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(71) **Applicant**: **CEMPRA PHARMACEUTICALS, INC.** [US/US]; 6320 Quadrangle Drive, Suite 360, Chapel Hill, North Carolina 27517 (US).

(72) **Inventor**: **PEREIRA, David E.**; 103 Lansbrooke Lane, Apex, North Carolina 27502 (US).

(74) **Agent**: **MCLAREN, Kevin L.**; Barnes & Thornburg LLP, 11 South Meridian Street, Indianapolis, Indiana 46204 (US).

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) **Title**: CONVERGENT PROCESSES FOR PREPARING MACROLIDE ANTIBACTERIAL AGENTS

(57) **Abstract**: The invention described herein relates to processes for preparing ketolide antibacterial agents. In particular, the invention relates to intermediates and processes for preparing ketolides that include a 1,2,3-triazole substituted side chain.

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CONVERGENT PROCESSES FOR PREPARING MACROLIDE ANTIBACTERIAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims, under 35 U.S.C. § 119(e), the benefit of and priority to U.S. Provisional Application No. 61/786,914 filed March 15, 2013, which is hereby incorporated herein by reference.

TECHNICAL FIELD

The invention described herein relates to processes for preparing ketolide antibacterial agents. In particular, the invention relates to intermediates and processes for preparing ketolides that include a 1,2,3-triazole substituted side chain.

BACKGROUND AND SUMMARY

The use of macrolides for various infectious diseases is well known. Erythromycin was the first compound of this class to be introduced into clinical practice. Since then, additional macrolides, including ketolides have garnered much attention for their ability to treat a wide range of disease states. In particular, macrolides are an important component of therapies for treating bacterial, protozoal, and viral infections. In addition, macrolides are often used in patients allergic to penicillins.

Illustrative of their wide ranging uses, macrolide compounds have been found to be effective for the treatment and prevention of infections caused by a broad spectrum of bacterial and protozoal pathogens. They are also useful for treating respiratory tract infections and soft tissue infections. Macrolide antibiotics are found to be effective on beta-hemolytic streptococci, pneumococci, staphylococci, and enterococci. They are also found to be effective against mycoplasma, mycobacteria, some rickettsia, and chlamydia.

Macrolide compounds are characterized by the presence of a large lactone ring, which is generally a 14, 15, or 16-membered macrocyclic lactone, to which one or more saccharides, including deoxy sugars such as cladinose and desosamine, may be attached. For example, erythromycin is a 14-membered macrolide that includes two sugar moieties. Spiramycin belongs to a second generation of macrolide compounds that include a 16-membered ring. Third generation macrolide compounds include for example semi-synthetic derivatives of erythromycin A, such as azithromycin and clarithromycin. Finally, ketolides represent a newer class of macrolide antibiotics that have received much attention recently due to their acid stability, and most importantly due to their excellent activity against organisms that are resistant to other macrolides. Like erythromycins, ketolides are 14-membered ring macrolide derivatives characterized by a keto group at the C-3 position (Curr. Med. Chem., "Anti-Infective Agents," 1:15-34 (2002)). Ketolide compounds are also currently under clinical investigation.

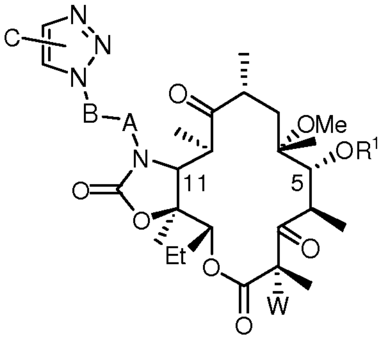
Liang et al. in U.S. Patent Appl. Pub. No. 2006/0100164, the disclosure of which is incorporated herein by reference, describes a new series of triazole-containing ketolide compounds, and an illustrative synthesis thereof. These new compounds show excellent activity against pathogenic organisms, including those that have already exhibited resistance to current therapies. However, it has been discovered herein that side-reactions occur in the processes disclosed by Liang et al leading to impurities that are difficult to remove, and low yields. In addition, starting material impurities are also difficult to remove. Those side-reactions decrease the overall yield of the desired compounds, and those side-products and impurities may complicate the purification of the desired compounds. The occurrence of such side reactions and the presence of such impurities are exacerbated on large commercial scales. In addition, the processes disclosed by Liang et al. include an azide intermediate, which at larger commercial manufacturing scales, may be undesirable, or represent a safety issue. Due to the importance of these triazole-containing ketolide compounds for use in providing beneficial therapies for the treatment of pathogenic organisms, alternative and/or improved processes for their preparation are needed.

The azide intermediate may be avoided by a process that incorporates the side chain intact. However, it has also been reported that introduction of an intact side chain is not a viable process (see, Lee et al., "Process Development of a Novel Azetidinyl Ketolide Antibiotic" Org. Process Res Dev 16:788–797 (2012)). In particular, it has been reported that introduction of an intact side chain leads to an isomeric mixture of products. In addition, it has been reported that introduction of the intact side chain provides only a low yield (<20%).

It has been unexpectedly discovered herein that triazole-containing side chains do not result in an isomeric mixture of products. It has also been unexpectedly discovered herein that triazole-containing side chains provide high yielding reactions. It has also been unexpectedly discovered herein that if the side chain is introduced before the removal of the cladinose, then a single isomer is obtained. It has also been unexpectedly discovered herein that if the side chain is introduced before the removal of the cladinose, then the process provides a high yield.

Described herein are new processes that may be advantageous in preparing compounds of formula (I) that avoid such side-products, and/or may be purified to higher levels of purity. In addition, the processes described herein avoid the azide intermediate by proceeding through a convergent synthetic route.

In one illustrative embodiment of the invention, processes and intermediates are described for preparing compounds of formula (I):



(I)

and pharmaceutically acceptable salts, solvates, and hydrates thereof; wherein

R^1 is a desosamine or a desosamine derivative;

A is $-CH_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-S(O)_2-$, $-S(O)_2NH-$, $-C(O)NHS(O)_2-$;

B is $-(CH_2)_n-$ where n is an integer ranging from 0-10; or B is saturated C_2-C_{10}; or B is unsaturated C_2-C_{10}, which may contain one or more alkenyl or alkynyl groups; or -A-B- taken together is alkylene, cycloalkylene, or arylene;

C represents 1 or 2 substituents independently selected in each instance from hydrogen, halogen, hydroxy, acyl, acyloxy, sulfonyl, ureyl, and carbamoyl, and alkyl, alkoxy, heteroalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, , each of which is optionally substituted; and

W is hydrogen, F, Cl, Br, I, or OH.

In another illustrative embodiment, processes and intermediates are described herein for preparing 11-N-[[4-(3-aminophenyl)-1,2,3-triazol-1-yl]-butyl]-5-desosaminyl-2-fluoro-3-oxoerythronolide A, 11,12-cyclic carbamate, also known as OP-1068, CEM-101, and solithromycin.

In another embodiment of the compounds of formula (I), R^1 is a desosamine that includes an optionally protected 2'-hydroxy group. In another embodiment, R^1 is a desosamine that includes a protected 2'-hydroxy group. In another embodiment, the protecting group is an acyl group. In another embodiment, the protecting group is a sterically hindered acyl group, such as a branched alkyl, aryl, heteroaryl, arylalkyl, arylalkyl, or heteroarylalkyl acyl group, each of which is optionally substituted. In another embodiment, the protecting group is an optionally substituted benzoyl group. In another embodiment, the protecting group is a benzoyl group. In another embodiment, -A-B- is alkylene, cycloalkylene, or arylene. In another embodiment, -A-B- is alkylene. In another embodiment, -A-B- is C_3-C_5 alkylene. In another embodiment, -A-B- is C_4 alkylene. In another embodiment, -A-B- is $-(CH_2)_4-$. In another embodiment, C is optionally substituted aryl, heteroaryl, arylalkyl, or heteroarylalkyl. In another embodiment, C is optionally substituted aryl or heteroarylalkyl. In another embodiment, C is optionally substituted aryl. In another embodiment, C is substituted aryl. In another embodiment, C is amino substituted aryl. In another embodiment, C is amino substituted phenyl. In another embodiment, C is 3-aminophenyl. In another embodiment, W is H or F. In another embodiment, W is F.

It is to be understood that each and every combination, and each and every selection, and combination thereof, of the forgoing and following embodiments is described herein. For example, in another embodiment, R^1 is a desosamine that includes a protected 2'-hydroxy group, where the protecting group is an acyl group; or R^1 is a desosamine that includes a protected 2'-hydroxy group, where the protecting group is a sterically hindered acyl group; or R^1 is a desosamine that includes a protected 2'-hydroxy group, where the protecting group is a benzoyl group, and -A-B- is C_3-C_5 alkylene; or R^1 is a desosamine that includes a protected 2'-hydroxy group, where the protecting group is a benzoyl group, and -A-B- is $-(CH_2)_4-$; or R^1 is a desosamine that includes a protected 2'-hydroxy group, where the protecting group is a benzoyl group, and -A-B- is $-(CH_2)_4-$, and C is optionally substituted aryl; or R^1 is a desosamine that includes a protected 2'-hydroxy group, where the protecting group is a benzoyl group, and -A-B- is $-(CH_2)_4-$, and C is 3-aminophenyl; and so forth.

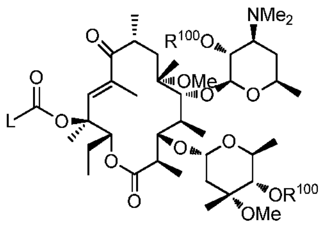
It is to be understood that the processes described herein may be advantageously performed simply and cost-effectively. It is further to be understood that the processes described herein may be scaled to large production batches. It is further to be understood that the processes described herein are performed in fewer steps than conventional processes. It is further to be understood that the processes described herein are performed are more convergent, and/or require shorter linear sub-processes, than conventional processes. It is further to be understood that the processes described herein may concomitantly produce fewer or different side products than known processes. It is further to be understood that the processes described herein may yield compounds described herein in higher purity than known processes.

DETAILED DESCRIPTION

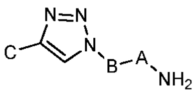
Several illustrative embodiments of the invention are described by the following enumerated clauses:

1A. A process for preparing a compound of formula (I) as described herein, the process comprising the step of

(A) contacting a compound of formula



or a salt thereof, where R^{100} is a hydroxyl protecting group, and L is a leaving group, with a compound of formula



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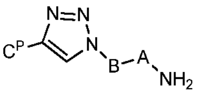
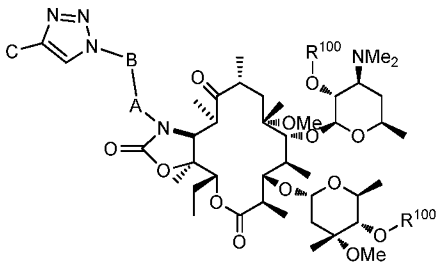


or a salt thereof, where C is as defined herein, and C^P is a protected form of C, and a base, to prepare a compound of formula



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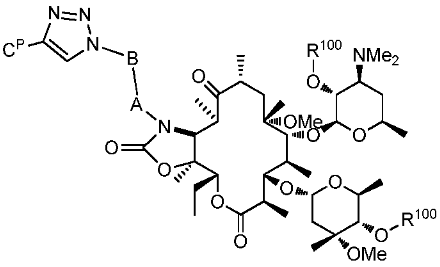
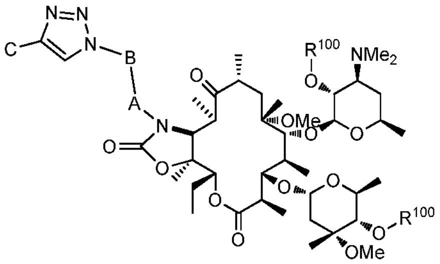
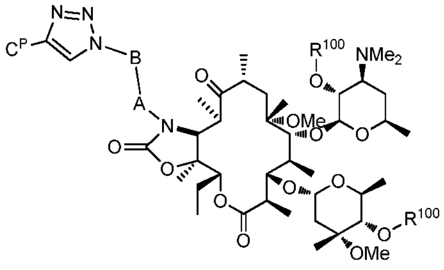


or a salt thereof; or

(B) contacting a compound of formula

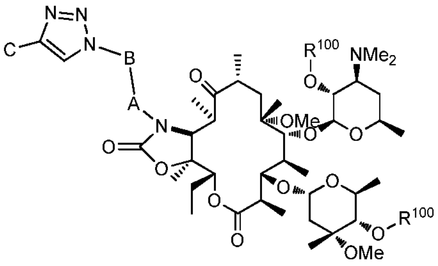


or a salt thereof, with one or more protecting group forming agents to prepare a compound of formula



or a salt thereof; or

(C) contacting a compound of formula



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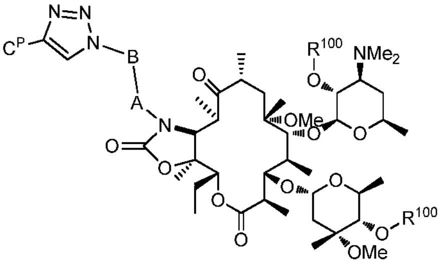
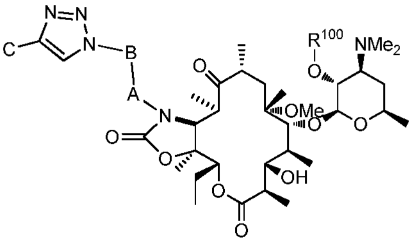


or a salt thereof, with an acid to prepare a compound of formula



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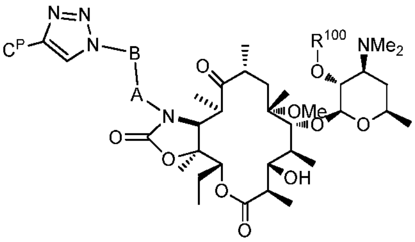
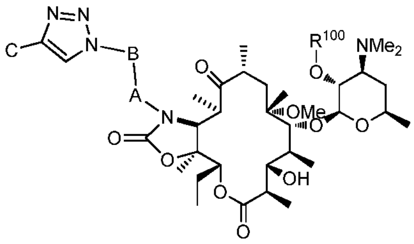
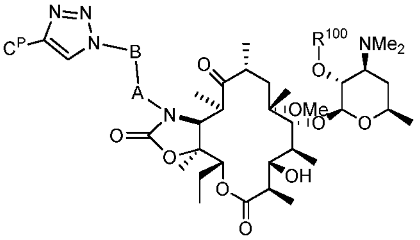


or a salt thereof; or

(D) contacting a compound of formula

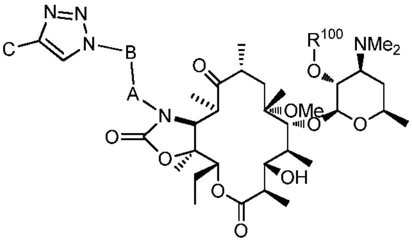


or a salt thereof, with one or more protecting group forming agents to prepare a compound of formula



or a salt thereof; or

(E) contacting a compound of formula



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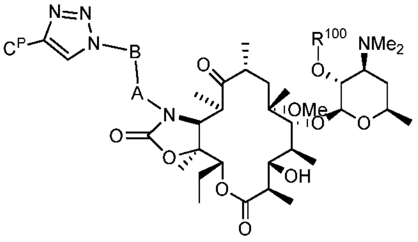
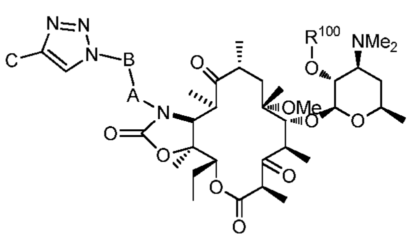


or a salt thereof, with an oxidizing agent to prepare a compound of formula



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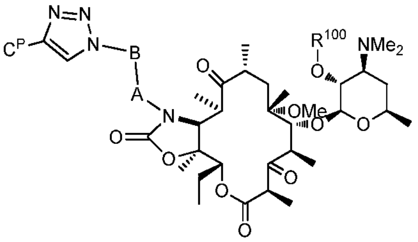
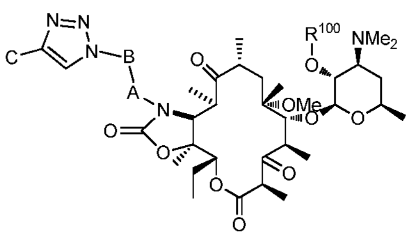


or a salt thereof; or

(F) contacting a compound of formula



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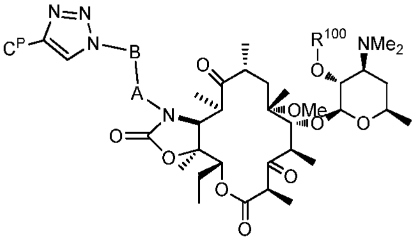
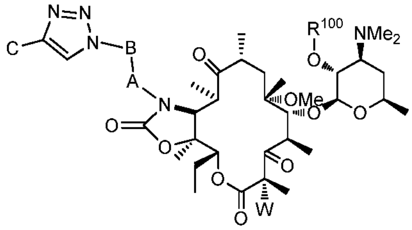


or a salt thereof, with a hydroxylating or halogenating agent to prepare a compound of formula



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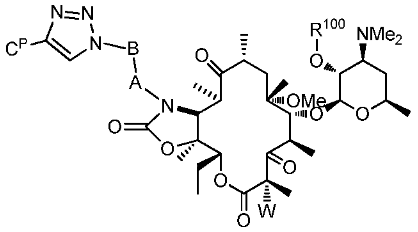
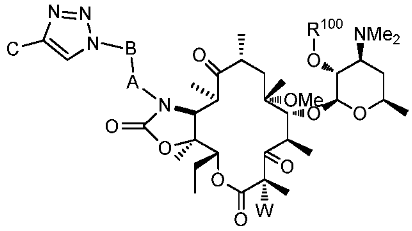


or a salt thereof; or

(G1) contacting a compound of formula



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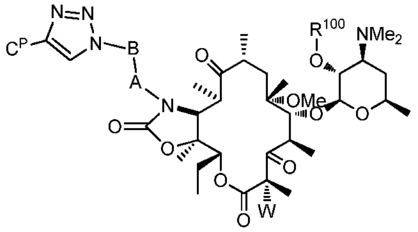
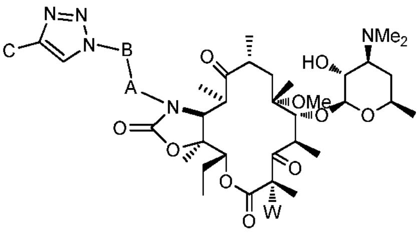


or a salt thereof, with a hydroxy deprotecting agent to prepare a compound of formula



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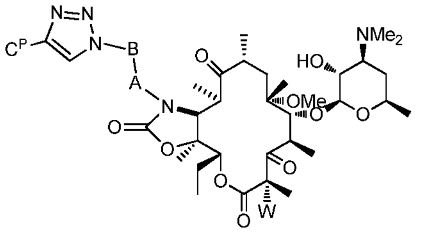
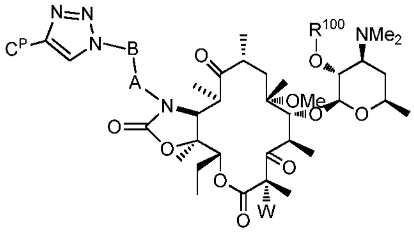
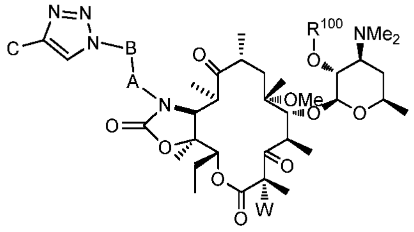


or a salt thereof; or

(G2) contacting a compound of formula



or a salt thereof, with one or more deprotecting agents to prepare the corresponding deprotected compound of formula



or a salt thereof; or

any combination of the foregoing.

1B. The process of clause 1A wherein steps (G1) and (G2) are performed sequentially, contemporaneously, or simultaneously.

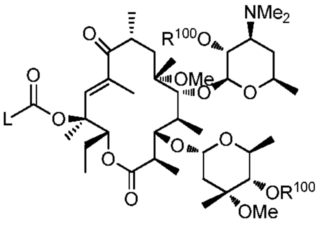
1C. The process of clause 1A wherein steps (G1) and (G2) are performed simultaneously.

1D. The process of clauses 1 wherein the deprotecting agent and the hydroxy deprotecting agent are the same.

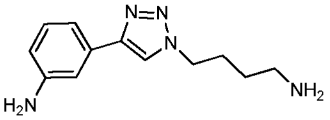
1E. The process of clauses 1 wherein C^P is N^P-substituted phenyl.

2A. A process for preparing a compound of formula (I) as described herein, the process comprising the step of

(a) contacting a compound of formula



or a salt thereof, where R^{100} is a hydroxyl protecting group, and L is a leaving group, with a compound of formula



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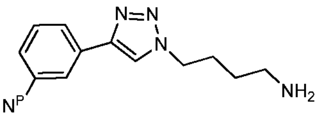
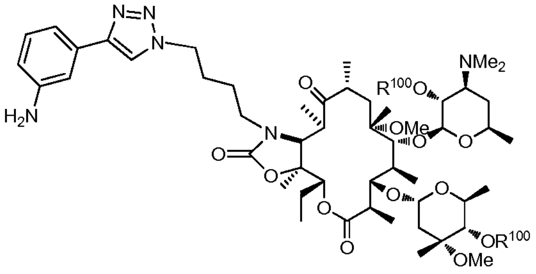


or a salt thereof, where N^P is a protected amine, and a base; to prepare a compound of formula



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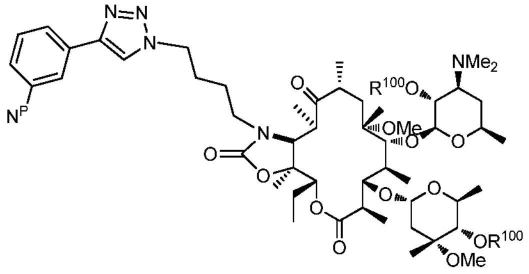
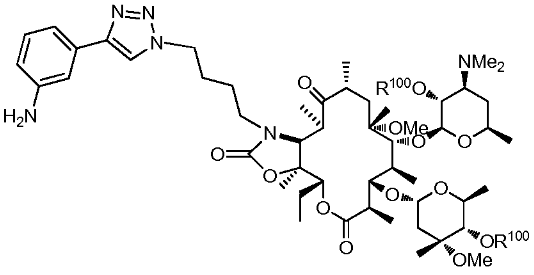
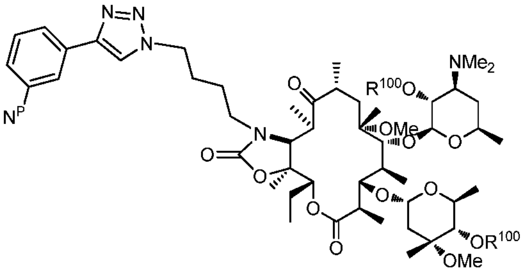


or a salt thereof; or

(b) contacting a compound of formula

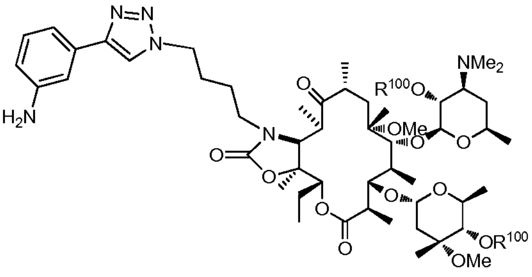


or a salt thereof, with an amine protecting group forming agent to prepare a compound of formula



or a salt thereof; or

(c) contacting a compound of formula



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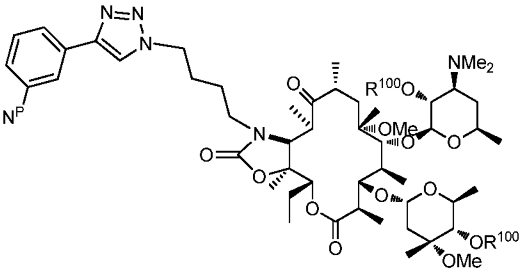
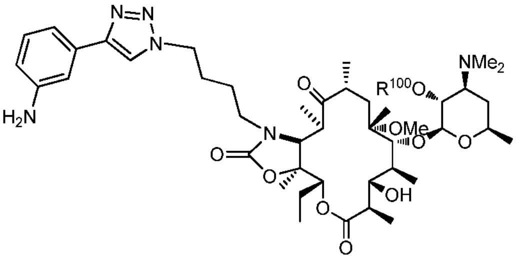


or a salt thereof, with an acid to prepare a compound of formula



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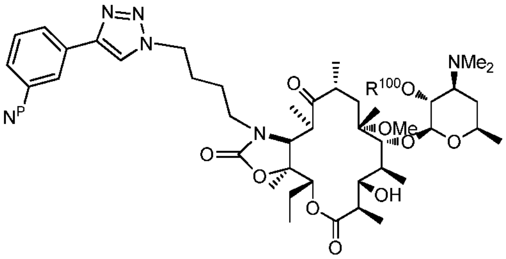
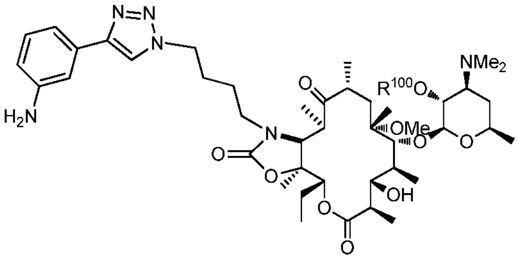
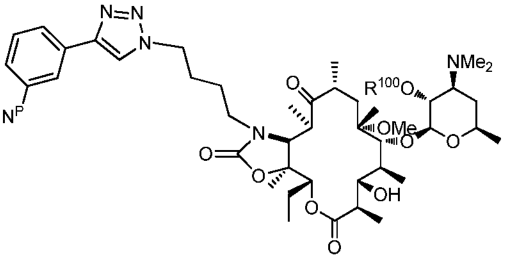


or a salt thereof; or

(d) contacting a compound of formula

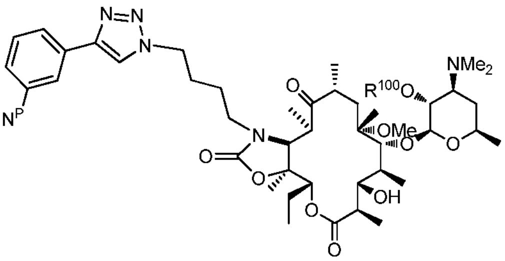


or a salt thereof, with an amine protecting group forming agent to prepare a compound of formula

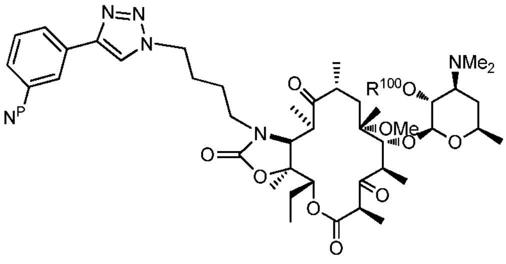


or a salt thereof; or

(e) contacting a compound of formula

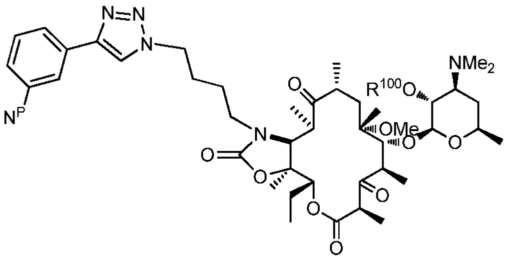


or a salt thereof, with an oxidizing agent to prepare a compound of formula

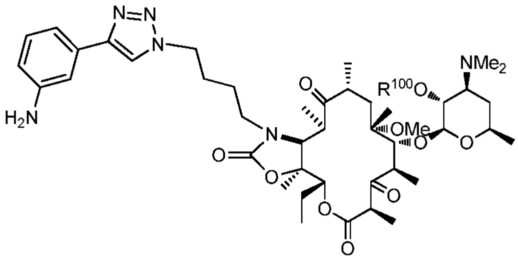


or a salt thereof; or

(f) contacting a compound of formula

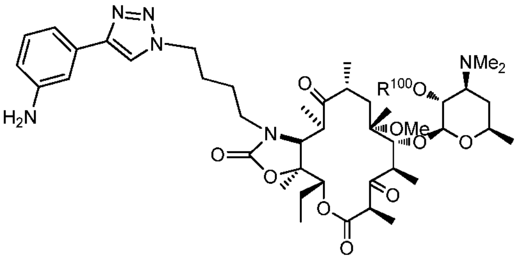


or a salt thereof, with an amine deprotecting agent to prepare a compound of formula



or a salt thereof; or

(g) contacting a compound of formula



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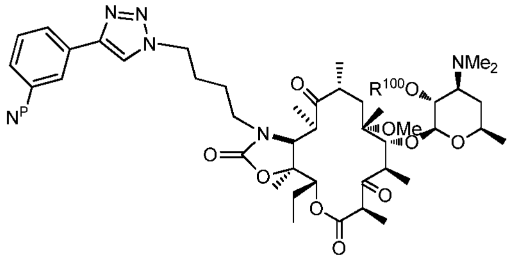
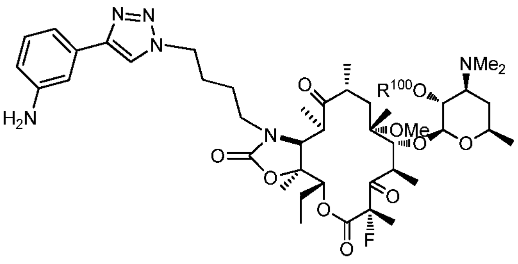


or a salt thereof, with a fluorinating agent to prepare a compound of formula



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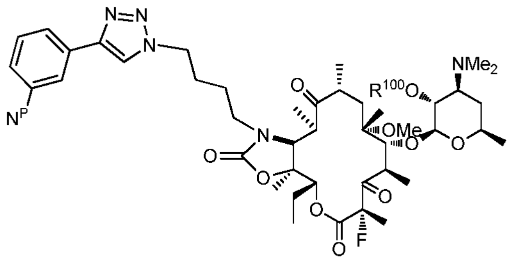
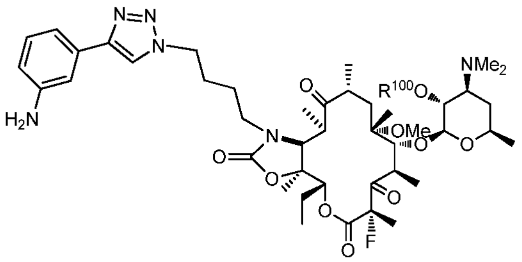


or a salt thereof; or

(h1) contacting a compound of formula



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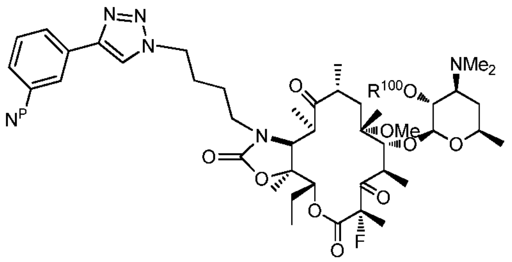
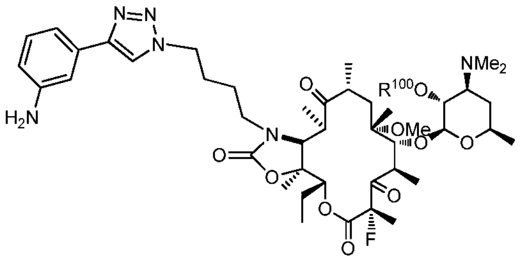


or a salt thereof, with a hydroxy deprotecting agent to prepare a compound of formula



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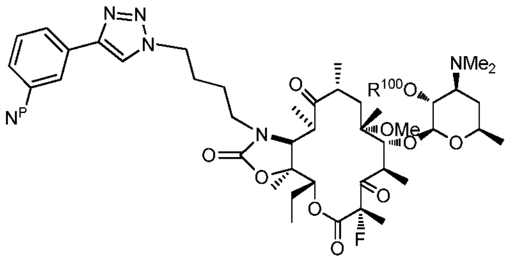
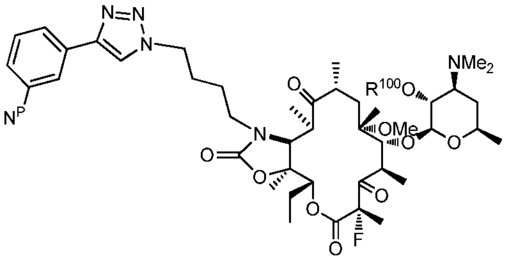
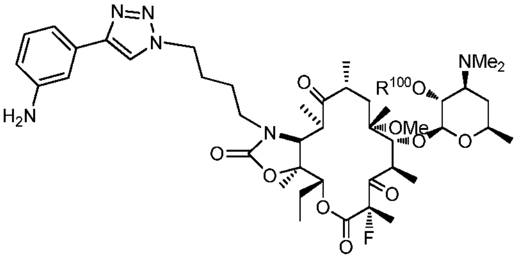


or a salt thereof; or

(h2) contacting a compound of formula



or a salt thereof, with an amine deprotecting agent to prepare a compound of formula



or a salt thereof; or

any combination of the foregoing.

2B. The process of clause 2A wherein steps (h1) and (h2) are performed sequentially, contemporaneously, or simultaneously.

2C. The process of clause 2A wherein steps (h1) and (h2) are performed simultaneously.

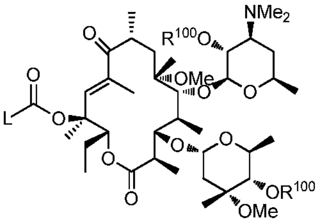
3. The process of clauses 2 wherein the amine protecting group forming agent is an acylating agent or amide, carbamate, or urea forming agent.

4. The process of any one of clauses 2 to 3 wherein the amine deprotecting agent and the hydroxyl deprotecting agent are the same, such as ammonia or ammonium hydroxide and a solvent.

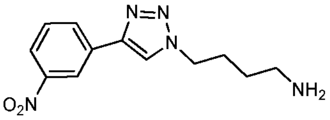
5. The process of any one of clauses 1 to 4 wherein N^P is $NHC(O)CF_3$.

6A. A process for preparing a compound of formula (I) as described herein, the process comprising the step of

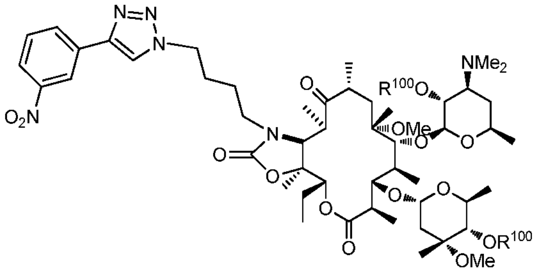
(a') contacting a compound of formula



or a salt thereof, where R^{100} is a hydroxyl protecting group, and L is a leaving group, with a compound of formula

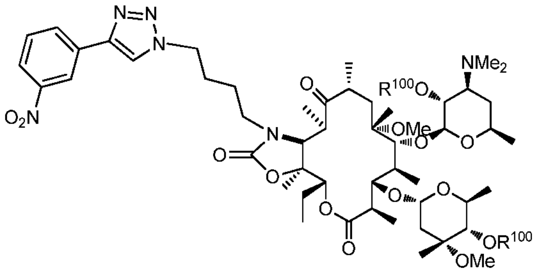


or a salt thereof, and a base; to prepare a compound of formula

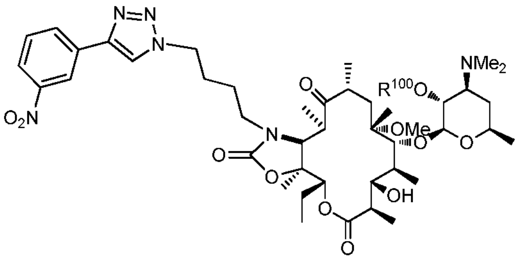


or a salt thereof; or

(b') contacting a compound of formula

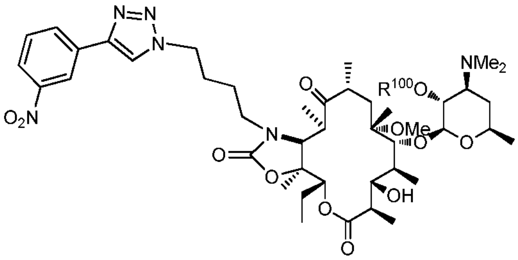


or a salt thereof, with an acid to prepare a compound of formula

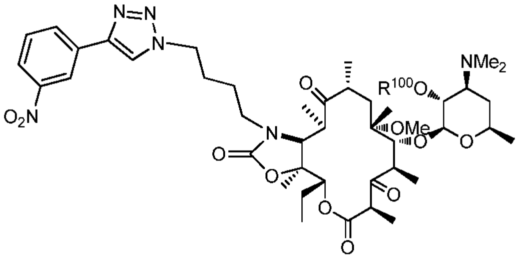


or a salt thereof; or

(c') contacting a compound of formula

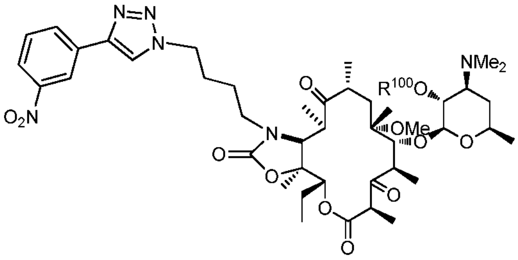


or a salt thereof, with an oxidizing agent to prepare a compound of formula

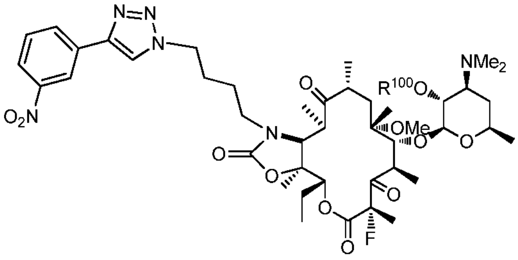


or a salt thereof; or

(d') contacting a compound of formula

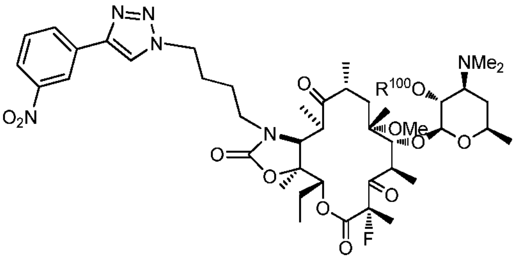


or a salt thereof, with a fluorinating agent to prepare a compound of formula



or a salt thereof; or

(e') contacting a compound of formula



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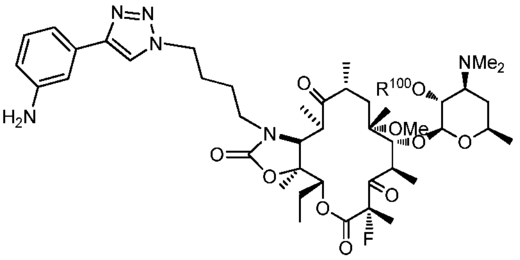
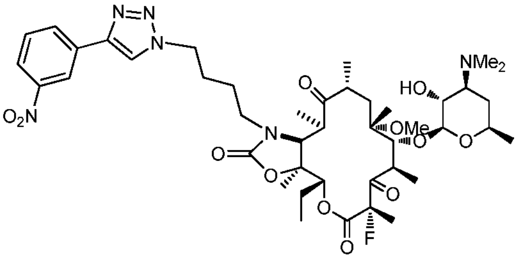


or a salt thereof, with a hydroxy deprotecting agent to prepare a compound of formula



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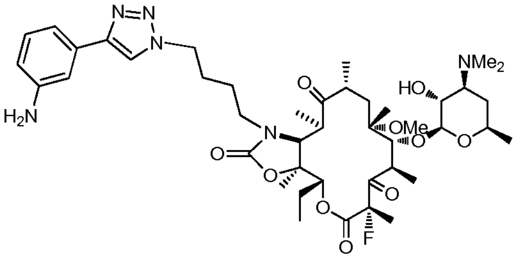
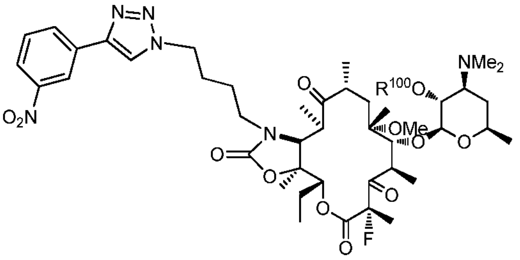


or a salt thereof; or

(f') contacting a compound of formula



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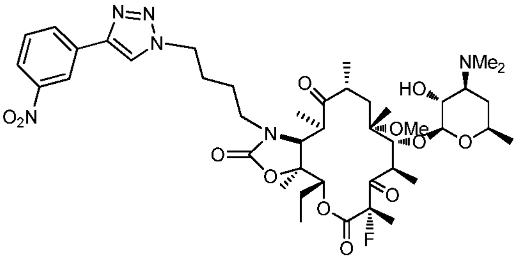
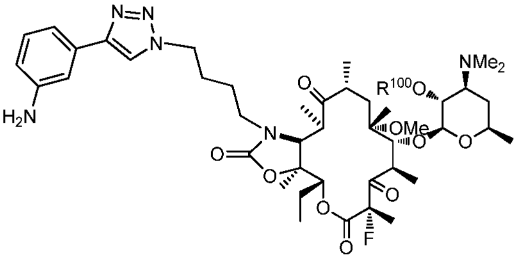


or a salt thereof, with a reducing agent to prepare a compound of formula



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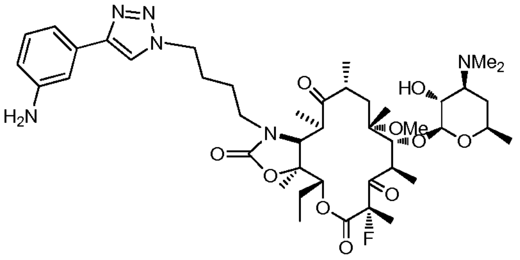


or a salt thereof; or

any combination of the foregoing.

6B. The process of clause 6A wherein steps (e') and (f') are performed sequentially, contemporaneously, or simultaneously.

6C. The process of clause 6A wherein steps (e') and (f') are performed simultaneously.

7. The process of clauses 6 wherein the hydroxy deprotecting agent and the reducing agent are the same.

8. The process of any one of clauses 1 to 7 wherein the leaving group is halo, pentafluorophenoxy, a sulfonate, such as triflate, a hydroxyamino, such as an HOBt, or imidazol-1-yl.

9. The process of any one of clauses 1 to 8 wherein the leaving group is imidazol-1-yl.

10. The process of any one of clauses 1 to 9 wherein the base is DBU.

11A. The process of any one of clauses 1 to 10 wherein the acid is aqueous HCl, such as 5% HCl, optionally with an organic cosolvent, such as a ketone, such as acetone.

11B. The process of any one of clauses 1 to 10 wherein the acid is HCl in an organic cosolvent, such as a ketone, such as acetone, or an alcohol, such as methanol, or a combination thereof.

12. The process of any one of clauses 1 to 11 wherein N^P is an amide or carbamate, such as Bz-NH, $CF_3C(O)$-NH, Cbz-NH, Boc-NY, Fmoc-NY, BsMoc-NH, Trityl-NH, MeOTrityl-NH, and the like

13. The process of any one of clauses 1 to 12 wherein the amine protecting group forming agent is TFAA.

14. The process of any one of clauses 1 to 12 wherein the amine protecting group forming agent is benzoyl chloride.

15. The process of any one of clauses 1 to 12 wherein the amine protecting group forming agent is Boc-anhydride.

16. The process of any one of clauses 1 to 12 wherein the amine protecting group forming agent is Fmoc chloride.

17. The process of any one of clauses 1 to 12 wherein the protected amine is formed in the presence of base, such a TEA.

18. The process of any one of clauses 1 to 17 wherein the oxidizing agent is trifluoroacetic anhydride in pyridine, PCC, Jones oxidation, TEMPO/NaOCl, Swern oxidation, Dess-Martin reagent, or Corey-Kim reagent.

19. The process of any one of clauses 1 to 17 wherein the oxidizing agent is N-chlorosuccinimide (NCS)/DMS.

20. The process of any one of clauses 1 to 19 wherein the fluorinating agent is NFSI, F-TEDA, or Selectfluor.

21. The process of any one of clauses 1 to 20 wherein the amine deprotecting agent is an amide hydrolyzing, cleaving, or removing agent.

22. The process of any one of clauses 1 to 20 wherein the amine deprotecting agent is hydrogen, such as hydrogen gas or hydrogen produced in situ, such as by transfer hydrogenation, such as by a transfer hydrogenation agent like formic acid, ammonium formate, and the like, and a metal catalyst.

23. The process of any one of clauses 1 to 20 wherein the amine deprotecting agent is ammonia, aqueous ammonia, or ammonia or aqueous ammonia with an organic cosolvent, such as an alcohol, such as methanol.

24. The process of any one of clauses 1 to 20 wherein the amine deprotecting agent is a carbamate hydrolyzing, cleaving, or removing agent.

25. The process of any one of clauses 1 to 24 wherein the deprotecting agent is an acid, such as TFA.

26. The process of any one of clauses 1 to 25 wherein the hydroxy deprotecting agent is an ester hydrolyzing, cleaving, or removing agent.

27. The process of any one of clauses 1 to 25 wherein the hydroxy deprotecting agent is an alcohol, such as methanol.

28. The process of any one of clauses 1 to 27 wherein the reducing agent is hydrogen, such as hydrogen gas or hydrogen produced in situ, such as by transfer hydrogenation, such as by a transfer hydrogenation agent like formic acid, ammonium formate, and the like, and a metal catalyst.

29. The process of clause 28 wherein the metal catalyst is 5% Pd-C, 5% Pt-C, 10% Pd-C, 10% Pd-C, Pearlman's Catalyst, 20% Pd(OH)2, Raney-Ni, nickel sponge, iron, and the like.

30. The process of any one of clauses 1 to 29 wherein C is aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

31. The process of any one of clauses 1 to 30 wherein A is CH_2.

32. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$.

33. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$, and n is an integer between 2 and 6.

34. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$, and n is an integer between 2 and 5.

35. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$, and n is an integer between 3 and 6.

36. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$, and n is an integer between 3 and 5.

37. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$, and n is an integer between 3 and 4.

38. The process of any one of clauses 1 to 31 wherein B is $(CH_2)_n$, and n is 3.

39. The process of any one of clauses 1 to 38 wherein R^{100} is acyl.

40. The process of any one of clauses 1 to 38 wherein R^{100} is alkylcarbonyl or optionally substituted benzoyl.

41. The process of any one of clauses 1 to 38 wherein R^{100} is acetyl or benzoyl, or R^{100} is benzoyl.

42. The process of any one of clauses 1 to 41 wherein W is H or F.

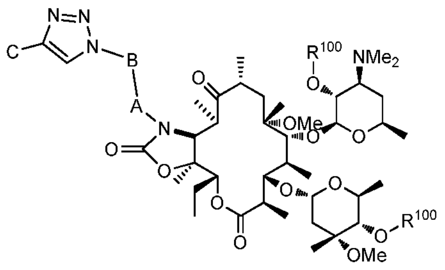
43. The process of any one of clauses 1 to 41 wherein W is F.

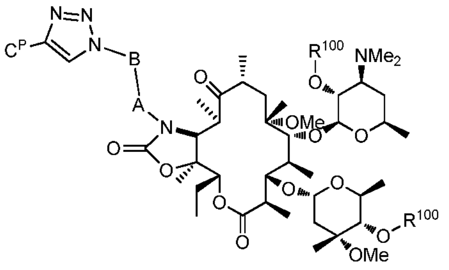
In another illustrative embodiment, R^{100} is a hydroxy protecting group, such as an acyl group. Additional hydroxyl protecting groups are described in Greene & Wuts, "Protective Groups in Organic Synthesis," 2nd Ed. John Wiley & Sons, Inc., the disclosure of which is incorporated herein by reference. In another embodiment, R100 is such an additional hydroxyl protecting. In another illustrative embodiment, R^{100} is a sterically hindered acyl group; formed with a sterically hindered acylating agent R^{100}-L, wherein R^{100} is a sterically hindered acyl group and L is a leaving or activating group, to form the corresponding 2'-acyl derivative.

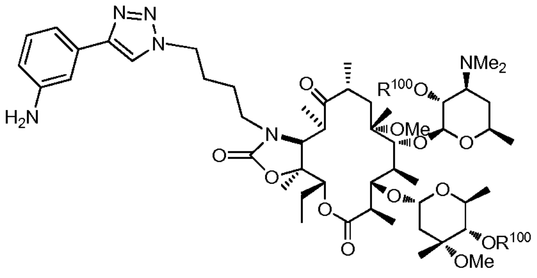
Illustrative sterically hindered acyl or diacyl derivatives include but are not limited to cyclohexylcarbonyl, benzoyl, neopentoyl, pivaloyl, and the like. A wide variety of activating groups for forming the acyl derivative may be used to prepare the required acylating agent, including but not limited to anhydrides, chlorides, triflates, bromides, and the like. In one aspect, the sterically hindered acylating agent is benzoic anhydride, or an equivalent activated benzoyl reagent capable of forming a benzoyl ester at the 2' or both the 2' and 4' positions. In another embodiment R^{100} is an optionally substituted benzoyl group, and the process includes an optionally substituted benzoic anhydride, or an equivalent activated optionally substituted benzoylating reagent capable of forming the optionally substituted benzoyl ester.

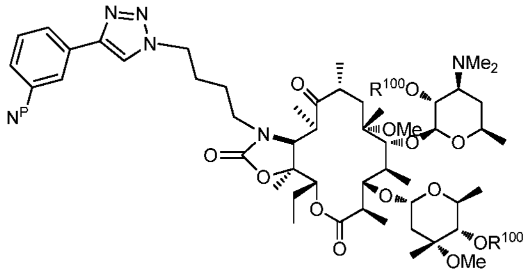
Acylation is generally performed in the presence of a solvent and a base. Illustrative solvents include, but are not limited to, ethyl acetate, dichloromethane, acetone, pyridine and the like, and mixtures thereof. Illustrative bases include but are not limited to inorganic bases, such as sodium and potassium bicarbonates and carbonates, sodium and potassium hydroxides, and the like, and mixtures thereof; and amine bases, such as pyridine, dimethylaminopyridine (DMAP), triethylamine (TEA), diisopropylethylamine (DIPEA, Hünigs base), 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like, and mixtures thereof. The reaction may be performed at a variety of temperatures, such as in the range from about 0°C to about 60°C, and illustratively at about 10°C to about 30°C.

