

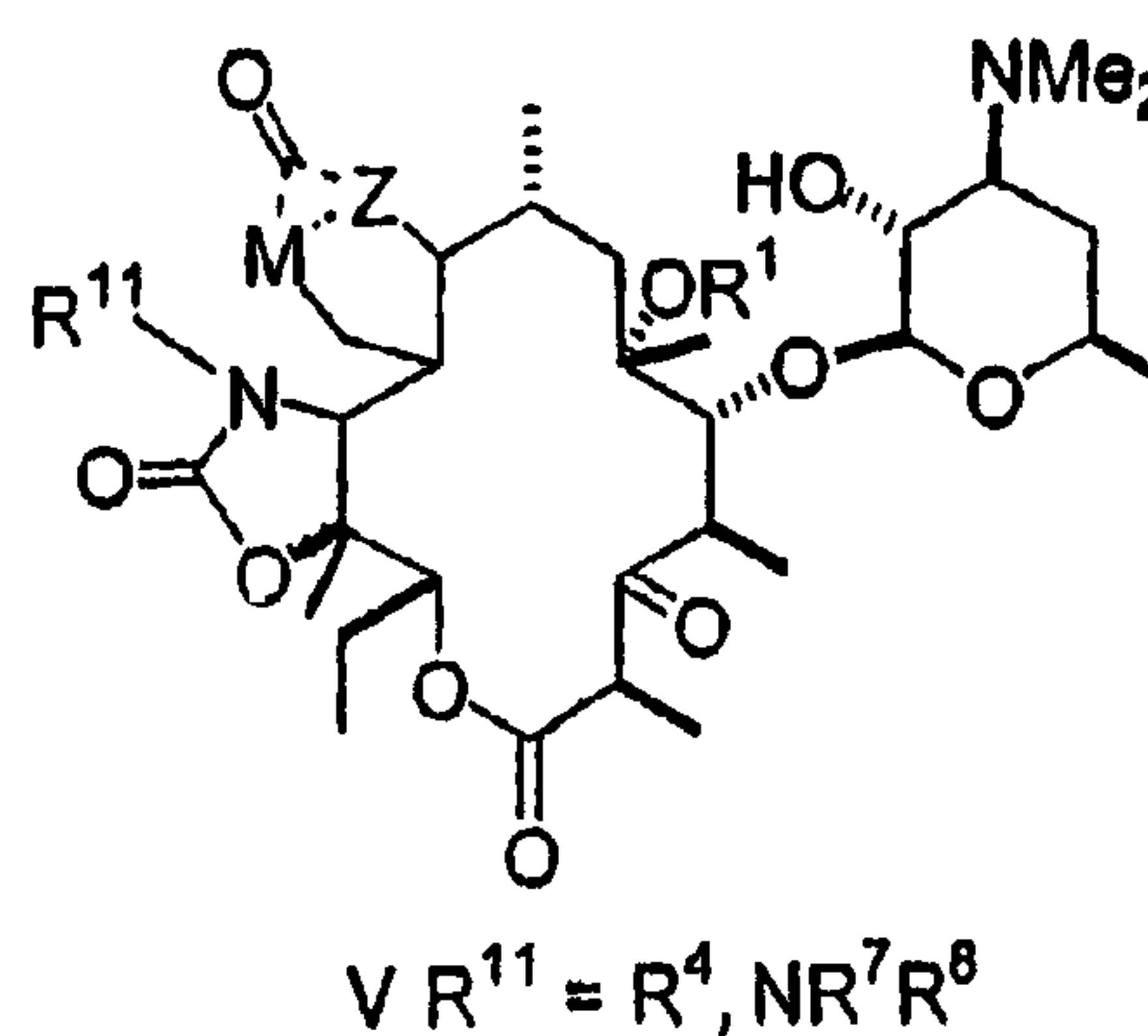
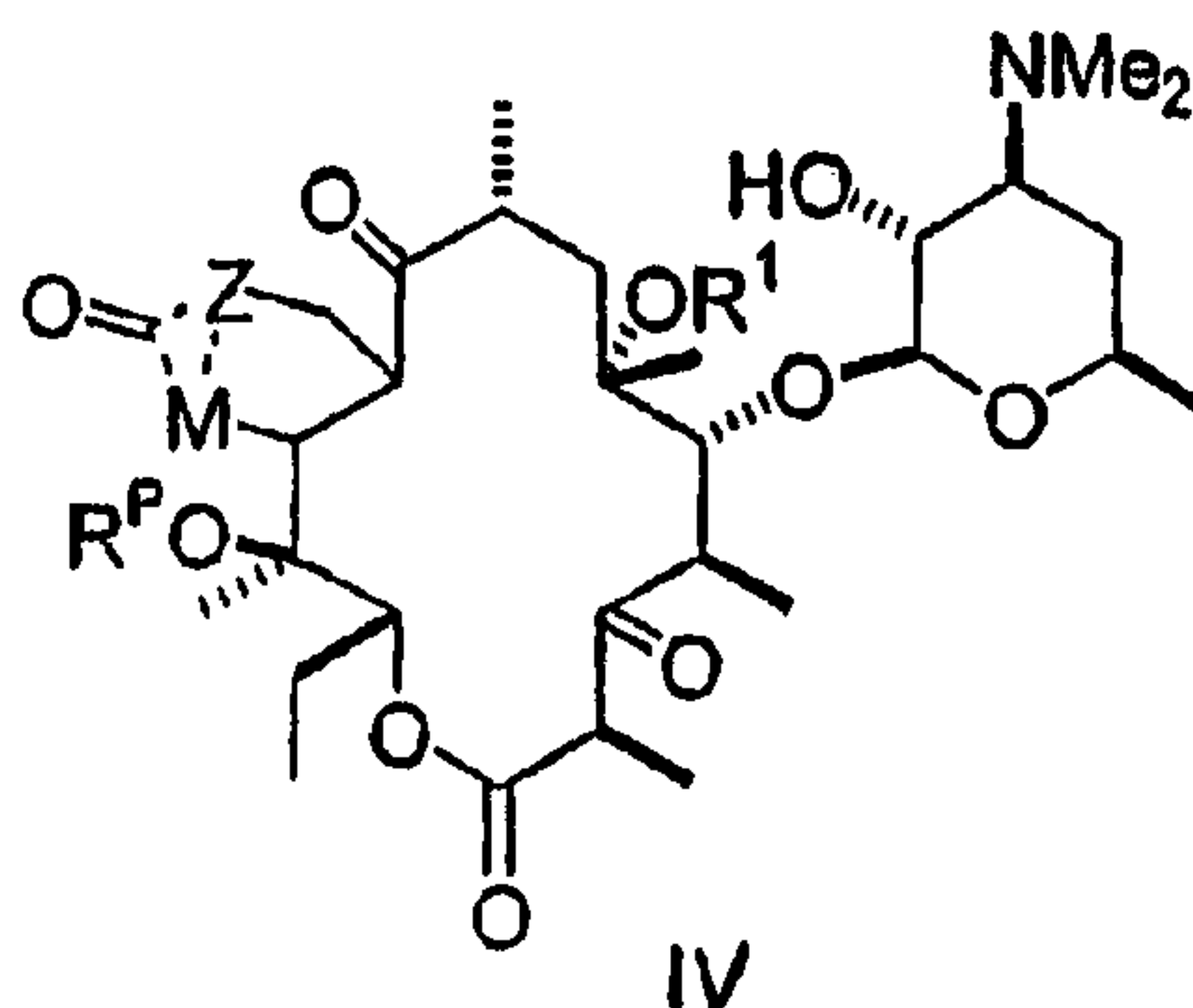
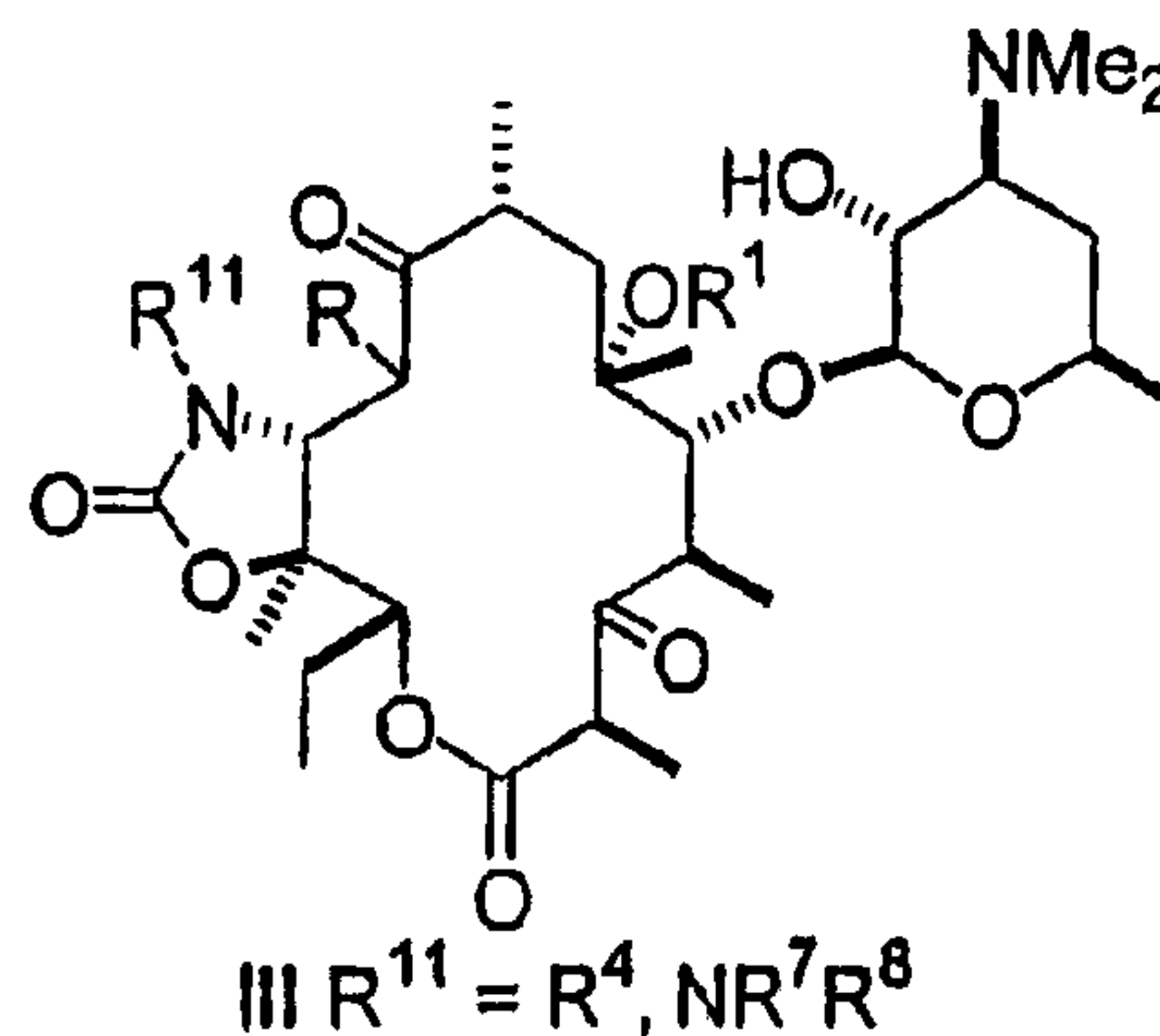
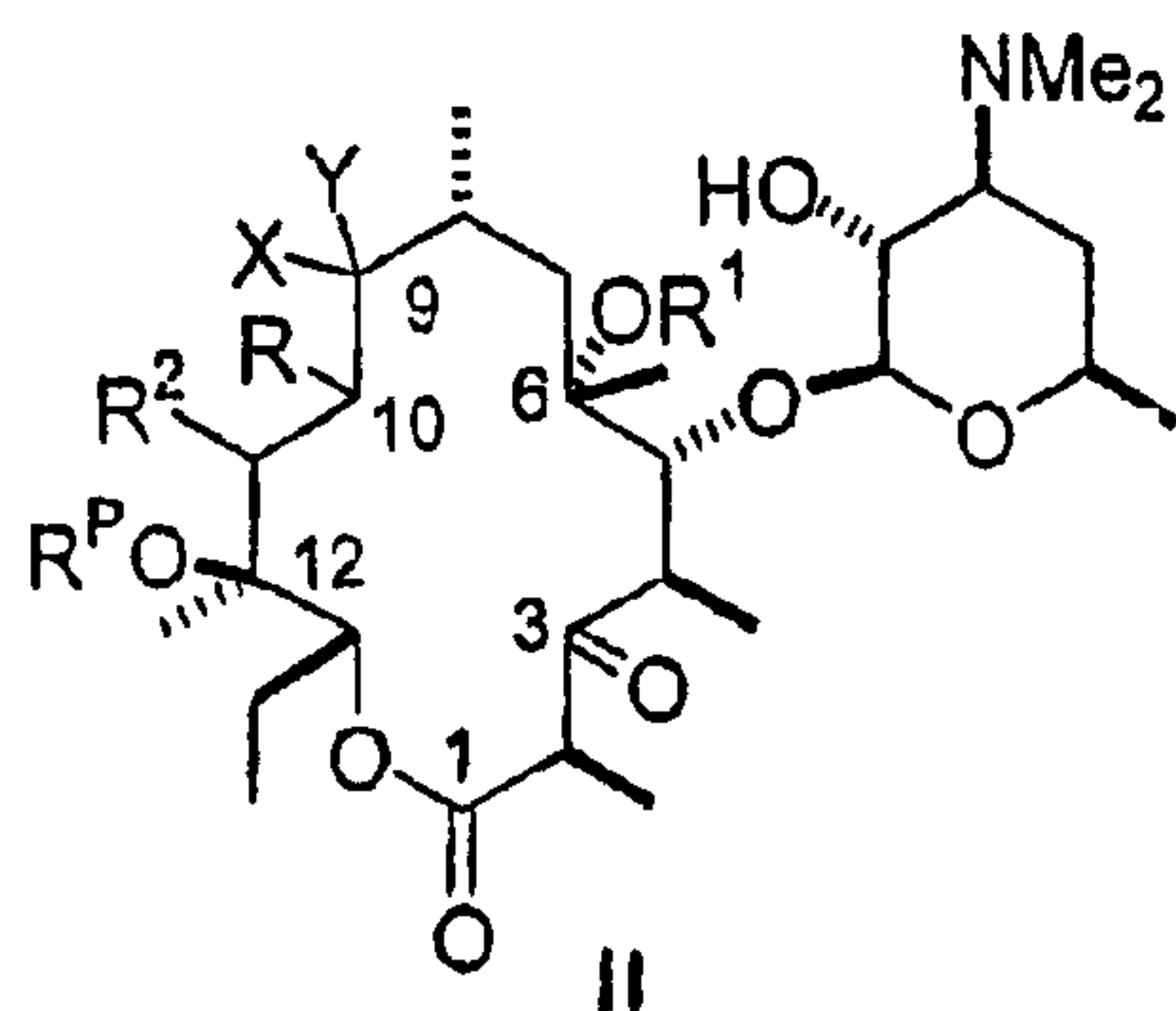


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(54) Titre : MACROLIDES

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(57) Abrégé/Abstract:

The application provides antibiotic 10-substituted 10-desmethyl macrolides. In a preferred embodiment the macrolides have an erythromycin basic structure according the formula, wherein the variable substituents have the meaning indicated in the description.



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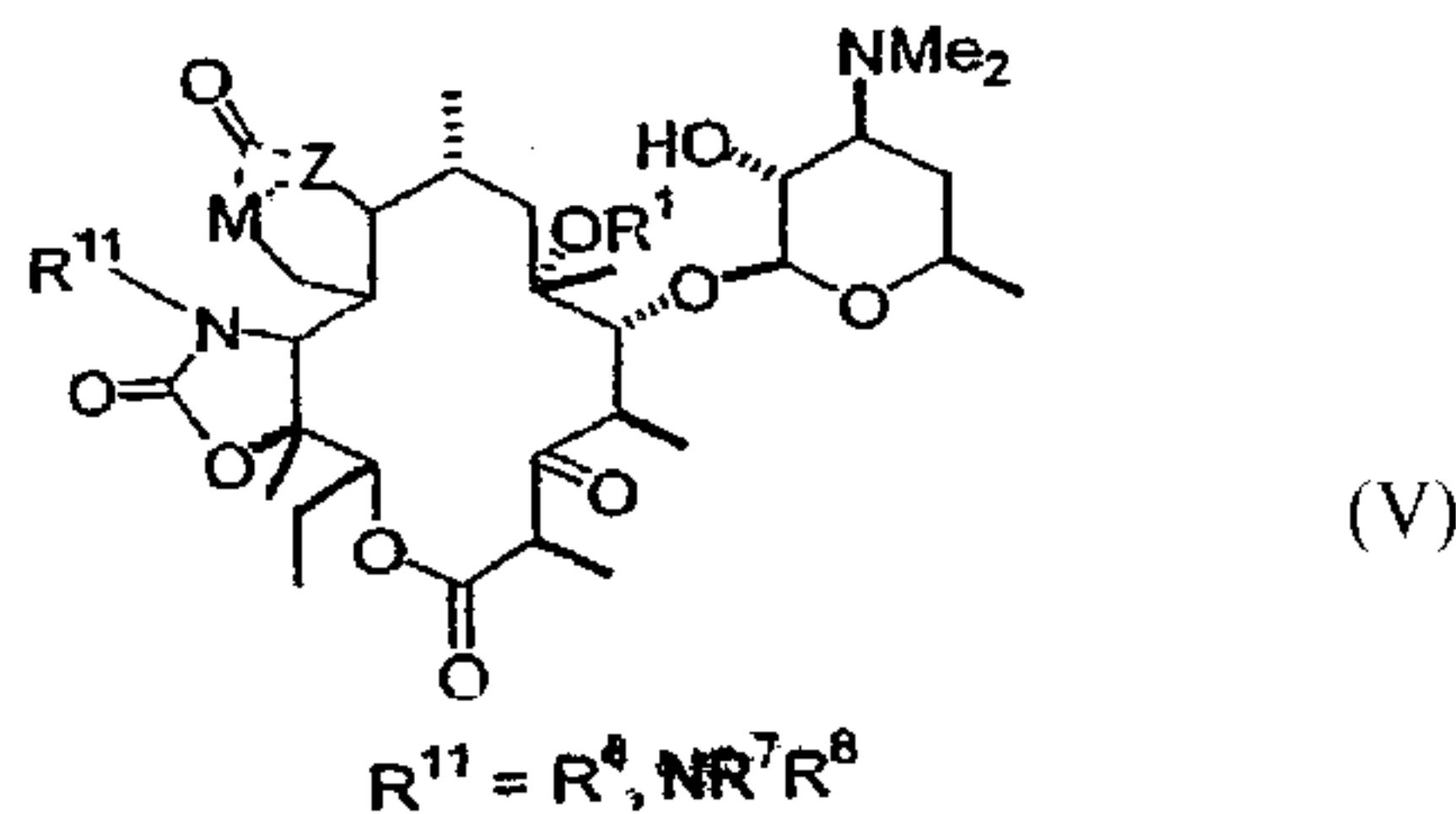
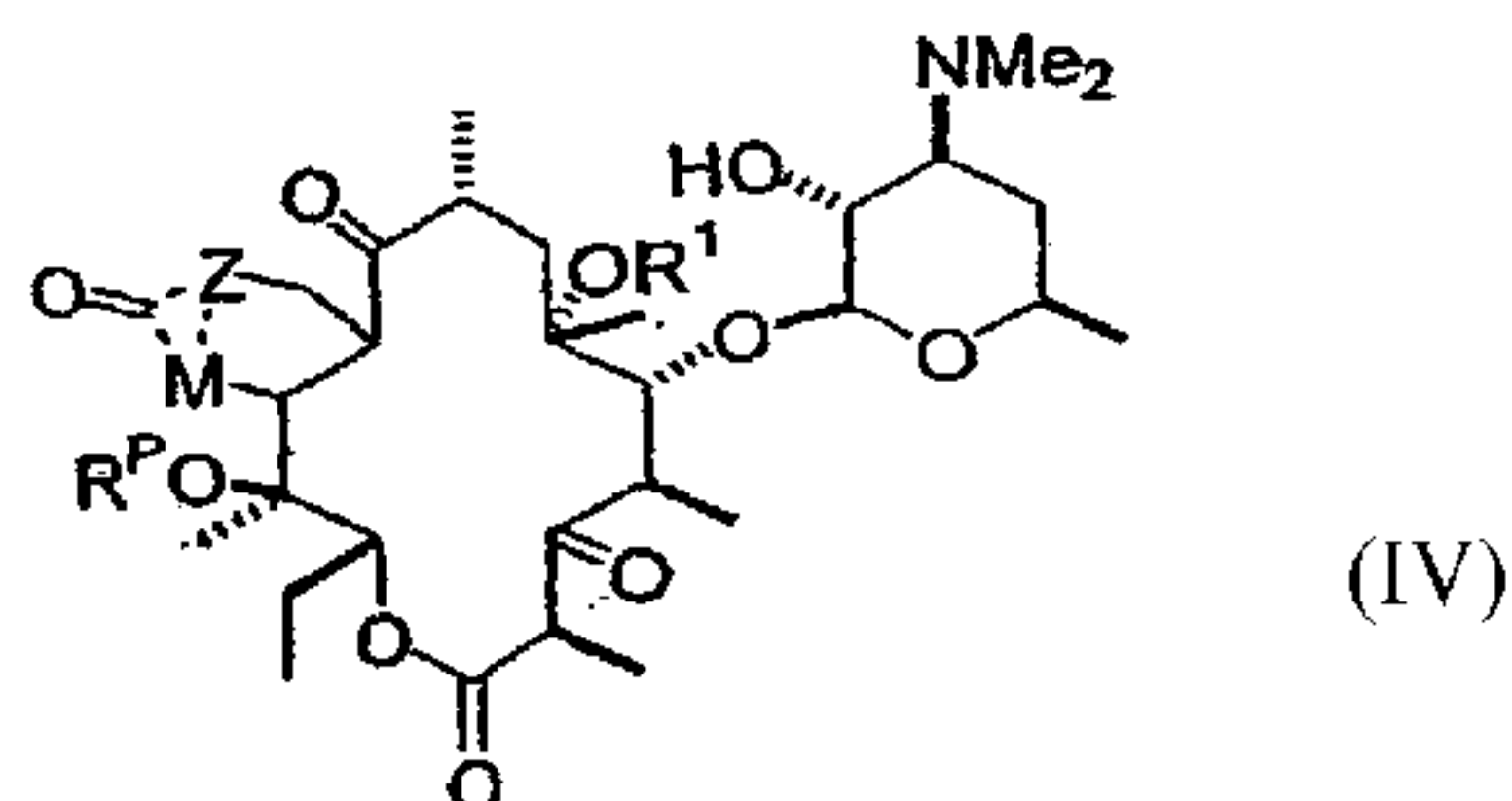
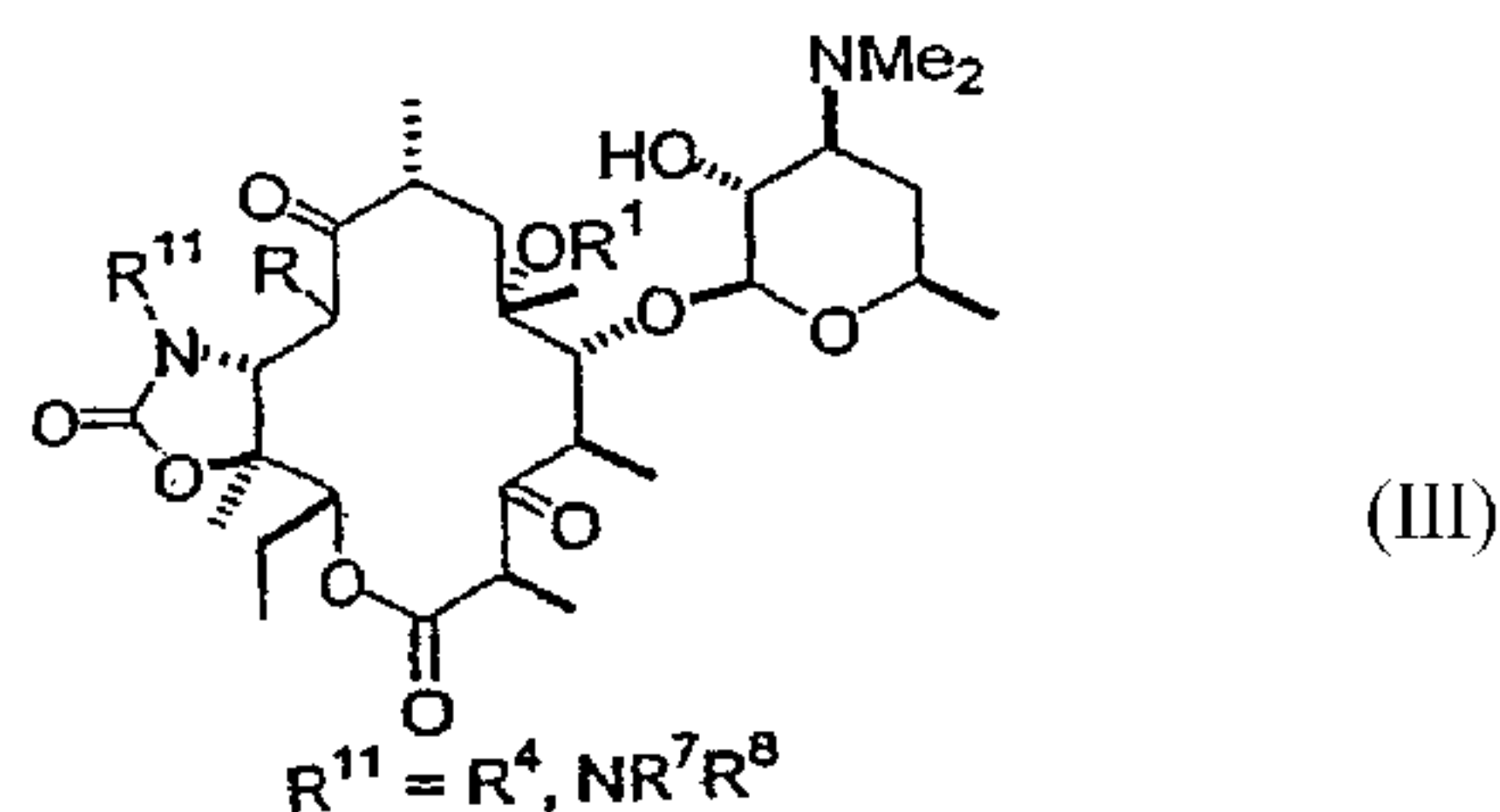
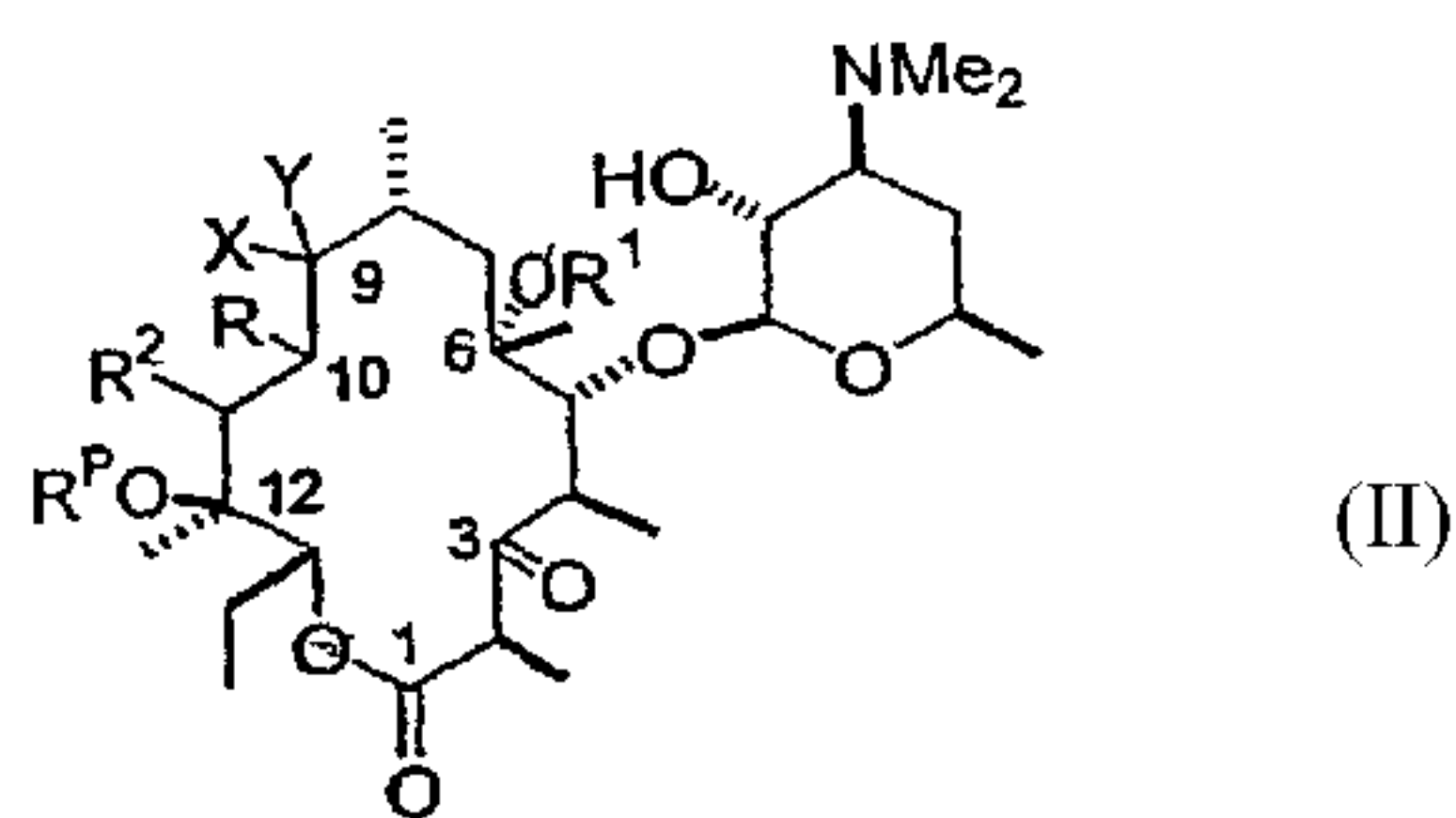
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(54) Title: 10-SUBSTITUTED MACROLIDE ANTIBIOTICS



(57) Abstract: The application provides antibiotic 10-substituted 10-desmethyl macrolides. In a preferred embodiment the macrolides have an erythromycin basic structure according the formula, wherein the variable substituents have the meaning indicated in the description.

WO 2004/056843 A3

Macrolides

5 This invention relates to a novel class of antibiotic agents, more specifically 10-desmethyl, 10-substituted-macrolides, their preparation, pharmaceutical compositions containing them, their use and methods of treatment using them.

10 The macrolide antibiotics are a large class of compounds, many derived from *Streptomyces* spp, which comprise a saturated $C_{13}ON_x$ (where x is 0 or 1) macrocyclic lactone ring substituted by one or more sugars, generally at the 5-carbon and optionally also at
15 the 3-carbon. One early example is erythromycin A which has a $C_{13}O$ ring substituted by sugars at the 3 and 5 ring carbons (the ester carbonyl is at the 1 position and the ester ring oxygen at the 14 position).

 Later generation macrolide antibiotics include
20 clarithromycin (which is methoxy substituted at the 6-carbon), azithromycin (which has a ring nitrogen between the 9- and 10- carbons, i.e. at the 9a position), telithromycin (which is oxo-substituted at the 3-carbon, methoxy-substituted at the 6- carbon, and has
25 the 11- and 12- carbons substituted by a bridging N-(4-(pyridin-3-yl)-imidazol-1-yl-butyl) cyclic carbamate group), roxithromycin (which is substituted at the 9 position an O-alkylated oxime group), dirithromycin (which is substituted at the 9 and 11 positions by a
30 substituted oxazine group), flurithromycin (which is 8-substituted by fluorine), CP 544372 (which is substituted on the 4' position of the 3-attached sugar by a 2-methoxyphenyleth-1-yl-N-ethyl- aminoethyl-aminocarbonyloxy group and at the 9 position by an amino
35 group), and cethromycin (which is substituted at the 3 position by an oxo group, at the 6 position by a quinolin-3-yl allyloxy group and at the 11 and 12

positions by a cyclic urethane group). Further known antibiotic macrolides include A20316, A69334, A66321, A60565, A216599, A217213, A229339, A241550, CP642959, CP654743, CP642957, CP647762, CP647763, FMA122, FMA174, 5 FMA187, FMA199, FMA367, FMA481, HMR3004, HMR3562, HMR3787, L701677, RWJ415663, RWJ415667, TE604, TE802, TE810, TEA777 and TEA824. Other examples may be found in Asaka et al. Current Topics in Medicinal Chemistry 3: 961-989 (2003) and Wu et al Current Medicinal Chemistry 10 8: 1727-1758 (2001) and the references therein.

The 3-oxo-substituted macrolides are also referred to as ketolides.

15 A further general feature of the known macrolides is that the 5-sugar is 3'-substituted by a secondary nitrogen (e.g. by a $-N(CH_3)_2$ group), that the 6-carbon carries a hydroxy or substituted hydroxy group, and that they are methyl-substituted at the 2, 4, 6, 8, 10 and 20 12- carbons.

As with antibiotics in general, there is an ongoing need for novel macrolide antibiotics as drug resistance to the existing compounds appear. There is also a need to increase the activity profile, i.e. the antibacterial 25 toxicity and the range of bacteria against which the macrolide antibiotics are toxic.

While modifying the ring substitution of the macrolides at many ring positions, in particular at the 3, 5, 6, 8, 9, 11 and 12 carbons and between the 9- and 30 11- carbons and between the 11- and 12- carbons, has been widely suggested, in the over 50 years since the development of erythromycin it has not to our knowledge been suggested that useful new macrolide antibiotics can be produced by modifying the substitution of the 10- 35 carbon. Methyl substitution at the 10- carbon appears to have been uniformly considered to be essential. This is nicely illustrated by Chiron's recent PCT application

WO 03/004509 which shows optional substitutional
modification at the 2, 4, 6, 9, 11, 12 and 13 carbons
(and remember the known macrolide flurithromycin has
substitutional modification at the 8- carbon) but still
5 mandates retention of the methyl groups at the 2, 4, 6,
8 and 10 carbons.

We have now surprisingly found that 10-desmethyl
macrolides, i.e. macrolides carrying a substituent (but
one other than methyl) at the 10- carbon, have desirable
10 antibiotic properties.

Thus viewed from one aspect this invention provides
10-substituted-10-desmethyl macrolides.

Viewed from a further aspect the invention provides
a pharmaceutical composition comprising an antibiotic
15 10-substituted-10-desmethyl macrolide together with at
least one pharmaceutical excipient.

Viewed from a still further aspect the invention
provides the use of an antibiotic 10-substituted-10-
desmethyl macrolide for the manufacture of a medicament
20 for use in the treatment or prevention of infection in
animals, preferably mammals.

Viewed from a yet still further aspect the
invention provides a method of treatment of a human or
animal (preferably mammalian) subject to combat
25 bacterial infection thereof, which method comprises
administering to said subject an antibacterially
effective amount of an antibiotic 10-substituted-10-
desmethyl macrolide.

Where referred to herein, a 10-desmethyl macrolide
30 is a macrolide having a non CH₃ substituent at the 10-
carbon of a C₁₃ON_x lactone ring, preferably one having a
carbon-attached substituent at the 10-carbon.

In the 10-desmethyl macrolides of the invention,
substitution at all other ring positions may be as
35 described in the literature for 10-methyl macrolides.
Particularly preferably the substitution pattern, other
than at the 10-carbon, for each position is selected

from the set of substituents present in the known macrolides mentioned above. Thus the 2 carbon is preferably methyl or methyl and fluorine substituted, the 3 carbon preferably is oxo, or optionally substituted hydroxy (e.g. sugar (e.g. cladinosyl) or acyloxy-substituted), the 4 carbon is preferably methyl substituted, the 5 carbon is preferably sugar substituted (especially substituted by an oxygen-attached desosamine), the 6- carbon is preferably methyl and hydroxy or substituted hydroxy (e.g. methoxy or arylalkyloxy) substituted, the 7 carbon is preferably unsubstituted, the 8 carbon is preferably methyl or methyl and fluorine substituted, the 9 carbon is preferably unsubstituted (where the ring is C₁₃ON) or oxo, amino or imino substituted (which groups themselves may be substituted or form part of a bridging structure), especially oxo substituted, the 11 carbon is preferably hydroxyl, amino or substituted hydroxyl or amino substituted, the 12 carbon is preferably methyl and hydroxy or amino or substituted hydroxy or amino substituted, or more preferably the 11 and 12 carbons and optionally also the 10 carbon are substituted by groups forming a fused ring, and the 13 carbon is preferably ethyl substituted. The substituting groups, especially at the 6, 11 and/or 12 carbons or a 9a nitrogen may optionally together form a fused cyclic group, e.g. at the 11 and 12 carbons, and may desirably carry pendant aromatic groups, especially aromatic rings containing 5 to 10 ring atoms.

Such substituents at the positions conventionally substituted in the known macrolides may be introduced by synthetic techniques conventional in macrolide synthesis or by using a correspondingly substituted conventional macrolide as a starting material.

The group at the 10 carbon is preferably methylene (=CH₂), CHO or an optionally substituted carboxy group or a substituted methyl group, e.g. a methyl group

substituted by one or more groups selected from N₃, halo, cyano, carboxy, substituted carboxy, amino, substituted amino (e.g. alkylamino, aralkylamino, etc.), C₁₋₆ alkyl, alkenyl or alkylaryl, aryl, aralkyl, arylkenyl, aralkynyl, hydroxy, substituted hydroxy (e.g. acyloxy) or a group forming a bridge to a substituent on the 11 carbon or, less preferably, the 9 carbon. The 10-substituent however is desirably either polar (e.g. nitrogen containing) or small, e.g. having a total of no more than 6 non-hydrogen atoms.

Unless otherwise specified herein, alkyl, alkenyl, alkynyl moieties preferably contain up to 6 carbons; aryl moieties preferably contain 5 to 10 ring atoms selected from C, N, O and S, especially C and N, especially preferably 0, 1 or 2 being heteroatoms, especially N atoms; and acyl groups are preferably alkylcarbonyl or aralkylcarbonyl groups, optionally ones in which the alkylene group is interrupted by aza groups.

