ATCC 19606	MP-15	8	16	32	16	16	16	32	>64
	A. baumannii	Clinical - AZT low	MP-577	32	32	64	64	32	32	>64	>64

	A. baumannii	Clinical - MDR	MP-576	>64	>64	>64	>64	>64	>64	>64	>64

[00634] Table B12 below shows MIC data for FSM-100426 compared with solithromycin. The data suggests that incorporating a rigidified linker between the cyclic carbamate and the triazole (*i.e.*, the alkynylene linker moiety of FSM-10042) can provide a more potent analog. The rigid alkynyl linker of FSM-10042 corresponds to the linking group L^{C1} as described herein.

Table B12.

	Species	Strain or Genotype	Solithro	FSM-100426
Gram-positive	*S. aureus*	ATCC 29213	0.125	0.0625
	S. aureus	MRSA: USA300	1	0.5
	S. aureus	MRSA: USA100	> 32	> 32
	S. aureus	erm A genotype	> 32	> 32
	S. aureus	USA600, GISA	> 32	32
	S. pneumoniae	ATCC 49619	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	< 0.03125	< 0.03125
	S. pneumoniae	mef A genotype	0.125	< 0.03125
	S. pneumoniae	erm B + tet(M,O) genotype	< 0.03125	< 0.03125
	S. pneumoniae	erm B + mef A genotype	0.25	< 0.03125
	S. pyogenes	ATCC 19615	< 0.03125	< 0.03125
	S. pyogenes	Macrolide-resistant	0.0625	< 0.03125
	E. faecalis	ATCC 29212	< 0.03125	< 0.03125
	E. faecalis	Vancomycin-resistant	32	8
Gram-negative	*E. coli*	ATCC 25922	32	32
	E. coli	NDM-1	> 32	> 32
	E. coli	TEM-1	32	> 32
	E. coli	CTX-M-14	> 32	> 32
	A. baumannii	ATCC 19606	8	16
	A. baumannii	imipenem-resistant	4	8
	A. baumannii	chromosomal class C	8	32
	A. baumannii	IMP-4	> 32	> 32
	K. pneumoniae	ATCC 10031	8	8
	K. pneumoniae	KPC-2	> 32	> 32
	K. pneumoniae	TEM-10	> 32	> 32
	K. pneumoniae	SHV-12	> 32	> 32
	P. aeruginosa	ATCC 27853	> 32	> 32
	P. aeruginosa	HPA101-1477	> 32	> 32
	H. influenzae	Erythro >4, Azithro 1	2	4

	H. influenzae	ATCC49247	4	4

[00635] Table B13 below shows MIC data for FSM-100573 compared with solithromycin. The data suggests that incorporating a rigidified linker between the cyclic carbamate and the triazole (linking group L^{C1} as defined herein), in addition to a heteroaryl triazole substituent (group R^{23} as defined herein), provides an even more potent analog.

Table B13.

	Species	Strain No.	Solithro	FSM-100573
Gram-positive	*S. aureus*	MP-12	0.125	0.06
	S. aureus (MRSA)	MP-549	0.125	0.06
	S. aureus (MRSA)	MP-618 UNT-096	>32	16
	S. aureus (MRSA)	MP-620 UNT-146	>32	16
	S. aureus (MRSA)	MP-619 UNT-120	>32	16
	S. pneumoniae	MP-21	<0.015	<0.03
	S. pneumoniae	MP-626 UNT-038	<0.015	<0.03
	S. pneumoniae	MP-627 UNT-039	<0.015	<0.03
	S. pneumoniae			
	S. pneumoniae			
	S. pyogenes	MP-19	<0.015	<0.03
	S. pyogenes	MP-625 UNT-014	0.03	<0.03
	E. faecalis	MP-24	0.03	<0.03
	E. faecalis	UNT-039	8	1
Gram-negative	*H. influenzae*			
	H. influenzae			
	A. baumannii	MP-15	8	2
	K. pneumoniae	MP-14	4	2
	P. aeruginosa	MP-3	>32	16
	E. coli	MP-4	16	8
New Strains	*E. coli*	MP-9	4	2
	P. aeruginosa	MP-7	>32	32
	P. aeruginosa	MP-8	8	4
	S. aureus	MP-17	0.125	0.06
	S. aureus (MRSA)	MP-513	>32	16
	E. coli	MP541	16	16
	E. coli	MP532	>32	64
	K. pneumoniae	MP548	32	32
	K. pneumoniae	MP546	>32	64
	A. baumannii	MP577	32	16

	A. baumannii	MP576	>32	64

OTHER EMBODIMENTS

[00636] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00637] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00638] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims.

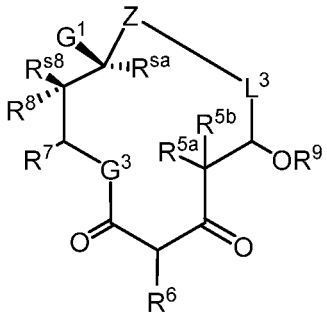
Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00639] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of formula: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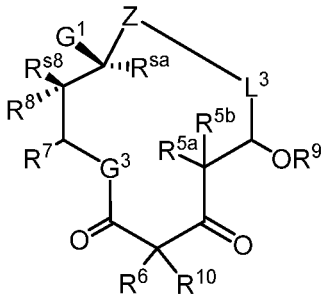
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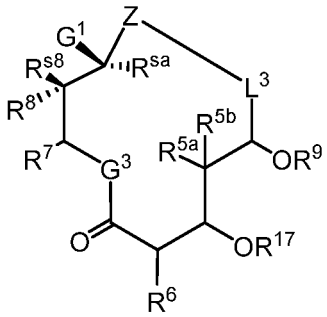
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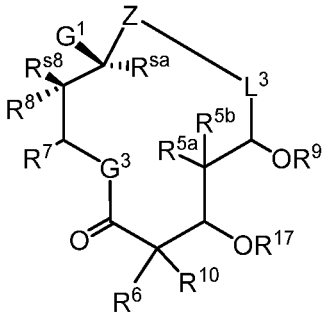
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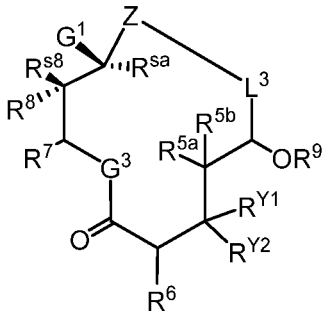
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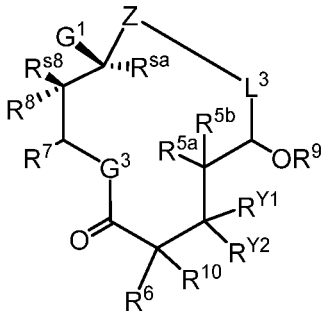
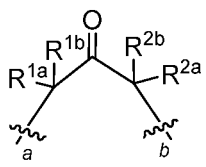
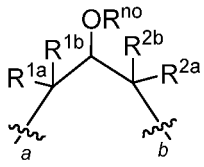
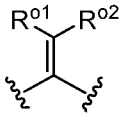

(N-7)

or a salt thereof;

wherein:

Z is of the formula  (z-i) or  (z-ii);

each instance of R^{1a}, R^{1b}, R^{2a}, and R^{2b} is independently hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl, or wherein R^{1a} and R^{1b} or

R^{2a} and R^{2b} are taken together to form  ;

a indicates the point of attachment to the carbon substituted by G1;

b indicates the point of attachment to L^3;

each of R^{o1} and R^{o2} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl;

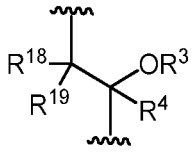
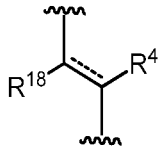
R^{no} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group;

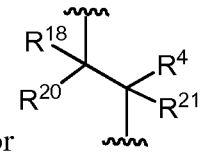
R^{sa} is hydrogen, hydrogen, halogen, carbonyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, optionally substituted heteroaryl;

or R^{sa} and R^{1a} or R^{sa} and R^{1b} are taken together to form a bond;

R^{s8} is hydrogen or OR^{11};

L^3 is a group of formula:

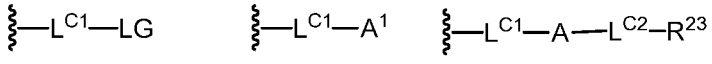
 **(L^3-i)**,  **(L^3-ii)**,



or **(L^3-iii)**;

====== represents a single or double bond;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a group of formula:



(L^{C1}-i) **(L^{C1}-ii)** **(L^{C1}-iii)** ;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl;

each instance of R^{18} and R^{19} independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of R^{20} and R^{21} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, halogen, carbonyl, or R^{20} and R^{21} are joined to form an optionally substituted cyclopropyl or an oxiranyl ring;

each instance of R^{5a} and R^{5b} is independently hydrogen, halogen, silyl, optionally substituted alkyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

R^{Y1} is $-OR^{17}$ and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is hydrogen, or R^{Y1} is halogen and R^{Y2} is halogen, or R^{Y1} and R^{Y2} are joined to form an oxo (=O) group;

R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

R^7 and R^8 are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^9 and R^{17} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)R^{Z8}$, $-C(=O)OR^{Z8}$, $-C(=O)N(R^{Z8})_2$, an oxygen protecting group, or a carbohydrate;

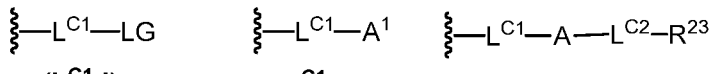
R^{10} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,

optionally substituted aryl, optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, and halogen;

G^3 is –O–, –S–, or $–N(R^{G1})–$, wherein R^{G1} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

G^1 is hydrogen, $–OR^{12}$ or $–NR^{13}R^{14}$;

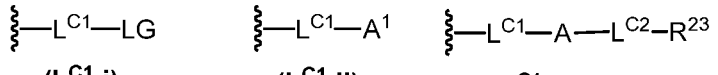
provided when G^1 is $–OR^{12}$, then R^{11} and R^{12} are joined as a group of formula –C(=O)- to provide a cyclic carbonate, or R^{11} and R^{12} are not joined, and R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, and R^{12} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group, or a group of formula:



$(L^{C1}\text{-i})$ $(L^{C1}\text{-ii})$ $(L^{C1}\text{-iii})$;

or provided when G^1 is $–NR^{13}R^{14}$, then R^{11} and R^{13} are joined as a group of formula –C(=O)- to provide a cyclic carbamate, or R^{11} and R^{13} are not joined, R^{11} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group, R^{13} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group;

R^{14} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group, $-C(=O)R^{Z8}$, or $-C(=O)OR^{Z8}$, or a group of formula:



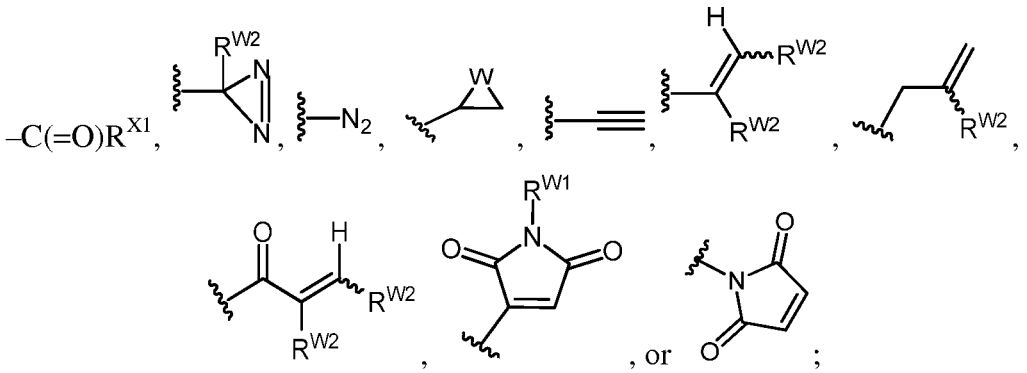
$(L^{C1}\text{-i})$ $(L^{C1}\text{-ii})$ $(L^{C1}\text{-iii})$

or R^{13} and R^{14} are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl;