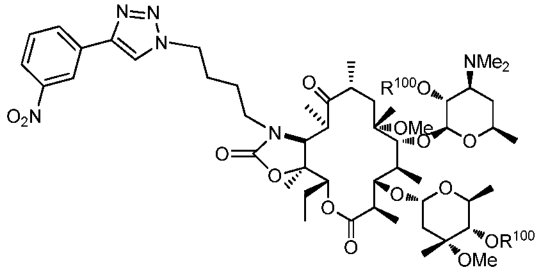
In another illustrative embodiment, processes are described for preparing compounds of formulae

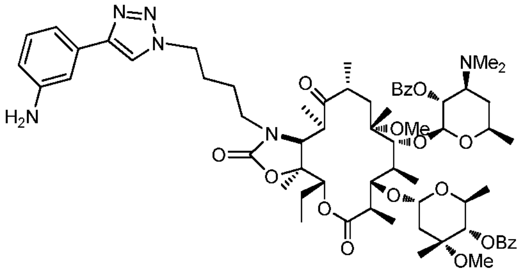


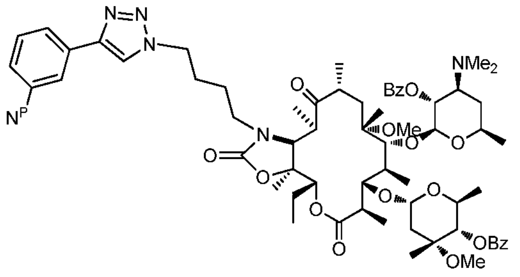


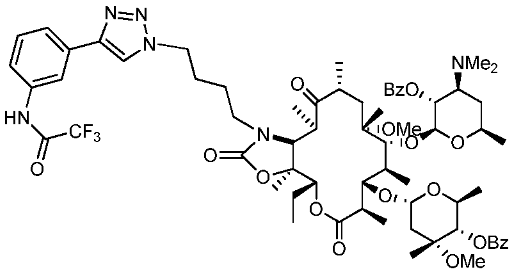


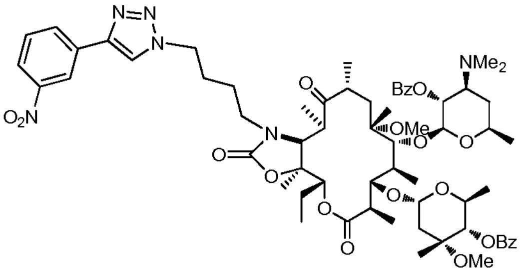






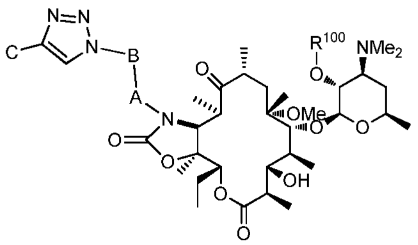
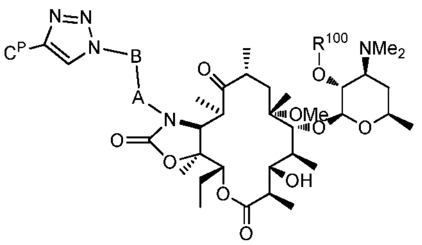
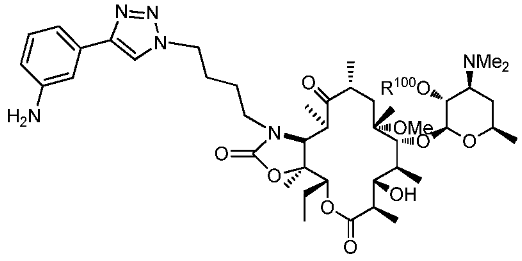
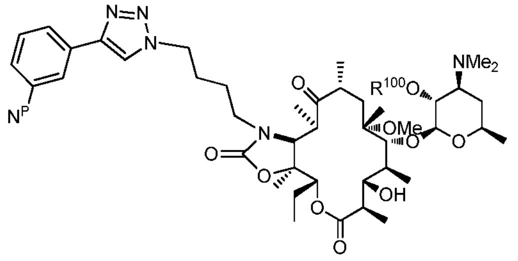
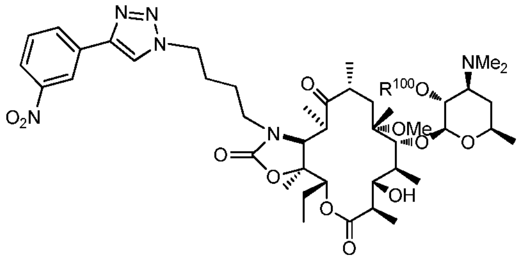
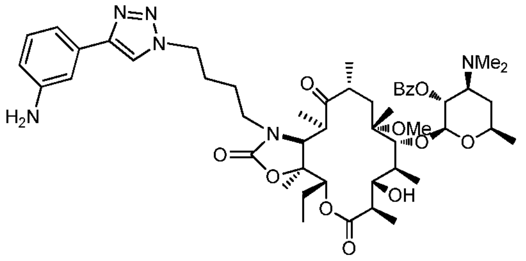
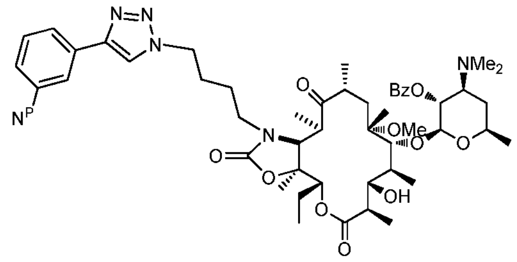
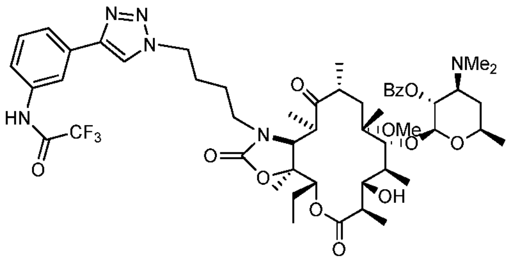
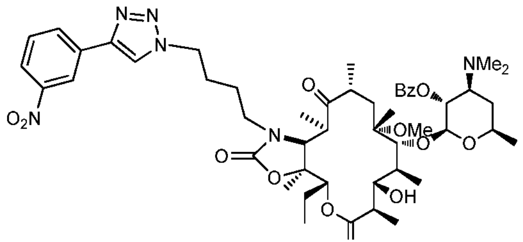






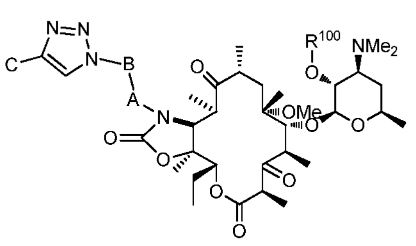
and salts thereof. The processes are generally performed in the presence of a polar solvent, including polar protic and polar aprotic solvents, or a mixture thereof. Illustrative polar protic solvents include, but are not limited to water, alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butyl alcohol, tert-butyl alcohol, methoxyethanol, ethoxyethanol, pentanol, neo-pentyl alcohol, tert-pentyl alcohol, cyclohexanol, ethylene glycol, propylene glycol, benzyl alcohol, formamide, N-methylacetamide, N-methylformamide, glycerol, and the like, and mixtures thereof. Illustrative polar aprotic solvents include, but are not limited to dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), acetonitrile, dimethylsulfoxide (DMSO), propionitrile, ethyl formate, methyl acetate, hexachloroacetone, HMPA, HMPT, acetone, ethyl methyl ketone, ethyl acetate, isopropyl acetate, t-butyl acetate, sulfolane, N,N-dimethylpropionamide, nitromethane, nitrobenzene, tetrahydrofuran (THF), methyl tetrahydrofuran, dioxane, polyethers, and the like, and mixtures thereof. The processes may also be performed in the presence of an additional base. Illustrative bases include, but are not limited to DBU, DABCO, TEA, DIPEA, piperidine, and the like, and mixtures thereof.

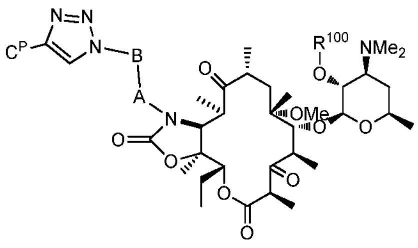
In another illustrative embodiment, processes are described for preparing compounds of formulae

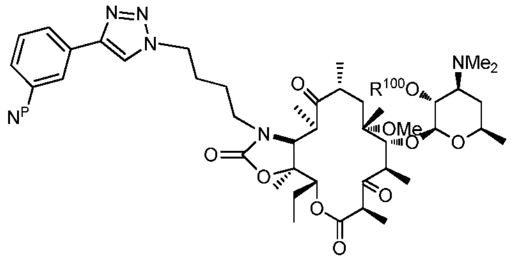










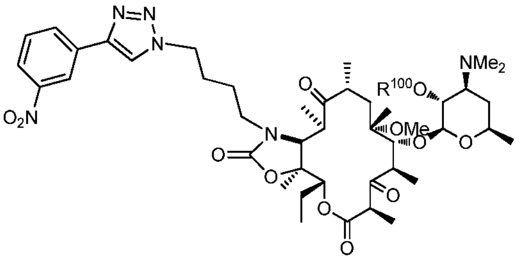
and salts thereof. The processes are generally performed in the presence of an acid. Illustrative acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, trifluoroacetic acid, formic acid, hydrofluoric acid, and the like, and mixtures thereof. In one variation, the acid is hydrochloric acid. The processes are generally performed in a solvent such as water, a polar organic solvent, including alcohols such as methanol, ethanol, isopropanol, n-propanol, tert-butanol, n-butanol, and the like, and mixtures thereof. The processes may be performed at a wide variety of temperatures, including temperatures in the range from about 0°C to about 70°C, and illustratively in the range from about 20°C to about 60°C.

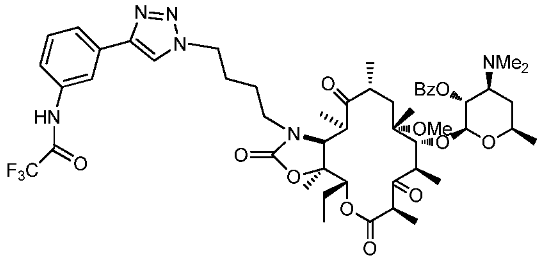
In another illustrative embodiment, processes are for preparing compounds of formula

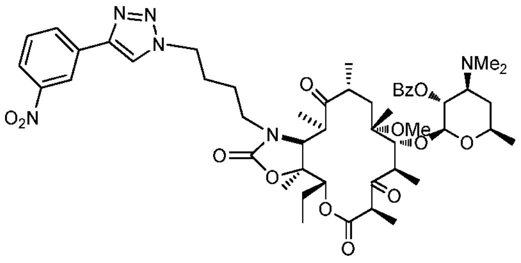






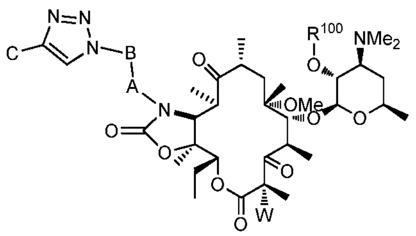


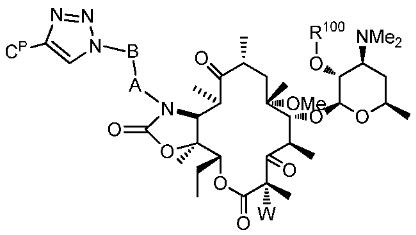


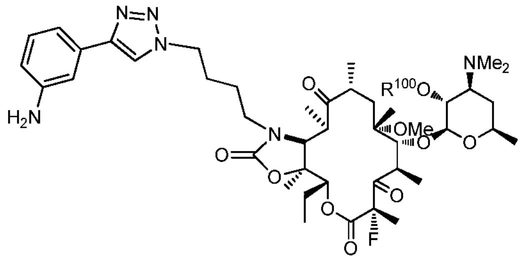


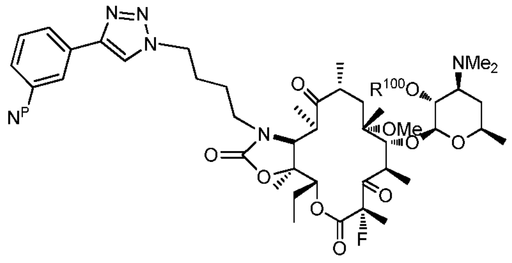
and salts thereof. The processes are generally performed in the presence of an oxidizing agent. Illustrative oxidizing reagents and conditions, include but are not limited to Corey-Kim oxidation, such as dimethylsulfide/N-chlorosuccinimide (DMS/NCS), di-n-butylsulfide/N-chlorosuccinimide, Dess-Martin reagent, Pfitzner-Moffat methods and modifications thereof, Swern conditions, such as DMSO/oxalyl chloride, DMSO/phosphorous pentoxide, DMSO/p-toluene sulfonyl chloride, DMSO/acetic anhydride, DMSO/trifluoroacetic anhydride, and DMSO/thionyl chloride, manganese, chromium and selenium reagents, tertiary amine oxides, $Ni(Ac)_2$/hypochlorite, DMSO/EDAC·HCl/pyridine.TFA and the like, and variations thereof, such as by including one or more phase-transfer catalysts.

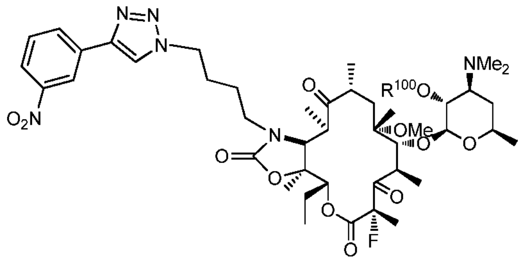
In another illustrative embodiment, process are described for preparing compounds of formulae

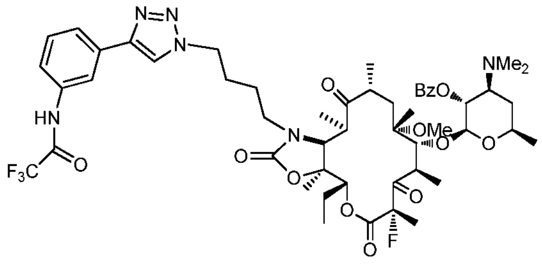


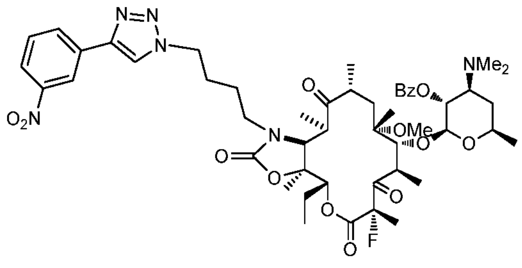






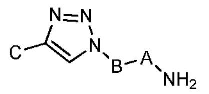


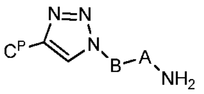


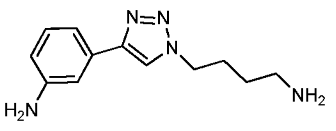


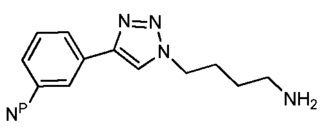
and salts thereof. The processes are generally performed in the presence of a fluorinating agent. Illustrative fluorinating agents include $(PhSO_2)_2N$-F (NFSI or N-fluorosulfonimide), F-TEDA, F-TEDA-BF_4, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), and the like, in the presence of solvent and base, such as t-BuOK.

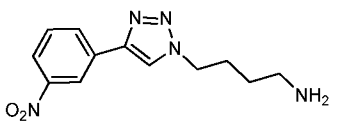
In another illustrative embodiment, processes are described for preparing compounds of formulae





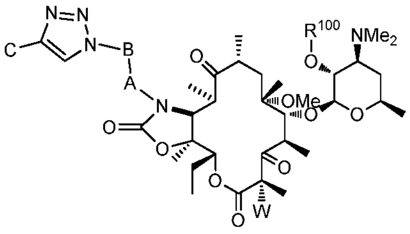


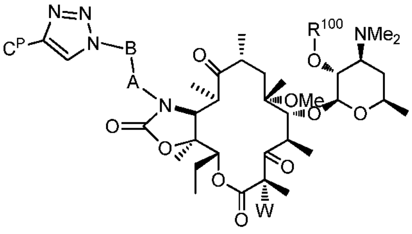


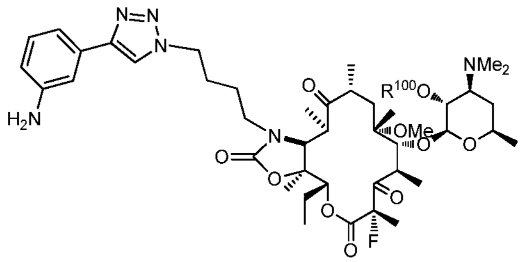


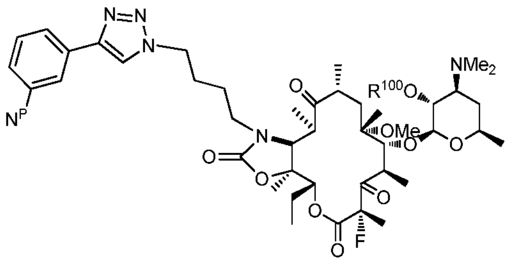
and salts thereof via Huisgen cyclization in the presence of a copper catalyst and base. The Huisgen cyclization is generally performed either solvent-free, in water or in an organic solvent such as acetonitrile or toluene, in the presence of base. Illustrative bases include but are not limited to organic bases, including alkyl and heteroaryl bases, such as triethylamine, diisopropylethylamine, DABCO, pyridine, lutidine, and the like, and inorganic bases, such as NaOH, KOH, K_2CO_3, $NaHCO_3$, and the like. The base is illustratively diisopropyl ethyl amine (DIPEA). The reaction is carried out at temperatures ranging from 20°C to 80°C. The reaction may also be promoted with the use of a catalyst, including but not limited to a copper halide, illustratively copper iodide. The ratio of CuI to azide is illustratively from about 0.01 to 1 to about 0.1 to 1. In an alternate embodiment, the catalyst is an organic catalyst, such as phenolphthalein. Additional reaction conditions are described by Sharpless et al. in U.S. Patent Application Publication No. US 2005/0222427, Liang et al. in Bioorg. Med. Chem. Lett. 15 (2005) 1307–1310, and Romero et al. in Tetrahedron Letters 46 (2005) 1483–1487, the disclosures of which are incorporated herein by reference.

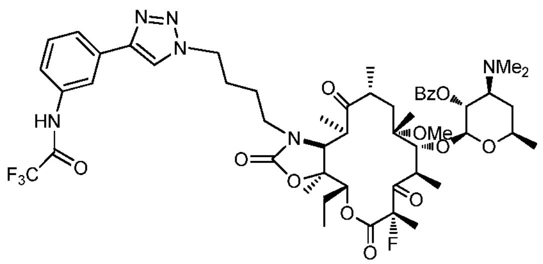
In another illustrative embodiment, processes are described for deprotecting compounds of formula

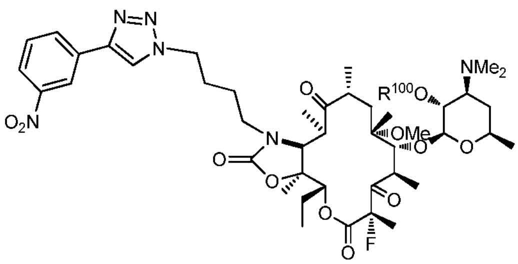


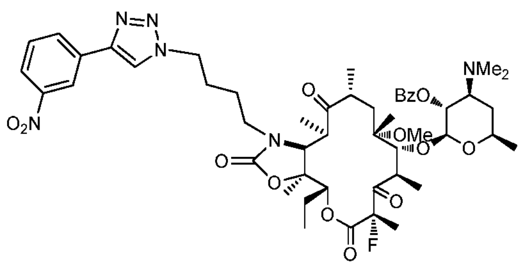






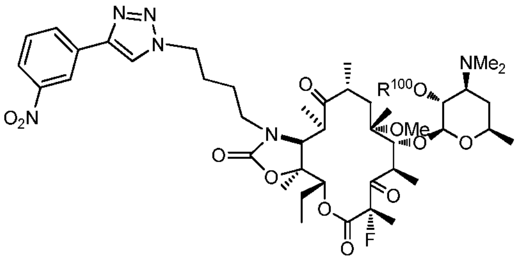


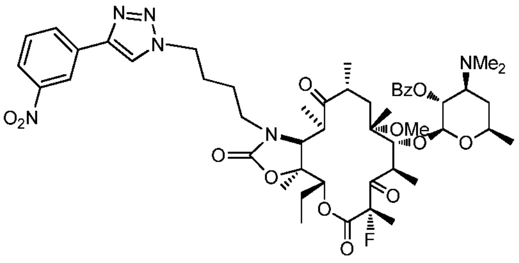


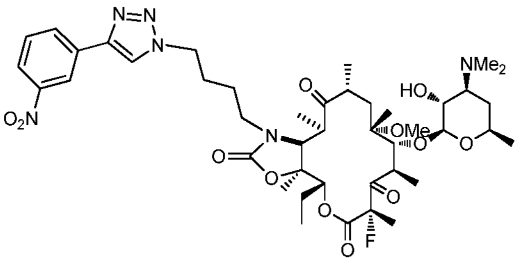


and salts thereof with an alcohol to prepare the corresponding deprotected compound of formula (I). Illustrative alcohols include, but are not limited to, methanol, ethanol, n-propanol, isopropanol, tert-butanol, n-butanol or mixtures thereof. Illustratively, the alcohol is methanol. The reaction may be performed at a temperature of about 0°C to about 100°C, or at about 20°C to about 70°C. The reaction may also be performed in the presence of mineral acid, such as a mineral acid selected from HCl, H_2SO_4 and the like, and mixtures thereof. In one illustrative embodiment the reaction is carried out in methanol at a temperature of about 55°C.

In another illustrative embodiment, processes are described for reducing compounds of formula

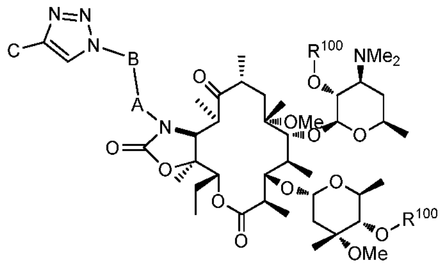


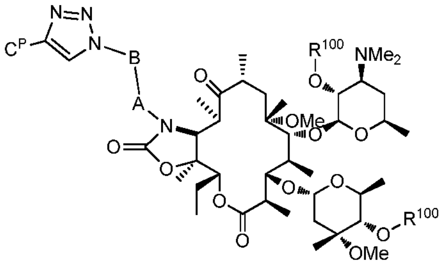


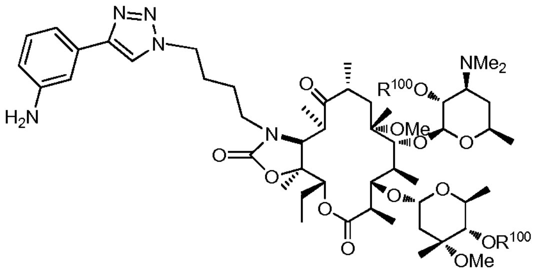


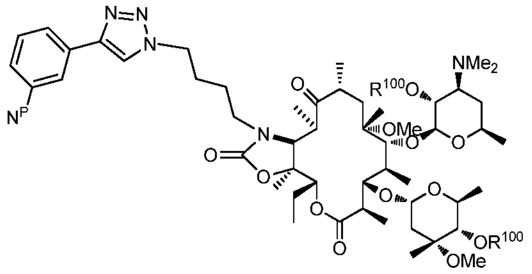
and salts thereof. The processes are generally performed in the presence of a reducing agent. Illustrative reducing agents include, but are not limited to, hydrogen gas, iron and an acid, transfer hydrogenation agents, Raney-Ni, nickel sponge, metal catalysts, such as Pt, Pd, and the like.

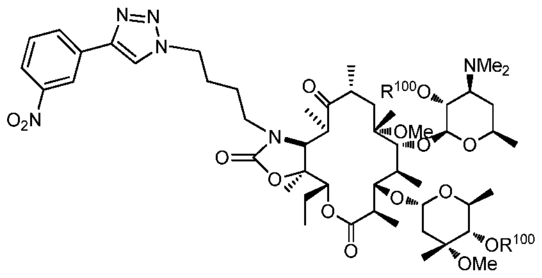
In another illustrative embodiment, described herein are compounds of formulae

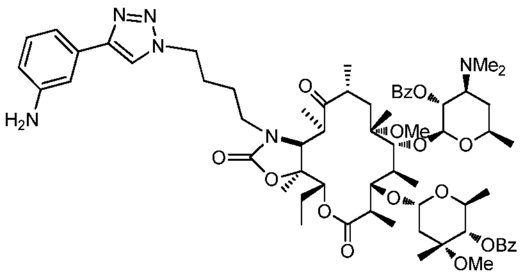


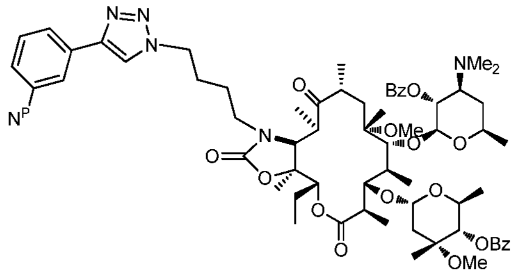


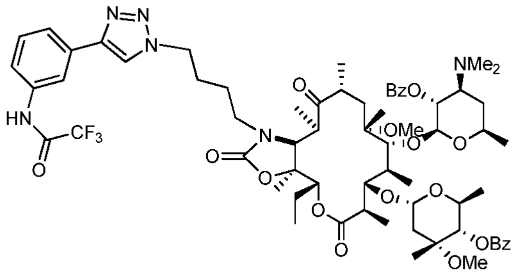


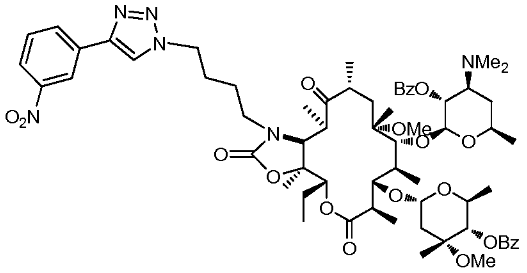






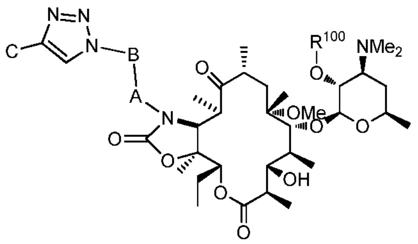


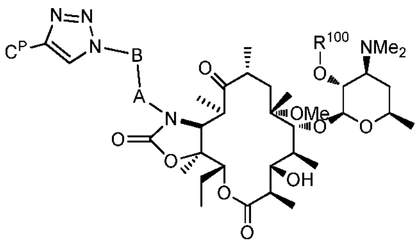


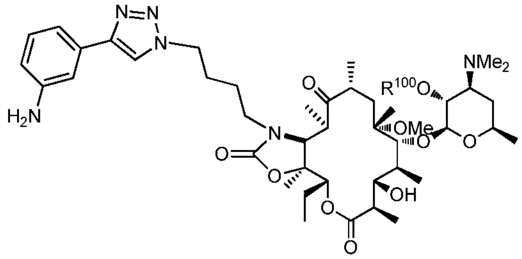


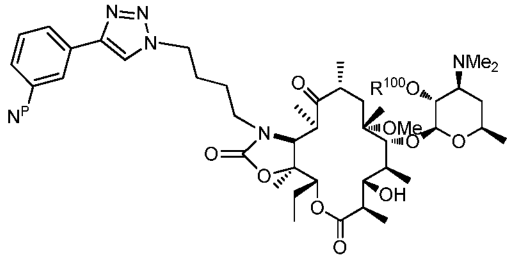
and salts thereof.

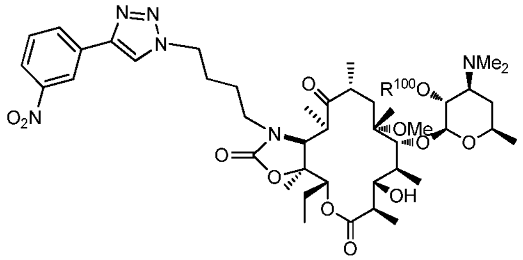
In another illustrative embodiment, described herein are compounds of formulae

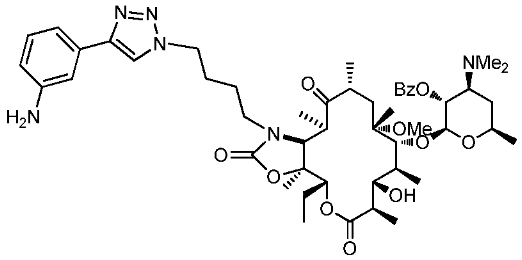


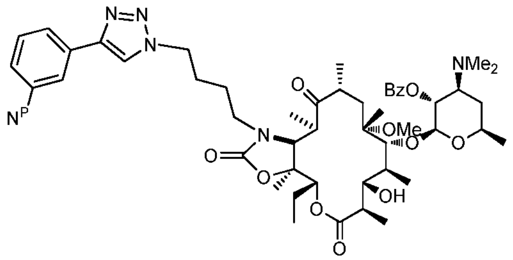


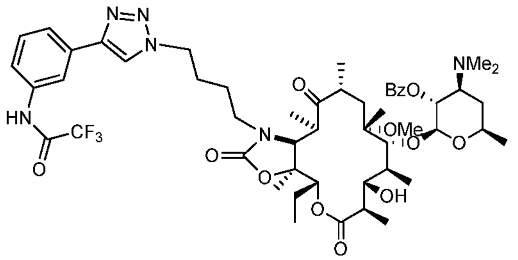


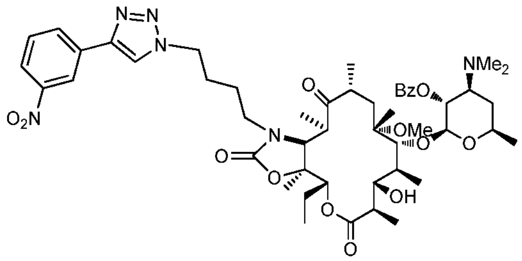






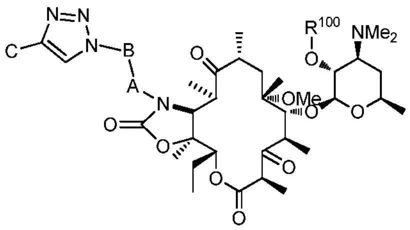


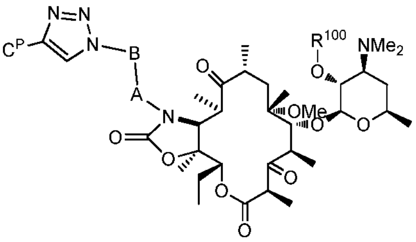


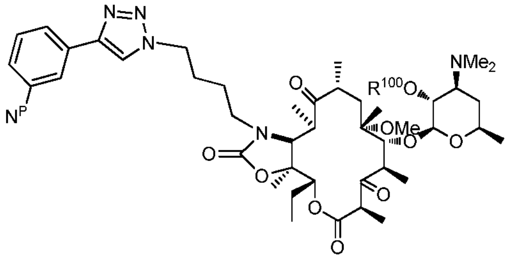


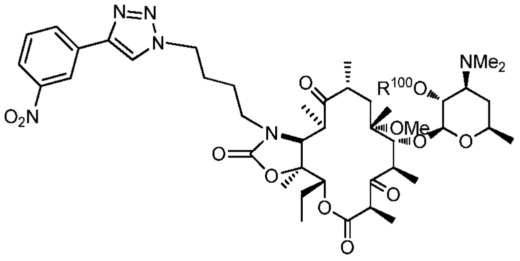
and salts thereof.

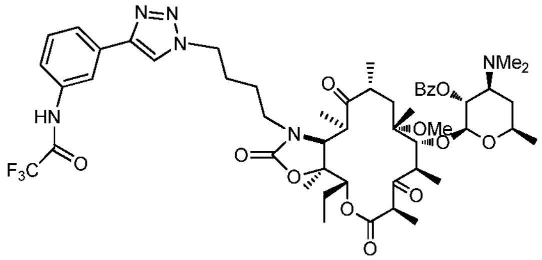
In another illustrative embodiment, described herein are compounds of formulae

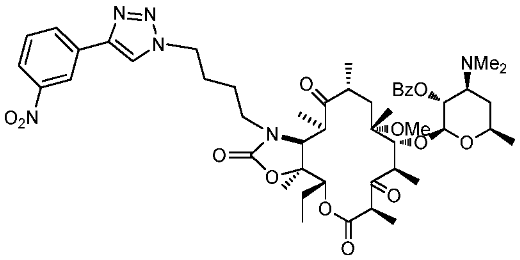






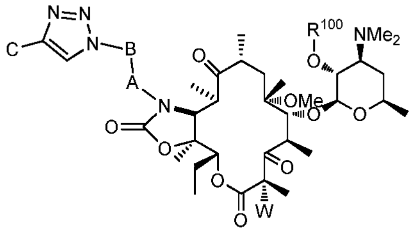


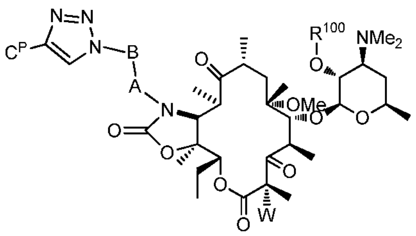


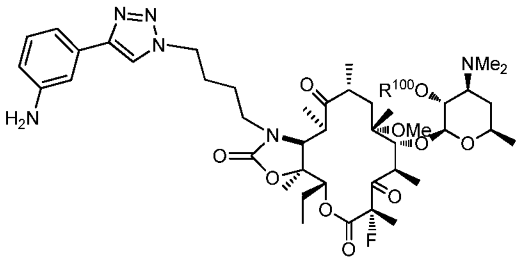


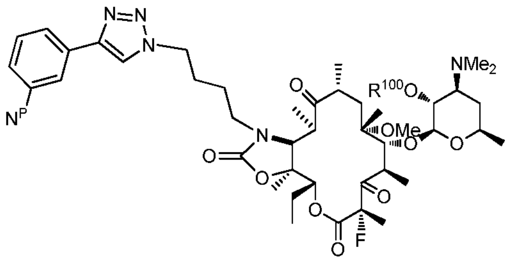
and salts thereof.

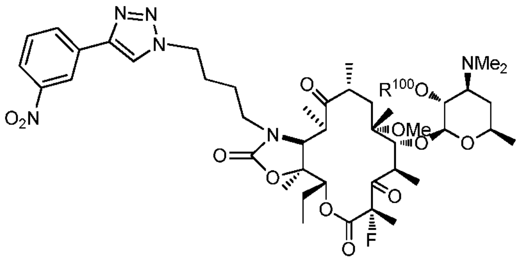
In another illustrative embodiment, described herein are compounds of formulae

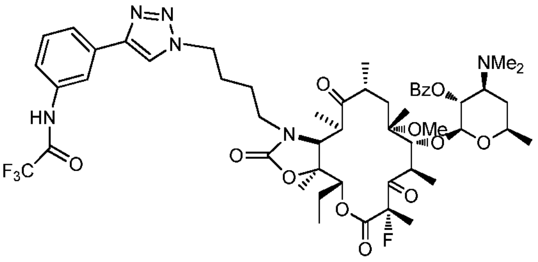


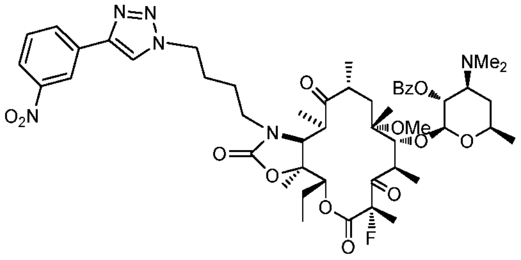






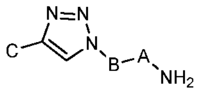


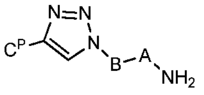


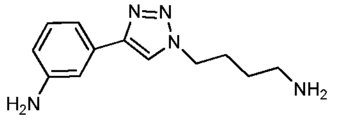


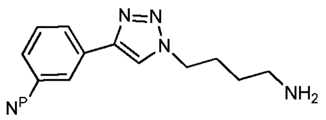
and salts thereof.

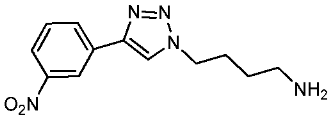
In another illustrative embodiment, described herein are compounds of formulae





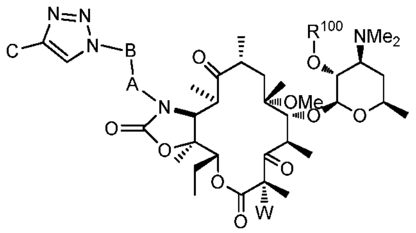


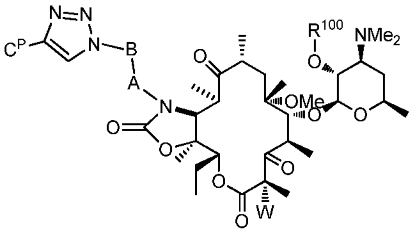


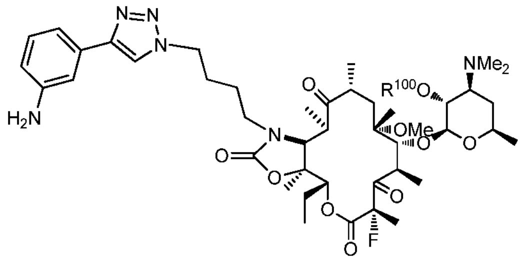


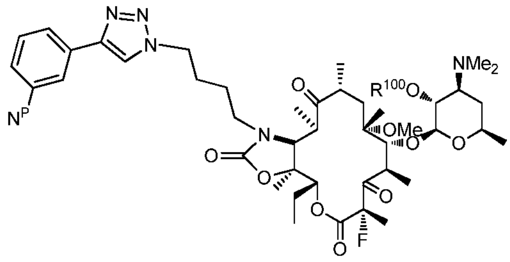
and salts thereof. In another embodiment, N^P is an amide, or carbamate, such as Bz-NH, $CF_3C(O)$-NH, Cbz-NH, Boc-NY, Fmoc-NY, BsMoc-NH, Trityl-NH, MeOTrityl ((4-methoxyphenyl)diphenylmethyl)-NH, and the like.

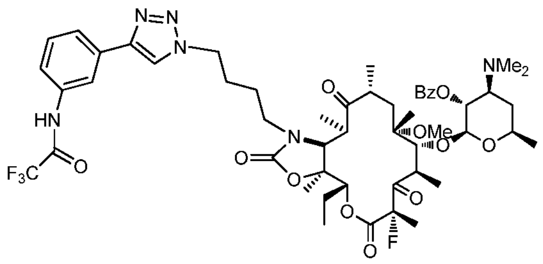
In another illustrative embodiment, described herein are compounds of formulae

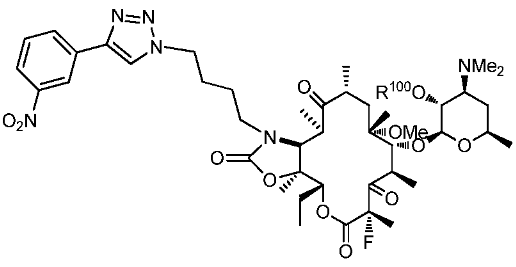


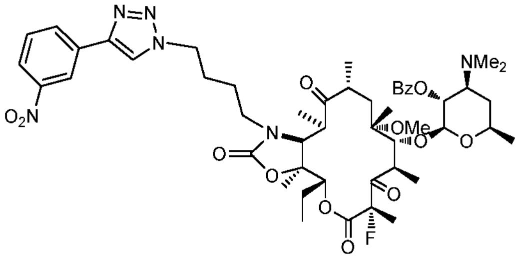






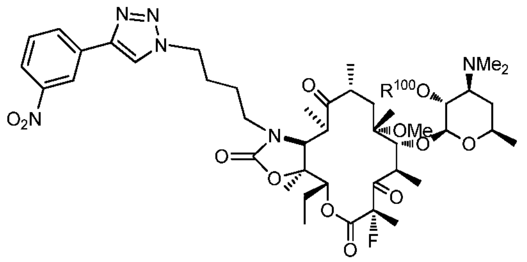


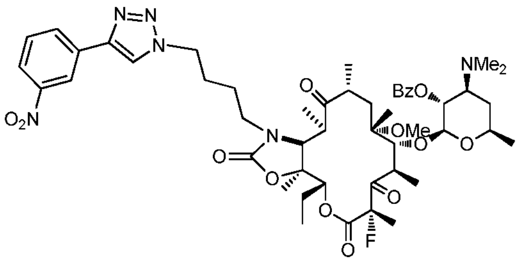


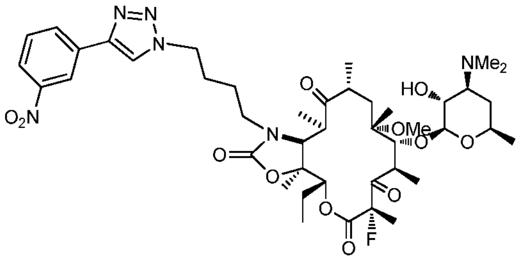


and salts thereof.

In another illustrative embodiment, described herein are compounds of formulae







and salts thereof.

It is to be understood that in each of the foregoing embodiments, in each instance, the selection of each of R^{100}, N^P, A, B, C, C^P, W, and L is independently made from any of the species, subgenera, and genera described herein. In addition, it is to be understood that every combination of each of those selections of R^{100}, N^P, A, B, C, C^P, W, and L is described herein, including any combinations of species thereof, subgenera thereof, and genera thereof.

In each of the foregoing and each of the following embodiments, it is also to be understood that the formulae include and represent any and all crystalline forms, partially crystalline forms, and non-crystalline and/or amorphous forms of the compounds.

In each of the foregoing and each of the following embodiments, it is also to be understood that the formulae include and represent not only all pharmaceutically acceptable salts of the compounds, but also include any and all hydrates and/or solvates of the compound formulae. It is appreciated that certain functional groups, such as the hydroxy, amino, and like groups form complexes and/or coordination compounds with water and/or various solvents, in the various physical forms of the compounds. Accordingly, the above formulae are to be understood to be a description of such hydrates and/or solvates, including pharmaceutically acceptable solvates.

As used herein, the term "solvates" refers to compounds described herein complexed with a solvent molecule. It is appreciated that compounds described herein may form such complexes with solvents by simply mixing the compounds with a solvent, or dissolving the compounds in a solvent. It is appreciated that where the compounds are to be used as pharmaceuticals, such solvents are pharmaceutically acceptable solvents. It is further appreciated that where the compounds are to be used as pharmaceuticals, the relative amount of solvent that forms the solvate should be less than established guidelines for such pharmaceutical uses, such as less than International Conference on Harmonization (ICH) Guidelines. It is to be understood that the solvates may be isolated from excess solvent by evaporation, precipitation, and/or crystallization. In some embodiments, the solvates are amorphous, and in other embodiments, the solvates are crystalline.

As used herein, the term "alkyl" includes a chain of carbon atoms, which is optionally branched. As used herein, the terms "alkenyl" and "alkynyl" each include a chain of carbon atoms, which is optionally branched, and include at least one double bond or triple bond, respectively. It is to be understood that alkynyl may also include one or more double bonds. It is to be further understood that in certain embodiments, alkyl is advantageously of limited length, including C_1-C_{24}, C_1-C_{12}, C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and the like Illustratively, such particularly limited length alkyl groups, including C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_8, C_2-C_6, and C_2-C_4, and the like may be referred to as lower alkyl. It is to be further understood that in certain embodiments alkenyl and/or alkynyl may each be advantageously of limited length, including C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_3-C_4, and the like Illustratively, such particularly limited length alkenyl and/or alkynyl groups, including C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_8, C_3-C_6, and C_3-C_4, and the like may be referred to as lower alkenyl and/or alkynyl. It is appreciated herein that shorter alkyl, alkenyl, and/or alkynyl groups may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkyl refers to alkyl as defined herein, and optionally lower alkyl. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkenyl refers to alkenyl as defined herein, and optionally lower alkenyl. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkynyl refers to alkynyl as defined herein, and optionally lower alkynyl. Illustrative alkyl, alkenyl, and alkynyl groups are, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, heptyl, octyl, and the like, and the corresponding groups containing one or more double and/or triple bonds, or a combination thereof.

As used herein, the term “alkylene” includes a divalent chain of carbon atoms, which is optionally branched. As used herein, the term “alkenylene” and “alkynylene” includes a divalent chain of carbon atoms, which is optionally branched, and includes at least one double bond or triple bond, respectively. It is to be understood that alkynylene may also include one or more double bonds. It is to be further understood that in certain embodiments, alkylene is advantageously of limited length, including C_1-C_{24}, C_1-C_{12}, C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and the like. Illustratively, such particularly limited length alkylene groups, including C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_8, C_2-C_6, and C_2-C_4, and the like may be referred to as lower alkylene. It is to be further understood that in certain embodiments alkenylene and/or alkynylene may each be advantageously of limited length, including C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_3-C_4, and the like. Illustratively, such particularly limited length alkenylene and/or alkynylene groups, including C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_8, C_3-C_6, and C_3-C_4, and the like may be referred to as lower alkenylene and/or alkynylene. It is appreciated herein that shorter alkylene, alkenylene, and/or alkynylene groups may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkylene, alkenylene, and alkynylene refers to alkylene, alkenylene, and alkynylene as defined herein, and optionally lower alkylene, alkenylene, and alkynylene. Illustrative alkyl groups are, but not limited to, methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, sec-butylene, pentylene, 1,2-pentylene, 1,3-pentylene, hexylene, heptylene, octylene, and the like.

As used herein, the term “cycloalkyl” includes a chain of carbon atoms, which is optionally branched, where at least a portion of the chain in cyclic. It is to be understood that cycloalkylalkyl is a subset of cycloalkyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkyl include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 2-methylcyclopropyl, cyclopentyleth-2-yl, adamantyl, and the like. As used herein, the term “cycloalkenyl” includes a chain of carbon atoms, which is optionally branched, and includes at least one double bond, where at least a portion of the chain in cyclic. It is to be understood that the one or more double bonds may be in the cyclic portion of cycloalkenyl and/or the non-cyclic portion of cycloalkenyl. It is to be understood that cycloalkenylalkyl and cycloalkylalkenyl are each subsets of cycloalkenyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkenyl include, but are not limited to, cyclopentenyl, cyclohexylethen-2-yl, cycloheptenylpropenyl, and the like. It is to be further understood that chain forming cycloalkyl and/or cycloalkenyl is advantageously of limited length, including C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_5-C_6. It is appreciated herein that shorter alkyl and/or alkenyl chains forming cycloalkyl and/or cycloalkenyl, respectively, may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior.

As used herein, the term “heteroalkyl” includes a chain of atoms that includes both carbon and at least one heteroatom, and is optionally branched. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. As used herein, the term “cycloheteroalkyl” including heterocyclyl and heterocycle, includes a chain of atoms that includes both carbon and at least one heteroatom, such as heteroalkyl, and is optionally branched, where at least a portion of the chain is cyclic. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. Illustrative cycloheteroalkyl include, but are not limited to, tetrahydrofuryl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl, quinuclidinyl, and the like.

As used herein, the term “aryl” includes monocyclic and polycyclic aromatic carbocyclic groups, each of which may be optionally substituted. Illustrative aromatic carbocyclic groups described herein include, but are not limited to, phenyl, naphthyl, and the like. As used herein, the term “heteroaryl” includes aromatic heterocyclic groups, each of which may be optionally substituted. Illustrative aromatic heterocyclic groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, quinolinyl, quinazolinyl, quinoxalinyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, benzisothiazolyl, and the like.

As used herein, the term “amino” includes the group NH_2, alkylamino, and dialkylamino, where the two alkyl groups in dialkylamino may be the same or different, i.e. alkylalkylamino. Illustratively, amino includes methylamino, ethylamino, dimethylamino, methylethylamino, and the like. In addition, it is to be understood that when amino modifies or is modified by another term, such as aminoalkyl, or acylamino, the above variations of the term amino are included therein. Illustratively, aminoalkyl includes H_2N-alkyl, methylaminoalkyl, ethylaminoalkyl, dimethylaminoalkyl, methylethylaminoalkyl, and the like. Illustratively, acylamino includes acylmethylamino, acylethylamino, and the like.

As used herein, the term “amino and derivatives thereof” includes amino as described herein, and alkylamino, alkenylamino, alkynylamino, heteroalkylamino, heteroalkenylamino, heteroalkynylamino, cycloalkylamino, cycloalkenylamino, cycloheteroalkylamino, cycloheteroalkenylamino, arylamino, arylalkylamino, arylalkenylamino, arylalkynylamino, heteroarylamino, heteroarylalkylamino, heteroarylalkenylamino, heteroarylalkynylamino, acylamino, and the like, each of which is optionally substituted. The term “amino derivative” also includes urea, carbamate, and the like.

As used herein, the term “hydroxy and derivatives thereof” includes OH, and alkyloxy, alkenyloxy, alkynyloxy, heteroalkyloxy, heteroalkenyloxy, heteroalkynyloxy, cycloalkyloxy, cycloalkenyloxy, cycloheteroalkyloxy, cycloheteroalkenyloxy, aryloxy, arylalkyloxy, arylalkenyloxy, arylalkynyloxy, heteroaryloxy, heteroarylalkyloxy, heteroarylalkenyloxy, heteroarylalkynyloxy, acyloxy, and the like, each of which is optionally substituted. The term “hydroxy derivative” also includes carbamate, and the like.

As used herein, the term “thio and derivatives thereof” includes SH, and alkylthio, alkenylthio, alkynylthio, heteroalkylthio, heteroalkenylthio, heteroalkynylthio, cycloalkylthio, cycloalkenylthio, cycloheteroalkylthio, cycloheteroalkenylthio, arylthio, arylalkylthio, arylalkenylthio, arylalkynylthio, heteroarylthio, heteroarylalkylthio, heteroarylalkenylthio, heteroarylalkynylthio, acylthio, and the like, each of which is optionally substituted. The term “thio derivative” also includes thiocarbamate, and the like.

As used herein, the term “acyl” includes formyl, and alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, heteroalkylcarbonyl, heteroalkenylcarbonyl, heteroalkynylcarbonyl, cycloalkylcarbonyl, cycloalkenylcarbonyl, cycloheteroalkylcarbonyl, cycloheteroalkenylcarbonyl, arylcarbonyl, arylalkylcarbonyl, arylalkenylcarbonyl, arylalkynylcarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl, heteroarylalkenylcarbonyl, heteroarylalkynylcarbonyl, acylcarbonyl, and the like, each of which is optionally substituted.

As used herein, the term “carbonyl and derivatives thereof” includes the group C(O), C(S), C(NH) and substituted amino derivatives thereof.

As used herein, the term “carboxylic acid and derivatives thereof” includes the group CO_2H and salts thereof, and esters and amides thereof, and CN.

As used herein, the term “sulfinic acid or a derivative thereof” includes SO_2H and salts thereof, and esters and amides thereof.

As used herein, the term “sulfonic acid or a derivative thereof” includes SO_3H and salts thereof, and esters and amides thereof.

As used herein, the term “sulfonyl” includes alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, heteroalkylsulfonyl, heteroalkenylsulfonyl, heteroalkynylsulfonyl, cycloalkylsulfonyl, cycloalkenylsulfonyl, cycloheteroalkylsulfonyl, cycloheteroalkenylsulfonyl, arylsulfonyl, arylalkylsulfonyl, arylalkenylsulfonyl, arylalkynylsulfonyl, heteroarylsulfonyl, heteroarylalkylsulfonyl, heteroarylalkenylsulfonyl, heteroarylalkynylsulfonyl, acylsulfonyl, and the like, each of which is optionally substituted.