In a particularly preferred embodiment the substitution pattern on a C₁₃O macrolide according to the invention (where the 7-carbon is unsubstituted) is substituted: in the 2-position by methyl and hydrogen or fluorine; in the 3-position by oxo or optionally substituted hydroxy; in the 4-position by methyl; in the 5-position by an oxygen-attached desosamine; in the 6-position by methyl and an optionally substituted hydroxyl; in the 8-position by methyl and hydrogen or fluorine; in the 9-position by oxo; in the 10-position by methylene, CHO, substituted methyl, or carboxy or substituted carboxy; in the 11- and 12-positions by a group forming a fused ring at the 11, 12 and optionally 10-positions; at the 12-position additionally by a methyl group; and at the 13-position by an ethyl group.

The 10-desmethyl macrolides of the invention may, depending on their substitution pattern, be in the form of salts with physiologically tolerable counterions.

Such counterions, e.g. sodium, chloride, ammonium, meglumine, etc, are well known in the pharmacological field.

- Further examples of substituents at the 10 carbon
- 5 include
- (1) methyl substituted with one or more substituents selected from the group consisting of
- (i) CN,
- (ii) F,
- 10 (iii) CO_2R^3 wherein R^3 is selected from hydrogen, C_1 - C_3 -alkyl or aryl substituted C_1 - C_3 -alkyl, or heteroaryl substituted C_1 - C_3 -alkyl,
- (iv) OR^4 wherein R^4 is selected from hydrogen, C_1 - C_4 -alkyl or aryl substituted C_1 - C_4 -alkyl, or heteroaryl
- 15 substituted C_1 - C_4 -alkyl, heterocycloalkyl and optionally substituted cycloalkyl, C_1 - C_3 -alkoxy- C_1 - C_3 -alkoxy, C_1 - C_4 -alkenyl or aryl substituted C_1 - C_4 -alkenyl, or heteroaryl substituted C_1 - C_4 -alkenyl, heterocycloalkyl and optionally substituted cycloalkyl, aryl or optionally
- 20 substituted aryl, heteroaryl or optionally substituted heteroaryl,
- (v) $\text{S}(\text{O})_n\text{R}^3$ wherein $n = 0, 1$ or 2 and R^3 is as previously defined
- (vi) $\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined
- 25 (vii) $\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 is defined as defined previously, and R^5 and R^6 are independently selected from hydrogen, C_1 - C_3 -alkyl, C_1 - C_3 alkyl substituted with aryl, substituted aryl, heteroaryl, substituted heteroaryl
- (viii) NR^7R^8 wherein R^7 and R^8 are independently selected
- 30 from the group consisting of
- (a) hydrogen
- (b) C_1 - C_{12} -alkyl, and optionally substituted C_1 - C_{12} -alkyl
- (c) C_2 - C_{12} -alkenyl, and optionally substituted C_2 - C_{12} -alkenyl
- 35 (d) C_2 - C_{12} -alkynyl, and optionally substituted C_2 - C_{12} -alkynyl
- (e) aryl, and optionally substituted aryl

- (f) heteroaryl, and optionally substituted heteroaryl
- (g) heterocycloalkyl, and optionally substituted heterocycloalkyl
- (h) C₁-C₁₂ alkyl substituted with aryl, and optionally substituted with substituted aryl
- (i) C₁-C₁₂ alkyl substituted with heteroaryl, and optionally substituted with substituted heteroaryl
- (j) C₁-C₁₂ alkyl substituted with heterocycloalkyl, and with optionally substituted heterocycloalkyl, and
- (k) R⁷ and R⁸ taken together with the atom to which they are attached from a 3-10- membered heterocycloalkyl ring which may contain one or more additional heteroatoms and may be substituted with one or more substituents independently selected from the group consisting of
 - (aa) halogen, hydroxy, C₁-C₃-alkoxy, alkoxy-C₁-C₃-alkoxy, oxo, C₁-C₃-alkyl, aryl and optionally substituted aryl, heteroaryl and optional substituted heteroaryl
 - (bb) CO₂R³ wherein R³ is as previously defined, and
 - (cc) C(O)NR⁵R⁶ wherein R⁵ and R⁶ are as previously defined,
 - (ix) aryl, and optionally substituted aryl, and
 - (x) heteroaryl, and optionally substituted heteroaryl,
 - (2) C₂-C₁₀-alkyl,
 - (3) C₂-C₁₀-alkyl substituted with one or more substituents selected from the group consisting of
 - (i) halogen,
 - (ii) OR⁴ wherein R⁴ is as defined previously
 - (iii) -CHO,
 - (iv) oxo,
 - (v) NR⁷R⁸ wherein R⁷ and R⁸ are defined as previously
 - (vi) =N-O-R⁴ is wherein R³ is as previously defined
 - (vii) -CN
 - (viii) -S(O)_nR³ wherein n = 0, 1 or 2 and R³ is as previously defined
 - (ix) aryl, and optionally substituted aryl
 - (x) heteroaryl, and optionally substituted heteroaryl

- (xi) C₃-C₈-cycloalkyl, and optionally substituted C₃-C₈-cycloalkyl
- (xii) heterocycloalkyl, and optionally substituted heterocycloalkyl
- 5 (xiii) NR⁴C(O)R³ where R³ and R⁴ are as previously defined
- (xiv) NR⁴C(O)NR⁵R⁶ wherein R⁴, R⁵ and R⁶ are as previously defined
- (xv) =N-NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
- (xvi) =N-R⁴ wherein R⁴ is as previously defined
- 10 (xvii) =N-NR⁴C(O)R³ wherein R³ and R⁴ are as previously defined, and
- (xviii) =N-NR⁴C(O)NR⁵R⁶ wherein R⁴, R⁵ and R⁶ are as previously defined,
- (4) C₂-C₁₀-alkenyl,
- 15 (5) C₂-C₁₀-alkenyl substituted with one or more substituents selected from the group consisting of
- (i) halogen,
- (ii) OR⁴ wherein R⁴ is as previously defined
- (iii) O-S(O)_nR³ where n and R³ are as previously defined
- 20 (iv) -CHO,
- (v) oxo,
- (vi) -CO₂R³ where R³ is as previously defined
- (vii) -C(O)-R⁴ where R⁴ is as previously defined
- (viii) -CN
- 25 (ix) aryl, and optionally substituted aryl
- (x) heteroaryl, and optionally substituted heteroaryl
- (xi) C₃-C₇-cycloalkyl
- (xii) C₁-C₁₂-alkyl substituted with heteroaryl
- (xiii) NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
- 30 (xiv) NR⁴C(O)R³ where R³ and R⁴ are as previously defined
- (xv) NR⁴C(O)NR⁵R⁶ where R⁴, R⁵ and R⁶ are as previously defined
- (xvi) =N-O-R⁴ where R⁴ is as previously defined
- (xvii) =N-NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
- 35 (xviii) =N-NR⁴ wherein R⁴ is as previously defined
- (xix) =N-NR⁴C(O)R³ wherein R³ and R⁴ are as previously defined, and

- (xx) =N-NR⁴C(O)NR⁵R⁶ wherein R⁴, R⁵ and R⁶ are as previously defined,
- (6) C₂-C₁₀-alkynyl
- (7) C₂-C₁₀-alkynyl substituted with one or more
- 5 substituents selected from the group consisting of
- (i) trialkylsilyl
- (ii) halogen,
- (iii) -CN
- (iv) OR⁴ where R⁴ is defined as previously
- 10 (v) -CHO,
- (vi) oxo,
- (vii) -CO₂R³ where R³ is as previously defined
- (viii) -C(O)NR⁵R⁶ wherein R⁵ and R⁶ are as previously defined
- 15 (ix) NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
- (x) O-S(O)_nR³ where n and R³ are as previously defined
- (xi) C₃-C₇-cycloalkyl
- (xii) C₁-C₁₂-alkyl substituted with heteroaryl
- (xiii) aryl, and optionally substituted aryl
- 20 (xiv) heteroaryl, and optionally substituted heteroaryl
- (xv) NR⁴C(O)R³ where R³ and R⁴ are as previously defined
- (xvi) NR⁴C(O)NR⁵R⁶ where R⁴, R⁵ and R⁶ are as previously defined
- (xvii) =N-O-R⁴ where R⁴ is as previously defined
- 25 (xviii) =N-NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
- (xix) =N-NR⁴C(O)R³ wherein R³ and R⁴ are as previously defined, and
- (xx) =N-NR⁴C(O)NR⁵R⁶ wherein R⁴, R⁵ and R⁶ are as previously
- 30 defined,
- (8) cyclic substituents
- (i) aryl, and optionally substituted aryl
- (ii) heteroaryl, and optionally substituted heteroaryl
- (iii) heterocycloalkyl, and optionally substituted
- 35 heterocycloalkyl, and
- (iv) C₃-C₇-cycloalkyl, and optionally substituted C₃-C₇-cycloalkyl, and

(9) C_1 substituents with the exception of 10-methyl derivatives which are part of the above definitions under (1)

(i) $-CHO$

5 (ii) $-CN$

(iii) CO_2R^3 wherein R^3 is as previously defined

(iv) $C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(v) $C(S)NR^5R^6$ wherein R^5 and R^6 are as previously defined

10 (vi) $C(NR^4)NR^5R^6$ wherein R^4 , N^5 and R^6 are as previously defined

(vii) $CH=N-O-R^4$ wherein R^4 is as previously defined

(viii) $CH=N-R^4$ is wherein R^4 is as previously defined

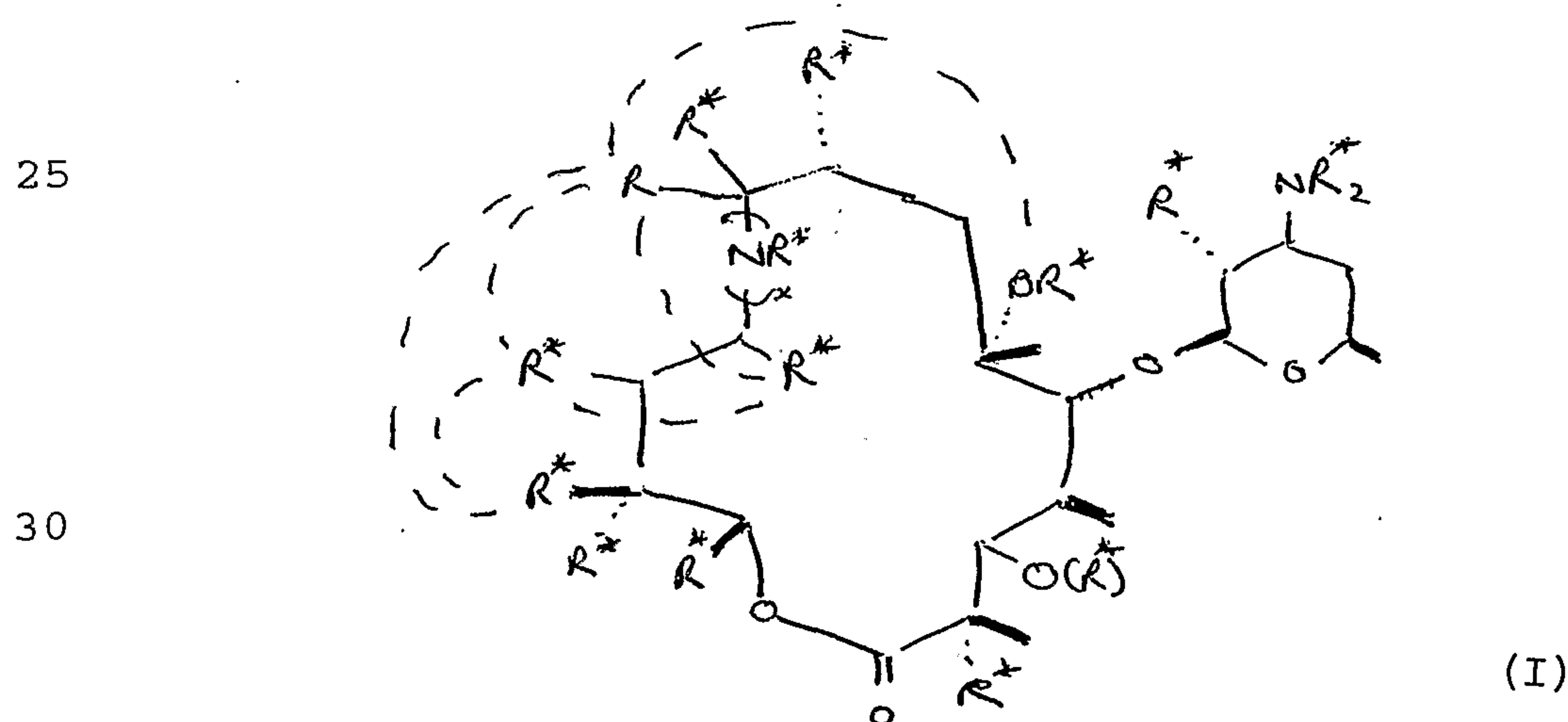
(ix) $CH=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined

15 (x) $CH=N-NR^4C(O)R^3$ wherein R^3 and R^4 are as previously defined, and

(xi) $CH=N-NR^4C(O)NR^5R^6$ wherein R^4 , R^5 and R^6 are as previously defined.

20 The identities 1(iv), 1(viii), 2 and 5(ix) are particularly preferred.

Thus for example the macrolides of the invention may typically be of formula I



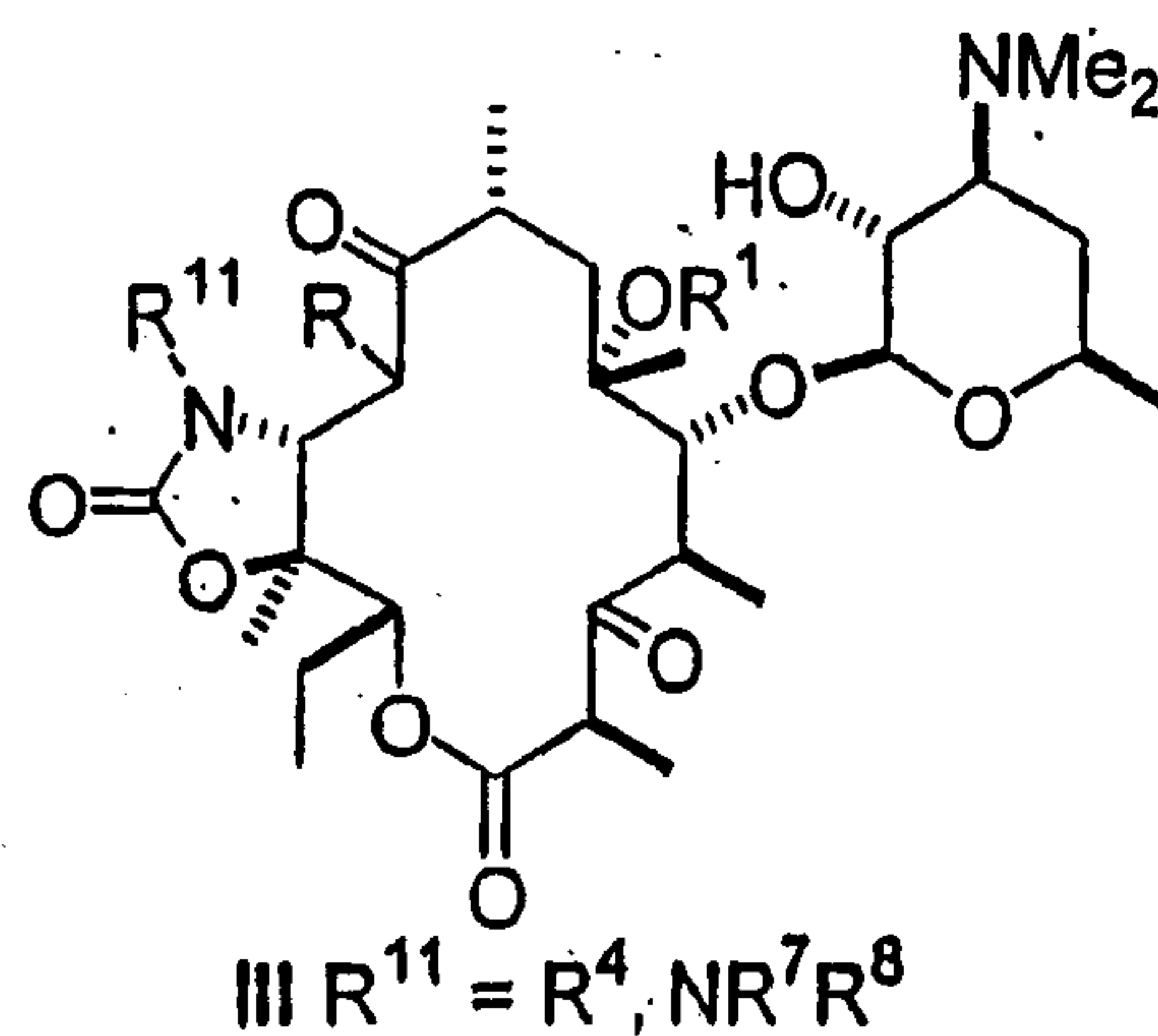
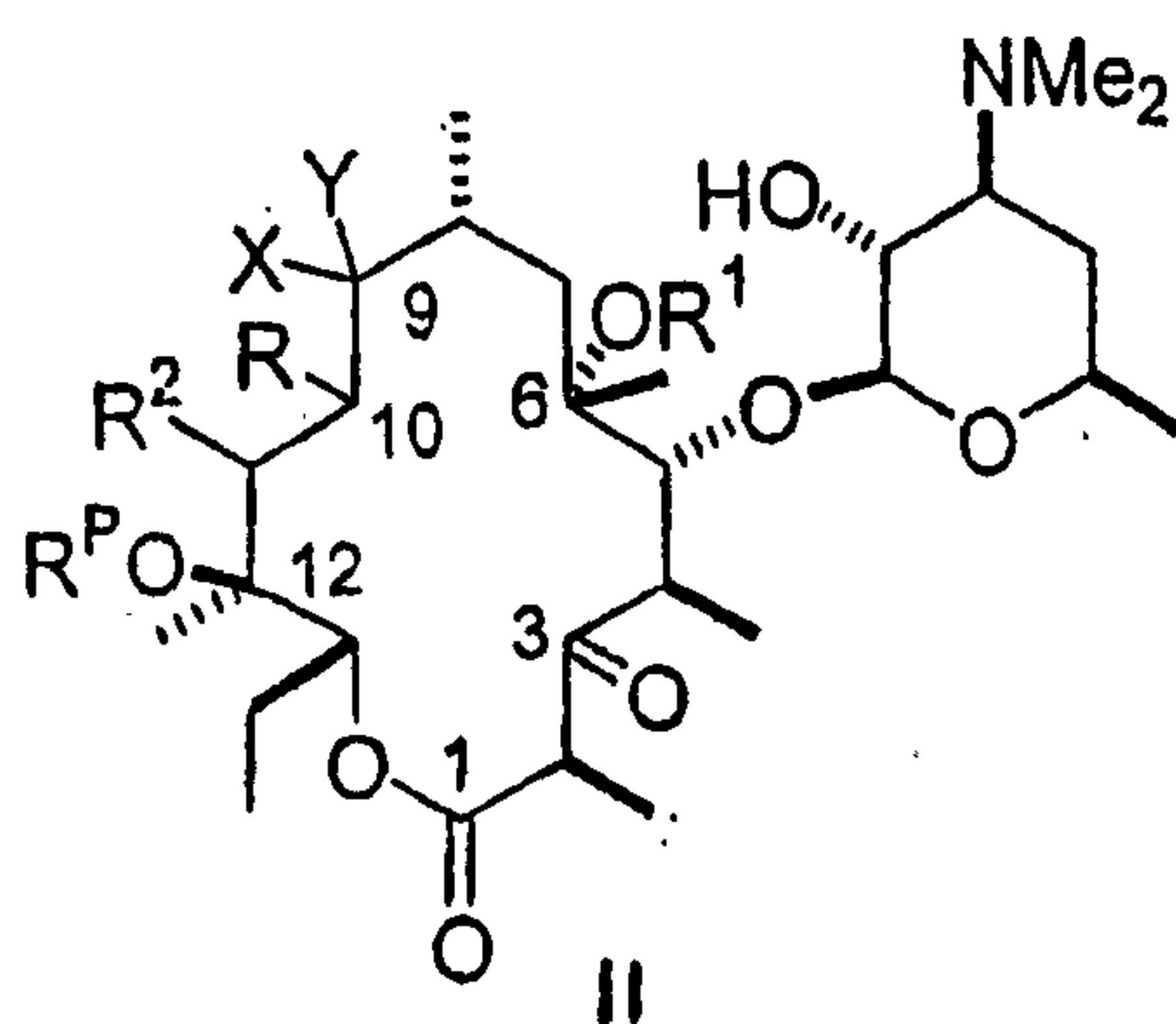
35 (where the 3 position R^* is an oxo, acyloxy or sugar (preferably cladinose) moiety, and the dashed lines indicate possible bridging between substituents at two ring positions). The " R^* " groups are not defined in

relation to formula I as this formula is used for illustrative purposes. Such groups, except the R at the 10 carbon may be as in the earlier published descriptions of 10-methyl macrolides, e.g. as in WO 03/004509, the documents cited therein and in the Search Report issued in relation thereto, or in Martindale - The Computer Drug Reference, 32nd Edition, 1999, the Antibacterials chapter at page 112 et seq. and in Asaka et al (supra) and Wu et al (supra).

Particular embodiments of formula I are given by formulae II, III, IV and V below

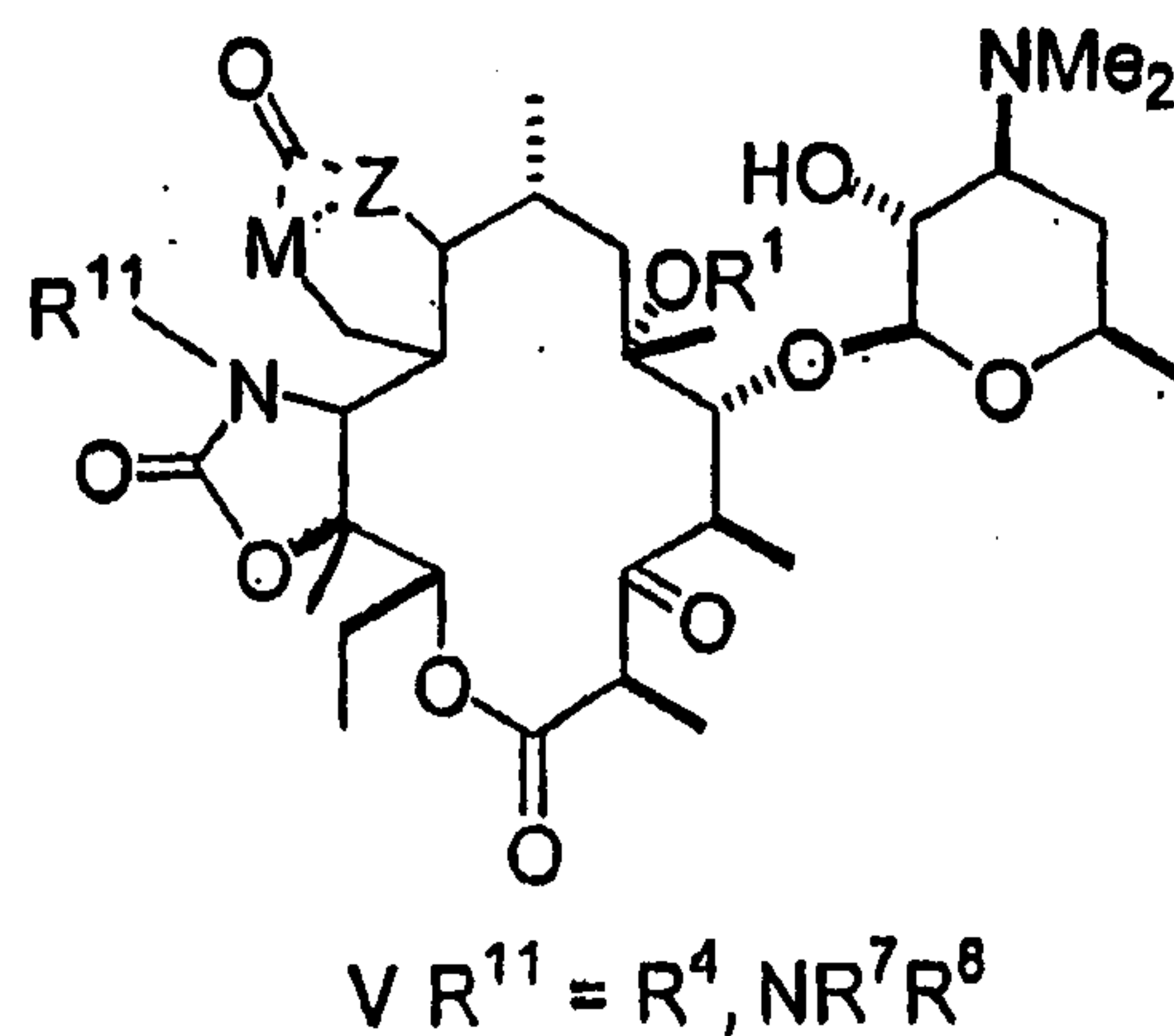
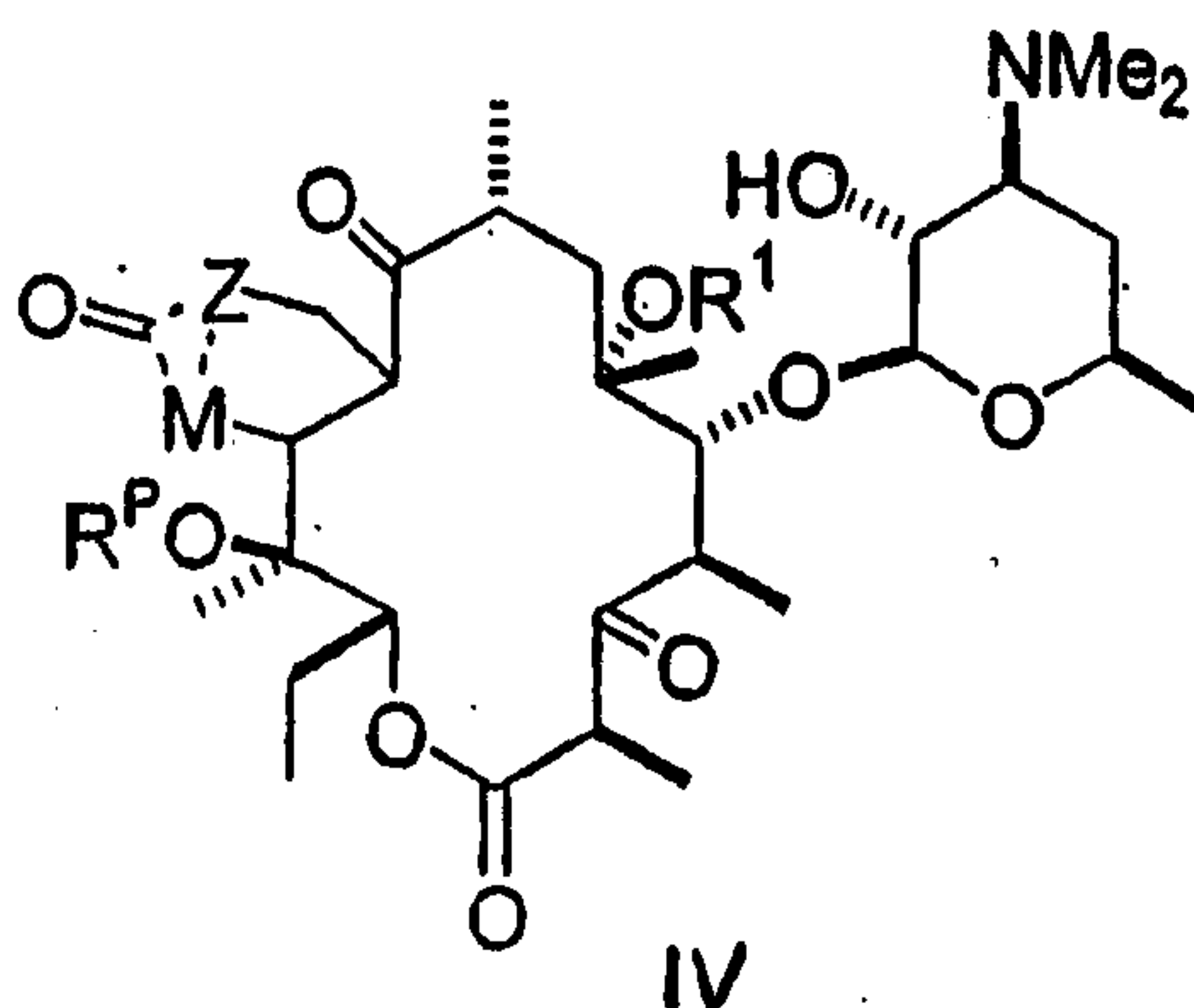
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- (1) methyl substituted with one or more substituents selected from the group consisting of
- (i) CN,
 - (ii) F,
 - 5 (iii) CO_2R^3 wherein R^3 is selected from hydrogen, C_1 - C_3 -alkyl or aryl substituted C_1 - C_3 -alkyl, or heteroaryl substituted C_1 - C_3 -alkyl,
 - (iv) OR^4 wherein R^4 is selected from hydrogen, C_1 - C_4 -alkyl or aryl substituted C_1 - C_4 -alkyl, or heteroaryl
 - 10 substituted C_1 - C_4 -alkyl, heterocycloalkyl and optionally substituted cycloalkyl, C_1 - C_3 -alkoxy- C_1 - C_3 -alkoxy, C_1 - C_4 -alkenyl or aryl substituted C_1 - C_4 -alkenyl, or heteroaryl substituted C_1 - C_4 -alkenyl, heterocycloalkyl and optionally substituted cycloalkyl, aryl or optionally
 - 15 substituted aryl, heteroaryl or optionally substituted heteroaryl,
 - (v) $\text{S}(\text{O})_n\text{R}^3$ wherein $n = 0, 1$ or 2 and R^3 is as previously defined
 - (vi) $\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined
 - 20 (vii) $\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 is defined as defined previously, and R^5 and R^6 are independently selected from hydrogen, C_1 - C_3 -alkyl, C_1 - C_3 alkyl substituted with aryl, substituted aryl, heteroaryl, substituted heteroaryl
 - (viii) NR^7R^8 wherein R^7 and R^8 are independently selected
 - 25 from the group consisting of
 - (a) hydrogen
 - (b) C_1 - C_{12} -alkyl, and optionally substituted C_1 - C_{12} -alkyl
 - (c) C_2 - C_{12} -alkenyl, and optionally substituted C_2 - C_{12} -alkenyl
 - 30 (d) C_2 - C_{12} -alkynyl, and optionally substituted C_2 - C_{12} -alkynyl
 - (e) aryl, and optionally substituted aryl
 - (f) heteroaryl, and optionally substituted heteroaryl
 - (g) heterocycloalkyl, and optionally substituted
 - 35 heterocycloalkyl
 - (h) C_1 - C_{12} alkyl substituted with aryl, and optionally substituted with substituted aryl

- (i) C_1-C_{12} alkyl substituted with heteroaryl, and optionally substituted with substituted heteroaryl
- (j) C_1-C_{12} alkyl substituted with heterocycloalkyl, and with optionally substituted heterocycloalkyl, and
- 5 (k) R^7 and R^8 taken together with the atom to which they are attached from a 3-10- membered heterocycloalkyl ring which may contain one or more additional heteroatoms and may be substituted with one or more substituents independently selected from the group consisting of
- 10 (aa) halogen, hydroxy, C_1-C_3 -alkoxy, alkoxy- C_1-C_3 -alkoxy, oxo, C_1-C_3 -alkyl, aryl and optionally substituted aryl, heteroaryl and optional substituted heteroaryl
- (bb) CO_2R^3 wherein R^3 is as previously defined, and
- 15 (cc) $C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined,
- (ix) aryl, and optionally substituted aryl, and
- (x) heteroaryl, and optionally substituted heteroaryl,
- (2) C_2-C_{10} -alkyl,
- 20 (3) C_2-C_{10} -alkyl substituted with one or more substituents selected from the group consisting of
- (i) halogen,
- (ii) OR^4 wherein R^4 is as defined previously
- (iii) $-CHO$,
- 25 (iv) oxo,
- (v) NR^7R^8 wherein R^7 and R^8 are defined as previously
- (vi) $=N-O-R^4$ is wherein R^3 is as previously defined
- (vii) $-CN$
- (viii) $-S(O)_nR^3$ wherein $n = 0, 1$ or 2 and R^3 is as
- 30 previously defined
- (ix) aryl, and optionally substituted aryl
- (x) heteroaryl, and optionally substituted heteroaryl
- (xi) C_3-C_8 -cycloalkyl, and optionally substituted C_3-C_8 -cycloalkyl
- 35 (xii) heterocycloalkyl, and optionally substituted heterocycloalkyl
- (xiii) $NR^4C(O)R^3$ where R^3 and R^4 are as previously defined

- (xiv) $\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined
- (xv) $=\text{N}-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined
- (xvi) $=\text{N}-\text{R}^4$ wherein R^4 is as previously defined
- 5 (xvii) $=\text{N}-\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined, and
- (xviii) $=\text{N}-\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined,
- (4) C_2-C_{10} -alkenyl,
- 10 (5) C_2-C_{10} -alkenyl substituted with one or more substituents selected from the group consisting of
- (i) halogen,
- (ii) OR^4 wherein R^4 is as previously defined
- (iii) $\text{O}-\text{S}(\text{O})_n\text{R}^3$ where n and R^3 are as previously defined
- 15 (iv) $-\text{CHO}$,
- (v) oxo,
- (vi) $-\text{CO}_2\text{R}^3$ where R^3 is as previously defined
- (vii) $-\text{C}(\text{O})-\text{R}^4$ where R^4 is as previously defined
- (viii) $-\text{CN}$
- 20 (ix) aryl, and optionally substituted aryl
- (x) heteroaryl, and optionally substituted heteroaryl
- (xi) C_3-C_7 -cycloalkyl
- (xii) C_1-C_{12} -alkyl substituted with heteroaryl
- (xiii) NR^7R^8 wherein R^7 and R^8 are as previously defined
- 25 (xiv) $\text{NR}^4\text{C}(\text{O})\text{R}^3$ where R^3 and R^4 are as previously defined
- (xv) $\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ where R^4 , R^5 and R^6 are as previously defined
- (xvi) $=\text{N}-\text{O}-\text{R}^4$ where R^4 is as previously defined
- (xvii) $=\text{N}-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined
- 30 (xviii) $=\text{N}-\text{NR}^4$ wherein R^4 is as previously defined
- (xix) $=\text{N}-\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined, and
- (xx) $=\text{N}-\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined,
- 35 (6) C_2-C_{10} -alkynyl
- (7) C_2-C_{10} -alkynyl substituted with one or more substituents selected from the group consisting of

- (i) trialkylsilyl
(ii) halogen,
(iii) -CN
(iv) OR⁴ where R⁴ is defined as previously
5 (v) -CHO,
(vi) oxo,
(vii) -CO₂R³ where R³ is as previously defined
(viii) -C(O)NR⁵R⁶ wherein R⁵ and R⁶ are as previously
defined
10 (ix) NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
(x) O-S(O)_nR³ where n and R³ are as previously defined
(xi) C₃-C₇-cycloalkyl
(xii) C₁-C₁₂-alkyl substituted with heteroaryl
(xiii) aryl, and optionally substituted aryl
15 (xiv) heteroaryl, and optionally substituted heteroaryl
(xv) NR⁴C(O)R³ where R³ and R⁴ are as previously defined
(xvi) NR⁴C(O)NR⁵R⁶ where R⁴, R⁵ and R⁶ are as previously
defined
(xvii) =N-O-R⁴ where R⁴ is as previously defined
20 (xviii) =N-NR⁷R⁸ wherein R⁷ and R⁸ are as previously
defined
(xix) =N-NR⁴C(O)R³ wherein R³ and R⁴ are as previously
defined, and
(xx) =N-NR⁴C(O)NR⁵R⁶ wherein R⁴, R⁵ and R⁶ are as previously
25 defined,
(8) cyclic substituents
(i) aryl, and optionally substituted aryl
(ii) heteroaryl, and optionally substituted heteroaryl
(iii) heterocycloalkyl, and optionally substituted
30 heterocycloalkyl, and
(iv) C₃-C₇-cycloalkyl, and optionally substituted C₃-C₇-
cycloalkyl, and
(9) C₁ substituents with the exception of 10-methyl
derivatives which are part of the above definitions
35 under (1)
(i) -CHO
(ii) -CN

- (iii) CO_2R^3 wherein R^3 is as previously defined
 - (iv) $\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are as previously defined
 - (v) $\text{C}(\text{S})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are as previously defined
 - (vi) $\text{C}(\text{NR}^4)\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined
 - (vii) $\text{CH}=\text{N}-\text{O}-\text{R}^4$ wherein R^4 is as previously defined
 - (viii) $\text{CH}=\text{N}-\text{R}^4$ wherein R^4 is as previously defined
 - (ix) $\text{CH}=\text{N}-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined
 - (x) $\text{CH}=\text{N}-\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined, and
 - (xi) $\text{CH}=\text{N}-\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined;
- R^1 is selected from the group consisting of
- (1) H
 - (2) methyl
 - (3) methyl substituted with one or more substituents selected from the group consisting of
 - (i) F
 - (ii) -CN
 - (iii) $-\text{CO}_2\text{R}^{11}$ where R^{11} is C_1 - C_3 -alkyl or aryl substituted C_1 - C_3 -alkyl, or heteroalkyl substituted C_1 - C_3 -alkyl
 - (iv) $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are defined as previously
 - (v) aryl, and optionally substituted aryl, and
 - (vi) heteroaryl, and optionally substituted heteroaryl
 - (4) C_2 - C_{10} -alkyl
 - (5) substituted C_2 - C_{10} -alkyl with one or more substituents selected from the group consisting of
 - (i) halogen,
 - (ii) OR^4 where R^4 is defined as previously
 - (iii) C_1 - C_3 -alkoxy- C_1 - C_3 -alkoxy
 - (iv) -CHO
 - (v) oxo
 - (vi) NR^7R^8 wherein R^7 and R^8 are as previously defined
 - (vii) $=\text{N}-\text{O}-\text{R}^4$ where R^4 is as previously defined
 - (viii) -CN

- (ix) $-S(O)_nR^3$ where $n = 0, 1, \text{ or } 2$ and R^3 is as previously defined
- (x) aryl, and optionally substituted aryl
- (xi) heteroaryl, and optionally substituted heteroaryl
- 5 (xii) C_3-C_8 -cycloalkyl, and optionally substituted C_3-C_8 -cycloalkyl
- (xiii) C_1-C_{12} -alkyl substituted with heteroaryl, and optionally substituted heteroaryl
- (xiv) heterocycloalkyl
- 10 (xv) $NHC(O)R^3$ where R^3 is as previously defined
- (xvi) $NHC(O)NR^5R^6$ where R^5 and R^6 are as previously defined
- (xvii) $=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined
- (xviii) $=N-R^4$ wherein R^4 as previously defined, and
- 15 (xix) $=N-NHC(O)R^3$ wherein R^3 is as previously defined,
- (4) C_1-C_{10} -alkenyl substituted with one or more substituents selected from the group consisting of
- (i) halogen,
- (ii) OR^4 where R^4 is as previously defined
- 20 (iii) $-CHO$
- (iv) oxo
- (v) $-S(O)_nR^3$ where n and R^3 are as previously defined
- (vi) $-CN$
- (vii) $-CO_2R^3$ where R^3 is as previously defined
- 25 (viii) NR^7R^8 wherein R^7 and R^8 are as previously defined
- (ix) $=N-O-R^4$ where R^4 is as previously defined
- (x) $-C(O)-R^4$ where R^4 is as previously defined
- (xi) $-C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined
- 30 (xii) aryl, and optionally substituted aryl
- (xiii) heteroaryl, and optionally substituted heteroaryl
- (xiv) C_3-C_7 -cycloalkyl
- (xv) C_1-C_{12} -alkyl substituted with heteroaryl
- (xvi) $NHC(O)R^3$ where R^3 is as previously defined
- 35 (xvii) $NHC(O)NR^5R^6$ where R^5 and R^6 are as previously defined
- (xviii) $=N-NR^7R^8$ wherein R^7 and R^8 are as previously

defined

(xix) $=N-R^4$ wherein R^4 is as previously defined,

(xx) $=N-NHC(O)R^3$ wherein R^3 is as previously defined, and

5 (xxi) $=N-NHC(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined,

(5) C_2-C_{10} -alkynyl, and

(6) C_2-C_{10} -alkynyl substituted with one or more substituents selected from the group consisting of

(i) halogen,

10 (ii) OR^4 where R^4 is defined as previously

(iii) $-CHO$

(iv) oxo

(v) $-CO_2R^3$ where R^3 is as previously defined

15 (vi) $-C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined

(vii) $-CN$

(viii) NR^7R^8 wherein R^7 and R^8 are as previously defined

(ix) $=N-O-R^4$ where R^4 is as previously defined

(x) $-S(O)_nR^3$ where n and R^3 are as previously defined

20 (xi) aryl, and optionally substituted aryl

(xii) heteroaryl, and optionally substituted heteroaryl

(xiii) C_3-C_7 -cycloalkyl

(xiv) C_1-C_{12} -alkyl substituted with heteroaryl

(xv) $NHC(O)R^3$ where R^3 is as previously defined

25 (xvi) $NHC(O)NR^5R^6$ where R^5 and R^6 are as previously defined

(xvii) $=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined

(xviii) $=N-R^4$ wherein R^4 is as previously defined

(xix) $=N-NHC(O)R^3$ wherein R^3 is as previously defined, and

30 (xx) $=N-NHC(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined;

R^2 is selected from the group consisting of

(1) hydrogen

(2) OH

35 (3) OR^3 where R^3 is as previously defined

(4) $OC(O)R^3$ where R^3 is as previously defined, and

(5) $O(CO)OR^3$ where R^3 is as previously defined;

and X and Y taken together are selected from the group consisting of

- (1) O
- (2) NOR^4 wherein R^4 is as defined previously
- 5 (3) $\text{N-O C(R}^9\text{)(CR}^{10}\text{)-O-R}^4$ where R^4 is as previously defined and
 - (i) R^9 and R^{10} are each independently defined as R^4 , or
 - (ii) R^9 and R^{10} are taken together with the atom to
- 10 which they are attached form a $\text{C}_3\text{-C}_{12}$ cycloalkyl ring,
- (4) NR^4 wherein R^4 is as previously defined, and
- (5) $\text{N-NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined, or one of X and Y is hydrogen and the other is selected
- 15 from the group consisting of

- (1) $-\text{OR}^4$ wherein R^4 is as previously defined, and
- (2) $-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined.