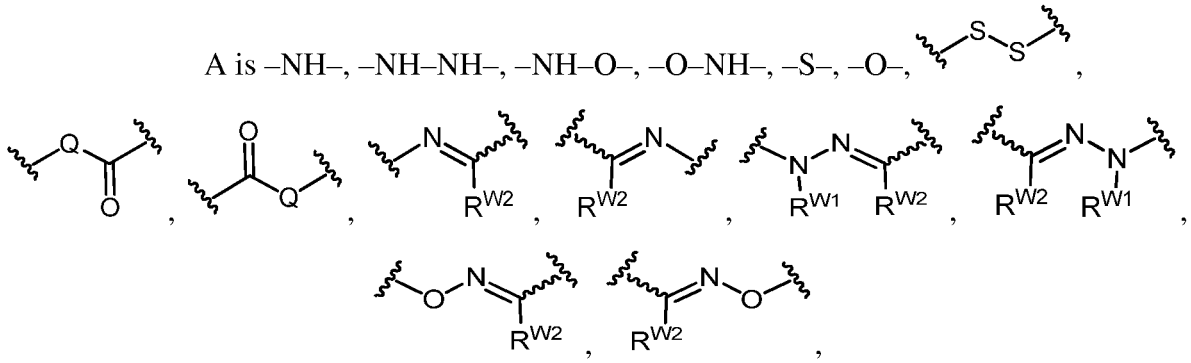
each instance of L^{C1} and L^{C2} is independently a bond, or a linking group selected from the group consisting of optionally substituted alkylene, optionally substituted alkenylene,

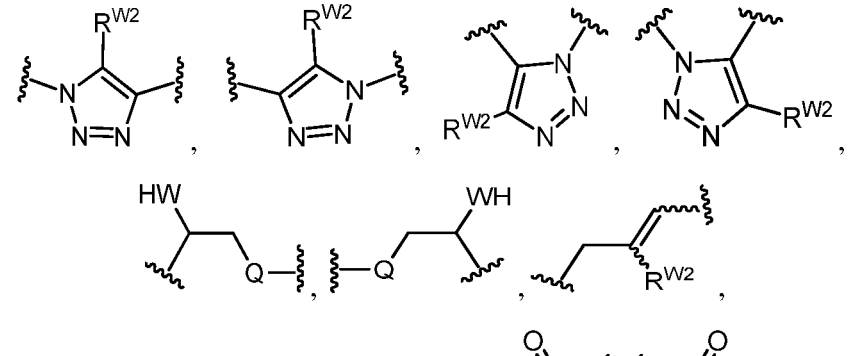
optionally substituted alkynylene; optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene, optionally substituted carbocyclylene, optionally substituted heterocyclylene, and combinations thereof;

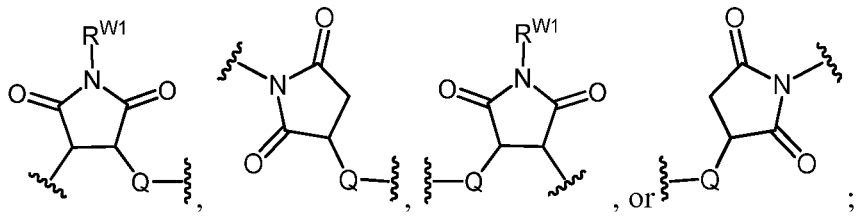
each instance of A^1 is independently a leaving group (LG), –SH, –OH, $–NH_2$, –NH–NH_2, $–N_3$, –O–NH_2,



A is –NH–, –NH–NH–, –NH–O–, –O–NH–, –S–, –O–,







Q is –NH–, –NH–NH–, –O–NH–,–NH–O–,–S–, –O–;

W is O, S, or NR^{W1};

R^{W1} is hydrogen, substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or a nitrogen protecting group;

R^{W2} is hydrogen, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl, or two R^{W2} groups are joined to form an optionally substituted cyclic moiety;

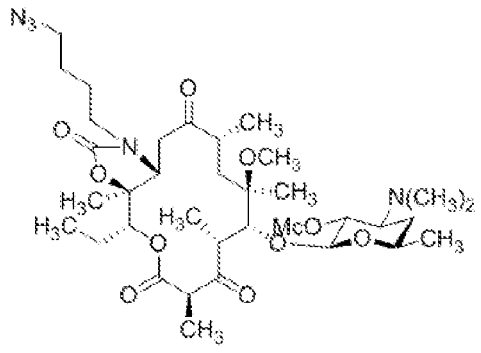
R^{X1} is hydrogen, halogen, or $–OR^{X2}$, wherein R^{X2} is hydrogen; optionally substituted alkyl; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; optionally substituted heteroaryl; or an oxygen protecting group;

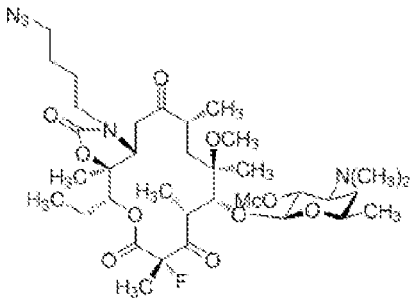
R^{23} is optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted carbocyclyl; optionally substituted heterocyclyl; optionally substituted aryl; or optionally substituted heteroaryl; and

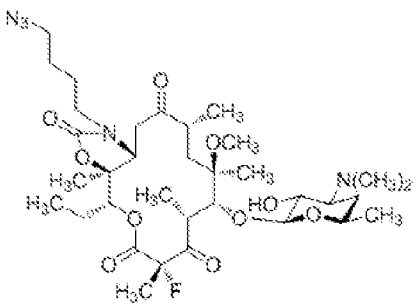
each instance of R^{Z8} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocylyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{Z8} groups are joined to form an optionally substituted heterocylyl or optionally substituted heteroaryl ring;

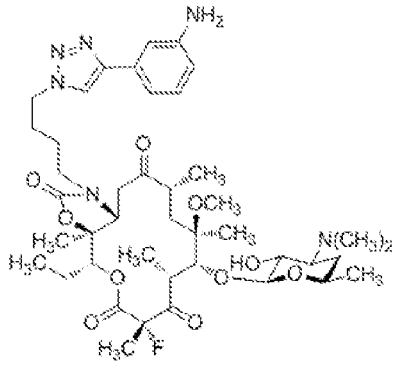
or A is a cyclic moiety selected from the group consisting of optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

provided the compound is not one of the following:

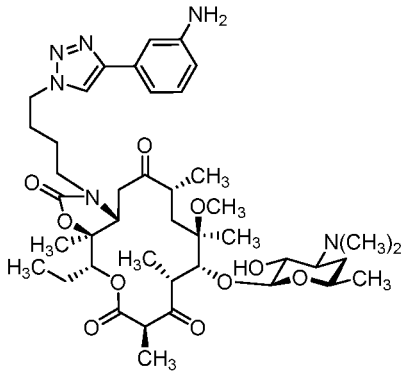




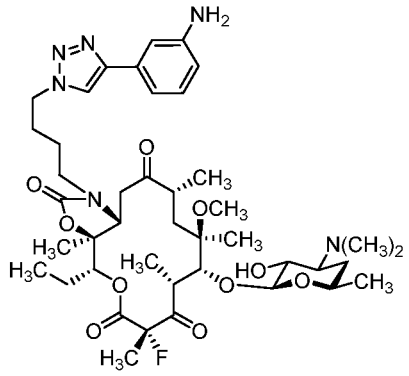




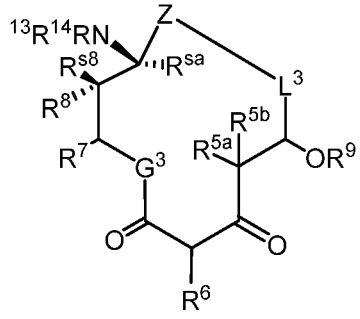
FSM-21535



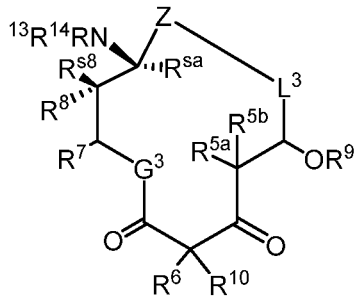
FSM-21598



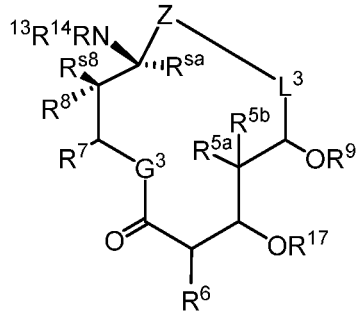
2. The compound of claim 1, wherein the compound is of Formula:



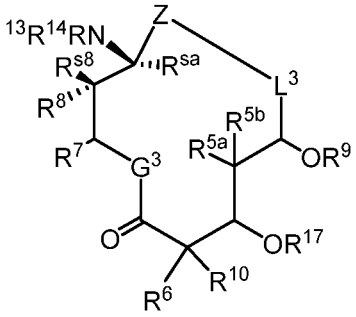
(N-2-A),



(N-3-A),



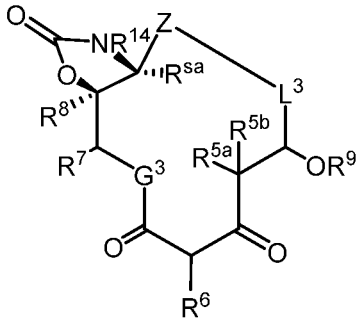
(N-4-A),

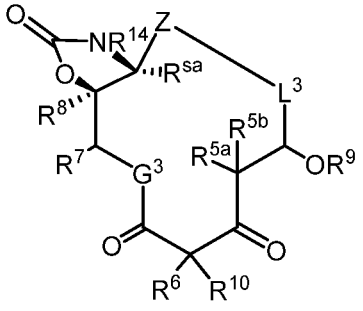


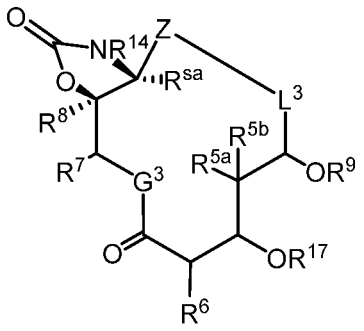
(N-5-A),

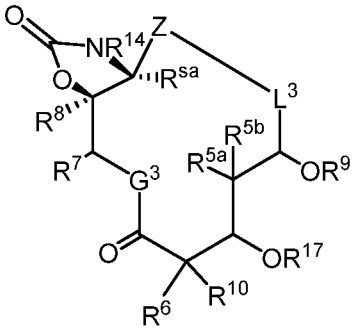
or a salt thereof.

3. The compound of claim 1, wherein the compound is of formula:


(N-2-B),

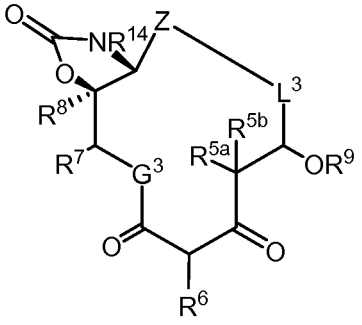

(N-3-B),

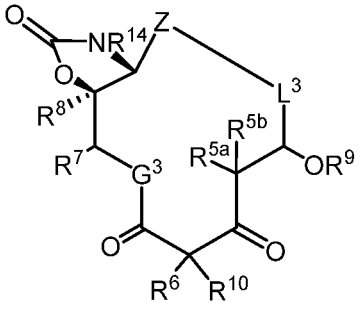

(N-4-B),

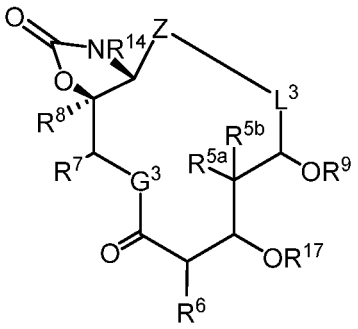

(N-5-B),

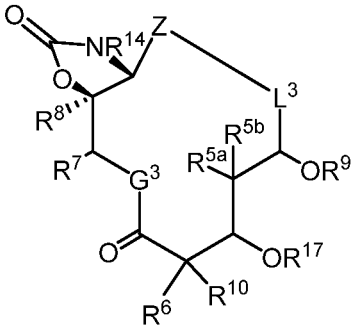
or a salt thereof.