The term "optionally substituted" as used herein includes the replacement of hydrogen atoms with other functional groups on the radical that is optionally substituted. Such other functional groups illustratively include, but are not limited to, amino, hydroxyl, halo, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxyl, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

As used herein, the terms "optionally substituted aryl" and "optionally substituted heteroaryl" include the replacement of hydrogen atoms with other functional groups on the aryl or heteroaryl that is optionally substituted. Such other functional groups illustratively include, but are not limited to, amino, hydroxy, halo, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxy, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

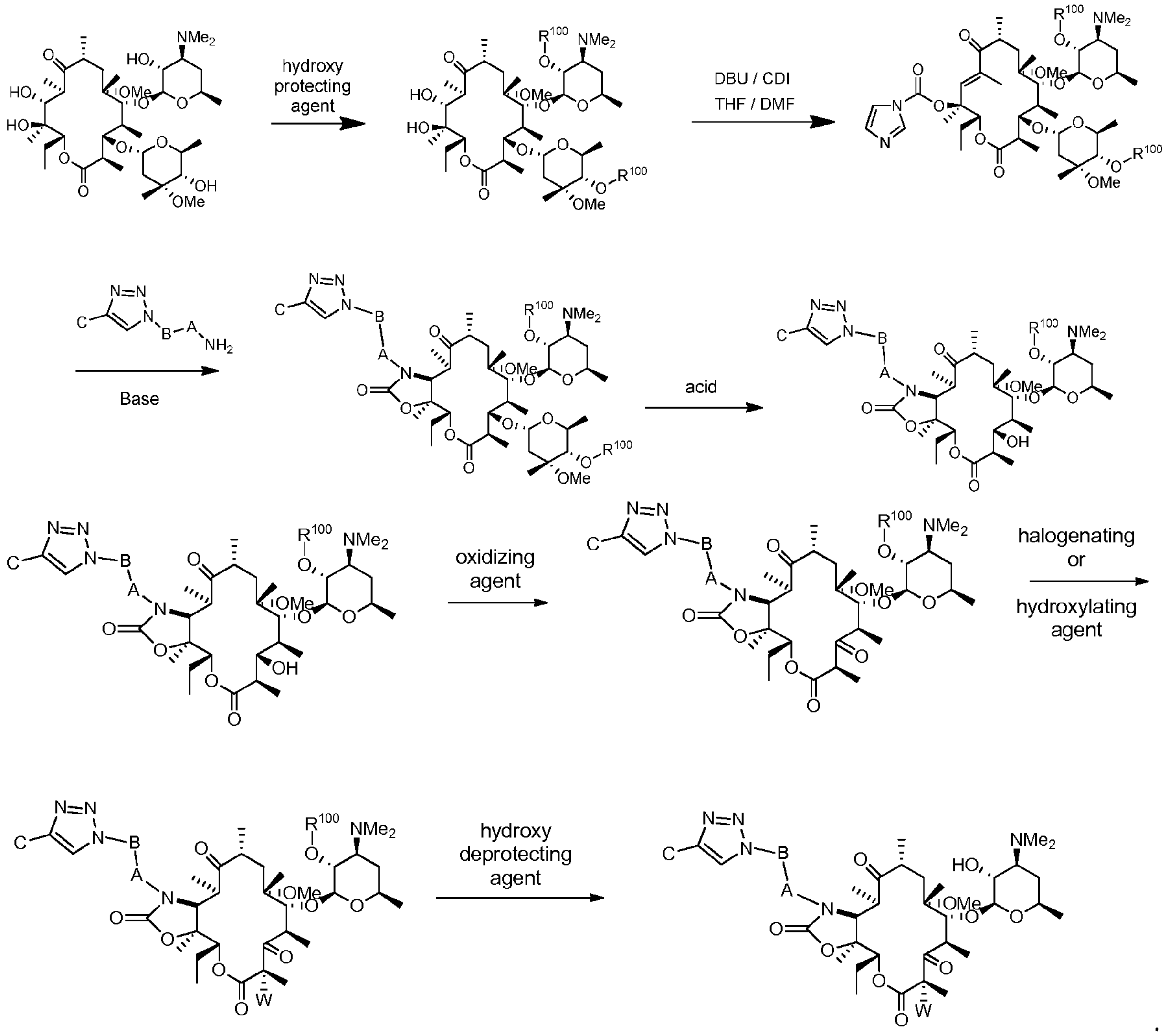
Illustrative substituents include, but are not limited to, a radical $-(CH_2)_xZ^X$, where x is an integer from 0-6 and Z^X is selected from halogen, hydroxy, alkanoyloxy, including C_1-C_6 alkanoyloxy, optionally substituted aroyloxy, alkyl, including C_1-C_6 alkyl, alkoxy, including C_1-C_6 alkoxy, cycloalkyl, including C_3-C_8 cycloalkyl, cycloalkoxy, including C_3-C_8 cycloalkoxy, alkenyl, including C_2-C_6 alkenyl, alkynyl, including C_2-C_6 alkynyl, haloalkyl, including C_1-C_6 haloalkyl, haloalkoxy, including C_1-C_6 haloalkoxy, halocycloalkyl, including C_3-C_8 halocycloalkyl, halocycloalkoxy, including C_3-C_8 halocycloalkoxy, amino, C_1-C_6 alkylamino, (C_1-C_6 alkyl)(C_1-C_6 alkyl)amino, alkylcarbonylamino, N-(C_1-C_6 alkyl)alkylcarbonylamino, aminoalkyl, C_1-C_6 alkylaminoalkyl, (C_1-C_6 alkyl)(C_1-C_6 alkyl)aminoalkyl, alkylcarbonylaminoalkyl, N-(C_1-C_6 alkyl)alkylcarbonylaminoalkyl, cyano, and nitro; or Z^X is selected from $-CO_2R^4$ and $-CONR^5R^6$, where R^4, R^5, and R^6 are each independently selected in each occurrence from hydrogen, C_1-C_6 alkyl, aryl-C_1-C_6 alkyl, and heteroaryl-C_1-C_6 alkyl.

Illustrative heterocycles include, but are not limited to pyrrolidines, piperidines, oxazolidines, isoxazolidines, thiazolidines, isothiazolidines, pyrrolidinones, piperidinones, oxazolidinones, isoxazolidinones, thiazolidinones, isothiazolidinones, and succinimides.

As used herein, the term “leaving group” refers to a reactive functional group that generates an electrophilic site on the atom to which it is attached such that nucleophiles may be added to the electrophilic site on the atom. Illustrative leaving groups include, but are not limited to, halogens, optionally substituted phenols, acyloxy groups, sulfonoxy groups, and the like. It is to be understood that such leaving groups may be on alkyl, acyl, and the like. Such leaving groups may also be referred to herein as activating groups, such as when the leaving group is present on acyl. In addition, conventional peptide, amide, and ester coupling agents, such as but not limited to PyBop, BOP-Cl, BOP, pentafluorophenol, isobutylchloroformate, and the like, form various intermediates that include a leaving group, as defined herein, on a carbonyl group.

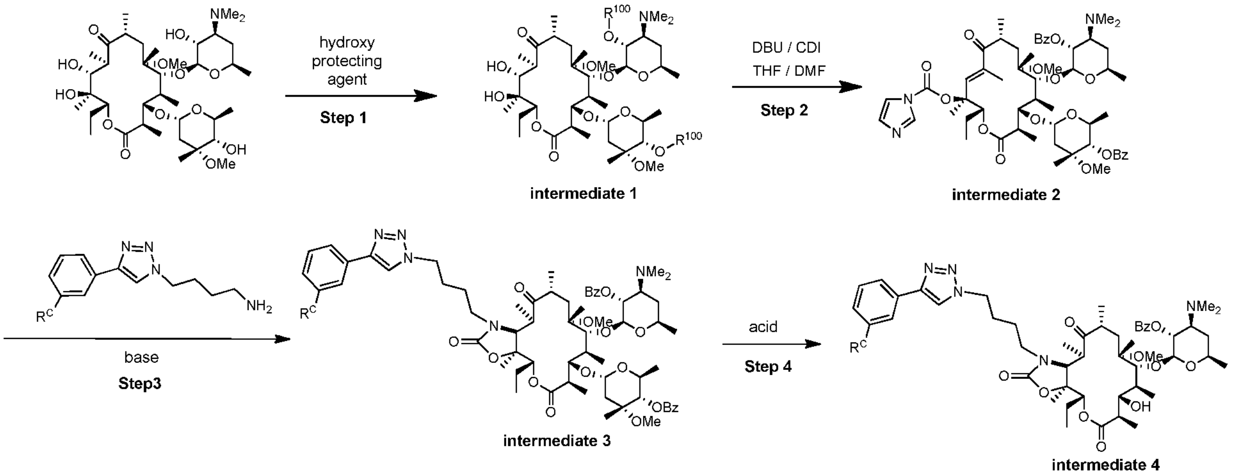
It is to be understood that where members are grouped together in a common manner, such as in a Markush group, the present invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group. Accordingly, for all purposes, the present invention encompasses not only the main group, but also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

In another embodiment, the following process steps and compounds are each individually described herein.



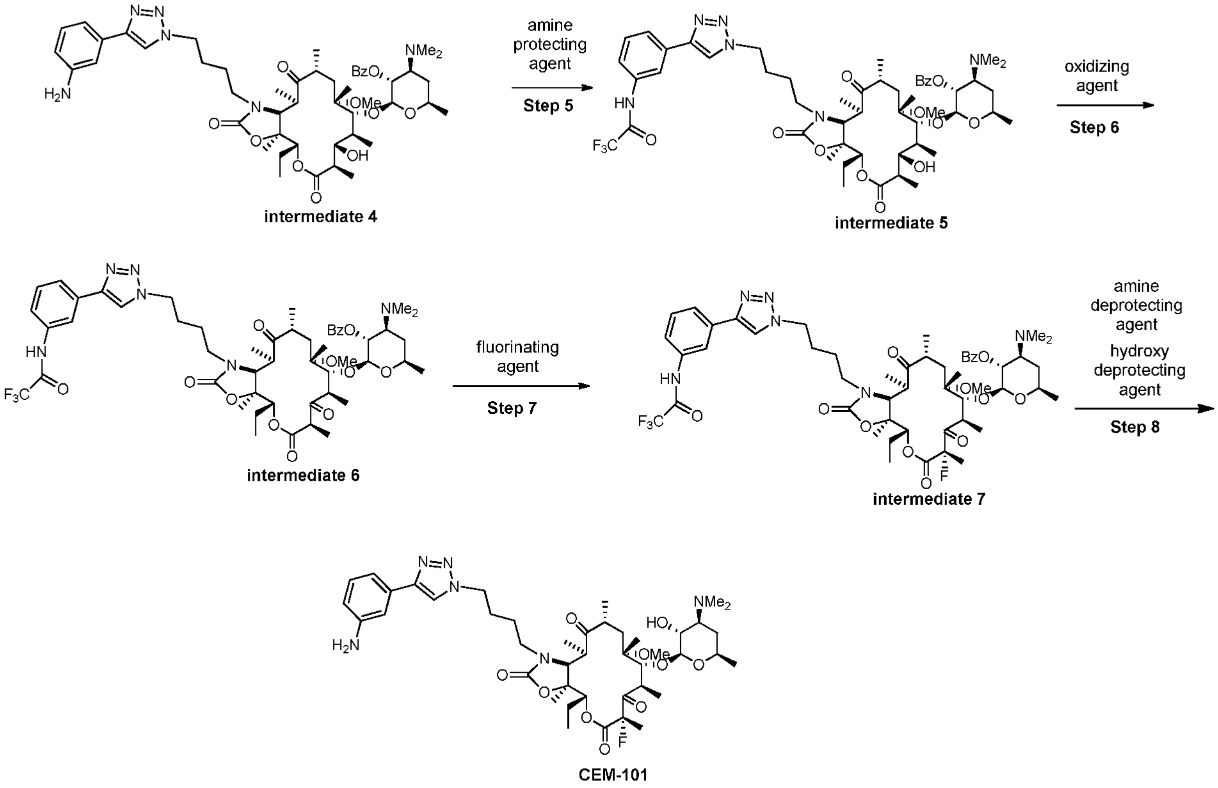
The corresponding process where C is replace by C^P in one or more steps is also described herein.

In another embodiment, the following process steps and compounds are each individually described herein.

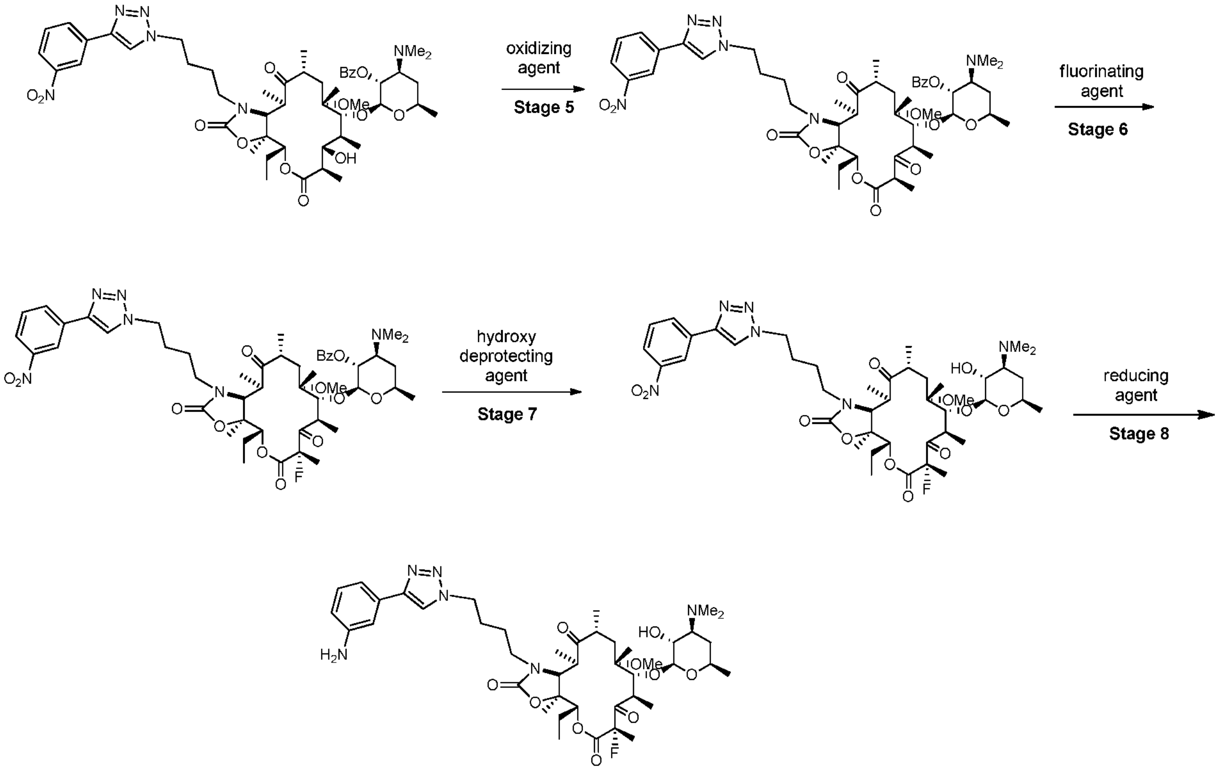


where R^C is amino, or a protected amino derivative such as N^P, or nitro. The corresponding process where R^C is N^P is also described herein.

In another embodiment, the following process steps and compounds are each individually described herein.



In another embodiment, the following process steps and compounds are each individually described herein.

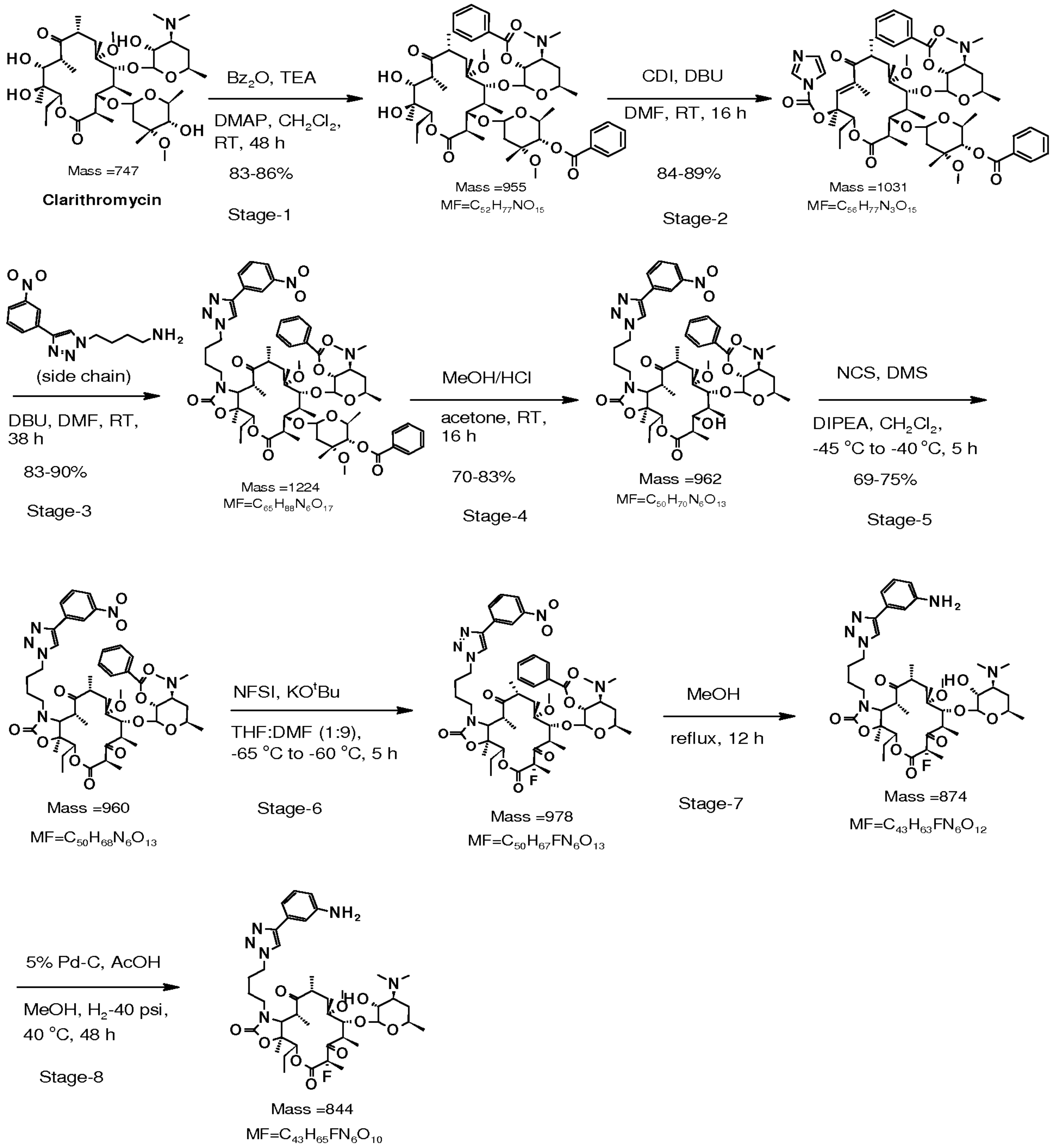


CEM-101

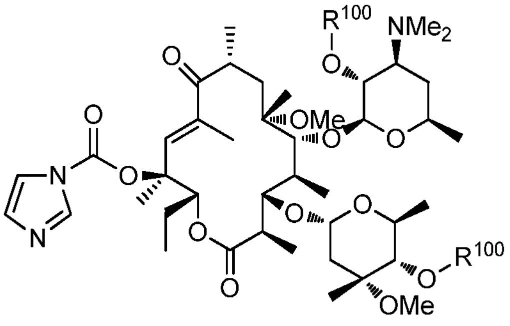
The processes and compounds described herein are further illustrated by the following examples. The following examples are intended to be illustrative and should not be construed or considered to be limiting in any manner.

EXAMPLES

EXAMPLE. CEM-101 is prepared according to the following process.

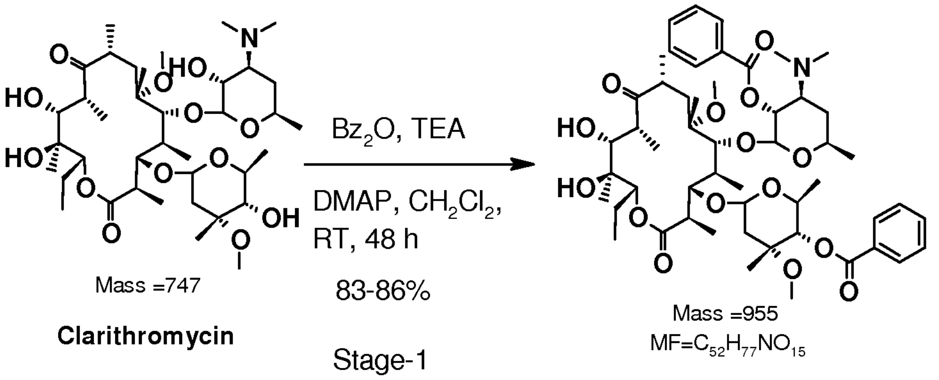


EXAMPLE. Compounds of the formula



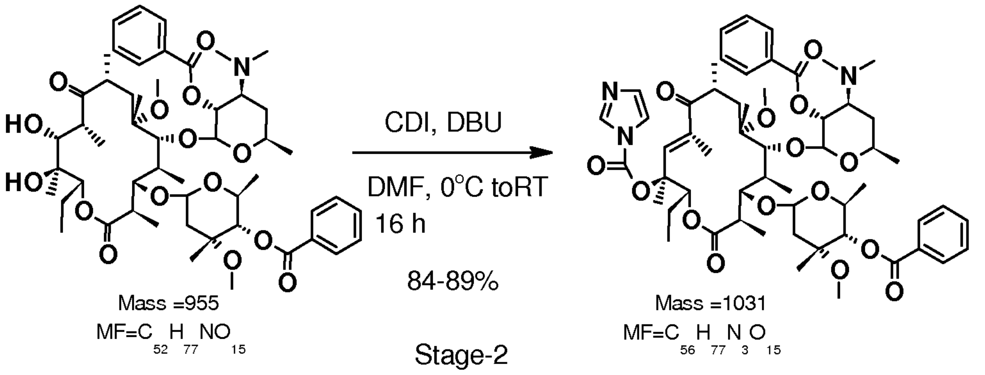
where R^{100} is a hydroxy protecting group, such as an acyl group, including acetyl, benzoyl, and the like, are prepared using conventional processes, such as but not limited to processes described in PCT International Publication Nos. WO/2009/055557 and WO/2011/146829, the disclosures of which are incorporated herein by reference, in their entirety.

EXAMPLE. Stage 1.



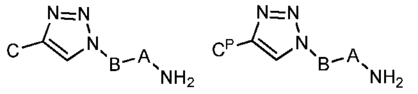
Preparation of 2',4"-di-O-benzoyl-6-O-methylerythromycin A. 125 mL of ethyl acetate was added to 25 g clarithromycin A. 26.5 g benzoic anhydride, 5.7 g 4-dimethylamino pyridine and 6.7 g triethylamine were added to the reaction mixture at 25°C to 35°C. The reaction mixture was stirred for about 70 hours at ambient temperature. After completion of the reaction, ethyl acetate was distilled out to obtain the title compound.

EXAMPLE. Stage 2.



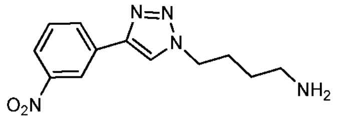
Preparation of 10,11-anhydro-2',4"-di-O-benzoyl-12-O-imidazolylcarbonyl-6-O-methylerythromycin A. Dimethylformamide (DMF, 100 mL) was added to 2',4"-di-O-benzoyl-6-O-methylerythromycin A at 25-35°C, then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU 6.4 g) was added to the reaction mixture and stirred at ambient temperature. 1,1'-Carbonyldiimidazole (CDI, 17 g) was added to the reaction and it was stirred until completion at ambient temperature. The title compound is isolated by addition of water, and collecting the resulting precipitate.

EXAMPLE. Compounds of formulae (A)



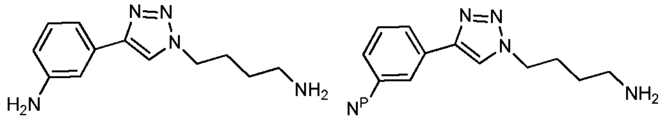
(A)

where A, B, C, and C^P are as defined herein in each of the embodiments described herein, are prepared using conventional processes. Similarly, compounds of formula (A1)



(A1)

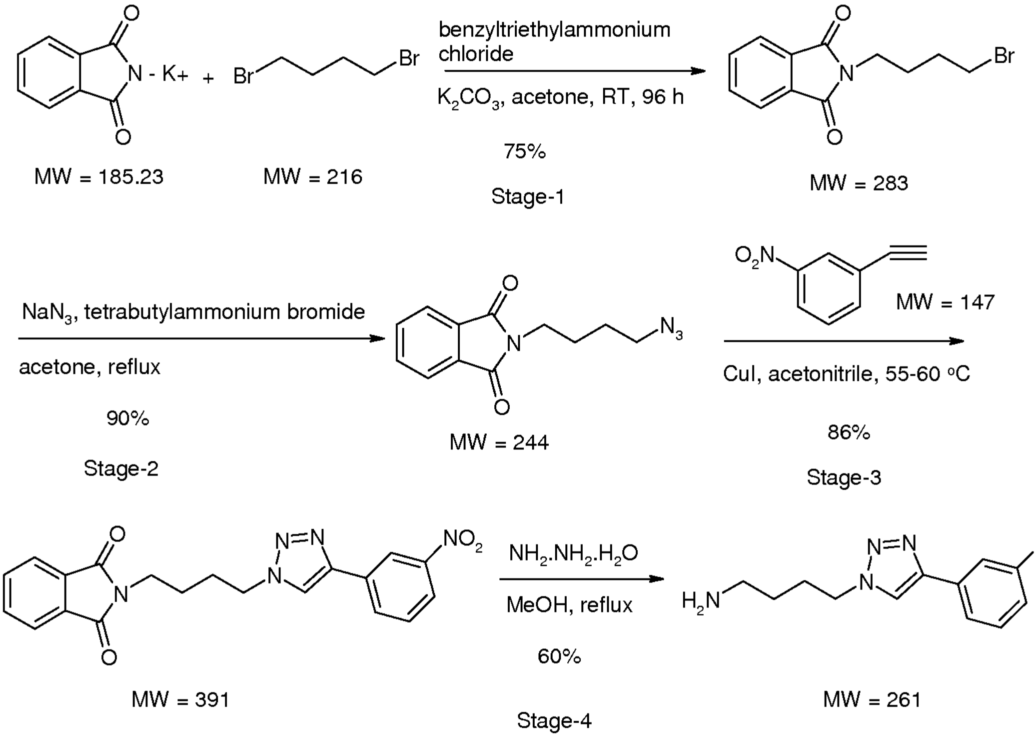
are prepared using conventional processes. Similarly, compounds of formula (A2)



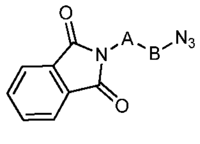
(A2)

where N^P is as defined herein in each of the embodiments described herein, are prepared using conventional processes. It is appreciated that the aminophenyl group of the compounds of formula (A2) may be protected prior to addition to Intermediate 3. Amino protected amide, carbamate, and urea derivatives are also prepared using conventional processes.

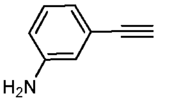
EXAMPLE. Illustratively, the foregoing compounds may be prepared by the following processes, illustrated for compounds of formula (A1) :

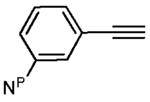


It is to be understood that the foregoing process may be used to prepare compounds of the formula (A) and/or (A1), including amino-protected derivatives thereof by the appropriate selection of starting materials, such as



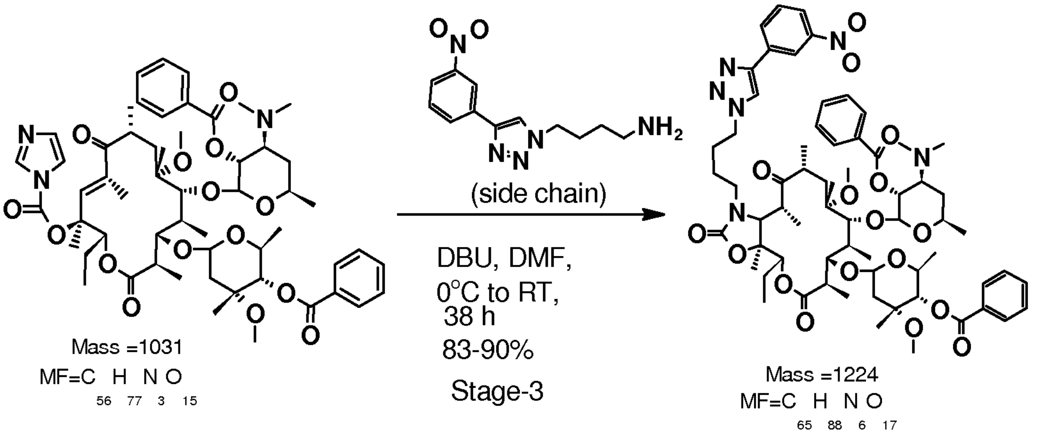
and

$C-\equiv$ $C^P-\equiv$


and


and the like, where A, B, C, C^P, and N^P are as defined herein in each of the embodiments described herein.

EXAMPLE. Stage 3.

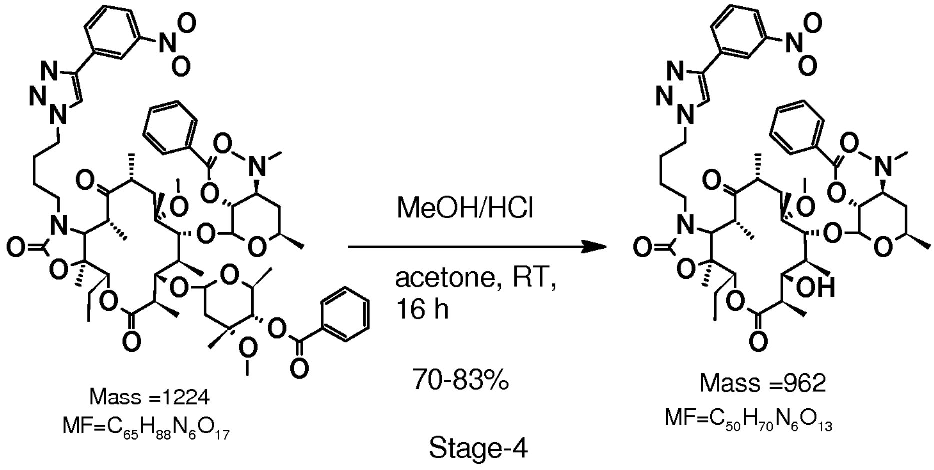


To a solution Stage-2 compound dissolved in 3000 mL of DMF (5.0 v, M/C <1.0%) at 0-5°C was added drop wise DBU followed by side chain in portions. The reaction mixture was allowed to come to room temperature and stirred for 36 h. The HPLC recorded after 36 h showed <1% of un-reacted Stage-2 compound.

The reaction mixture was poured into ice cold water (6000 mL) and stirred for 2 h. The solid was filtered, washed with water (2500 mL) and suck dried for 2 h to obtain 650 g of crude product with 85% HPLC purity.

The crude product was added at room temperature to a bi-phasic solution of ethyl acetate (1500 mL) and 1 N aqueous HCl (1500 mL) and stirred for 1h. The solid was filtered, washed with ethyl acetate (600 mL) and suck dried for 2 h. The solid was suspended again in ethyl acetate (1500 mL), stirred for 1h at room temperature and filtered. The filter cake was dried in a vacuum oven at 40-45 °C till the moisture content was not more than 3%. The pure product was obtained as a white solid in 88% yield (620 g) and 98% purity.

EXAMPLE. Stage 4.



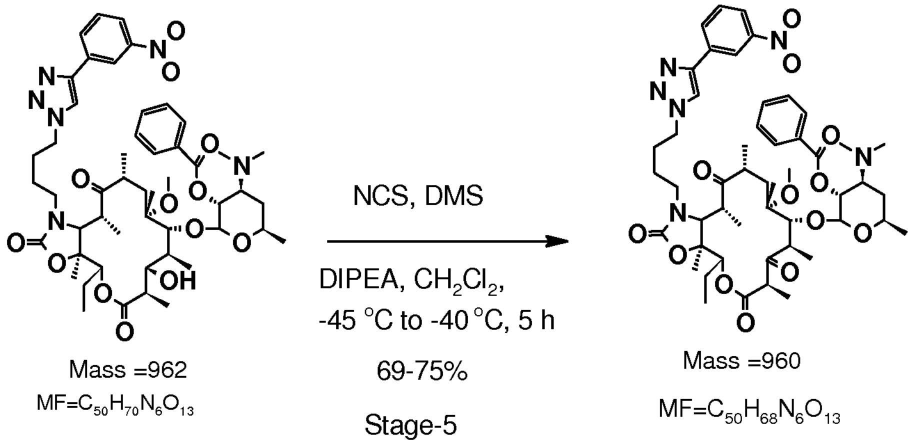
To a solution of Stage-3 compound in 1800 mL of acetone at 0 to 5 °C was added 272 mL of methanolic HCl slowly and the reaction mixture was stirred for additional 30 min at the same temperature. The reaction was then allowed to come to room temperature and stirred for 16 h.

After completion of the reaction, the reaction mixture was distilled under reduced pressure and obtained the product as a gummy residue. The crude mass was stirred with ethyl acetate and decanted to remove benzoyl cladinose and other impurities. Alternately, the gummy residue was dissolved in water and then extracted with toluene to remove benzoyl cladinose and other impurities. Then the aqueous layer was basified using 10% aqueous sodium hydroxide solution, then extracted with ethyl acetate to get decladinose product. Optionally, the distillation was performed after adjusting the pH with aqueous sodium bicarbonate solution.

The suspension was filtered and washed with acetone (200 mL). The pH of the filtrate was adjusted to 5 using saturated aqueous sodium bicarbonate solution and the solvents acetone and methanol were distilled under reduced pressure (below 40-45 °C). The residue was extracted with dichloromethane (3x 200 mL) and the combined organic layer was dried over anhydrous sodium sulphate and distilled dichloromethane to obtain 130 g of crude product. The HPLC showed benzoyl cladinose and the desired product as major peaks (together showed 98% by area).

The crude product was stirred at room temperature in 5% ethyl acetate in hexanes (40 mL of ethyl acetate and 760 mL of hexanes) for 2 h and filtered. The filter cake was washed with 5% ethyl acetate in hexanes (10 mL of ethyl acetate and 190 mL of hexanes) and dried in a vacuum oven at 40-45 °C till the LOD was note more than 1% and M/C not more than 0.5%. The pure was obtained as a white solid in 86.6 % yield (132 g) and 92.0% HPLC purity.

EXAMPLE. Stage 5.

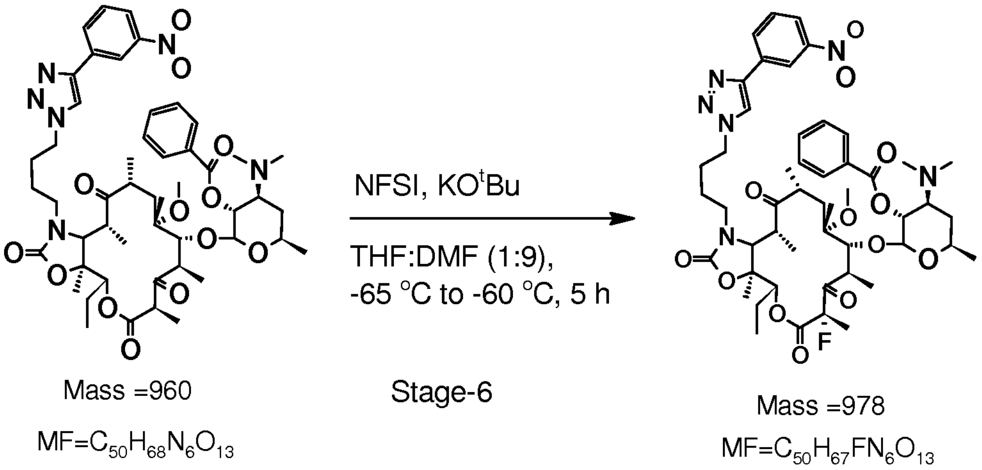


To a solution of N- chlorosuccinimide dissolved in 1600 mL of dichloromethane at -50°C was added dimethyl sulfide over a period of 30 min, maintaining the temperature between -40 to -35°C. After stirring the reaction mixture for 60 min, a solution of Stage-4 compound in 1400 mL of dichloromethane was added over a period of 2 h maintaining the internal temperature between -40 to -35°C. The reaction mixture was stirred for further 90 min at -45°C (HPLC showed <1% of the un-reacted starting material) and 177 mL of N-diisopropylethylamine was added cautiously over a period of 1h maintaining the internal temperature between -45 to-40°C. The reaction mixture was warmed to 10 °C and stirred for 90 min.

To the reaction mixture 3000 mL of water was added and warmed the reaction mass to room temperature (25-30°C). The organic layer was separated and washed successively with 1N aqueous HCl (2000 mL), water (2000 mL) followed by 10% aqueous sodium bi-carbonate solution (2000 mL). The organic layer was then dried over anhydrous sodium sulphate and the solvent was distilled under reduced pressure to obtain 190 g of crude product having 85% HPLC purity.

The crude product was suspended in 400 mL of MTBE and heated at 55°C for 2 h. The suspension was cooled to room temperature and stirred for 1 h. The solid was filtered and dried in a vacuum oven at 40-45°C to obtain the pure product with LOD not more than 1.0% and M/C not more than 0.5%. The pure was obtained as a white solid in 89.1% yield (178 g) and 93.0% HPLC purity.

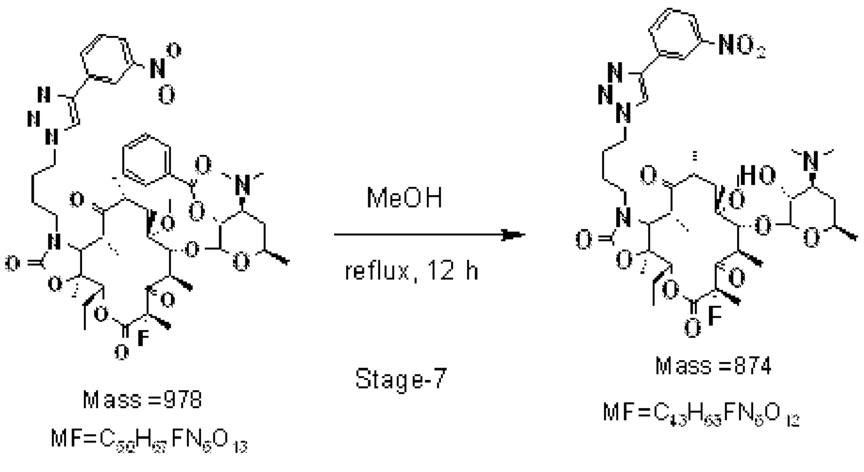
EXAMPLE. Stage 6.



To a solution of Stage-5 compound dissolved in 9:1 mixture of DMF: THF (1350 mL of DMF and 150 mL of THF) at -65 to -60°C was added K^{t}OBu in 10 equal portions and stirred the reaction mixture for 60 min at the same temperature. A solution of NFSI dissolved in 9:1 mixture of DMF: THF (900 mL of DMF and 100 mL of THF) was added to the reaction mixture over a period of 3-4 h maintaining the internal temperature between -65 to -60°C. The contents were stirred for further 60 min at the same temperature.

The reaction mixture was poured into 1000 mL of saturated aqueous $NaHCO_3$ solution maintained at 0°C and stirred for 30 min. The precipitated solid was filtered, washed with 2x100 mL of water and dried in a vacuum oven at 45-50°C till LOD was not more than 3.0% and M/C not more than 3%. The crude product was obtained a brown solid in 87.6 % yield (90 g) and 80-90% HPLC purity. Further purification may be performed using column chromatography on fluorisil

EXAMPLE. Stage 7.

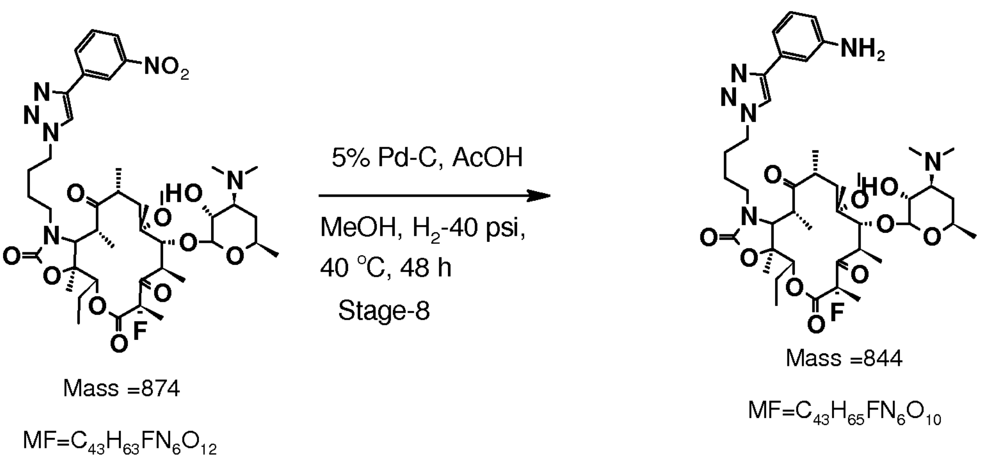


A solution of Stage-6 compound dissolved in 765 mL of methanol was heated at reflux temperature for 12 h. The HPLC after 12 h showed <1% of the starting material and at this stage charcoal was added and stirred for further 2 h at reflux temperature.

The suspension was filtered over a celite bed and the filtrate was concentrated under reduced pressure (at < 45 °C) to obtain the crude product as brown gummy solid.

The crude product was stirred at room temperature in 5% MTBE in hexanes (14 mL of MTBE and 255 mL of hexanes) for 2 h. The solid was filtered and the purification was repeated two more times with 5% MTBE in hexanes (14 mL of MTBE and 255 mL of hexanes each time) to obtain 73 g of product (90% yield) as pale brown solid with 90.54 % purity.

EXAMPLE. Stage 8.

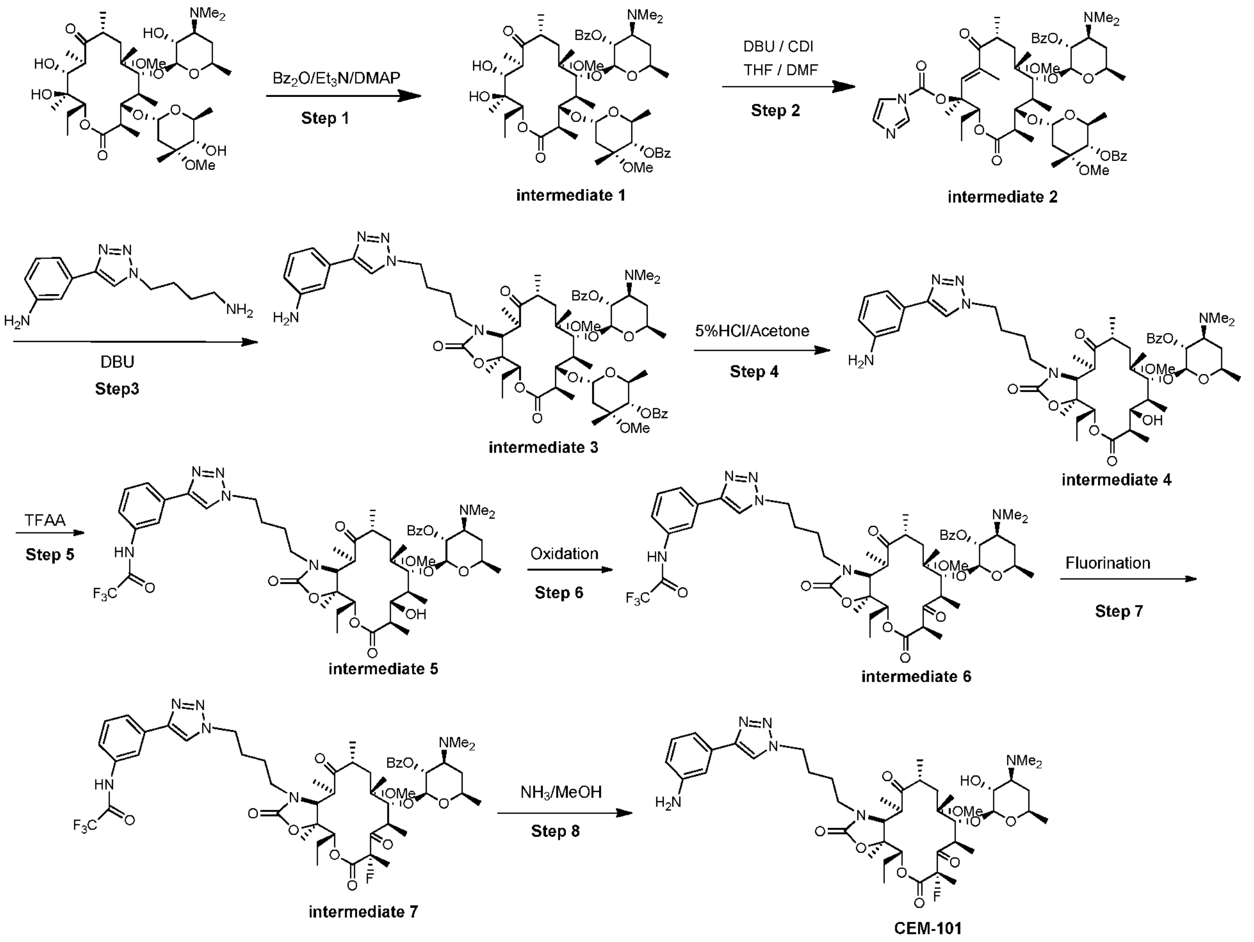


To a solution of Stage-7 compound dissolved in 450 mL of methanol was added 1.0 equiv of acetic acid followed by 3.3 w/w % of Pd-C. The suspension was stirred at 40 °C under 40 psi of hydrogen pressure for 6 h and HPLC showed 15% conversion of the starting material. The second lot of 6.6% w/w of Pd-C was added and continued to stir the reaction at 40°C under 40 psi of hydrogen pressure for 24 h. At this stage HPLC showed 55% conversion of the starting material. The third lot of 3.3% Pd-C was added to the reaction mixture and after 12 h <1% of un-reacted starting material was observed.

The reaction mixture was cooled to room temperature and the suspension was filtered through a celite bed. The filter cake was washed with 200 mL of methanol and the combined filtrates were subjected to distillation under reduced pressure (below 45°C temperature) to obtain gummy solid. The gummy solid was dissolved in 125 mL of dichloromethane and washed with 25 mL of aqueous ammonia solution. The organic layer was dried over sodium sulphate and dichloromethane was distilled to obtain crude product as pale brown solid (21 g) in 80% HPLC purity.

The crude product was suspended in 50 mL of IPA and stirred at 55-60°C for 3 days. The suspension was allowed to cool to room temperature and filtered. The filter cake was washed with 25 mL of cold IPA and dried under vacuum at 40-45°C to obtain 12.6 g (52 % yield) of the product with 94% purity.

EXAMPLE. CEM-101is prepared according to the following process.



EXAMPLE. Intermediate 4. Intermediate 4 is prepared as described in PCT International Publication Nos. WO/2009/055557 and WO/2011/146829 from clarithromycin, and generally according to the process shown in Scheme 1. 62 g of Intermediate 1 was prepared in 80% yield from clarithromycin. 15 g of Intermediate 2 was prepared from Intermediate 1 in 93% yield. Cyclization of Intermediate 2 gave 6.6 g of intermediate 3 in 86% yield. Removal of cladinose from intermediate 3 Step 4 gave 4.4 g of Intermediate 4 in 85% yield. The product identity was confirmed by mass spectrometry and NMR.

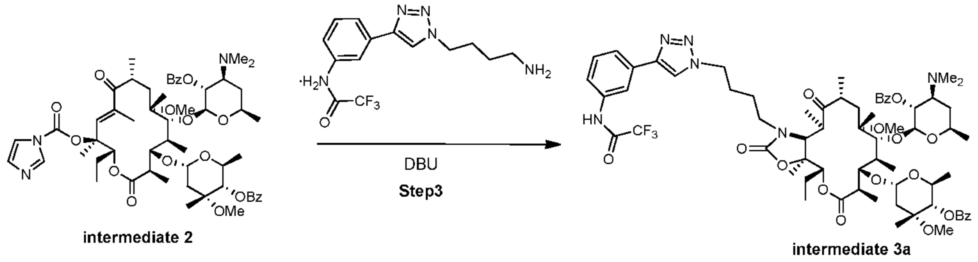
EXAMPLE. Intermediate 5. Trifluoroacetic anhydride (113 mg, 0.54 mmol) was added dropwise to a solution of Intermediate 4 (500 mg, 0.54 mmol) in anhydrous DCM (9 mL) at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM, washed successively with dilute aqueous $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated to dryness to give 450 mg of crude Intermediate 5 as a light brown solid. Mass spectroscopy analysis of crude Intermediate 5 showed the desired product peak as the major component. The ^{1}H-NMR spectrum of crude Intermediate 5 showed peaks corresponding to the desired structure of the product. The ^{1}H-NMR spectrum also showed the presence of unreacted Intermediate 4. The material (~85% purity) was used without further purification.

EXAMPLE. Intermediate 6. To a solution of Intermediate 5 (100 mg, 0.097 mmol, ~85% purity) in anhydrous DCM (3 mL) was added Dess-Martin periodinane (50 mg, 0.116 mmol, 1.2 eq). The resulting reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with DCM, washed successively with dilute aqueous sodium thiosulfate solution and brine, and dried over anhyd $MgSO_4$. After filtration, the filtrate concentrated to dryness. The crude product was subjected to silica gel column chromatography (eluent: acetone/DCM, 20/80, v/v) to afford 55 mg of pure Intermediate 6 as a white solid in 72% yield. The ^{1}H-NMR spectrum of Intermediate 6 confirmed the structure of the product and its good purity.

EXAMPLE. Intermediate 7. A solution of Intermediate 6 (82 mg, 0.08 mmol) in DMF (1 mL) was cooled to -30 °C. DBU (14 mg, 0.088 mmol) was added, and the resulting mixture was stirred at -30 °C for 20 min. To the reaction mixture stirring at -30 °C was added dropwise a solution of NSFI (25 mg, 0.08 mmol) in DMF (1 mL). After the addition, the reaction mixture was stirred at -30 °C for 20 min. The reaction mixture was quenched with dilute aqueous solution of $NaHCO_3$ and extracted with DCM. The combined DCM extract was washed with brine, and dried over anhyd $MgSO_4$. After filtration, the filtrate was concentrated to dryness. The crude product was subjected to silica gel column chromatography (eluent: acetone/DCM, 20/80, v/v) to afford 61 mg of pure Intermediate 7 as a white solid in 86% yield. The ^{1}H-NMR spectrum of Intermediate 7 confirmed the desired structure of the product and its good purity.