R^p is selected from the group consisting of

- (1) hydrogen
- 20 (2) R^3 as previously defined
- (3) COR^3 where R^3 is as previously defined;

subject to the proviso that when the structure is IV, Z and M are part of a five- or six- membered ring, said rings optionally being fully or partially unsaturated;

25 for the six- membered ring, the bonding between Z and M is through a carbonyl group; for the five- membered ring, the bonding is directly between Z and M excluding CO; Z and M are independently selected from the group consisting of carbon, oxygen or N; and when $\text{M} = \text{N}$ a

30 second bridge may exist between this nitrogen and the oxygen of the 12-OH group whereby either an additional annulated oxazole or oxazine ring constitutes part of the molecule; and subject to the proviso that when the structure is V, Z and M are part of a five- or six-

35 membered ring, said rings optionally being fully saturated or fully or partially unsaturated; for the six-membered ring, the bonding between Z and M is

through a carbonyl group; for the five-membered ring, the bonding is directly between Z and M excluding CO; Z and M are independently selected from the group consisting of carbon, oxygen or nitrogen; and when M = N
5 a second bridge may exist between this nitrogen and the urethane nitrogen.

In formulae II to V, the substituent at the 10 carbon may also be as described earlier herein. The particularly preferred identities of the substituent at
10 the 10-carbon are those shown for the end products in the reaction schemes set out below.

The macrolides of the invention may, but preferably do not have an oxygen bridge linking the 6 and 9 carbons.

15 Where the macrolide ring is set out as shown in the formulae drawings herein, the 2-methyl, 4-methyl, 6-methyl, 13-ethyl and 3- optionally substituted hydroxy groups are preferably above the plane, and the 5-sugar, the 6- optionally substituted hydroxy and the 8 and 12
20 methyl groups are preferably below the plane. The 10-substituent is also preferably below the plane.

Examples of processes for the preparation of the macrolides of the invention are set out below in reaction schemes and Examples. Preferably the processes
25 involve dehydration of a 6-substituted hydroxy, 10-methyl, 11-hydroxyl macrolide and subsequent substitution of the 10 methyl group, e.g. by reaction with NBS (preferably after oxidation of the 3' nitrogen in the 5-sugar), followed if necessary by further
30 reaction, e.g. to modify the 10-substituent, to transform the 10-11 bond to a single bond, to remove protecting groups or to introduce substituents elsewhere on the molecule. Such a process forms a further aspect of the present invention.

35 The novel macrolides of the invention may be formulated in conventional administration forms, e.g. tablets, coated tablets, powders, granulates, solutions,

dispersions, syrups, emulsions, sprays, suppositories, pessaries, etc using conventional excipients, e.g. solvents, diluents, binders, sweeteners, aromas, pH modifiers, viscosity modifiers, antioxidants, etc.

5 Conventional formulation techniques, well known in the art, may be used. The compositions may likewise be administered by conventional administration routes, e.g. orally, by injection, infusion, nasally, rectally, etc. The use of orally administrable compositions, e.g.
10 tablets, coated tablets, syrups, etc is especially preferred.

The macrolides of the invention may be administered in dosage amounts, over dosage periods and at dosage intervals conventional in the use of macrolide
15 antibiotics (e.g. see Martindale, supra and the references for macrolide entries therein). Typical daily dosages for a human or other mammal, given in a single dose or at multiple (e.g. 2, 3 or 4) times per day will generally lie in the range 0.01 to 50 mg/kg
20 bodyweight, especially 0.1 to 25 mg/kg bodyweight.

Many of the intermediates described herein are themselves novel and useful compounds and these form a further aspect of the invention. Thus viewed from a further aspect the invention provides 6-substituted
25 hydroxy-10-acetyloxy-macrolide analogs having a carbon-carbon double bond between the 10 and 11 carbons; macrolide analogs oxidized at the 3' nitrogen of the 5-sugar; 10-desmethyl macrolide analogs having a carbon-carbon double bond between the 10 and 11 carbons and
30 having a substituted hydroxy group at the 12-carbon; and 10-desmethyl macrolides, hydroxy protected at the 2' position of the 5-sugar. Specific examples of such intermediates may be found in the reaction schemes below. Other intermediates which form a further aspect
35 of the invention include those in the reaction schemes below identified by the numbers 3, 4, 5, 5a, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23,

24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37,
38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51,
52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65,
66 and 66a, especially 3, 4, 5, 5a, 6, 7, 8, 9, 10, 11,
5 12, 13, 14, 15, 16, 17, 18, 29, 30, 31, 32, 33 and 37.

In this context, the term analog is used to mean a
compound which, by virtue only of the specified
substitution pattern (e.g. the ring unsaturation or 3'-N-
substituent oxidation) may fall outside the definition
10 herein of a macrolide.

Where the processes of the invention involve use of
protecting groups, the invention is not limited to the
use of the protecting groups specifically mentioned. A
wide range of suitable protecting groups is known in
15 conventional organic synthesis (see for example Greene
et al. "Protective Groups in Organic Synthesis", 3rd
Edition, Wiley, NY, 1999 and McOmie "Protective Groups
in Organic Chemistry", Plenum, 1973 and more recent
publications on protecting groups).

20 Thus for example other protecting groups such as
simple esters, ethers removable by hydrogenolysis or
mild oxidative conditions, mixed acetals, etc may be
used.

The following abbreviations are used herein:

25 TMS/TMS-triflate: Trimethylsilyl/(Trimethylsilyl)-methyl
trifluoromethanesulfonate
TEA: Triethylamine
TES-O: Triethylsilyl trifluoromethanesulfonate
NMP: N-methylpyrrolidone
30 NBS: N-Bromosuccinimide
TFP: Tri-(2-furyl)phosphine
NaHMDS: Sodium bis(trimethylsilyl) amide
CDI: Carbonyldiimidazole
BSTFA: N,O-Bis(trimethylsilyl)trifluoroacetamide
35 Pd₂(dba)₃ CHCl₃: tris(dibenzylideneacetone)dipalladium
chloroform complex
DMAP: Dimethylaminopyridine

TBAF: Tetrabutyl ammonium fluoride

TMS-O: Trimethylsilyl-ether

Boc₂O: benzyloxy carbonyl anhydride

P(o-tol)₃: Tri-ortho-toluenephosphine

5 BnNH₂: Benzylamine

TBDMS-triflate/TBDMS: tert-butyl dimethylsilyl
trifluoromethanesulfonate

mCPBA: m-chloroperbenzoic acid.

dppe: 1,2 bis(diphenylphosphino)ethane

10 MeI: Methyl iodide

Scheme 1

Chemoselective N-oxidation of the spirane **2** was carried
15 out using H₂O₂ as the oxidising agent in methanol at room
temperature. The product was the desired N-oxide **3** in
close to quantitative yield. The N-oxide moiety can be
regarded as a protected form of the tertiary amino group
for a subsequent chemoselective reaction in the 10-
20 methyl group. The bromination was effected by NBS in
acetic acid at room temperature. When bromination was
attempted with the amine **2** without the protection by the
N-oxide function, several products were formed. The
structure of the bromination product **4** has been verified
25 by a single crystal X-ray analysis. Deprotection with
removal of the N-oxide function was effected by
triphenylphosphine under reflux in THF. The product was
the 10-bromomethyl derivative **5**. Therefore both the
latter, and its N-oxide bromomethyl precursor **4**, have
30 been substrates (or intermediates) for the subsequent
reactions. The 2', 3-hydroxy groups in structure **5** are
accessible for reactions. Structure **5a** shows silyl
ether formation.

35 Scheme 2

In another embodiment of this invention for the
preparation of key intermediates as substrates for the

target compounds, the 3-ketolide **8** was prepared as shown in Scheme 2. For many reactions it was necessary to protect the reactive 2', 3-hydroxy groups in structures **2**. Therefore a number of silyl ethers **2a-2c** have been
5 prepared as intermediate reactants.

The substrate was erythralosamine **2**. Selective protection of the 2'-OH group, as an acetyl derivative **6**, was achieved using acetic anhydride with
10 triethylamine. Corey-Kim oxidation of the 3-OH group provided the 3'-ketolide **7**. Deprotection of the 2'-OH group was by methanol at room temperature. The ketolide **8** (R=Me) can be oxidised to its N-oxide **9** using hydrogen peroxide (*vide supra*) and brominated to furnish the
15 bromomethyl derivative **10**. Phosphine deoxygenation of the N-oxide provides the amine **11**. The bromomethyl ketolide **10** is also available by oxidation of the alcohol **5**, e.g. under Corey-Kim or related conditions.

20 Scheme 3

Carbylations by cross-coupling reactions are shown in Scheme 3. The N-oxide **4** was the substrate for the coupling under Stille conditions with tributyl(2-furyl)stannane, tris(2-furyl)phosphine (TFP),
25 Pd₂dba₃.CHCl₃ in NMP at 80°C to furnish a furyl derivative which was isolated in 51% yield. Under these conditions concurrent phosphine deoxygenation of the N-oxide function occurred. The product was the amine **13**. The
30 substrate for the phenylation reaction was the amine **5**. Satisfactory cross-coupling under the same conditions with tributylphenylstannane gave the 10-benzyl derivative **12** in 60% yield. By these reactions we have shown that either the amine **5** or the N-oxide **4** can be
35 the substrate for cross-coupling reactions.

Optionally, a triple bond derivative may be produced. In

the simplest case phenylacetylene has been coupled under Stille conditions to provide the alkyne **14**. Sonogashira methodology would provide the same product.

5 A target in this work has been the preparation of the 10-ethyl derivative, e.g. as the silyl protected derivative **15**. The reaction has been successfully achieved using trimethylaluminium under palladium-mediated catalysis with the silyl protected substrate **5a**
10 as shown in Scheme 3. The methylated product **15** was obtained in high yield, 84%. Simple silyl deprotection provides the parent dihydroxy compound.

Scheme 4

15

A functionalized alkene **16** has been introduced under Stille conditions as shown in Scheme 4.

The tin reagent was tributyl(1-ethoxyethenyl)stannane.
20 The desired coupling product **16** was isolated in 54% yield. Acid catalysed cleavage of the vinyl ether provides the corresponding methyl ketone **17**.

Scheme 5

25

Either bromo compound **4** or **5** under hydrolytic conditions will furnish the corresponding hydroxymethyl derivative indicated in Scheme 5. The hydrolysis product **18** from the amine **5** is shown. As an allylic alcohol **18** is
30 selectively oxidised, first to the aldehyde **19** that can be further oxidised to the carboxylic acid **20** and subsequently converted into new derivatives via the carboxy function. Alternatively, the aldehyde **19** is converted into a ketone **22** via adduct **21** formation with
35 an organometallic reagent and a subsequent oxidation.

In this manner the 10-methyl group has been

functionalised to aldehyde, ketone and carboxylic acid carbonyl groups for further manipulations towards desired derivatives.

5 Scheme 6

10 In Scheme 6 are outlined transformations of 10-carbonyl substituents into five- and six-membered heterocycles at C-10. Aryl derivatives are similarly prepared by ring forming reactions. In this case the products are drawn as heteroaryl derivatives **24** and **25**. The reactions will in most cases run via a dihydro or even tetrahydro heterocycle that can be further oxidised and aromatised by standard methodology.

15

Scheme 7

20 An aldehyde or ketone in the 10-position as in structure **26** (Scheme 7) are suitable substrates for the introduction of alkenes by the family of Wittig reactions, or related reactions. Alternatively, the polarization in this reaction can be reversed in which case the bromomethyl substrate must be converted into an ylide for reactions with appropriate aldehydes and
25 ketones to form the same alkenes **27**. It will be recalled, however, that complete chemoselectivity was achieved for N-deoxygenation of the bromomethyl derivative **4** using tris(2-furyl)phosphine or triphenylphosphine (Scheme 1). Therefore ylide
30 formation requires stronger reaction conditions or more reactive phosphines or phosphites.

Scheme 8

35 In another embodiment of the invention, heterosubstituents are substituted into the 10-methyl

group shown in the case of the bromide 5 in Scheme 8. Structure 28 represents ether and sulfide derivatives that may be formed in reactions with the bromide 5 and metal olates or thiolates. Both alkyl and aryl derivatives become available in this manner. When the bromide 5 in a first step has been converted into an alcohol 18 in Scheme 5 or the corresponding thiol, the same products 28 are available by alkylation reactions.

The methyl ethers 29 would be important synthetic intermediates, to provide compounds with a minimum of structural changes from the bioactive macrolides.

A convenient method for the preparation of 10-methylamino derivatives, is to react the bromide 4 or 5 with an amine. The amination can be run either with the free amine 5 or its N-oxide 4. In the reaction with benzylamine, the amine 5 was the substrate used to provide the benzylaminomethyl derivative 30. With p-chloroaniline in one experiment, the substrate was the N-oxide 4 which furnished the anilino derivative 31.

In order to provide 9-oxo derivatives, the 9-acetal function is to be opened under acidic conditions using catalysis. Due to high resistance towards the acidic conditions tried, indirect methods for acetal cleavage are also to be used.

Scheme 9

30

Scheme 9 outlines some reactions on saturation of the carbon-carbon double bond. After saturation, modified reactivity will be realized in chemical transformations at C-9. Besides catalytic hydrogenation, diboron addition can be used to provide the adduct 33. Substituted boron hydride reagents failed because of

serious steric shielding. When the diboron adduct **33** was treated with a carboxylic acid, in this case acetic acid, C-protonation gave the product **34**. Oxidation of the 3-hydroxy derivative **35** to its ketolide **36** can be effected by several reagents. A suitable process involves selective O-acetyl protection of the 2'-OH group. The macrolide aglycone hydroxy groups are less reactive for steric reasons. Oxidation of the sugar protected macrolide takes place selectively in the 3-position to furnish the corresponding 3-ketone. The acetyl protecting group is removed by methanol treatment with formation of the product **36**.

Scheme 10

Erythromycin carries a hydroxy group at C-11. In the present case a hydroxy group at C-11 can be reintroduced by treatment of the diborane adduct **33** with hydrogen peroxide under alkaline conditions (Scheme 10). For steric reasons adduct formation is expected to occur from the less shielded alpha-face thereby providing a compound **37** with stereochemistry of the hydroxy group as in erythromycin. A large excess of the oxidising agent is used in generating the alcohol. Concurrent oxidation of the amino group therefore occurs. The resultant N-oxide, however, is readily and cleanly deoxygenated on treatment of the product with triphenylphosphine, the product being structure **37**.

In the subsequent reaction, the acetal function at C-9 has to be cleaved and the 3-OH group oxidised to its ketone **39** as outlined in Scheme 10.

Scheme 11

In an alternative oxygen insertion reaction, epoxide

formation was successfully achieved using m-chloroperbenzoic acid as shown in Scheme 11. The product is the N-oxidised structure **40**. N-Deoxygenation occurred readily by heating the latter with triphenylphosphine at reflux temperature in THF. The product was the amine epoxide **41**. In the subsequent reaction step, the epoxide **40** can be rearranged to the 11-ketone **42** by Lewis acid catalysis or under the influence of palladium catalysis and reflux conditions in toluene. Various catalytic hydrogenation procedures or metal hydrides can be used to reduce the 11-keto function to a hydroxy group. The choice of reducing conditions will determine the prevalent hydroxy epimer being formed. Cleavage of the 9-acetal and oxidation of the 3-hydroxy group are the next steps to be carried out as above. Alternatively, hydrolytic cleavage of the 9-acetal function can be carried out at the level of the 11-ketone **42** before reductions.

20 Scheme 12

Macrolides based on an oxime function in the 9-position have been commercialised. A classical synthesis of analogues based on the intermediate substrate **45** is outlined in Scheme 12. Oxime formation by treatment with hydroxylamine provides the oxime **46**. The oxime oxygen is alkylated under strongly basic conditions to provide the O-alkyl oxime **47**. A subsequent oxidation as carried out above, provides the desired 3-ketolide **48**.

30

Scheme 13

Scheme 13 gives an outline of the preparation of 9-oxo-6-OMe-3-ketolides **52**. The 9-oxime is protected by reactions as above leading to the O-protected oxime **49**. The 6-OH group can be O-methylated under strongly basic

conditions to furnish the 6-methoxy derivative 50. Subsequently, the oxime function is removed (vide infra) to furnish the 9-oxo derivative 51. A subsequent oxidation provides the 3-ketolide 52 as a target
5 compound.

Scheme 14

A more detailed synthesis of a 6-O allyl derivative 59
10 is outlined in Scheme 14. Oximation under standard conditions provides the substrate 53 which is protected as an oxime mixed acetal 54 under experimental conditions related to published methodology. This substrate is allylated under strongly alkaline
15 conditions as shown in Scheme 14. The product is the 6-allyloxy derivative 55. Subsequently, the oxime protecting function is removed. In the first step, cleavage of the acetal function is effected by acetic acid to furnish the oxime 56. The N-O bond is cleaved
20 by bisulfite-formic acid and the resultant imine hydrolysed by aqueous ethanol at elevated temperature to furnish the 9-ketone 57. Before the oxidation of the 3-hydroxy function, the sugar 2'-hydroxy group has to be protected, in this case by selective acetylation. The
25 oxidation can be effected by several methods including the Corey-Kim oxidation, the Dess-Martin oxidation, Jones oxidation and the Pfitzner-Moffat oxidation to furnish the 3-ketolide 58. The Corey-Kim oxidation is shown in Scheme 13. Among other methods, substitution
30 in the allylic moiety can be effected under Heck conditions to furnish target compounds 59.

Scheme 15

35 The same oxime protection has also been used in reported 6-O methylation work. In clarithromycin work strongly

basic solution of aqueous KOH was used. In Scheme 15 this is shown for a transformation of structure 54 to its 6-methoxy derivative 60. Subsequently, the oxime protection is removed as discussed in Scheme 14.

5

Scheme 16

Scheme 16 shows oxime protection by analogy to literature for the preparation of clarithromycin. The oxime oxygen in substrate 46 is alkylated by 2-chlorobenzyl chloride to furnish structure 62. TMS-protection is used for the 2'-hydroxyl group in the sugar and in the 3-position, structure 63. 6-O-Methylation is effected by methyl iodide in DMSO-THF with sodium hydroxide as base. The product will be the 6-methoxy derivative 64. Removal of the benzyl function by hydrogenolysis over palladium on charcoal provides the oxime 61. Reductive hydrolysis as above yields the 9-ketone 65. Protection of 3-OH is by an acetyl function as in structure 66. Oxidation of 3-OH and acetyl removal by methanol is effected with the same procedure as above. The product is the ketolide 66a.

15

20

Scheme 17

25

30

2-Substituted ketolides are potentially useful analogues, in particular 2-halogen derivatives with emphasis on 2-fluoro derivatives. Fluorine can be introduced by an electrophilic substitution on an enolate of the ketolide. The reaction is exemplified by the series shown in Scheme 17, but the fluorination can also be carried out at later steps in a reaction sequence.

35

Scheme 18

Several ketolide drug candidates are 11,12-cyclic carbamates. The present invention also includes cyclic carbamate structures. One such preparation starts with structure 70 in Scheme 18. Reaction with
5 carbonyldiimidazole leads to the carbonyl activated urethane 71. The latter, when reacted with an amine or ammonia forms an 11,12 cyclic carbamate 72. When the N-substituent is hydrogen, N-alkylation reactions under basic conditions will provide derivatives of the type
10 alkyl-heteroaryl. Alternatively, the side-chain is anchored to the amino nitrogen before it is involved in cyclic carbamate formation to furnish structures 72.

In another series, the amino nitrogen is part of a
15 hydrazine structure or hydrazine itself as shown in the formation of the hydrazide 73 in Scheme 18. A subsequent cyclisation provides the 11,12-cyclic carbazate 74, probably as a mixture of epimers at C-10. Epimerisation to the natural configuration can take
20 place under the basic conditions caused by excess of hydrazine. The hydrazone 75 is probably an intermediate in a subsequent reductive alkylation with sodium cyanoborohydride and an aldehyde corresponding to the desired side-chain product 76.

25

Scheme 19

In Scheme 19 substrate 77 is available by a Stille
coupling or a Sonogashira coupling between one of the
30 10-bromomethyl substrates and a terminal alkyne. In a reaction with palladium diacetate together with triphenylphosphine, initial adduct formation over the triple bond leads to intermediate 78. A Pd-effected cyclisation reaction subsequently occurs. The
35 hydridopalladium elimination from the cyclisation adduct requires a cis-arrangement of the outgoing substituents

which means that double bond isomer 79 is expected. In this manner pharmacophoric groups, as in the new ketolides, may be anchored through the new ring structure to the macrolide. The annulation may also
5 affect the conformational preferences of the macrolide ring in a manner that facilitates hydrolytic cleavage of the acetal. In an atmosphere of carbon monoxide, CO insertion leads to annulated six-membered ring derivatives indicated by structure 80, or in its more
10 stable phenolic form 81.

A bromomethyl substrate can also be made to react with a geminal diheterofunctional- C_1 reagent. Such reagents could be thiourea or its equivalents, urea or its
15 equivalents, guanidins or its equivalents as indicated in Scheme 20. Of special interest are reagents derived from amidine that will provide annulated pyrimidine derivatives 88 carrying a pyrimidine 2-substituent for additional manipulations.

20 With thiourea substitution at the bromomethyl carbon by the sulfur is to be expected. The initially formed onium salt 84 can then react further by attack at the acetal carbon with structure 85 as an intermediate. The
25 opening could also take another course resulting in liberation of the 6-hydroxy group (not drawn). In structure 87 both hydroxy groups have been set free. When an amidine was used instead, the annulated dihydropyrimidine 88 would be provided.

30 If the initial cyclisation instead takes place over the double bond, structure 84 would be the initial product

Scheme 21

35

When the reagent is a hydroxylamine or hydrazine, five-

membered heterocycles can be formed. Scheme 21 shows some reactions using reagents derived from hydroxylamine. Oxygen has been introduced at the allylic carbon in structure 89. The nitrogen must be protected for the oxygen to be the nucleophile. An appropriate reagent in this case is an aldoxime. Mild acid hydrolysis will furnish the aminoxy derivative 90. Cyclisation under acid catalysis takes place towards the acetal carbon with formation of the cyclic oxime 91 that is an annulated dihydroisoxazole derivative. If desirable, the latter is readily cleaved by hydrogenolysis to provide the hydroxymethyl derivative 92.

15 Scheme 22

When the cyclisation takes place over the carbon-carbon double bond, a tetrahydroisoxazole 93 is obtained as in Scheme 22. The isoxazole can be cleaved by hydrogenolysis, or as shown, be N-alkylated as in structure 94. Further manipulations are indicated from structures 95.

25 Scheme 23

Similar reactions with hydrazines are shown in Scheme 23. Allylic N-alkylation provides structure 96. Acid catalysed cyclic hydrazone formation at the acetal carbon is expected to furnish the dihydropyrrazole derivative 97. The latter can be further manipulated starting by an N-alkylation reaction to provide structure 98. Hydrogenolysis can be used to cleave the nitrogen-nitrogen bond as in structure 99.

35 Scheme 24

In Scheme 24 cyclisation over the carbon-carbon double bond is shown to lead to the tetrahydropyrrazole 101 that can be further manipulated as indicated in structures 102 and 103.

5

Scheme 25

Starting with a macrolide 104 in which the 6-hydroxy group is protected and which has 10-methyl and 11-hydroxy substitution, water is eliminated creating a 10-11 double bond by reaction with ethyl carbonate. The product is then transformed into the corresponding 3-hydroxy macrolide 105 by acidic hydrolysis.

Chemoselective N-oxidation of the 10,11-anhydro substrate 105 was carried out using H₂O₂ as the oxidising agent in methanol at room temperature. The product was the desired N-oxide 106 in high yield. The N-oxide moiety can be regarded as a protected form of the tertiary amino group for a subsequent chemoselective reaction in the 10-methyl group. The bromination was effected by NBS in acetic acid at room temperature. When bromination was attempted with the amine 105 without the protection by the N-oxide function, several products were formed. In the 6-O-methyl derivative 106 the product was the corresponding 10-acyloxymethyl derivative 107. The product formation may be rationalised as an initial bromination followed by fast solvolysis, in this case with acetic acid, to furnish the allylic acetate 107.

Deprotection with removal of the N-oxide function was effected by triphenylphosphine under reflux in THF. The product was the 10-acetoxymethyl amine 108. For some of the subsequent reactions the reactive hydroxyl in the sugar moiety was protected. Acetyl protection was effected with acetic anhydride in the presence of triethylamine to provide the 2'-O-acetyl derivative 109.

Oxidation of the 3-OH group to furnish the ketolide 110 was effected with periodinane under Dess-Martin conditions. Removal of the O-acetyl function in the 2'-position readily takes place in methanol with formation of the 10-acetoxymethyl derivative 111.

Scheme 26

The allylic acetate 111 was deacetylated with sodium methoxide in methanol. The methanolysis could be effected without heating at room temperature. Under these conditions the reaction was slow but gave a satisfactory high yield of the allylic alcohol 112.

Scheme 27

Scheme 3 shows methodology for the preparation of 11,12-annulated cyclic urethanes. In this case the original methyl group has been modified into a methylene group, structure 115. The appropriately protected substrate 111 was metallated using NaHMDS at -40°C and treated with carbonyl-diimidazole (CDI). The product was the imidazolocarbonyl derivative 113. With aqueous ammonia the latter reacts to form the oxazolidinone product 114. This is a novel, unique reaction in that it also involves a concurrent elimination of acetic acid and formation of the 10-methylene function in structure 114. Methanolysis was used to remove the acetyl group in the sugar protected derivative 114 with formation of target ketolide compound 115.

Scheme 28

In Scheme 27 ammonia was used to effect the concurrent annulation reaction and methylene generation. When a

primary amine is used as the amine substrate, an N-substituted annulated ring results. The reaction is illustrated with benzylamine when the N-benzyl derivative **116a** is obtained. Other alkylamines react similarly. Of special interest is the 4-phenylbutane derivative **116b**. Removal of the acetyl protecting group in the sugar moiety is readily effected by methanolysis as demonstrated for the preparation of the sugar hydroxy compound **117**.

Scheme 29

The methylene group in the novel structure **115** is part of an α,β -unsaturated carbonyl system. Such a substrate can be used both for Michael additions and for Heck coupling reactions. In Scheme 29, Michael additions with benzylamine and with 3-phenylpropane-1-amine are shown. The products **118a** and **118b** are 10-methylamino derivatives. Other substitutions on the amino nitrogen may also be used to introduce pharmacophoric functions similar to those attached to the 11'-N-position in known macrolides.

Scheme 30

In Scheme 30 a bifunctional amine reagent, ethane-1,2-diamine, is used. The reaction is rationalised as an initial aminolysis of the imidazolo carbonyl group followed by addition and cyclic carbamate formation. Acetate elimination occurs concurrent with the cyclisation generating the methylene function. The second amino group becomes attached in a Michael fashion to the methylene carbon. Thereby cyclisation occurs with formation of the product **119**.

Scheme 31

Scheme 31 shows an example of substitution at the allylic carbon in the acetoxy derivative 109.

Chemoselective attack with sodium azide occurred at the allylic carbon, the product being the azidomethyl derivative 120. Protection of the 2'-OH group was effected with acetic anhydride as reagent to form the acetoxy derivative 121. A subsequent Dess-Martin periodinane oxidation provided the 3-ketolide 122 which is metallated and acylated by CDI to form the imidazolocarbonyl derivative 123. As an intermediate as such or after prior conversion to amino functions for further reactions towards target compounds.

Scheme 32

Carbylations in the allylic acetate moiety can be effected with transition metal catalysis. The methodology is exemplified with a methylation reaction shown in Scheme 32. The methodology requires a fully protected substrate. In the present case persilylation has been used. BSTFA is a mild reagent for introduction of trimethylsilyl groups and provided the persilylated structure 124. The carbylation was effected with trimethylaluminium and palladium catalysis resulting in formation of the 10-ethyl derivative 125. In this manner the methyl group in the original substrate can be converted into larger carbon substituents. In the present series, the silyl protecting groups are removed with fluoride ions in form of the TBAF reagent to yield the deprotected ethyl derivative 126. For further applications the latter can be protected in the sugar moiety as a 2'-O-benzoyl derivative 127 using benzoic anhydride and is subsequently converted into the 3-ketolide 128 by Dess-Martin periodinane oxidation.

Scheme 33

Another example of carbonylation is provided by the reaction of the substrate **109** with the tributyltin derivative of phenylacetylene under Pd-catalysis. The product was the 10-propyne derivative **129**. The product, even without any protection of the substrate **109**, was isolated in 33% yield.

Scheme 34

Scheme 34 shows a conversion of the 10-ethyl derivative **126** into its oxazolidinone derivative **134**. With acetic anhydride the reactive hydroxyl group in the sugar moiety is protected, structure **130**. Dess-Martin oxidation provides the 3-ketolide **131** which is subsequently metallated and acylated using CDI with formation of the imidazolocarbonyl derivative **132**. Aqueous ammonia leads to oxazolidinone formation and derivative **133** from which deacetylation to compound **134** is effected by methanolysis.

Scheme 35

Carbazate analogues, or N11-amino derivatives, are available by the reaction of hydrazine or a substituted hydrazine with intermediate 12'-O-imidazolocarbonyl derivatives. Scheme 35 shows a reaction between the imidazolocarbonyl derivative **135** and excess hydrazine hydrate which provides the 3-aminooxazolidinone derivative **136**. Reductive alkylation between the amino group and a heterocyclic aldehyde with sodium cyanoborate provides an alkylated product such as structure **137**. The benzoyl protection in the sugar moiety is removed by methanolysis to provide target compound **138**.

Scheme 36

A scheme for the preparation of some compounds of the final target families is shown in Scheme 36. For the preparation of the 4-[4-(3-pyridinyl)imidazolyl]butyl derivative **140** the substrate is the sugar protected ethyl 3-ketolide **128**. Metallation and a subsequent reaction with CDI provides the imidazolocarbonyl derivative **135** which is reacted with a butylamine substituted at the terminal carbon by a heterocycle, in this case by 4-(3-pyridinyl)imidazole, in aqueous acetonitrile at elevated temperature. The product is the N-substituted oxazolidinone **139**. The target compound **140** is available by removal of the benzoyl protection in the sugar moiety by methanolysis. In an alternative approach compounds of this family can be prepared by an alkylation reaction on a preformed oxazolidinone derivative such as structure **133** in Scheme 34.

Scheme 37

In Scheme 37 is indicated a route for the preparation of the cethromycin family analogs which carry new substituents in the 10 position. A route to a key allylic acetate intermediate **146** is shown. The starting material is the O6-allyl derivative **141** which has been described in patents and other publications. To avoid any interference from the double bond in the allylic moiety in the oxidation step, and in the bromination reaction, the double bond is initially protected as a dibromide. Thereafter a series of reactions follow the standard methodology set out herein until the allyl group can be regenerated. Several methods exist for the vicinal debromination, e.g. by zinc or by the iodide ion. In the latter case triphenylphosphine is used for deoxygenation of the N-oxide. In the former case the metal reaction is assumed to include deoxygenation. Intermediate **146** is subsequently modified on the allylic

carbon for the desired target compound and reacted further by analogy to literature.

Transformations at C-10

5

From 10-AcOCH₂-: A number of transformations have been given above, e.g. hydrolysis, carbylations, amination.

10

10-CH₂=: In Scheme 29 is demonstrated amination of the double bond in the α,β -unsaturated carbonyl structure **115** by a Michael addition. The Michael addition proceeds readily with thiol reactants to form thioethers. Alcohols will also be Michael reactants providing corresponding ethers. For carbylation reactions, Heck coupling conditions are used, e.g. in introduction of aryl or heteroaryl substituents at the methylene carbon. The Heck products can be taken further to target molecules with or without saturation of the double C-C bond.

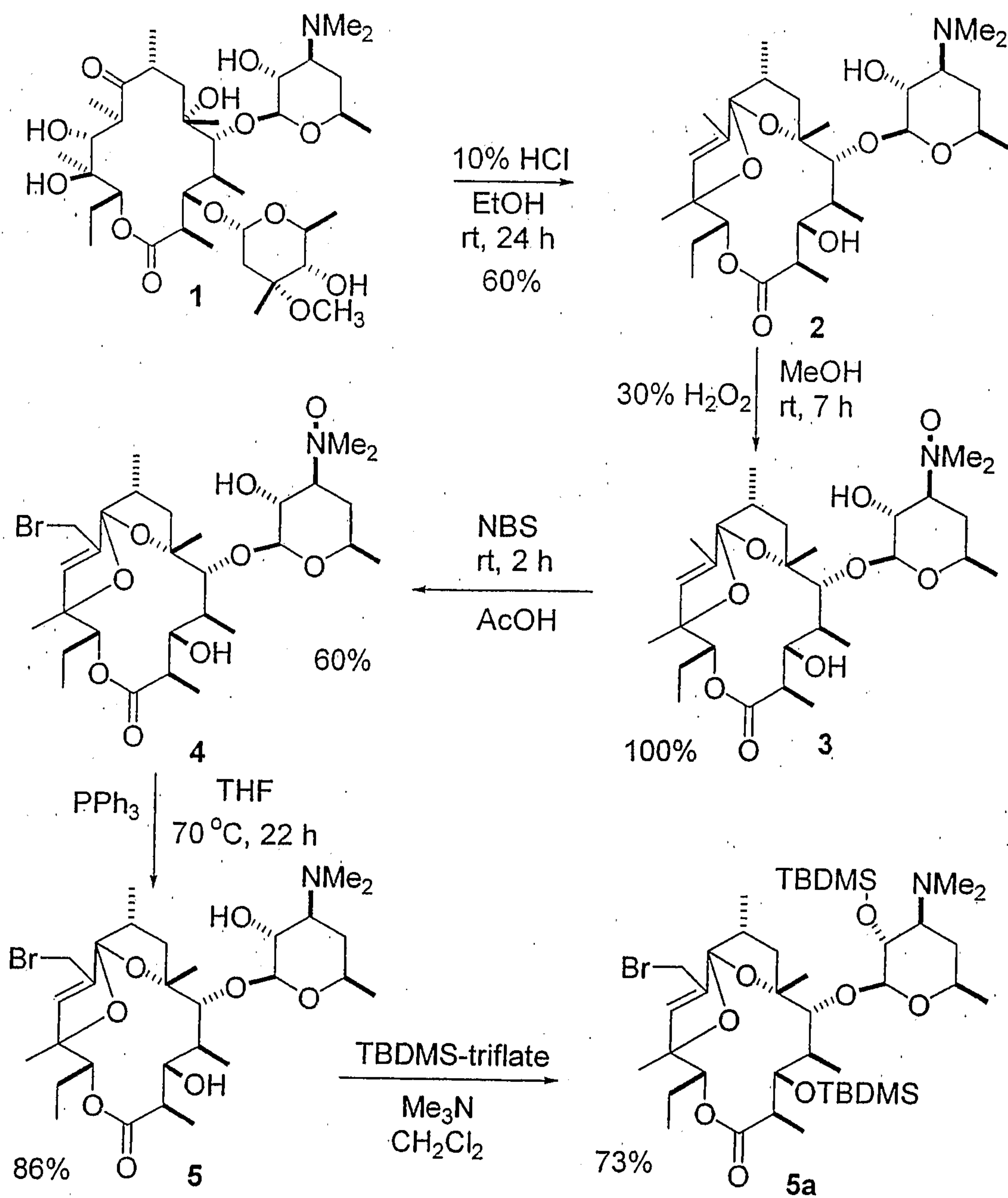
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CH₂N₃: An azide function is a common intermediate function in the synthesis of amines. Reductive procedures are used. Examples shown include hydrogenolysis over Pd/C, or use of certain types of Raney-Ni. Convenient is also the use of low-valent metals, several examples exist. A good reagent is SnCl₂ which will provide a primary amine.