4. The compound of claim 1, wherein the compound is of formula:


(N-2-B1),

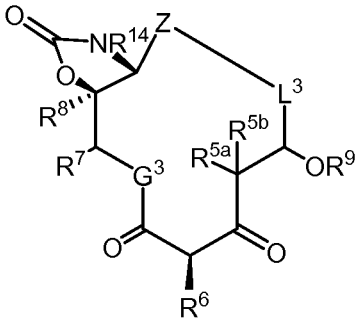

(N-3-B1),


(N-4-B1),

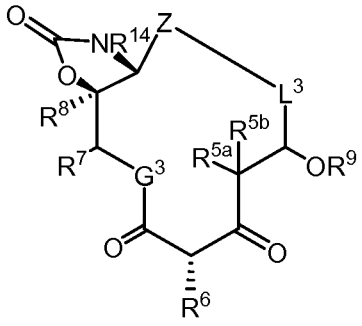

(N-5-B1),

or a salt thereof.

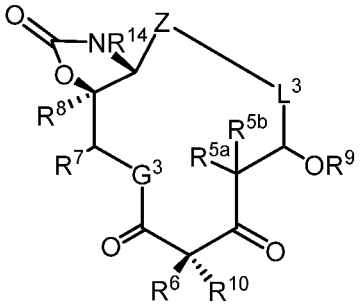
5. The compound of claim 1, wherein the compound is of formula:



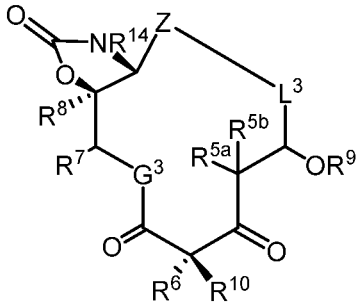
(N-2-B1-i)



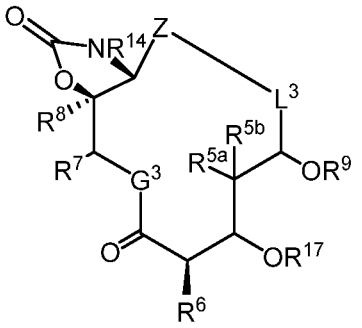
(N-2-B1-ii)



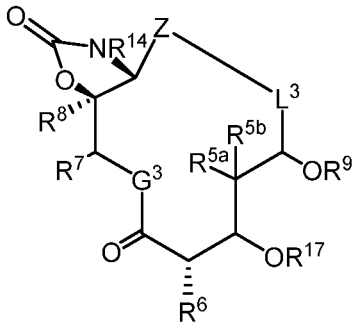
(N-3-B1-i),



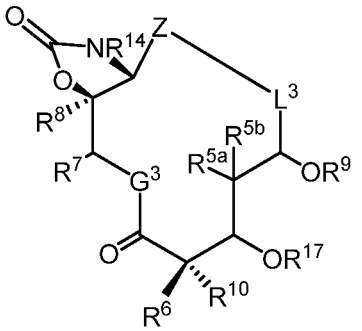
(N-3-B1-ii),



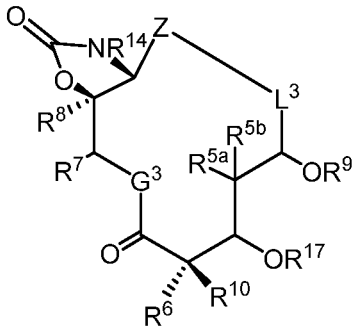
(N-4-B1-i)



(N-4-B1-ii)



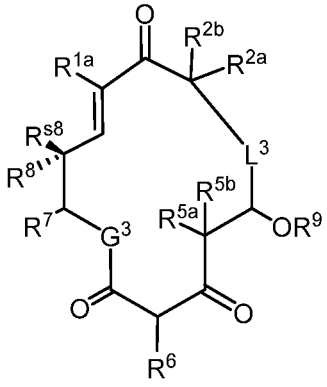
(N-5-B1-i)



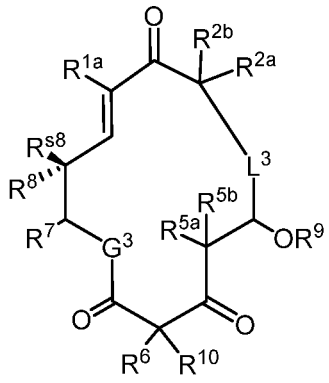
(N-5-B1-ii)

or a salt thereof.

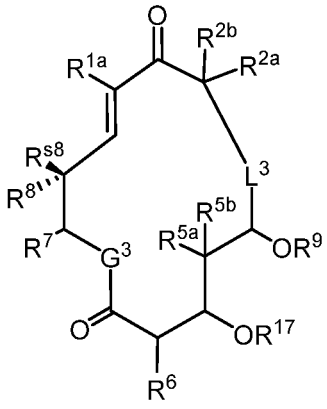
6. The compound of any one of preceding claims, wherein R^{sa} and R^{1b} are taken together to form a bond, and the compound is of the Formula:



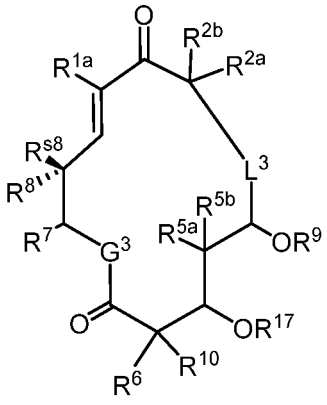
(N-2-C),



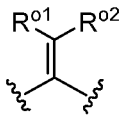
(N-3-C),



(N-4-C),



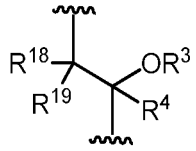
(N-5-C).

7. The compound of any one of claims 1-6, wherein R^{1a} and R^{1b} are taken together to form 

.

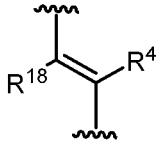
8. The compound of claim 7, wherein R^{o1} and R^{o2} are hydrogen.

9. The compound of any one of claims 1-8, wherein L^3 is a group of formula:



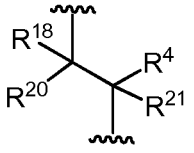
($\mathbf{L^3}$-**i**).

10. The compound of any one of claims 1-8, wherein L^3 is a group of formula:



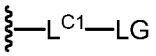
.

11. The compound of any one of claims 1-8, wherein L^3 is a group of formula:

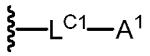


; and R^{21} is hydrogen.

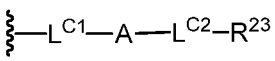
12. The compound of claim 1, wherein R^3 is a group of formula:



(L^{C1}-i)



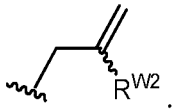
(L^{C1}-ii)



(L^{C1}-iii)

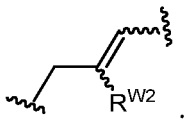
.

13. The compound of claim 12, wherein A^1 is:



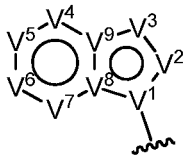
.

14. The compound of claim 12, wherein A is:

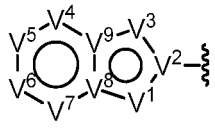


.

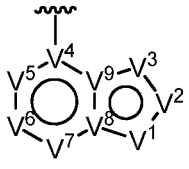
15. The compound of claim 12, wherein R^{23} is



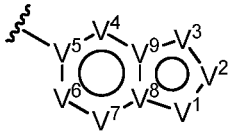
(e–1)



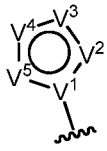
(e–2)



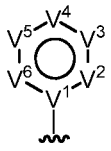
(e–3)



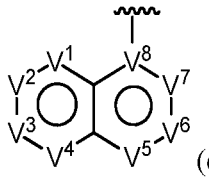
(e–4)

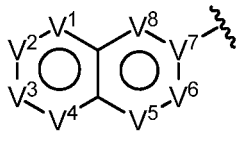


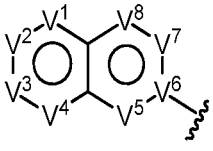
(e–5),



(e–6),


(e-7),


(e-8),


(e-9),

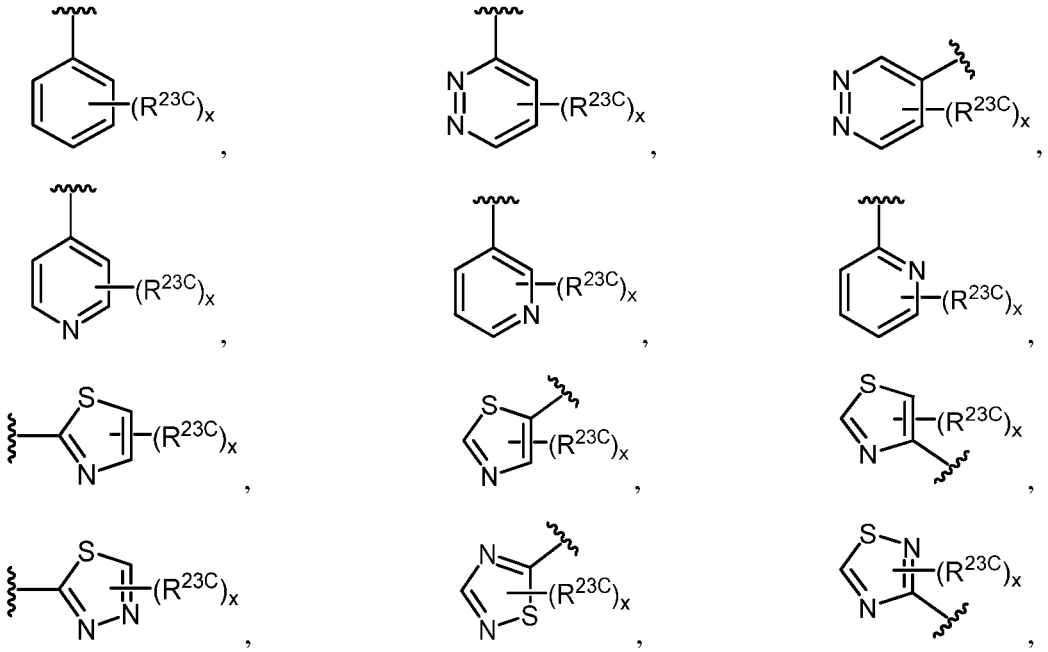
wherein:

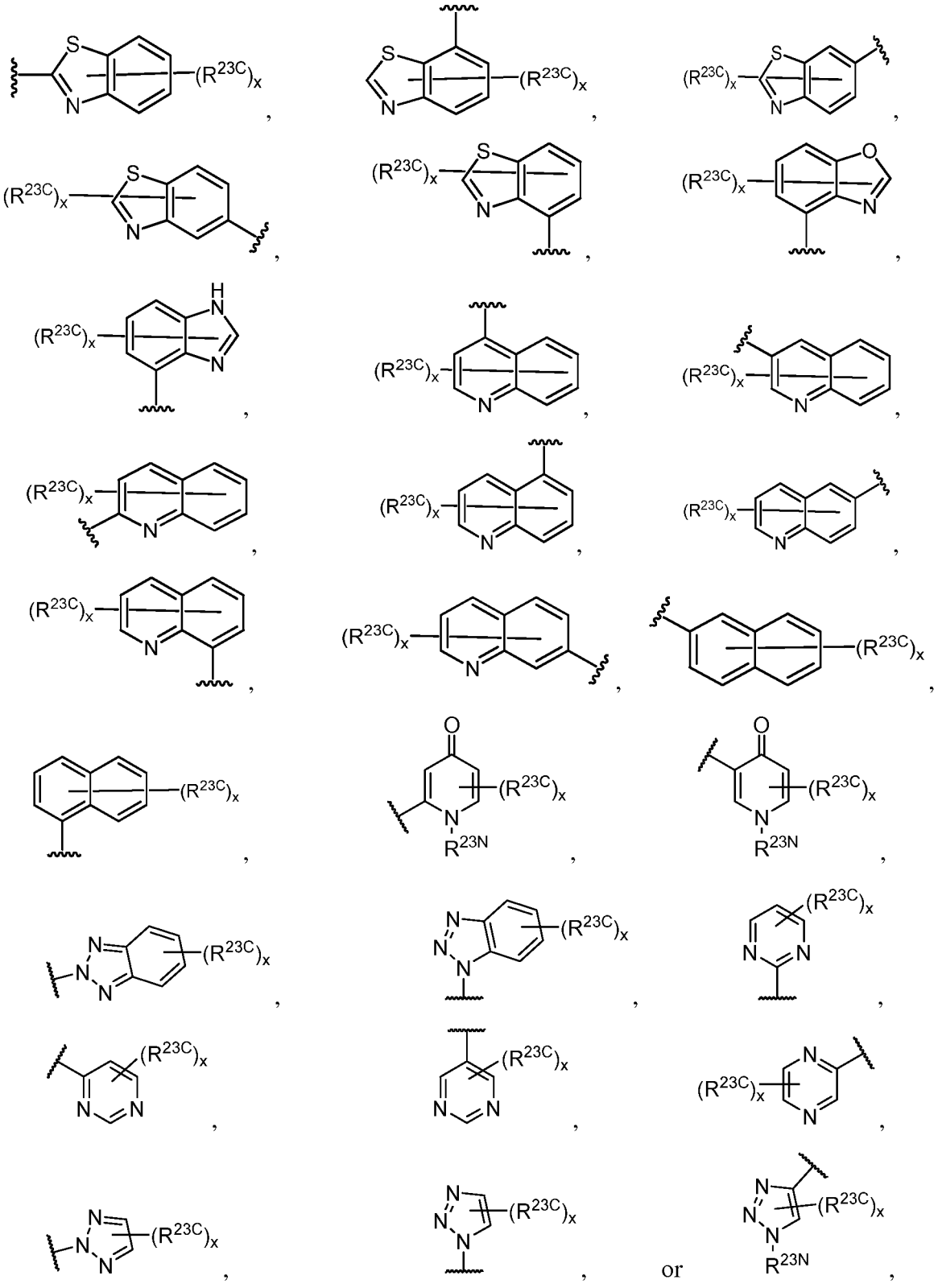
each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 may independently be O, S, N, NR^{23N}, C, or CR^{23C}, as valency permits;

R^{23N} is independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or a nitrogen protecting group; and

R^{23C} is hydrogen, halogen, –CN, $–NO_2$, $–N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, or carbonyl.