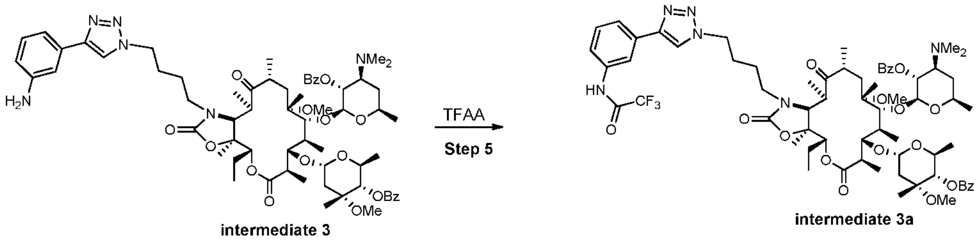
EXAMPLE. CEM-101. A solution of Intermediate 7 (60 mg) in methanol (1 mL) containing 0.3 mL of NH_4OH was stirred at room temperature overnight. Mass spectroscopy analysis of an aliquot of the reaction mixture showed a peak with a Mw corresponding to CEM-101 as the major component along with unreacted Intermediate 7. The reaction mixture was diluted with DCM, washed successively with water and brine, and dried over anhyd $MgSO_4$. After filtration, the filtrate was concentrated to dryness. The crude product was dissolved in methanol (10 mL) and heated at reflux for one hour. The reaction mixture was concentrated to a small volume and the residue was subjected to silica gel column chromatography (eluent: DCM/MeOH/NH_4OH, 95/5/0.5, by volume) to afford 40 mg of CEM-101. The ^{1}H-NMR spectrum confirmed the desired structure of the product.

EXAMPLE. Synthesis of Intermediate 3a.



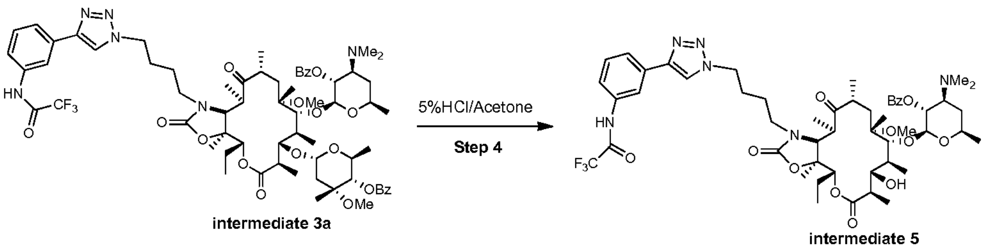
A mixture of intermediate 2 (1.0 g), protected side chain-HCl salt (1.3 eq.), DBU (2.5 eq.), and DMF was heated at 40-70°C with stirring under nitrogen. Reaction progress was monitored by TLC, HPLC, and MS. When complete, the mixture was partitioned between DCM and brine, washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by HPLC to give ≥90% yield of the title compound. ^{1}H NMR spectra and mass spectra (MW 1292) were consistent with the title compound.

EXAMPLE. Synthesis of Intermediate 3a



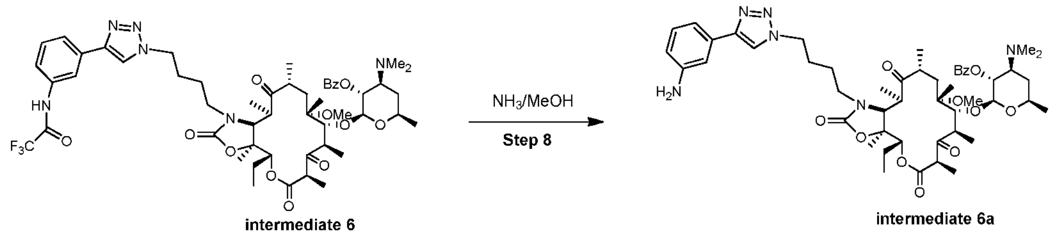
A solution of Intermediate 3 (650 mg, 0.544 mmol) in anhydrous DCM (10 mL) was cooled to 5°C with an ice-bath. To this was added trifluoroacetic anhydride (172 mg, 0.82 mmol, 1.5 equivalent), and the resulting reaction mixture was stirred for 10 min at 5°C, before gradual warming to ambient temperature over 1.5 hr. The reaction was quenched with ice cold diluted aqueous $NaHCO_3$ and extracted with DCM. The combined DCM extract was washed with brine and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the filtrate was concentrated to dryness. The crude product was purified through silica gel column chromatography (eluent: DCM/MeOH/NH4OH = 95/5/0.5, by volume) to give 540 mg of product in 77% yield. Both the ^{1}H-NMR spectrum and mass spectrum of the product showed peaks conforming to the desired structure of Intermediate 3a.

EXAMPLE. Synthesis of Intermediate 5



To a solution of Intermediate 3a (150 mg, 0.116 mmol) in acetone (3 mL) was added DBU (35 mg, 0.233 mmol, 2.0 equivalent), followed by conc. HCl (300 μL). The resulting reaction mixture was stirred at room temperature for 5 hrs. Mass analysis of an aliquot of the reaction mixture showed complete reaction with clean reaction profile. The reaction mixture was poured into a mixture of DCM and ice water. The mixture was made basic by the addition of dilute NH_4OH and extracted with DCM. The combined DCM extract was washed with brine, dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the filtrate was concentrated to dryness. The crude product was purified through silica gel column chromatography (eluent: DCM/MeOH/NH4OH = 95/5/0.5, by volume) to give 103 mg of Intermediate 5 in 86% of yield. The ^{1}H-NMR spectrum and mass spectrum of the product showed peaks corresponding to those expected for the desired structure of intermediate 5 with good purity.

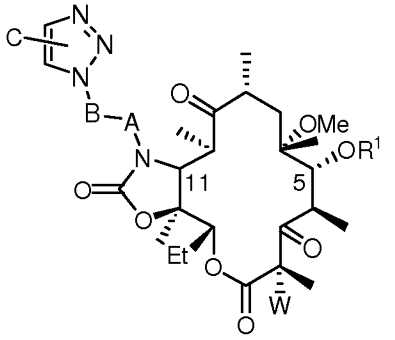
EXAMPLE. Synthesis of Intermediate 6a



To a solution of Intermediate 6, (1.0 mmol) in methanol (10 mL) is added ammonium hydroxide solution (NH_4OH, 30 mmol). The resulting clear solution is stirred at ambient temperature overnight to give a turbid reaction mixture. The reaction mixture is concentrated to dryness, dissolved in DCM, washed successively with diluted aqueous $NaHCO_3$ solution and brine, and then dried over anhydrous. $MgSO_4$. After filtration to remove the drying agent, the filtrate is concentrated to dryness to afford 0.8 mmol of Intermediate 6a(90% yield). The 1H-NMR spectrum and mass spectrum are consistent with the title compound.

WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof; wherein

R^1 is a desosamine or a desosamine derivative;

A is -CH_2-, -C(O)-, -C(O)O-, -C(O)NH-, -$S(O)_2$-, -$S(O)_2NH$-, -C(O)$NHS(O)_2$-;

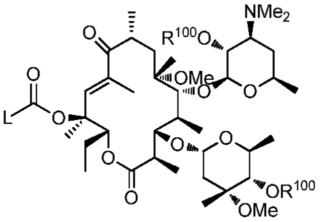
B is -$(CH_2)_n$- where n is an integer ranging from 0-10; or B is saturated C_2-C_{10}; or B is unsaturated C_2-C_{10} comprising one or more alkenyl or alkynyl groups; or -A-B- taken together is alkylene, cycloalkylene, or arylene;

C represents 1 or 2 substituents independently selected in each instance from the group consisting of hydrogen, halogen, hydroxy, acyl, acyloxy, sulfonyl, ureyl, and carbamoyl, and alkyl, alkoxy, heteroalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, , each of which is optionally substituted; and

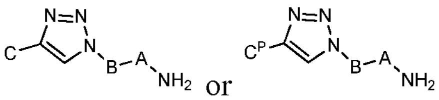
W is hydrogen, F, Cl, Br, I, or OH;

the process comprising the step of

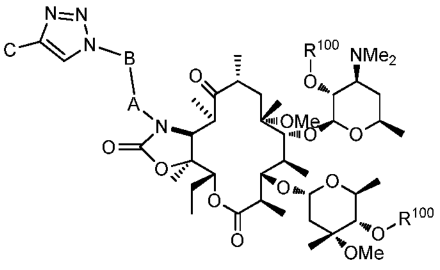
(A) contacting a compound of formula



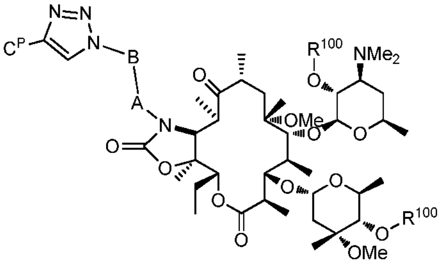
or a salt thereof, where R^{100} is a hydroxyl protecting group, and L is a leaving group, with a compound of formula



or a salt thereof, where C is as defined herein, and C^P is a protected form of C, and a base, to prepare a compound of formula

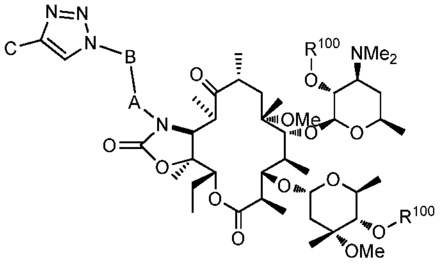


or

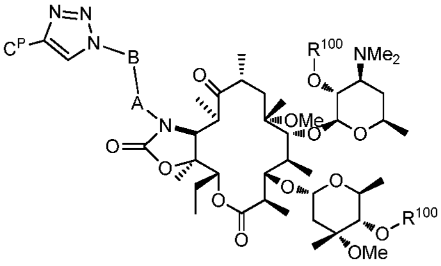


or a salt thereof; or

(B) contacting a compound of formula

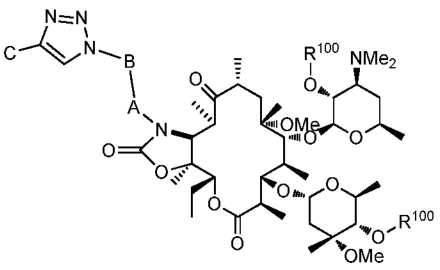


or a salt thereof, with one or more protecting group forming agents to prepare a compound of formula



or a salt thereof; or

(C) contacting a compound of formula



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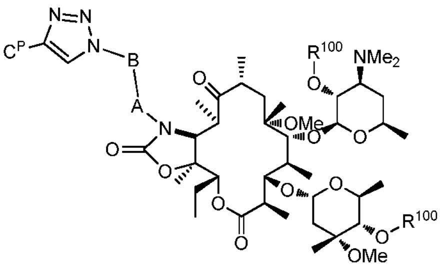
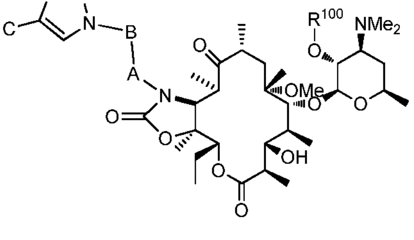


or a salt thereof, with an acid to prepare a compound of formula



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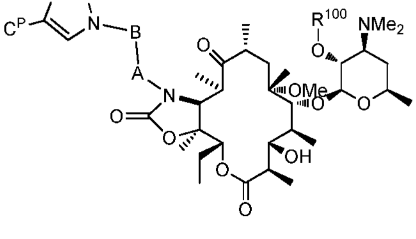
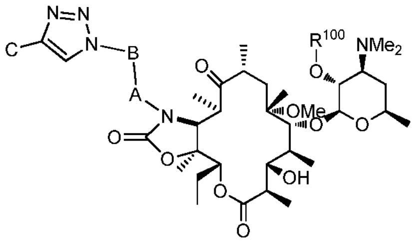
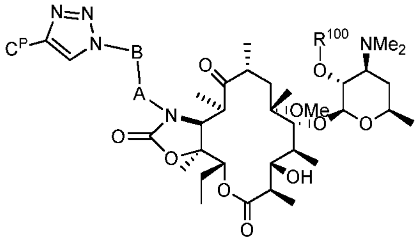


or a salt thereof; or

(D) contacting a compound of formula

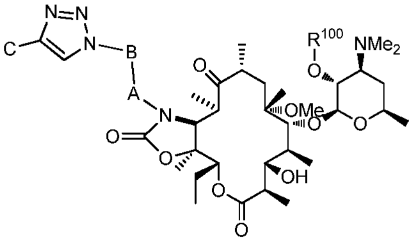


or a salt thereof, with one or more protecting group forming agents to prepare a compound of formula

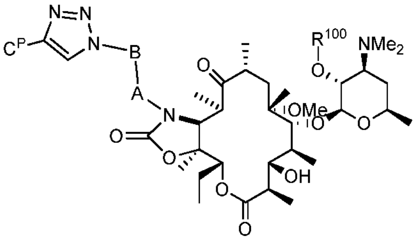


or a salt thereof; or

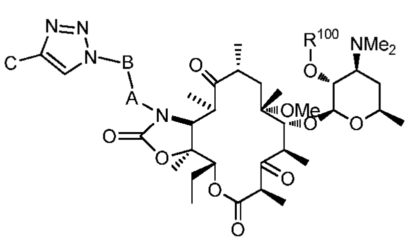
(E) contacting a compound of formula



or



or a salt thereof, with an oxidizing agent to prepare a compound of formula



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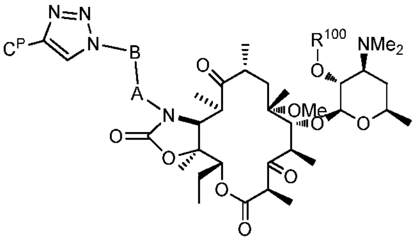
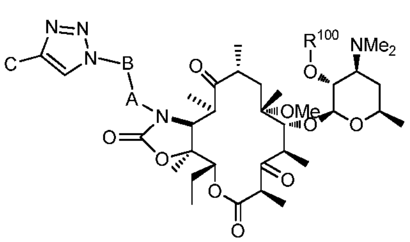


or a salt thereof; or

(F) contacting a compound of formula



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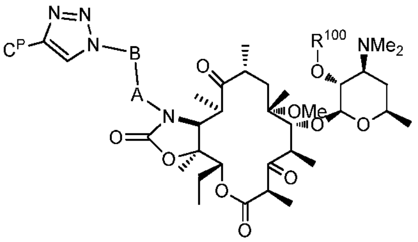
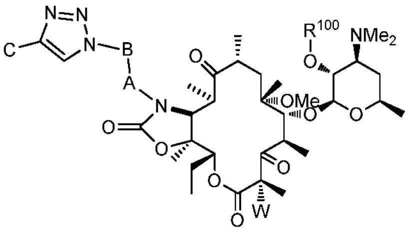


or a salt thereof, with a hydroxylating or halogenating agent to prepare a compound of formula



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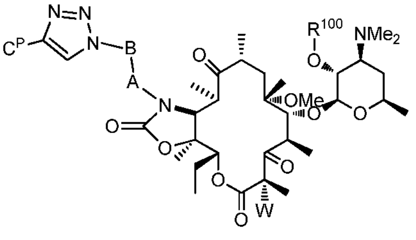
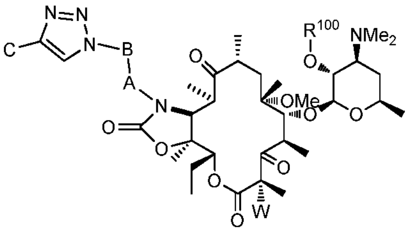


or a salt thereof; or

(G1) contacting a compound of formula



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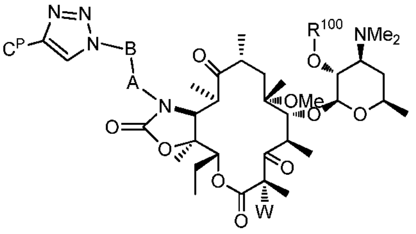
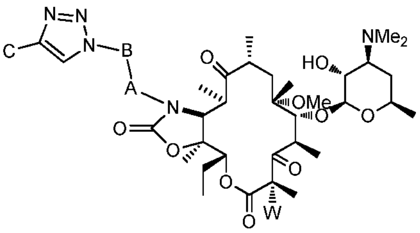


or a salt thereof, with a hydroxy deprotecting agent to prepare a compound of formula



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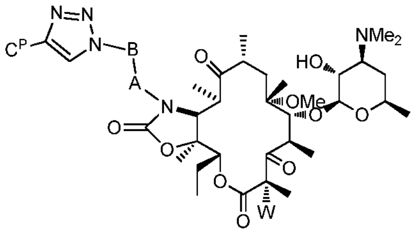
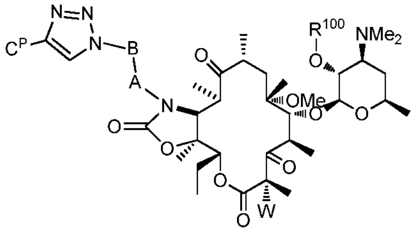
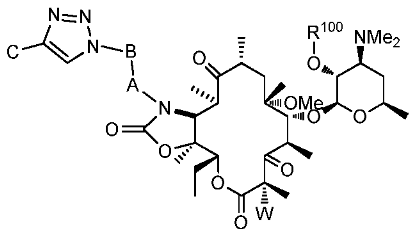


or a salt thereof; or

(G2) contacting a compound of formula



or a salt thereof, with one or more deprotecting agents to prepare the corresponding deprotected compound of formula

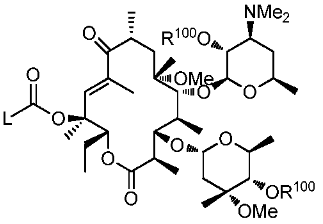


or a salt thereof; or

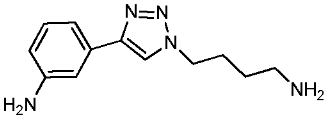
any combination of the foregoing.

2. A process for preparing a compound of formula (I) as defined in claim 1, the process comprising the step of

(a) contacting a compound of formula



or a salt thereof, where R^{100} is a hydroxyl protecting group, and L is a leaving group, with a compound of formula



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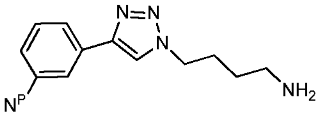
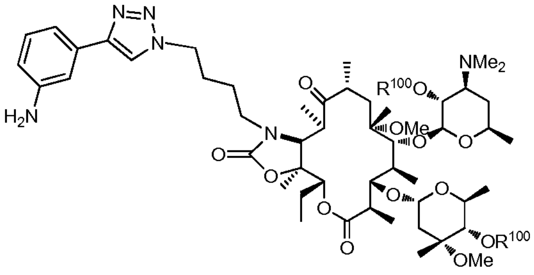


or a salt thereof, where N^P is a protected amine, and a base; to prepare a compound of formula



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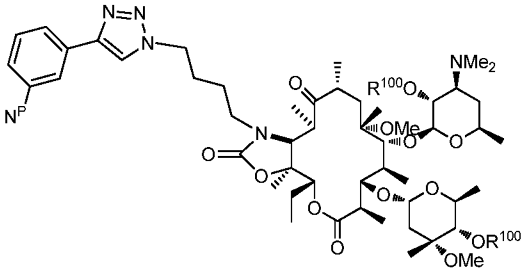
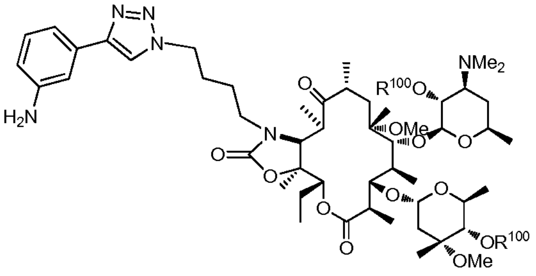
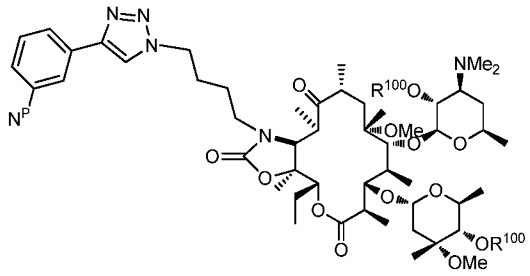


or a salt thereof; or

(b) contacting a compound of formula

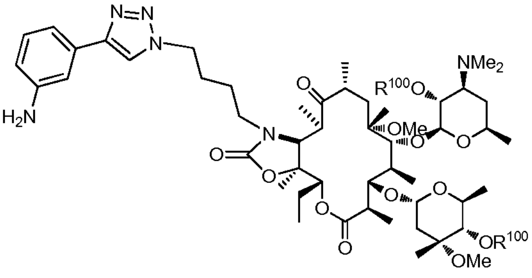


or a salt thereof, with an amine protecting group forming agent to prepare a compound of formula



or a salt thereof; or

(c) contacting a compound of formula



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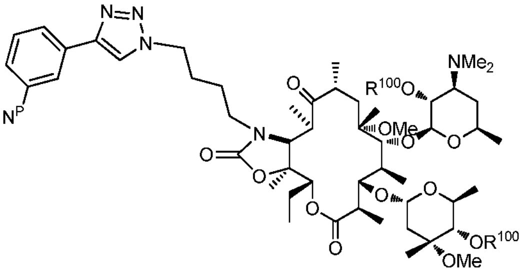
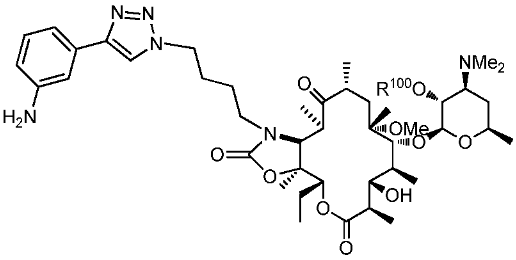


or a salt thereof, with an acid to prepare a compound of formula



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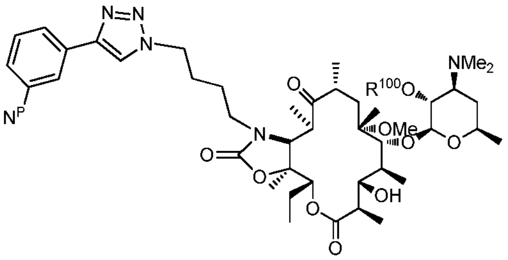
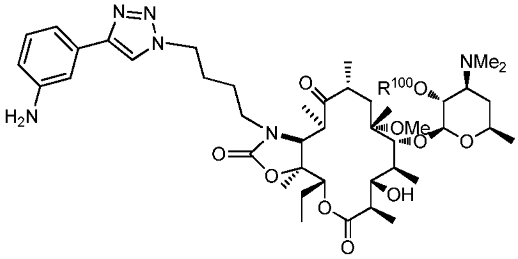
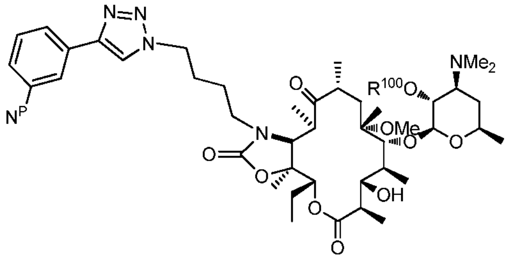


or a salt thereof; or

(d) contacting a compound of formula

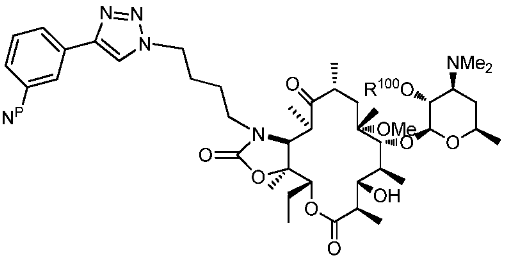


or a salt thereof, with an amine protecting group forming agent to prepare a compound of formula

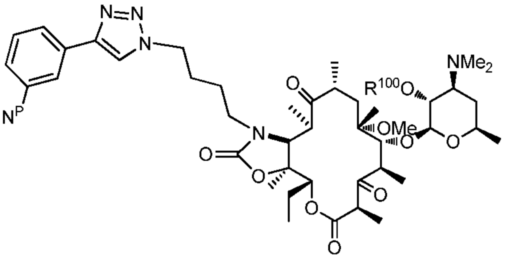


or a salt thereof; or

(e) contacting a compound of formula

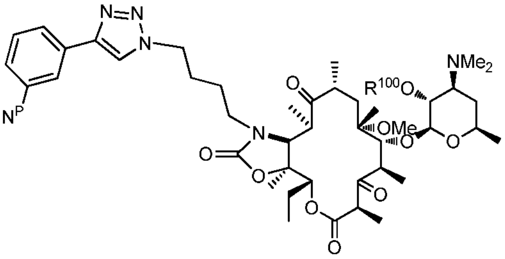


or a salt thereof, with an oxidizing agent to prepare a compound of formula

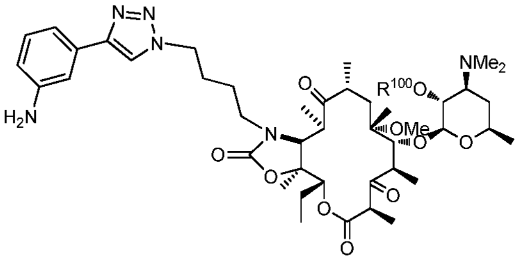


or a salt thereof; or

(f) contacting a compound of formula

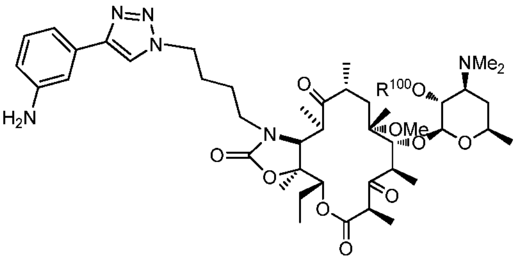


or a salt thereof, with an amine deprotecting agent to prepare a compound of formula



or a salt thereof; or

(g) contacting a compound of formula



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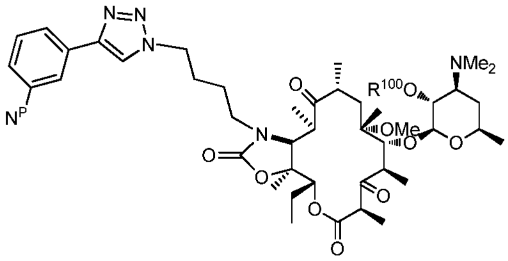
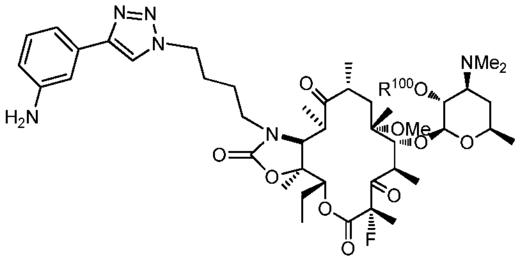


or a salt thereof, with a fluorinating agent to prepare a compound of formula



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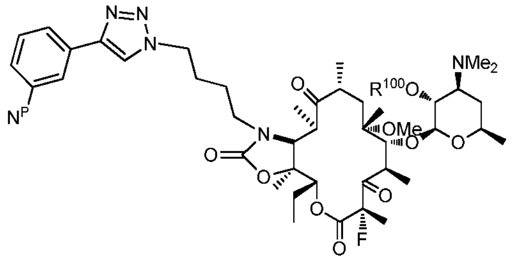
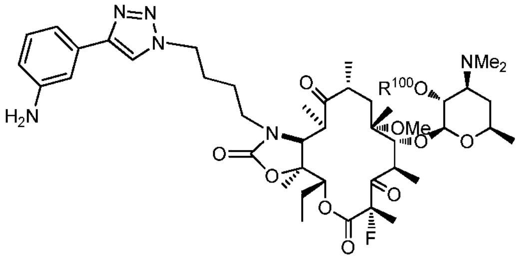


or a salt thereof; or

(h1) contacting a compound of formula



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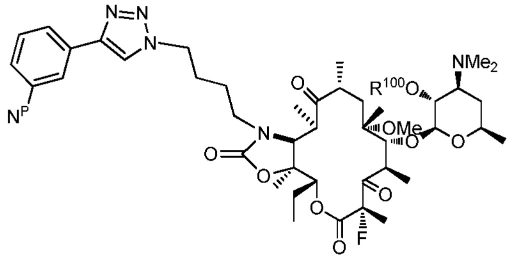
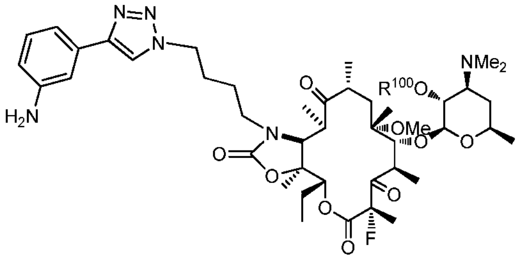


or a salt thereof, with a hydroxy deprotecting agent to prepare a compound of formula



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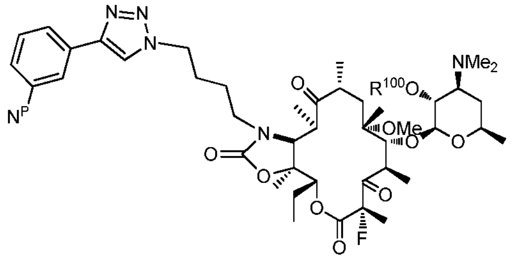
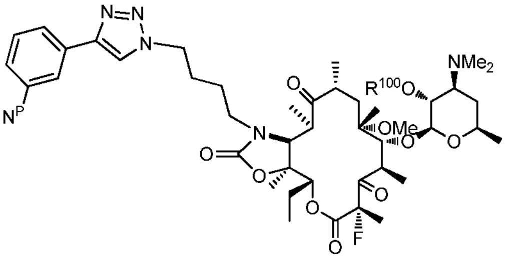
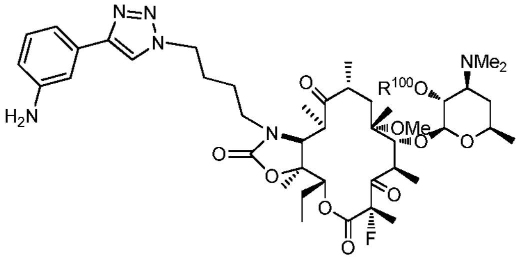


or a salt thereof; or

(h2) contacting a compound of formula



or a salt thereof, with an amine deprotecting agent to prepare a compound of formula



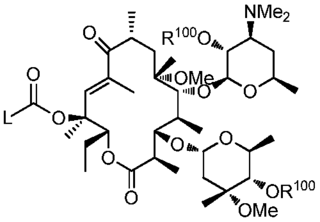
or a salt thereof; or

any combination of the foregoing.

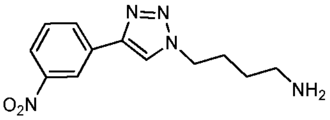
3. The process of claim 2 wherein N^P is $NHC(O)CF_3$.

4. A process for preparing a compound of formula (I) as defined in claim 1, the process comprising the step of

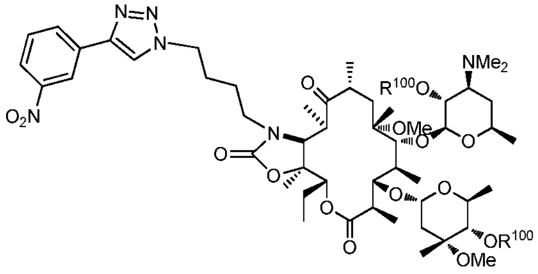
(a') contacting a compound of formula



or a salt thereof, where R^{100} is a hydroxyl protecting group, and L is a leaving group, with a compound of formula

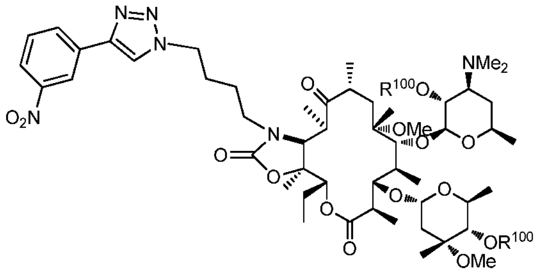


or a salt thereof, and a base; to prepare a compound of formula

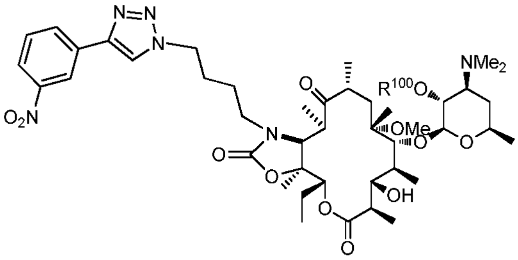


or a salt thereof; or

(b') contacting a compound of formula

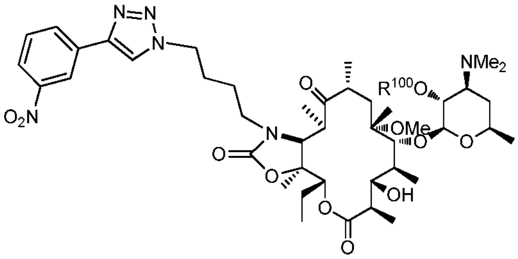


or a salt thereof, with an acid to prepare a compound of formula

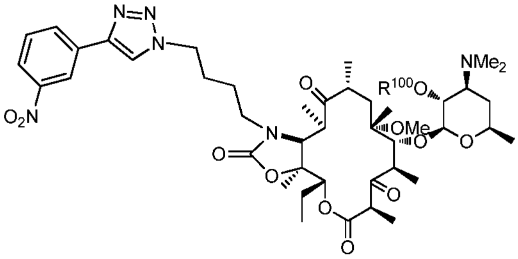


or a salt thereof; or

(c’) contacting a compound of formula

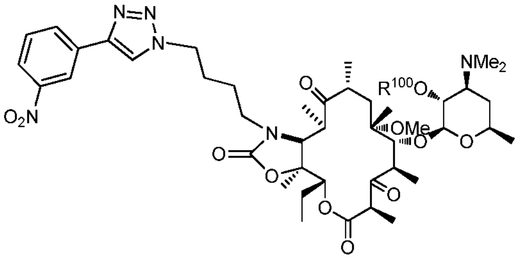


or a salt thereof, with an oxidizing agent to prepare a compound of formula

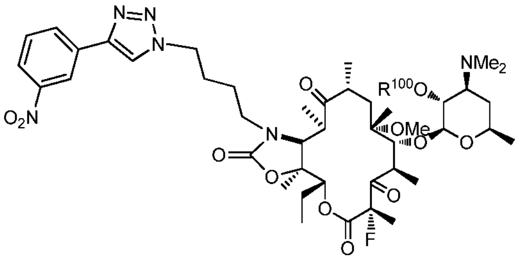


or a salt thereof; or

(d’) contacting a compound of formula

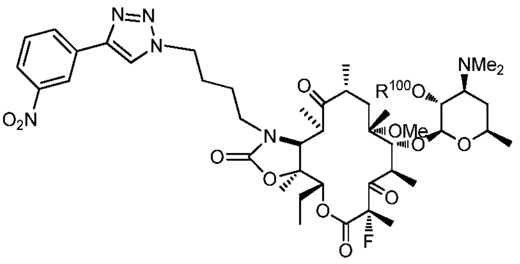


or a salt thereof, with a fluorinating agent to prepare a compound of formula



or a salt thereof; or

(e’) contacting a compound of formula



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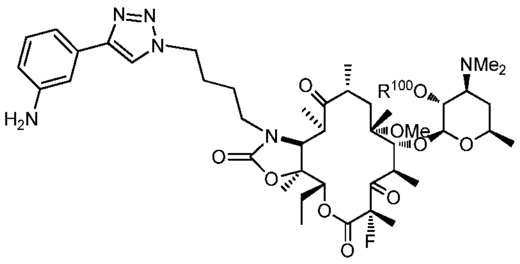
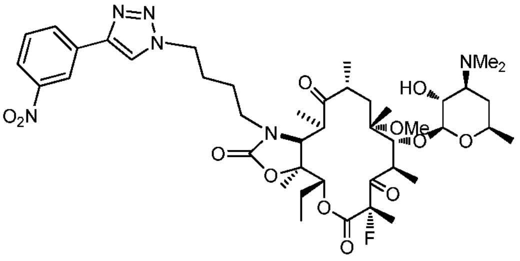


or a salt thereof, with a hydroxy deprotecting agent to prepare a compound of formula



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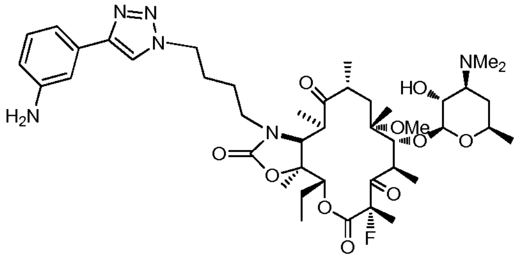
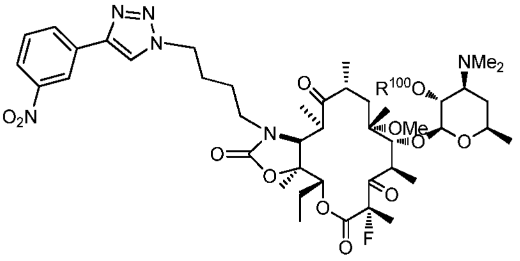


or a salt thereof; or

(f') contacting a compound of formula



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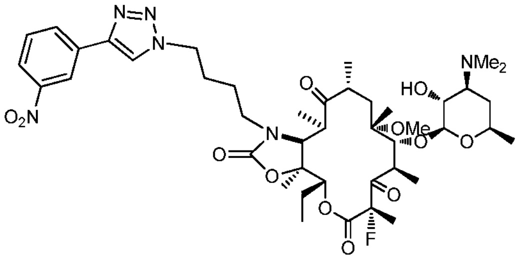
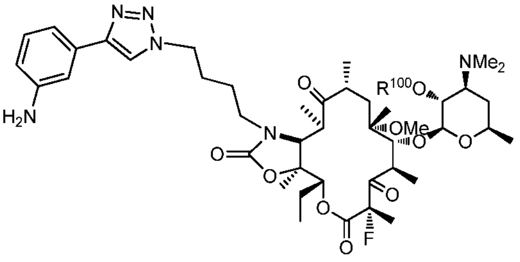


or a salt thereof, with a reducing agent to prepare a compound of formula



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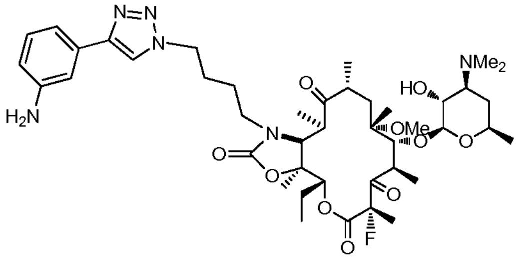

or a salt thereof; or

any combination of the foregoing.

5. The process of any one of claims 1 to 4 wherein the leaving group is halo, pentafluorophenoxy, a sulfonate, such as triflate, a hydroxyamino, such as an HOBt, or imidazol-1-yl.

6. The process of any one of claims 1 to 4 wherein the leaving group is imidazol-1-yl.

7. The process of any one of claims 1 to 4 wherein the base is DBU.

8. The process of any one of claims 1 to 4 wherein the acid is aqueous HCl, such as 5% HCl, optionally with an organic cosolvent, such as a ketone, such as acetone.

9. The process of any one of claims 1 to 4 wherein the amide forming agent is TFAA.

10. The process of any one of claims 1 to 4 wherein the oxidizing agent is trifluoroacetic anhydride in pyridine, PCC, Jones oxidation, TEMPO/NaOCl, Swern oxidation, Dess-Martin reagent, or Corey-Kim reagent.

11. The process of any one of claims 1 to 4 wherein the fluorinating agent is NFSI, F-TEDA, or Selectfluor.

12. The process of any one of claims 1 to 4 wherein the amine deprotecting agent is hydrogen and a metal catalyst.

13. The process of any one of claims 1 to 4 wherein the amine deprotecting agent is ammonia.

14. The process of any one of claims 1 to 4 wherein the hydroxy deprotecting agent is an alcohol.

15. The process of any one of claims 1 to 4 wherein the reducing agent is hydrogen and a metal catalyst.

16. The process of any one of claims 1 to 4 wherein C is aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

17. The process of any one of claims 1 to 4 wherein A is CH_2.

18. The process of any one of claims 1 to 4 wherein B is $(CH_2)_n$.

19. The process of any one of claims 1 to 4 wherein B is $(CH_2)_n$, and n is an integer between 3 and 4.

20. The process of any one of claims 1 to 4 wherein B is $(CH_2)_n$, and n is 3.

21. The process of any one of claims 1 to 4 wherein R^{100} is acyl.

22. The process of any one of claims 1 to 4 wherein R^{100} is alkylcarbonyl or optionally substituted benzoyl.

23. The process of any one of claims 1 to 4 wherein R^{100} is acetyl or benzoyl.

24. The process of any one of claims 1 to 4 wherein W is H or F.

25. The process of any one of claims 1 to 4 wherein W is F.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/29932

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7056; C07H 17/08 (2014.01)
USPC - 514/29; 536/7.4
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): A61K 31/7056; C07H 17/08 (2014.01)
USPC: 514/29; 536/7.4

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)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: ketolide, macrolide, antibacterial, triazole, intermediate, leaving group, imidazolyl, DBU, amine, deprotecting, reducing, oxidation, fluorinating

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0216731 A1 (PEREIRA, DE et al.) 26 August 2010; paragraphs [0017], [0020], [0022] and [0024]	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4
Y	US 2009/0005325 A1 (BAS, B et al.) 01 January 2009; paragraphs [0007], [0030]-[0031], [0040] and [0114]	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4
Y	US 7,951,905 B2 (SCHWEIZER, F et al.) 31 May 2011; column 14, lines 25-27; column 34, lines 49-51	9/1-4, 13/1-4
Y	US 2008/0132546 A1 (BASARAB, GS et al.) 05 June 2008; paragraph [0216]	12/1-4
Y	US 2010/0143505 A1 (GANT, TG et al.) 10 June 2010; paragraph [0118]	15/1-4

☒ Further documents are listed in the continuation of Box C. ☐

* 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
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"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
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"&" document member of the same patent family

Date of the actual completion of the international search 25 June 2014 (25.06.2014)	Date of mailing of the international search report 11 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/29932

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 2012/0071429 A1 (DUFFIELD, J et al.) 22 March 2012; entire document	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4
A	WO 2004/080391 A2 (LIANG, CH et al.) 23 September 2004; entire doucment	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4
A	US 2006/0100164 A1 (LIANG, CH et al.) 11 May 2006; entire document	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4
A	US 2013/0066056 A1 (PEREIRA, DE) 14 March 2013; entire document	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4
A	US 2009/0209593 A1 (LIANG, CH et al.) 20 August 2009; entire document	1-4, 5/1-4, 6/1-4, 7/1-4, 8/1-4, 9/1-4, 10/1-4, 11/1-4, 12/1-4, 13/1-4, 14/1-4, 15/1-4, 16/1-4, 17/1-4, 18/1-4, 19/1-4, 20/1-4, 21/1-4, 22/1-4, 23/1-4, 24/1-4, 25/1-4

(19)中华人民共和国国家知识产权局

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(71)申请人 森普拉制药公司
地址 美国加利福尼亚州

(72)发明人 D·E·佩雷拉

(74)专利代理机构 北京市铸成律师事务所 11313
代理人 孟锐

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C07H 17/08(2006.01)

权利要求书12页 说明书44页

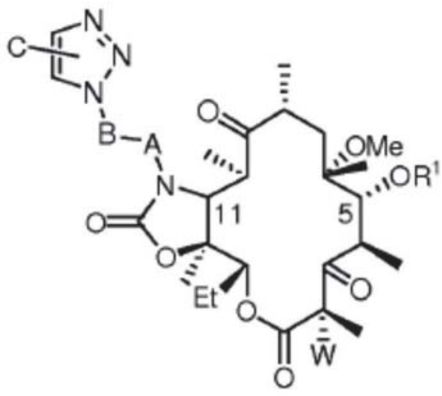
(54)发明名称

用于制备大环内酯抗菌剂的收敛方法

(57)摘要

本文所述的发明涉及用于制备酮内酯抗菌剂的方法。具体说来，本发明涉及用于制备包括1,2,3-三唑取代的侧链的酮内酯的中间体和方法。

1.一种用于制备式(I)化合物



(I)

或其药学上可接受的盐的方法;其中

R^1是德糖胺或德糖胺衍生物;

A是$-CH_2-$、$-C(O)-$、$-C(O)O-$、$-C(O)NH-$、$-S(O)_2-$、$-S(O)_2NH-$、$-C(O)NHS(O)_2-$;

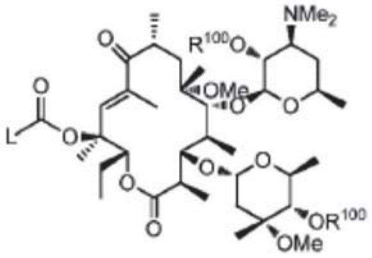
B是$-(CH_2)_n-$,其中n是在0-10范围内的整数;或B是饱和的C_2-C_{10};或B是包含一个或多个烯基或炔基的不饱和的C_2-C_{10};或-A-B-合起来是亚烷基、亚环烷基、或亚芳基;

C代表1或2个在各情况下独立地选自由以下组成的组的取代基:氢、卤素、羟基、酰基、酰氧基、磺酰基、脲基、及氨基甲酰基,以及烷基、烷氧基、杂烷基、芳基、杂芳基、芳基烷基、及杂芳基烷基,其各自任选被取代;并且

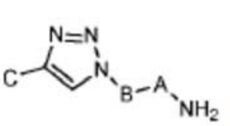
W是氢、F、Cl、Br、I、或OH;

