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[11] **Patent Number: 5,621,108**

[45] **Date of Patent: Apr. 15, 1997**

[54] **PROCESSES AND INTERMEDIATES FOR PREPARING MACROCYCLES**

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[51] **Int. Cl.**^{6} **C07D 405/06**

[52] **U.S. Cl.** **546/207**; 549/20

[58] **Field of Search** 546/207

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Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris

[57] **ABSTRACT**

Novel processes for the preparation of lactam- and lactone-containing macrocyles are provided. In preferred embodiments, rapamycin and demethoxyrapamycin are prepared by a convergent synthesis regime. Intermediates useful in the synthetic processes are also provided.

10 Claims, 10 Drawing Sheets

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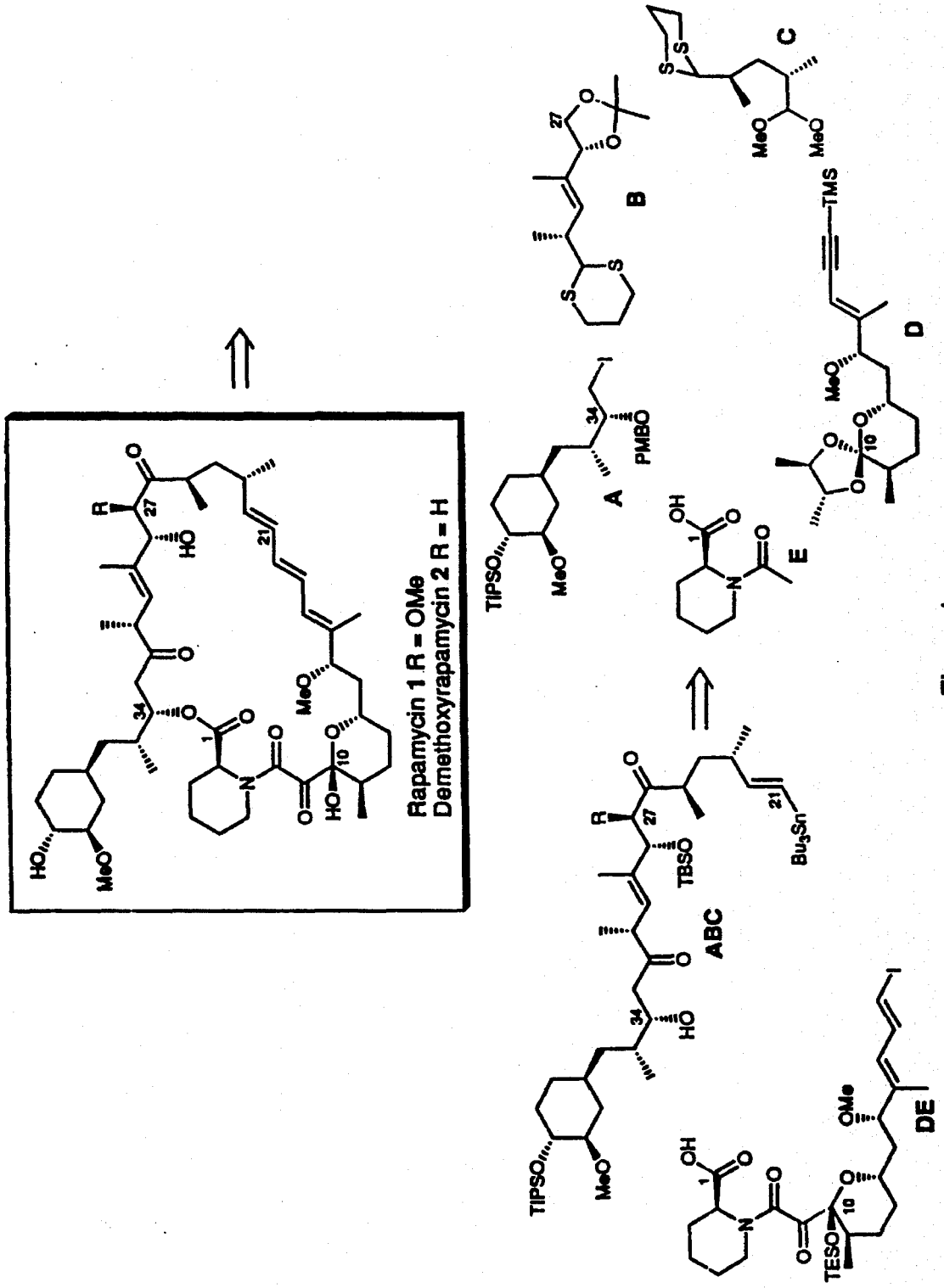