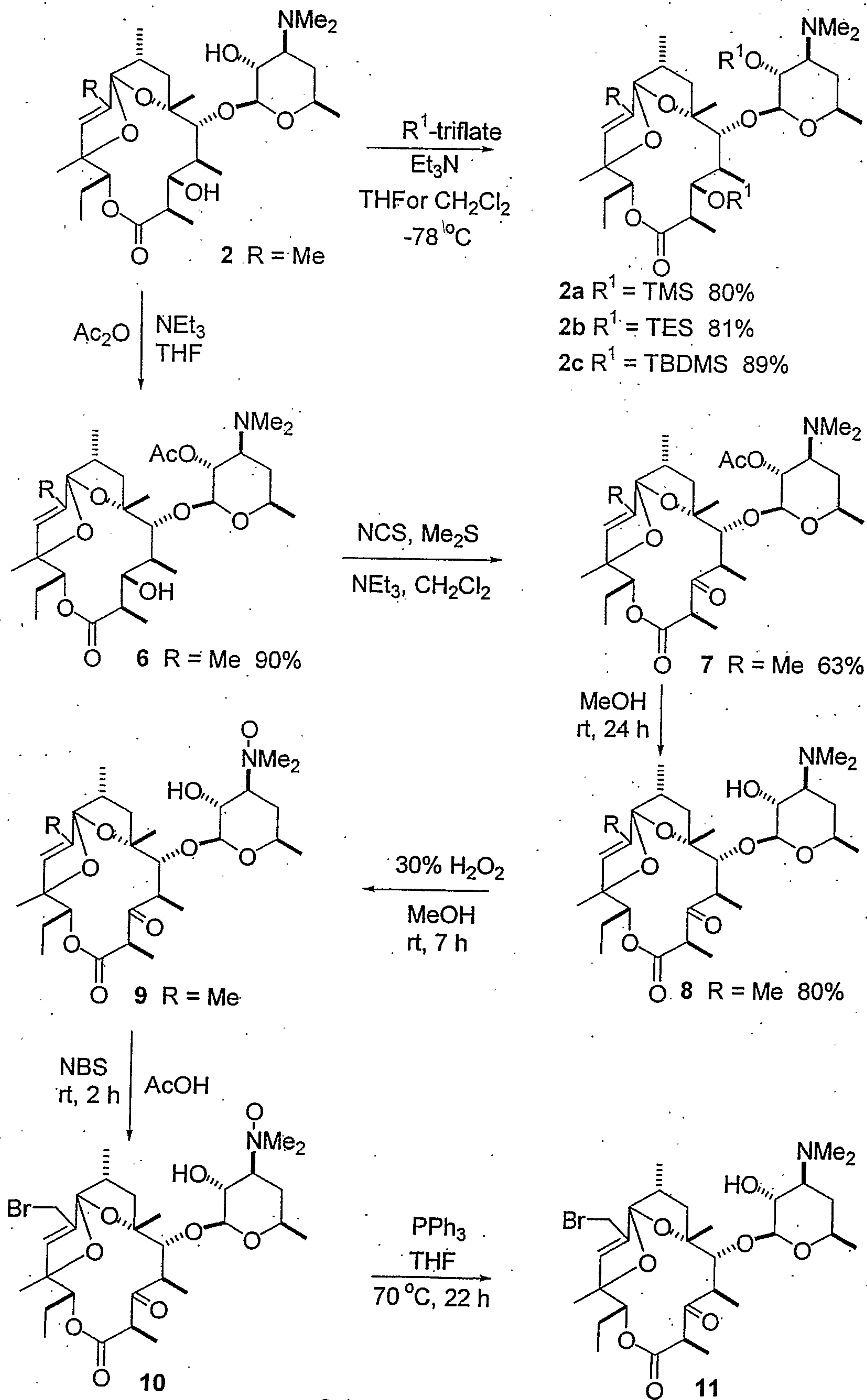
25

The 10-HOCH₂- group can be transformed by gentle oxidation to a 10-CHO group which in turn can be oxidized to the 10-carboxylic acid which can, if desired be transformed to an amide or ester, optionally one having a pendant aryl-(or heteroaryl)-alkyl group.

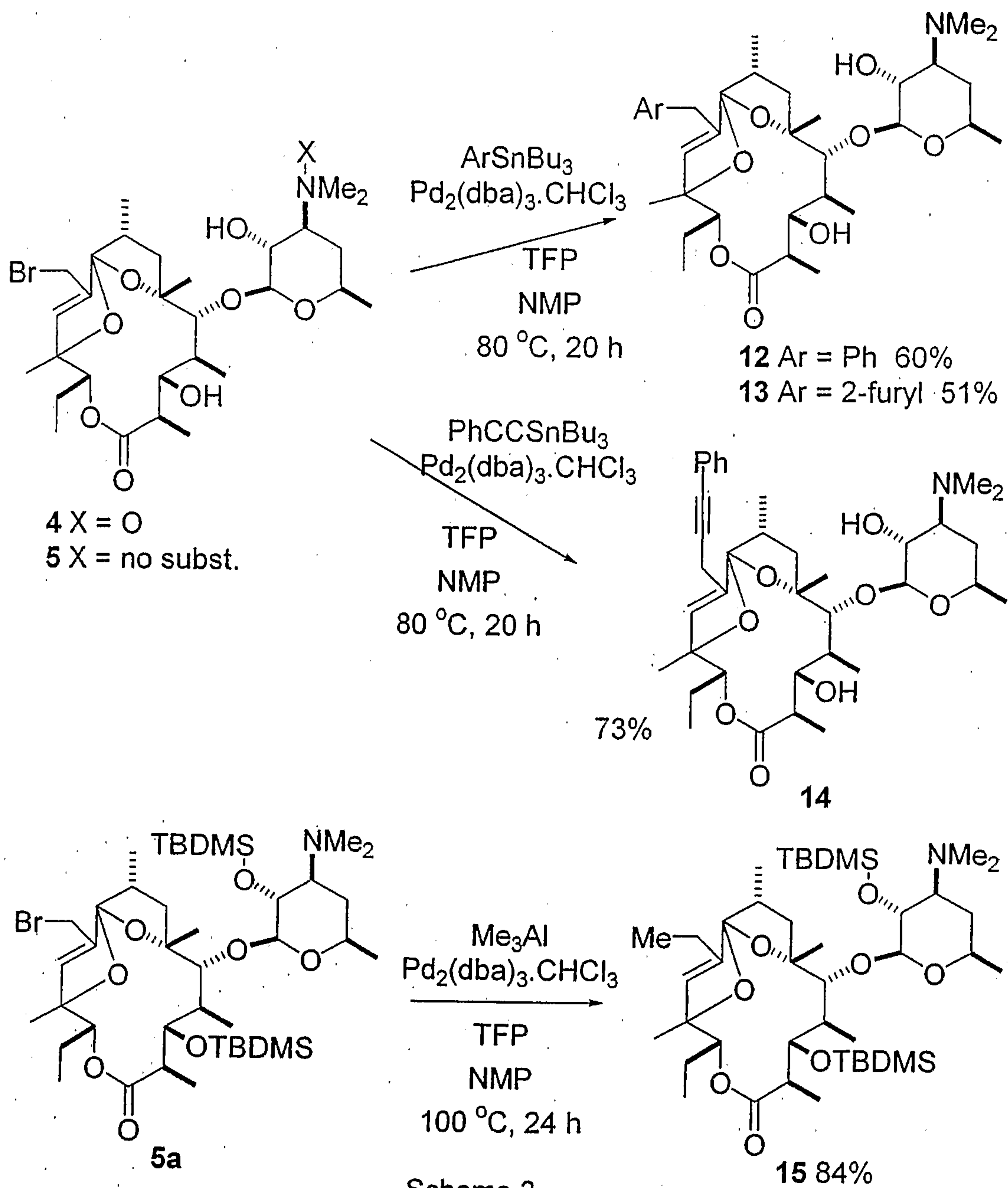
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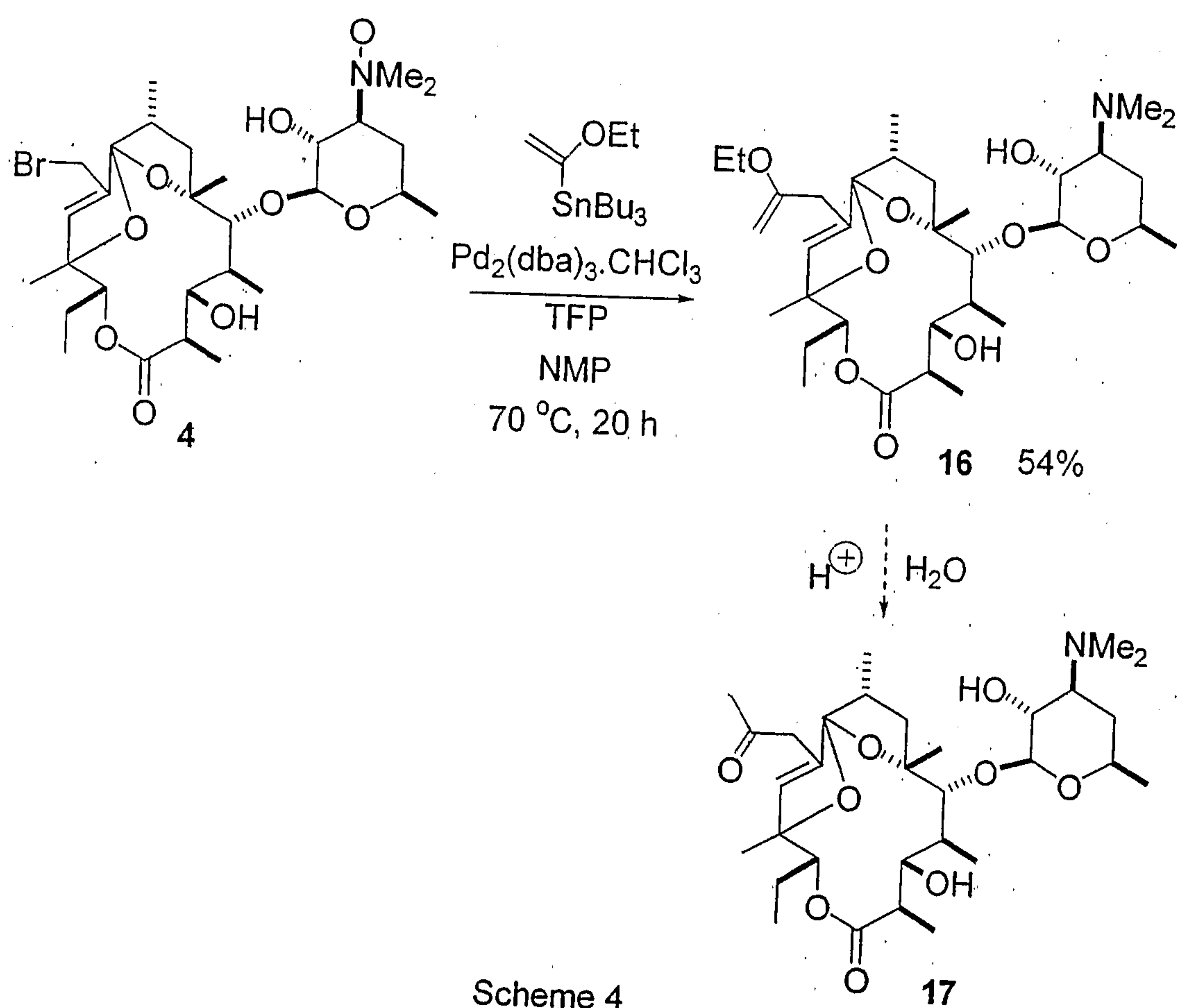