所述方法包括以下步骤

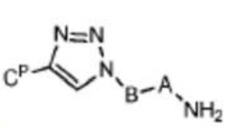
(A)使下式的化合物



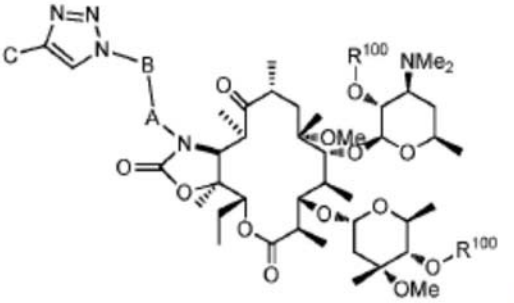
或其盐,其中R^{100}是羟基保护基且L是离去基团,与下式的化合物



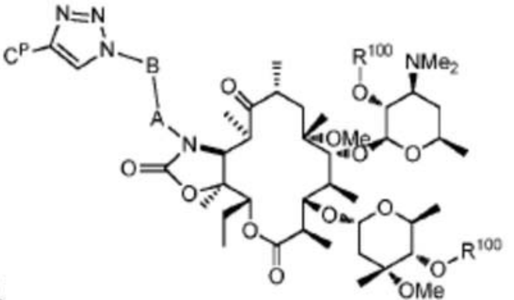
或



或其盐,其中C如本文中所定义且C^P是C的保护形式,和碱接触,以制备下式的化合物

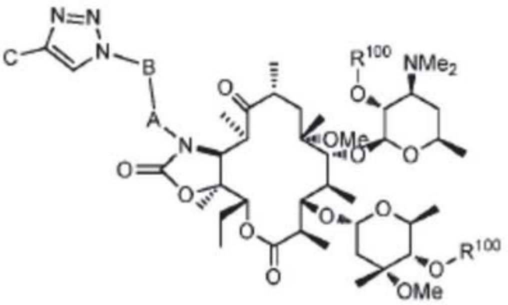


或

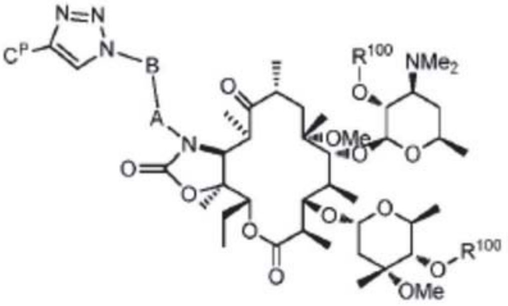


或其盐；或

(B) 使下式的化合物

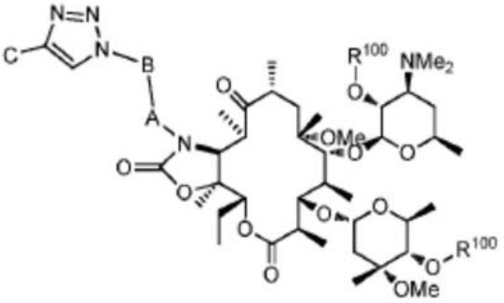


或其盐，与一种或多种保护基形成剂接触以制备下式的化合物

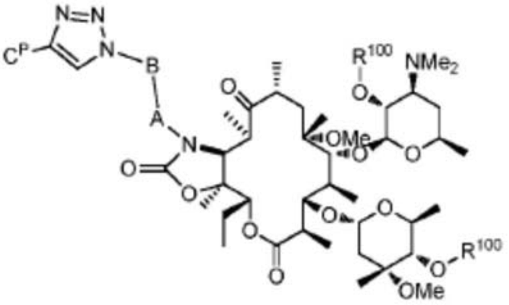


或其盐；或

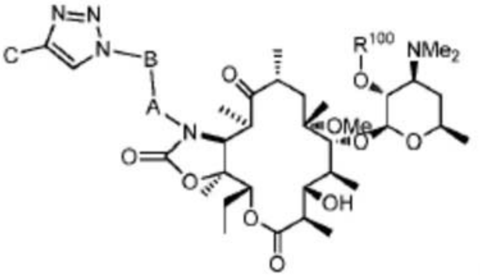
(C) 使下式的化合物



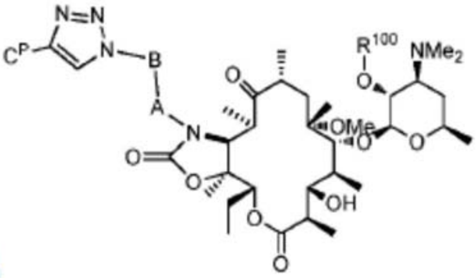
或



或其盐，与酸接触以制备下式的化合物

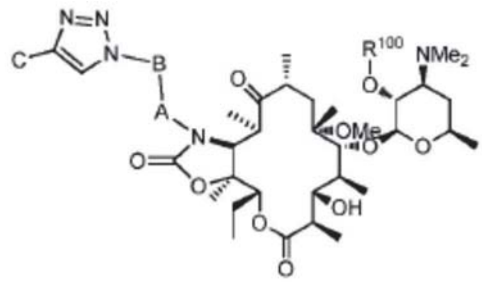


或

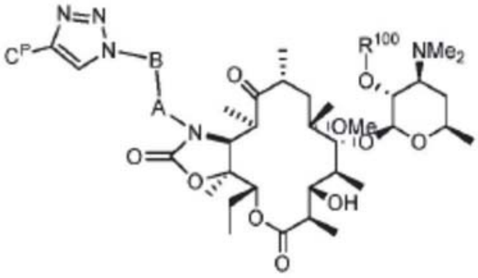


或其盐；或

(D) 使下式的化合物

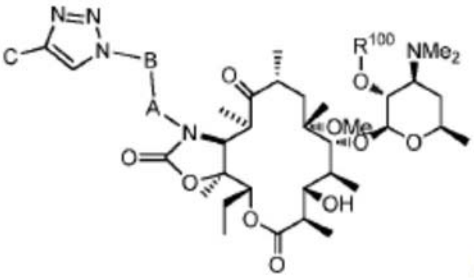


或其盐，与一种或多种保护基形成剂接触以制备下式的化合物

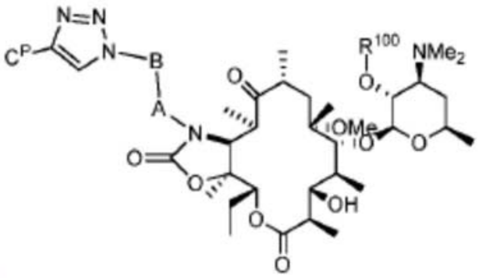


或其盐；或

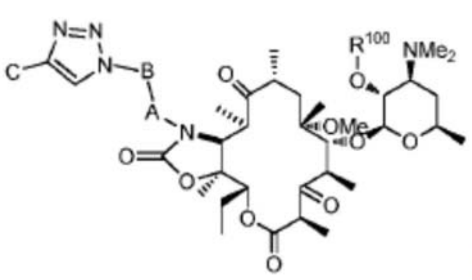
(E) 使下式的化合物



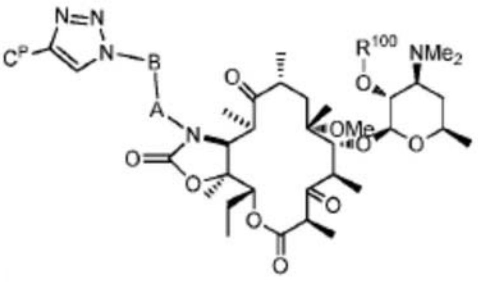
或



或其盐，与氧化剂接触以制备下式的化合物

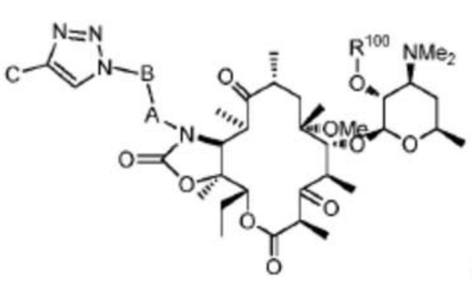


或

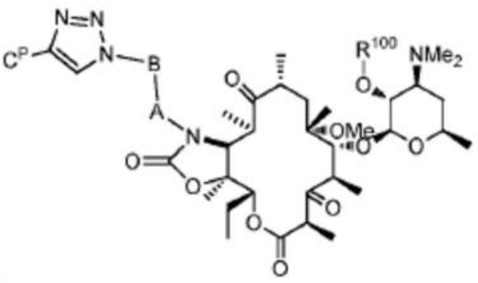


或其盐；或

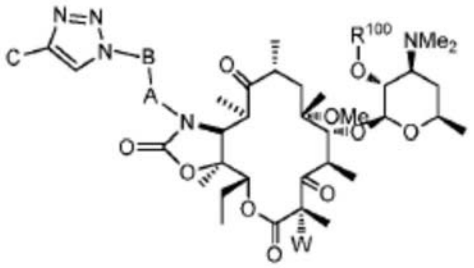
(F) 使下式的化合物



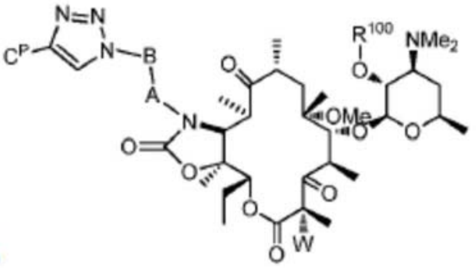
或



或其盐，与羟基化剂或卤化剂接触以制备下式的化合物

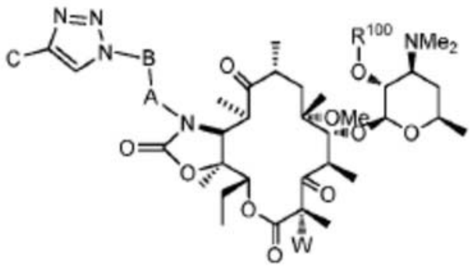


或

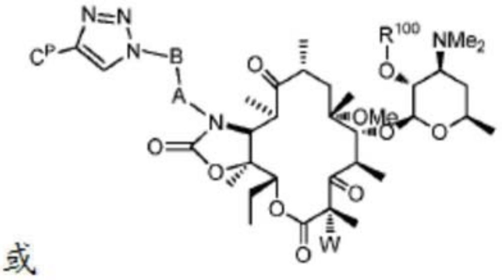


或其盐；或

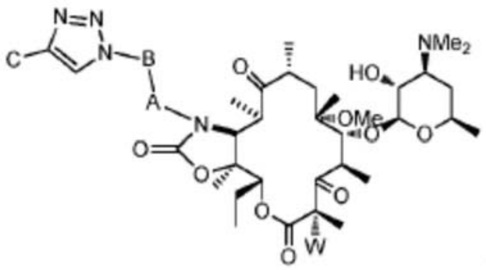
(G1) 使下式的化合物



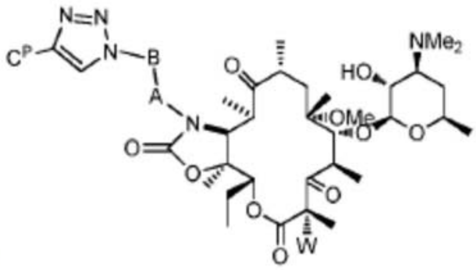
或



或其盐，与羟基去保护剂接触以制备下式的化合物

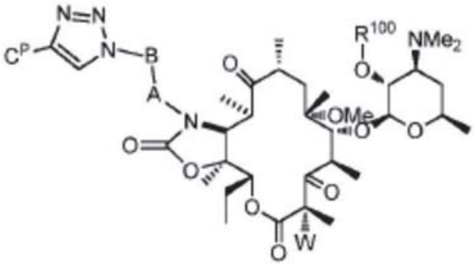


或

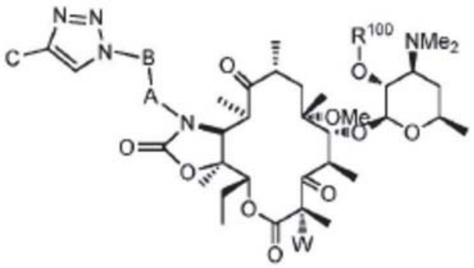


或其盐；或

(G2) 使下式的化合物



或其盐，与一种或多种去保护剂接触以制备相应的去保护的下式化合物

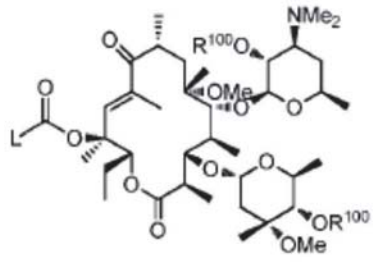


或其盐；或

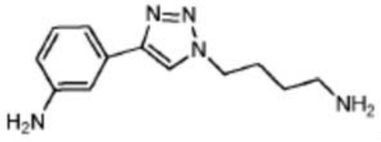
前述的任何组合。

2. 一种用于制备如权利要求 1 所定义的式 (I) 化合物的方法，所述方法包括以下步骤

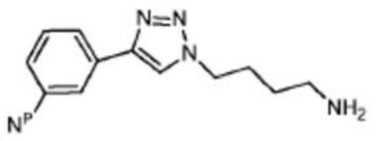
(a) 使下式的化合物



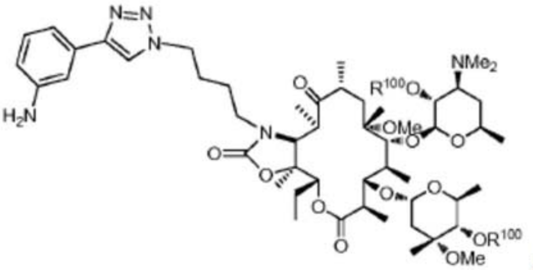
或其盐，其中 R^{100}是羟基保护基，且 L 是离去基团，与下式的化合物



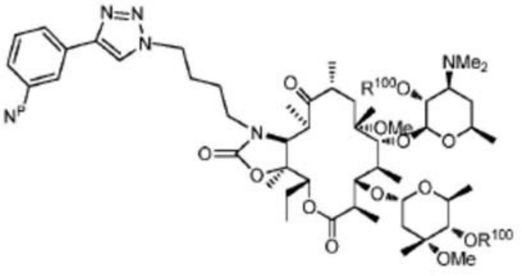
或



或其盐，其中 N^{P}是受保护的胺，和碱接触；以制备下式的化合物

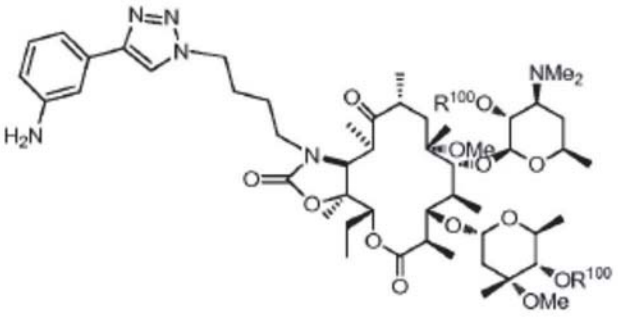


或

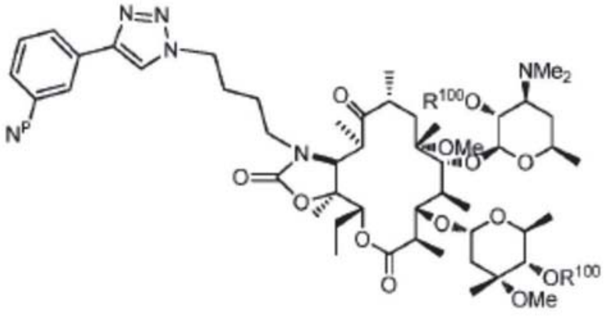


或其盐；或

(b) 使下式的化合物

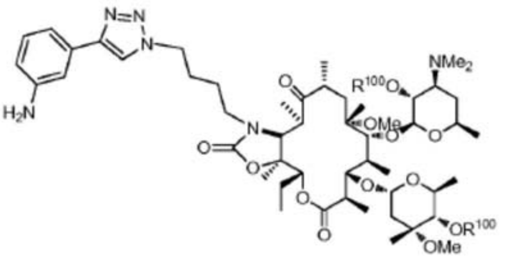


或其盐，与胺保护基形成剂接触以制备下式的化合物

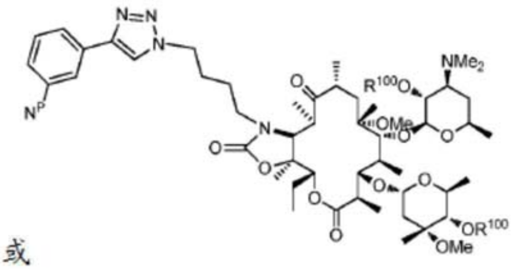


或其盐；或

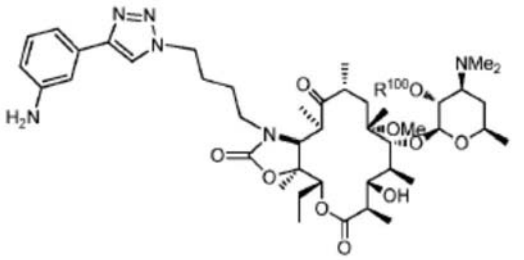
(c) 使下式的化合物



或



或其盐，与酸接触以制备下式的化合物



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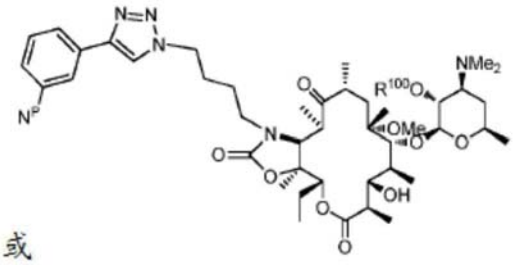
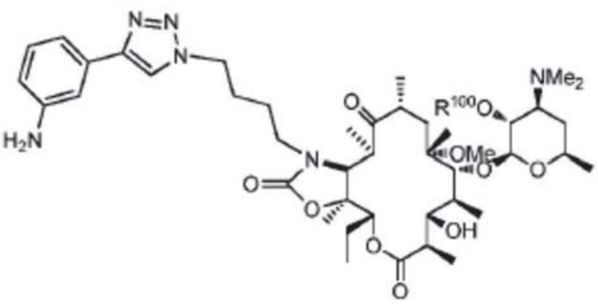
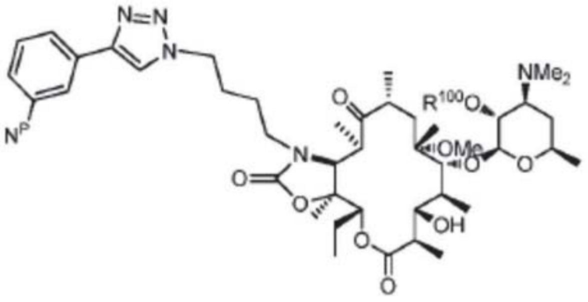


或其盐；或

(d) 使下式的化合物

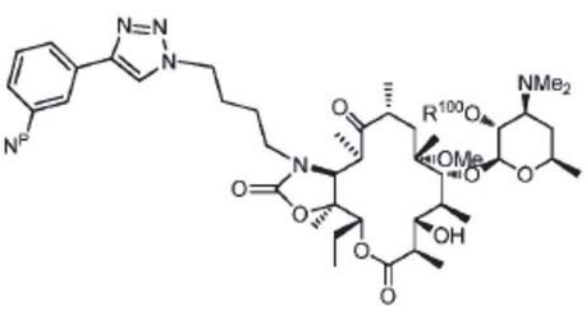


或其盐，与胺保护基形成剂接触以制备下式的化合物

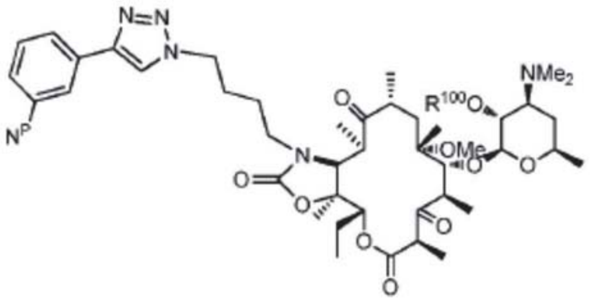


或其盐；或

(e) 使下式的化合物

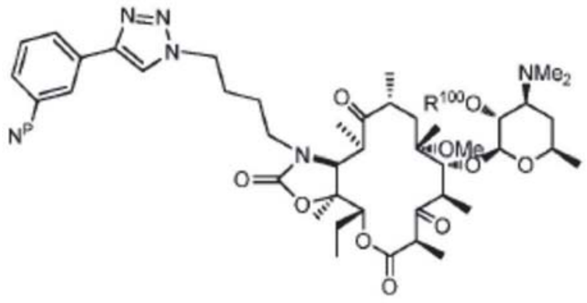


或其盐，与氧化剂接触以制备下式的化合物

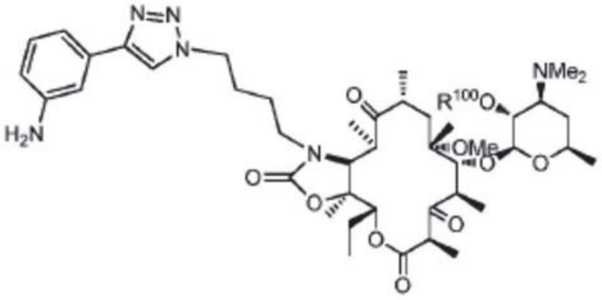


或其盐；或

(f) 使下式的化合物

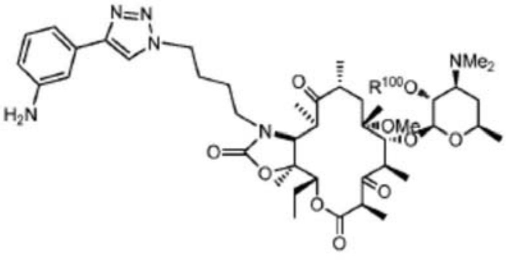


或其盐，与胺去保护剂接触以制备下式的化合物



或其盐；或

(g) 使下式的化合物



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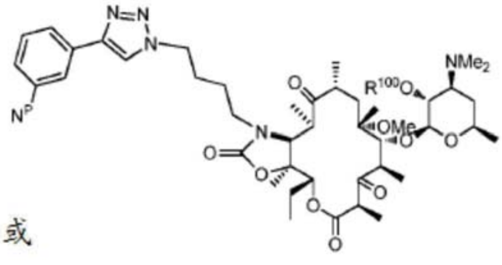
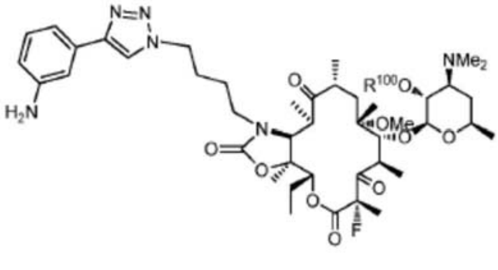


或其盐，与氟化剂接触以制备下式的化合物



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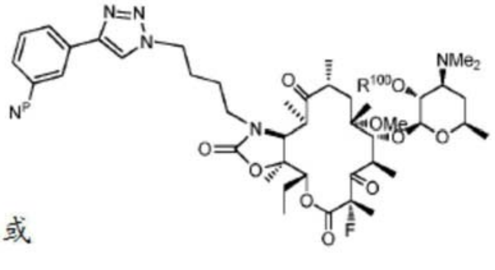
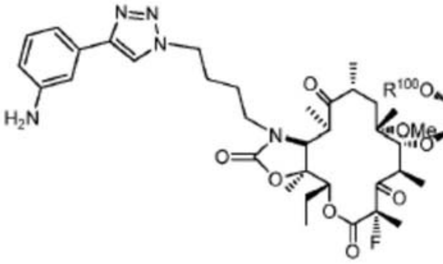


或其盐；或

(h1) 使下式的化合物



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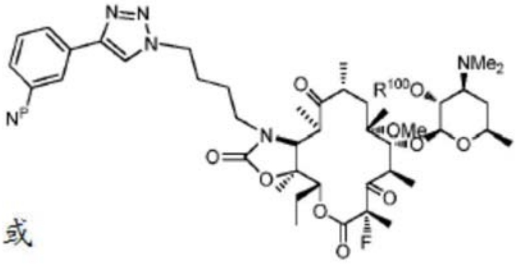
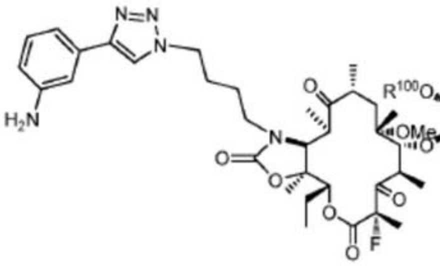


或其盐，与羟基去保护剂接触以制备下式的化合物



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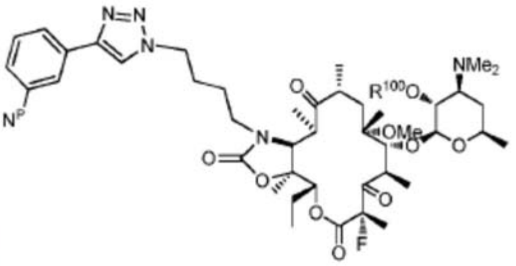
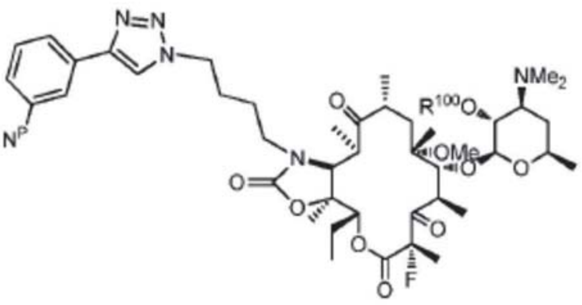
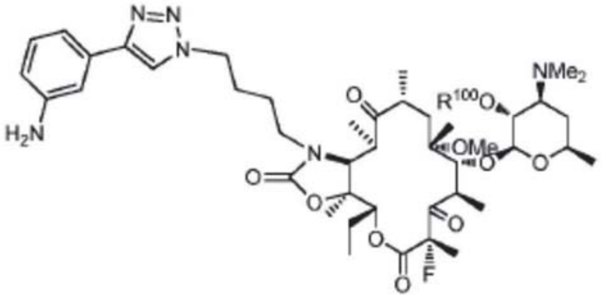


或其盐；或

(h2) 使下式的化合物



或其盐，与胺去保护剂接触以制备下式的化合物

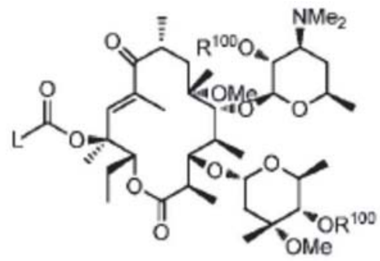


或其盐；或

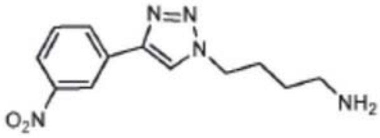
前述的任何组合。

3.如权利要求2所述的方法，其中N^P是$NHC(O)CF_3$。

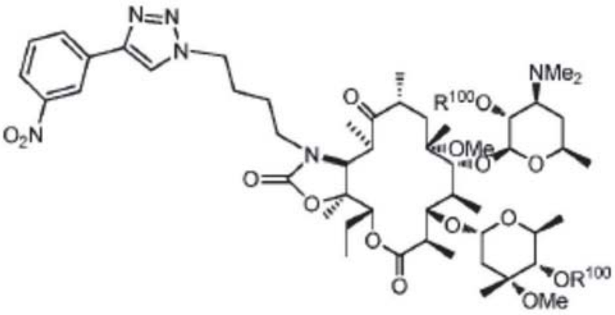
4.一种用于制备如权利要求1所定义的式(I)化合物的方法，所述方法包括以下步骤(a’)使下式的化合物



或其盐，其中 R^{100}是羟基保护基且 L 是离去基团，与下式的化合物

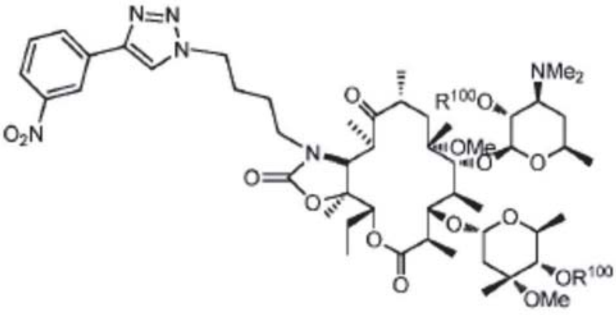


或其盐，和碱接触；以制备下式的化合物

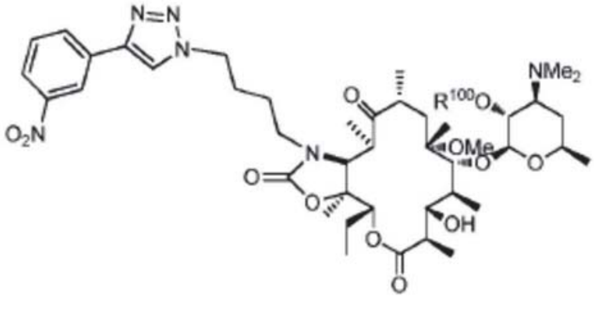


或其盐；或

(b’) 使下式的化合物

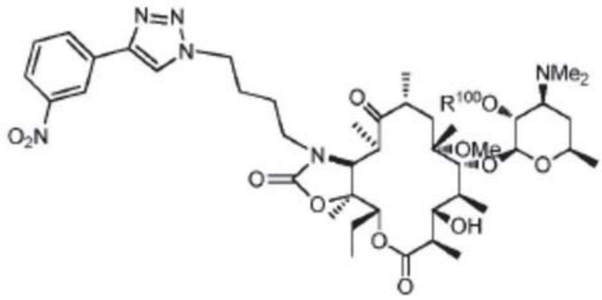


或其盐，与酸接触以制备下式的化合物

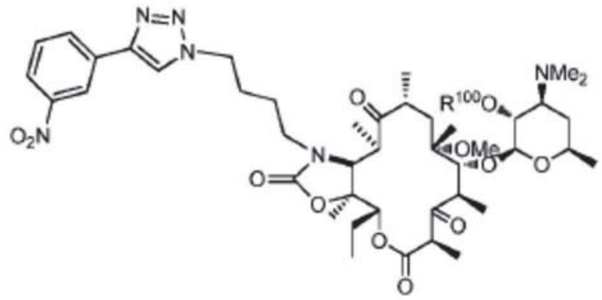


或其盐；或

(c’) 使下式的化合物

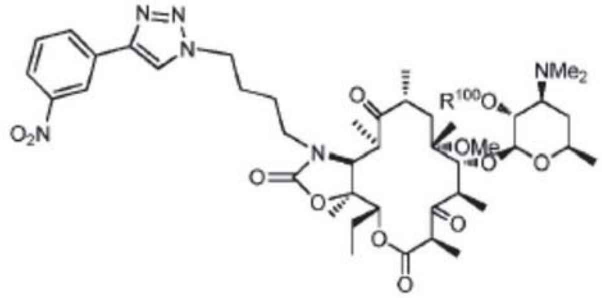


或其盐，与氧化剂接触以制备下式的化合物

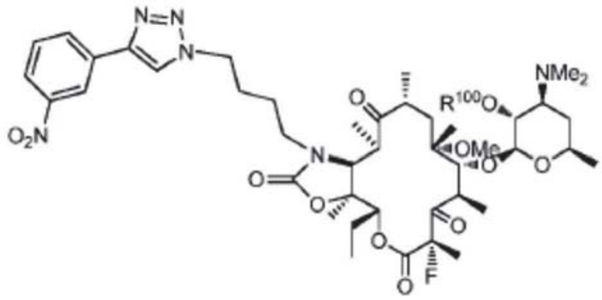


或其盐；或

(d’)使下式的化合物

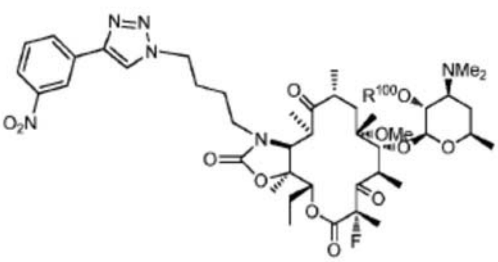


或其盐，与氟化剂接触以制备下式的化合物



或其盐；或

(e’)使下式的化合物



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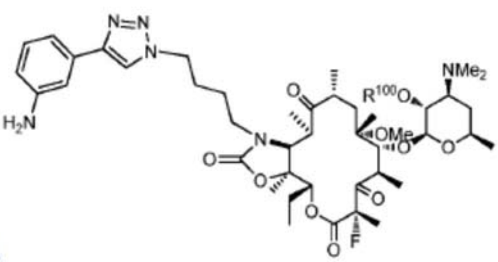
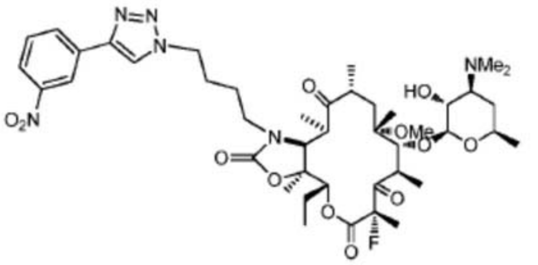


或其盐，与羟基去保护剂接触以制备下式的化合物



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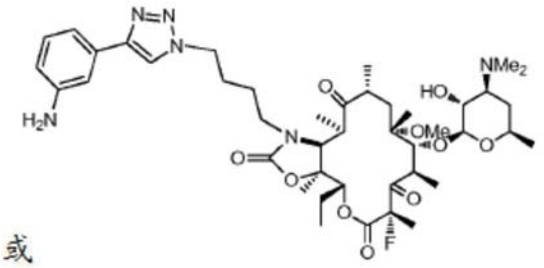
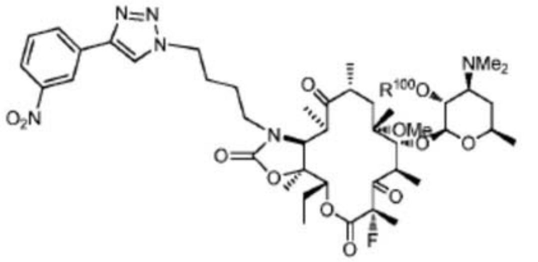
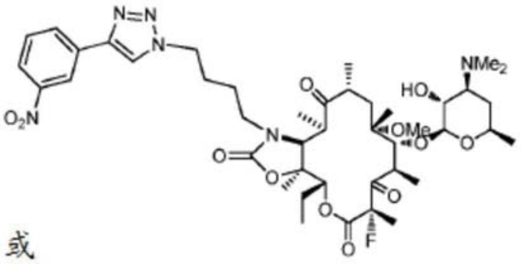


或其盐；或

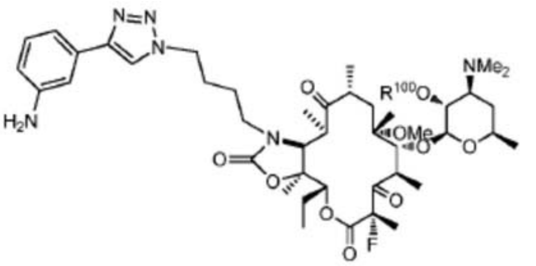
(f’)使下式的化合物



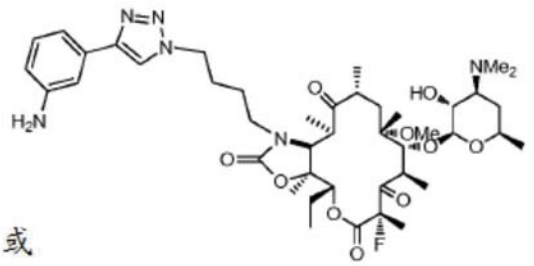
或



或其盐，与还原剂接触以制备下式的化合物



或



或其盐；或

前述的任何组合。

5. 如权利要求1至4中任一项所述的方法，其中所述离去基团是卤基、五氟苯氧基、磺酸酯基如三氟甲磺酸酯基、羟氨基如HOBt或咪唑-1-基。

6. 如权利要求1至4中任一项所述的方法，其中所述离去基团是咪唑-1-基。

7. 如权利要求1至4中任一项所述的方法，其中所述碱是DBU。

8. 如权利要求1至4中任一项所述的方法，其中所述酸是水性HCl，如5％HCl，任选地具有有机共溶剂，如酮，如丙酮。

9. 如权利要求1至4中任一项所述的方法，其中所述酰胺形成剂是TFAA。

10. 如权利要求1至4中任一项所述的方法，其中所述氧化剂是在吡啶、PCC、琼斯氧化、TEMPO/NaOCl、Swern氧化、Dess-Martin试剂或Corey-Kim试剂中的三氟乙酸酐。

11. 如权利要求1至4中任一项所述的方法，其中所述氟化剂是NFSI、F-TEDA、或Selectfluor。

12. 如权利要求1至4中任一项所述的方法，其中所述胺去保护剂是氢和金属催化剂。

13. 如权利要求1至4中任一项所述的方法，其中所述胺去保护剂是氨。

14. 如权利要求1至4中任一项所述的方法，其中所述羟基去保护剂是醇。

15. 如权利要求1至4中任一项所述的方法，其中所述还原剂是氢和金属催化剂。

16. 如权利要求1至4中任一项所述的方法，其中C是芳基、杂芳基、芳基烷基、或杂芳

基烷基，其的每一个任选被取代。

17.如权利要求1至4中任一项所述的方法，其中A是CH_2。

18.如权利要求1至4中任一项所述的方法，其中B是$(CH_2)_n$。

19.如权利要求1至4中任一项所述的方法，其中B是$(CH_2)_n$，且n是在3与4之间的整数。

20.如权利要求1至4中任一项所述的方法，其中B是$(CH_2)_n$，且n是3。

21.如权利要求1至4中任一项所述的方法，其中R^{100}是酰基。

22.如权利要求1至4中任一项所述的方法，其中R^{100}是烷基羰基或任选取代的苯甲酰基。

23.如权利要求1至4中任一项所述的方法，其中R^{100}是乙酰基或苯甲酰基。

24.如权利要求1至4中任一项所述的方法，其中W是H或F。

25.如权利要求1至4中任一项所述的方法，其中W是F。

用于制备大环内酯抗菌剂的收敛方法

[0001] 相关申请的交叉引用

[0002] 本申请根据 35U.S.C.§119(e) 要求 2013 年 3 月 15 日提交的美国临时申请号 61/786,914 的权益和优先权，该申请据此以引用的方式并入本文。

技术领域

[0003] 本文所述的发明涉及用于制备酮内酯抗菌剂的方法。具体说来，本发明涉及用于制备包括 1,2,3- 三唑取代的侧链的酮内酯的中间体和方法。

[0004] 发明背景和概述

[0005] 大环内酯用于各种感染性疾病的用途是众所周知的。红霉素是被引入临床实践中的首个此类化合物。从那时起，另外的大环内酯（包括酮内酯）就因其治疗大范围疾病状态的能力而引起了很多关注。具体说来，大环内酯是用于治疗细菌、原生动物、及病毒感染的疗法的重要组分。另外，大环内酯经常用于对青霉素过敏的患者中。

[0006] 作为其广泛使用的示例，大环内酯化合物被认为能有效用于治疗和预防由广谱细菌和原生动物病原体引起的感染。它们还适用于治疗呼吸道感染和软组织感染。发现大环内酯类抗生素对 β- 溶血性链球菌、肺炎球菌、葡萄球菌、及肠道球菌是有效的。还发现它们对于支原体、分枝杆菌、一些立克次氏体、及衣原体是有效的。

[0007] 大环内酯化合物的特征在于存在大的内酯环，其一般是 14 元、15 元或 16 元大环内酯，一种或多种糖可连接于其上，包括脱氧糖，如克拉定糖和德糖胺。例如，红霉素是包括两个糖部分的 14 元大环内酯。螺旋霉素属于第二代大环内酯化合物，其包括 16 元环。第三代大环内酯化合物包括例如红霉素 A 的半合成衍生物，如阿奇霉素和克拉霉素。最终，酮内酯代表一种较新类别的大环内酯类抗生素，其最近由于其酸稳定性且最重要的是由于其对于对其他大环内酯有耐药性的生物体的优良活性而引起了许多关注。像红霉素一样，酮内酯是以在 C-3 位处的酮基为特征的 14 元环大环内酯衍生物 (Curr.Med.Chem.,“Anti-Infective Agents,”1:15-34(2002))。酮内酯化合物目前还处于临床研究中。

[0008] 在美国专利申请公布号 2006/0100164（其公开内容以引用的方式并入本文）中，Liang 等人描述了一种新的含有三唑的酮内酯化合物系列及其示例性合成。这些新的化合物显示出针对病原生物体的优良活性，包括早已展现对当前疗法的耐药性的那些病原生物体。然而，在本文中已发现，在由 Liang 等人所公开的方法中出现的副反应导致难以去除的杂质和低产率。另外，起始材料杂质也难以去除。那些副反应降低所需化合物的总产率，且那些副产物和杂质可使所需化合物的纯化复杂化。所述副反应的出现和所述杂质的存在在大工业规模下加剧。另外，由 Liang 等人公开的方法包括叠氮化物中间体，其在更大的工业制造规模下可能是不合需要的或代表一个安全问题。由于这些含有三唑的酮内酯化合物在提供用于治疗病原生物体的有益疗法中使用的重要性，所以需要用于其制备的替代和 / 或改进的方法。

[0009] 叠氮化物中间体可通过并入完整侧链的方法而避免。然而，还据报道引入完整的

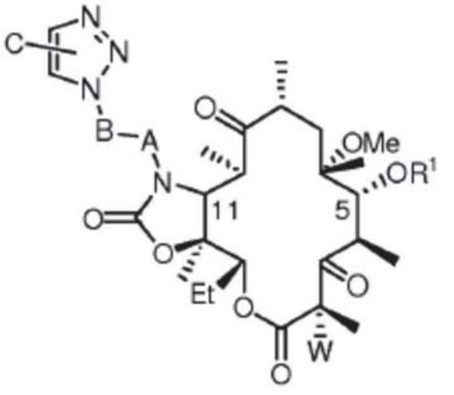
侧链不是可行的方法（参见，Lee 等人，“Process Development of a Novel Azetidinyl Ketolide Antibiotic”Org.Process Res Dev 16:788-797(2012)）。具体说来，据报道引入完整的侧链得到产物的异构混合物。另外，据报道引入完整的侧链仅提供低产率（<20％）。

[0010] 在本文中已出乎意料地发现含有三唑的侧链不会产生产物的异构混合物。在本文中还出乎意料地发现含有三唑的侧链提供高产反应。在本文中还出乎意料地发现如果在除去克拉定糖之前引入侧链，那么获得单一异构体。在本文中还出乎意料地发现如果在除去克拉定糖之前引入侧链，那么所述方法提供高产率。

[0011] 本文描述可在制备式（I）化合物中避免所述副产物的有利的和/或可纯化至更高纯度水平的新方法。另外，本文所述的方法通过继续进行收敛合成路线避免了叠氮化物中间体。

[0012] 在本发明的一个示例性实施方案中，描述用于制备式（I）化合物：

[0013]



(I)

[0014] 及其药学上可接受的盐、溶剂化物、和水合物的方法和中间体；其中

[0015] R^1是德糖胺（desosamine）或德糖胺衍生物；

[0016] A 是 $-CH_2-$、$-C(O)-$、$-C(O)O-$、$-C(O)NH-$、$-S(O)_2-$、$-S(O)_2NH-$、$-C(O)NHS(O)_2-$；

[0017] B 是 $-(CH_2)_n-$，其中 n 是在 0-10 范围内的整数；或 B 是饱和的 C_2-C_{10}；或 B 是可含有一个或多个烯基或炔基的不饱和的 C_2-C_{10}；或 -A-B- 合起来是亚烷基、亚环烷基、或亚芳基；

[0018] C 代表 1 或 2 个在各情况下独立地选自以下的取代基：氢、卤素、羟基、酰基、酰氧基、磺酰基、脲基、及氨基甲酰基，以及烷基、烷氧基、杂烷基、芳基、杂芳基、芳基烷基、及杂芳基烷基，其各自任选被取代；并且

[0019] W 是氢、F、Cl、Br、I、或 OH。

[0020] 在另一示例性实施方案中，在本文中描述用于制备 11-N-[[4-(3-氨基苯基)-1,2,3-三唑-1-基]-丁基]-5-脱氧糖胺基-2-氟-3-氧代红诺霉素 A,11,12-环状氨基甲酸酯的方法和中间体，所述化合物又名 OP-1068、CEM-101、及索利霉素(solithromycin)。

[0021] 在式（I）化合物的另一实施方案中，R^1是包括任选保护的 2’-羟基的德糖胺。在另一实施方案中，R^1是包括受保护的 2’-羟基的德糖胺。在另一实施方案中，保护基是酰基。在另一实施方案中，保护基是空间位阻酰基，如支链烷基、芳基、杂芳基、芳基烷基、芳基烷基、或杂芳基烷基酰基，其各自任选被取代。在另一实施方案中，保护基是任选取代的苯

甲酰基。在另一实施方案中，保护基是苯甲酰基。在另一实施方案中，-A-B- 是亚烷基、亚环烷基、或亚芳基。在另一实施方案中，-A-B- 是亚烷基。在另一实施方案中，-A-B- 是 C_3-C_5 亚烷基。在另一实施方案中，-A-B- 是 C_4亚烷基。在另一实施方案中，-A-B- 是 $-(CH_2)_4-$。在另一实施方案中，C 是任选取代的芳基、杂芳基、芳基烷基、或杂芳基烷基。在另一实施方案中，C 是任选取代的芳基或杂芳基烷基。在另一实施方案中，C 是任选取代的芳基。在另一实施方案中，C 是取代的芳基。在另一实施方案中，C 是氨基取代的芳基。在另一实施方案中，C 是氨基取代的苯基。在另一实施方案中，C 是 3- 氨基苯基。在另一实施方案中，W 是 H 或 F。在另一实施方案中，W 是 F。

[0022] 应理解的是，本文描述先前和之后实施方案的每个组合、和每个选择、及其组合。例如，在另一实施方案中，R^1是包括受保护的 2’- 羟基的德糖胺，其中保护基是酰基；或 R^1是包括受保护的 2’- 羟基的德糖胺，其中保护基是空间位阻酰基；或 R^1是包括受保护的 2’- 羟基的德糖胺，其中保护基是苯甲酰基，且 -A-B- 是 C_3-C_5亚烷基；或 R^1是包括受保护的 2’- 羟基的德糖胺，其中保护基是苯甲酰基，且 -A-B- 是 $-(CH_2)_4-$；或 R^1是包括受保护的 2’- 羟基的德糖胺，其中保护基是苯甲酰基，且 -A-B- 是 $-(CH_2)_4-$，且 C 是任选取代的芳基；或 R^1是包括受保护的 2’- 羟基的德糖胺，其中保护基是苯甲酰基，且 -A-B- 是 $-(CH_2)_4-$，且 C 是 3- 氨基苯基；等等。

[0023] 应理解的是本文所述的方法可有利地以简便和成本有效的方式进行。进一步应理解的是，本文所述的方法可扩大规模至大批量生产。进一步应理解的是，本文所述的方法以比常规方法更少的步骤进行。进一步应理解的是，本文所述的方法以比常规方法更收敛地进行和 / 或需要更短的线性子方法。进一步应理解的是，本文所述的方法可比已知方法伴随地产生更少或不同的副产品。进一步应理解的是，本文所述的方法可以产生比已知方法更高的纯度的本文所述的化合物。

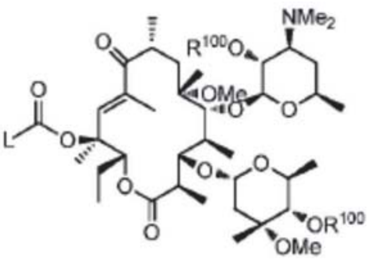
[0024] 发明详述

[0025] 本发明的若干示例性实施方案是通过以下列举的条款来描述：

[0026] 1A. 一种用于制备如本文所述的式 (I) 化合物的方法，所述方法包括以下步骤

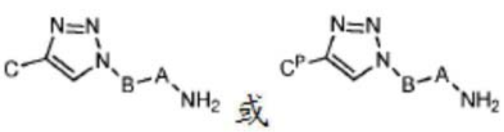
[0027] (A) 使下式的化合物

[0028]



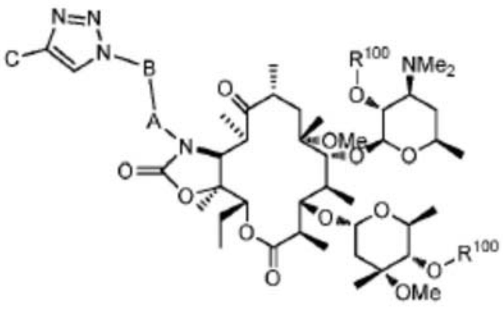
[0029] 或其盐，其中 R^{100}是羟基保护基，且 L 是离去基团，与下式的化合物

[0030]



[0031] 或其盐，其中 C 如本文中所定义，且 C^P是 C 的保护形式，和碱接触以制备下式的化合物

[0032]



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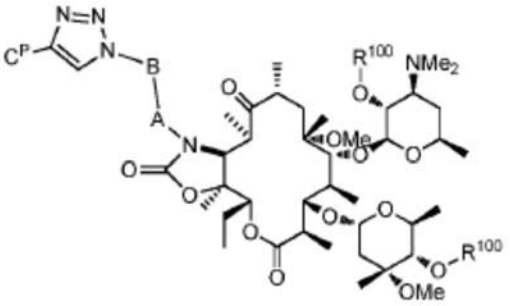
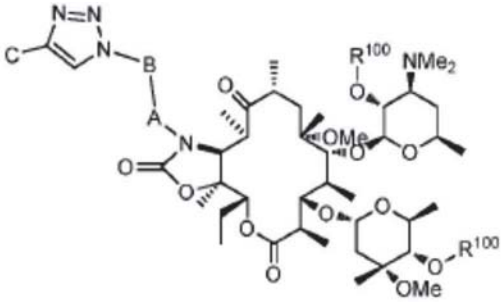


[0033]　或其盐；或

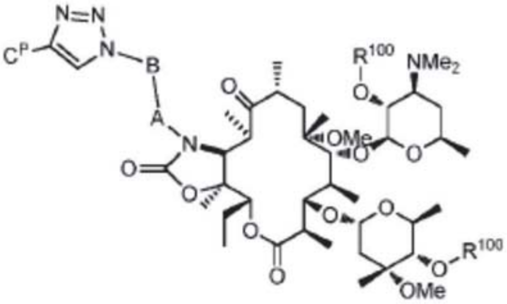
[0034]　(B) 使下式的化合物

[0035]



[0036]　或其盐，与一种或多种保护基形成剂接触以制备下式的化合物

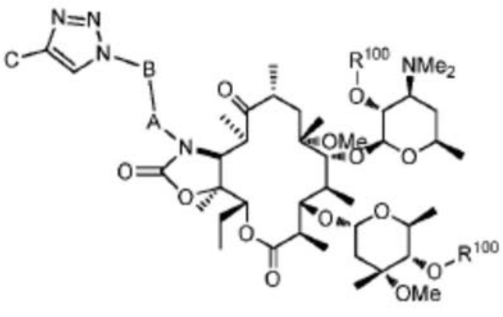
[0037]



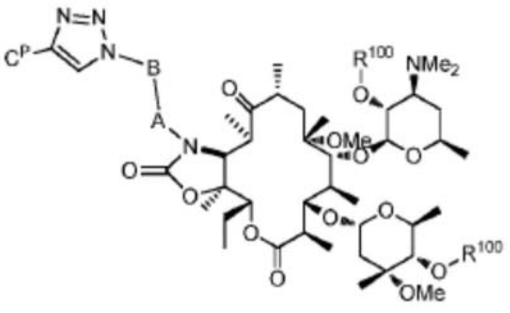
[0038]　或其盐；或

[0039]　(C) 使下式的化合物

[0040]

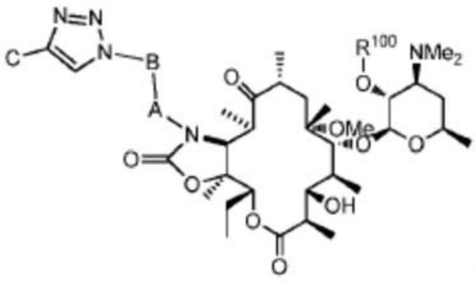


或



[0041]　或其盐，与酸接触以制备下式的化合物

[0042]



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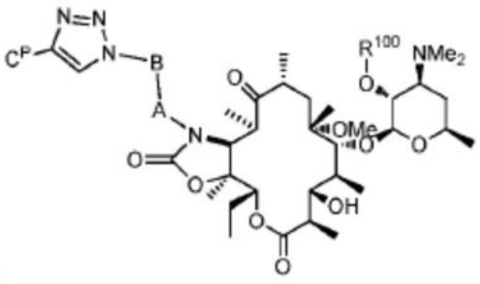
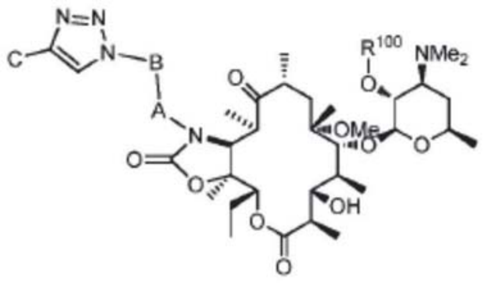


[0043] 或其盐；或

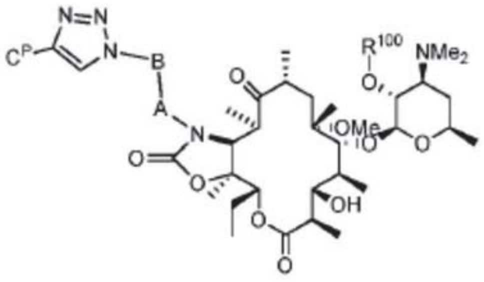
[0044] (D) 使下式的化合物

[0045]



[0046] 或其盐，与一种或多种保护基形成剂接触以制备下式的化合物

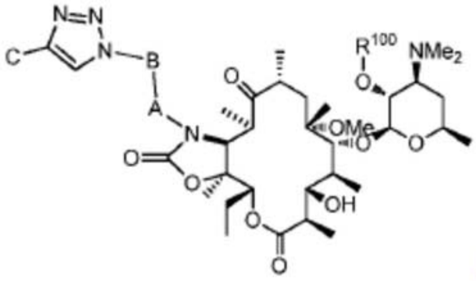
[0047]



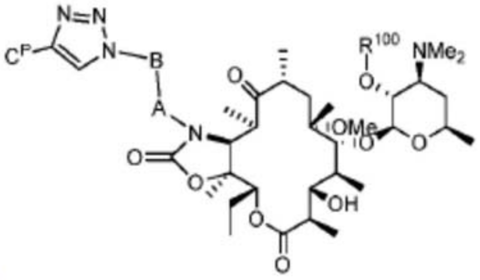
[0048] 或其盐；或

[0049] (E) 使下式的化合物

[0050]

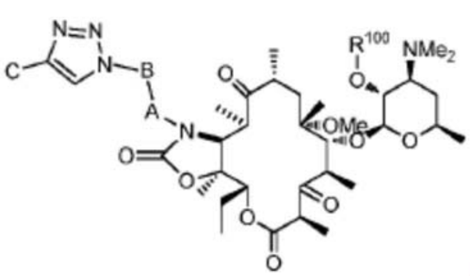


或



[0051] 或其盐，与氧化剂接触以制备下式的化合物

[0052]



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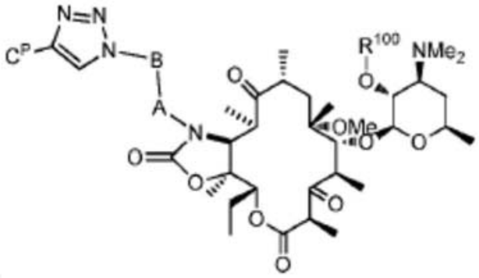
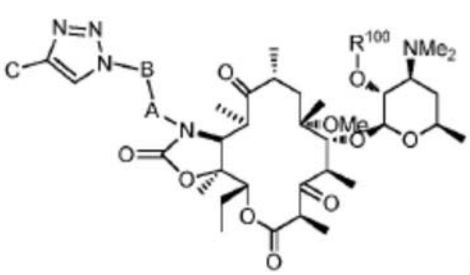