Rapamycin 1 R = OMe
Demethoxyrapamycin 2 R = H
A
B
C
D
E
ABC
DE
TIPSO
MeO
PMBO
TBSO
TMS
TESO
OMe
Bu3Sn
HO
OH

Figure 1

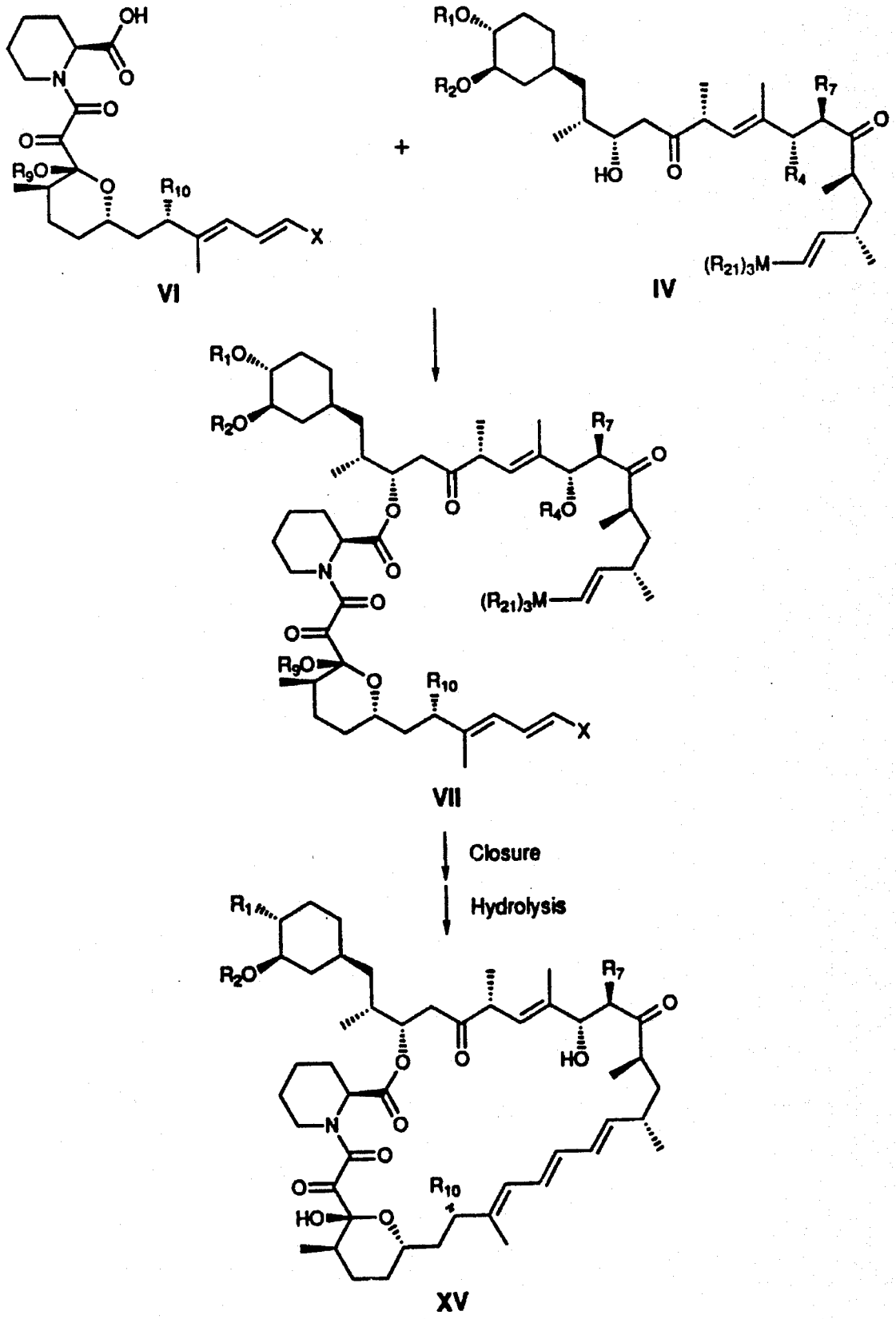


Figure 2