Scheme 1

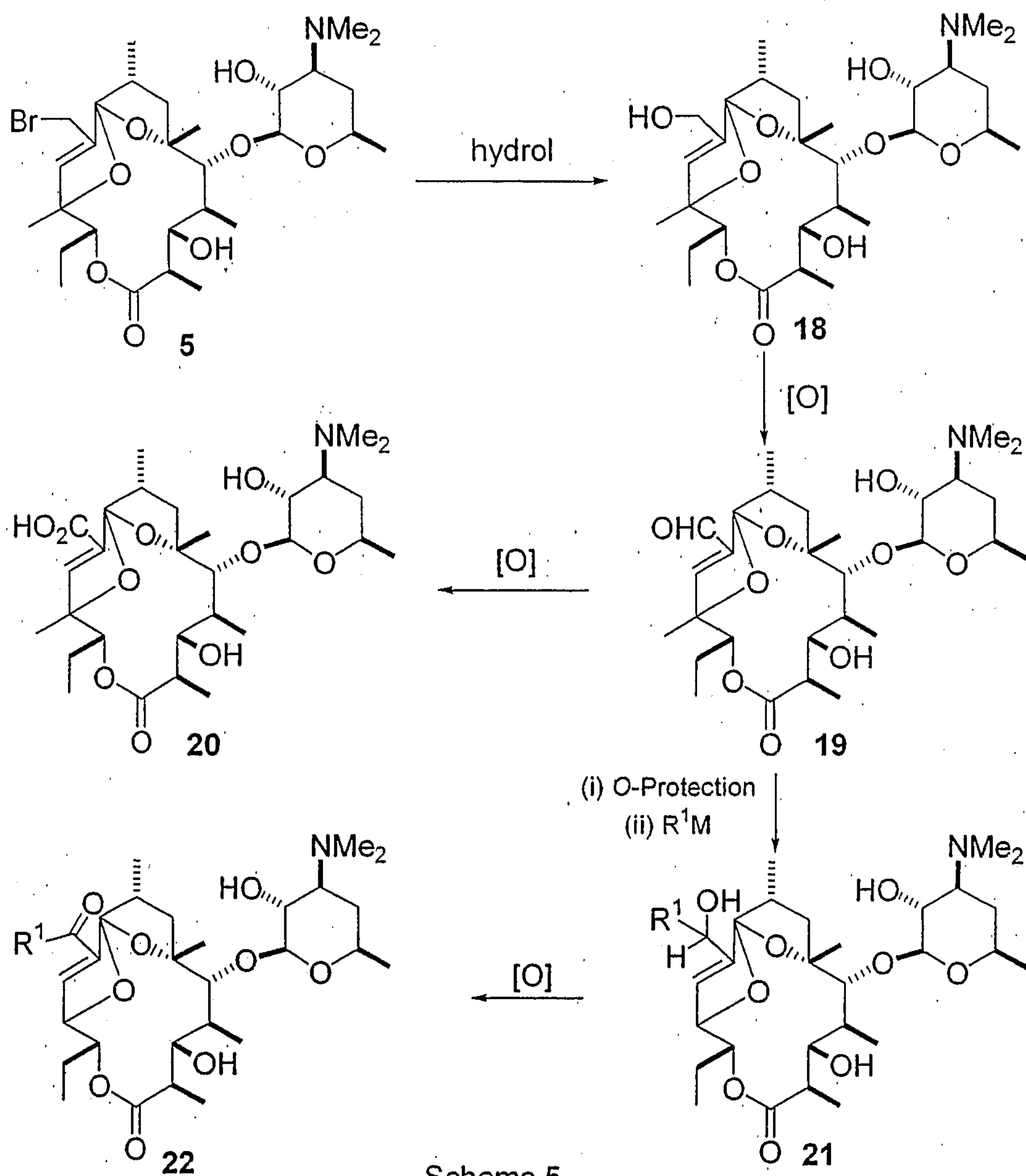


Scheme 2

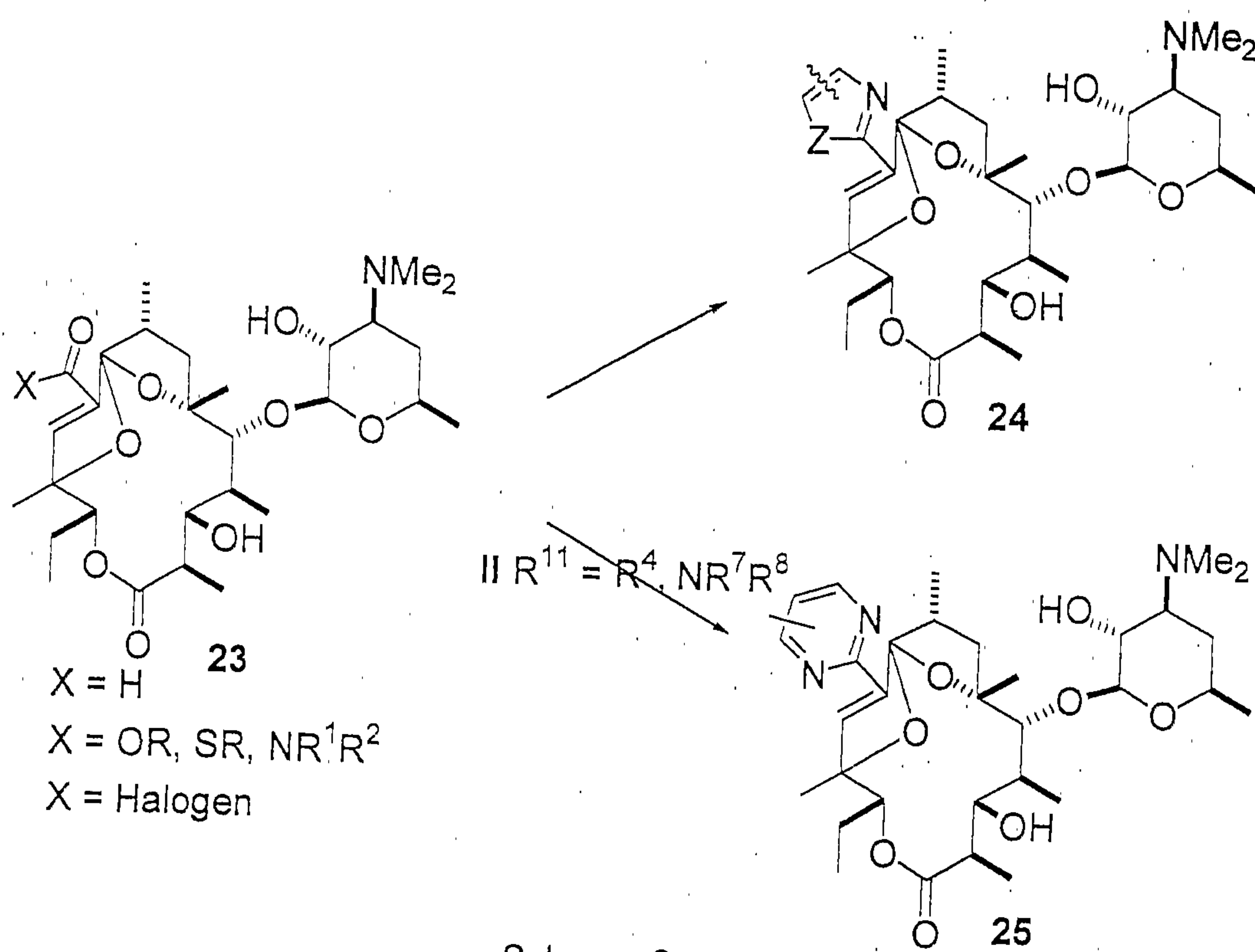




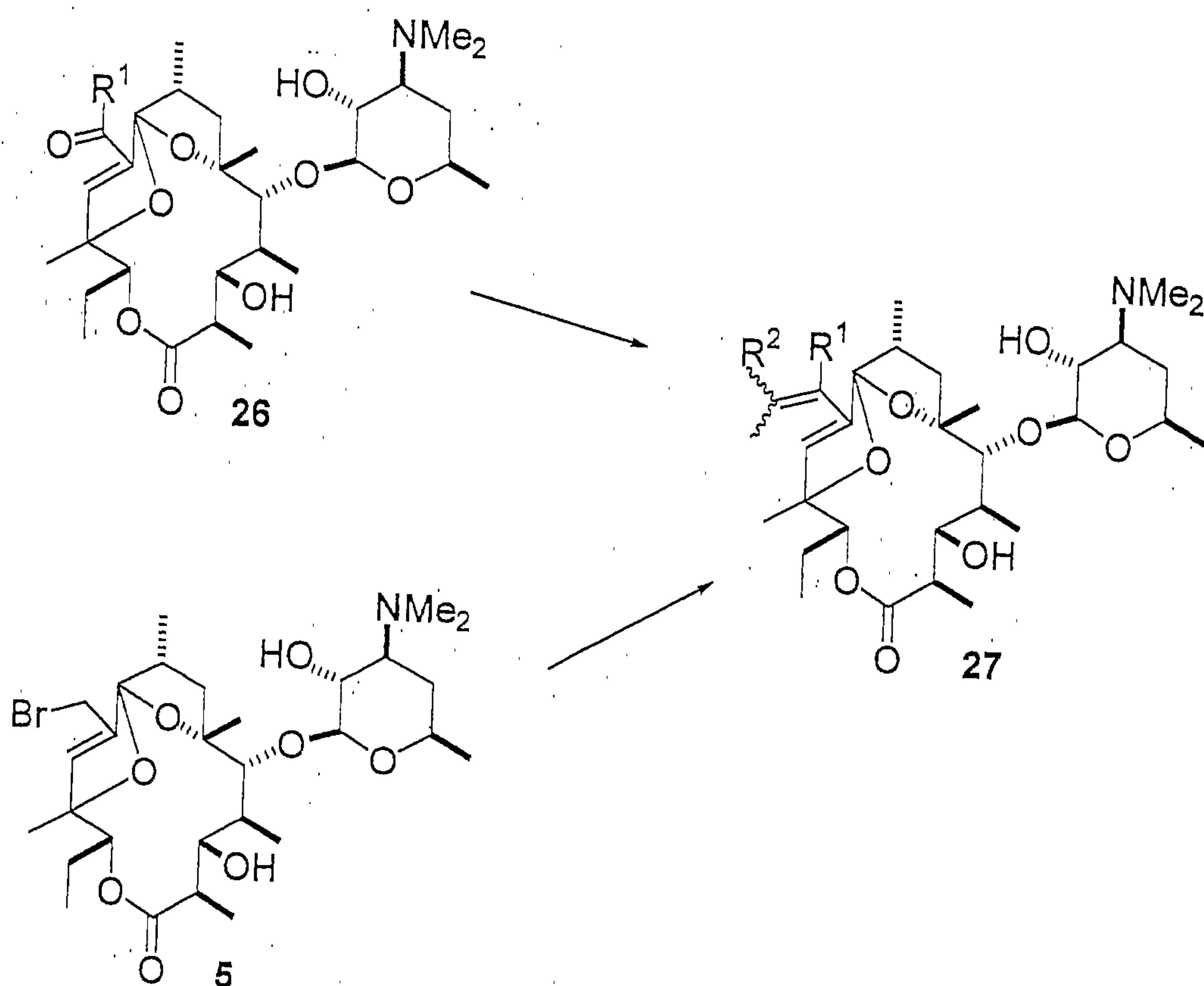
Scheme 4



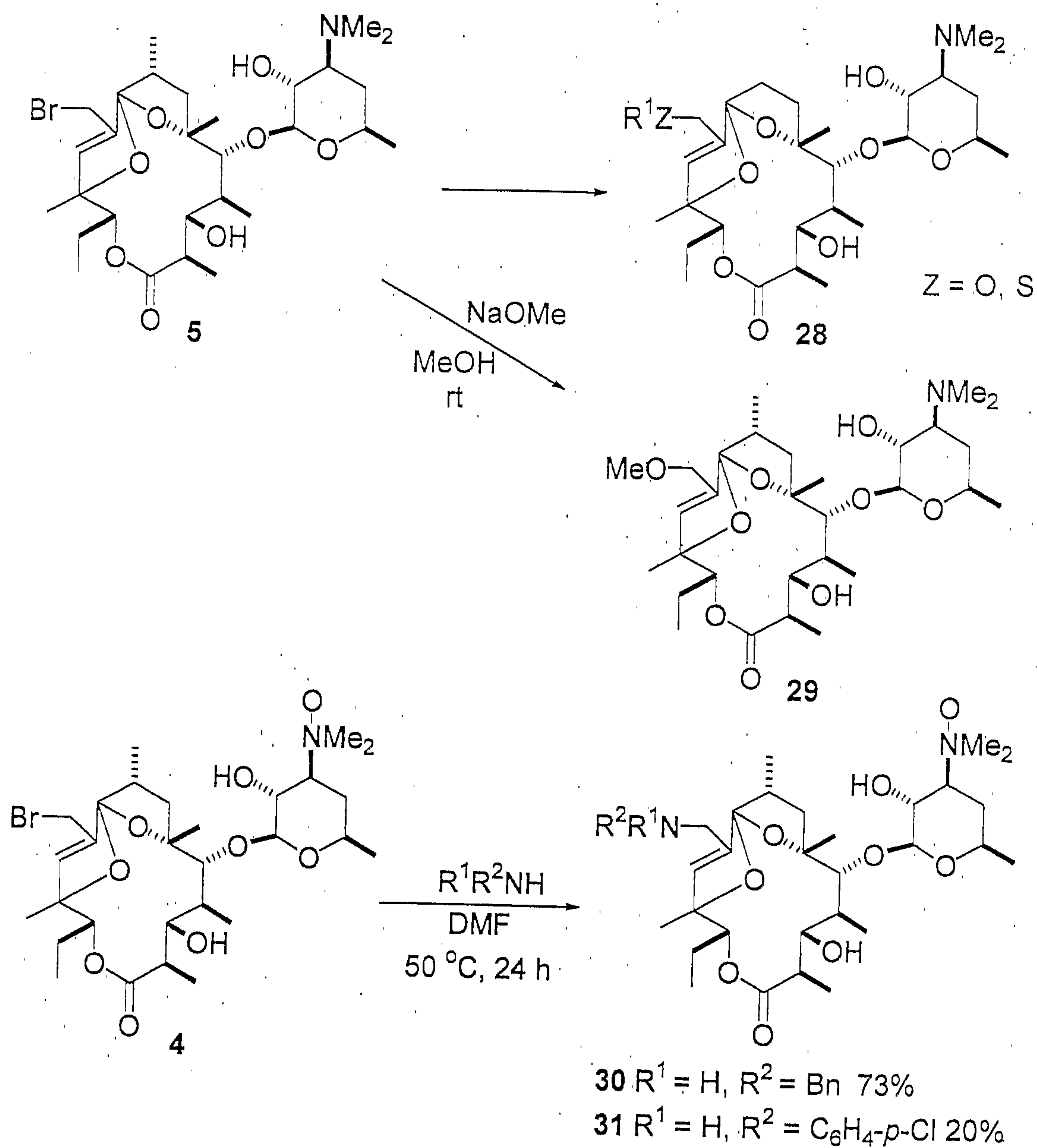
Scheme 5



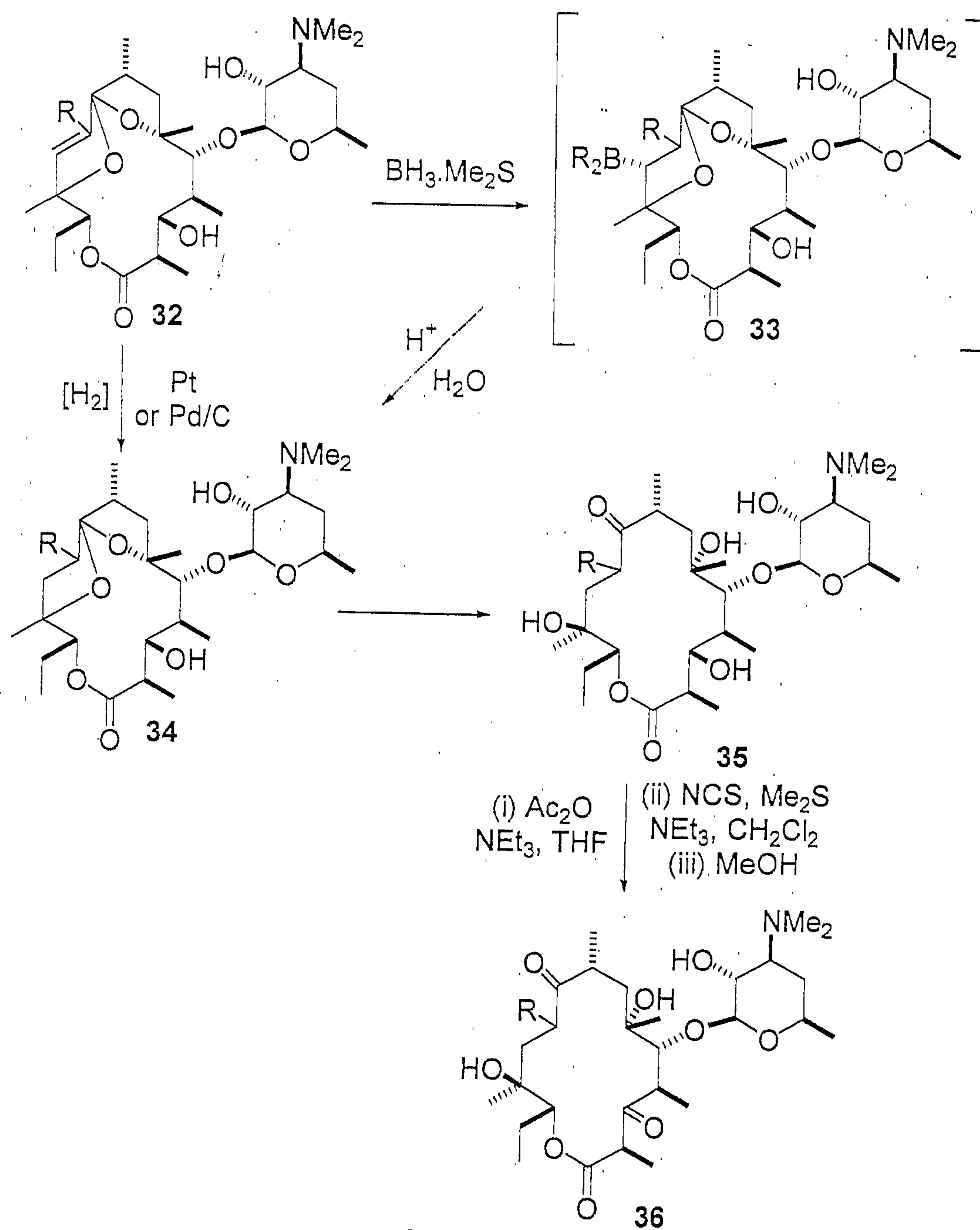
Scheme 6



Scheme 7

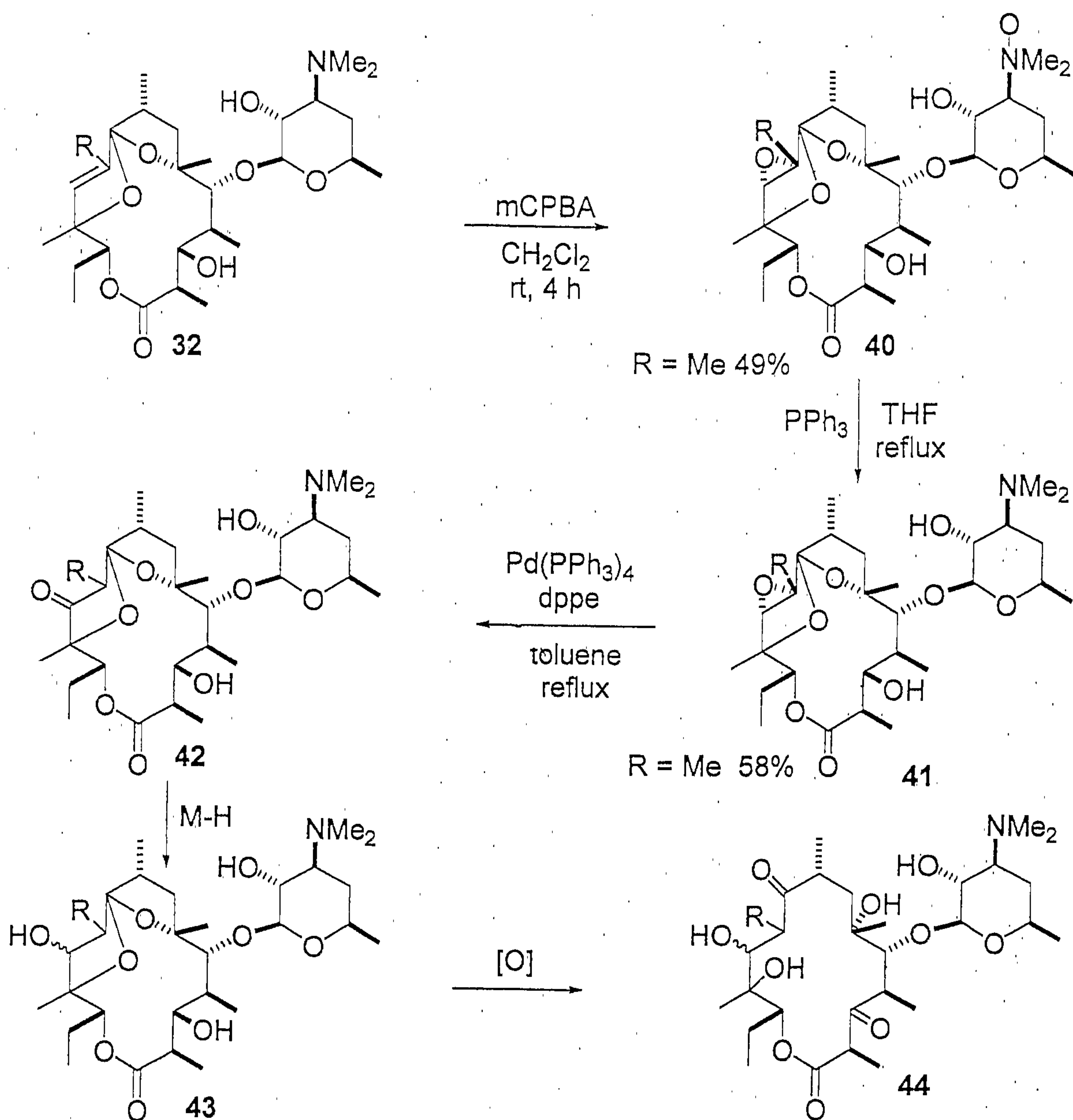


Scheme 8

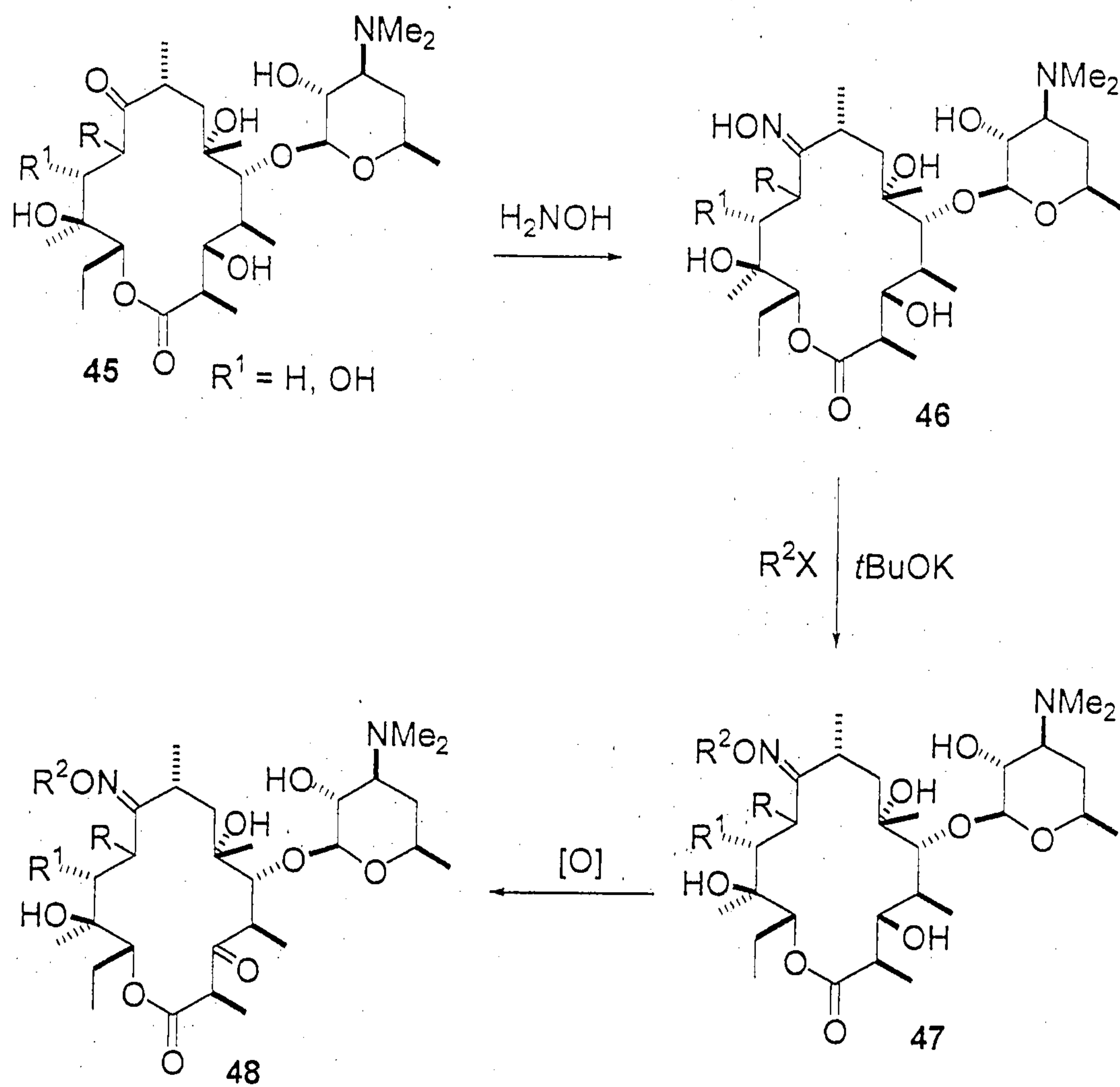


Scheme 9

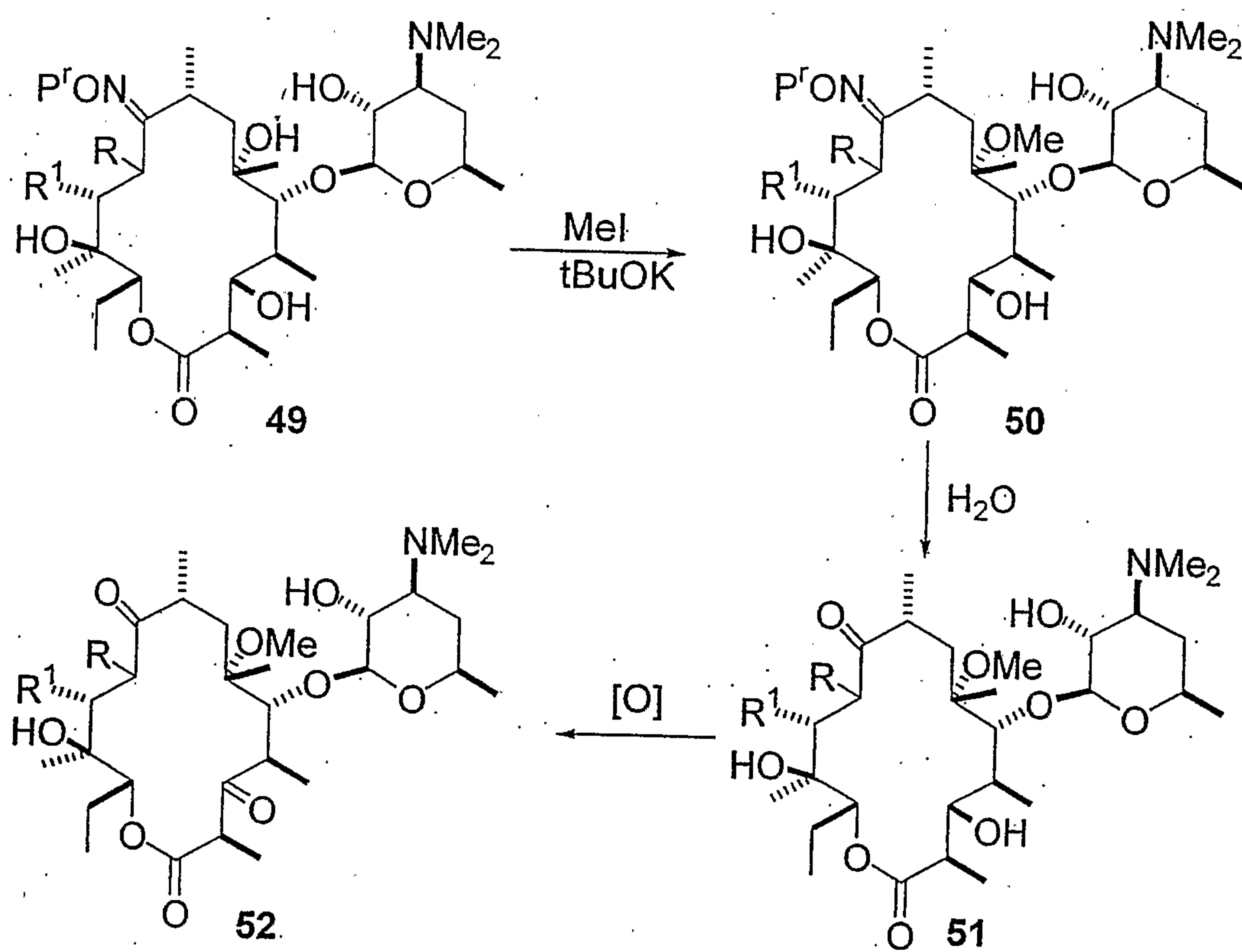




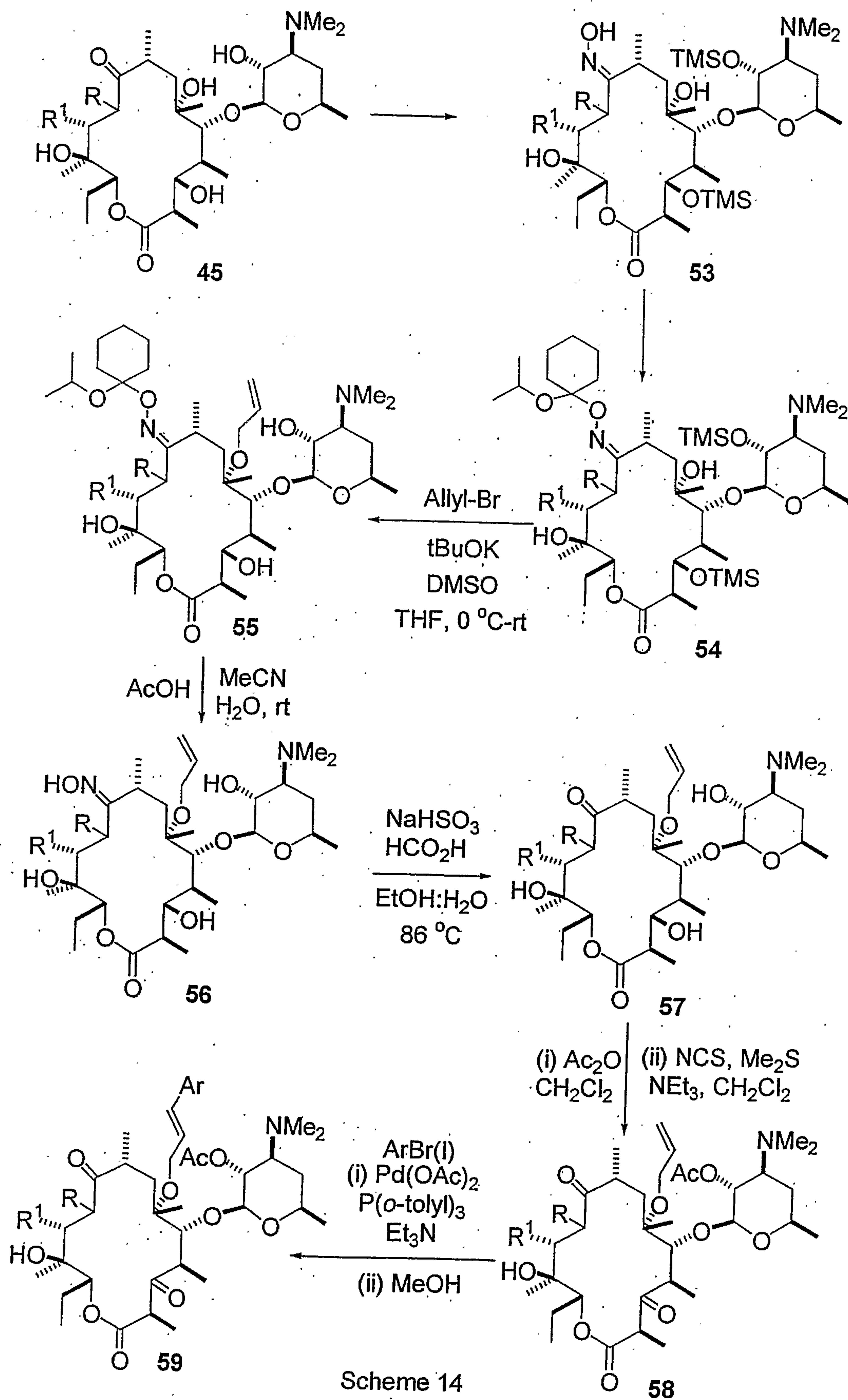
Scheme 11.