[0053] 或其盐;或

[0054] (F) 使下式的化合物

[0055]



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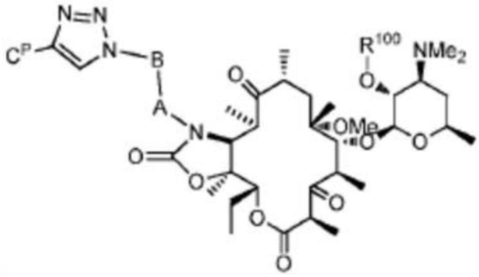
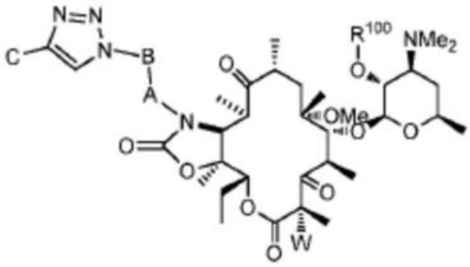


[0056] 或其盐,与羟基化剂或卤化剂接触以制备下式的化合物

[0057]



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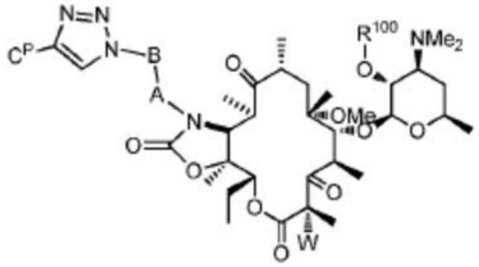
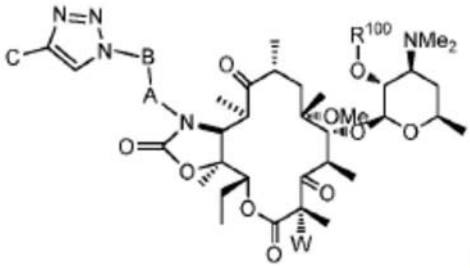


[0058] 或其盐;或

[0059] (G1) 使下式的化合物

[0060]



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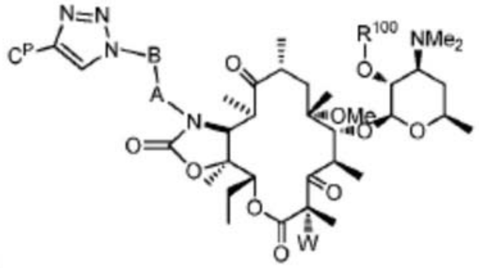
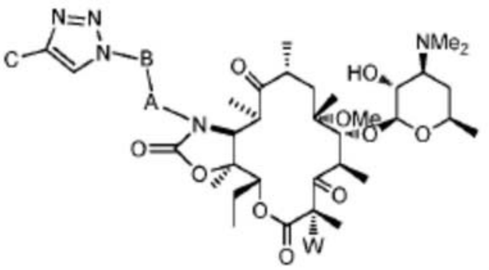


[0061] 或其盐,与羟基去保护剂接触以制备下式的化合物

[0062]



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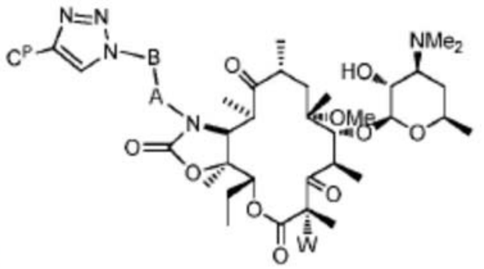
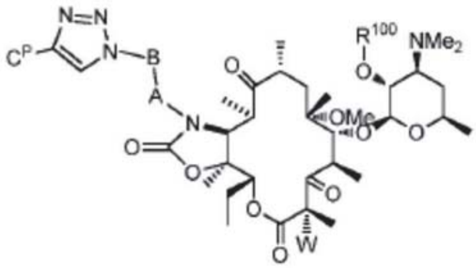


[0063] 或其盐；或

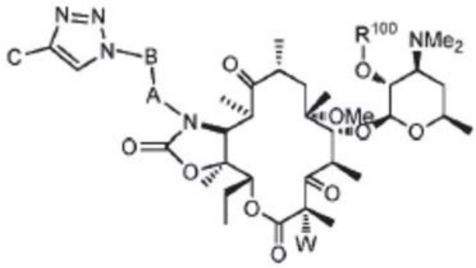
[0064] (G2) 使下式的化合物

[0065]



[0066] 或其盐，与一种或多种去保护剂接触以制备下式的相应的去保护化合物

[0067]



[0068] 或其盐；或

[0069] 前述的任何组合。

[0070] 1B. 如条款 1A 所述的方法，其中步骤 (G1) 和 (G2) 依次地、同时、或同时地进行。

[0071] 1C. 如条款 1A 所述的方法，其中步骤 (G1) 和 (G2) 同时地进行。

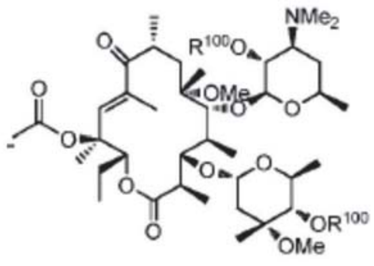
[0072] 1D. 如条款 1 所述的方法，其中所述去保护剂和所述羟基去保护剂是相同的。

[0073] 1E. 如条款 1 所述的方法，其中 C^P是 N^P取代的苯基。

[0074] 2A. 一种用于制备如本文所述的式 (I) 化合物的方法，所述方法包括以下步骤

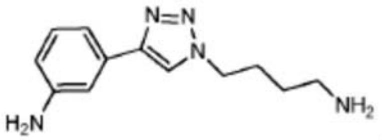
[0075] (a) 使下式的化合物

[0076]

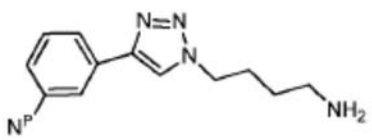


[0077] 或其盐，其中 R^{100}是羟基保护基，且 L 是离去基团，与下式的化合物

[0078]

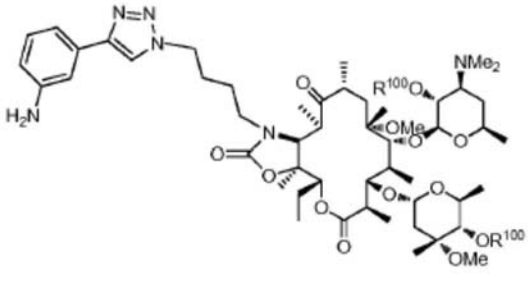


或

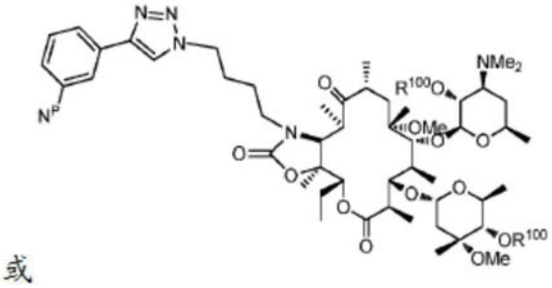


[0079] 或其盐，其中 N^P是受保护的胺，和碱接触；以制备下式的化合物

[0080]



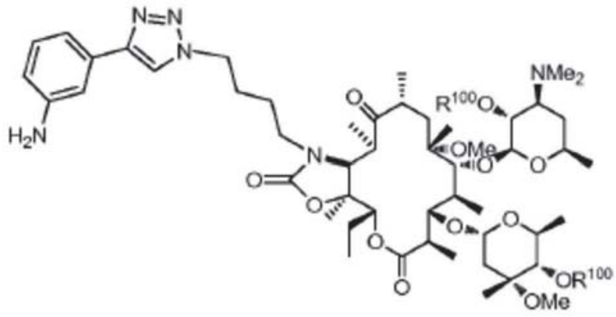
或



[0081] 或其盐；或

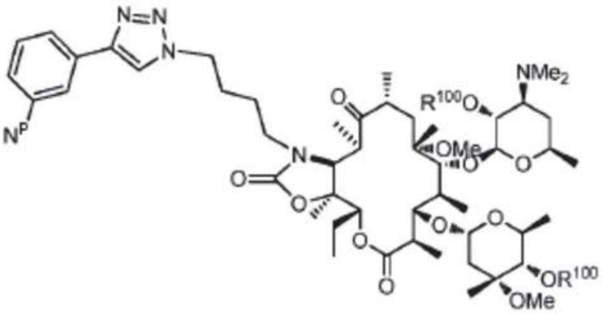
[0082] (b) 使下式的化合物

[0083]



[0084] 或其盐，与胺保护基形成剂接触以制备下式的化合物

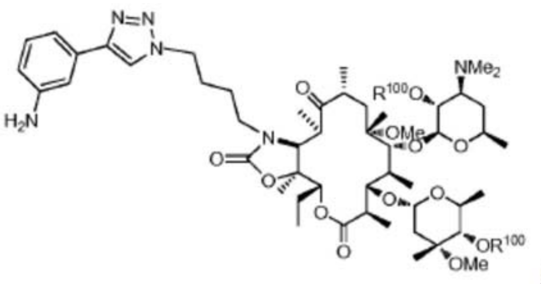
[0085]



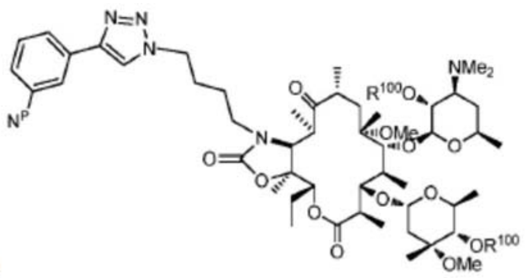
[0086] 或其盐；或

[0087] (c) 使下式的化合物

[0088]

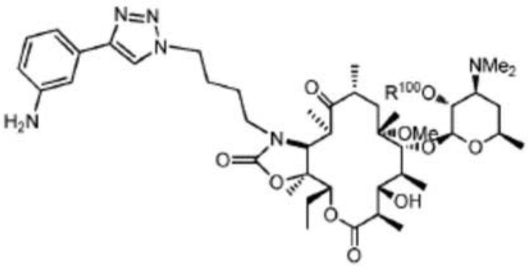


或

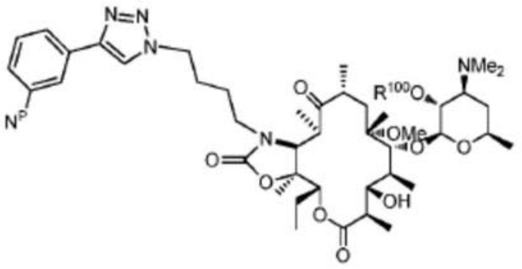


[0089] 或其盐，与酸接触以制备下式的化合物

[0090]



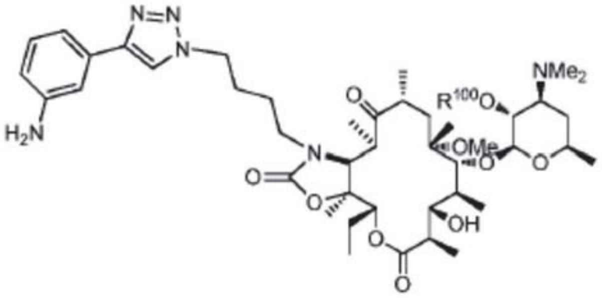
或



[0091] 或其盐；或

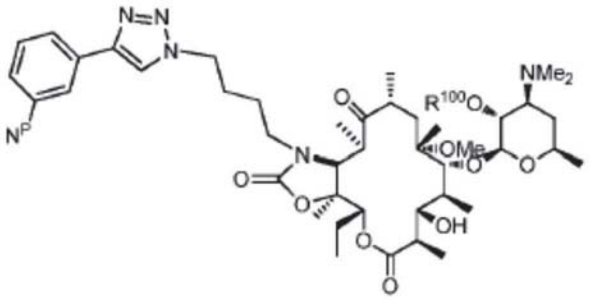
[0092] (d) 使下式的化合物

[0093]



[0094] 或其盐，与胺保护基形成剂接触以制备下式的化合物

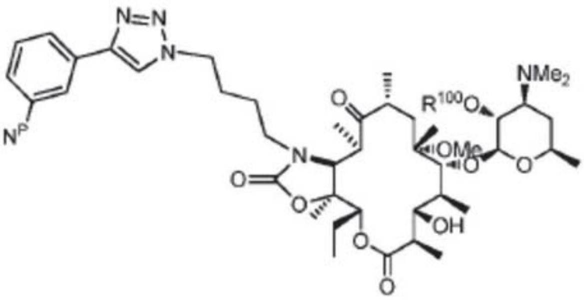
[0095]



[0096] 或其盐；或

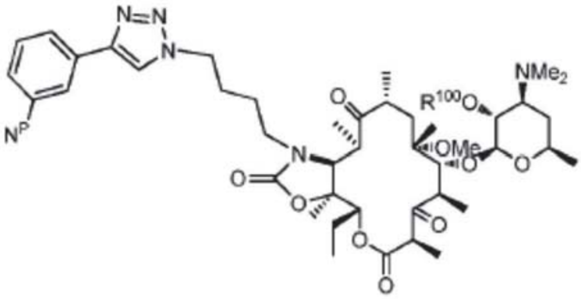
[0097] (e) 使下式的化合物

[0098]



[0099] 或其盐，与氧化剂接触以制备下式的化合物

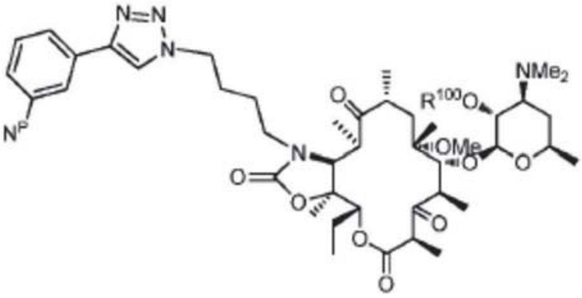
[0100]



[0101] 或其盐；或

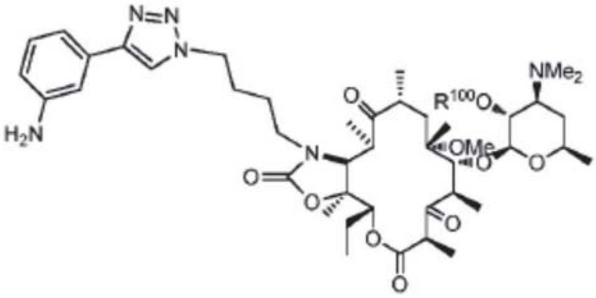
[0102] (f) 使下式的化合物

[0103]



[0104] 或其盐，与胺去保护剂接触以制备下式的化合物

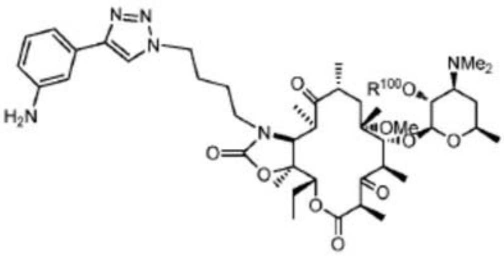
[0105]



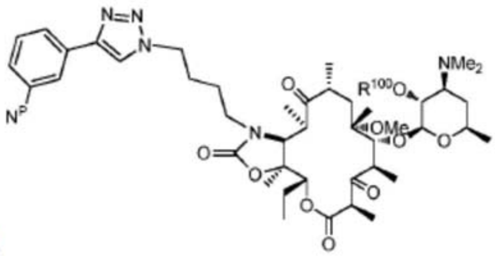
[0106] 或其盐；或

[0107] (g) 使下式的化合物

[0108]

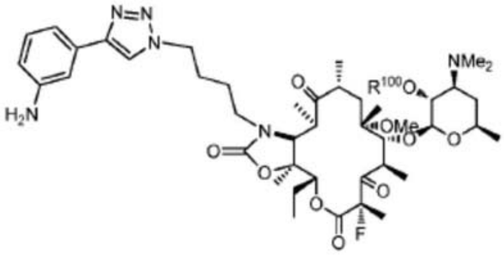


或

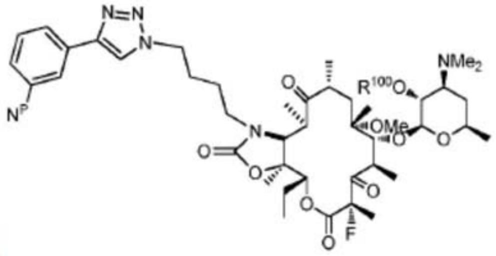


[0109] 或其盐，与氟化剂接触以制备下式的化合物

[0110]



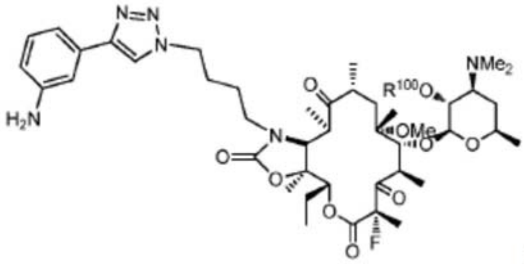
或



[0111] 或其盐；或

[0112] (h1) 使下式的化合物

[0113]



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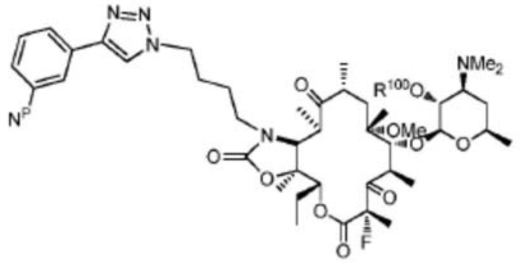
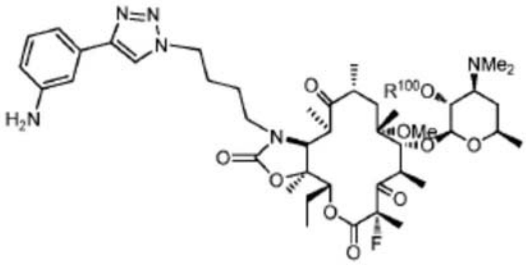


[0114] 或其盐，与羟基去保护剂接触以制备下式的化合物

[0115]



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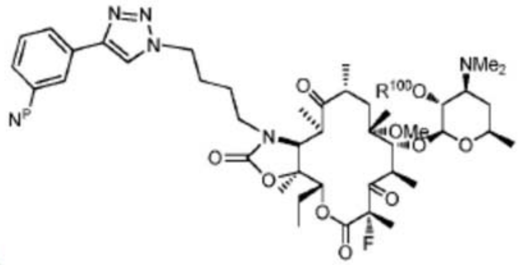
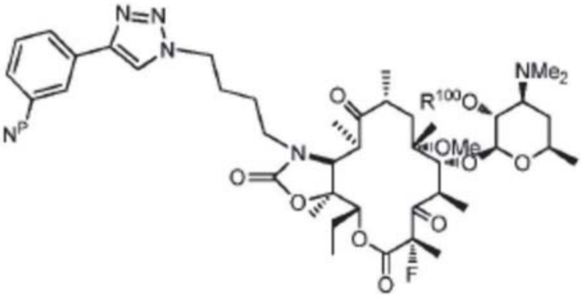


[0116] 或其盐；或

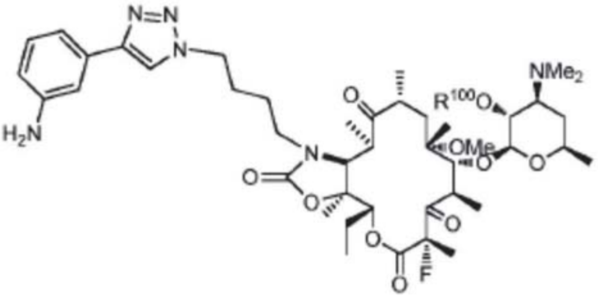
[0117] (h2) 使下式的化合物

[0118]



[0119] 或其盐，与胺去保护剂接触以制备下式的化合物

[0120]



[0121] 或其盐；或

[0122] 前述的任何组合。

[0123] 2B. 如条款 2A 所述的方法，其中步骤 (h1) 和 (h2) 依次地、同时、或同时地进行。

[0124] 2C. 如条款 2A 所述的方法，其中步骤 (h1) 和 (h2) 同时地进行。

[0125] 3. 如条款 2 所述的方法，其中所述胺保护基形成剂是酰化剂或酰胺、氨基甲酸酯、或脲形成剂。

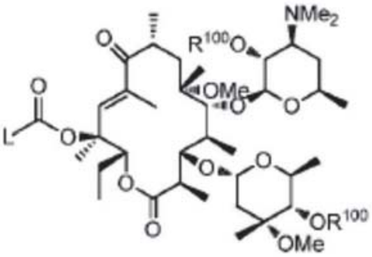
[0126] 4. 如条款 2 至 3 中任一项所述的方法，其中所述胺去保护剂和所述羟基去保护剂是相同的，如氨或氢氧化铵和溶剂。

[0127] 5. 如条款 1 至 4 中任一项所述的方法，其中 N^P是 $NHC(O)CF_3$。

[0128] 6A. 一种用于制备如本文所述的式 (I) 化合物的方法，所述方法包括以下步骤

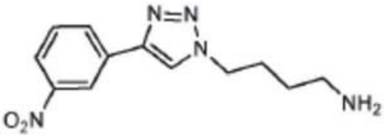
[0129] (a’) 使下式的化合物

[0130]



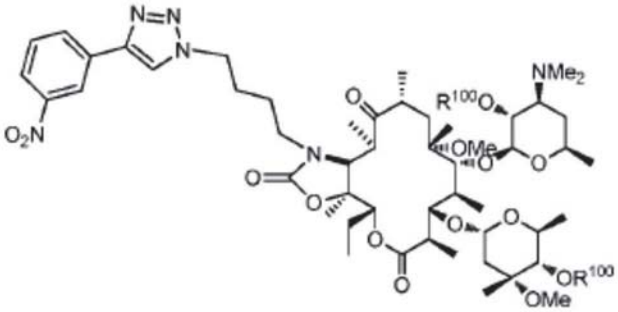
[0131] 或其盐，其中 R^{100}是羟基保护基，且 L 是离去基团，与下式的化合物

[0132]



[0133] 或其盐，和碱接触；以制备下式的化合物

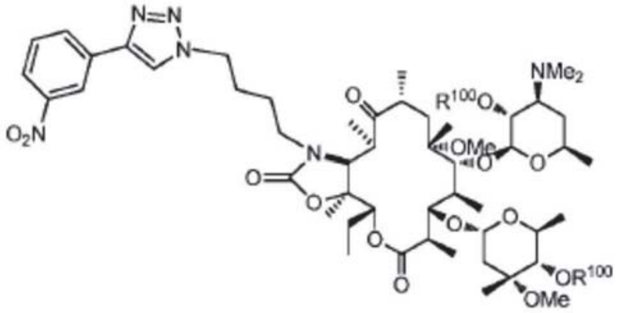
[0134]



[0135] 或其盐；或

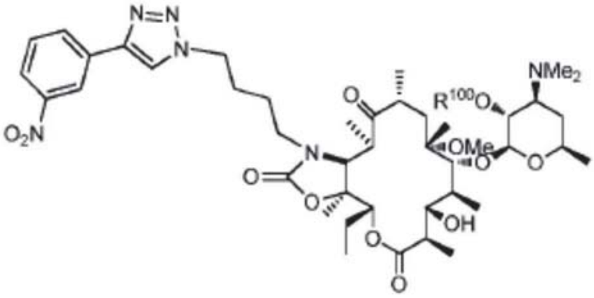
[0136] (b’)使下式的化合物

[0137]



[0138] 或其盐，与酸接触以制备下式的化合物

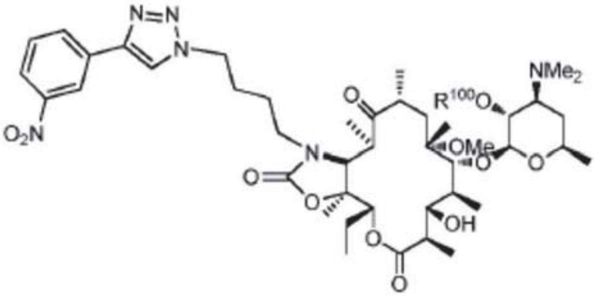
[0139]



[0140] 或其盐；或

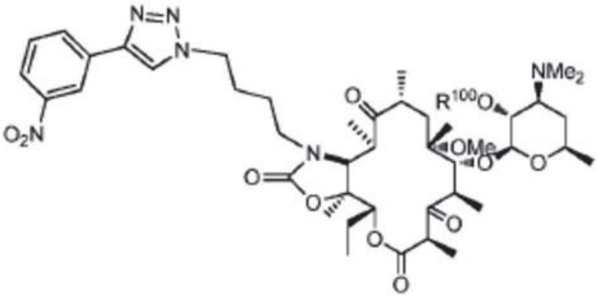
[0141] (c’)使下式的化合物

[0142]



[0143] 或其盐，与氧化剂接触以制备下式的化合物

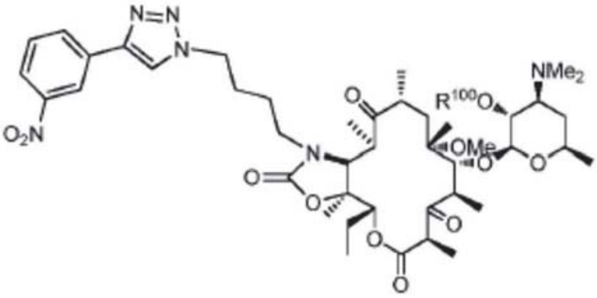
[0144]



[0145] 或其盐；或

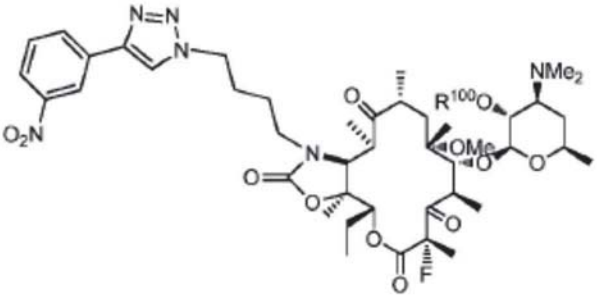
[0146] (d’)使下式的化合物

[0147]



[0148] 或其盐，与氟化剂接触以制备下式的化合物

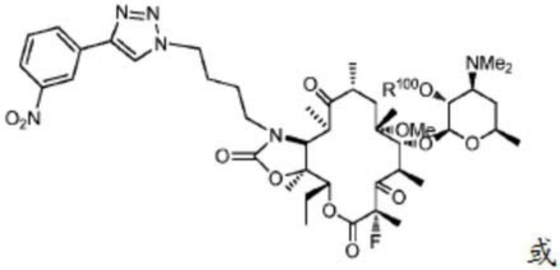
[0149]



[0150] 或其盐；或

[0151] (e’)使下式的化合物

[0152]



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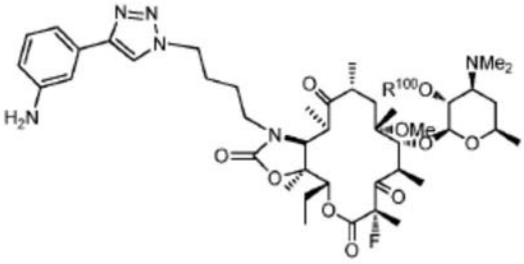
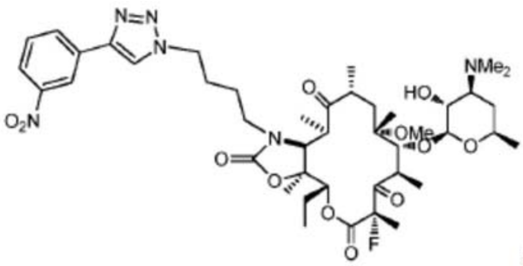


[0153] 或其盐，与羟基去保护剂接触以制备下式的化合物

[0154]



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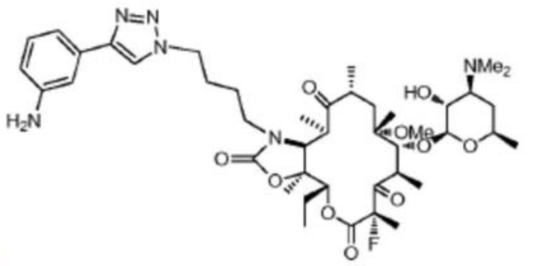
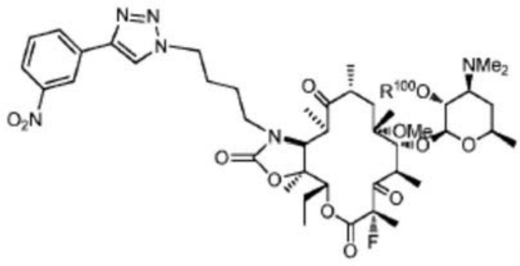


[0155]　或其盐 ;或

[0156]　(f’) 使下式的化合物

[0157]



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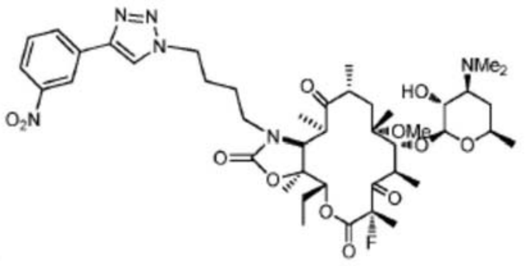
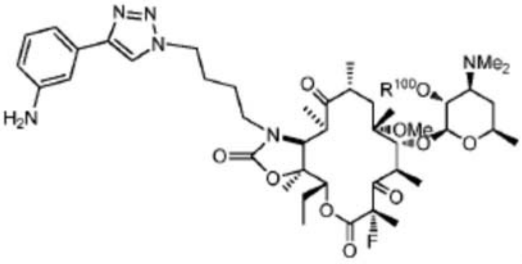


[0158]　或其盐,与还原剂接触以制备下式的化合物

[0159]



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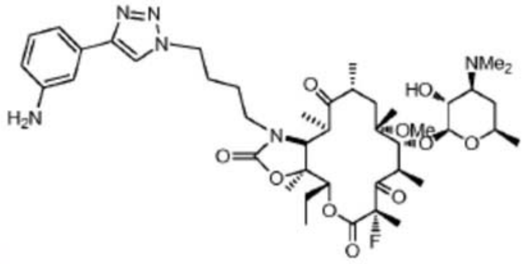


[0160]　或其盐 ;或

[0161]　前述的任何组合。

[0162]　6B. 如条款 6A 所述的方法,其中步骤 (e’) 和 (f’) 依次地、同时、或同时地进行。

[0163]　6C. 如条款 6A 所述的方法,其中步骤 (e’) 和 (f’) 同时地进行。

[0164]　7. 如条款 6 所述的方法,其中所述羟基去保护剂和所述还原剂是相同的。

[0165]　8. 如条款 1 至 7 中任一项所述的方法,其中所述离去基团是卤基、五氟苯氧基、磺酸酯基如三氟甲磺酸酯基、羟氨基如 HOBt、或咪唑 -1- 基。

[0166]　9. 如条款 1 至 8 中任一项所述的方法,其中所述离去基团是咪唑 -1- 基。

[0167]　10. 如条款 1 至 9 中任一项所述的方法,其中所述碱是 DBU。

[0168]　11A. 如条款 1 至 10 中任一项所述的方法,其中所述酸是水性 HCl,如 5% HCl,任选地具有有机共溶剂,如酮,如丙酮。

[0169]　11B. 如条款 1 至 10 中任一项所述的方法,其中所述酸是在有机共溶剂中的 HCl,所述有机共溶剂如,酮如丙酮、或醇如甲醇、或其组合。

[0170]　12. 如条款 1 至 11 中任一项所述的方法,其中 N^P是酰胺或氨基甲酸酯,如 Bz-NH、$CF_3C(O)$-NH、Cbz-NH、Boc-NY、Fmoc-NY、BsMoc-NH、三苯甲基 -NH、MeO 三苯甲基 -NH 等等。

[0171]　13. 如条款 1 至 12 中任一项所述的方法,其中所述胺保护基形成剂是 TFAA。

[0172] 14. 如条款 1 至 12 中任一项所述的方法，其中所述胺保护基形成剂是苯甲酰氯。

[0173] 15. 如条款 1 至 12 中任一项所述的方法，其中所述胺保护基形成剂是 Boc- 酸酐。

[0174] 16. 如条款 1 至 12 中任一项所述的方法，其中所述胺保护基形成剂是 Fmoc 氯化物。

[0175] 17. 如条款 1 至 12 中任一项所述的方法，其中所述受保护的胺是在碱如 TEA 的存在下形成。

[0176] 18. 如条款 1 至 17 中任一项所述的方法，其中所述氧化剂是在吡啶、PCC、琼斯氧化、TEMPO/NaOCl、Swern 氧化、Dess-Martin 试剂或 Corey-Kim 试剂中的三氟乙酸酐。

[0177] 19. 如条款 1 至 17 中任一项所述的方法，其中所述氧化剂是 N- 氯代琥珀酰亚胺 (NCS)/DMS。

[0178] 20. 如条款 1 至 19 中任一项所述的方法，其中所述氟化剂是 NFSI、F-TEDA、或 Selectfluor。

[0179] 21. 如条款 1 至 20 中任一项所述的方法，其中所述胺去保护剂是酰胺水解剂、裂解剂、或除去剂。

[0180] 22. 如条款 1 至 20 中任一项所述的方法，其中所述胺去保护剂是氢，如氢气或原位产生的氢，如通过转移氢化、如通过转移氢化剂像甲酸、甲酸铵等等、以及金属催化剂。

[0181] 23. 如条款 1 至 20 中任一项所述的方法，其中所述胺去保护剂是氨、氨水、或含有有机共溶剂如醇（如甲醇）的氨或氨水。

[0182] 24. 如条款 1 至 20 中任一项所述的方法，其中所述胺去保护剂是氨基甲酸酯水解剂、裂解剂、或除去剂。

[0183] 25. 如条款 1 至 24 中任一项所述的方法，其中所述去保护剂是酸，如 TFA。

[0184] 26. 如条款 1 至 25 中任一项所述的方法，其中所述羟基去保护剂是酯水解剂、裂解剂、或除去剂。

[0185] 27. 如条款 1 至 25 中任一项所述的方法，其中所述羟基去保护剂是醇，如甲醇。

[0186] 28. 如条款 1 至 27 中任一项所述的方法，其中所述还原剂是氢，如氢气或原位产生的氢，如通过转移氢化、如通过转移氢化剂像甲酸、甲酸铵等等、以及金属催化剂。

[0187] 29. 如条款 28 所述的方法，其中所述金属催化剂是 5％ Pd-C、5％ Pt-C、10％ Pd-C、10％ Pd-C、Pearlman 氏催化剂、20％ Pd(OH)2、兰尼镍、海绵镍、铁等等。

[0188] 30. 如条款 1 至 29 中任一项所述的方法，其中 C 是芳基、杂芳基、芳基烷基、或杂芳基烷基，其各自任选被取代。

[0189] 31. 如条款 1 至 30 中任一项所述的方法，其中 A 是 CH_2。

[0190] 32. 如条款 1 至 31 中任一项所述的方法，其中 B 是 $(CH_2)_n$。

[0191] 33. 如条款 1 至 31 中任一项所述的方法，其中 B 是 $(CH_2)_n$，且 n 是在 2 与 6 之间的整数。

[0192] 34. 如条款 1 至 31 中任一项所述的方法，其中 B 是 $(CH_2)_n$，且 n 是在 2 与 5 之间的整数。

[0193] 35. 如条款 1 至 31 中任一项所述的方法，其中 B 是 $(CH_2)_n$，且 n 是在 3 与 6 之间的整数。

[0194] 36. 如条款 1 至 31 中任一项所述的方法，其中 B 是 $(CH_2)_n$，且 n 是在 3 与 5 之间的

整数。

[0195] 37. 如条款1至31中任一项所述的方法，其中B是$(CH_2)_n$，且n是在3与4之间的整数。

[0196] 38. 如条款1至31中任一项所述的方法，其中B是$(CH_2)_n$，且n是3。

[0197] 39. 如条款1至38中任一项所述的方法，其中R^{100}是酰基。

[0198] 40. 如条款1至38中任一项所述的方法，其中R^{100}是烷基羰基或任选取代的苯甲酰基。

[0199] 41. 如条款1至38中任一项所述的方法，其中R^{100}是乙酰基或苯甲酰基，或R^{100}是苯甲酰基。

[0200] 42. 如条款1至41中任一项所述的方法，其中W是H或F。

[0201] 43. 如条款1至41中任一项所述的方法，其中W是F。

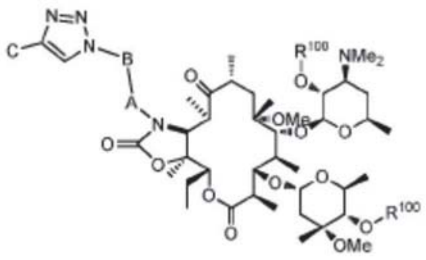
[0202] 在另一示例性实施方案中，R^{100}是羟基保护基，如酰基。另外的羟基保护基描述于Greene&Wuts，“Protective Groups in Organic Synthesis，”第2版John Wiley&Sons，Inc.中，其公开内容以引用的方式并入本文。在另一实施方案中，R100是这样一种另外的羟基保护基。在另一示例性实施方案中，R^{100}是空间位阻酰基；用空间位阻酰化剂R^{100}-L形成，其中R^{100}是空间位阻酰基且L是离去基团或活化基团，以形成相应的2’-酰基衍生物。

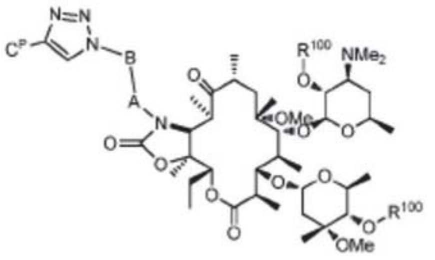
[0203] 示例性空间位阻酰基或二酰基衍生物包括但不限于环己基羰基、苯甲酰基、新戊酰基(neopentoyl)、新戊酰基(pivaloyl)等等。用于形成酰基衍生物的广泛多种活化基团可用于制备所需的酰化剂，包括但不限于酸酐、氯化物、三氟甲磺酸酯、溴化物等等。一方面，空间位阻酰化剂是苯甲酸酐、或等价活化的苯甲酰基试剂，其能够在2’或2’和4’位处形成苯甲酰酯。在另一实施方案中，R^{100}是任选取代的苯甲酰基，且所述方法包括任选取代的苯甲酸酐、或等价活化的任选取代的苯甲酰化试剂，其能够形成任选取代的苯甲酰酯。

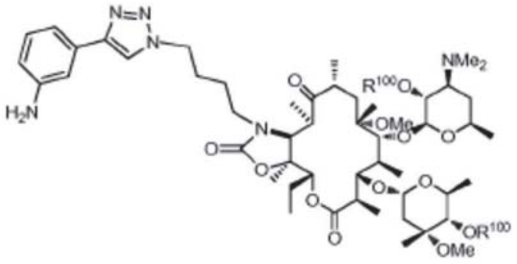
[0204] 酰化一般在溶剂和碱存在下进行。示例性溶剂包括但不限于乙酸乙酯、二氯甲烷、丙酮、吡啶等等，及其混合物。示例性碱包括但不限于无机碱，如碳酸氢钠和碳酸氢钾及碳酸钠和碳酸钾、氢氧化钠和氢氧化钾等等，及其混合物；及胺碱，如吡啶、二甲基氨基吡啶(DMAP)、三乙胺(TEA)、二异丙基乙胺(DIPEA，Hünigs碱)、1,4-二氮杂二环[2.2.2]辛烷(DABCO)等等，及其混合物。反应可在多个温度下进行，如在约0℃至约60℃的范围内，且示例性地，在约10℃至约30℃的范围内。

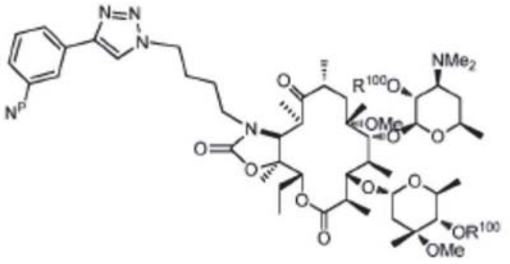
[0205] 在另一示例性实施方案中，描述用于制备下式化合物

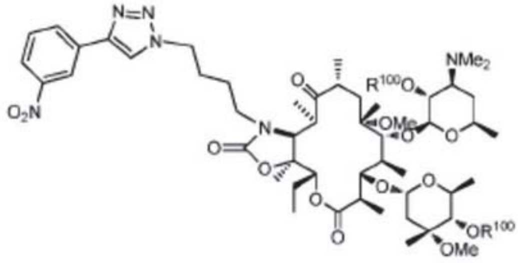
[0206]

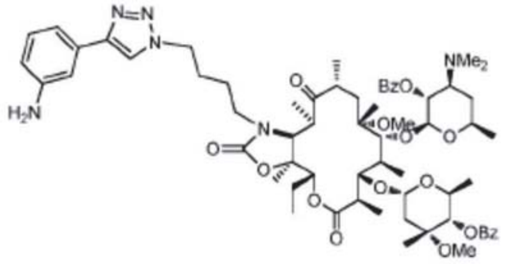




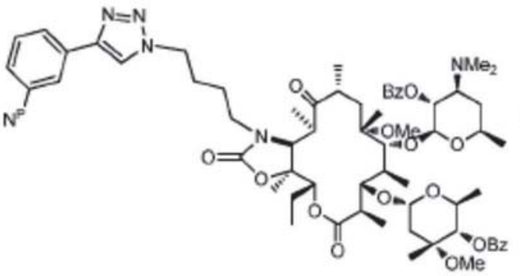


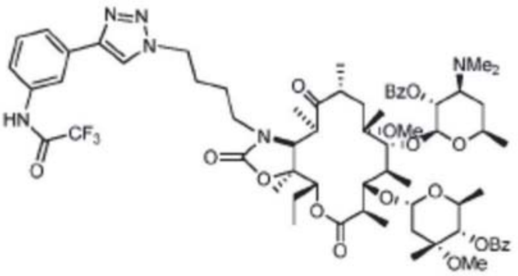


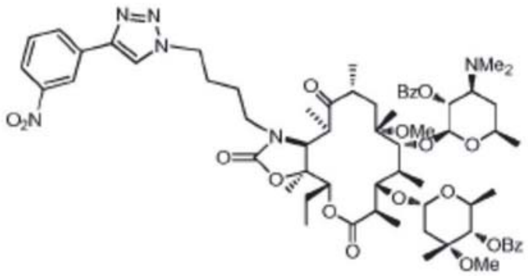




[0207]





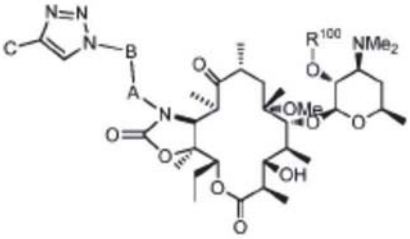


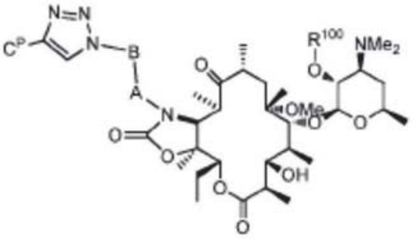
[0208]　及其盐的方法。所述方法一般在极性溶剂存在下进行，包括极性质子和极性非质子溶剂，或其混合物。示例性极性质子溶剂包括但不限于水；醇类，如甲醇、乙醇、异丙醇、正丙醇、正丁醇、异丁醇、叔丁醇、甲氧基乙醇、乙氧基乙醇、戊醇、新戊醇、叔戊醇、环己醇、乙二醇、丙二醇、苯甲醇、甲酰胺、N-甲基乙酰胺、N-甲基甲酰胺、甘油等等，及其混合物。示例性极性非质子溶剂包括但不限于二甲基甲酰胺(DMF)、二甲基乙酰胺(DMAC)、1,3-二甲基-3,4,5,6-四氢-2(1H)-嘧啶酮(DMPU)、1,3-二甲基-2-咪唑啉酮(DMI)、N-甲基吡咯烷酮(NMP)、乙腈、二甲亚砜(DMSO)、丙腈、甲酸乙酯、乙酸甲酯、六氯丙酮、HMPA、HMPT、丙酮、乙基甲基酮、乙酸乙酯、乙酸异丙酯、乙酸叔丁酯、环丁砜、N,N-二甲基丙酰胺、硝基甲烷、硝基苯、四氢呋喃(THF)、甲基四氢呋喃、二噁烷、聚醚等等，及其混合物。所述方法还可在另外

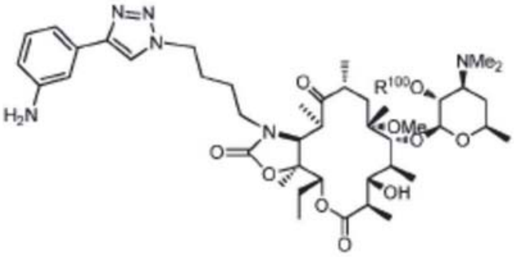
的碱存在下进行。示例性碱包括但不限于DBU、DABCO、TEA、DIPEA、哌啶等等，及其混合物。

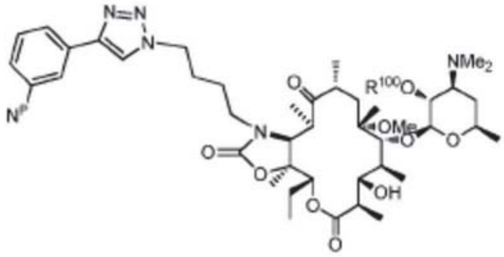
[0209] 在另一示例性实施方案中，描述用于制备下式化合物

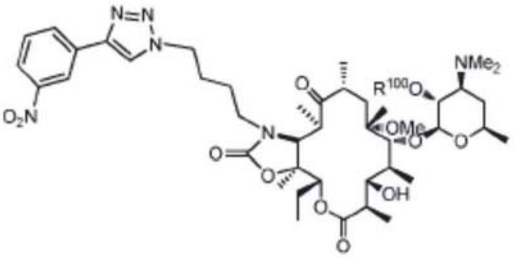
[0210]

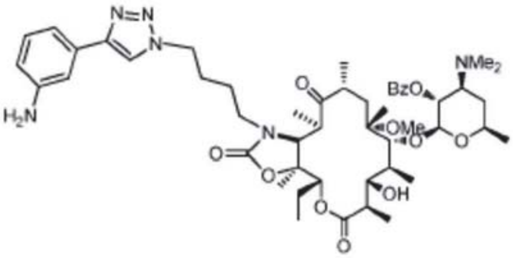


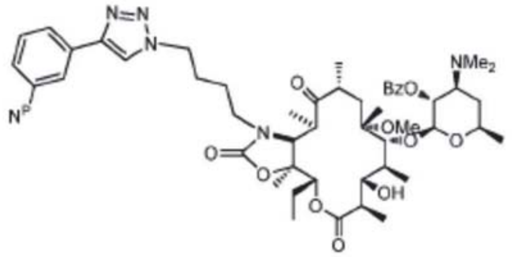


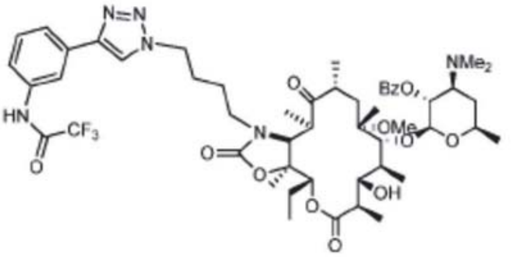


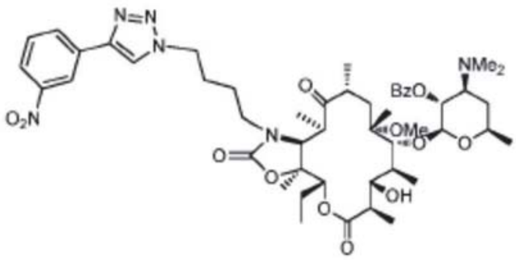








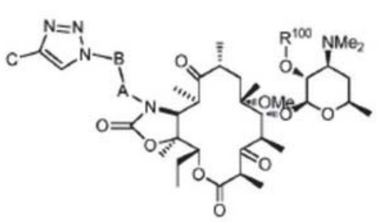


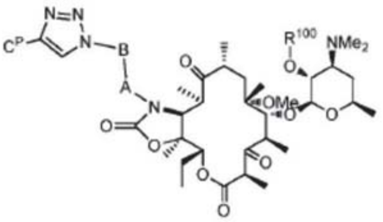


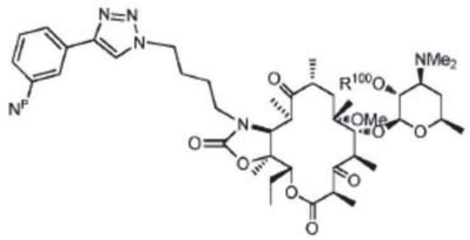
[0211] 及其盐的方法。所述方法一般在酸存在下进行。示例性酸包括但不限于盐酸、氢溴酸、硫酸、硝酸、磷酸、高氯酸、三氟乙酸、甲酸、氢氟酸等等，及其混合物。在一个变型中，所述酸是盐酸。所述方法一般在溶剂如水、包括醇类如甲醇、乙醇、异丙醇、正丙醇、叔丁醇、正丁醇等等的极性有机溶剂及其混合物中进行。所述方法可在多个温度下进行，包括在约0℃至约70℃范围内的温度，且示例性地，在约20℃至约60℃的范围内。

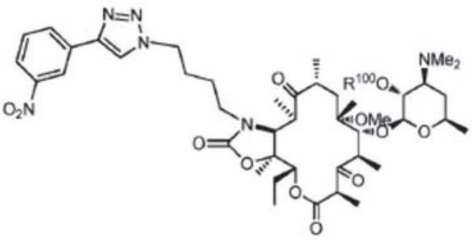
[0212] 在另一示例性实施方案中，描述用于制备下式化合物

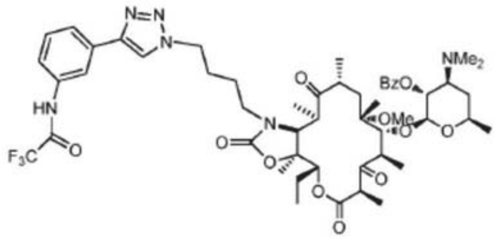
[0213]