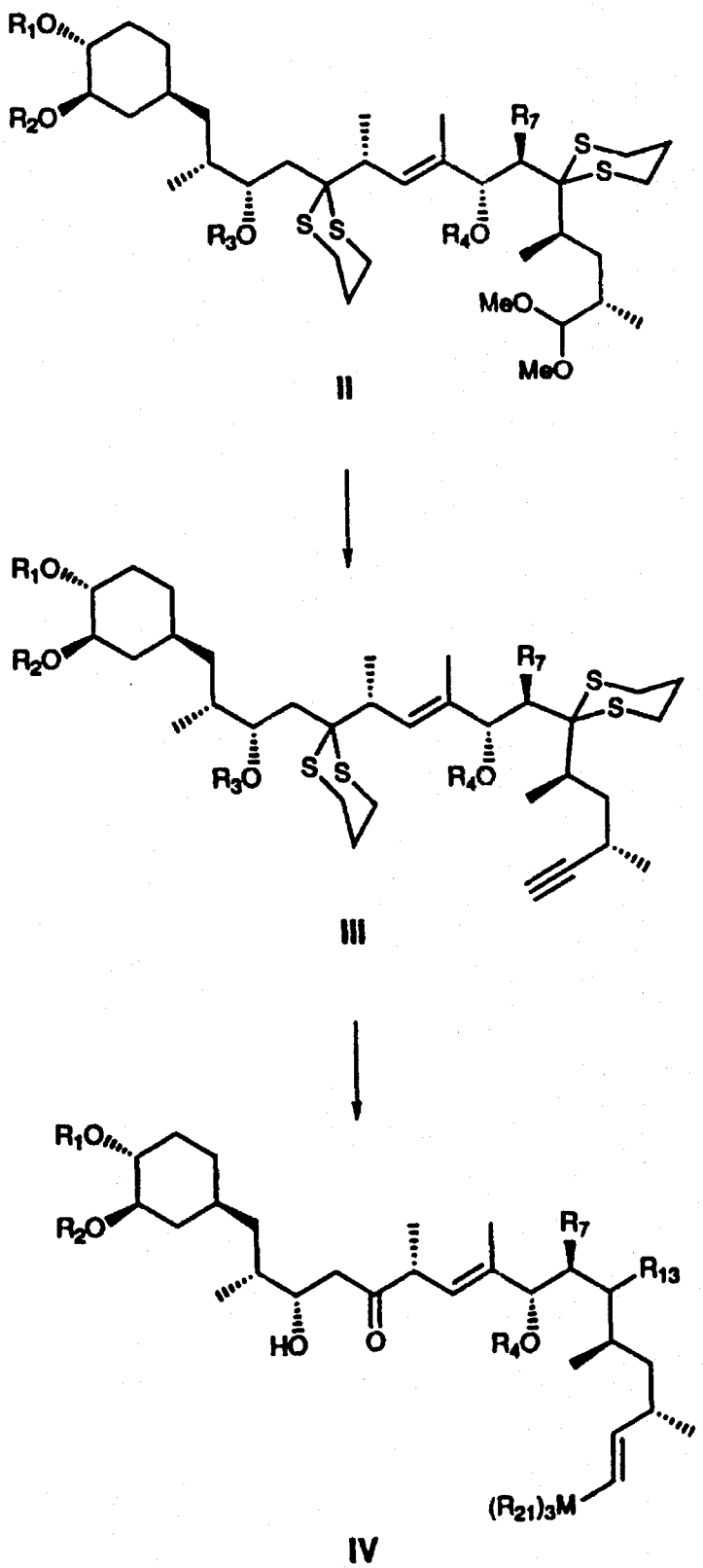

R1O
R2O
R3O
R4O
R7
S
S
S
S
MeO
MeO
II
R1O
R2O
R3O
R4O
R7
S
S
S
S
III
R1O
R2O
HO
O
R4O
R7
R13
(R21)3M
IV

Figure 3

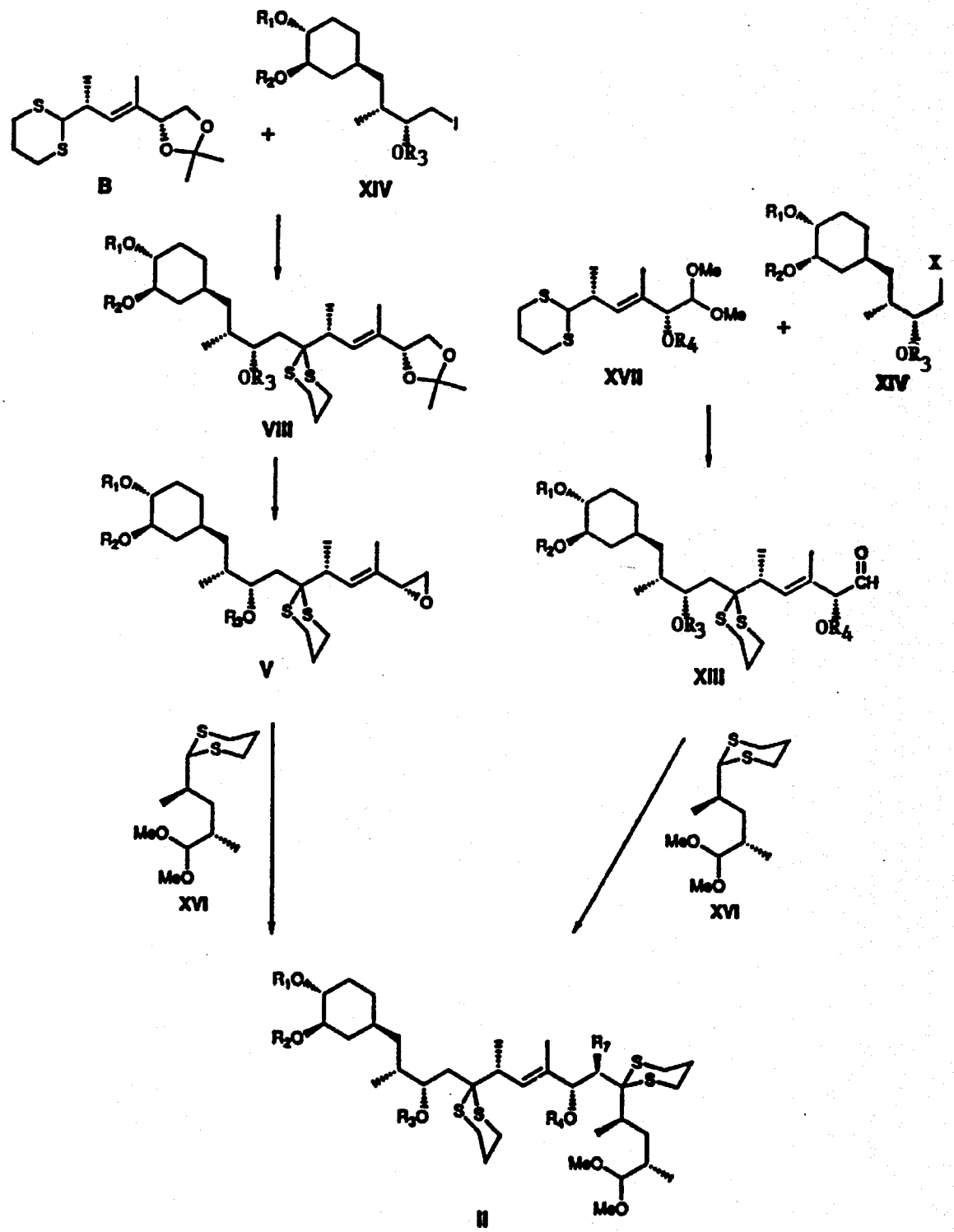


Figure 4