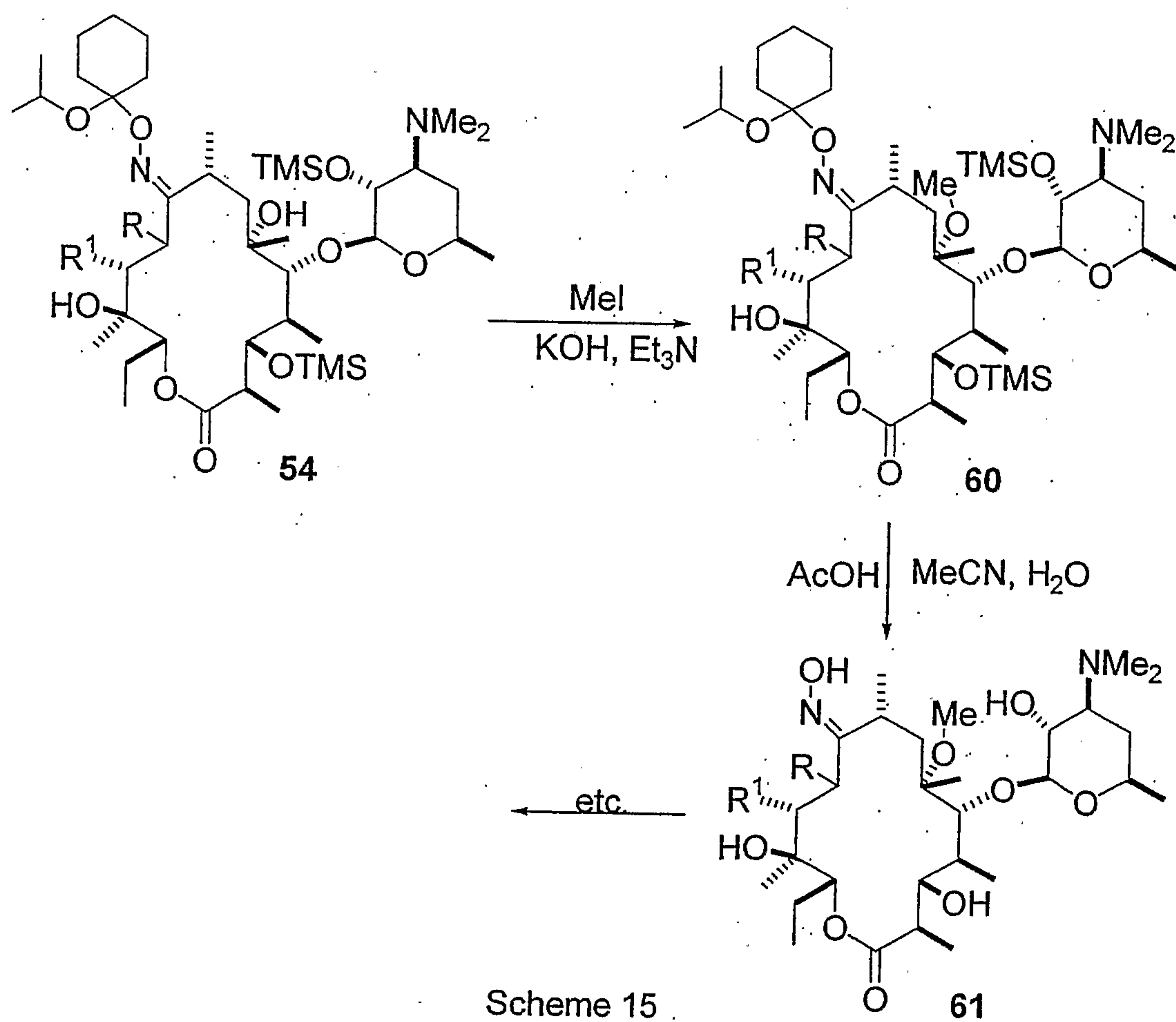


Scheme 12

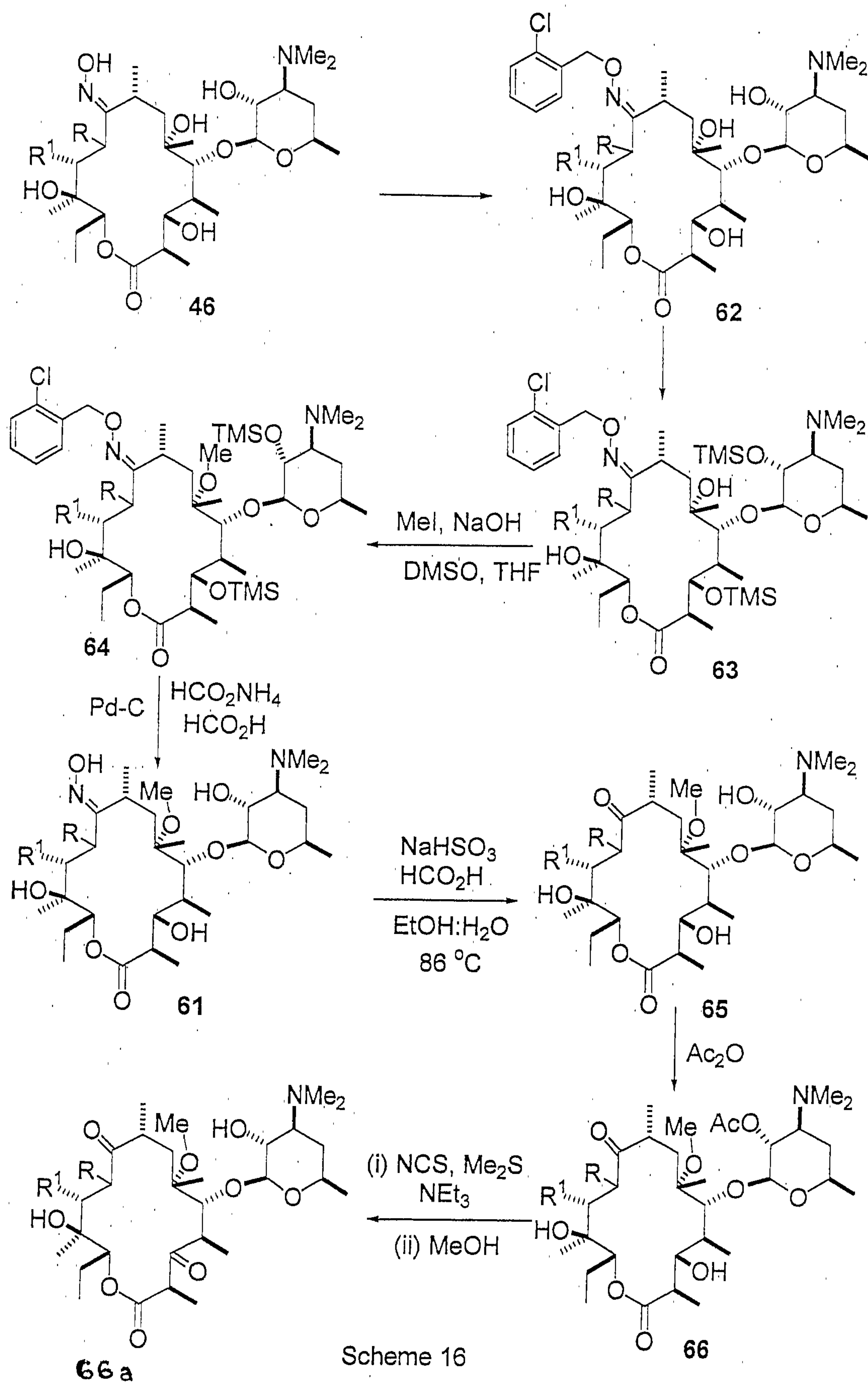


Scheme 13

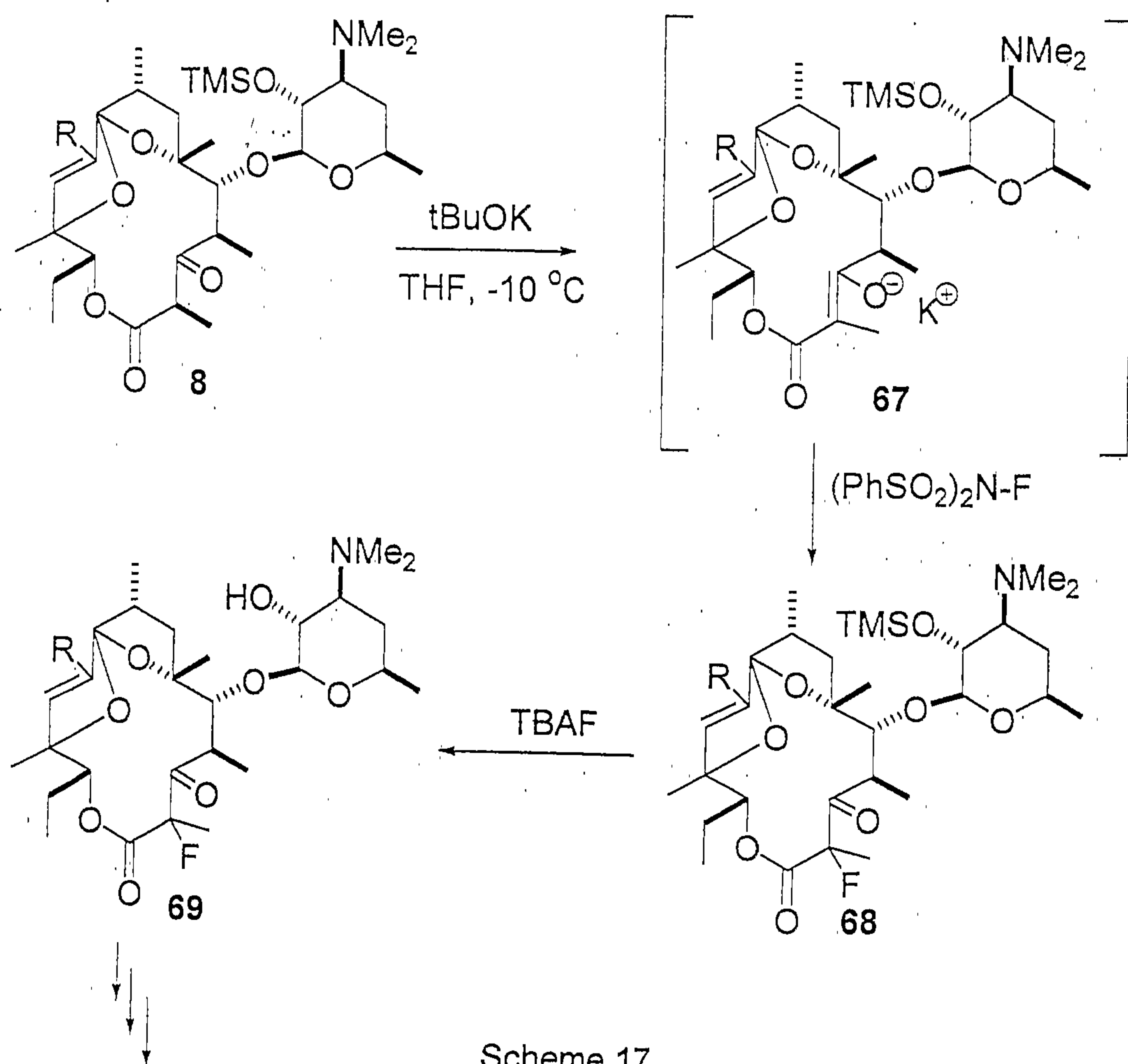




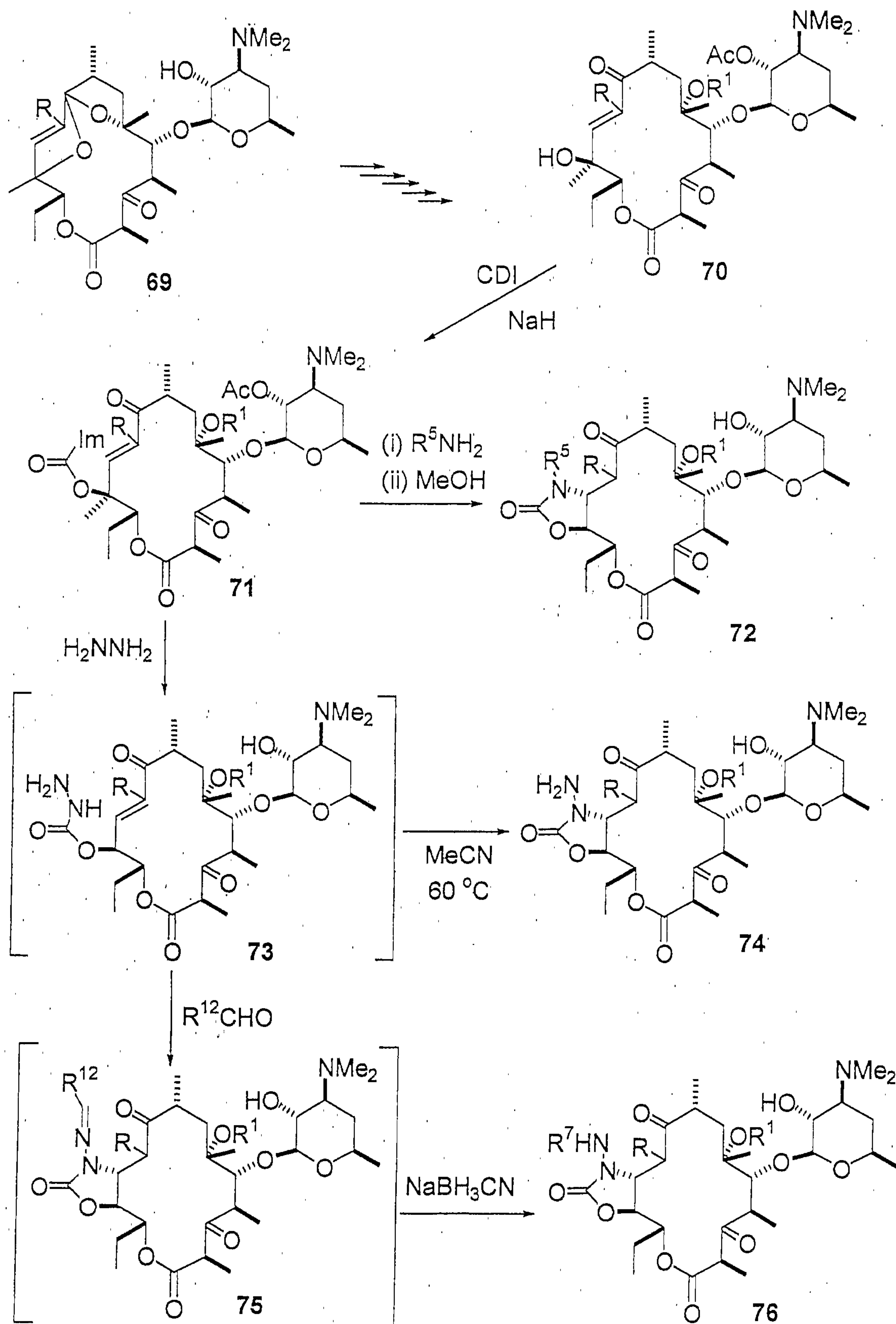
Scheme 15



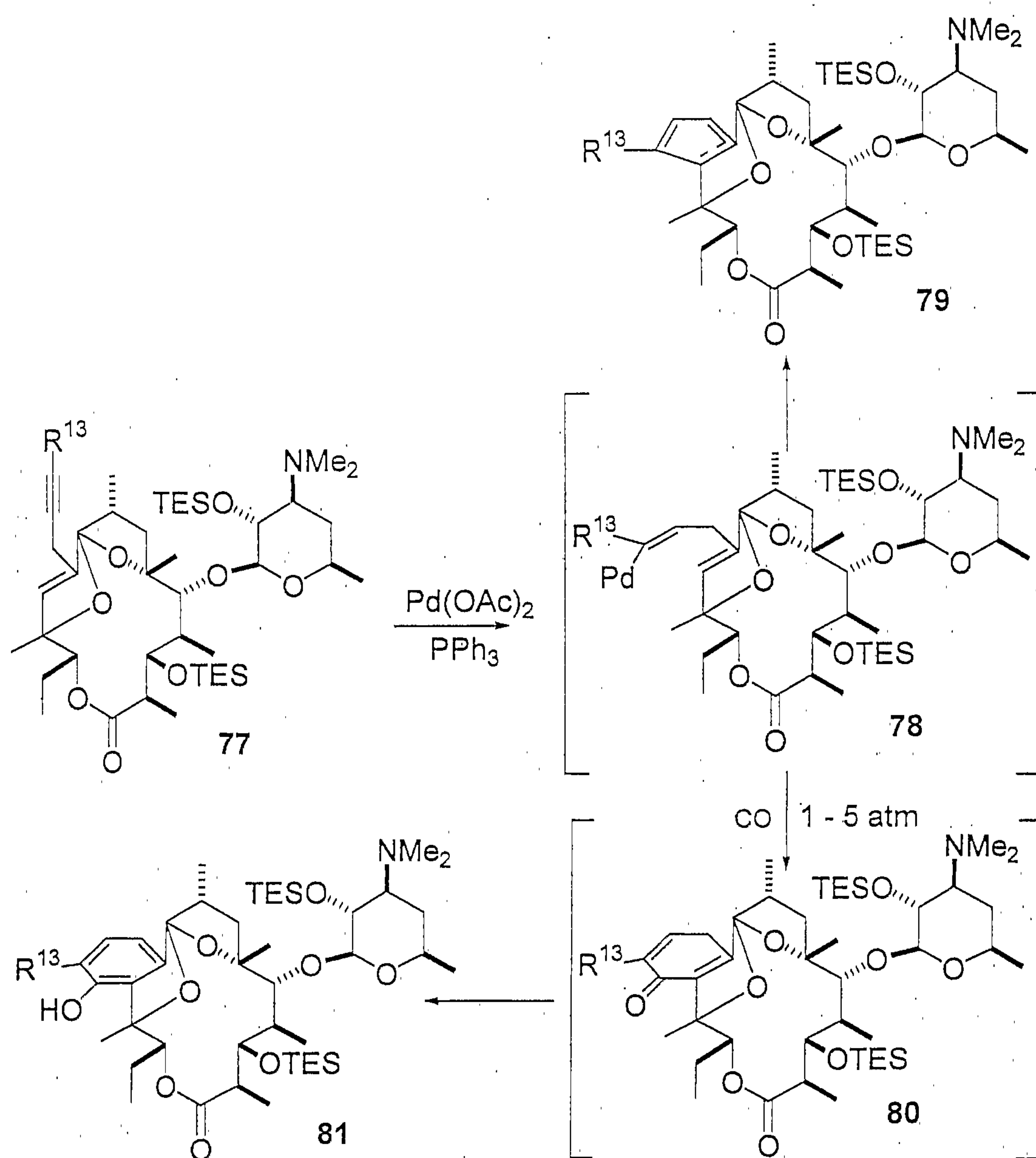
Scheme 16



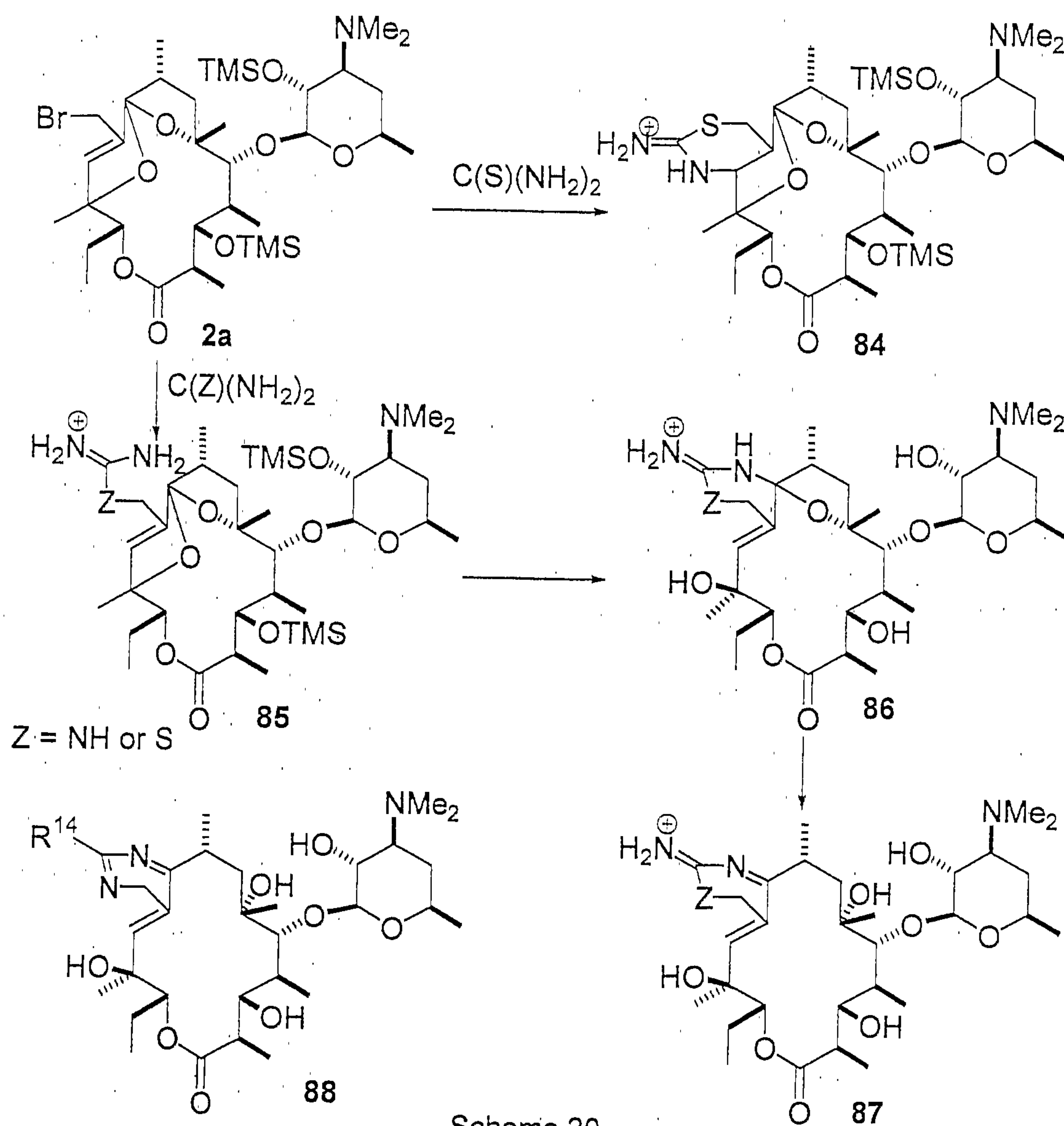
Scheme 17



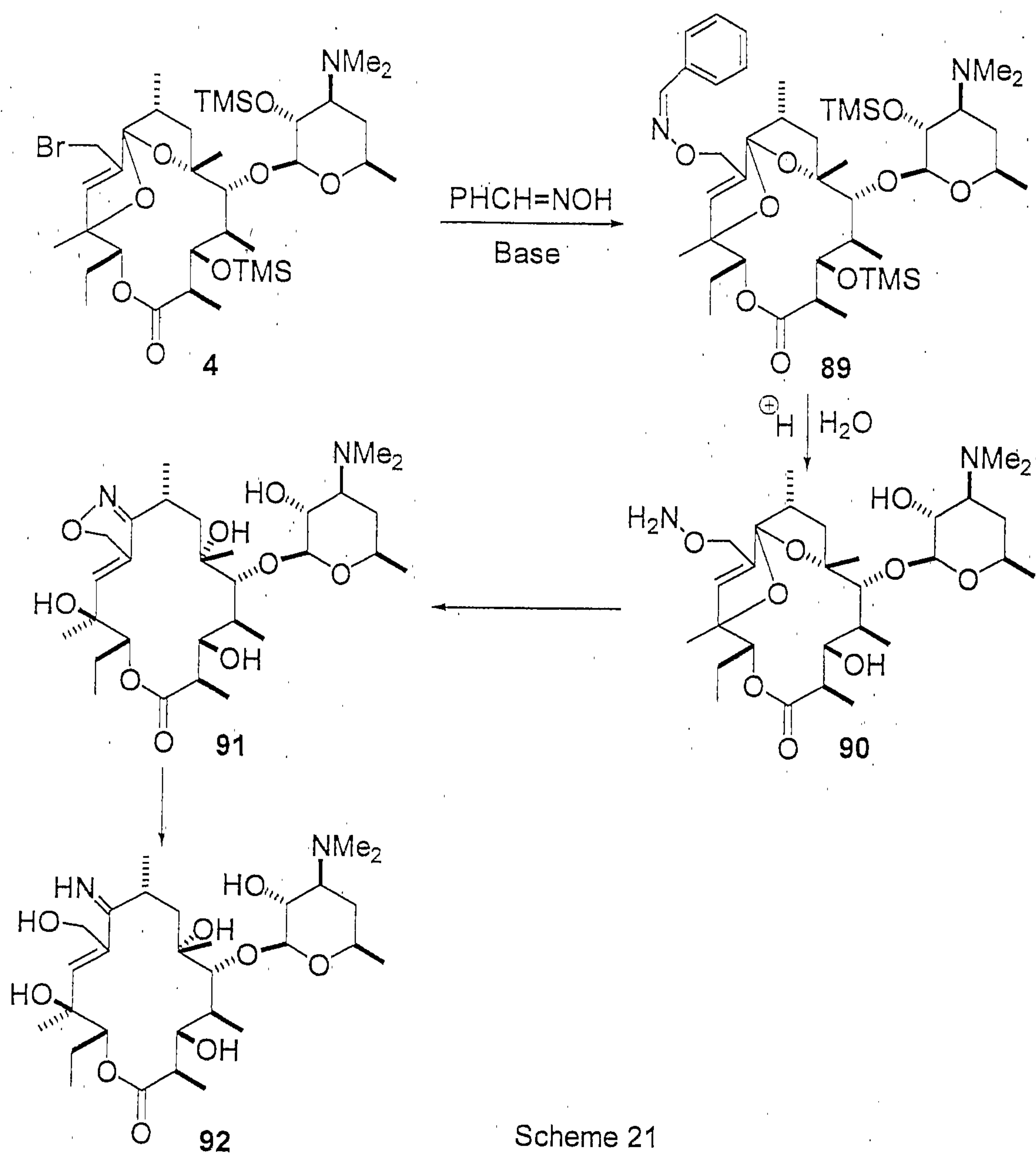
Scheme 18



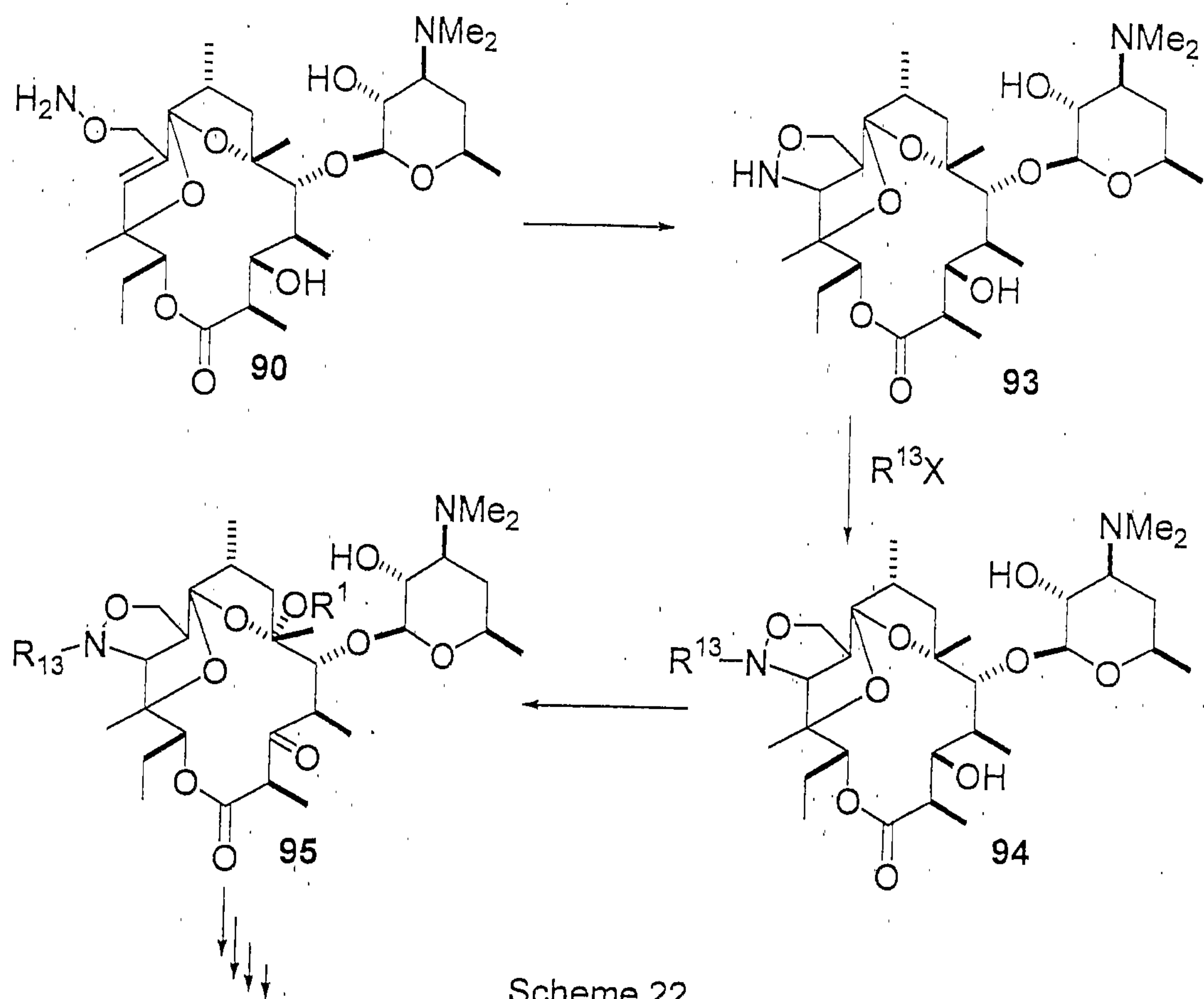
Scheme 19



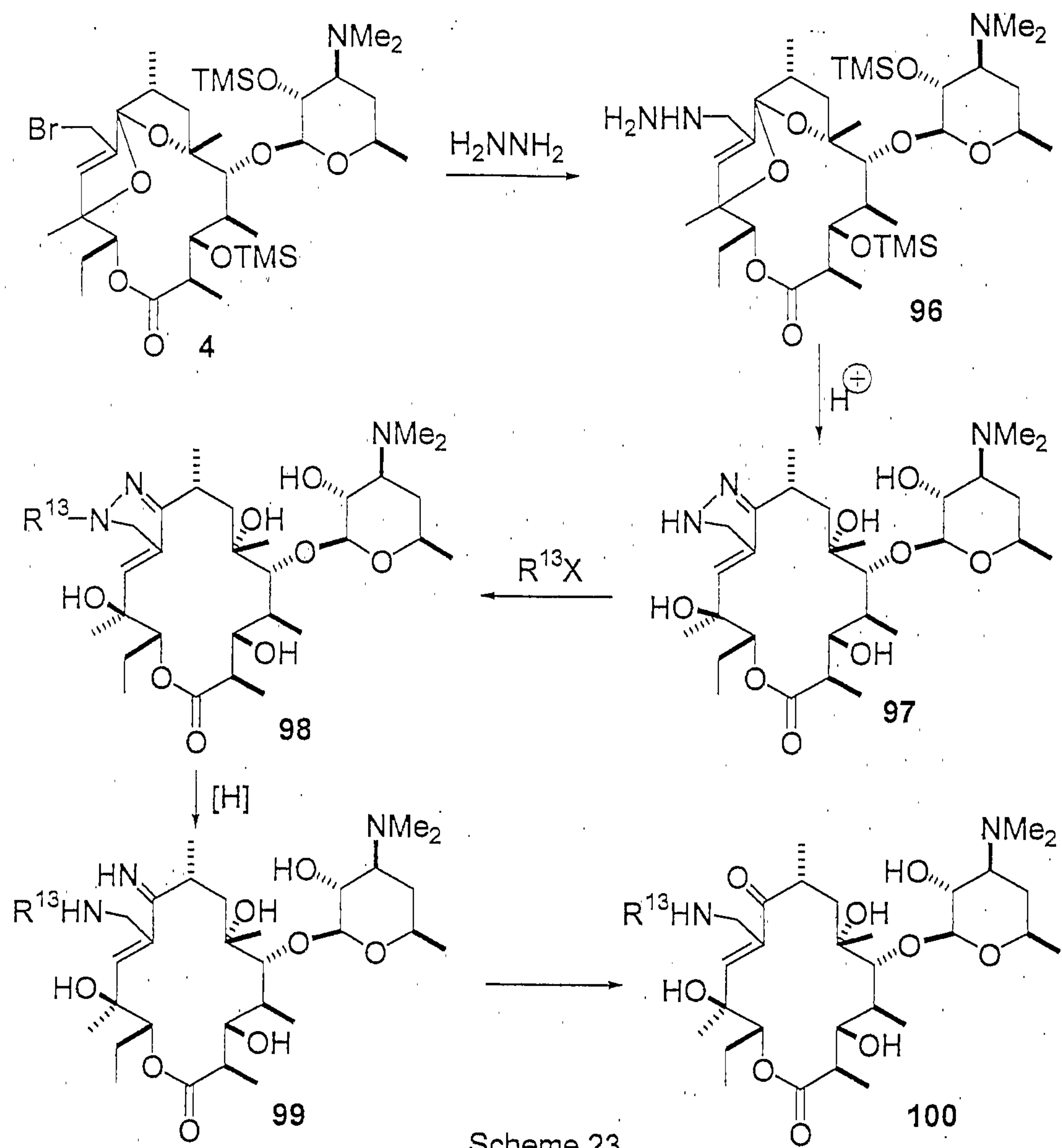
Scheme 20



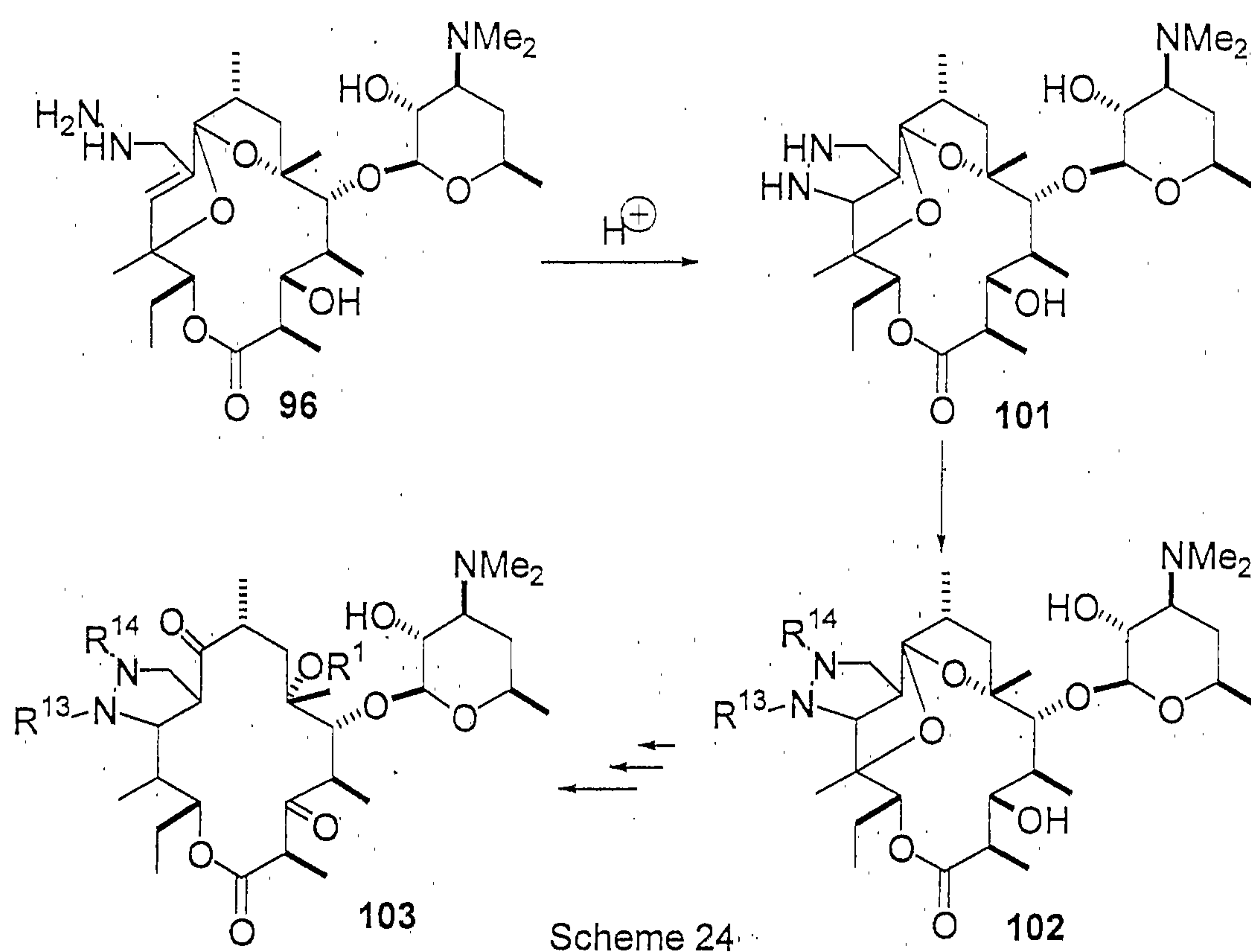
Scheme 21

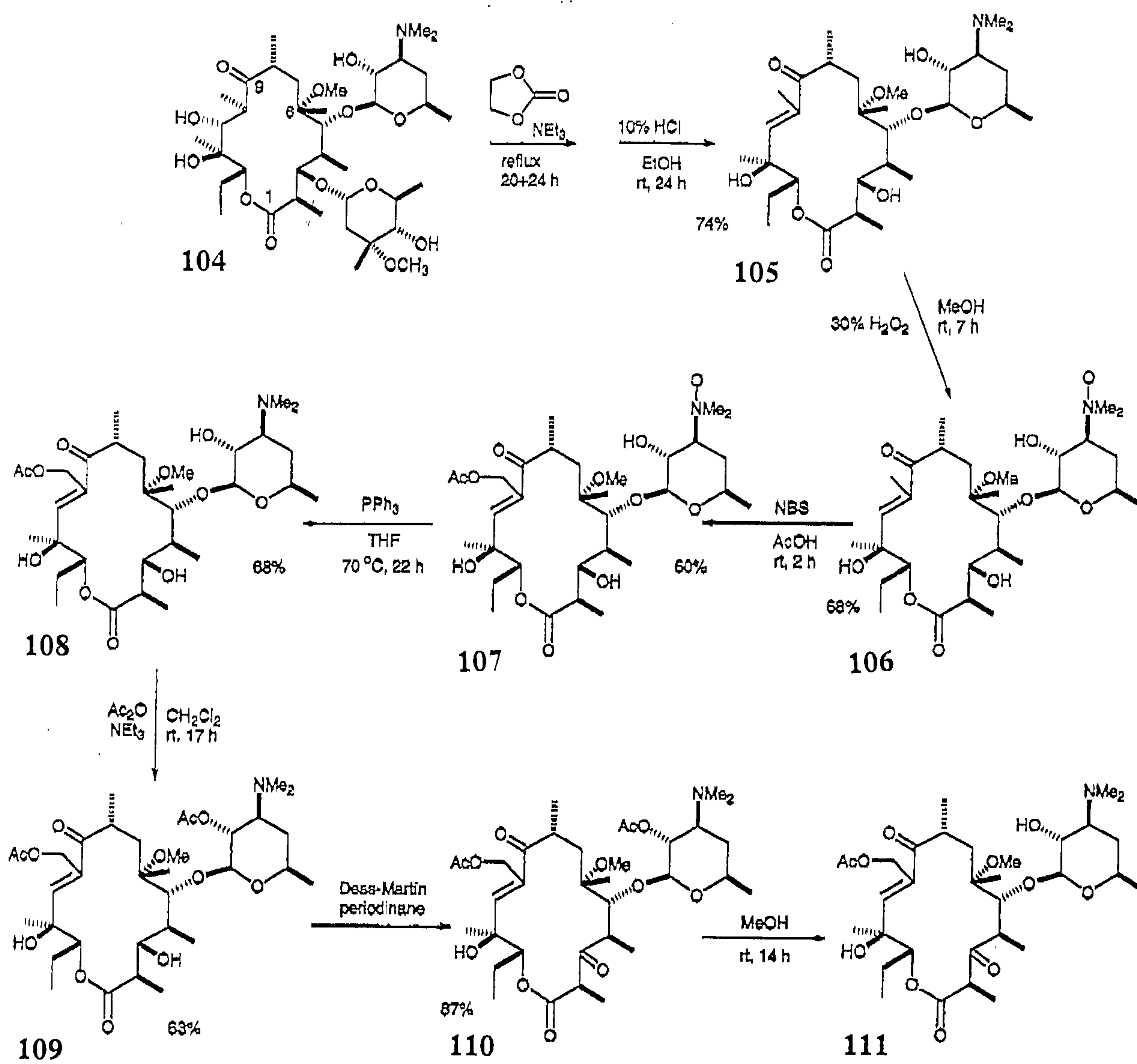


Scheme 22

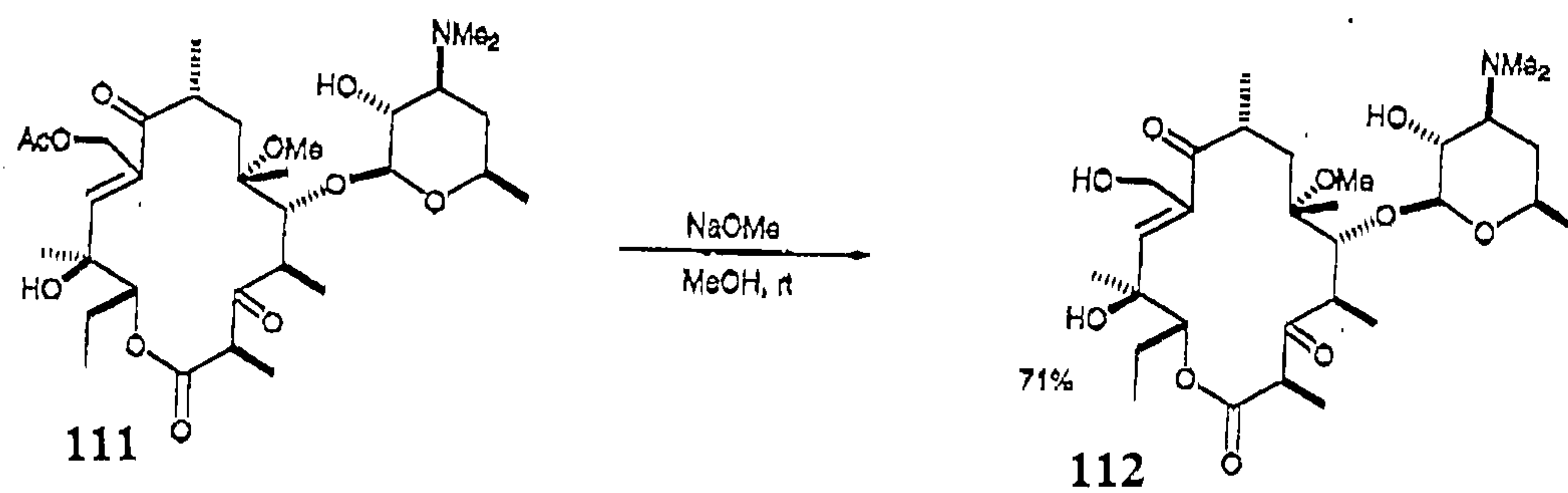


Scheme 23

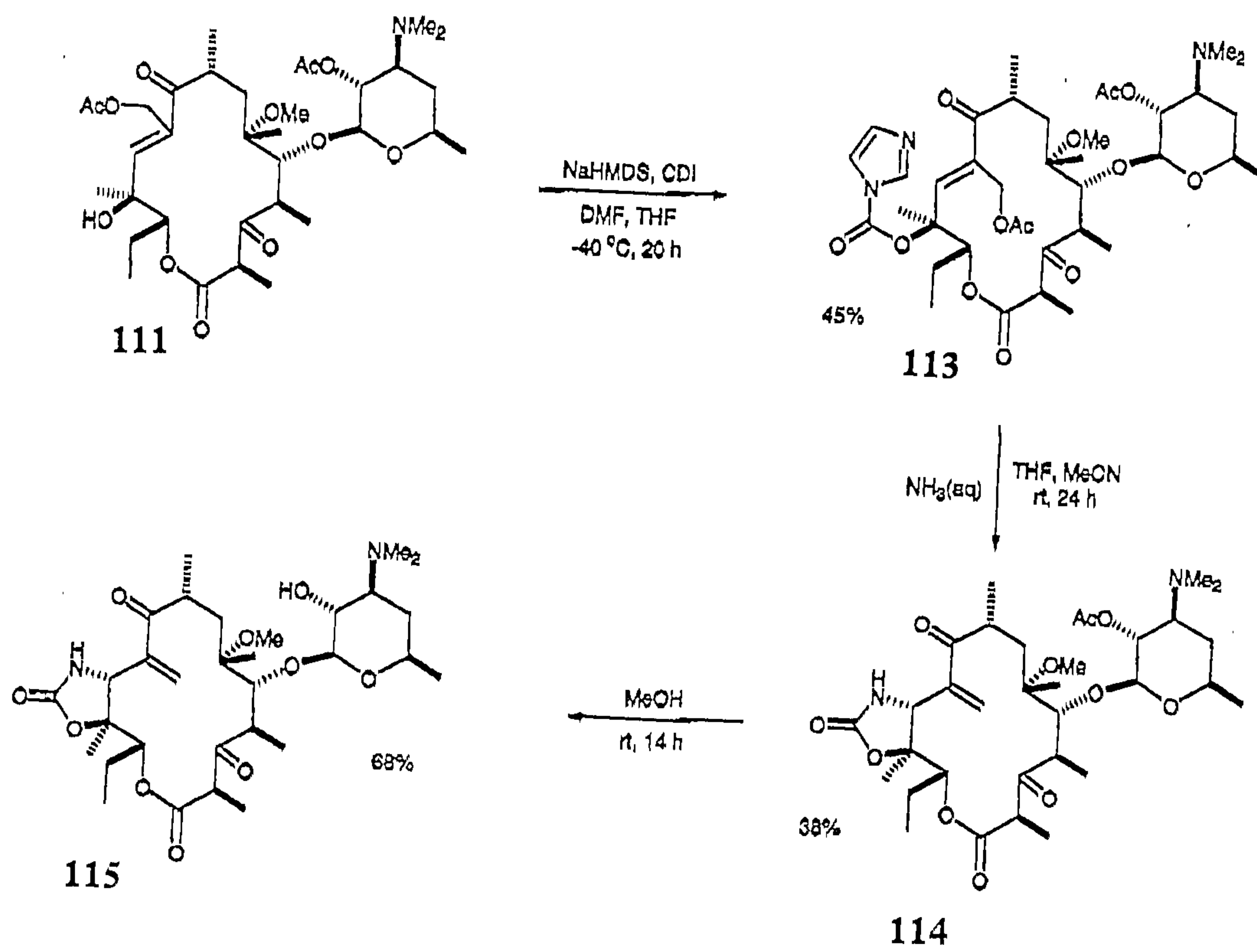




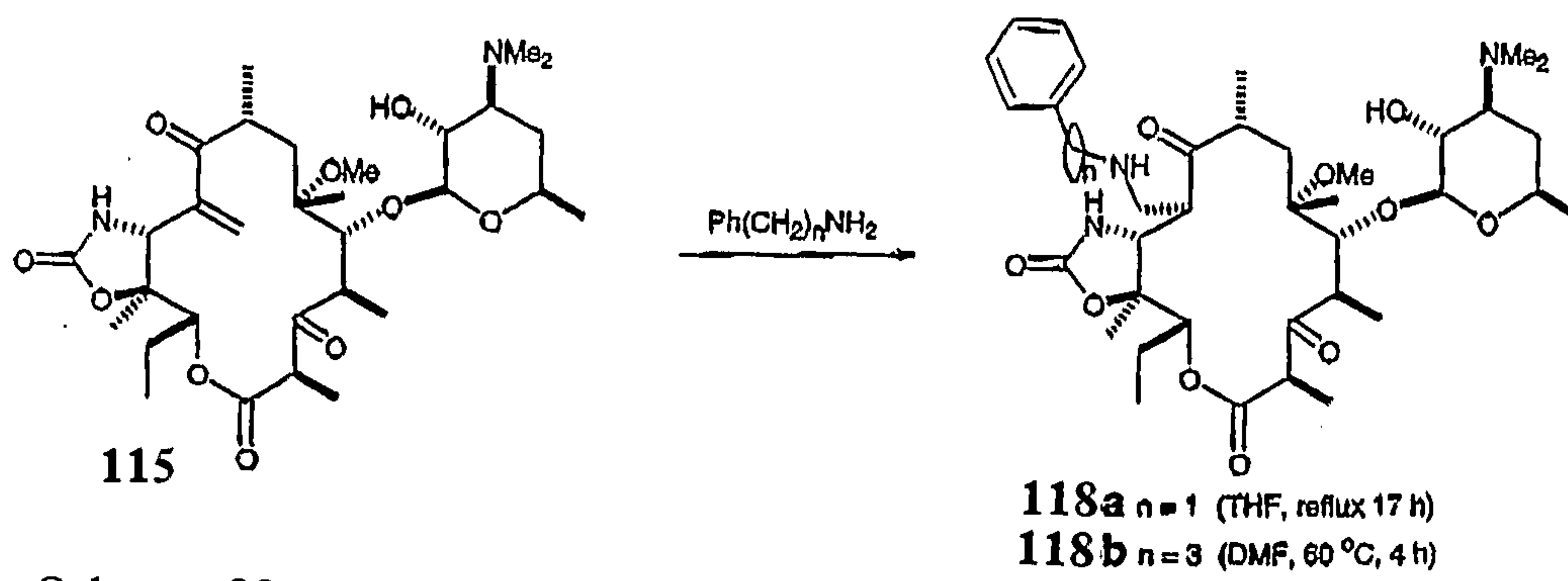
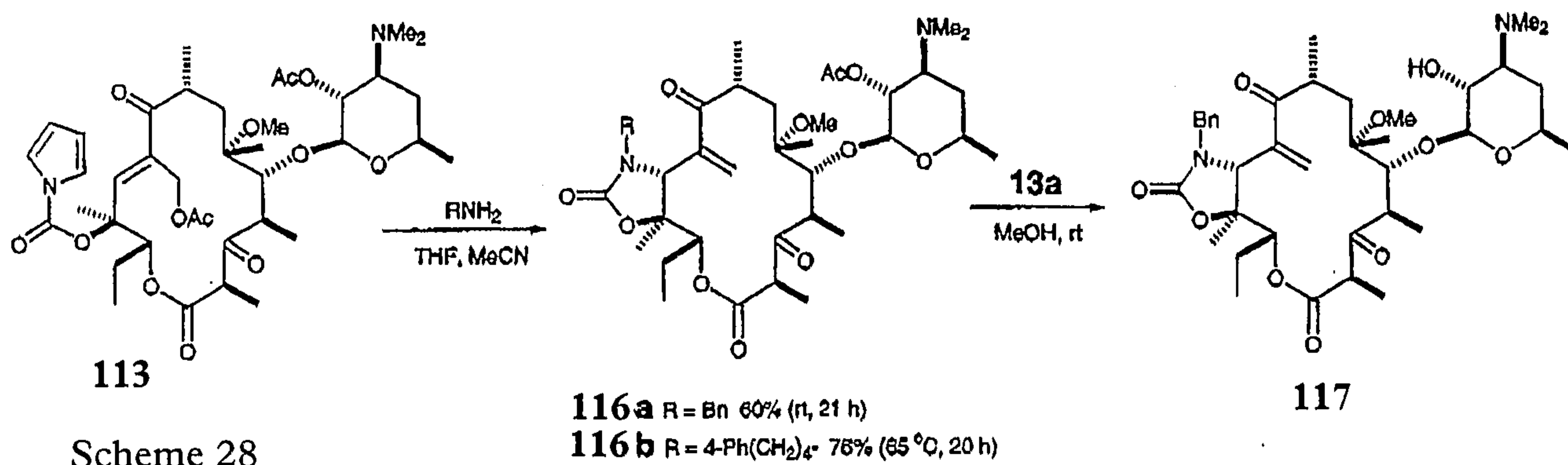
Scheme 25

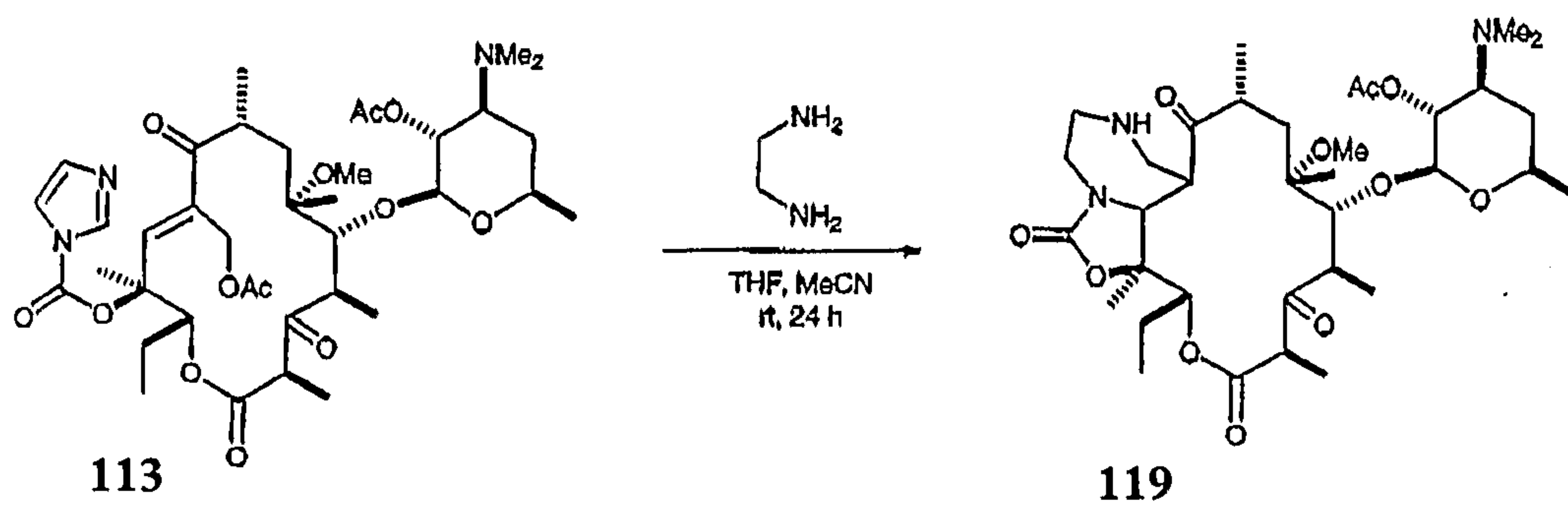
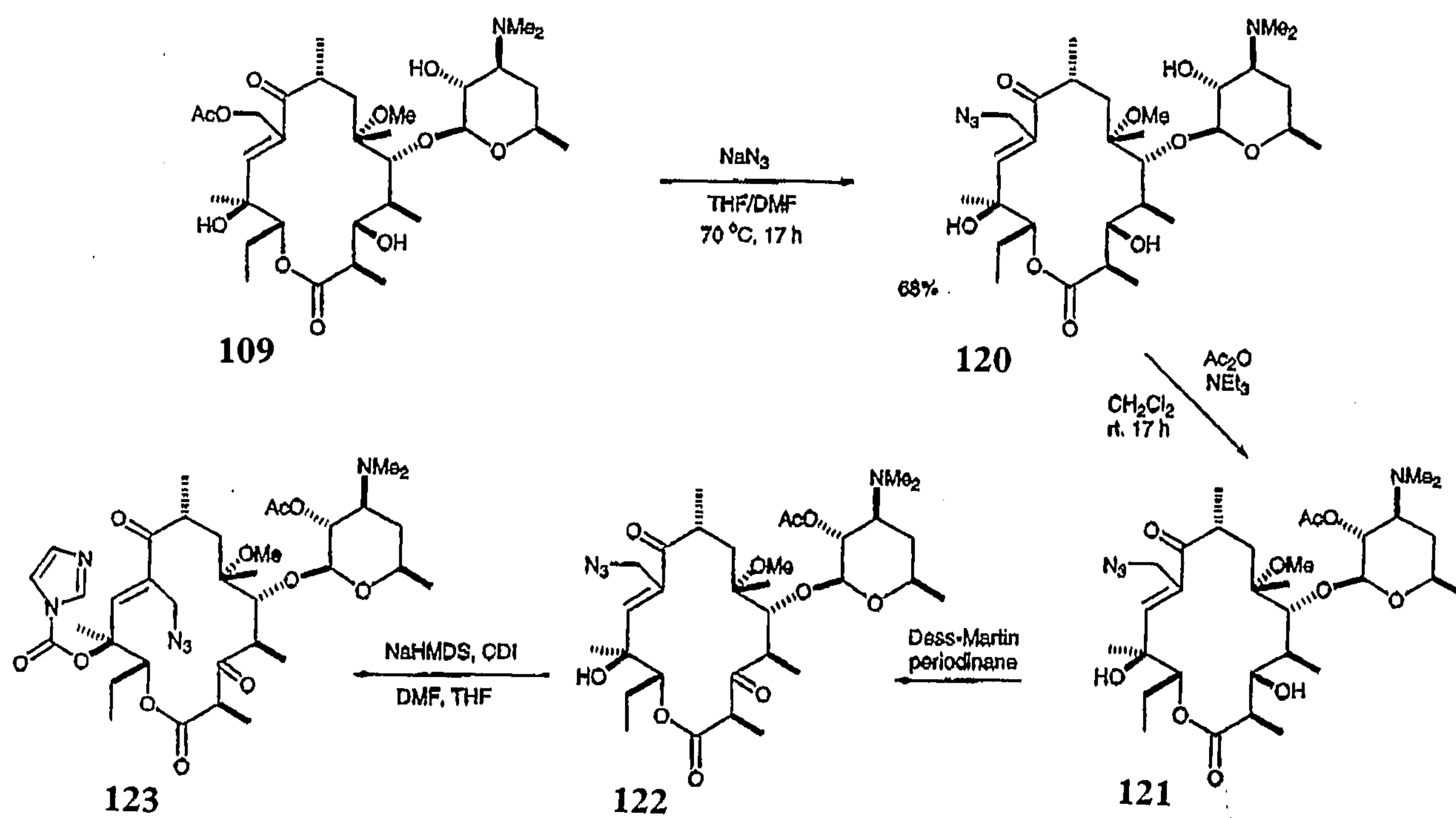