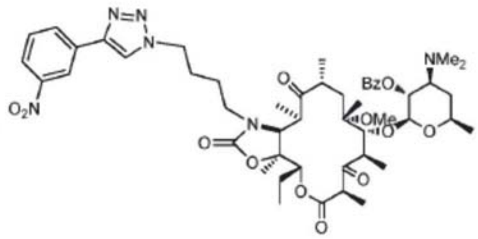








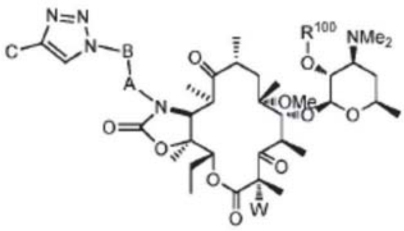


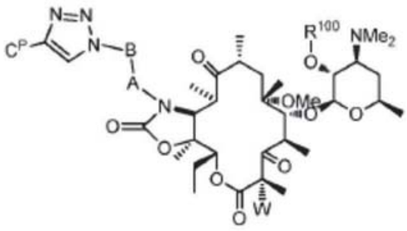


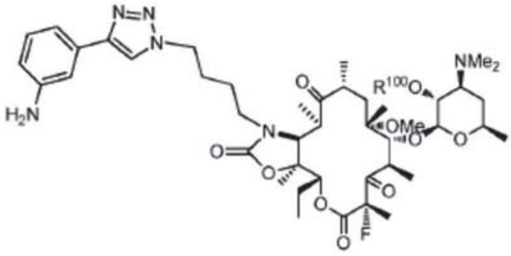
[0214] 及其盐的方法。所述方法一般在氧化剂存在下进行。示例性的氧化剂和条件包括但不限于 Corey-Kim 氧化，如甲硫醚 /N- 氯代琥珀酰亚胺（DMS/NCS）、二 - 正丁基硫醚 /N- 氯代琥珀酰亚胺、Dess-Martin 试剂、Pfitzner-Moffat 方法和其改良法、Swern 条件如 DMSO/ 草酰氯、DMSO/ 五氧化二磷、DMSO/ 对甲苯磺酰氯、DMSO/ 乙酸酐、DMSO/ 三氟乙酸酐、及 DMSO/ 亚硫酰氯、锰、铬及硒试剂、叔胺氧化物、$Ni(Ac)_2$/ 次氯酸盐、DMSO/EDAC·HCl/ 吡啶 .TFA 等等、及其变型，如通过包括一种或多种相转移催化剂。

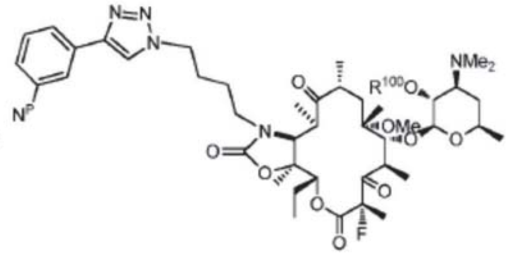
[0215] 在另一示例性实施方案中，描述用于制备下式化合物

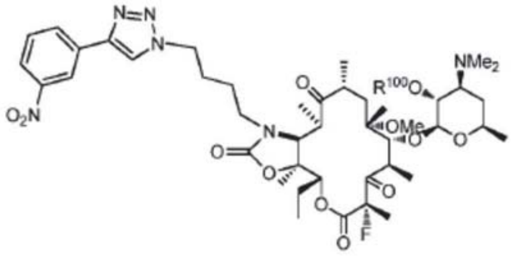
[0216]

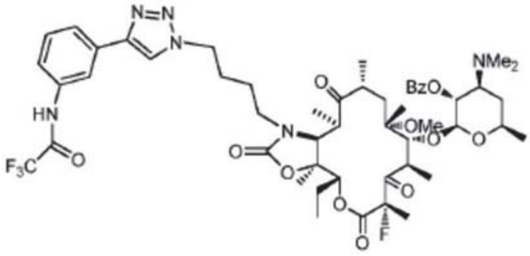


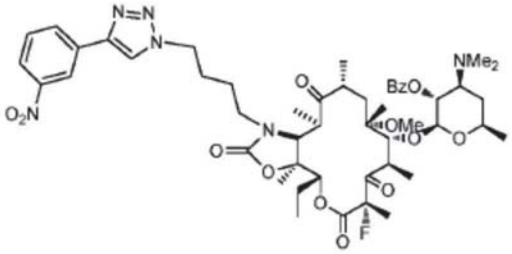








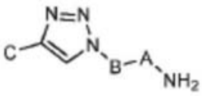


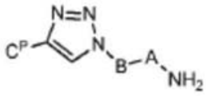


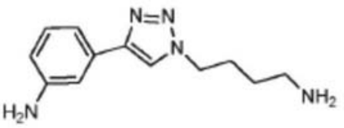
[0217] 及其盐的方法。所述方法一般在氟化剂存在下进行。示例性氟化剂包括$(PhSO_2)_2$N-F(NFSI或N-氟代磺酰亚胺)、F-TEDA、F-TEDA-BF_4、1-氟-4-羟基-1,4-二氮酮二环[2.2.2]辛烷双(四氟硼酸酯)等等,在溶剂和碱如t-BuOK的存在下。

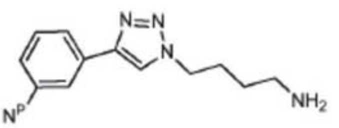
[0218] 在另一示例性实施方案中,描述用于在铜催化剂和碱存在下经由Huisgen环化制备下式化合物

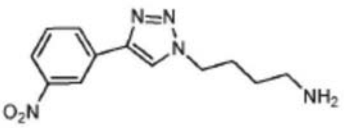
[0219]









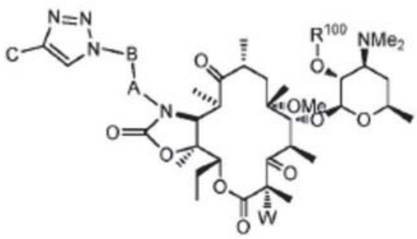


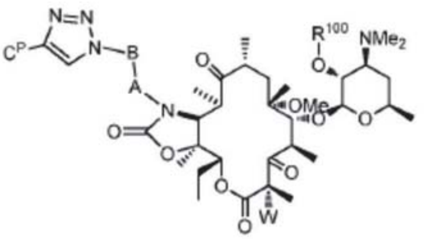
[0220] 及其盐的方法。Huisgen环化一般无溶剂地、在水中或在有机溶剂如乙腈或甲苯中在碱存在下进行。示例性碱包括但不限于有机碱,包括烷基和杂芳基碱,如三乙胺、二异丙基乙胺、DABCO、吡啶、二甲基吡啶等等;以及无机碱,如NaOH、KOH、K_2CO_3、$NaHCO_3$等等。所述碱示例性地是二异丙基乙胺(DIPEA)。反应是在从20℃到80℃范围内的温度下进行。反应还可通过使用催化剂来促进,包括但不限于卤化铜,示例性地碘化亚铜。CuI与叠氮化物的

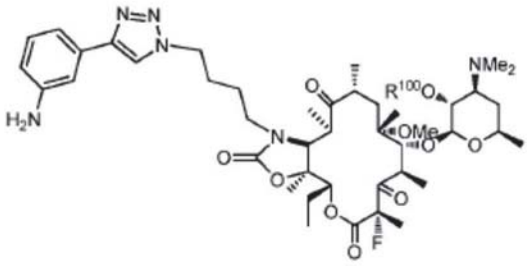
比率示例性地从约 0.01 到 1 至约 0.1 到 1。在一个替代实施方案中，所述催化剂是有机催化剂，如酚酞。另外的反应条件描述于以下文献中：Sharpless 等人的美国专利申请公布号 US 2005/0222427；Liang 等人的 Bioorg. Med. Chem. Lett. 15(2005)1307-1310；以及 Romero 等人的 Tetrahedron Letters 46(2005)1483-1487，其公开内容以引用的方式并入本文。

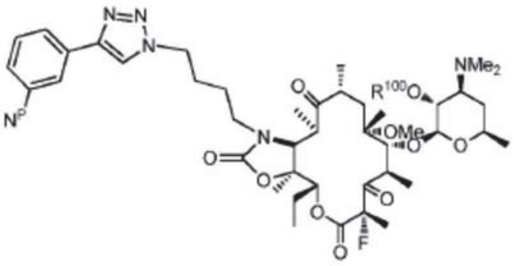
[0221] 在另一示例性实施方案中，描述用醇去保护下式化合物

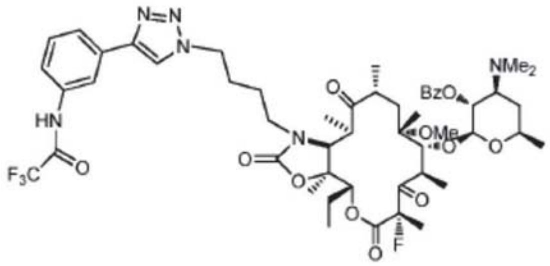
[0222]

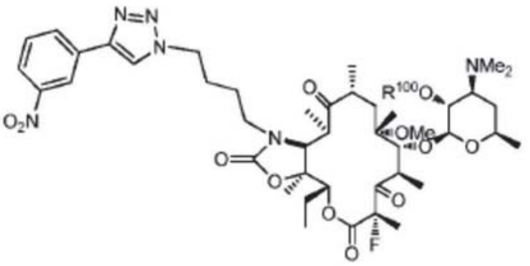


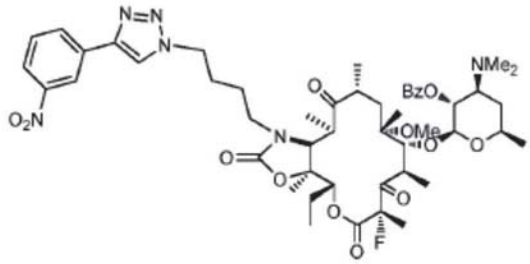








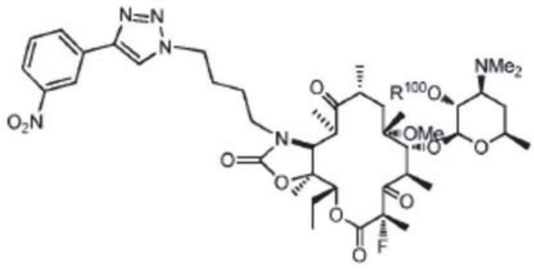


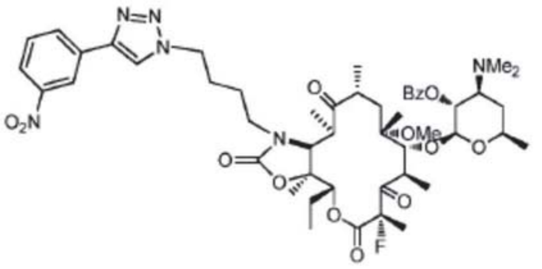


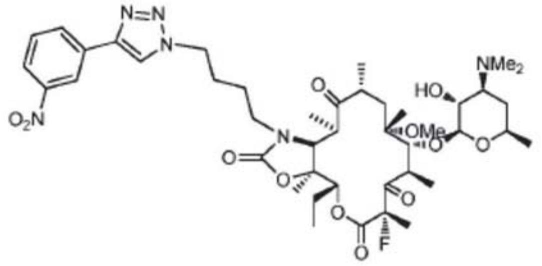
[0223] 及其盐以制备式 (I) 的相应的去保护化合物的方法。示例性醇包括但不限于甲醇、乙醇、正丙醇、异丙醇、叔丁醇、正丁醇或其混合物。示例性地，所述醇是甲醇。反应可在约 0℃到约 100℃的温度下，或在约 20℃到约 70℃下进行。反应也可在无机酸如选自 HCl、H_2SO_4等等及其混合物的无机酸存在下进行。在一个示例性实施方案中，反应在甲醇中在约 55℃的温度下进行。

[0224] 在另一示例性实施方案中，描述用于还原下式化合物

[0225]



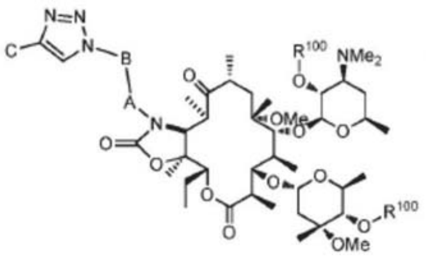


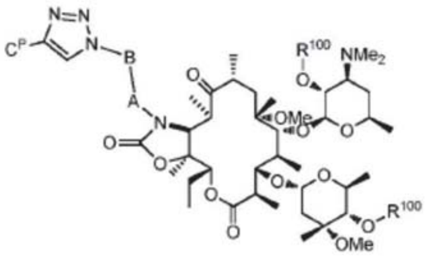


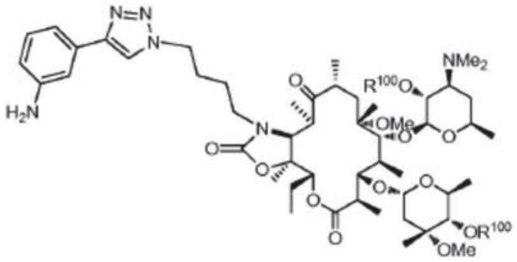
[0226]　及其盐的方法。所述方法一般在还原剂存在下进行。示例性还原剂包括但不限于氢气、铁和酸、转移氢化剂、兰尼镍、海绵镍、金属催化剂如 Pt、Pd 等等。

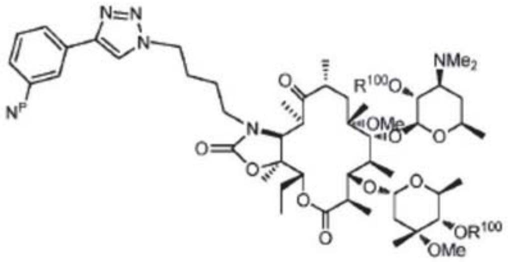
[0227]　在另一示例性实施方案中，在本文中描述下式的化合物

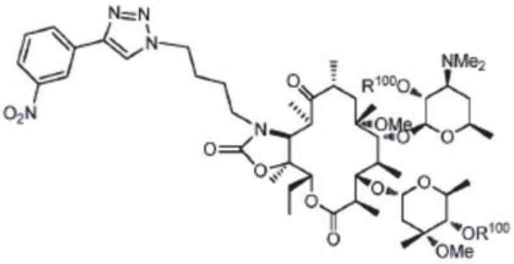
[0228]

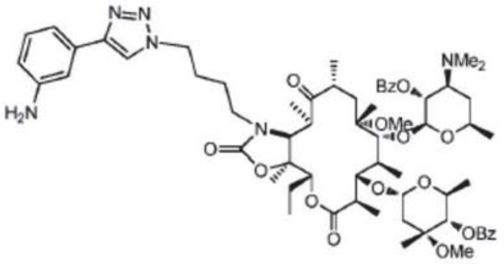


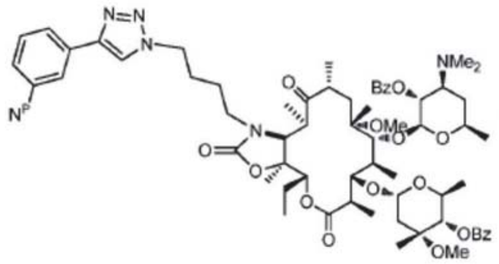


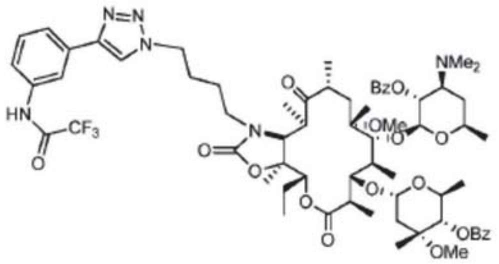


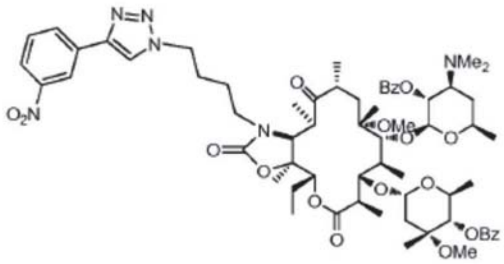








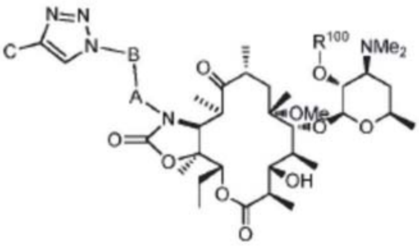


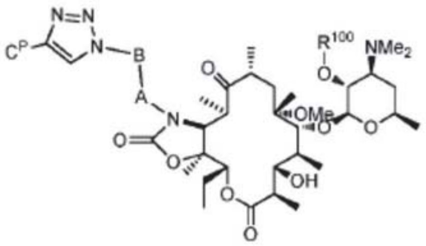


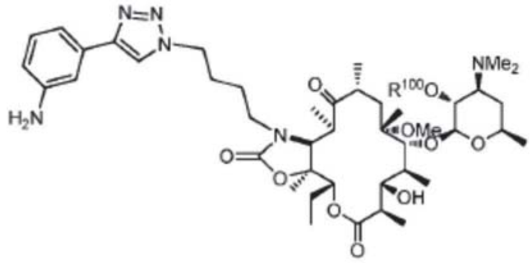
[0229] 及其盐。

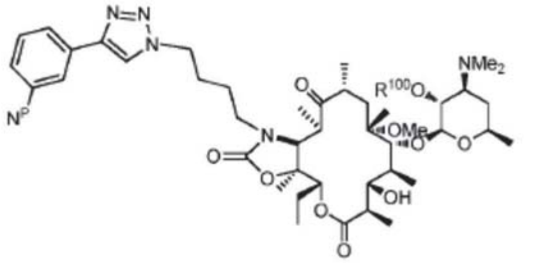
[0230] 在另一示例性实施方案中，在本文中描述下式的化合物

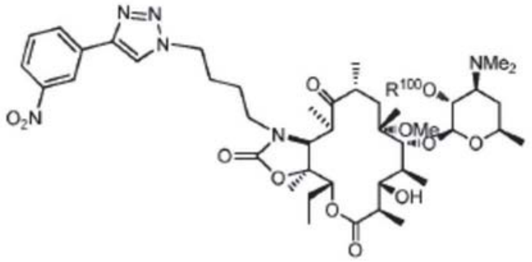
[0231]

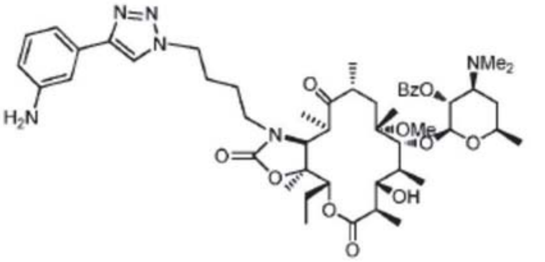


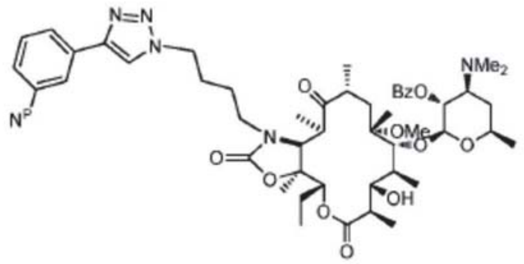


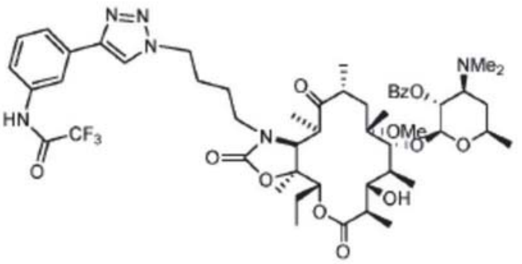


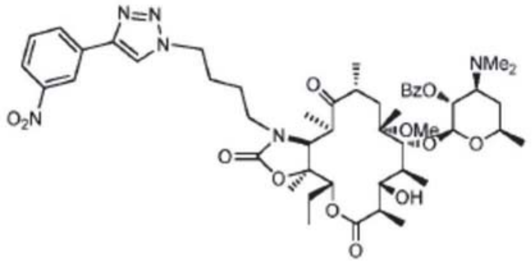








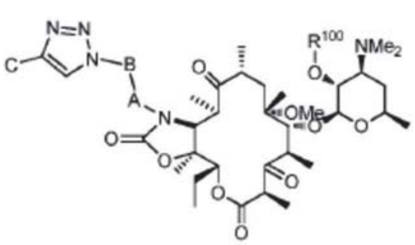


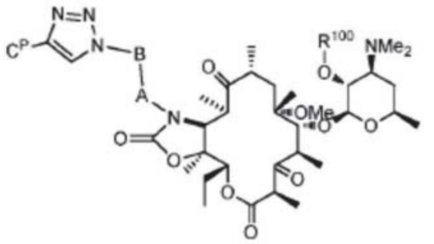


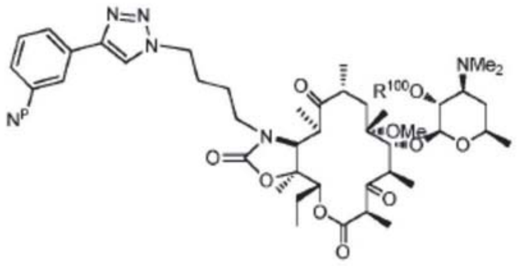
[0232] 及其盐。

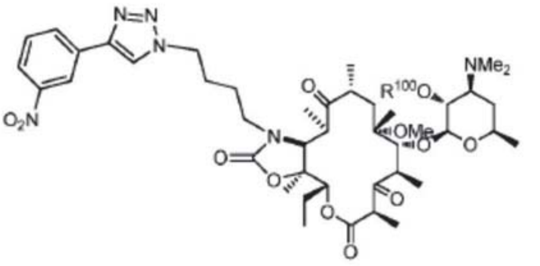
[0233] 在另一示例性实施方案中,在本文中描述下式的化合物

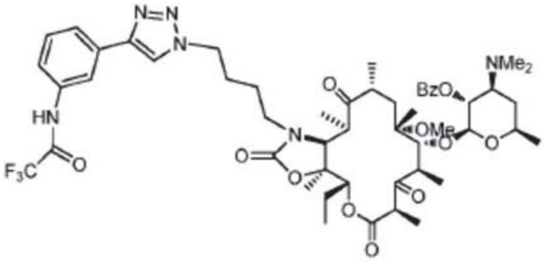
[0234]

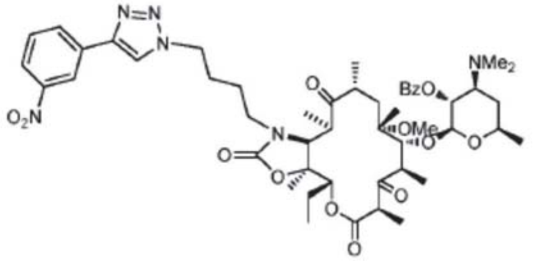








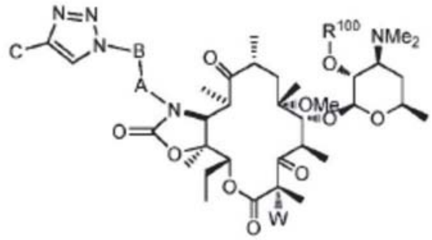


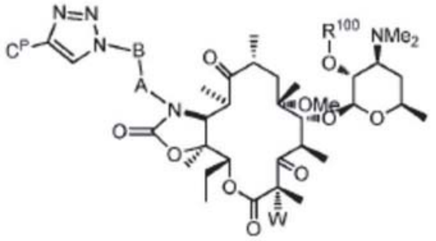


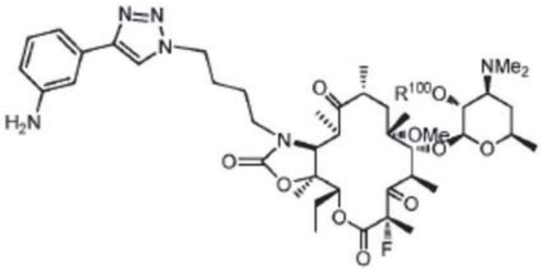
[0235]　及其盐。

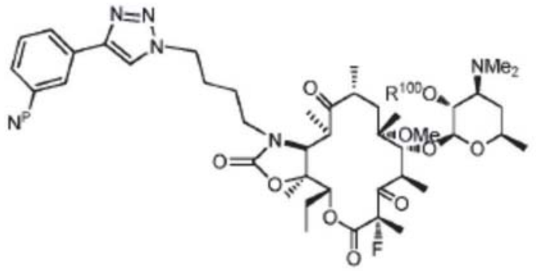
[0236]　在另一示例性实施方案中，在本文中描述下式的化合物

[0237]

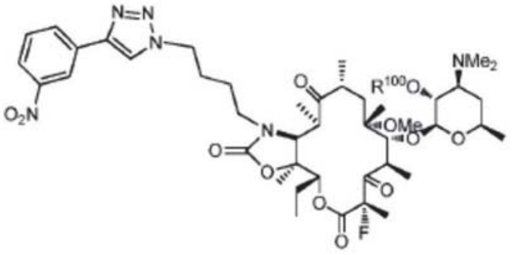


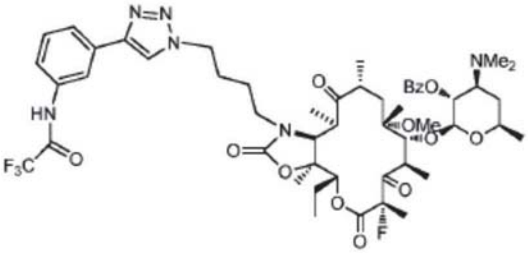


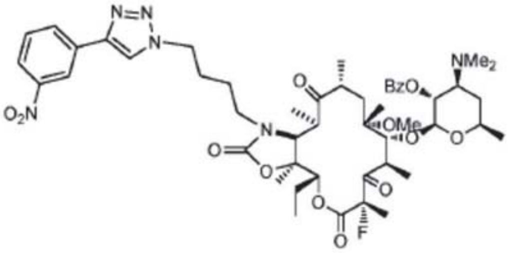




[0238]



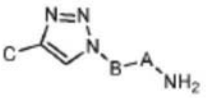


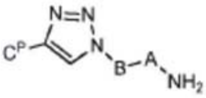


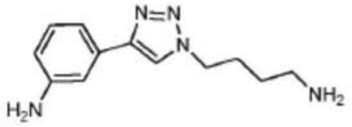
[0239] 及其盐。

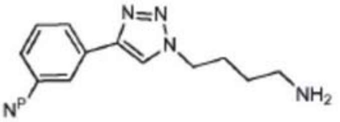
[0240] 在另一示例性实施方案中,在本文中描述下式的化合物

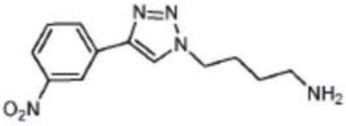
[0241]







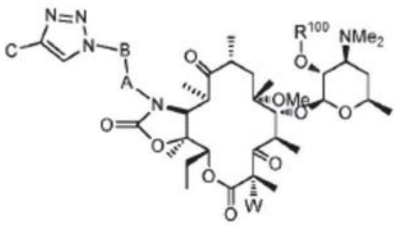


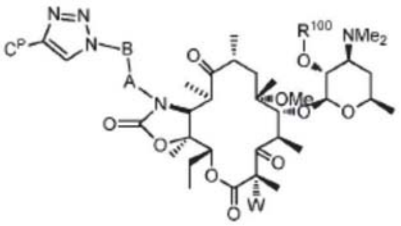


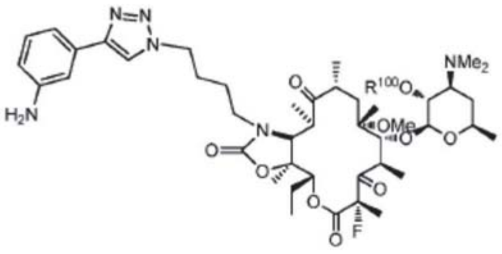
[0242] 及其盐。在另一实施方案中,N^{P}是酰胺、或氨基甲酸酯,如Bz-NH、CF$_3$C(O)-NH、Cbz-NH、Boc-NY、Fmoc-NY、BsMoc-NH、三苯甲基-NH、MeO三苯甲基((4-甲氧基苯基)二苯基甲基)-NH等等。

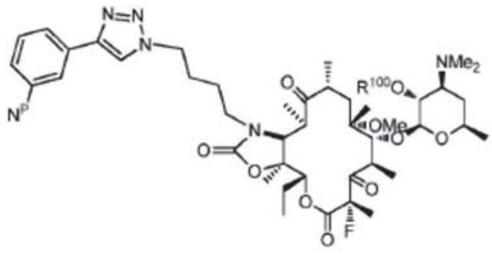
[0243] 在另一示例性实施方案中,在本文中描述下式的化合物

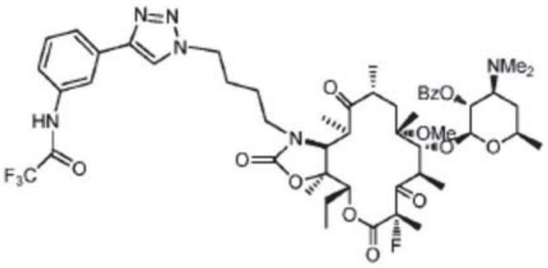
[0244]

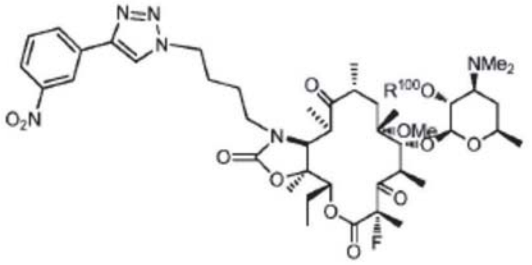


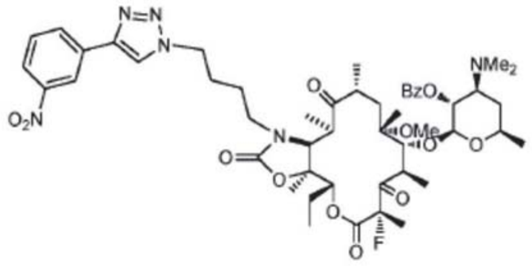








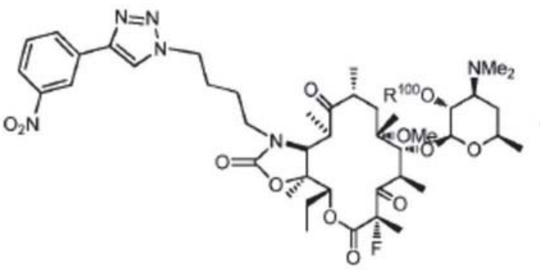


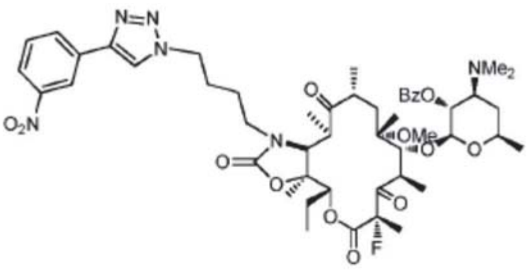


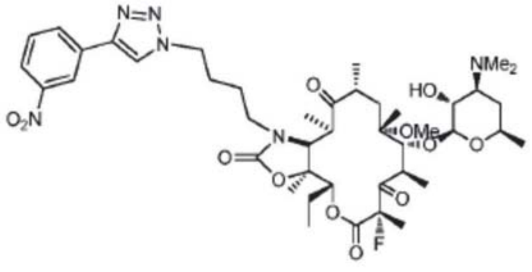
[0245]　及其盐。

[0246]　在另一示例性实施方案中，在本文中描述下式的化合物

[0247]







[0248]　及其盐。

[0249] 应理解的是，在每一先前实施方案中，在各情况下，R^{100}、N^P、A、B、C、C^P、W 及 L 各自的选择独立地由本文所述的任何种、亚属、和属构成。另外，应理解的是，在本文中描述 R^{100}、N^P、A、B、C、C^P、W 及 L 的那些选择各自的每个组合，包括其种、其亚属、及其属的任何组合。

[0250] 在每个之前和每个之后的实施方案中，还应理解的是，结构式包括并代表化合物的任何及所有结晶形式、部分结晶形式、以及非结晶和／或无定形形式。

[0251] 在每个之前和每个之后的实施方案中，还应理解的是，结构式不仅包括并代表化合物的所有药学上可接受的盐，而且包括化合物结构式的任何及所有水合物和／或溶剂化物。应了解，某些官能团，如羟基、氨基及类似基团与水和／或各种溶剂形成复合物和／或配位化合物，呈化合物的各种物理形式。因此，应理解以上结构式是作为所述水合物和／或溶剂化物（包括药学上可接受的溶剂化物）的描述。

[0252] 如本文所用，术语“溶剂化物”是指与溶剂分子复合的本文所述的化合物。应当理解，本文所述的化合物可通过仅仅将化合物与溶剂混合或将化合物溶解于溶剂中而与溶剂形成所述复合物。应当理解，当化合物将被用作药物时，所述溶剂是药学上可接受的溶剂。进一步应理解，当化合物将被用作药物时，形成溶剂化物的溶剂的相对量应小于为所述药物用途建立的指导原则，如小于国际协调会议 (ICH) 指导原则。应理解，溶剂化物可通过蒸发、沉淀和／或结晶从过量的溶剂中分离。在一些实施方案中，溶剂化物是无定形的，且在其他实施方案中，溶剂化物是结晶的。

[0253] 如本文所用，术语“烷基”包括任选支化的碳原子链。如本文所用，术语“烯基”和“炔基”各自包括任选支化的碳原子链且分别包括至少一个双键或三键。应理解，炔基也可包括一个或多个双键。进一步应理解，在某些实施方案中，烷基有利地具有有限的长度，包括 C_1-C_{24}、C_1-C_{12}、C_1-C_8、C_1-C_6、及 C_1-C_4，以及 C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6、及 C_2-C_4等等。示例性地，所述特别有限长度的烷基（包括 C_1-C_8、C_1-C_6、及 C_1-C_4，以及 C_2-C_8、C_2-C_6、及 C_2-C_4等等）可被称为低级烷基。进一步应理解，在某些实施方案中，烯基和／或炔基可各自有利地具有有限的长度，包括 C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6、及 C_2-C_4，以及 C_3-C_{24}、C_3-C_{12}、C_3-C_8、C_3-C_6、及 C_3-C_4等等。示例性地，所述特别有限长度的烯基和／或炔基（包括 C_2-C_8、C_2-C_6、及 C_2-C_4，以及 C_3-C_8、C_3-C_6、及 C_3-C_4等等）可被称为低级烯基和／或炔基。在本文中应理解，较短的烷基、烯基、和／或炔基可向化合物添加更小的亲油性且因此将具有不同的药物动力学行为。在本文所述发明的实施方案中，应理解，在各情况下，烷基是指如本文中所定义的烷基，且任选地低级烷基。在本文所述发明的实施方案中，应理解，在各情况下，烯基是指如本文中所定义的烯基，且任选地低级烯基。在本文所述发明的实施方案中，应理解，在各情况下，炔基是指如本文中所定义的炔基，且任选地低级炔基。示例性烷基、烯基、及炔基是但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、戊基、2- 戊基、3- 戊基、新戊基、己基、庚基、辛基等等，以及含有一个或多个双键和／或三键的相应基团，或其组合。

[0254] 如本文所用，术语“亚烷基”包括任选支化的二价碳原子链。如本文所用，术语“亚烯基”和“亚炔基”包括任选支化的二价碳原子链且分别包括至少一个双键或三键。应理解，亚炔基也可包括一个或多个双键。进一步应理解，在某些实施方案中，亚烷基有利地具有有限的长度，包括 C_1-C_{24}、C_1-C_{12}、C_1-C_8、C_1-C_6、及 C_1-C_4，以及 C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6、及 C_2-C_4等等。示例性地，所述特别有限长度的亚烷基（包括 C_1-C_8、C_1-C_6、及 C_1-C_4，以及 C_2-C_8、C_2-C_6、及 C_2-C_4等等）可被称为低级亚烷基。进一步应理解，在某些实施方案中，亚烯基和／或亚

炔基可各自有利地具有有限的长度，包括 C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6、及 C_2-C_4，以及 C_3-C_{24}、C_3-C_{12}、C_3-C_8、C_3-C_6、及 C_3-C_4等等。示例性地，所述特别有限长度的亚烯基和／或亚炔基（包括C_2-C_8、C_2-C_6、及C_2-C_4，以及C_3-C_8、C_3-C_6、及C_3-C_4等等）可被称为低级亚烯基和／或亚炔基。在本文中应理解，较短的亚烷基、亚烯基、和／或亚炔基可向化合物添加更小的亲油性且因此将具有不同的药物动力学行为。在本文所述发明的实施方案中，应理解，在各情况下，亚烷基、亚烯基、及亚炔基是指如本文中所定义的亚烷基、亚烯基、及亚炔基，且任选地是低级亚烷基、亚烯基、及亚炔基。示例性烷基是但不限于亚甲基、亚乙基、正亚丙基、异亚丙基、正亚丁基、异亚丁基、仲亚丁基、亚戊基、1,2- 亚戊基、1,3- 亚戊基、亚己基、亚庚基、亚辛基等等。

[0255] 如本文所用，术语“环烷基”包括任选支化的碳原子链，其中链的至少一部分呈环状。应理解，环烷基烷基是环烷基的子集。应理解，环烷基可以是多环的。示例性环烷基包括但不限于环丙基、环戊基、环己基、2- 甲基环丙基、环戊基乙 -2- 基、金刚烷基等等。如本文所用，术语“环烯基”包括任选支化的碳原子链，且包括至少一个双键，其中链的至少一部分呈环状。应理解，一个或多个双键可处于环烯基的环状部分和／或环烯基的非环状部分中。应理解，环烯基烷基和环烷基烯基各自是环烯基的子集。应理解，环烷基可以是多环的。示例性环烯基包括但不限于环戊烯基、环己基乙烯 -2- 基、环庚烯基丙烯基等等。进一步应理解，形成环烷基和／或环烯基的链有利地具有有限的长度，包括 C_3-C_{24}、C_3-C_{12}、C_3-C_8、C_3-C_6、及 C_5-C_6。在本文中应理解，分别形成环烷基和／或环烯基的较短的烷基和／或烯基链可向化合物添加更小的亲油性且因此将具有不同的药物动力学行为。

[0256] 如本文所用，术语“杂烷基”包括含有碳及至少一个杂原子且任选支化的原子链。示例性杂原子包括氮、氧、及硫。在某些变型中，示例性杂原子还包括磷和硒。如本文所用，术语“环杂烷基”包括杂环基和杂环，包括含有碳及至少一个杂原子（如杂烷基）且任选支化的原子链，其中链的至少一部分呈环状。示例性杂原子包括氮、氧、及硫。在某些变型中，示例性杂原子还包括磷和硒。示例性环杂烷基包括但不限于四氢呋喃基、吡咯烷基、四氢吡喃基、哌啶基、吗啉基、哌嗪基、高哌嗪基、奎宁环基等等。

[0257] 如本文所用，术语“芳基”包括单环和多环芳族碳环基团，其各自可任选被取代。本文所述的示例性芳族碳环基团包括但不限于苯基、萘基等等。如本文所用，术语“杂芳基”包括芳族杂环基团，其各自可任选被取代。示例性芳族杂环基团包括但不限于吡啶基、嘧啶基、吡嗪基、三嗪基、四嗪基、喹啉基、喹唑啉基、喹喔啉基、噻吩基、吡唑基、咪唑基、噁唑基、噻唑基、异噁唑基、异噻唑基、噁二唑基、噻二唑基、三唑基、苯并咪唑基、苯并噁唑基、苯并噻唑基、苯并异噁唑基、苯并异噻唑基等等。

[0258] 如本文所用，术语“氨基”包括基团 NH_2、烷基氨基、及二烷基氨基，其中二烷基氨基中的两个烷基可以是相同或不同的，即烷基烷基氨基。示例性地，氨基包括甲基氨基、乙基氨基、二甲基氨基、甲基乙基氨基等等。另外，应理解当氨基修饰或被另一个术语修饰时，如氨基烷基或酰氨基，术语氨基的以上变型包括在其中。示例性地，氨基烷基包括 H_2N- 烷基、甲基氨基烷基、乙基氨基烷基、二甲基氨基烷基、甲基乙基氨基烷基等等。示例性地，酰氨基包括酰基甲基氨基、酰基乙基氨基等等。

[0259] 如本文所用，术语“氨基及其衍生物”包括如本文所述的氨基，以及烷基氨基、烯基氨基、炔基氨基、杂烷基氨基、杂烯基氨基、杂炔基氨基、环烷基氨基、环烯基氨基、环杂烷基

氨基、环杂烯基氨基、芳基氨基、芳基烷基氨基、芳基烯基氨基、芳基炔基氨基、杂芳基氨基、杂芳基烷基氨基、杂芳基烯基氨基、杂芳基炔基氨基、酰胺基等等，其各自任选被取代。术语“氨基衍生物”还包括脲、氨基甲酸酯等。

[0260] 如本文所用，术语“羟基及其衍生物”包括 OH，以及烷氧基、烯氧基、炔氧基、杂烷氧基、杂烯氧基、杂炔氧基、环烷氧基、环烯氧基、环杂烷氧基、环杂烯氧基、芳氧基、芳基烷氧基、芳基烯氧基、芳基炔氧基、杂芳氧基、杂芳基烷氧基、杂芳基烯氧基、杂芳基炔氧基、酰氧基等等，其各自任选被取代。术语“羟基衍生物”还包括氨基甲酸酯等。

[0261] 如本文所用，术语“硫基及其衍生物”包括 SH，以及烷硫基、烯硫基、炔硫基、杂烷硫基、杂烯硫基、杂炔硫基、环烷硫基、环烯硫基、环杂烷硫基、环杂烯硫基、芳硫基、芳基烷硫基、芳基烯硫基、芳基炔硫基、杂芳硫基、杂芳基烷硫基、杂芳基烯硫基、杂芳基炔硫基、酰硫基等等，其各自任选被取代。术语“硫基衍生物”还包括硫代氨基甲酸酯等。

[0262] 如本文所用，术语“酰基”包括甲酰基，以及烷基羰基、烯基羰基、炔基羰基、杂烷基羰基、杂烯基羰基、杂炔基羰基、环烷基羰基、环烯基羰基、环杂烷基羰基、环杂烯基羰基、芳基羰基、芳基烷基羰基、芳基烯基羰基、芳基炔基羰基、杂芳基羰基、杂芳基烷基羰基、杂芳基烯基羰基、杂芳基炔基羰基、酰基羰基等等，其各自任选被取代。

[0263] 如本文所用，术语“羰基及其衍生物”包括基团 C(O)、C(S)、C(NH) 及其取代的氨基衍生物。

[0264] 如本文所用，术语“羧酸及其衍生物”包括基团 CO_2H 及其盐，以及其酯和酰胺，及 CN。

[0265] 如本文所用，术语“亚磺酸或其衍生物”包括 SO_2H 及其盐，以及其酯和酰胺。

[0266] 如本文所用，术语“磺酸或其衍生物”包括 SO_3H 及其盐，以及其酯和酰胺。

[0267] 如本文所用，术语“磺酰基”包括烷基磺酰基、烯基磺酰基、炔基磺酰基、杂烷基磺酰基、杂烯基磺酰基、杂炔基磺酰基、环烷基磺酰基、环烯基磺酰基、环杂烷基磺酰基、环杂烯基磺酰基、芳基磺酰基、芳基烷基磺酰基、芳基烯基磺酰基、芳基炔基磺酰基、杂芳基磺酰基、杂芳基烷基磺酰基、杂芳基烯基磺酰基、杂芳基炔基磺酰基、酰基磺酰基等等，其各自任选被取代。

[0268] 如本文所用的术语“任选取代的”包括在任选被取代的基团上用其他官能团置换氢原子。所述其他官能团示例性地包括但不限于氨基、羟基、卤基、硫醇、烷基、卤烷基、杂烷基、芳基、芳基烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基、硝基、磺酸及其衍生物、羧酸及其衍生物等等。示例性地，氨基、羟基、硫醇、烷基、卤烷基、杂烷基、芳基、芳基烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基、和 / 或磺酸中的任一者是任选被取代的。

[0269] 如本文所用，术语“任选取代的芳基”和“任选取代的杂芳基”包括在任选取代的芳基或杂芳基上用其他官能团置换氢原子。所述其他官能团示例性地包括但不限于氨基、羟基、卤基、硫基、烷基、卤烷基、杂烷基、芳基、芳基烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基、硝基、磺酸及其衍生物、羧酸及其衍生物等等。示例性地，氨基、羟基、硫基、烷基、卤烷基、杂烷基、芳基、芳基烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基、和 / 或磺酸中的任一者是任选被取代的。

[0270] 示例性取代基包括但不限于基团 $-(CH_2)_xZ^X$，其中 x 是从 0-6 的整数且 Z^X 选自卤素；

羟基；烷酰氧基，包括 C_1-C_6烷酰氧基，任选取代的芳酰氧基；烷基，包括 C_1-C_6烷基；烷氧基，包括 C_1-C_6烷氧基；环烷基，包括 C_3-C_8环烷基；环烷氧基，包括 C_3-C_8环烷氧基；烯基，包括 C_2-C_6烯基；炔基，包括 C_2-C_6炔基；卤烷基，包括 C_1-C_6卤烷基；卤烷氧基，包括 C_1-C_6卤烷氧基；卤环烷基，包括 C_3-C_8卤环烷基；卤环烷氧基，包括 C_3-C_8卤环烷氧基；氨基、C_1-C_6烷基氨基、(C_1-C_6烷基)(C_1-C_6烷基)氨基、烷基羰基氨基、N-(C_1-C_6烷基)烷基羰基氨基、氨基烷基、C_1-C_6烷基氨基烷基、(C_1-C_6烷基)(C_1-C_6烷基)氨基烷基、烷基羰基氨基烷基、N-(C_1-C_6烷基)烷基羰基氨基烷基、氰基、及硝基；或 Z^X选自 $-CO_2R^4$和 $-CONR^5R^6$，其中 R^4、R^5、及 R^6在每次出现时各自独立地选自氢、C_1-C_6烷基、芳基 $-C_1$-C_6烷基、及杂芳基 $-C_1$-C_6烷基。

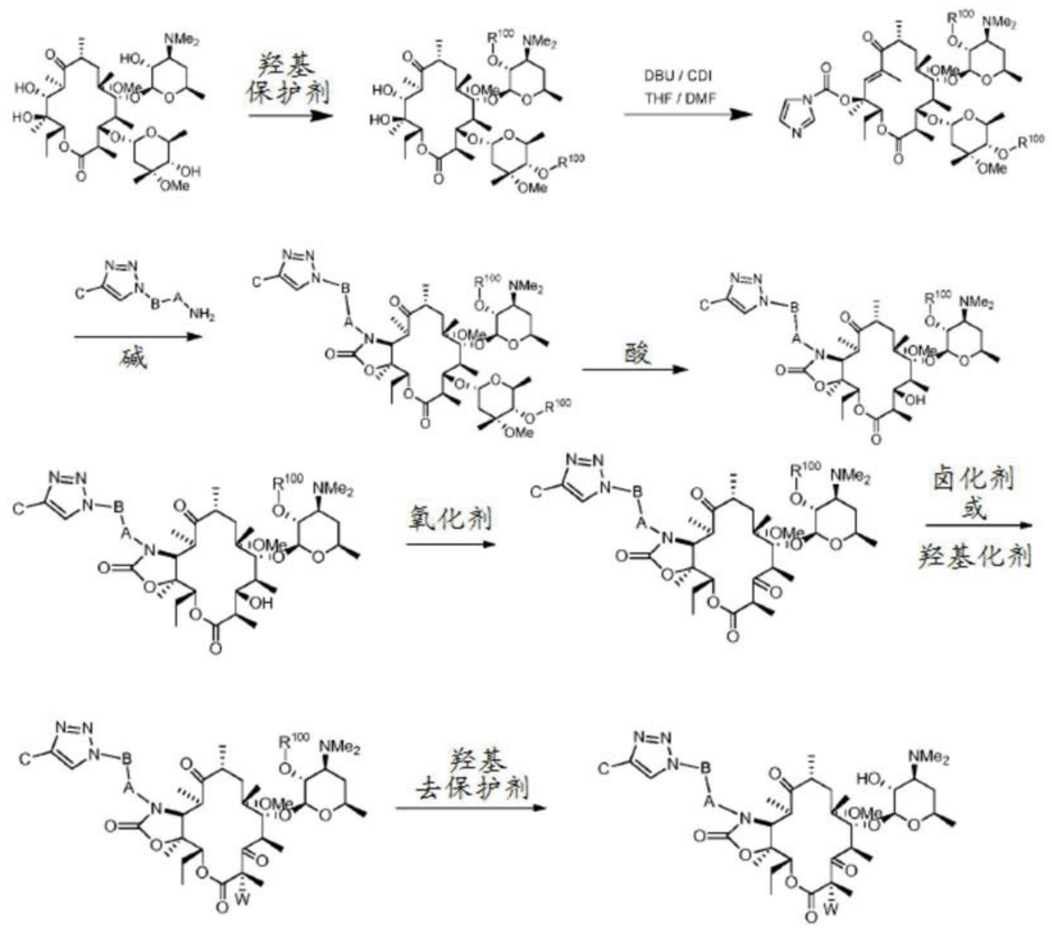
[0271]　示例性杂环化合物包括但不限于吡咯烷、哌啶、噁唑烷、异噁唑烷、噻唑烷、异噻唑烷、吡咯烷酮、哌啶酮、噁唑烷酮、异噁唑烷酮、噻唑烷酮、异噻唑烷酮、及琥珀酰亚胺。

[0272]　如本文所用，术语“离去基团”是指在其所连接的原子上生成亲电子位点以使得亲核试剂可添加到原子上的亲电子位点的反应性官能团。示例性离去基团包括但不限于卤素、任选取代的苯酚、酰氧基、磺酰氧基等等。应理解，所述离去基团可在烷基、酰基等上。所述离去基团在本文中还可称为活化基团，如当离去基团存在于酰基上时。另外，常规的肽、酰胺、及酯偶联剂如但不限于 PyBop、BOP-Cl、BOP、五氟苯酚、异丁基氯甲酸酯等等形成各种中间体，包括在羰基上的如本文所定义的离去基团。

[0273]　应理解，当以常规方式将成员集合在一起时，如在马库什 (Markush) 组中，本发明不仅包括作为整体列出的整个组，而且包括各自的每个组成员和主组的所有可能的亚组。因此，出于所有目的，本发明不仅包括主组，而且包括缺乏一个或多个组成员的主组。本发明还设想在要求保护的发明中明确排除任何一个或多个组成员。

[0274]　在另一实施方案中，以下方法步骤和化合物各自单独地在本文中描述。

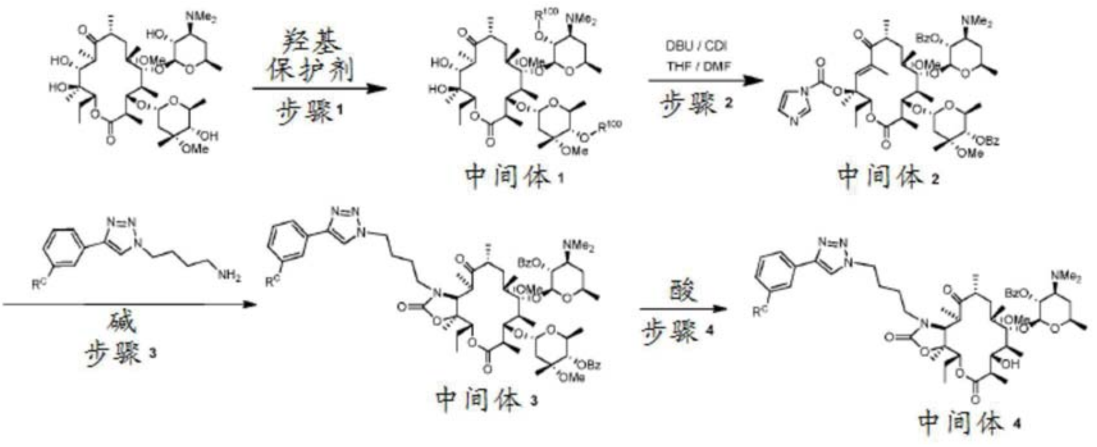
[0275]