16. The compound of claim 15, wherein R^{23} is of formula:





wherein x is 0, 1, or 2.

17. The compound of any one of claims 1-16, wherein R^4 is hydrogen, optionally substituted C_{1-6}alkyl, or optionally substituted C_{2-6}alkenyl.

18. The compound of any one of claims 1-16, wherein R^4 is $–CH_3$, $–CH_2CH_2OH$, $–CH_2C(H)=O$, $–CH_2CH_2N(R^{22})_2$, or $–CH_2CH_2NHR^{22}$, wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl.

19. The compound of any one of claims 1-16, wherein R^4 is optionally substituted allyl or unsubstituted allyl.

20. The compound of any one of claims 1-16, wherein R^4 is hydrogen, optionally substituted $C_{1–6}$alkyl, or optionally substituted $C_{2–6}$alkenyl; and R^{21} is hydrogen.

21. The compound of any one of claims 1-16, wherein R^4 is $–CH_3$, $–CH_2CH_2OH$, $–CH_2C(H)=O$, $–CH_2CH_2N(R^{22})_2$, or $–CH_2CH_2NHR^{22}$, wherein each instance of R^{22} is independently hydrogen or optionally substituted alkyl; and R^{21} is hydrogen.

22. The compound of any one of claims 1-16, wherein R^4 is optionally substituted allyl or unsubstituted allyl; and R^{21} is hydrogen.

23. The compound of any one of claims 1-16, wherein each instance of R^{5a} and R^{5b} is independently hydrogen, optionally substituted alkyl, or halogen.

24. The compound of any one of claims 1-16, wherein R^{5a} and R^{5b} are both hydrogen.

25. The compound of any one of claims 1-16, wherein R^{5a} is $–CH_3$; and R^{5b} is hydrogen.

26. The compound of any one of claims 1-16, wherein R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl.

27. The compound of any one of claims 1-16, wherein R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aralkyl, or optionally substituted heteroaralkyl; and R^{10} is fluorine.

28. The compound of any one of claims 1-16, wherein R^6 is optionally substituted pyrazolylalkyl, imidazolylalkyl, thiazolylalkyl, oxazolylalkyl, pyridinylalkyl, pyrimidinylalkyl, or pyrazinylalkyl.

29. The compound of any one of claims 1-16, wherein R^6 is optionally substituted pyrazolylalkyl, imidazolylalkyl, thiazolylalkyl, oxazolylalkyl, pyridinylalkyl, pyrimidinylalkyl, or pyrazinylalkyl; and R^{10} is fluorine.

30. The compound of any one of claims 1-16, wherein R^6 is optionally substituted allyl, optionally substituted allyl or optionally substituted benzyl.

31. The compound of any one of claims 1-16, wherein R^6 is optionally substituted allyl, optionally substituted allyl or optionally substituted benzyl; and R^{10} is fluorine.

32. The compound of any one of claims 1-16 wherein R^6 is $–CH_2CN$ or $–CH_2C(=O)OR^{32}$, wherein R^{32} is hydrogen or optionally substituted alkyl.

33. The compound of any one of claims 1-16, wherein R^7 is optionally substituted alkyl.

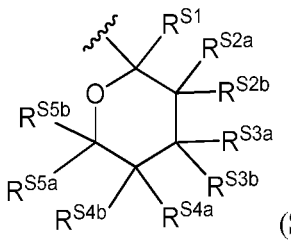
34. The compound of any one of claims 1-16, wherein R^7 is $–CH_2CH_3$.

35. The compound of any one of claims 1-16, wherein R^8 is optionally substituted alkyl.

36. The compound of any one of claims 1-16, wherein R^8 is $–CH_3$.

37. The compound of any one of claims 1-16, wherein R^{18} and R^{19} are hydrogen.

38. The compound of any one of claims 1-16, wherein R^9 is a group of formula:



(S-1)

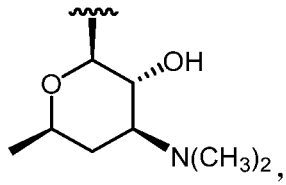
wherein:

each of R^{S1}, R^{S2a}, R^{S2b}, R^{S3a}, R^{S3b}, R^{S4a}, R^{S4b}, R^{S5a}, and R^{S5b} is independently hydrogen, optionally substituted alkyl, $-OR^{SO}$, $-N(R^{SN})_2$, or wherein R^{S2a} or R^{S2b} may be taken together with R^{S3a} or R^{S3b} to form an optionally substituted fused heterocyclic ring;

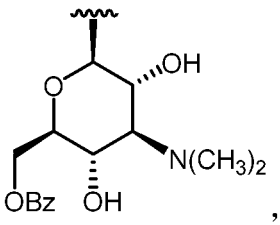
each instance of R^{SO} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted heterocyclyl, or an oxygen protecting group; and

each instance of R^{SN} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; or optionally two R^{SN} are taken with the intervening atoms to form a heterocyclic ring.

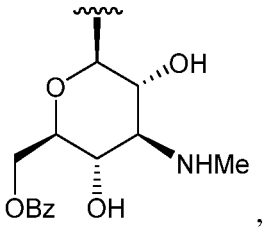
39. The compound of any one of claims 1-16, wherein R^9 is a group of formula:



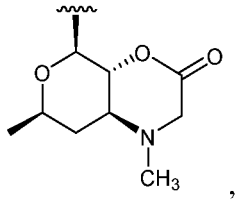
(S–2a–i–2),



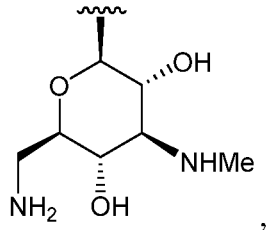
(S–2a–iii–4),



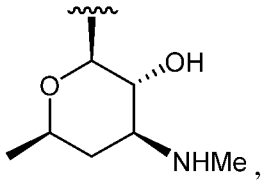
(S-2a-vii-5),



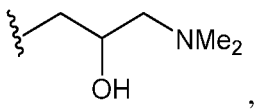
(S–2a–vii–3),



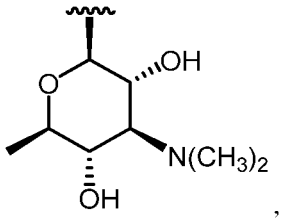
(S-2a-vii-5),



(S-2a-vii-5),

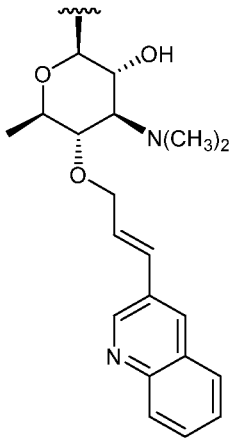


(S-2a-vii-5),



(S–2a–i–3),

or



(S–2a–vii–4).

40. The compound of any one of claims 1-16, wherein R^{14} is hydrogen.

41. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is optionally substituted C_{1-6}alkyl, optionally substituted haloalkyl, optionally substituted aralkyl, optionally substituted C_{2-6}alkenyl, or optionally substituted C_{3-6}carbocyclyl.

42. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is $-CH_3$, $-CF_3$, $-CH_2CH_2OH$, $-CH_2C(H)=O$, $-CH_2CH_2N(R^{22})_2$, or $-CH_2CH_2NHR^{22}$.

43. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is optionally substituted vinyl or optionally substituted allyl.

44. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is unsubstituted vinyl or unsubstituted allyl.

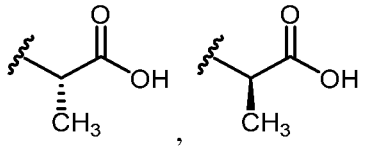
45. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is optionally substituted benzyl or unsubstituted benzyl.

46. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is monosubstituted benzyl.

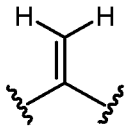
47. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is benzyl substituted by one instance of halogen.

48. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is optionally substituted cyclopropyl or unsubstituted cyclopropyl.

49. The compound of any one of claims 1-16, wherein R^{1a} or R^{1b} is $-CH_2CH_2N(R^{22})_2$ or $-CH_2CH_2NHR^{22}$; and each instance of R^{22} is independently hydrogen,$-CH_2C(=O)OH$,



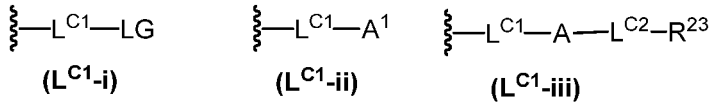
, $-CH_3$.

50. The compound of any one of claims 1-16, wherein R^{1a} and R^{1b} are taken together to form  .

51. The compound of any one of claims 1-16, wherein R^{2a} is optionally substituted C_{1-6}alkyl, optionally substituted haloalkyl, or halogen.

52. The compound any one of of claims 1-16, wherein R^{2a} is $-CH_3$, $-CF_3$, or –F.

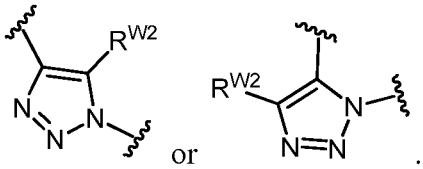
53. The compound of any one of claims 1-16, wherein R^{14} is a group of formula:



.

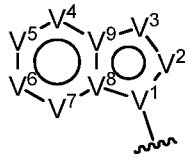
54. The compound of claim 53, wherein A^1 is $-N_3$.

55. The compound of claim 53, wherein A is:

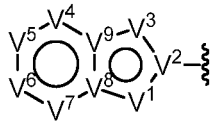


.

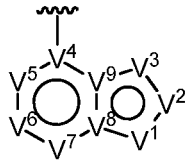
56. The compound of claim 53, wherein R^{23} is of formula:



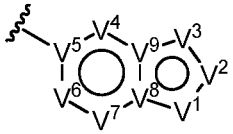
(e–1)



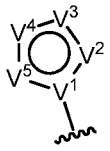
(e–2)



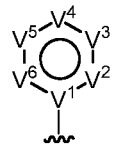
(e–3)



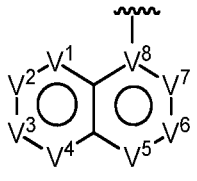
(e–4)

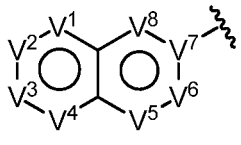


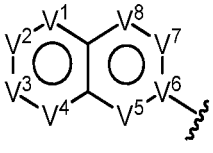
(e–5),



(e–6),


(e-7),


(e-8),


(e-9),

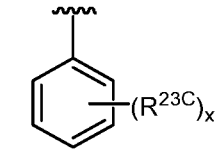
wherein:

each instance of V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, and V^9 may independently be O, S, N, NR^{23N}, C, or CR^{23C}, as valency permits;

R^{23N} is independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or a nitrogen protecting group; and

R^{23C} is hydrogen, halogen, –CN, $–NO_2$, $–N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, hydroxyl, substituted hydroxyl, amino, substituted amino, thiol, substituted thiol, or carbonyl.