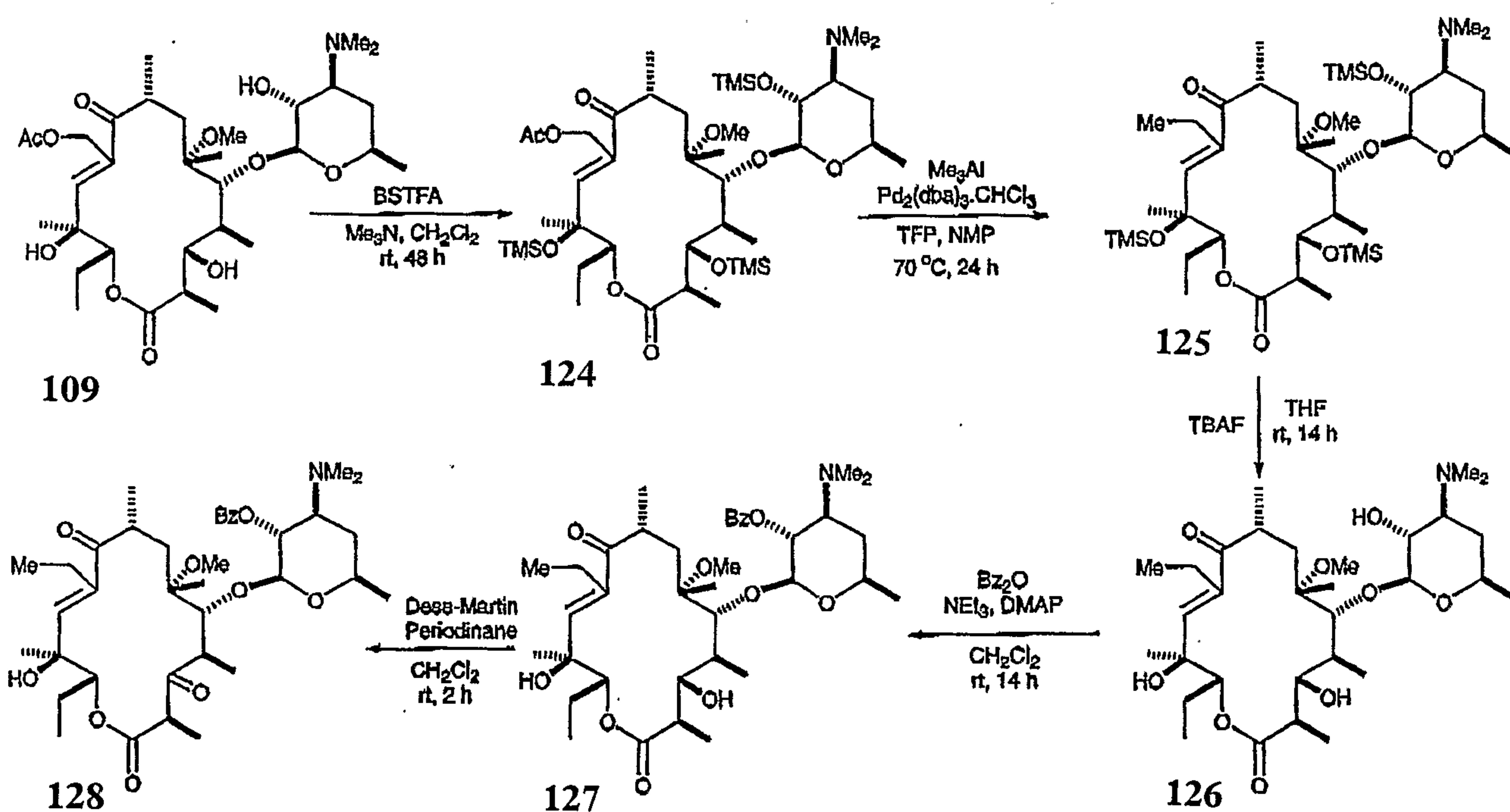
Scheme 26



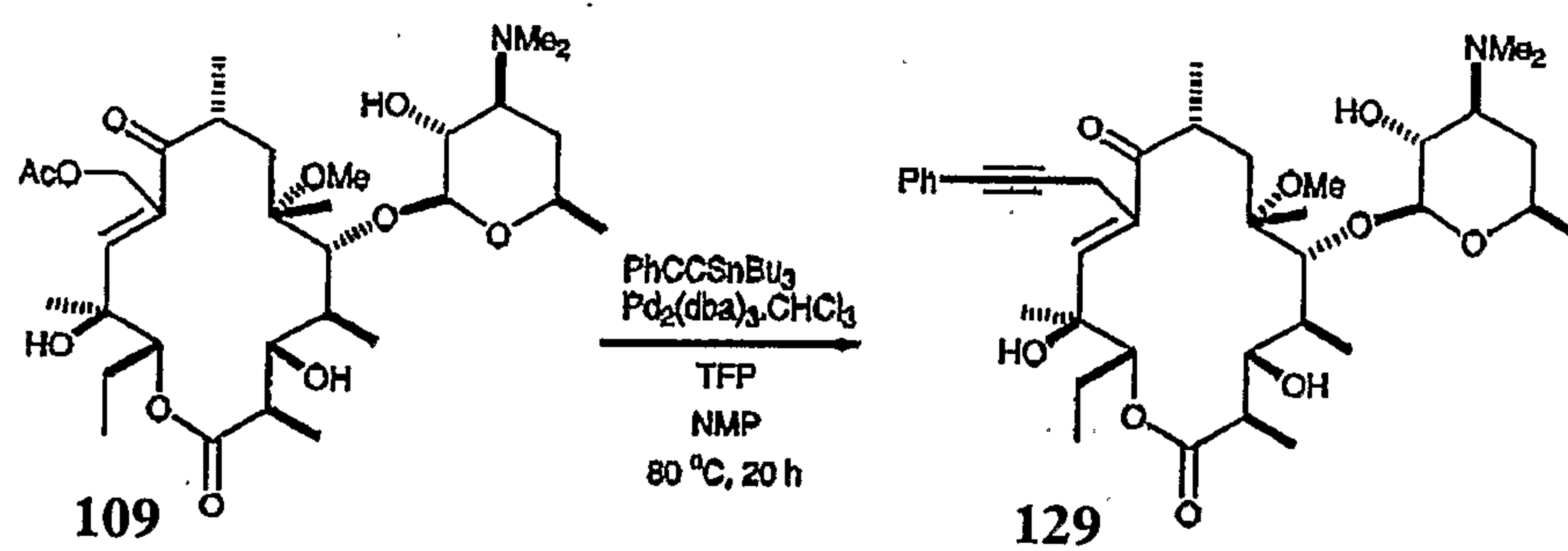
Scheme 27



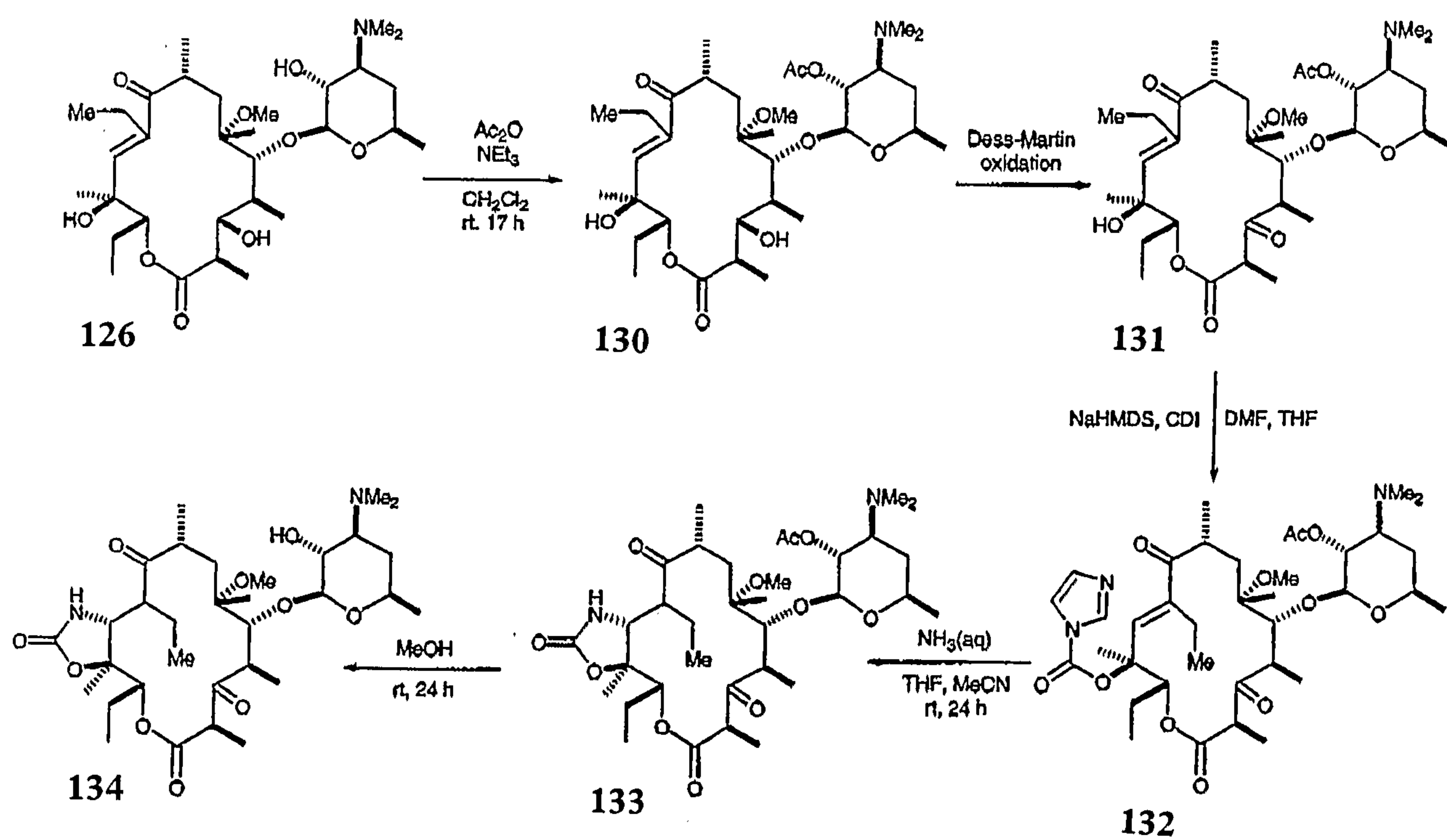
Scheme 30Scheme 31

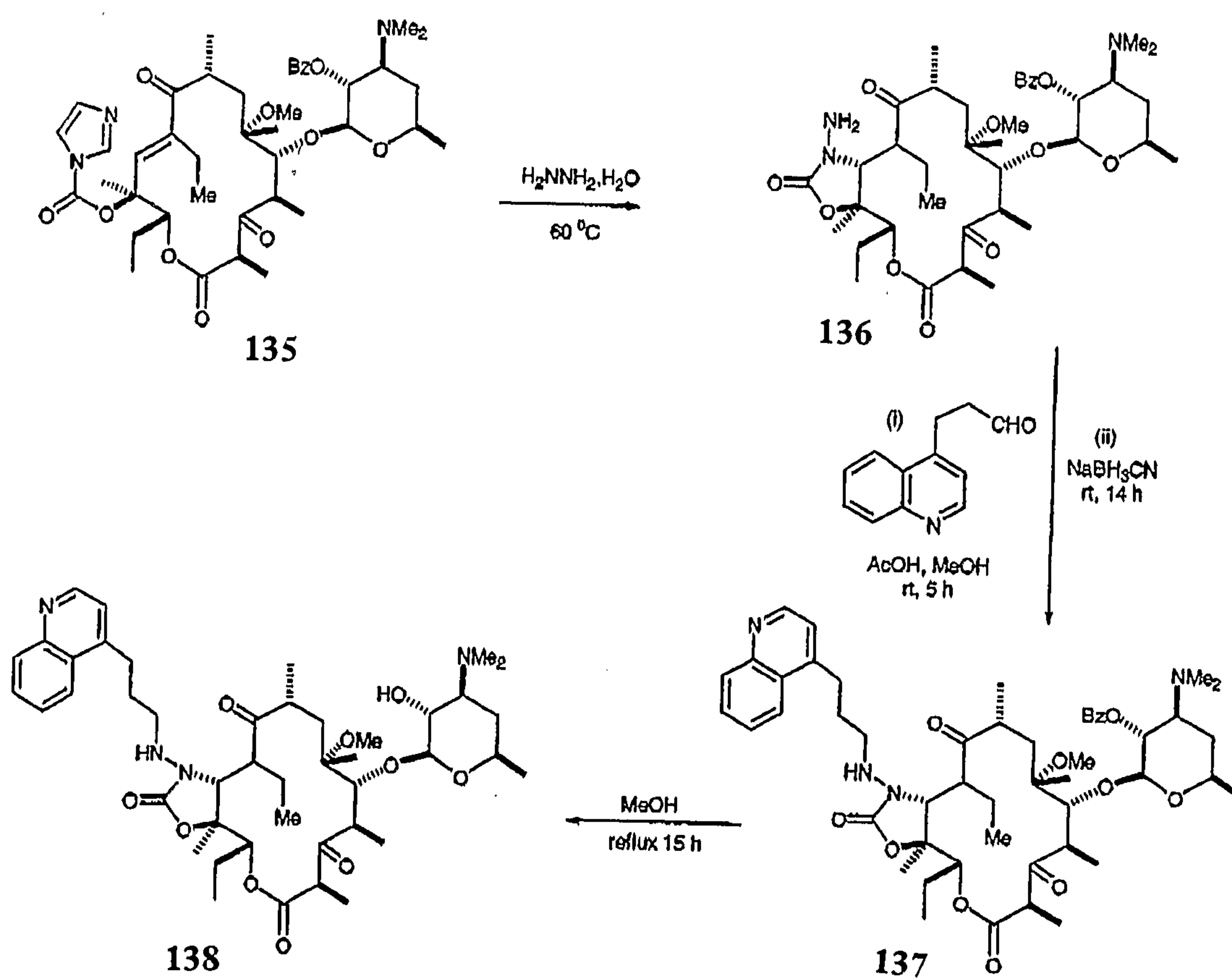


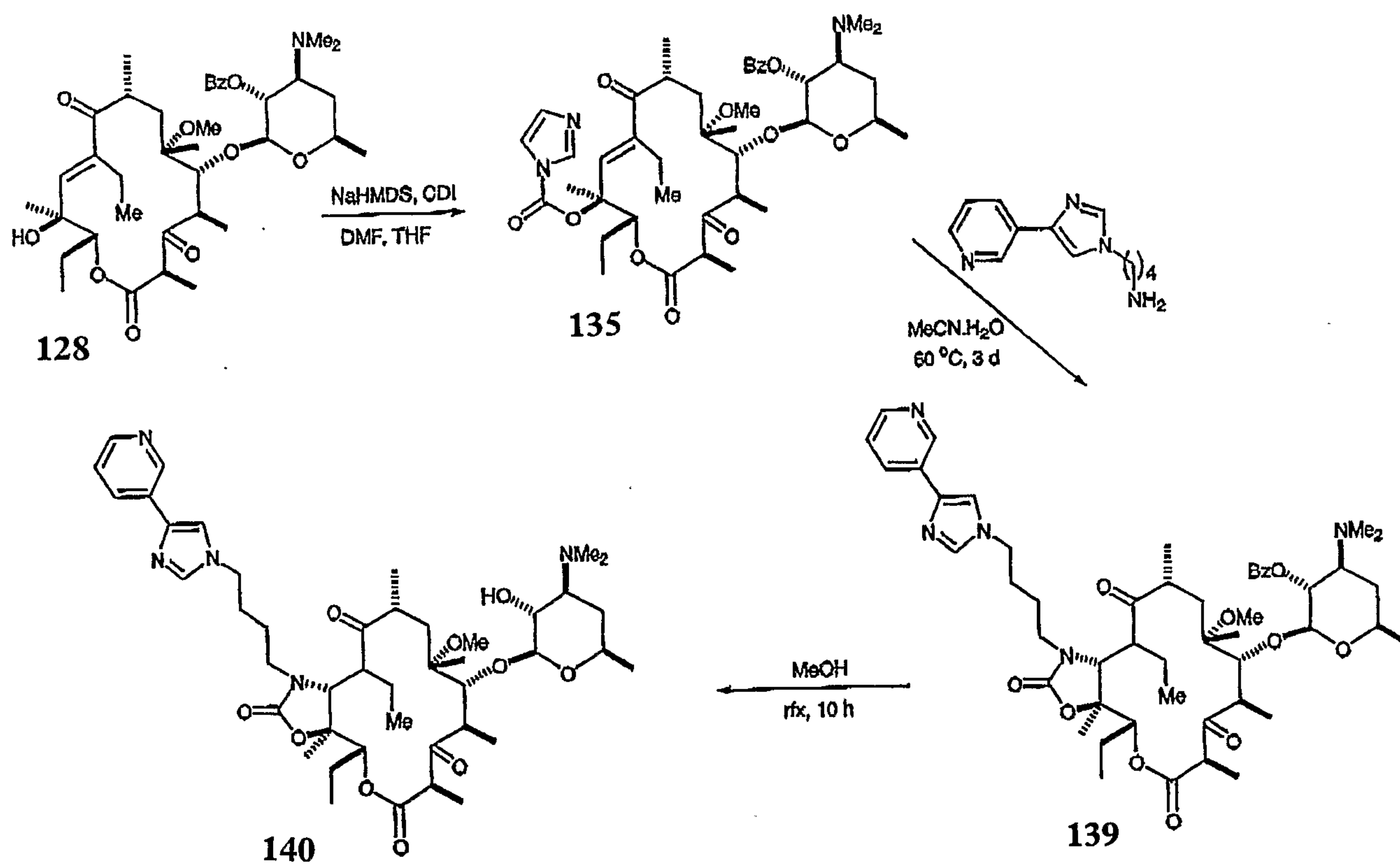
Scheme 32

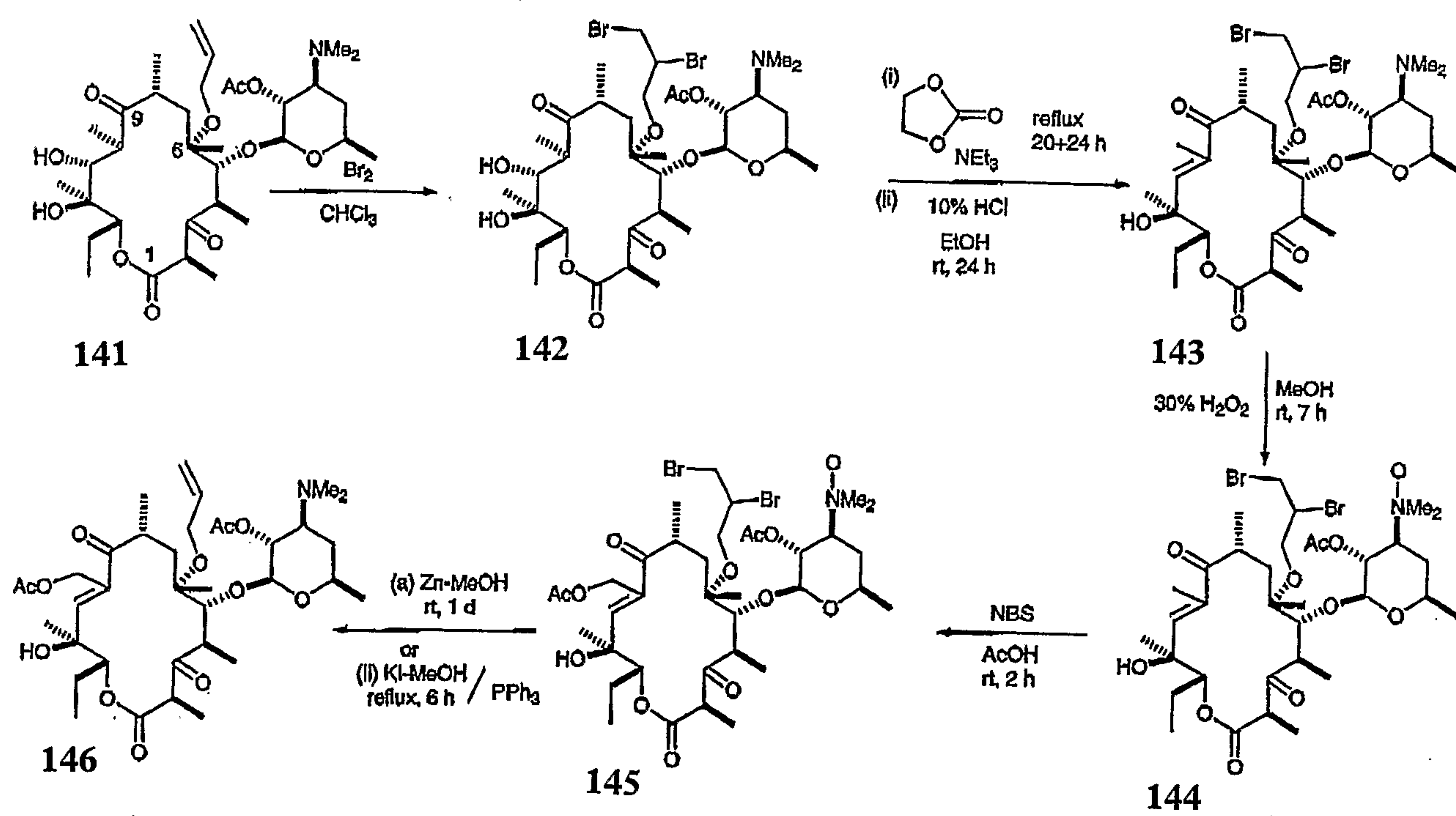


Scheme 33

Scheme 34

Scheme 35

Scheme 36



Scheme 37

Embodiments of the invention, which illustrate the invention in a non-limiting fashion, are set out below in the following Examples.

5 Example 1

Erythralosamine (2) [Flynn et al. J. Am. Chem. Soc. 76: 3121-3131 (1954)]

10 A solution of erythromycin A (6.66 g, 9.1 mmol) in a mixture of EtOH (60 ml) and 10 % HCl (200 ml) was stirred at ambient temperature for 24 h. The mixture was diluted with ethyl acetate (3 x 200 ml), washed with water (3 x 200 ml), dried (MgSO₄) and the solvent was evaporated. The residual material was subjected to flash
15 chromatography on silica gel using CH₂Cl₂:MeOH:aq.NH₃, initially in ratio 90:4:1, then in ratio 90:8:2. Rf 0.19. The product was a white crystalline solid; yield 3.22 g (66%), mp 208°C.

20 HRMS: M 539.3412. Calc. for C₂₉H₄₉NO: 539.3458.

Example 2

O^{2',3'}-Bis (trimethylsilyl) erythralosamine (2a)

25 A solution of erythralosamine (2) (1.59 g, 0.0029 mol) and triethylamine (2.4 ml, 0.0174 mol) in THF (40 ml) under argon was cooled to -78°C and trimethylsilyl trifluoromethanesulfonate (1.59 ml, 0.0088 mol) added dropwise. The mixture was stirred for 20 h, extracted
30 into ethyl acetate, the solution shaken with brine, dried (MgSO₄) and evaporated. The residual material was subjected to flash chromatography on silica gel using hexane:Et₂O 3:1 with 1% Et₃N; yield: 1.59 g (80%) of a crystalline material.

35

HRMS: M 684.4338. Calc. for C₃₅H₆₅NO₈Si₂: 684.4321.

Example 3O^{2',3}-Bis(triethylsilyl)erythralosamine (2b)

A solution of erythralosamine (2) (0.673 g, 0.0012 mol) and triethylamine (0.50 ml, 0.0036 mmol) in dichloromethane (10 ml) under argon was cooled to -78 °C and TES-triflate (0.81 ml, 0.0036 mmol) was added dropwise. Ethyl acetate was added after 24h, the solution shaken brine and dried (MgSO₄) before evaporation to dryness. The residual material was subjected to flash chromatography on silica gel using hexane:Et₂O 3:1 and 1% Et₃N; yield 0.75 g (81%) of a white crystalline material.

HRMS: M 768.5248. Calc. for C₄₁H₇₇NO₈Si₂: 768.5260.

Example 4O^{2',3}-Bis(t-butyldimethylsilyl)erythralosamine (2c)

A solution of erythralosamine (2) (0.475 g, 0.880 mmol) and triethylamine (0.37 ml, 2.640 mmol) in CH₂Cl₂ (5 ml) was cooled to 0°C and TBDMS-triflate (0.50 ml, 2.640 mmol) was added dropwise to the reaction mixture. Water was added to the cold reaction mixture after 22 h, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO₄) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using hexane:Et₂O 3:1; yield 0.593 g (89%) of a white crystalline solid, mp 92-93°C.

HRMS: [M+1] 768.5297. Calc. for C₄₁H₇₇NO₈Si₂: 768.5260.

Example 5Erythralosamine N-Oxide (3)

30% Hydrogen peroxide (1 ml) was added to a solution of

erythralosamine (2) (1.4 g, 2.52 mmol) in methanol (10 ml) and the reaction mixture stirred at ambient temperature for 7 h. Saturated aqueous sodium bisulfite was added slowly to the reaction mixture to remove
5 excess hydrogen peroxide before extraction with chloroform. The dried (MgSO_4) chloroform solution was evaporated. The residual material was the title compound that was sufficiently pure for use in the subsequent reaction. The product was a white crystalline solid with
10 mp 153-155°C; yield 100%.

HRMS: $[\text{M}+1]$ 556.3484. Calc. for $\text{C}_{29}\text{H}_{50}\text{BrNO}_9$: 556.3480.

Example 6

15

10-Bromomethyl-10-desmethyl-erythralosamine N-Oxide (4)

A solution of N-bromosuccinimide in acetic acid (15 ml) was added to a solution of erythralosamine N-oxide (3) (1.56 g, 2.5 mmol) in acetic acid (20 ml) and the
20 resultant solution stirred at room temperature for 3 h when TLC showed the reaction to be complete. Most of the acetic acid was removed under reduced pressure and aqueous potassium hydroxide was added to the reaction mixture until pH 9-11. The product was extracted into chloroform
25 that was washed and dried (MgSO_4) before the solvent was distilled off. The product was isolated after flash chromatography on silica gel using CH_2Cl_2 :MeOH: NH_3 , initially in ratio 9:1:0.1, and then 9:2:0.1; yield 0.95 g (60%) of a white crystalline material, mp 149-151°C.

30

HRMS: M 634.2556. Calc. for $\text{C}_{29}\text{H}_{49}\text{BrNO}_9$: 634.2591.

Example 7

35

10-Bromomethyl-10-desmethyl-erythralosamine (5)

A solution of 10-bromomethyl-10-desmethyl-

erythralosamine N-oxide (4) (2.60 g, 0.004 mol) and triphenylphosphine (2.20 g, 0.008 mol) in THF (30 ml) was heated under reflux for 17 h when TLC monitoring showed that the reaction had gone to completion. Most of
5 the THF was removed by distillation, the residual material extracted into ethyl acetate, the extracts shaken with aqueous sodium bicarbonate, washed with brine, dried (MgSO_4), the solution evaporated and the residual material subjected to flash chromatography on
10 silica gel using CH_2Cl_2 :MeOH: NH_3 90:8:2; yield 2.13 g (86%) of a white crystalline material, mp 88-90°C.

HRMS: M 618.2607. Calc. for $\text{C}_{29}\text{H}_{48}\text{BrNO}_8$: 618.2636.

15 Example 8

10-Bromomethyl- $\text{O}^{2',3}$ -Bis(t-butyldimethylsilyl)-10-desmethyl-erythralosamine (5a)

A solution of 10-bromomethyl-10-desmethyl-
20 erythralosamine (5) (0.250 g, 0.404 mmol) and trimethylamine (0.17 ml, 1.212 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C and TBDMS-triflate (0.23 ml, 1.212 mmol) added dropwise to the reaction mixture. Water was added to the cold reaction mixture after 17 h, the mixture
25 extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO_4) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using hexane: Et_2O 5:1; yield 0.25 g (73%) of a white
30 crystalline solid, mp 151-152°C.

HRMS: $[\text{M}+1]$, 846.4329. Calc. for $\text{C}_{41}\text{H}_{76}\text{NO}_8\text{Si}_2\text{Br}$: 846.4365.

Example 9O^{2'}-Acetyl-erythralosamine (6)

Acetic anhydride (0.88 ml, 9.30 mmol) and triethylamine
5 (129 ml, 9.30 mmol) were added to a solution of
erythralosamine (2) (2.50 g, 4.69 mmol) in CH₂Cl₂ (15 ml)
and the reaction mixture stirred at room temperature for
2h until TLC monitoring showed full conversion. The
reaction mixture was diluted with ethyl acetate, the
10 solution shaken with 5% Na₂CO₃ (aq), with brine, dried
(MgSO₄) and evaporated. The residual material was
subjected to flash chromatography using silica gel,
90:4:1 CH₂Cl₂:MeOH:NH₃ (aq); yield 2.30 g (84%) of a white
solid, mp 153-154°C

15

HRMS: M 581.3554. Calc. for C₂₉H₄₉NO₈: 581.3564.

Example 1020 O^{2'}-Acetyl-erythralosamine-3 ketolide (7)

Dimethyl sulfide (0.24 ml, 7.72 mmol) was added dropwise
from a syringe over 5 min to a stirred solution of N-
chlorosuccinimide (NCS) (0.363 g, 2.12 mmol) in
dichloromethane (8 ml) at 10°C under argon. The solution
25 was stirred at this temperature for 10 min before a
solution of O^{2'}-acetylerythralosamine (6) (1.05g, 1.81
mmol) in dichloromethane (12 mL) was added dropwise over
20 min. The mixture was stirred for 30 min at -10 to -
5°C when triethylamine (0.28 mL, 1.99 mmol) was added
30 over 5 min. The mixture was stirred for an additional 45
min at this temperature and then allowed to reach room
temperature and the solvent removed at reduced pressure.
The residual material was extracted into ethyl acetate,
the solution shaken with 5% Na₂CO₃, with brine, dried
35 (MgSO₄) and the solvent distilled off. The residual
material was subjected to flash chromatography on silica

gel using NEt_3 :acetone:hexane 1:25:75; yield 0.66 g (63%) of a white solid, mp 235°C. Rf 0.17.

HRMS: M 580.3480. Calc. for $\text{C}_{31}\text{H}_{49}\text{NO}_9$: 580.3480.

5

Example 11

Erythralosamine 3-ketolide (8)

10 $0^{2'}$ -Acetyl-erythralosamine-3 ketolide (7) (0.50 g, 0.86 mmol) was dissolved in methanol (10 ml) and the reaction mixture stirred at room temperature for 16 h until TLC monitoring showed full conversion. The solvent was removed under reduced pressure and the residual material purified by flash chromatography on silica gel using
15 NEt_3 :acetone:hexane 1:25:75. Rf 0.15. Yield 0.37 g (80%) of a white solid, mp 179°C.

HRMS: M 538.3354. Calc. for $\text{C}_{29}\text{H}_{47}\text{NO}_8$: 538.3374.

20 Example 12

Erythralosamine 3-ketolide N-Oxide (9)

30% Hydrogen peroxide (1 ml) was added to a solution of erythralosamine 3-ketolide (8) (0.307 g, 0.507 mmol) in
25 methanol (2 ml) and the reaction mixture stirred at ambient temperature for 4 h. Saturated aqueous sodium bisulfite was added slowly to the reaction mixture to remove excess hydrogen peroxide before extraction with ethyl acetate. The dried (MgSO_4) solution was
30 evaporated. The residual material was the title compound, which was sufficiently pure for use in the subsequent reaction. The product was a white crystalline solid with mp 139-141°C; yield 73%.

35 HRMS: $[\text{M}+1]$ 554.3315. Calc. for $\text{C}_{29}\text{H}_{47}\text{NO}_9$: 554.3323.

Example 1310-Benzyl-10-desmethyl-erythralosamine (12)

A solution of 10-bromomethyl-10-desmethyl-erythralosamine (5) (0.280 g, 0.453 mmol) in NMP (5 ml) was degassed and tris(2-furyl)phosphine (0.025 g, 0.109 mmol) and Pd₂dba₃.CHCl₃ (0.014 g, 0.014 mmol) added. The reaction mixture was heated at 50°C for 10 min before tributyl(phenyl)stannane (0.30 ml, 0.906 mmol) was added. The reaction mixture was heated at 100 °C for 20 h. The cold reaction mixture was extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO₄) and the solvents distilled off at reduced pressure. The residual material was subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH:NH₃ 90:4:1 and then CH₂Cl₂:MeOH (9:2); yield 0.168 g (60%) of a white crystalline material mp. 151-152°C.

HRMS: M 616.3847. Calc. for C₃₅H₅₃NO₈: 616.3843.

Example 1410-(2-Furylmethyl)-10-desmethyl-erythralosamine (13)

A solution of 10-bromomethyl-10-desmethyl-erythralosamine N-oxide (4) (0.196 g, 0.310 mmol) in NMP (3 ml) was degassed and tris(2-furyl)phosphine (0.018 g, 0.077 mmol) and Pd₂dba₃.CHCl₃ (0.010 g, 0.010 mmol) added. The reaction mixture was heated at 50 °C for 10 min and more tris(2-furyl)phosphine (0.12 ml, 0.372 mmol) added. The reaction mixture was heated at 80°C for 22 h. The product was extracted with ethyl acetate, the organic phase washed with aqueous sodium hydrogen carbonate, brine and dried (MgSO₄). The NMP was removed under reduced pressure and the residual material subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH:NH₃

90:4:1, yield 0.096 g (51%) of a white crystalline solid.

HRMS: [M+1] 606.3654. Calc. for $C_{33}H_{51}NO_9$: 606.3636.

5

Example 15

10-Phenylethynylmethyl-10-desmethyl-erythralosamine (14)
1-methyl-2-pyrrolidone was degassed and tris(2-furyl)phosphine (0.022 g, 0.096 mmol) and $Pd_2dba_3 \cdot CHCl_3$ (0.013 g, 0.012 mmol) added. The reaction mixture was heated at 50°C for 10 min before tributyl(phenylethynyl)stannane (0.21 ml, 0.589 mmol) was added. The reaction mixture was heated at 80°C for 17 h. The solvents were distilled off at reduced pressure. The crude product was subjected to flash chromatography on silica gel using $CH_2Cl_2:MeOH:NH_3$ 90:4:1 and then $CH_2Cl_2:MeOH$ (9:2); yield 0.240 g (76%) of a yellow foam.

20

HRMS: [M+1] 640.3817 (Calc. for $C_{37}H_{53}NO_8$: 640.3843).

Example 16

$O^{2',3}$ Bis(t-butyldimethylsilyl)-10-ethyl-10-desmethyl-erythralosamine (15)

A solution of 10-bromomethyl- $O^{2',3}$ -bis(t-butyldimethylsilyl)-10-desmethyl-erythralosamine (5a) (0.064 g, 0.080 mmol) in NMP (1 ml) was degassed for 1 h before tris(dibenzylideneacetone)dipalladium chloroform complex (0.002 g, 0.002 mmol) and tri(2-furyl)phosphine (0.004 g, 0.016 mmol) were added. The mixture was heated to 50°C to generate the active catalyst and trimethylaluminium 2 M in hexane (0.2 ml, 0.400 mmol) added carefully through a syringe. The resultant reaction mixture was heated at 100 °C for 24h. The cold

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reaction mixture was passed through a silica plug and the solvent was removed from the filtrate by distillation. The residual material was subjected to flash chromatography on silica gel using hexane:Et₂O 4:1; yield 0.053 g (84%) of a white crystalline material.

HRMS: [M+1] 782.5383. Calc. for C₄₂H₇₉NO₈Si₂: 782.5417.

Example 17

10

10-(2-Ethoxyprop-2-en-1-yl)-10-desmethyl-erythralosamine (16)

10-Bromomethyl-10-desmethyl-erythralosamine N-oxide (4) (0.100 g, 0.158 mmol) was deoxygenated when a solution with tris(2-furyl)phosphine (0.036 g, 0.158 mmol) in NMP (1 ml) was heated at 70 °C for 17 h. The catalyst Pd₂dba₃.CHCl₃ (0.005 g, 0.005 mmol) and tris(2-furyl)phosphine (0.009 g, 0.038 mmol) for the cross-coupling reaction were added to the reaction mixture together with tributyl(1-ethoxyethenyl)stannane (0.064 ml, 0.189 mmol). The resultant mixture was heated at 70°C for 24 h. The solvent was removed at reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO₄), evaporated and the residual material subjected to flash chromatography on silica gel CH₂Cl₂:MeOH:NH₃ 90:4:1; yield 0.052 g (54%) of a white crystalline material.

HRMS: [M+1] 610.3948. Calc. for C₃₃H₅₅NO₉: 610.3949.

Example 18

C-10 Benzylaminomethyl-10-desmethyl-erythralosamine (30)

A solution of 10-bromomethyl-10-desmethyl-erythralosamine (5) (0.502 g, 0.812 mmol) and

benzylamine (0.35 ml, 3.246 mmol) in DMF (4 ml) was heated at 60°C for 16 h. Water was added to the cold reaction mixture, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO₄) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH: aq.NH₃ 90:8:2; yield 0.40 g (78%) of a white crystalline solid, mp 151-152°C.

HRMS: M 645.4102. Calc. for C₂₉H₄₈BrNO₈: 645.4109.

Example 19

10-p-Chloroanilinomethyl-10-desmethyl-erythralosamine N-Oxide (31)

A solution of 10-bromomethyl-10-desmethyl-erythralosamine N-oxide (4) (0.613 g, 0.968 mmol) and p-chloroaniline (0.540 g, 3.872 mmol) in NMP (5 ml) was heated at 100°C for 20 h. Water was added to the cold reaction mixture, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, the solution dried (MgSO₄) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH:aq.NH₃ 90:4:1; yield 0.129 g (20%) of a white crystalline material. HRMS [H⁺] 665.3547 (calculated for C₃₅H₅₃N₂O₈Cl₁ 665.3563.

HRMS: [M+1] 665.3547. Calc. for C₃₅H₅₃NO₈Cl: 665.3547.

Example 20

11-Hydroxy-O^{2'3}-bis(trimethylsilyl)erythralosamine N-oxide (37)

O^{2'3}-Bis(trimethylsilyl) erythralosamine (2a) (0.409g,

0.598 mmol) was dissolved in a borane-methyl sulfide complex in THF (2M, 3 ml, 5.978 mmol) and the mixture stirred at ambient temperature for 17 h. Ethanol (0.5 ml) and 1 M sodium hydroxide (0.5 ml) were added to the resultant reaction mixture which was cooled to 0°C before addition of hydrogen (30%, 2 ml). Stirring was continued for 2 h, the mixture extracted with ethyl acetate, the extracts shaken with sodium hydrogen carbonate, brine, dried (MgSO₄), and evaporated. The residual material was subjected to flash chromatography on silica gel using hexane:Et₂O 1:1; yield 0.144 g (35%) of a white solid.

Example 21

15

10,11-Epoxy-erythralosamine N-oxide (40)

A solution of erythralosamine (0.573 g, 1.062 mmol) and MCPBA (1.66 g, 7.432 mmol) in dichloromethane (20 ml) was heated under reflux for 4 h, another portion of MCPBA added (0.55 g, 3.16 mmol) and the heating continued for another 4 h. Sodium hydrogen carbonate was added to the cold mixture, stirred overnight and extracted with dichloromethane. The organic phase was washed with Na₂SO₃, brine and dried (MgSO₄). The crude product was purified by flash chromatography (silica gel) CH₂Cl₂:MeOH 9:1; yield 0.298 g, (49%) of a white crystalline material.

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HRMS [M+1] 572.3456. Calc. for C₂₉H₄₉N₁O₁₀: 572.3456.

Example 22

10,11-Epoxy-erythralosamine (41)

A solution of 10,11-epoxy-erythralosamine N-oxide (37) (0.380g, 0.665 mmol) and triphenylphosphine (0.350 g, 1.33 mmol) in THF (5 ml) was heated at reflux for 17 h.

35

Most of the THF was removed by distillation, the residual material extracted into ethyl acetate, the extracts shaken with aqueous sodium bicarbonate, washed with brine and dried (MgSO_4). The solution was evaporated and the residual material subjected to flash chromatography on silica gel using $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_3$ 90:8:2; yield 0.216 g (60%) of a white crystalline material.

HRMS: M 556.3474. Calc. for $\text{C}_{29}\text{H}_{49}\text{NO}_9$: 556.3480.

Example 23

10,11-Anhydro-6-O-methyl-descladinosyl-erythromycin A (105)

A suspension of 6-O-methyl-erythromycin A (1.21 g, 1.60 mmol), ethylene carbonate (0.86 g, 9.70 mmol and triethylamine (5 ml) was refluxed with vigorous stirring for 24 h when more ethylene carbonate (0.43 g, 4.85 mmol) was added, and the reaction mixture was refluxed for an additional 20 h. Excess triethylamine was removed under reduced pressure, water (4 ml), 10% aqueous HCl (2 ml) and ethanol (0.5 ml) were added and the mixture was stirred at room temperature for 24 h. The pH was adjusted to 10-11 with aq. KOH. The mixture was extracted with EtOAc, the organic phase washed with brine, dried (MgSO_4) and concentrated to afford the crude product as a white solid mp 175-177°C; yield 0.68 g (74 %) after flash chromatography using $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_3(\text{aq})$ 90:4:2-90:10:2: HRMS [Electrospray, Na^+]: M 594.3626. Calc. for $\text{C}_{30}\text{H}_{53}\text{NO}_9$: 594.3612.

Example 24

10,11-Anhydro-6-O-methyl-descladinosyl-erythromycin A N-oxide (106)

Hydrogen peroxide (2.0 ml) was added to a solution of

10,11-anhydro-6-O-methyl-descladinosyl-erythromycin A
(105) (1.60 g, 2.80 mmol) in methanol (20 ml). The
reaction mixture was stirred at ambient temperature for
5 h. Cyclohexene (2 ml) was added to remove excess
hydrogen peroxide and the reaction mixture was stirred
at room temperature overnight. The solvents were removed
under reduced pressure and the crude product was
purified by flash chromatography using
CH₂Cl₂:MeOH:NH₃(aq) 90:20:2; yield 1.11 g (68%) of a
white crystalline material, mp. 192-193°C. HRMS
[Electrospray, H⁺]: M 588.3727. Calc. for C₃₀H₅₃NO₁₀:
588.3742.

Example 25

15

10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6-
O-methyl-descladinosyl-erythromycin A N-oxide (107)
NBS (1.00 g, 5.60 mmol) was added to a solution of the
N-oxide (106) (1.11 g, 1.90 mmol) in acetic acid (10 ml)
at room temperature and the mixture stirred at this
temperature overnight. The solvent was removed under
reduced pressure, the residual material dissolved in
CHCl₃, washed with NaHCO₃, dried (MgSO₄) and concentrated
to afford the crude product as a white solid, mp 154-
157°C; yield 0.995 g (80 %) after flash chromatography
using CH₂Cl₂:MeOH:NH₃(aq) 90:10:2. HRMS [Electrospray,
H⁺]: M 646.3800 (Calc. for C₃₂H₅₅NO₁₂: 646.3797).

Example 26

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10-Acetoxymethyl-10,11-anhydro-10-desmethyl- 6-
O-methyl-descladinosyl-erythromycin A (108)
The N-oxide (107) (0.69 g, 0.001 mol) and
triphenylphosphine (0.56 g, 0.003 mol) were heated under
refluxed with stirring in THF overnight. The cold
reaction mixture was extracted with EtOAc, the extracts

washed with NaHCO_3 , brine and dried (MgSO_4). The crude product was subjected to flash chromatography. (A simpler workup procedure is to remove the THF under reduced pressure and add the crude product onto the flash column) The product was obtained as a white solid, mp. 95-97°C; yield 0.43 g (68%). HRMS [Electrospray, M^+]:

M 652.3674. Calc. for $\text{C}_{32}\text{H}_{55}\text{NO}_{11}$: 652.3667.

Example 27

10-Acetoxymethyl-2'O-acetyl-10,11-anhydro-10-desmethyl-6-O-methyl-descladinosyl-erythromycin A (109)

A solution of the acetoxymethyl derivative (108) (0.35 g, 0.556 mmol), triethylamine (0.15 ml, 1.11 mmol) and acetic acid anhydride (0.10 ml, 1.11 mmol) in dichloromethane (10 ml) was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the product was extracted into ethyl acetate, the solution washed with NaHCO_3 , brine and dried (MgSO_4). The solution was evaporated and the residual material subjected to flash chromatography using acetone:hexane 1:2. The product was a white solid mp. 83-85°C; yield 0.24 g (63%) HRMS [Electrospray, Na^+]: M 694.3779 (Calc. for $\text{C}_{34}\text{H}_{57}\text{NO}_{12}$: 694.3773).

Example 28

10-Acetoxymethyl-2'O-acetyl-10,11-anhydro-10-desmethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (110)

The 3-OH compound (109) (1.50 g, 2.30 mmol) was dissolved in dichloromethane (40 ml) and Dess-Martin periodinane reagent (1.40 g, 3.10 mmol) was added. The reaction mixture was stirred at room temperature for 2 h before the reaction mixture was concentrated under

reduced pressure. The residual material was triturated with ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO₄). The crude product was subjected to flash chromatography using acetone:hexane 1:1. The product was a white solid, mp. 172-174°C, 0.93 g, (87%).

HRMS [Electrospray, Na⁺]: M 692.3586 (Calc. for C₃₄H₅₅NO₁₂: 692.3616).

10

Example 29

10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin (111)

A solution of 10-acetoxymethyl-2'-O-acetyl-10,11-anhydro-10-desmethyl-6-O-methyl-3-oxo-descladinosylerythromycin A (110) in methanol is stirred at room temperature overnight. The methanol is distilled off and the residual material subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH:NH₃(aq) 90:8:2 to provide the title compound as a white solid.

20

Example 30

10-hydroxymethyl-10-11-anhydro-10-desmethyl-6-O-methyl-descladinosyl-erythromycin A (112)

The allylic acetate (111) (0.045 g, 0.071 mmol) was dissolved in methanol (1 ml) and cooled to 0°C. Sodium methoxide (1 M) (0.09 ml, 0.086 mmol) was added slowly and the reaction mixture was stirred for 16 h. Two more portions of sodium methoxide was added over the next 2 days. TLC showed full conversion to the product after 3 days. The reaction mixture was quenched with sodium bicarbonate and the methanol removed under reduced pressure. The product was extracted with ethyl acetate and purified by flash chromatography using

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CH₂Cl₂:MeOH:NH₃ 90:10:2. The allylic alcohol was a white solid 0.030 g (71%) with mp 205-206°C. HRMS

[Electrospray, Na⁺]: M 610.3558 (Calc. for C₃₀H₅₃NO₁₀: 610.3561).

5

Example 31

10-Acetoxymethyl-2'-O-acetyl-10-desmethyl-12-O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-erythromycin A (113)

1 M NaHMDS (1.6 ml, 1.50 mmol) THF was added dropwise over 30 min to a cold (-40°C) solution of the ketolide (111) (0.887 g, 1.30 mmol) in THF (10 ml). The solution was stirred at this temperature for 45 min. A solution of carbonyl diimidazole (CDI) (0.843 g, 5.20 mmol) in THF (10 ml) and DMF (5 ml) was added dropwise over 30 min to the reaction mixture at room temperature. The reaction mixture was stirred at this temperature for 20 h and quenched with sodium bicarbonate at 0°C. The product was extracted with ethyl acetate, washed with water (pH 10-11), with brine and dried (Na₂SO₄). The crude product was subjected to flash chromatography using acetone:hexane 1:1. The product was a white foam; yield 0.37 g (45%). HRMS [Electrospray, Na⁺]: M 786.3778 (Calc. for C₃₈H₅₇N₃O₁₃: 786.3783).

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Example 32

2'-O-Acetyl-11-amino-[11N-12O]-carbonyl-11-deshydroxy-10-desmethyl-10-methylene-6-O-methyl-3-oxo-descladinosyl-erythromycin (114)

Ammonia (aq) (0.2 ml) was added to a solution of the imidazole derivative (113) (0.127 g, 0.166 mmol) in acetonitrile (2 ml) and THF (0.2 ml) and the mixture stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and the

35

residual material triturated with ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO₄). The solution was evaporated and the residual material subjected to flash chromatography using acetone:hexane initially 2:1, then 1:1. The product was a white solid, mp. 142-145°C; yield 0.042 g (38%). HRMS [Electrospray, H⁺]: M 653.3627 (Calc. for C₃₃H₅₂N₂O₁₁: 653.3643).

10 Example 33

11-Amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-10-methylene-6-O-methyl-3-oxo-descladinosyl-erythromycin A (115)

15 Methanol (2 ml) was added to the cyclic carbamate (114) (0.072 g, 0.11 mmol) and the mixture stirred at room temperature overnight. The methanol was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel using
20 CH₂Cl₂:MeOH:NH₃(aq) 90:8:2. The product was a white solid, mp. 161-163°C; yield 0.046 g, (68%). HRMS [Electrospray, H⁺]: M 611.3525 (Calc. for C₃₁H₅₀N₂O₁₀: 611.3538).