[0276] 在本文中还描述相应的方法，其中C在一个或多个步骤中被C^P置换。

[0277] 在另一实施方案中，以下方法步骤和化合物各自单独地在本文中描述。

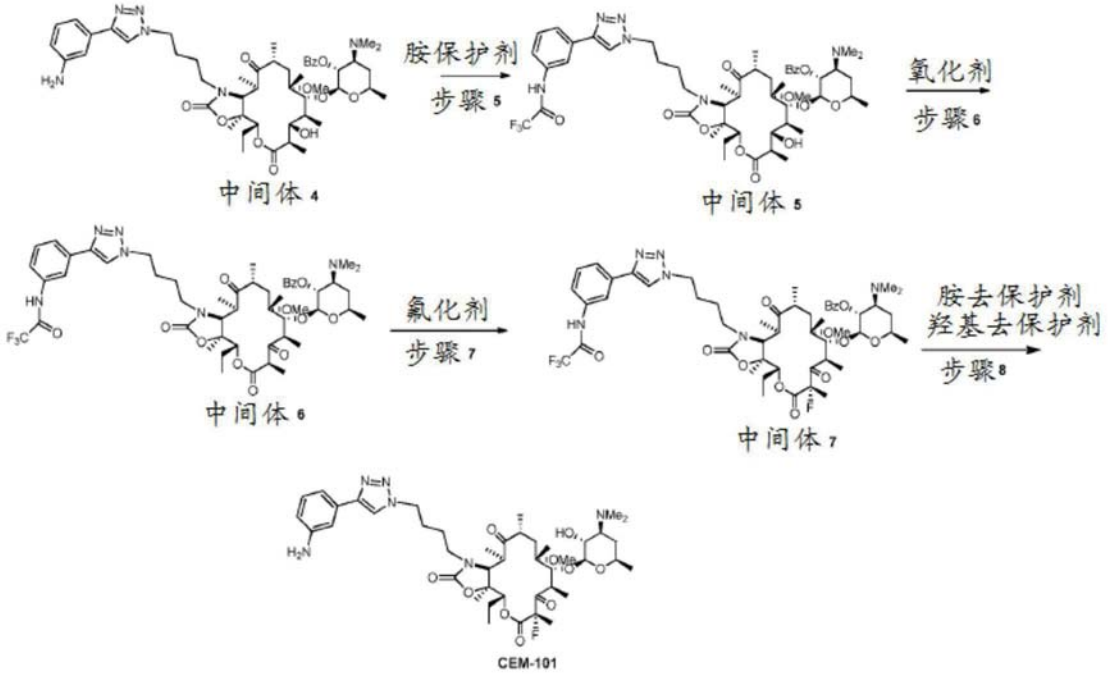
[0278]



[0279] 其中R^C是氨基、或受保护的氨基衍生物，如N^P、或硝基。在本文中还描述相应的方法，其中R^C是N^P。

[0280] 在另一实施方案中，以下方法步骤和化合物各自单独地在本文中描述。

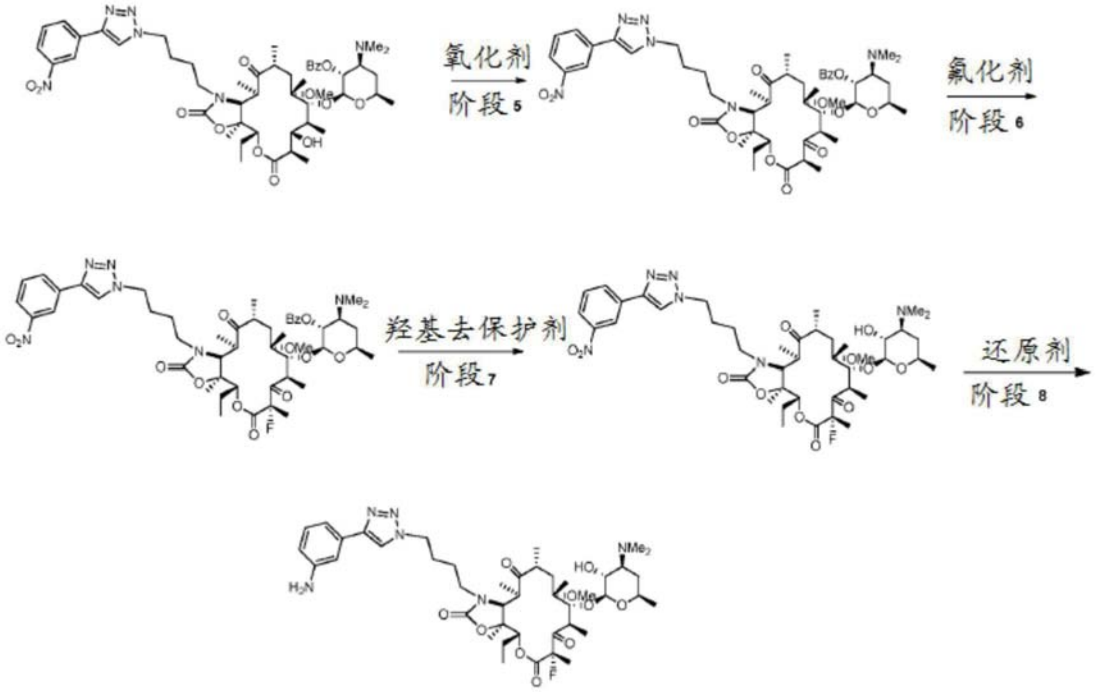
[0281]



CEM-101

[0282] 在另一实施方案中，以下方法步骤和化合物各自单独地在本文中描述。

[0283]



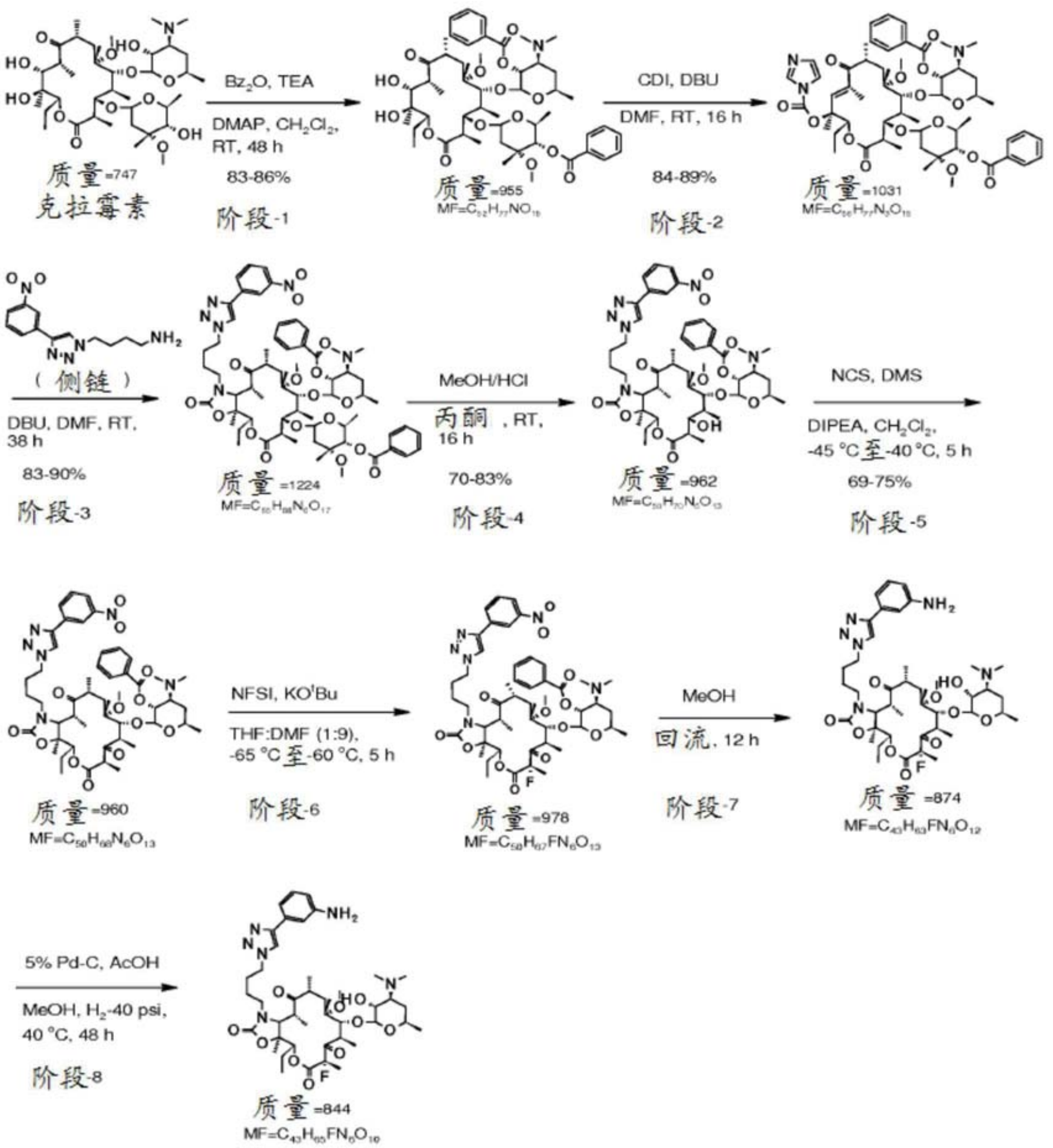
CEM-101

[0284] 本文所述的方法和化合物进一步由以下实施例来说明。以下实施例旨在是示例性的且不应被解释为或视为以任何方式进行限制。

实施例

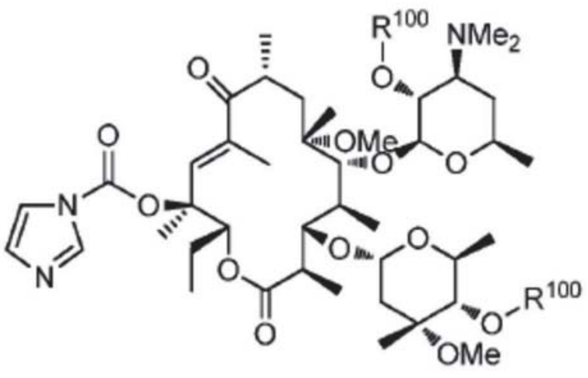
[0285] 实施例.CEM-101是根据以下方法来制备。

[0286]



[0287]　实施例．下式的化合物

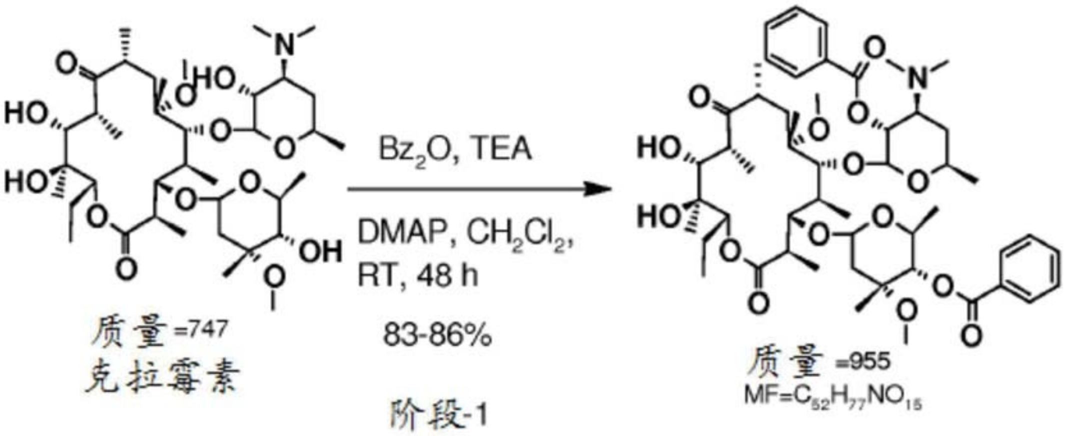
[0288]



[0289]　其中 R^{100} 是羟基保护基，如酰基，包括乙酰基、苯甲酰基等等，是使用常规方法如但不限于 PCT 国际公布号 WO/2009/055557 和 WO/2011/146829 中所述的方法来制备，所述文献的公开内容全部以引用的方式并入本文。

[0290]　实施例．阶段 1

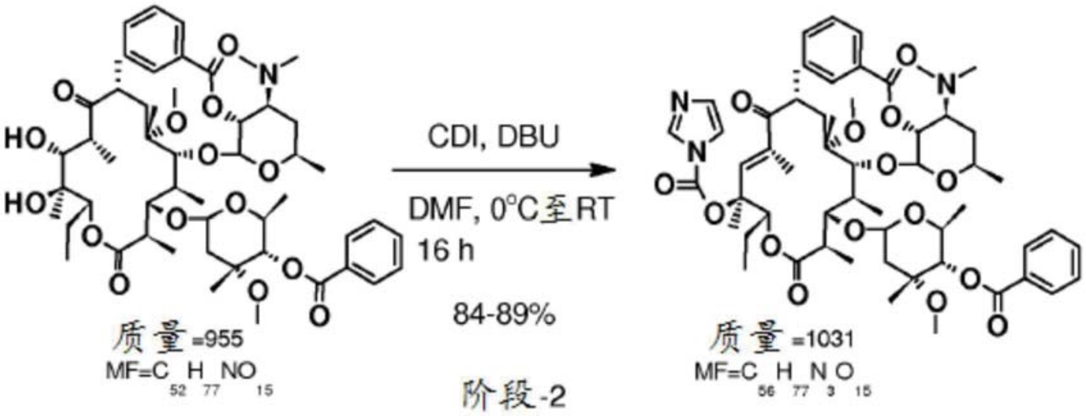
[0291]



[0292]　制备2',4"-二-O-苯甲酰基-6-O-甲基红霉素A。将125mL乙酸乙酯添加至25g克拉霉素A中。在25℃至35℃下将26.5g苯甲酸酐、5.7g 4-二甲基氨基吡啶及6.7g三乙胺添加至反应混合物中。在环境温度下搅拌反应混合物约70小时。反应完成之后，蒸馏出乙酸乙酯以获得标题化合物。

[0293]　实施例. 阶段2

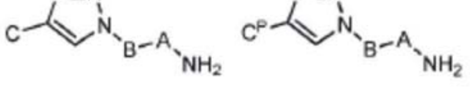
[0294]



[0295]　制备10,11-脱水-2',4"-二-O-苯甲酰基-12-O-咪唑基羰基-6-O-甲基红霉素A。在25-35℃下将二甲基甲酰胺(DMF,100mL)添加至2',4"-二-O-苯甲酰基-6-O-甲基红霉素A中，然后将1,8-二氮杂二环[5.4.0]十一碳-7-烯(DBU 6.4g)添加至反应混合物中并且在环境温度下搅拌。添加1,1'-羰基二咪唑(CDI,17g)到反应中并且在环境温度下将其搅拌直到完成。通过添加水并收集所得沉淀来分离标题化合物。

[0296]　实施例. 式(A)化合物

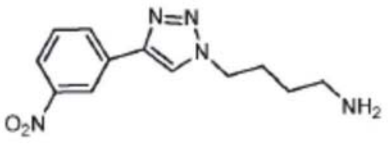
[0297]



(A)

[0298]　其中A、B、C及C^{P}在本文所述的每个实施方案中如本文中所定义，是使用常规方法来制备。类似地，式(A1)化合物

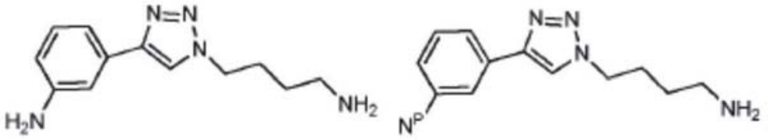
[0299]



(A1)

[0300] 是使用常规方法来制备。类似地，式(A2)化合物

[0301]

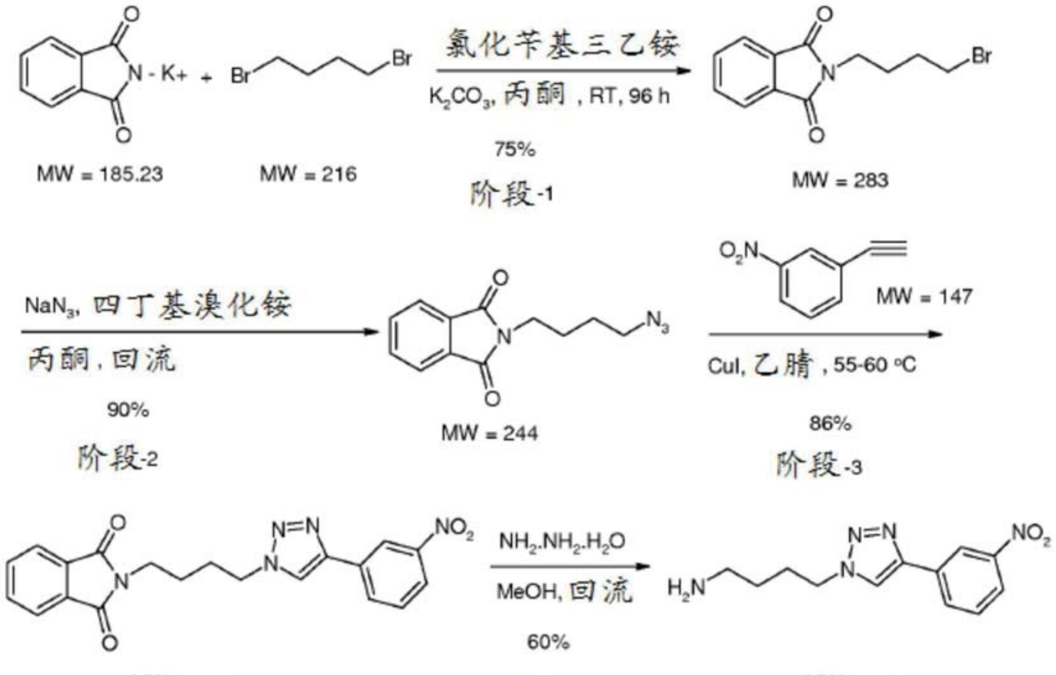


(A2)

[0302] 其中N^P在本文所述的每个实施方案中如本文中所定义，是使用常规方法来制备。应了解，式(A2)化合物的氨基苯基可在添加到中间体3之前被保护。氨基保护的酰胺、氨基甲酸酯、及脲衍生物也是使用常规方法来制备。

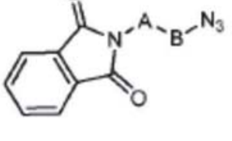
[0303] 实施例．示例性地，前述化合物可通过以下方法来制备，以式(A1)化合物作为示例：

[0304]



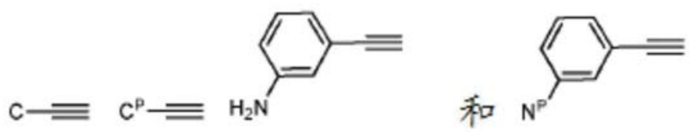
[0305] 应理解，前述方法可用于通过适当选择起始材料来制备式(A)和/或(A1)的化合物，包括其氨基保护的衍生物，所述起始材料如

[0306]



[0307] 及

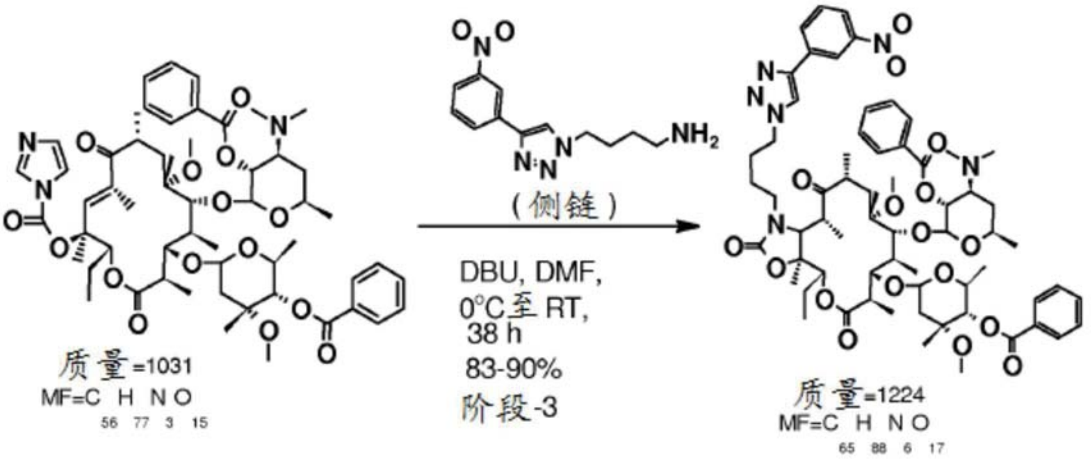
[0308]



[0309]　等等，其中 A、B、C、C^P、及 N^P 在本文所述的每个实施方案中如本文中所定义。

[0310]　实施例．阶段 3

[0311]



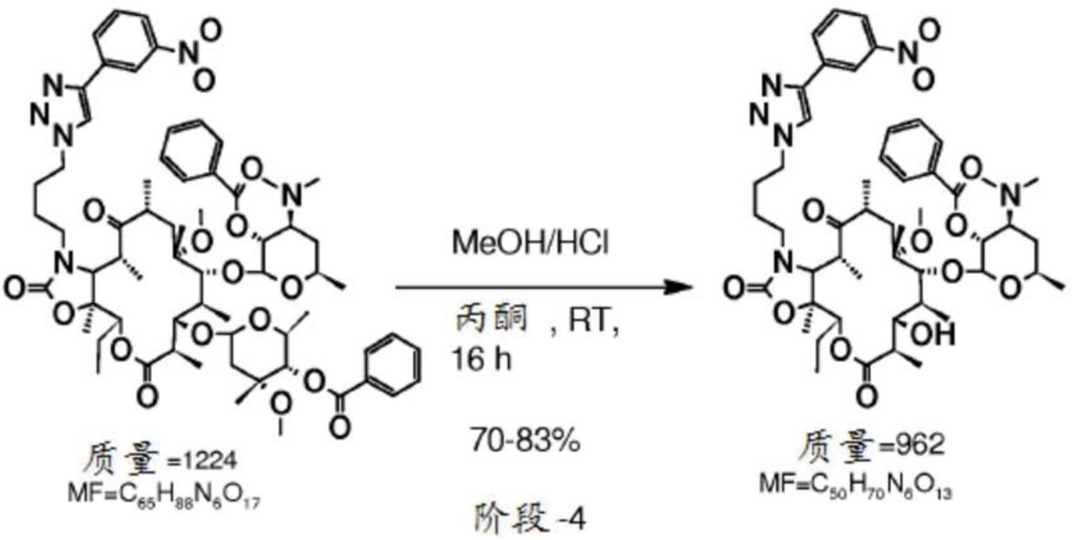
[0312]　在 0-5℃下向溶解于 3000mL DMF(5.0v，M/C<1.0％）中的溶液阶段 2 化合物中逐滴添加 DBU，接着逐份添加侧链。允许反应混合物达到室温并搅拌 36h。在 36h 之后记录的 HPLC 显示 <1％未反应的阶段 2 化合物。

[0313]　将反应混合物倾入冰冷水（6000mL）中并搅拌 2h。将固体过滤，用水（2500mL）洗涤并吸干 2h，获得 85％ HPLC 纯度的 650g 粗产物。

[0314]　将粗产物在室温下添加至乙酸乙酯（1500mL）与 1N 水性 HCl（1500mL）的双相溶液中并搅拌 1h。将固体过滤，用乙酸乙酯（600mL）洗涤并吸干持续 2h。将固体再次悬浮于乙酸乙酯（1500mL）中，在室温下搅拌 1h 并过滤。将滤饼在 40-45℃下在真空烘箱中干燥直到水分含量不超过 3％。获得 88％产率（620g）和 98％纯度的呈白色固体状的纯产物。

[0315]　实施例．阶段 4

[0316]



[0317]　在 0 至 5℃下向阶段 3 化合物在 1800mL 丙酮中的溶液中缓慢添加 272mL 甲醇 HCl

并且在相同温度下再搅拌反应混合物 30min。然后允许反应达到室温并搅拌 16h。

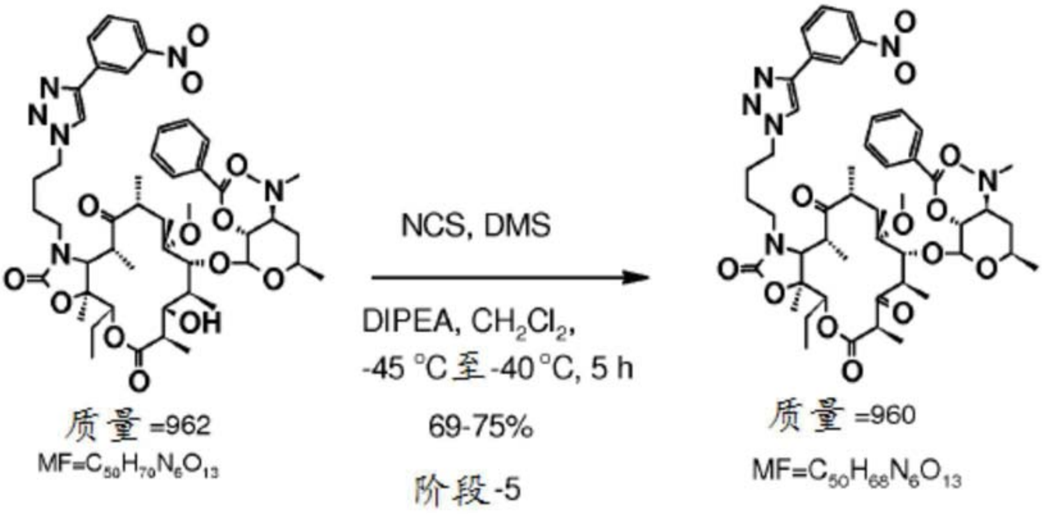
[0318]　反应完成之后，在减压下蒸馏反应混合物并获得呈树胶状残余物的产物。将粗物质与乙酸乙酯一起搅拌并且倾析以除去苯甲酰基克拉定糖及其他杂质。或者，将树胶状残余物溶解于水中，然后用甲苯萃取以除去苯甲酰基克拉定糖及其他杂质。接着，使用10％氢氧化钠水溶液碱化水层，然后用乙酸乙酯萃取以得到脱红霉糖产物。任选地，在用碳酸氢钠水溶液调整 pH 之后进行蒸馏。

[0319]　将悬浮液过滤并用丙酮(200mL)洗涤。使用碳酸氢钠饱和水溶液将滤液的pH调整至5并且在减压下(低于40-45℃)蒸馏溶剂丙酮和甲醇。将残余物用二氯甲烷(3×200mL)萃取并且将合并的有机层经无水硫酸钠干燥并蒸馏二氯甲烷以获得 130g 粗产物。HPLC 显示苯甲酰基克拉定糖和作为主峰的所要产物(总共显示 98 面积％)。

[0320]　在室温下在含 5％乙酸乙酯的己烷(40mL 乙酸乙酯和 760mL 己烷)中搅拌粗产物 2h 并过滤。将滤饼用含 5％乙酸乙酯的己烷(10mL 乙酸乙酯和 190mL 己烷)洗涤并在40-45℃下在真空烘箱中干燥直到注意到LOD超过1％且M/C不超过0.5％。获得 86.6％产率(132g)和 92.0％ HPLC 纯度的呈白色固体状的纯物质。

[0321]　实施例．阶段 5

[0322]



[0323]　在 -50℃下经 30 分钟时间向 N- 氯代琥珀酰亚胺溶解于 1600mL 二氯甲烷中的溶液中添加二甲基硫醚，维持温度在 -40 至 -35℃之间。在搅拌反应混合物 60min 之后，经 2h 时间添加阶段 4 化合物在 1400mL 二氯甲烷中的溶液，维持内部温度在 -40 至 -35℃之间。在 -45℃下将反应混合物再搅拌 90min(HPLC 显示<1％未反应的起始材料)且经 1h 时间小心地添加 177mL N- 二异丙基乙胺，维持内部温度在 -45 至 -40℃之间。将反应混合物升温至 10℃并搅拌 90min。

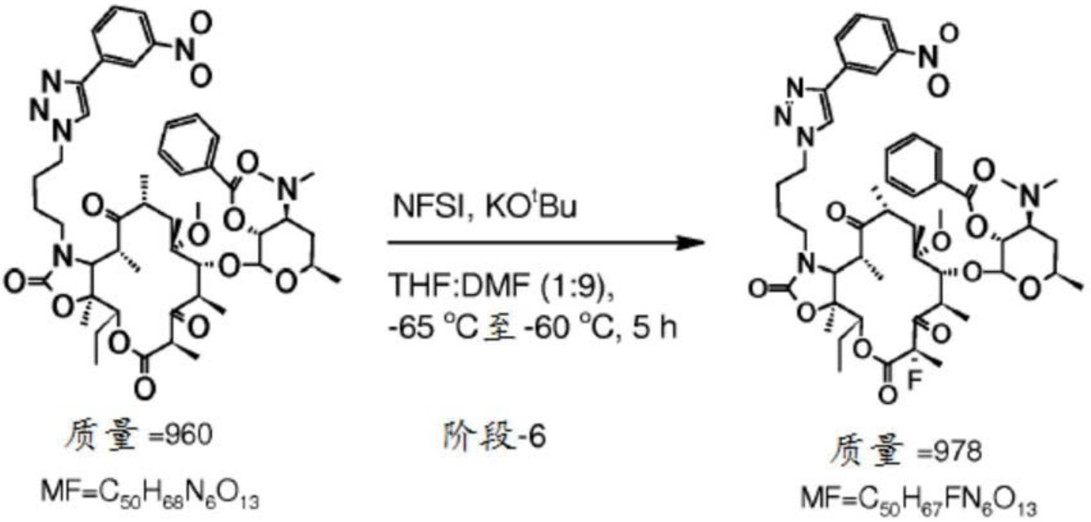
[0324]　向反应混合物中添加3000mL水并且将反应物质升温至室温(25-30℃)。将有机层分离并且用 1N 水性 HCl(2000mL)、水(2000mL)以及 10％碳酸氢钠水溶液(2000mL)相继地洗涤。然后将有机层经无水硫酸钠干燥并且在减压下蒸馏溶剂以获得 190g 具有 85％ HPLC 纯度的粗产物。

[0325]　将粗产物悬浮于 400mL MTBE 中并且在 55℃下加热 2h。将悬浮液冷却至室温并搅拌 1h。将固体过滤并且在 40-45℃下在真空烘箱中干燥以获得 LOD 不超过 1.0％且 M/C 不

超过 0.5%的纯产物。获得 89.1%产率 (178g) 和 93.0% HPLC 纯度的呈白色固体状的纯产物。

[0326] 实施例．阶段 6

[0327]

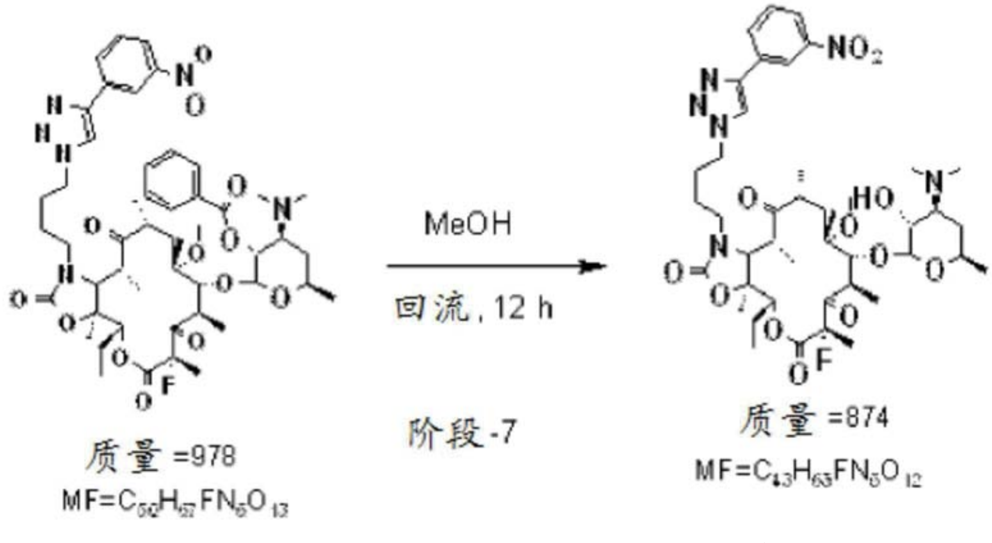


[0328] 在 -65 至 -60℃下向阶段 5 化合物溶解于 9:1DMF:THF(1350mL DMF 和 150mL THF) 混合物中的溶液中以 10 等份添加 K^{t}OBu 并且在相同温度下搅拌反应混合物 60min。将 NFSI 溶解于 DMF:THF(900mL DMF 和 100mL THF) 的 9:1 混合物中的溶液经 3-4h 的时间添加至反应混合物中，维持内部温度在 -65 至 -60℃之间。在相同温度下再搅拌内容物 60min。

[0329] 将反应混合物倾入 1000mL 饱和 $NaHCO_3$水溶液中，维持在 0℃下并搅拌 30min。将沉淀的固体过滤，用 2×100mL 水洗涤并且在 45-50℃下在真空烘箱中干燥直到 LOD 不超过 3.0%且 M/C 不超过 3%。获得 87.6%产率 (90g) 和 80-90% HPLC 纯度的呈棕色固体状的粗产物。可使用硅酸镁 (fluorisil) 上的柱色谱进行进一步纯化。

[0330] 实施例．阶段 7

[0331]



[0332] 将阶段 6 化合物溶解于 765mL 甲醇中的溶液在回流温度下加热 12h。12h 之后的 HPLC 显示 <1%的起始材料并且在此阶段添加木炭并在回流温度下再搅拌 2h。

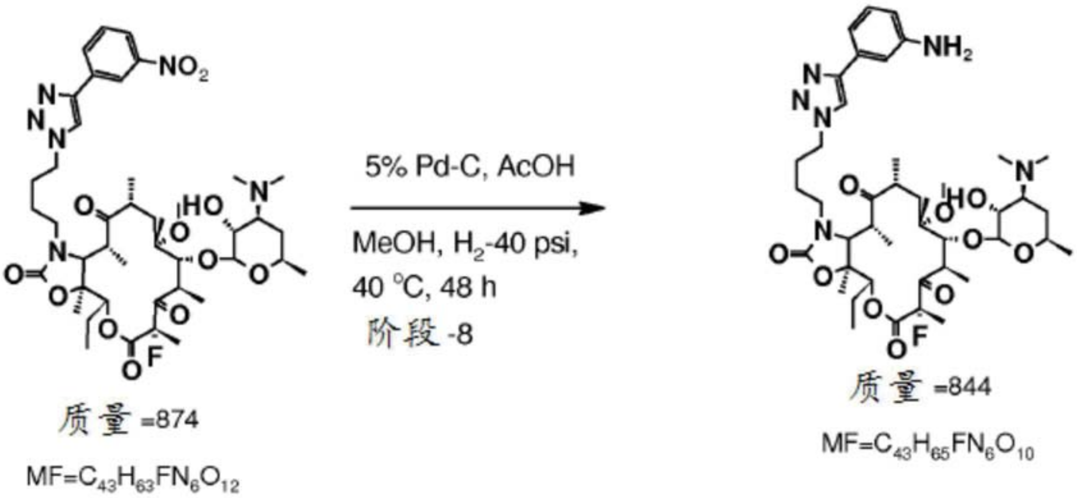
[0333] 将悬浮液经硅藻土床过滤并且将滤液在减压下（在 <45℃下）浓缩以得到呈棕色

树胶固体状的粗产物。

[0334] 在室温下在含 5% MTBE 的己烷（14mL MTBE 和 255mL 己烷）中搅拌粗产物 2h。过滤固体并且纯化用含 5% MTBE 的己烷（每次 14mL MTBE 和 255mL 己烷）再重复两次以获得 73g 的纯度为 90.54% 且呈浅棕色固体状的产物（90% 产率）。

[0335] 实施例．阶段 8

[0336]



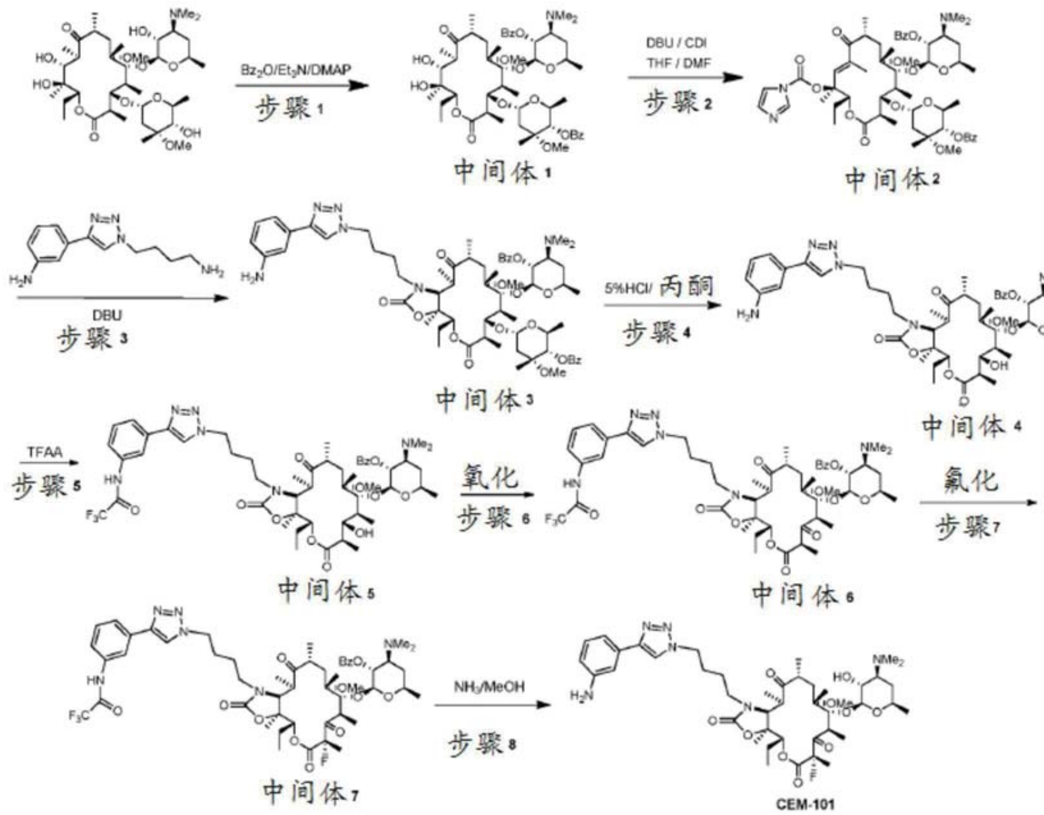
[0337] 向阶段 7 化合物溶解于 450mL 甲醇中的溶液中添加 1.0 当量乙酸，接着添加 3.3w/w% Pd-C。在 40℃下在 40psi 氢气压力下搅拌悬浮液 6h 并且 HPLC 显示 15% 的起始材料转化。添加第二批 6.6% w/w Pd-C 并且在 40℃下在 40psi 氢气压力下继续搅拌反应 24h。在此阶段，HPLC 显示 55% 的起始材料转化。添加第三批 3.3% Pd-C 至反应混合物中并且在 12h 之后观察到 <1% 未反应的起始材料。

[0338] 将反应混合物冷却至室温并且将悬浮液经由硅藻土床过滤。将滤饼用 200mL 甲醇洗涤并且使合并的滤液经受在减压下（低于 45℃温度）的蒸馏以获得树胶状固体。将该树胶状固体溶解于 125mL 二氯甲烷中并且用 25mL 氨水溶液洗涤。将有机层经硫酸钠干燥并且蒸馏二氯甲烷，获得 80% HPLC 纯度的呈浅棕色固体状的粗产物（21g）。

[0339] 将粗产物悬浮于 50mL IPA 中并且在 55-60℃下搅拌 3 天。允许悬浮液冷却至室温并过滤。将滤饼用 25mL 冷 IPA 洗涤并且在 40-45℃下在真空中干燥以获得 12.6g(52% 产率）的纯度为 94% 的产物。

[0340] 实施例．CEM-101 是根据以下方法来制备。

[0341]



[0342] 实施例．中间体4．中间体4是如PCT国际公布号WO/2009/055557和WO/2011/146829中所述由克拉霉素制备，且一般是根据流程1中所示的方法。62g中间体1是由克拉霉素制备，产率为80％。15g中间体2是由中间体1制备，产率为93％。中间体2的环化得到6.6g中间体3，产率为86％。克拉定糖从中间体3步骤4中的去除得到4.4g中间体4，产率为85％。产物的鉴定通过质谱法和NMR来证实。

[0343] 实施例．中间体5．在0℃下将三氟乙酸酐(113mg，0.54mmol)逐滴添加至中间体4(500mg，0.54mmol)在无水DCM(9mL)中的溶液中。添加之后，在0℃下搅拌反应混合物1h。将反应混合物用DCM稀释，用稀NaHCO$_3$水溶液和盐水连续洗涤，且经无水MgSO$_4$干燥。过滤之后，将滤液浓缩至干燥以得到450mg呈浅棕色固体状的粗中间体5。粗中间体5的质谱分析显示作为主要组分的所要产物峰。粗中间体5的^{1}H-NMR光谱显示对应于所要产物结构的峰。^{1}H-NMR光谱还显示存在未反应的中间体4。所述物质(～85％纯度)在未进一步纯化的情况下使用。

[0344] 实施例．中间体6．向中间体5(100mg，0.097mmol，～85％纯度)在无水DCM(3mL)中的溶液中添加Dess-Martin高碘烷(50mg，0.116mmol，1.2当量)。在室温下搅拌所得的反应混合物1.5h。将反应混合物用DCM稀释，用硫代硫酸钠水溶液和盐水连续洗涤，且经无水MgSO$_4$干燥。在过滤之后，将滤液浓缩至干燥。使粗产物经受硅胶柱色谱(洗脱剂：丙酮/DCM，20/80，v/v)得到55mg呈白色固体状的纯中间体6，产率为72％。中间体6的^{1}H-NMR光谱证实产物的结构及其良好的纯度。

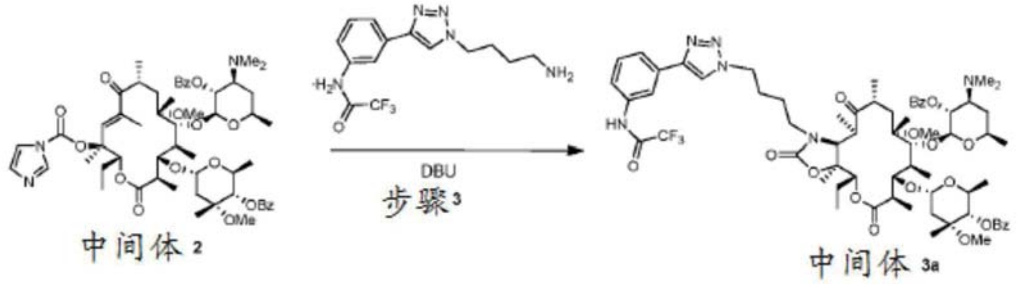
[0345] 实施例．中间体7．将中间体6(82mg，0.08mmol)在DMF(1mL)中的溶液冷却至-30℃。添加DBU(14mg，0.088mmol)，且在-30℃下搅拌所得的混合物20min。向在-30℃下搅拌的反应混合物中逐滴添加NSFI(25mg，0.08mmol)在DMF(1mL)中的溶液。添加之后，在-30℃下搅拌反应混合物20min。将反应混合物用稀NaHCO$_3$水溶液淬灭并用DCM萃取。

将合并的DCM萃取物用盐水洗涤，且经无水$MgSO_4$干燥。过滤之后，将滤液浓缩至干燥。使粗产物经受硅胶柱色谱（洗脱剂：丙酮/DCM，20/80，v/v），得到86％产率的61mg呈白色固体状的纯中间体7。中间体7的^{1}H-NMR光谱证实所要产物结构及其良好的纯度。

[0346] 实施例.CEM-101.在室温下搅拌中间体7(60mg)在含0.3mL NH_4OH的甲醇(1mL)中的溶液过夜。反应混合物的等分试样的质谱分析显示作为主要组分的具有对应于CEM-101的Mw的峰以及未反应的中间体7。将反应混合物用DCM稀释，用水和盐水连续洗涤，并且经由无水$MgSO_4$干燥。在过滤之后，将滤液浓缩至干燥。将粗产物溶解于甲醇(10mL)中并在回流下加热1小时。将反应混合物浓缩至小体积并使残余物经受硅胶柱色谱（洗脱剂：DCM/MeOH/NH_4OH，95/5/0.5，体积比）以得到40mg CEM-101。^{1}H-NMR光谱证实所要产物结构。

[0347] 实施例．合成中间体3a

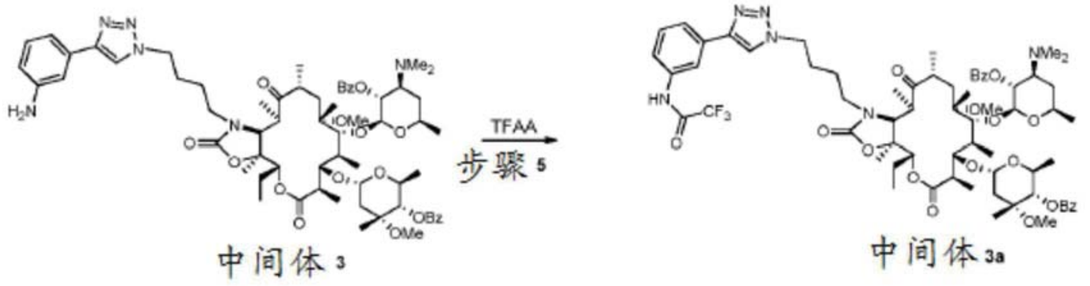
[0348]



[0349] 将中间体2(1.0g)、受保护的侧链-HCl盐(1.3当量)、DBU(2.5当量)、以及DMF的混合物在40-70℃下在氮气下加热伴随搅拌。反应进程通过TLC、HPLC、及MS来监测。完成时，将混合物分配在DCM与盐水之间，用水洗涤，经无水$MgSO_4$干燥，过滤并蒸发。将残余物通过HPLC纯化以得到≥90％产率的标题化合物。^{1}H NMR光谱和质谱(MW 1292)与标题化合物一致。

[0350] 实施例．合成中间体3a

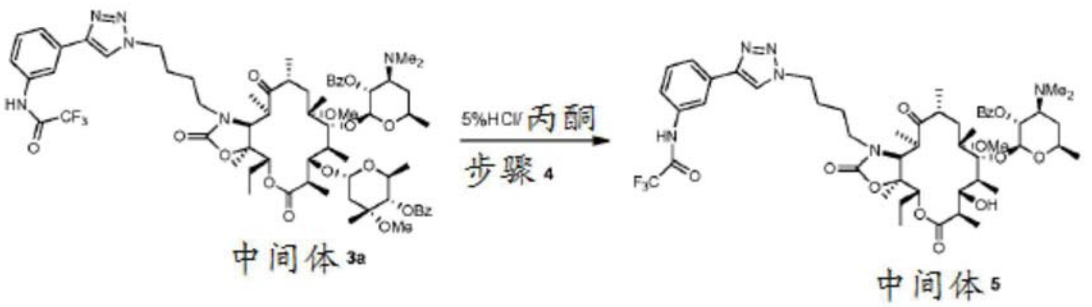
[0351]



[0352] 将中间体3(650mg，0.544mmol)在无水DCM(10mL)中的溶液用冰浴冷却至5℃。向其中添加三氟乙酸酐(172mg，0.82mmol，1.5当量)，并且在5℃下搅拌所得反应混合物10min，之后经1.5小时逐渐升温至环境温度。将反应用冰冷的稀$NaHCO_3$水溶液淬灭并用DCM萃取。将合并的DCM萃取物用盐水洗涤并经无水$MgSO_4$干燥。将干燥剂通过过滤除去，并且将滤液浓缩至干燥。将粗产物经由硅胶柱色谱（洗脱剂：DCM/MeOH/NH4OH＝95/5/0.5，体积比）纯化，以77％产率得到540mg产物。产物的^{1}H-NMR光谱和质谱都显示证实所要的中间体3a结构的峰。

[0353] 实施例．合成中间体5

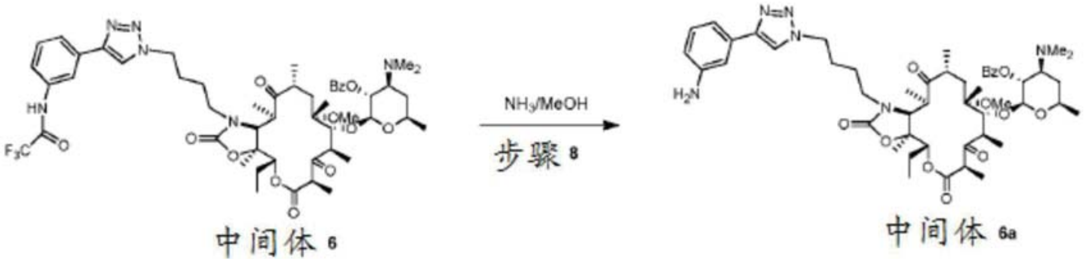
[0354]



[0355] 向中间体 3a(150mg,0.116mmol) 在丙酮 (3mL) 中的溶液中添加 DBU(35mg,0.233mmol,2.0 当量),接着添加浓 HCl(300μL)。在室温下搅拌所得反应混合物 5 小时。反应混合物的等分试样的质谱分析显示具有清楚反应特征的完全反应。将反应混合物倾入 DCM 与冰冷水的混合物中。通过添加稀 NH$_4$OH 使混合物变为碱性并用 DCM 萃取。将合并的 DCM 萃取物用盐水洗涤,经无水 MgSO$_4$干燥。通过过滤除去干燥剂,并将滤液浓缩至干燥。将粗产物经由硅胶柱色谱 (洗脱剂 :DCM/MeOH/NH4OH = 95/5/0.5,体积比) 纯化,以 86%产率得到 103mg 中间体 5。产物的 ^{1}H-NMR 光谱和质谱显示对应于预期具有良好纯度的所要中间体 5 的结构的峰。

[0356] 实施例 . 合成中间体 6a

[0357]



[0358] 向中间体 6(1.0mmol) 在甲醇 (10mL) 中的溶液中添加氢氧化铵溶液 (NH$_4$OH,30mmol)。在环境温度下搅拌所得的澄清溶液过夜以得到浑浊的反应混合物。将反应混合物浓缩至干燥,溶解于 DCM 中,用稀 NaHCO$_3$水溶液和盐水连续洗涤,然后经无水 MgSO$_4$干燥。在过滤以除去干燥剂之后,浓缩滤液至干燥,得到 0.8mmol 中间体 6a(90%产率)。1H-NMR 光谱和质谱与标题化合物一致。