57. The compound of claim 56, wherein R^{23} is of formula: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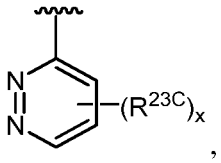
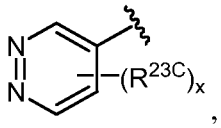
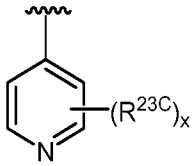

,

,

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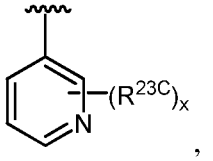
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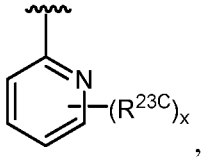
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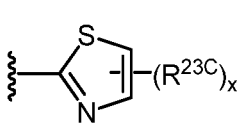
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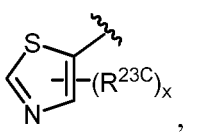
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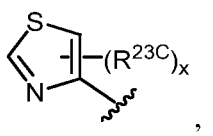
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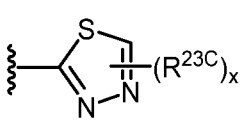
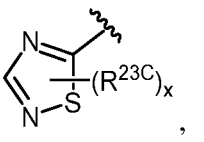
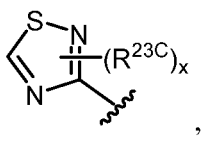

,

,

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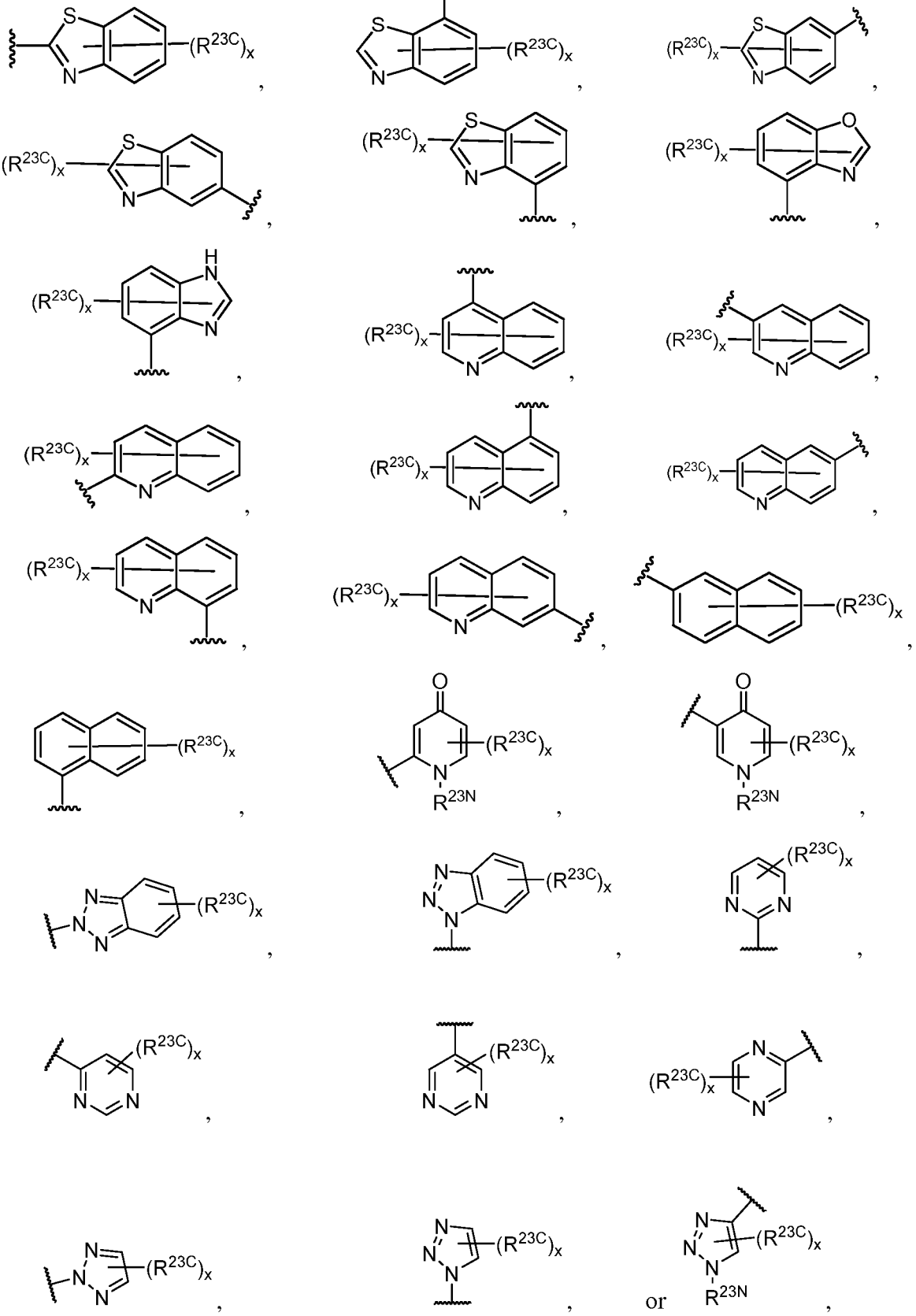


wherein x is 0, 1, or 2.

58. The compound of claim 1, wherein the compound is selected from any one of the compounds listed in Table 1 or salt thereof.

59. A pharmaceutical composition comprising a macrolide of any one of the preceeding claims, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

60. A method of treating an infectious disease comprising administering an effective amount of a macrolide of any one of the proceeding claims, or pharmaceutically acceptable salt thereof, to a subject in need thereof.

61. The method of claim 60, wherein the infectious disease is a bacterial infection.

62. The method of claim 60, wherein the bacterial infection is an infection with a Gram positive bacteria.

63. The method of claim 60, wherein the bacterial infection is an infection with a Gram negative bacteria.

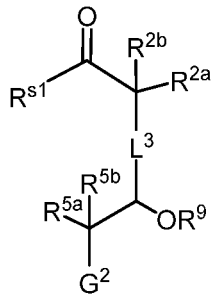
64. The method of claim 60, wherein the bacterial infection is a *Staphylococcus* infection, a *Bacillus* infection, a *Strepococcus* infection, an *Escherichia* infection, or a *Haemophilus* infection.

65. The method of claim 60, wherein the infectious disease is a parasitic infection.

66. A method of treating an inflammatory condition comprising administering an effective amount of a macrolide of any one of the proceeding claims, or pharmaceutically acceptable salt thereof, to a subject in need thereof.

67. The method of claim 66, wherein the inflammatory condition is a chronic pulmonary inflammatory syndrome.

68. A compound of Formula (**N-1a**):

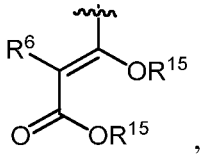
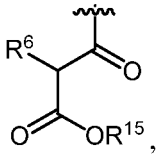
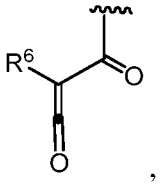


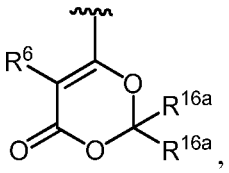
(**N-1a**)

or a salt thereof; wherein R^{2a}, R^{2b}, L^3, R^9, R^{5a}, R^{5b}, R^9, and L^3 are as defined in claim 1;

R^{s1} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

G^2 is a group of formula:

 ,  ,  ,

or  ,

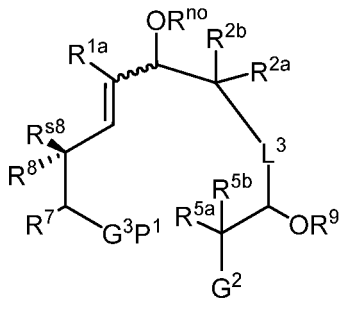
wherein:

R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

69. A compound of Formula (**N-1b**):



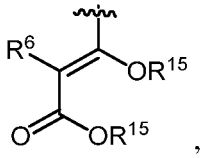
(**N-1c**)

or a salt thereof; wherein G^3, R^7, R^{s8}, R^8, R^{1a}, R^{2a}, R^{2b}, R^{5a}, R^{5b}, R^9, and L^3 are as defined in claim 1;

R^{no} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group;

P^1 is hydrogen, silyl, optionally substituted alkyl, or optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group; and

G^2 is a group of formula:



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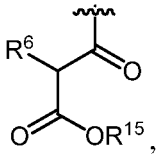

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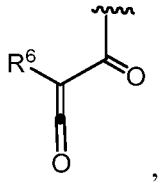

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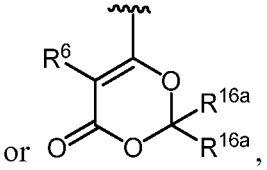


or ,

wherein:

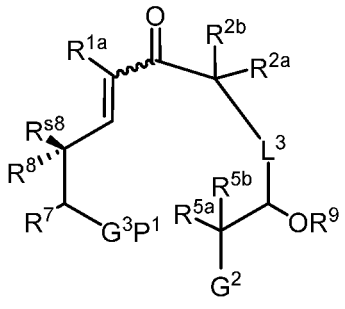
R^6 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, silyl, or halogen;

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl,

optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

70. A compound of Formula (**N-1d**):

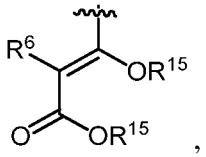


(**N-1d**)

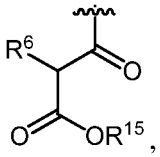
or a salt thereof; wherein G^3, R^{s8}, R^{1a}, R^{2a}, R^{2b}, R^8, R^7, R^{5a}, R^{5b}, R^9, and L^3 are as defined in claim 1;

P^1 is hydrogen, silyl, optionally substituted alkyl, or optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group; and

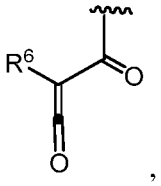
G^2 is a group of formula:



,

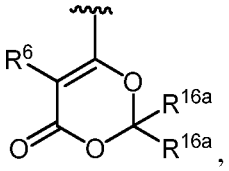


,



,

or



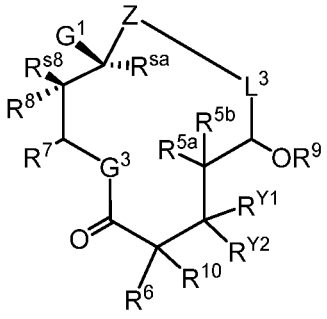
,

wherein:

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl; and

each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

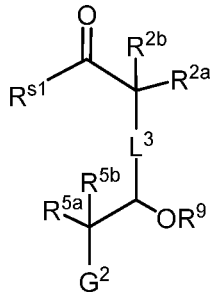
71. A method of preparing a compound of Formula (**N-7**):



(**N-7**),

or a salt thereof;

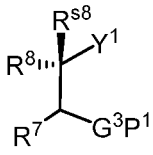
the method comprising coupling a compound of Formula (N-**1a**):



(**N-1a**),

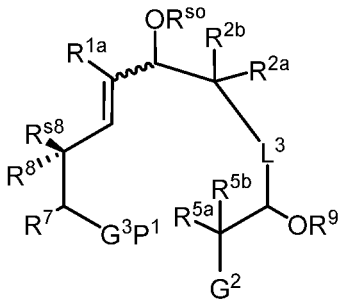
or salt thereof,

with a compound of Formula (**N-1b**)



(**N-1b**)

or salt thereof,

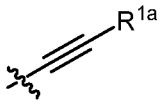
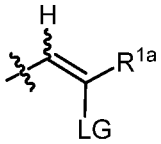


to give a compound of Formula (**N-1c**): (**N-1c**),

wherein:

Z, G^1, G^3, R^{1a}, R^{2a}, R^{2b}, R^{so}, R^{sa}, R^{s8}, R^{10}, R^9, R^8, R^7, R^6, R^{5a}, R^{5b}, R^9, R^{Y1}, R^{Y2}, and L^3 are as defined in claim 1;