25 Example 34

2'O-Acetyl-11-benzylamino-[11N-12O]-carbonyl-11-deshydroxy-10-desmethyl-10-methylene-6-O-methyl-3-oxo-descladinosyl-erythromycin A (116a)

30 Benzylamine (0.12 ml, 1.13 mmol) was added to a solution of the imidazole derivative (113) (172 mg, 0.225 mmol) in acetonitrile (2 ml) and THF (0.2 ml) and the mixture stirred at room temperature for 21 h. The reaction mixture was concentrated under reduced pressure and the
35 residual material triturated with ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11),

with brine and dried (MgSO_4). The solution was evaporated and the residual material subjected to flash chromatography using acetone:hexane, initially 2:1 and then 1:1. The product was a yellow oil; yield 100 mg (60%). HRMS [Electrospray, H^+]: M 743.4132 (Calc. for $\text{C}_{40}\text{H}_{58}\text{N}_2\text{O}_{11}$: 743.4113).

Example 35

2'-O-Acetyl-11-(4-phenylbut-1-yl-amino)-[11N-12O]-carbonyl-11-deshydroxy-10-desmethyl-10-methylene-6-O-methyl-3-oxo-descladinosyl-erythromycin A (116b)
4-Phenylbutane-1-amine (0.08 ml, 0.524 mmol) was added to a solution of the imidazole derivative (113) (100 mg, 0.131 mmol) in acetonitrile (3 ml) and THF (0.2 ml) and the mixture was stirred at 65°C for 20 h. The reaction mixture was concentrated under reduced pressure and the residual material triturated with ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO_4). The solution was evaporated and the residual material was subjected to flash chromatography using acetone:hexane, initially 2:1 and then 1:1. The product was a yellow oil; yield 83 mg (76%). HRMS [Electrospray, Na^+]: M 807.4 (Calc. for $\text{C}_{40}\text{H}_{58}\text{N}_2\text{O}_{11}$)

Example 36

11-Benzylamino-[11N-12O]-carbonyl-11-deshydroxy-10-desmethyl-10-methylene-6-O-methyl-3-oxo-descladinosyl-erythromycin A (117)

A solution of 2'-O-acetyl-11-benzylamino-[11N-12O]-carbonyl-11-deshydroxy-10-desmethyl-10-methylene-6-O-methyl-3-oxo-descladinosyl-erythromycin A (116a) in methanol (5 ml) was stirred at room temperature for 17 h. The solvent was removed under reduced pressure.

Evaporation of the solvent left the title compound as a yellow oil. HRMS [H⁺]: M 701.4011 (Calc. for C₃₈H₅₆N₂O₁₀ 701.4007).

5 Example 37

11-Amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-6-O-methyl-3-oxo-10-benzylaminomethyl-descladinosyl-erythromycin A (118a)

10 A solution of benzylamine (0.13 ml, 1.18 mmol) and 11-amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (115) (0.257 g, 3.39 mmol) in THF (4 ml) was heated at reflux for 17 h. Another portion of benzylamine (0.13 ml, 1.18 mmol)
15 was added and the solution heated for another 24 hours. The solution was concentrated at reduced pressure and the residual material extracted with ethyl acetate, the solution washed with NaHCO₃, with brine and dried (MgSO₄). The solution was evaporated and the residual
20 material was subjected to flash chromatography on silica gel using acetone:hexane 1:1. The product was a white solid with mp 185-187°C; yield 0.150 g (48%) HRMS [H⁺]: M 618.4273 (Calc. for C₃₈H₅₉N₃O₁₀: 718.4273).

25 Example 38

11-Amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-6-O-methyl-3-oxo-10-(3-phenylprop-1-yl-aminomethyl)-descladinosyl-erythromycin A (118b)

30 A solution of 3-phenylpropane-1-amine (1.2 mmol) and 11-amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (115) (1 mmol) in DMF (5 ml) was heated at 60°C for 4 h. The cold solution was taken into ethyl acetate, the acetate
35 solution washed with brine, dried (Na₂SO₄), evaporated and the product isolated from the residual material

after flash chromatography on silica gel using
CH₂Cl₂:MeOH 9:1.

Example 39

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10,11-Anhydro-10-azidomethyl-10-desmethyl-6-O-methyl-
descladinosyl-erythromycin A (120)

A solution of the descladinosyl-erythromycin allylic
acetate (109) (0.048 g, 0.076 mmol) and NaN₃ (0.010 g,
10 0.152 mmol) in THF (1ml)/DMF (5 ml) was heated at 70°C
for 17 h. The solution was concentrated at reduced
pressure and the residual material extracted with ethyl
acetate, the solution washed with NaHCO₃, with brine and
dried (MgSO₄). The solution was evaporated and the
15 residual material was subjected to flash chromatography
on silica gel using CH₂Cl₂:MeOH:NH₃(aq) initially 90:4:2,
then 90:8:2. The product was a white solid, mp. 98-
100°C; yield 0.022 g (68%) HRMS [M⁺]: M 613.3796 (Calc.
for C₃₀H₅₂N₄O₉: 613.3807).

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Example 40

2'O-Acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl- 6-
O-methyl-descladinosyl-erythromycin A (121)

25 10,11-Anhydro-10-azidomethyl-10-desmethyl-6-O-methyl-
descladinosyl-erythromycin A (120) (0.239 g, 0.390 mmol)
was dissolved in dichloromethane (3 ml). Triethylamine
(0.11 ml, 0.780 mmol) and acetic acid anhydride (0.07
ml, 0.780 mmol) were added. The reaction mixture was
30 stirred at ambient temperature for 15 h. The reaction
mixture was concentrated under reduced pressure and the
product was extracted with ethyl acetate and washed with
NaHCO₃, brine and dried (MgSO₄). The crude product was
subjected to flash chromatography using gradient elution
35 with acetone:hexane (1:2-1:1) as eluent. The phases were
concentrated to afford the product as a white solid, mp.

170-172°C, yield 0.136 g (54 %). HRMS [H⁺]: M 655.3928 (Calc. for C₃₂H₅₄N₄O₁₀ 655.3912).

Example 41

5

2'O-Acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (122)

The Dess-Martin periodinane reagent (0.140 g, 0.324 mmol) was added to a solution of 2'O-acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6-O-methyl-descladinosyl-erythromycin A (121) (0.106 g, 0.162 mmol) in dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure, the residual material dissolved in ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO₄) before evaporation. The product was isolated after flash chromatography of the residual material using gradient elution with acetone:hexane 2:1-1:1. The product was a white solid which was crystallized from diethyl ether and hexane, mp. 110-115°C, yield 0.079 g (75%). HRMS [Na⁺]: M 675.3608 (Calc. for C₃₂H₅₂N₄O₁₀ 675.3575).

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Example 42

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2'O-Acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-12-O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-erythromycin A (123)

2'O-Acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (112) (0.044 g, 0.067 mmol) in THF (2 ml) at 0°C was added to NaH (0.006 g, 0.2002 mmol). Carbonyl diimidazole (CDI) dissolved in THF (1 ml) was added dropwise over 5 min to the reaction mixture. The solution was stirred for 17 h and the reaction mixture was cooled to 0°C again before it was quenched with sodium bicarbonate and extracted

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with ethyl acetate and washed with water (pH 10-11),
with brine and dried (Na_2SO_4). The crude product was a
white solid, yield 0.050 g (98%). HRMS $[\text{Na}^+]$: M 769.3760
(Calc. for $\text{C}_{36}\text{H}_{54}\text{N}_6\text{O}_{11}$ 769.3742). (The crude product was
5 used without purification).

Example 43

10 10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6-O-methyl-
2',3,12- O_3 -trimethylsilyl-descladinosyl-erythromycin
A (124)

A solution of the descladinosyl-erythromycin allylic
acetate (109) (0.069 g, 0.110 mmol) and BSTFA (0.29 ml,
1.10 mmol) in pyridine (0.22 ml) under argon was stirred
15 at room temperature for 48 h. The solution was
evaporated to dryness under reduced pressure, the
residual material extracted into ethyl acetate, the
solution washed with NaHCO_3 , with brine and dried
(MgSO_4). The residual material was subjected to flash
20 chromatography on silica gel using acetone:hexane 1:4.
The product was a white foam, yield 0.036 g (40%). HRMS
[Electrospray, H^+]: M 846.5065 (Calc. for $\text{C}_{41}\text{H}_{79}\text{NO}_{11}\text{Si}_3$:
846.5033).

25 Example 44

10,11-Anhydro-10-desmethyl-10-ethyl-6-O-methyl- 2',3,
12- O_3 -trimethylsilyl-descladinosyl-erythromycin A (125)
Tris(2-furyl)phosphine (TFP) (0.002 g, 0.008 mmol) and
30 $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ (0.002 g, 0.002 mmol) were added to a
deoxygenated solution of 2',3,12- O_3 -trimethylsilyl-
descladinosyl-erythromycin (124) (0.070 g, 0.083 mmol)
in NMP (1 ml) under argon and the solution was heated at
50°C for 10 min to generate the catalyst. Subsequently,
35 a solution of trimethylaluminium in THF (2 M, 0.21 ml,
0.414 mmol) was added. The resultant mixture was heated

at 70°C for 24 h. The solvent was removed at reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO₄), evaporated and the residual material subjected to flash chromatography on silica gel to give 0.007g (10%) of a white crystalline material. HRMS [Electrospray, H⁺]: M 802.5140 (Calc. for C₄₁H₇₉NO₉Si₃: 802.5135).

10 Example 45

10,11-Anhydro-10-desmethyl-10-ethyl-6-O-methyl-descladinosyl-erythromycin A (126)

TBAF in THF (2.0 mmol, 2 ml) is added to a solution of 10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-2',3,12-O₃-trimethylsilyl-descladinosyl-erythromycin A (125) (0.5 mmol) in THF (10 ml) at 0°C. The mixture is stirred at this temperature for 30 min and at room temperature overnight. The solvent is then distilled off, and the residual material is subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH:NH₃(aq) 90:6:2.

Example 46

25 10,11-Anhydro-2'O-benzoyl-10-desmethyl-10-ethyl-6-O-methyl-descladinosyl-erythromycin A (127)

A solution of 10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-descladinosyl-erythromycin A (126), (0.5 mmol), benzoic anhydride (1.5 mmol), triethylamine (2 mmol) and DMAP (2 mmol) in dichloromethane (10 ml) is stirred at room temperature overnight. The reaction mixture is shaken with 5% aqueous sodium carbonate, the organic solution dried (Na₂SO₄) and the solution evaporated to dryness. The residual material is subjected to flash chromatography on silica gel using dichloromethane.

Example 4710,11-Anhydro-2'O-benzoyl-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (128)

5 The Dess-Martin periodinane reagent (3.0 mmol) is added to a solution of 10,11-anhydro-2'O-benzoyl-10-desmethyl-10-ethyl-6-O-methyl-descladinosyl-erythromycin A (127) (2.0 mmol) in dichloromethane (30 ml). The reaction mixture is stirred at room temperature for 2 h before
10 the reaction mixture is concentrated under reduced pressure. The residual material is triturated with ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO₄). The crude product is subjected to flash chromatography using
15 acetone:hexane 1:1 to provide the title compound.

Example 4810,11-Anhydro-10-desmethyl-6-O-methyl-10-(3-phenylprop-2-yn-1-yl)-descladinosyl-erythromycin A (129)

Tris(2-furyl)phosphine (0.007 g, 0.032 mmol) and Pd₂dba₃.CHCl₃ (0.004 g, 0.004 mmol) was added to a deoxygenated solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-6-O-methyl-descladinosyl-erythromycin A (109) (0.100 g, 0.159 mmol) in NMP (1 ml) under argon and the solution heated at 50°C for 10 min to generate the catalyst system. Subsequently, a solution of tributyl(phenylethynyl)tin (0.07 ml, 0.191
25 mmol) was added and the resultant mixture was heated at 80°C for 24 h. The solvent was removed under reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried (MgSO₄), evaporated and the residual
30 material subjected to flash chromatography on silica gel to give 0.035 g (33%) of a yellow oil. HRMS

[Electrospray, H⁺]: M 672.4120 (Calc. for C₃₈H₅₇NO₉: 672.4106).

Example 49

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2'O-Acetyl-10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-descladinosyl-erythromycin A (130)

A solution of 10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-descladinosyl-erythromycin A (126) (0.6 mmol),
10 triethylamine (0.16 ml, 1.2 mmol) and acetic acid anhydride (1.2 mmol) in dichloromethane (10 ml) is stirred at room temperature for 17 h. The reaction mixture is concentrated under reduced pressure and the product extracted into ethyl acetate, the solution
15 washed with NaHCO₃, brine and dried (MgSO₄). The solution is evaporated and the residual material subjected to flash chromatography on silica gel using acetone:hexane 1:1.

20 Example 50

2'O-Acetyl-10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (131)

The Dess-Martin periodinane reagent (3.10 mmol) is added
25 to a solution of 2'O-acetyl-10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-descladinosylerythromycin A (130) (2.30 mmol) in dichloromethane (40 ml). The reaction mixture is stirred at room temperature for 2 h, concentrated under reduced pressure, the residual
30 material triturated with ethyl acetate, the solution washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO₄) before evaporation. The product is isolated after flash chromatography of the residual material using acetone:hexane 1:1.

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Example 51

2'O-Acetyl-10,11-anhydro-10-desmethyl-10-ethyl-12-O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-erythromycin A (132)

1 M NaHMDS (1.6 ml, 1.50 mmol) in THF is added dropwise over 30 min to a cold (-40°C) solution of 2'O-acetyl-10,11-anhydro-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (131) (1.30 mmol) in THF (10 ml). The solution is stirred at this temperature for 45 min. A solution of carbonyl diimidazole (CDI) (5.20 mmol) in THF (10 ml) and DMF (5 ml) is added dropwise over 30 min to the reaction mixture at room temperature. The reaction mixture is stirred at this temperature for 20 h and quenched with sodium bicarbonate at 0°C. The reaction mixture is extracted with ethyl acetate, the organic solution washed with water (pH 10-11), with brine and dried (Na₂SO₄). The crude product is subjected to flash chromatography using acetone:hexane 1:1.

Example 52

2'O-Acetyl-11-amino-[11N-12-O]carbonyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (133)

Ammonia (aq) (0.2 ml) is added to a solution of 2'O-acetyl-10,11-anhydro-10-desmethyl-10-ethyl-12-O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-erythromycin A (132) (0.17 mmol) in acetonitrile (2 ml) and THF (0.2 ml) and the mixture stirred at room temperature for 24 h. The reaction mixture is concentrated under reduced pressure and the residual material triturated with ethyl acetate. The solution is washed with water/KOH (pH adjusted to 10-11), with brine and dried (MgSO₄). The solution is evaporated and the

residual material subjected to flash chromatography using acetone:hexane, initially 2:1, then 1:1.

Example 53

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11-Amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (134)

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A solution of 2'-O-acetyl-11-amino-[11N-12O]carbonyl -11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (133) in methanol is stirred at room temperature overnight. The methanol is distilled off and the residual material subjected to flash chromatography on silica gel using CH₂Cl₂:MeOH:NH₃ (aq) 90:8:2 to provide the title compound.

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Example 54

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10,11-Anhydro-2'-O-benzoyl-10-desmethyl-10 ethyl-12-O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-erythromycin A (135)

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1 M NaHMDS (1.50 mmol) THF is added dropwise over 30 min to a cold (-40°C) solution of 10,11-anhydro-2'-O-benzoyl-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-descladinosyl-erythromycin A (128) (1.30 mmol) in THF (10 ml). The solution is stirred at this temperature for 45 min. A solution of carbonyl diimidazole (CDI) (5.20 mmol) in THF (10 ml) and DMF (5 ml) is added dropwise over 30 min to the reaction mixture at room temperature. The reaction mixture is stirred at this temperature for 20 h and the reaction quenched with sodium bicarbonate at 0°C. The mixture is extracted with ethyl acetate, washed with water (pH 10-11), with brine and dried (Na₂SO₄). The pure title compound is obtained after flash chromatography of the crude product using acetone:hexane 1:1.

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Example 55

11-Amino-[11N-12O]carbonyl-N¹¹-amino-2'-O-benzoyl-11-
deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-
5 descladinosyl-erythromycin A (136)

Hydrazine hydrate (1.6 mmol) is added to a solution of
10,11-anhydro-2'-O-benzoyl-10-desmethyl-10 ethyl-12-
O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-
erythromycin A (135) (0.4 mmol) in DMF (5 ml) and the
10 resultant solution stirred at room temperature for 3 h.
The reaction mixture is taken up into ethyl acetate, the
resultant solution washed with water and brine, dried
(Na₂SO₄) and evaporated. The residual material is
purified by flash chromatography on silica gel using
15 hexane:EtOAc 5:2 with 2% NEt₃.

Example 56

11-Amino-[11N-12O]carbonyl-2'-O-benzoyl-11-deshydroxy-10-
20 desmethyl-10-ethyl-6-O-methyl-3-oxo-N¹¹-[3-(4-quinolinyl)
propylamino]-descladinosyl-erythromycin A (137)

Acetic acid (10 ml) is added to a solution of
11-amino-[11N-12O]carbonyl-N¹¹-amino-2'-O-benzoyl-11-
deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-
25 descladinosyl-erythromycin A (136) (1 mmol) and
3-(4-quinolinyl)propanal (1.2 mmol) in methanol (4 ml).
The solution is stirred at room temperature for 5 h
before sodium cyanoborohydride (2 mmol) is added. The
reaction mixture is stirred at room temperature
30 overnight before the reaction is quenched by addition of
saturated aqueous sodium carbonate and the reaction
mixture poured into ethyl acetate. The phases are
separated, the organic phase washed with brine, dried
(Na₂SO₄) and evaporated. The product is isolated after
35 flash chromatography on silica gel using hexane:EtOAc
1:1 with 2% Et₃N.

Example 57

11-Amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-N¹¹-[3-(4-quinolinyl)propylamino]-descladinosyl-erythromycin A (138)

A solution of 11-amino-[11N-12O]carbonyl-2'O-benzoyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-N¹¹-[3-(4-quinolinyl)propylamino]-descladinosyl-erythromycin A (137) (1 mmol) in methanol (10 ml) is heated under reflux for 15 h before the solution is evaporated to dryness. The solid title compound is isolated from the residual material after flash chromatography on silica gel using hexane:EtOAc 2:3 with 2% Et₃N.

Example 58

11-Amino-[11N-12O]carbonyl-2'O-benzoyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-N¹¹-4-[4-(3-pyridinyl)imidazolyl]butyl-descladinosyl-erythromycin A (139)

4-[4-(3-Pyridinyl)imidazolyl]butylamine (1.6 mmol) is added to a solution of 10,11-anhydro-2'O-benzoyl-10-desmethyl-10-ethyl-12-O-(imidazolocarbonyl)-6-O-methyl-3-oxo-descladinosyl-erythromycin A (135) (0.4 mmol) in wet acetonitrile (10 ml). The reaction mixture is stirred at 60°C for 3 d and taken up in ethyl acetate. The resulting mixture is washed with 5% NaOH, dried (Na₂SO₄) and evaporated. The residual material is purified by flash chromatography on silica gel using acetone:hexane 1:1.

Example 59

11-Amino-[11N-12O]carbonyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-N¹¹-4-[4-(3-pyridinyl)

imidazolyl]butyl-descladinosyl-erythromycin A (140)

A solution of 11-amino-[11N-12O]carbonyl-2'-O-benzoyl-11-deshydroxy-10-desmethyl-10-ethyl-6-O-methyl-3-oxo-N¹¹-4-[4-(3-pyridinyl)imidazolyl]butyl-descladinosyl-erythromycin A (139) in methanol is heated under reflux for 10 h. Evaporation of the solvent and flash chromatography of the residual material on a silica gel column using CH₂Cl₂:MeOH 9:1 provides the pure title compound.

In Examples 60 to 63, the active substance used is preferably the compound of Example 118b.

Example 60Tablets containing 50 mg of active substance

Composition:

active substance	50 mg
lactose	120 mg
maize starch	40 mg
magnesium stearate	2 mg
Povidone K 25	18 mg

The active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; and compressed in a tablet press. Weight of tablet 230 mg.

Example 61Capsules containing 50 mg active substance

Composition:

active substance	50 mg
maize starch	80 mg
highly dispersed silica	5 mg
magnesium stearate	2.5 mg

The active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; and the mixture is packed into hard gelatine capsules in a capsule filling machine.

5

Example 62Suppositories containing 50 mg of active substance

Composition:

10	active substance	50 mg
	hard fat q.s. ad	1700 mg

Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; and after cooling to about 35°C it is poured into chilled moulds.

15

Example 63Injectable solution containing 10 mg of active substance per 1 ml

Composition:

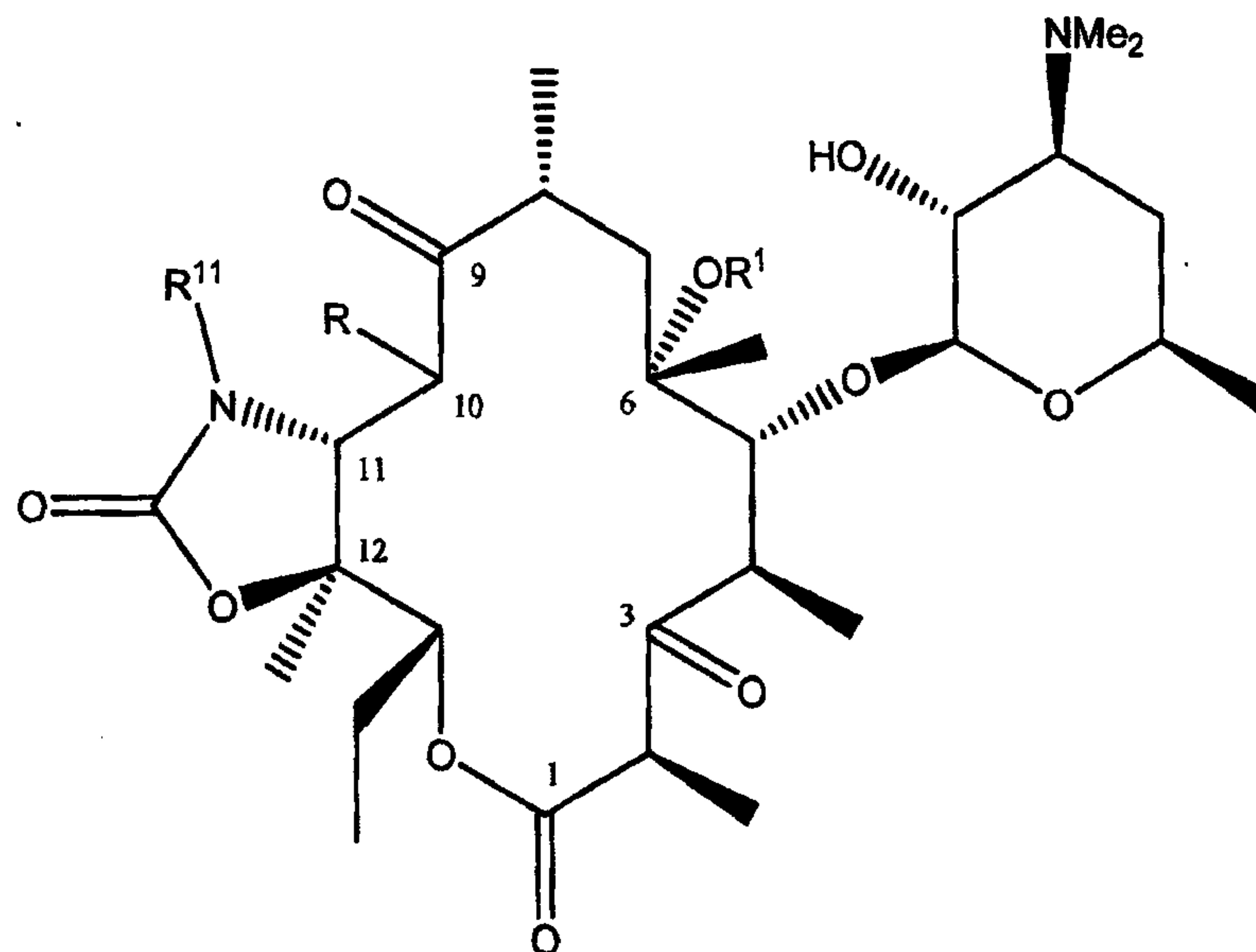
	active substance	10 mg
	mannitol	50 mg
25	human serum albumin	10 mg
	water for injections ad	1 ml

Mannitol is dissolved in water for injections; human serum albumin is added; the active ingredient is dissolved with heating; the solution is made up to the specified volume with water for injections and transferred into ampoules under nitrogen gas.

30

Claims:

1. A 10-Substituted-10-desmethyl macrolide of formula III:



III $R^{11} = R^4, NR^7R^8$

wherein R is selected from the group consisting of
 (1) methyl substituted with one or more substituents
 selected from the group consisting of
 (i) CN,
 (ii) F,
 (iii) CO_2R^3 wherein R^3 is selected from hydrogen, C_1 - C_3 -alkyl or aryl substituted C_1 - C_3 -alkyl, or heteroaryl substituted C_1 - C_3 -alkyl,
 (iv) OR^4 wherein R^4 is selected from hydrogen, C_1 - C_4 -alkyl or aryl substituted C_1 - C_4 -alkyl, or heteroaryl substituted C_1 - C_4 -alkyl, heterocycloalkyl and optionally substituted cycloalkyl, C_1 - C_3 -alkoxy- C_1 - C_3 -alkoxy, C_1 - C_4 -alkenyl or aryl substituted C_1 - C_4 -alkenyl, or heteroaryl substituted C_1 - C_4 -alkenyl, heterocycloalkyl and optionally substituted cycloalkyl, aryl or optionally substituted aryl, heteroaryl or optionally substituted heteroaryl,

- (v) $S(O)_nR^3$ wherein $n = 0, 1$ or 2 and R^3 is as previously defined
- (vi) $NR^4C(O)R^3$ wherein R^3 and R^4 are as previously defined
- (vii) $NR^4C(O)NR^5R^6$ wherein R^4 is defined as defined previously, and R^5 and R^6 are independently selected from hydrogen, C_1-C_3 -alkyl, C_1-C_3 alkyl substituted with aryl, substituted aryl, heteroaryl, substituted heteroaryl
- (viii) NR^7R^8 wherein R^7 and R^8 are independently selected from the group consisting of
- (a) hydrogen
 - (b) C_1-C_{12} -alkyl, and optionally substituted C_1-C_{12} -alkyl
 - (c) C_2-C_{12} -alkenyl, and optionally substituted C_2-C_{12} -alkenyl
 - (d) C_2-C_{12} -alkynyl, and optionally substituted C_2-C_{12} -alkynyl
 - (e) aryl, and optionally substituted aryl
 - (f) heteroaryl, and optionally substituted heteroaryl
 - (g) heterocycloalkyl, and optionally substituted heterocycloalkyl
 - (h) C_1-C_{12} alkyl substituted with aryl, and optionally substituted with substituted aryl
 - (i) C_1-C_{12} alkyl substituted with heteroaryl, and optionally substituted with substituted heteroaryl
 - (j) C_1-C_{12} alkyl substituted with heterocycloalkyl, and with optionally substituted heterocycloalkyl, and
 - (k) R^7 and R^8 taken together with the atom to which they are attached from a 3-10- membered heterocycloalkyl ring which may contain one or more additional heteroatoms and may be substituted with one or more substituents independently selected from the group consisting of
- (aa) halogen, hydroxy, C_1-C_3 -alkoxy, alkoxy- C_1-C_3 -alkoxy, oxo, C_1-C_3 -alkyl, aryl and optionally substituted aryl, heteroaryl and optional substituted heteroaryl
 - (bb) CO_2R^3 wherein R^3 is as previously defined, and

(cc)

$C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined,

(ix) aryl, and optionally substituted aryl, and

(x) heteroaryl, and optionally substituted heteroaryl,

(2) C_2-C_{10} -alkyl,

(3) C_2-C_{10} -alkyl substituted with one or more substituents selected from the group consisting of

(i) halogen,

(ii) OR^4 wherein R^4 is as defined previously

(iii)-CHO,

(iv) oxo,

(v) NR^7R^8 wherein R^7 and R^8 are defined as previously

(vi) $=N-O-R^4$ is wherein R^3 is as previously defined

(vii)-CN

(viii)- $S(O)_nR^3$ wherein $n = 0, 1$ or 2 and R^3 is as previously defined

(ix) aryl, and optionally substituted aryl

(x) heteroaryl, and optionally substituted heteroaryl

(xi) C_3-C_8 -cycloalkyl, and optionally substituted C_3-C_8 -cycloalkyl

(xii) heterocycloalkyl, and optionally substituted heterocycloalkyl

(xiii) $NR^4C(O)R^3$ where R^3 and R^4 are as previously defined

(xiv) $NR^4C(O)NR^5R^6$ wherein R^4 , R^5 and R^6 are as previously defined

(xv) $=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined

(xvi) $=N-R^4$ wherein R^4 is as previously defined

(xvii) $=N-NR^4C(O)R^3$ wherein R^3 and R^4 are as previously defined, and

(xviii) $=N-NR^4C(O)NR^5R^6$ wherein R^4 , R^5 and R^6 are as previously defined,

(4) C_2-C_{10} -alkenyl,

(5) C_2-C_{10} -alkenyl substituted with one or more substituents selected from the group consisting of

(i) halogen,

(ii) OR^4 wherein R^4 is as previously defined

- (iii) $O-S(O)_nR^3$ where n and R^3 are as previously defined
- (iv) $-CHO$,
- (v) oxo,
- (vi) $-CO_2R^3$ where R^3 is as previously defined
- (vii) $-C(O)-R^4$ where R^4 is as previously defined
- (viii) $-CN$
- (ix) aryl, and optionally substituted aryl
- (x) heteroaryl, and optionally substituted heteroaryl
- (xi) C_3-C_7 -cycloalkyl
- (xii) C_1-C_{12} -alkyl substituted with heteroaryl
- (xiii) NR^7R^8 wherein R^7 and R^8 are as previously defined
- (xiv) $NR^4C(O)R^3$ where R^3 and R^4 are as previously defined
- (xv) $NR^4C(O)NR^5R^6$ where R^4 , R^5 and R^6 are as previously defined
- (xvi) $=N-O-R^4$ where R^4 is as previously defined
- (xvii) $=N-NR^7R^8$ wherein R^7 and R^8 are as previously defined
- (xviii) $=N-NR^4$ wherein R^4 is as previously defined
- (xix) $=N-NR^4C(O)R^3$ wherein R^3 and R^4 are as previously defined, and
- (xx) $=N-NR^4C(O)NR^5R^6$ wherein R^4 , R^5 and R^6 are as previously defined,
- (6) C_2-C_{10} -alkynyl
- (7) C_2-C_{10} -alkynyl substituted with one or more substituents selected from the group consisting of
 - (i) trialkylsilyl
 - (ii) halogen,
 - (iii) $-CN$
 - (iv) OR^4 where R^4 is defined as previously
 - (v) $-CHO$,
 - (vi) oxo,
 - (vii) $-CO_2R^3$ where R^3 is as previously defined
 - (viii) $-C(O)NR^5R^6$ wherein R^5 and R^6 are as previously defined
 - (ix) NR^7R^8 wherein R^7 and R^8 are as previously defined
 - (x) $O-S(O)_nR^3$ where n and R^3 are as previously defined
 - (xi) C_3-C_7 -cycloalkyl
 - (xii) C_1-C_{12} -alkyl substituted with heteroaryl

- (xiii) aryl, and optionally substituted aryl
- (xiv) heteroaryl, and optionally substituted heteroaryl
- (xv) $\text{NR}^4\text{C}(\text{O})\text{R}^3$ where R^3 and R^4 are as previously defined
- (xvi) $\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ where R^4 , R^5 and R^6 are as previously defined
- (xvii) $=\text{N}-\text{O}-\text{R}^4$ where R^4 is as previously defined
- (xviii) $=\text{N}-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined
- (xix) $=\text{N}-\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined, and
- (xx) $=\text{N}-\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined,
- (8) cyclic substituents
 - (i) aryl, and optionally substituted aryl
 - (ii) heteroaryl, and optionally substituted heteroaryl
 - (iii) heterocycloalkyl, and optionally substituted heterocycloalkyl, and
 - (iv) C_3 - C_7 -cycloalkyl, and optionally substituted C_3 - C_7 -cycloalkyl, and
- (9) C_1 substituents with the exception of 10-methyl derivatives which are part of the above definitions under (1)
 - (i) $-\text{CHO}$
 - (ii) $-\text{CN}$
 - (iii) CO_2R^3 wherein R^3 is as previously defined
 - (iv) $\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are as previously defined
 - (v) $\text{C}(\text{S})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are as previously defined
 - (vi) $\text{C}(\text{NR}^4)\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined
 - (vii) $\text{CH}=\text{N}-\text{O}-\text{R}^4$ wherein R^4 is as previously defined
 - (viii) $\text{CH}=\text{N}-\text{R}^4$ is wherein R^4 is as previously defined
 - (ix) $\text{CH}=\text{N}-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined
 - (x) $\text{CH}=\text{N}-\text{NR}^4\text{C}(\text{O})\text{R}^3$ wherein R^3 and R^4 are as previously defined, and
 - (xi) $\text{CH}=\text{N}-\text{NR}^4\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^4 , R^5 and R^6 are as previously defined;

R^1 is selected from the group consisting of

- (1) H
- (2) methyl
- (3) methyl substituted with one or more substituents selected from the group consisting of
 - (i) F
 - (ii) -CN
 - (iii) $-CO_2R^{11}$ where R^{11} is C_1 - C_3 -alkyl or aryl substituted C_1 - C_3 -alkyl, or heteroalkyl substituted C_1 - C_3 -alkyl
 - (iv) $-C(O)NR^5R^6$ wherein R^5 and R^6 are defined as previously
 - (v) aryl, and optionally substituted aryl, and
 - (vi) heteroaryl, and optionally substituted heteroaryl
- (4) C_2 - C_{10} -alkyl
- (5) substituted C_2 - C_{10} -alkyl with one or more substituents selected from the group consisting of
 - (i) halogen,
 - (ii) OR^4 where R^4 is defined as previously
 - (iii) C_1 - C_3 -alkoxy- C_1 - C_3 -alkoxy
 - (iv) -CHO
 - (v) oxo
 - (vi) NR^7R^8 wherein R^7 and R^8 are as previously defined
 - (vii) $=N-O-R^4$ where R^4 is as previously defined
 - (viii) -CN
 - (ix) $-S(O)_nR^3$ where $n = 0, 1, \text{ or } 2$ and R^3 is as previously defined
 - (x) aryl, and optionally substituted aryl
 - (xi) heteroaryl, and optionally substituted heteroaryl
 - (xii) C_3 - C_8 -cycloalkyl, and optionally substituted C_3 - C_8 -cycloalkyl
 - (xiii) C_1 - C_{12} -alkyl substituted with heteroaryl, and optionally substituted heteroaryl
 - (xiv) heterocycloalkyl
 - (xv) $NHC(O)R^3$ where R^3 is as previously defined
 - (xvi) $NHC(O)NR^5R^6$ where R^5 and R^6 are as previously defined

- (xvii) =N-NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
 (xviii) =N-R⁴ wherein R⁴ as previously defined, and
 (xix) =N-NHC(O)R³ wherein R³ is as previously defined,
 (4) C₁-C₁₀-alkenyl substituted with one or more
 substituents selected from the group consisting of
 (i) halogen,
 (ii) OR⁴ where R⁴ is as previously defined
 (iii) -CHO
 (iv) oxo
 (v) -S(O)_nR³ where n and R³ are as previously defined
 (vi) -CN
 (vii) -CO₂R³ where R³ is as previously defined
 (viii) NR⁷R⁸ wherein R⁷ and R⁸ are as previously defined
 (ix) =N-O-R⁴ where R⁴ is as previously defined
 (x) -C(O)-R⁴ where R⁴ is as previously defined
 (xi) -C(O)NR⁵R⁶ wherein R⁵ and R⁶ are as previously defined
 (xii) aryl, and optionally substituted aryl
 (xiii) heteroaryl, and optionally substituted heteroaryl
 (xiv) C₃-C₇-cycloalkyl
 (xv) C₁-C₁₂-alkyl substituted with heteroaryl
 (xvi) NHC(O)R³ where R³ is as previously defined
 (xvii) NHC(O)NR⁵R⁶ where R⁵ and R⁶ are as previously
 defined
 (xviii) =N-NR⁷R⁸ wherein R⁷ and R⁸ are as previously
 defined
 (xix) =N-R⁴ wherein R⁴ is as previously defined,
 (xx) =N-NHC(O)R³ wherein R³ is as previously defined, and
 (xxi) =N-NHC(O)NR⁵R⁶ wherein R⁵ and R⁶ are as previously
 defined,
 (5) C₂-C₁₀-alkynyl, and
 (6) C₂-C₁₀-alkynyl substituted with one or more
 substituents selected from the group consisting of
 (i) halogen,
 (ii) OR⁴ where R⁴ is defined as previously
 (iii) -CHO
 (iv) oxo

- (v) $-\text{CO}_2\text{R}^3$ where R^3 is as previously defined
- (vi) $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are as previously defined
- (vii) $-\text{CN}$
- (viii) NR^7R^8 wherein R^7 and R^8 are as previously defined
- (ix) $=\text{N}-\text{O}-\text{R}^4$ where R^4 is as previously defined
- (x) $-\text{S}(\text{O})_n\text{R}^3$ where n and R^3 are as previously defined
- (xi) aryl, and optionally substituted aryl
- (xii) heteroaryl, and optionally substituted heteroaryl
- (xiii) C_3 - C_{12} -cycloalkyl
- (xiv) C_1 - C_{12} -alkyl substituted with heteroaryl
- (xv) $\text{NHC}(\text{O})\text{R}^3$ where R^3 is as previously defined
- (xvi) $\text{NHC}(\text{O})\text{NR}^5\text{R}^6$ where R^5 and R^6 are as previously defined
- (xvii) $=\text{N}-\text{NR}^7\text{R}^8$ wherein R^7 and R^8 are as previously defined
- (xviii) $=\text{N}-\text{R}^4$ wherein R^4 is as previously defined
- (xix) $=\text{N}-\text{NHC}(\text{O})\text{R}^3$ wherein R^3 is as previously defined, and
- (xx) $=\text{N}-\text{NHC}(\text{O})\text{NR}^5\text{R}^6$ wherein R^5 and R^6 are as previously defined.

2. A pharmaceutical composition comprising an antibiotic 10-desmethyl macrolide as claimed in claim 1 together with at least one pharmaceutical excipient.

3. The use of an antibiotic 10-desmethyl macrolide as claimed in claim 1 or claim 2 for the manufacture of a medicament for use in the treatment or prevention of infection in animals.

4. Use of an antibiotic 10-desmethyl macrolide as claimed in claim 1 or claim 2 as an agent to combat bacterial infection.

5. A 6-protected-hydroxy-10-acetyloxymethyl-10,11-unsaturated macrolide analog of a compound of formula (III) as defined in claim 1 for use as an intermediate in the synthesis of a said compound of formula (III).