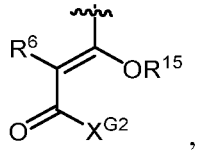
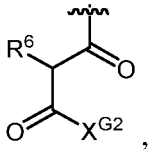
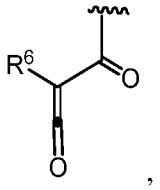
R^{s1} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

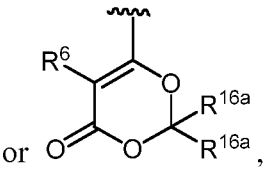
Y^1 is  or  ;

LG is a leaving group capable of being displaced by a nucleophile;

P^1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group; and

G^2 is a group of formula:

 ,  ,  ,

or  ,

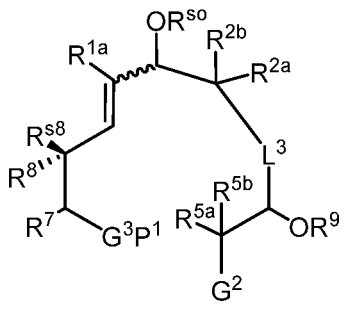
wherein:

each instance of X^{G2} is $-OR^{15}$, $-SR^{15}$, or $-N(R^{15})_2$;

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or two R^{15} groups are taken together to form an optionally substituted heteroaryl or heterocyclic ring; and

each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

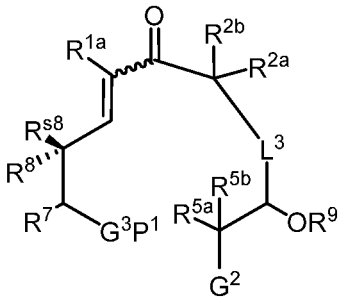
72. The method of claim 71 further comprising oxidizing, and optionally protecting a compound of Formula (**N-1c**):



(**N-1c**),

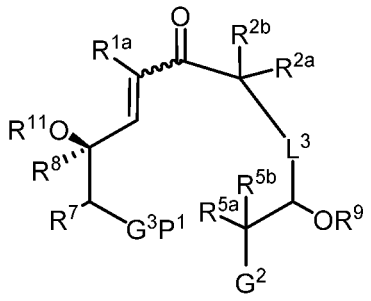
or a salt thereof;

to provide a compound of Formula (**N-1d**):



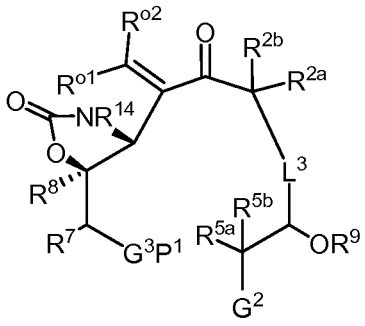
(**N-1d**).

73. The method of claim 72 further comprising protecting a compound of Formula (**N-1d-a**):



(**N-1d-a**),

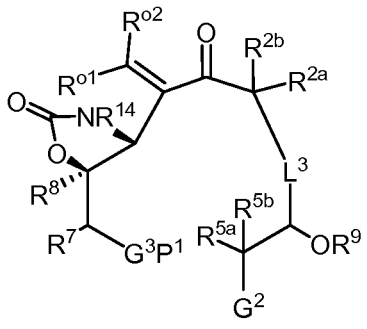
followed by an intramolecular nucleophilic addition to provide a compound of Formula (**N-1e**):



(**N-1e**),

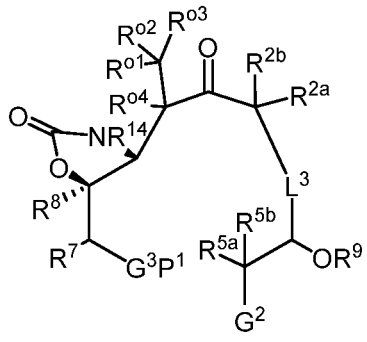
or a salt thereof; wherein R^{11}, R^{14}, R^{o1}, and R^{o2} are as defined in claim 1.

74. The method of claim 73 further comprising reacting a compound of Formula (**N-1e**)



(**N-1e**),

with a nucleophile to provide a compound of Formula (**N-1f**):



(**N-1f**),

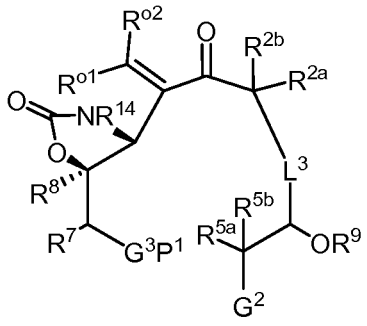
wherein

R^{o3} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl, $-OR^{n1}$, $-SR^{n1}$, or $-N(R^{n1})_2$;

R^{o4} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl; and

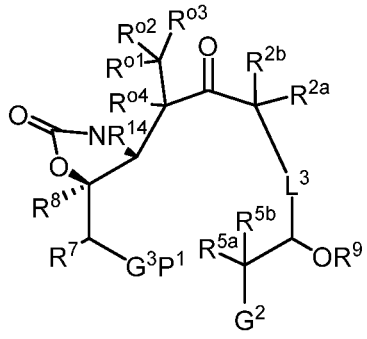
each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen; or a sulfur protecting group when attached to a sulfur; or a nitrogen protecting group when attached to nitrogen.

75. The method of claim 73 further comprising reducing and optionally protecting a compound of Formula (**N-1e**):



(**N-1e**),

to provide a compound of Formula (**N-1f**):



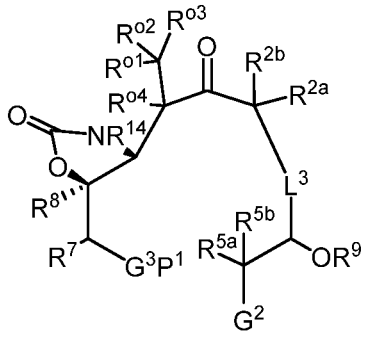
(**N-1f**),

wherein

each of R^{o3} and R^{o4} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl, $-OR^{n1}$, $-SR^{n1}$, or $-N(R^{n1})_2$; and

each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen; or a sulfur protecting group when attached to a sulfur; or a nitrogen protecting group when attached to nitrogen.

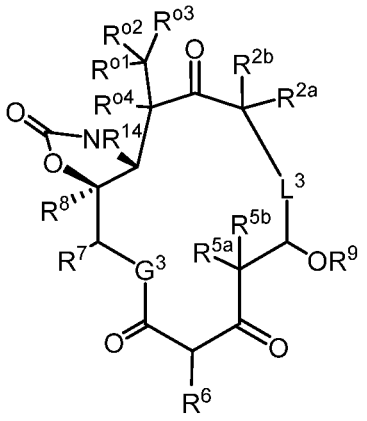
76. The method of claim 74 or 75 further comprising cyclizing a compound of Formula (**N-1f**):



(**N-1f**),

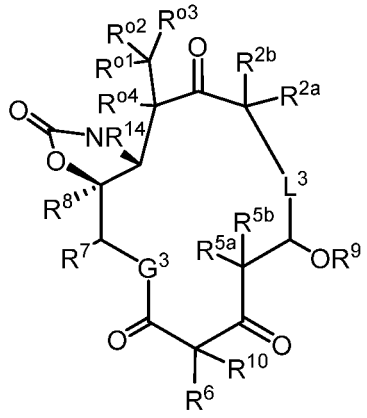
or a salt thereof;

to give a compound of Formula (**N-1g**):



(**N-1g**).

77. The method of claim 76 further comprising reacting a compound of Formula (**N-1g**) with an alkylating agent, R^{10}-LG, or a halogenating agent to provide a compound of Formula (**N-1h**):



(**N-1h**)

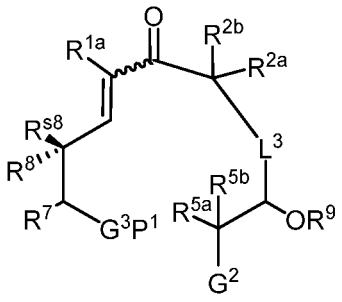
or a salt thereof; wherein R^{10} is halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl;

LG is a leaving group;

each of R^{o3} and R^{o4} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl, $-OR^{n1}$, $-SR^{n1}$, or $-N(R^{n1})_2$; and

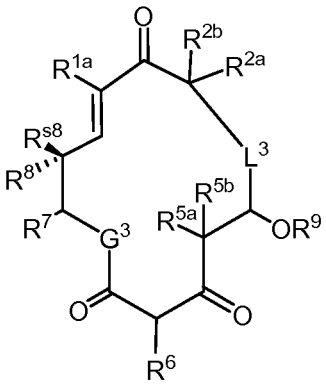
each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen; or a sulfur protecting group when attached to a sulfur; or a nitrogen protecting group when attached to nitrogen.

78. The method of claim 72, further comprising cyclizing a compound of Formula (**N-1d**):



(**N-1d**),

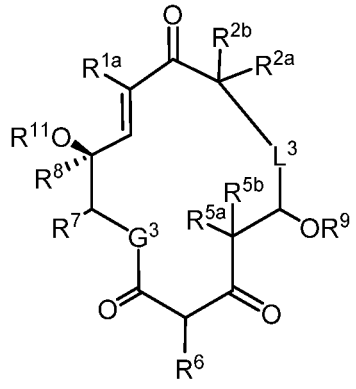
or a salt thereof, to provide a compound of Formula (**N-2-B**):



(**N-2-C**),

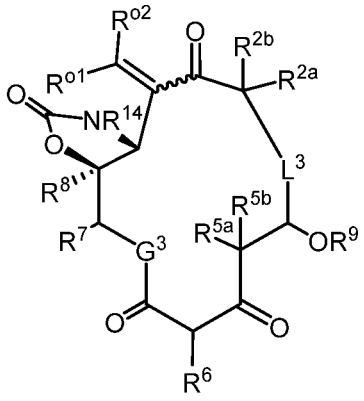
or salt thereof.

79. The method of claim 78, further comprising protecting a compound of Formula (**N-1i**):



(**N-1i**)

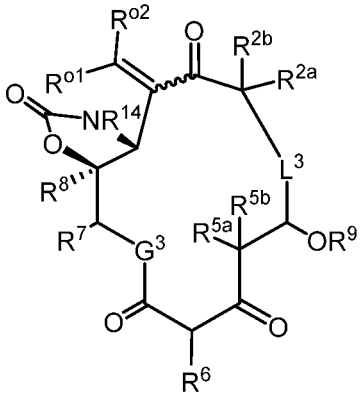
or salt thereof, followed by an intramolecular nucleophilic addition to provide a compound of Formula (**N-1j**):



(**N-1j**)

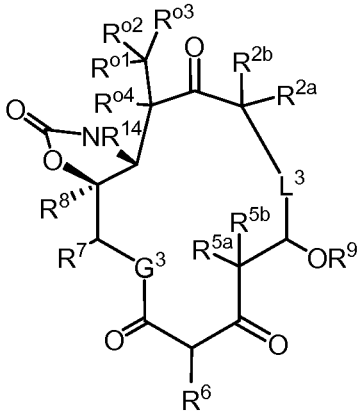
or salt thereof; wherein R^{o1}, R^{o2}, and R^{14} are as defined in claim 1.

80. The method of claim 79, further comprising reacting a compound of Formula (**N-1j**):



(**N-1j**)

or a salt thereof, with a nucleophile to provide a compound of Formula (**N-1k**):

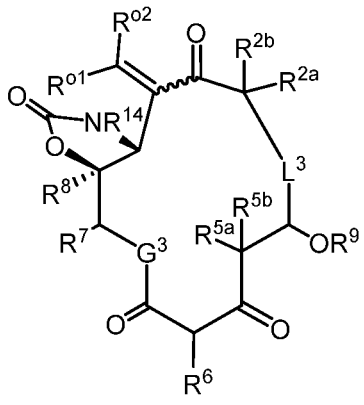


(**N-1k**);

each of R^{o3} and R^{o4} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl, $-OR^{n1}$, $-SR^{n1}$, or $-N(R^{n1})_2$; and

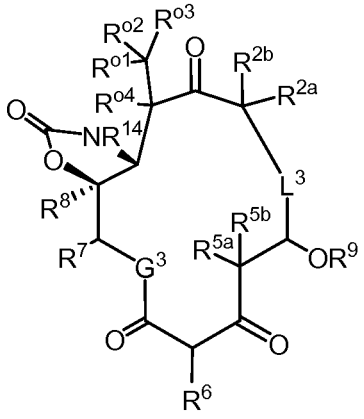
each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen; or a sulfur protecting group when attached to a sulfur; or a nitrogen protecting group when attached to nitrogen.

81. The method of claim 79, further comprising reducing a compound of Formula (**N-1j**):



(**N-1j**)

or a salt thereof, to provide a compound of Formula (**N-1k**):



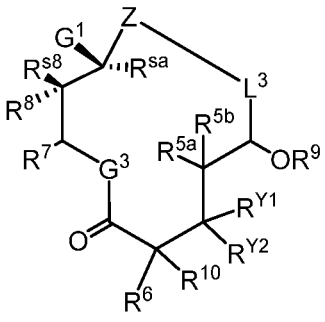
(**N-1k**),

wherein

each of R^{o3} and R^{o4} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or optionally substituted heteroaryl, $-OR^{n1}$, $-SR^{n1}$, or $-N(R^{n1})_2$; and

each instance of R^{n1} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen; or a sulfur protecting group when attached to a sulfur; or a nitrogen protecting group when attached to nitrogen.

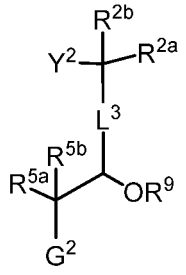
82. A method of preparing a compound of Formula (**N-7**):



(**N-7**),

or a salt thereof;

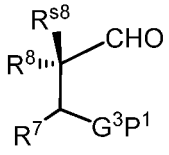
the method comprising coupling a compound of Formula (N-**1m**):



(**N-1m**),

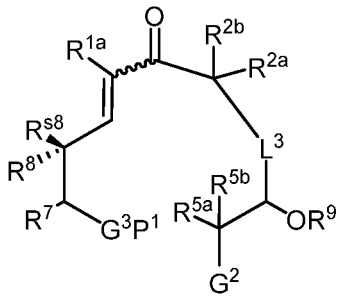
or salt thereof,

with a compound of Formula (**N-1n**)



(**N-1n**)

or salt thereof,



to give a compound of Formula (**N-1d**): (**N-1d**),

wherein:

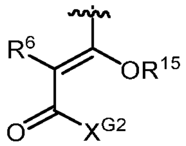
Z, G^1, G^3, R^{1a}, R^{2a}, R^{2b}, R^{sa}, R^{s8}, R^{10}, R^9, R^8, R^7, R^6, R^{5a}, R^{5b}, R^9, R^{Y1}, R^{Y2}, and L^3 are as defined in claim 1;

Y^2 is –C(=O)-CH=P(R^{P1})(R^{P2})(R^{P3}) or –C(=O)-CH_2-P(O)(OR^{P2})(OR^{P3}),

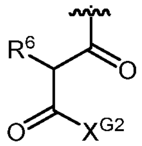
each of R^{P1}, R^{P2}, and R^{P3} is independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocycyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

P^1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group; and

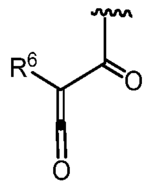
G^2 is a group of formula:



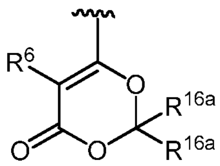
,



,



,

or 

,

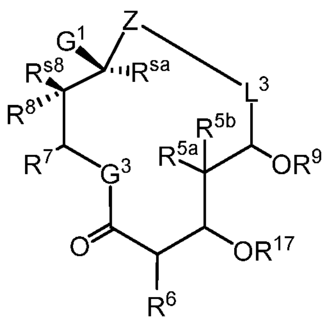
wherein:

each instance of X^{G2} is $-OR^{15}$, $-SR^{15}$, or $-N(R^{15})_2$;

each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or two R^{15} groups are taken together to form an optionally substituted heteroaryl or heterocyclic ring; and

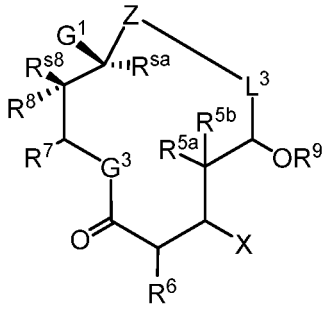
each instance of R^{16a} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

83. The method of any one of claims 71-82, further comprising halogenating a compound of Formula (**N-4**):



(**N-4**)

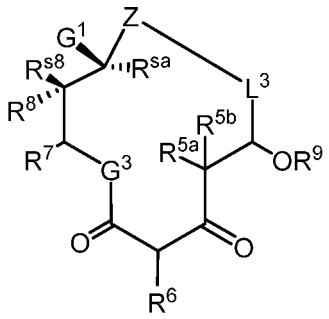
or a salt thereof, to provide a compound of Formula (**N-7a**):



(**N-7a**)

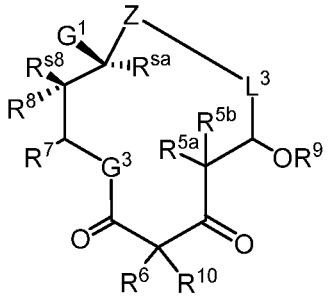
or salt thereof, wherein X is a halogen.

84. The method of any one of claims 71-82, further comprising treating a compound of Formula (**N-2**):



(**N-2**),

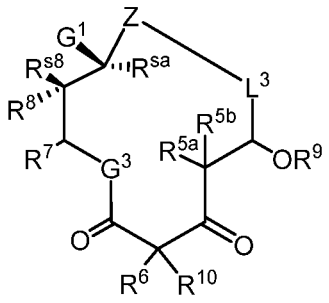
or a salt thereof, with an alkylating agent, R^{10}-LG, or a halogenating agent to provide a compound of Formula (**N-3**):



(**N-3**)

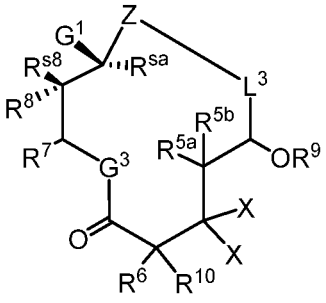
or salt thereof, wherein R^{10} is halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, or optionally substituted heterocyclyl.

85. The method of any one of claims 71-82, further comprising halogenating a compound of Formula (N-**3**):



(**N**-3),

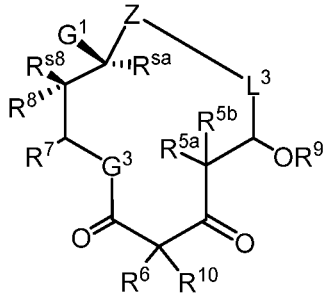
or a salt thereof, to provide a compound of Formula (**N-6b**):



(**N-6b**)

or salt thereof, wherein R^{10} is as defined in claim M7 and each instance of X is independently a halogen.

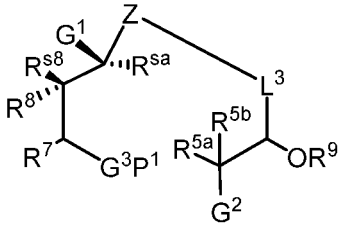
86. A method of preparing a compound of Formula (**N-3**):



(**N-3**)

or a salt thereof; wherein Z, G^1, G^3, R^8, R7, R^6, R^{10}, R^{5a}, R^{5b}, R^9, and L^3 are as defined in claim 1;

the method comprising cyclizing a compound of Formula (N-**1o**):



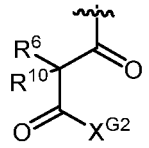
(**N-1o**)

or salt thereof;

wherein:

P^1 is hydrogen, silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen, nitrogen, or thiol protecting group; and

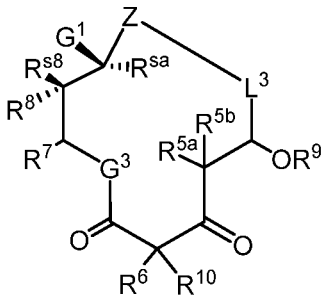
G^2 is a group of formula:



each instance of X^{G2} is $-OR^{15}$, $-SR^{15}$, or $-N(R^{15})_2$; and

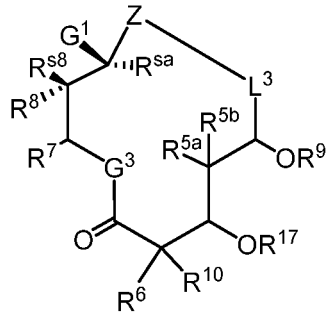
each instance of R^{15} is independently silyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or two R^{15} groups are taken together to form an optionally substituted heteroaryl or heterocyclic ring.

87. The method of claim 86, further comprising reducing, and optionally protecting, a compound of Formula (**N-3**):



(**N-3**),

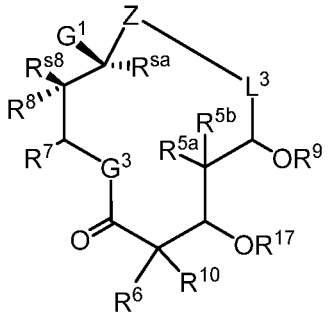
or a salt thereof, to provide a compound of Formula (**N-5**):



(**N-5**)

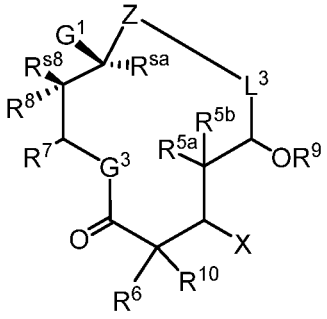
or salt thereof, wherein R^{17} is as defined in claim 1.

88. The method of claim 80, further comprising halogenating a compound of Formula (**N-5**):



(**N-5**)

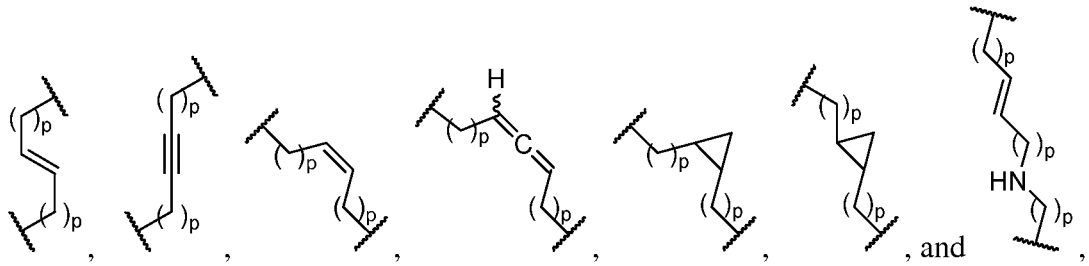
or a salt thereof, to provide a compound of Formula (**N-7b**):



(**N-7b**)

or salt thereof, wherein X is a halogen.

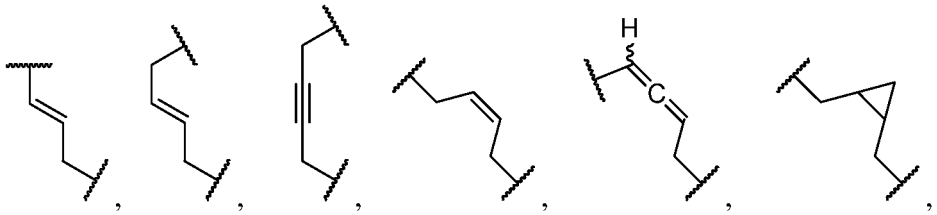
89. The compound of any one of claims 1-58, wherein each of L^{C1} and L^{C2} are independently of one of the following formulae:

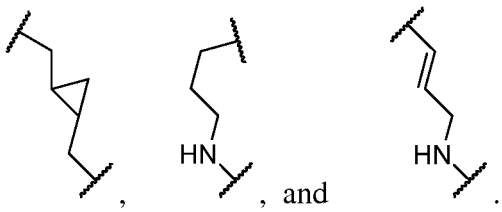


, and

wherein each instance of p is 0, 1, or 2.

90. The compound of any one of claims 1-58, wherein each of L^{C1} and L^{C2} are independently of one of the following formulae:

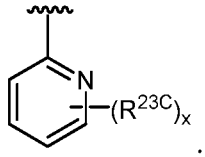




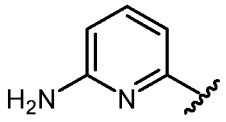
91. The compound of any one of claims 1-58 or 89-90, wherein R^{1a} is optionally substitutd C_{1-6} alkyl.

92. The compound of claim 91, wherein R^{1a} is methyl.

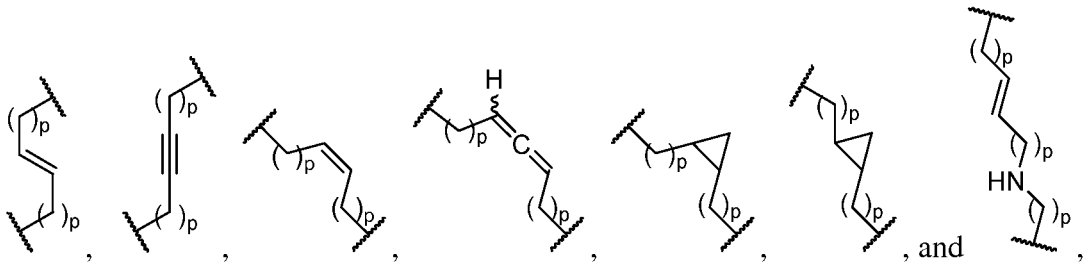
93. The compound of any one of claims 1-58 or 89-91, wherein R^{23} is of the following formula:



94. The compound of claim 93, wherein R^{23} is of the formula:

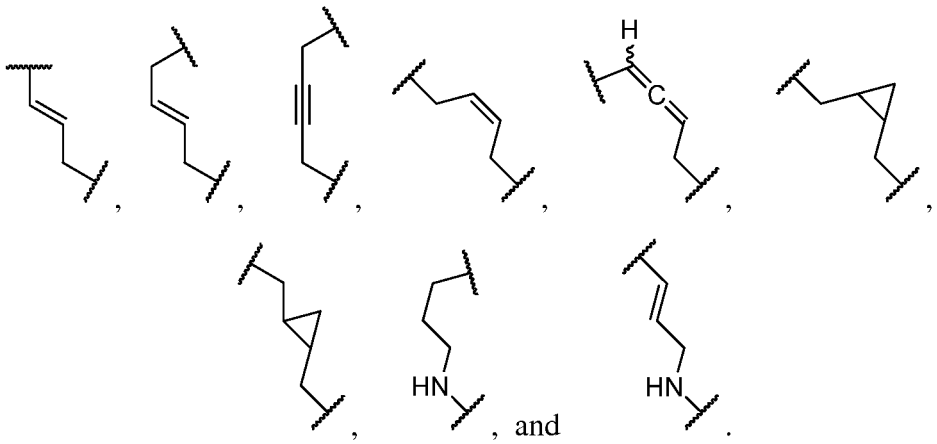


95. The method of any one of claims 71-88, wherein each of L^{C1} and L^{C2} are independently of one of the following formulae:



wherein each instance of p is 0, 1, or 2.

96. The method of any one of claims 71-88, wherein each of L^{C1} and L^{C2} are independently of one of the following formulae:

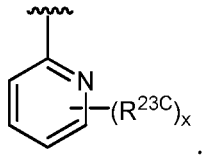


, and .

97. The method of any one of claims 71-88, wherein R^{1a} is optionally substitutd C_{1-6} alkyl.

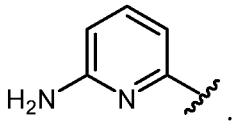
98. The compound of claim 97, wherein R^{1a} is methyl.

99. The method of any one of claims 71-88 or 95-98, wherein R^{23} is of the following formula:

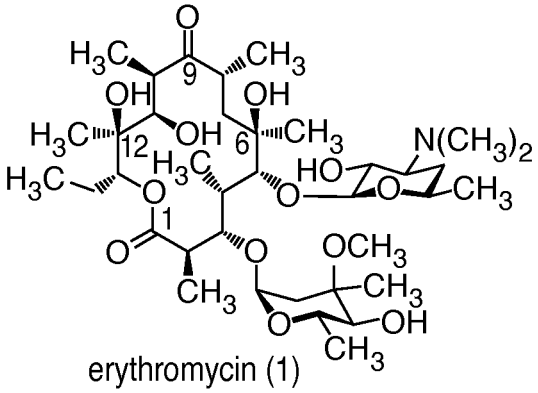


.

100. The method of claim 99, wherein R^{23} is of the formula:

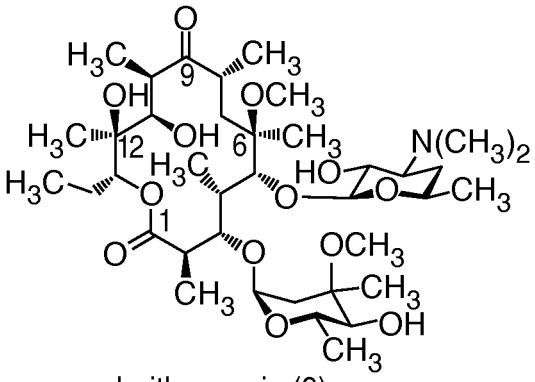


.

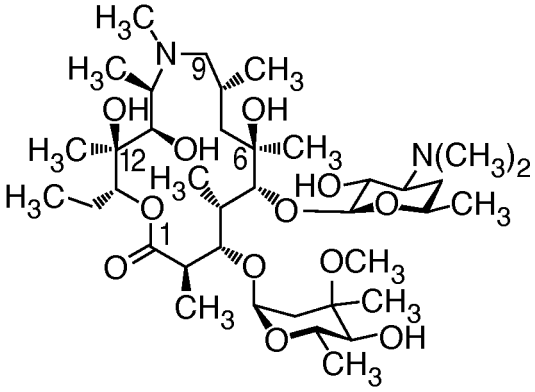


erythromycin (1)
14-membered macrolide
fermentation from *S. erythraea*
1952

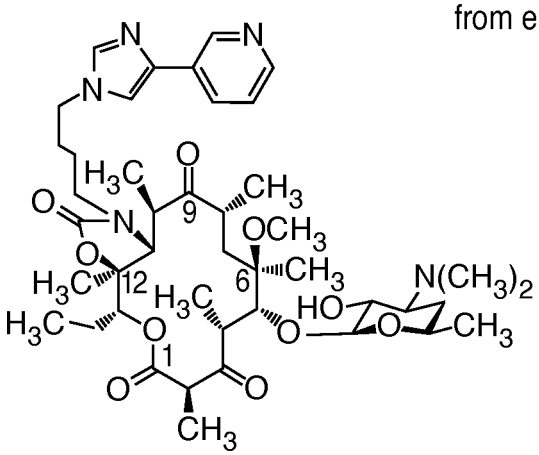
Preparation:
US FDA Approval:



clarithromycin (2)
14-membered macrolide
semi-synthesis: 6 steps
from erythromycin
1991

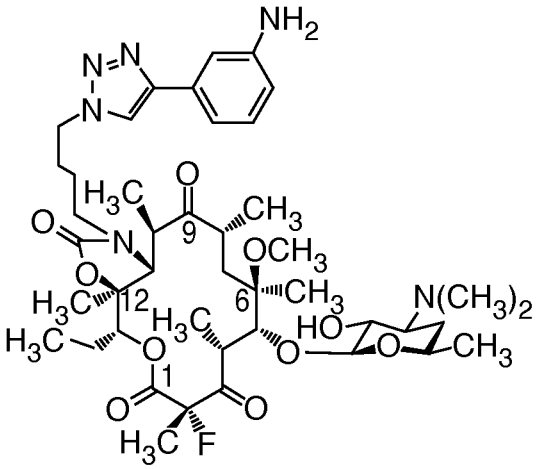


azithromycin (3)
15-membered azalide
semi-synthesis: 4 steps
from erythromycin
1991

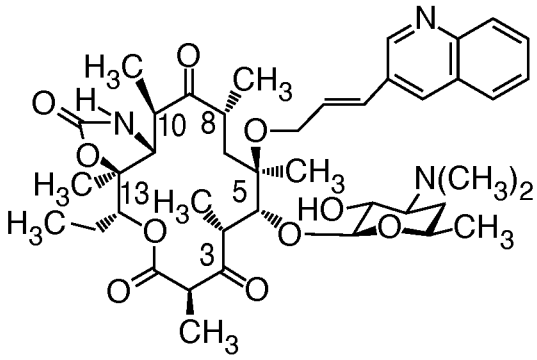


telithromycin (4)
14-membered ketolide
semi-synthesis: 12 steps from erythromycin
2004

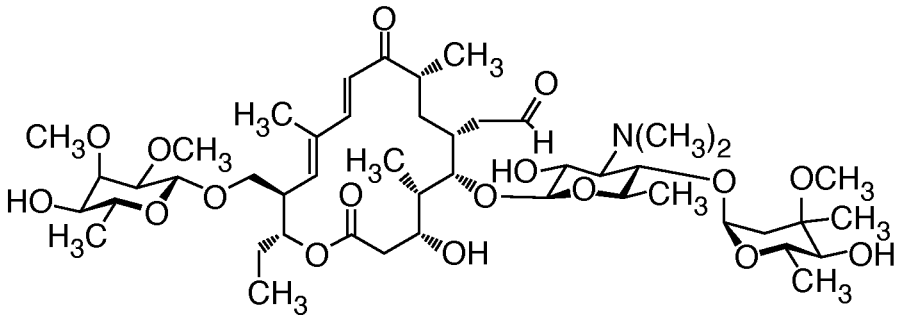
Figure 1



solithromycin (5)
14-membered ketolide
semi-synthesis: 16 steps from erythromycin
(Clinic Phase II)



cethromycin (7)
14-membered ketolide
(Clinic Phase III)



tylosin (6)
16-membered macrolide
fermentation from *S. fradiae*
(veterinary medicine)

Figure 1
(continued)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/54700

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/02; A61K 31/335, 31/365 (2015.01)
CPC - A61K 31/335; C12P 17/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A01N 43/02; A61K 31/335, 31/365 (2015.01)
CPC: A61K 31/335; C12P 17/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: ketolide, macrocyclization, infectious, inflammatory, macrolide, antibiotic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2005/0090461 A1 (LEADLAY, PF et al.) 28 April 2005; claim 26	1 --- 2-5, 6/1-5, 12-16
Y	US 2010/0035832 A1 (HEGGELUND, A et al.) 11 February 2010; paragraphs [0010]-[0013]	2-5, 6/2-5
Y	US 2002/0128212 A1 (OR, YS et al.) 12 September 2002; paragraph [0034]	6/1-5, 58
Y	WO 2011/131749 A1 (GLAXO GROUP LIMITED) 27 October 2011; page 2, lines 24-35; page 3, lines 1-5	12-16
Y	US 2012/0058963 A1 (ALIHODZIC, S et al.) 08 March 2012; paragraphs [0022], [0027]	13-14
Y	WU, YJ et al. "Recent Developments on Ketolides and Macrolides" Current Medicinal Chemistry, Vol. 8, 2001, pages 1727-1758; figure 1	15-16
A	US 8,796,474 B1 (WILLIAMS, LJ et al.) 05 August 2014; entire document	1-5, 6/1-5, 12-16, 58, 68-75, 76/74-75, 77/76/74-75, 78-82, 86-88
A	US 2014/0213515 A1 (LIU, DR et al.) 31 July 2014; entire document	1-5, 6/1-5, 12-16, 58, 68-75, 76/74-75, 77/76/74-75, 78-82, 86-88

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2015 (19.11.2015)	11 JAN 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/54700

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/0141589 A1 (OKUDA, A et al.) 29 June 2006; entire document	1-5, 6/1-5, 12-16, 58, 68-75, 76/74-75, 77/76/74-75, 78-82, 86-88
A	US 2013/0178429 A1 (LIU, DR et al.) 11 July 2013; entire document	1-5, 6/1-5, 12-16, 58, 68-75, 76/74-75, 77/76/74-75, 78-82, 86-88
A	WO 2012/127351 A1 (WOCKHARDT LIMITED) 27 September 2012; entire document	1-5, 6/1-5, 12-16, 58, 68-75, 76/74-75, 77/76/74-75, 78-82, 86-88
A	US 2009/0170790 A1 (DAS, B et al.) 02 July 2009; entire document	1-5, 6/1-5, 12-16, 58, 68-75, 76/74-75, 77/76/74-75, 78-82, 86-88

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/54700

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 7-11, 17-57, 59-67, 83-85, 89-100
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

摘要

本申请提供的是通过以下方式制备新的 14-元酮内酯的方法：使东半部与西半部偶联，然后大环化，并任选的官能化。本申请还提供在合成这些酮内酯中的中间体，包括东半部和西半部。本申请还提供药物组合物和使用这些酮内酯治疗感染性疾病和炎症性病症的方法。