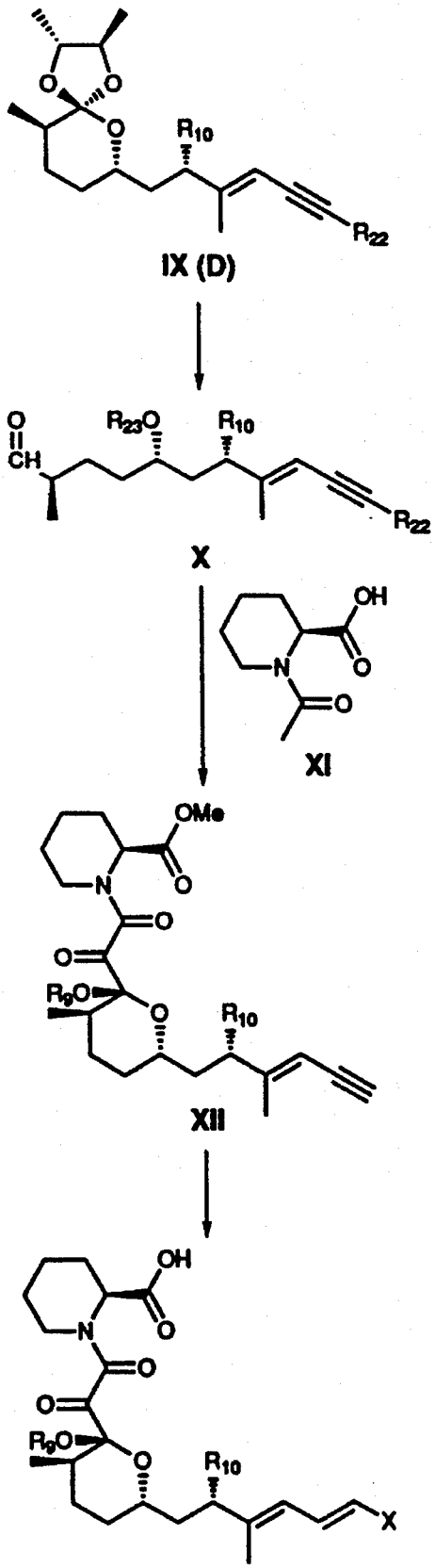

R10
R22
IX (D)
R23O
R10
CH
R22
X
OH
N
O
XI
OMe
R9O
R10
XII
OH
R9O
R10
X
VI (DE)

Figure 5

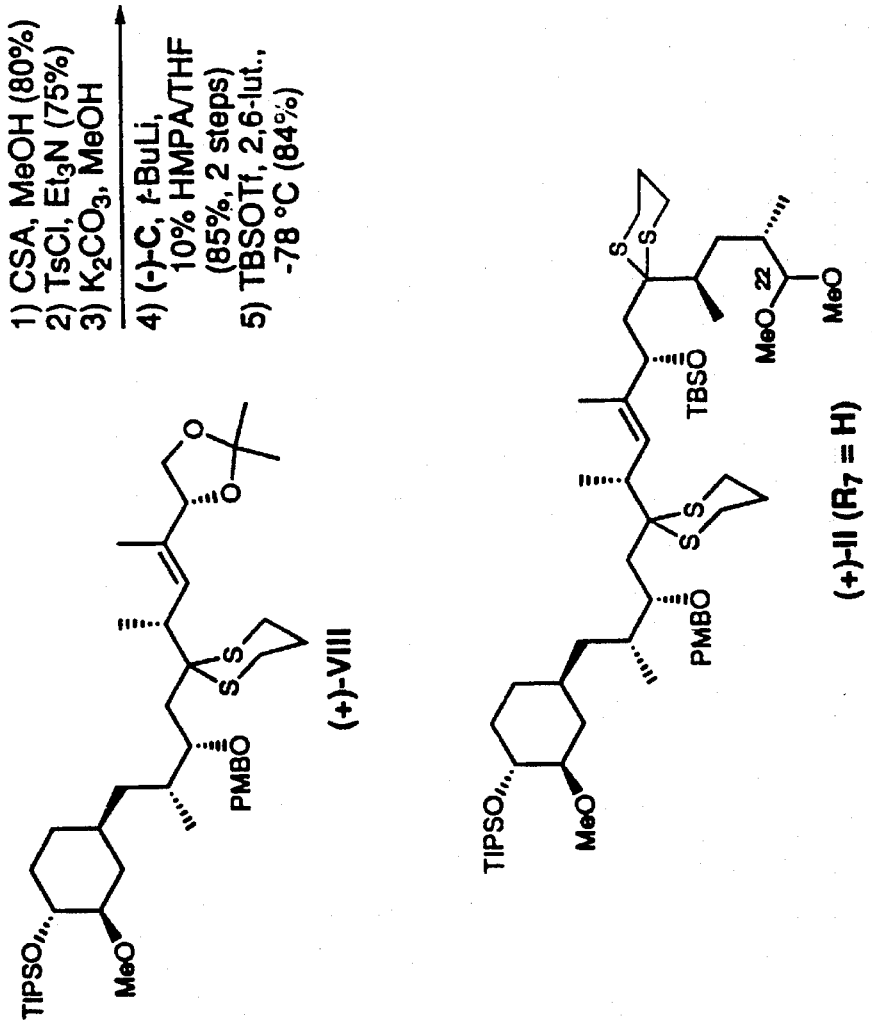

1) CSA, MeOH (80%)
2) TsCl, Et_3N (75%)
3) K_2CO_3, MeOH
4) (-)-C, t-BuLi, 10% HMPA/THF (85%, 2 steps)
5) TBSOTf, 2,6-lut., -78 °C (84%)
(+)-VIII
(+)-II (R_7 = H)
TIPSO
MeO
PMBO
TBSO
MeO
22
MeO

Figure 6

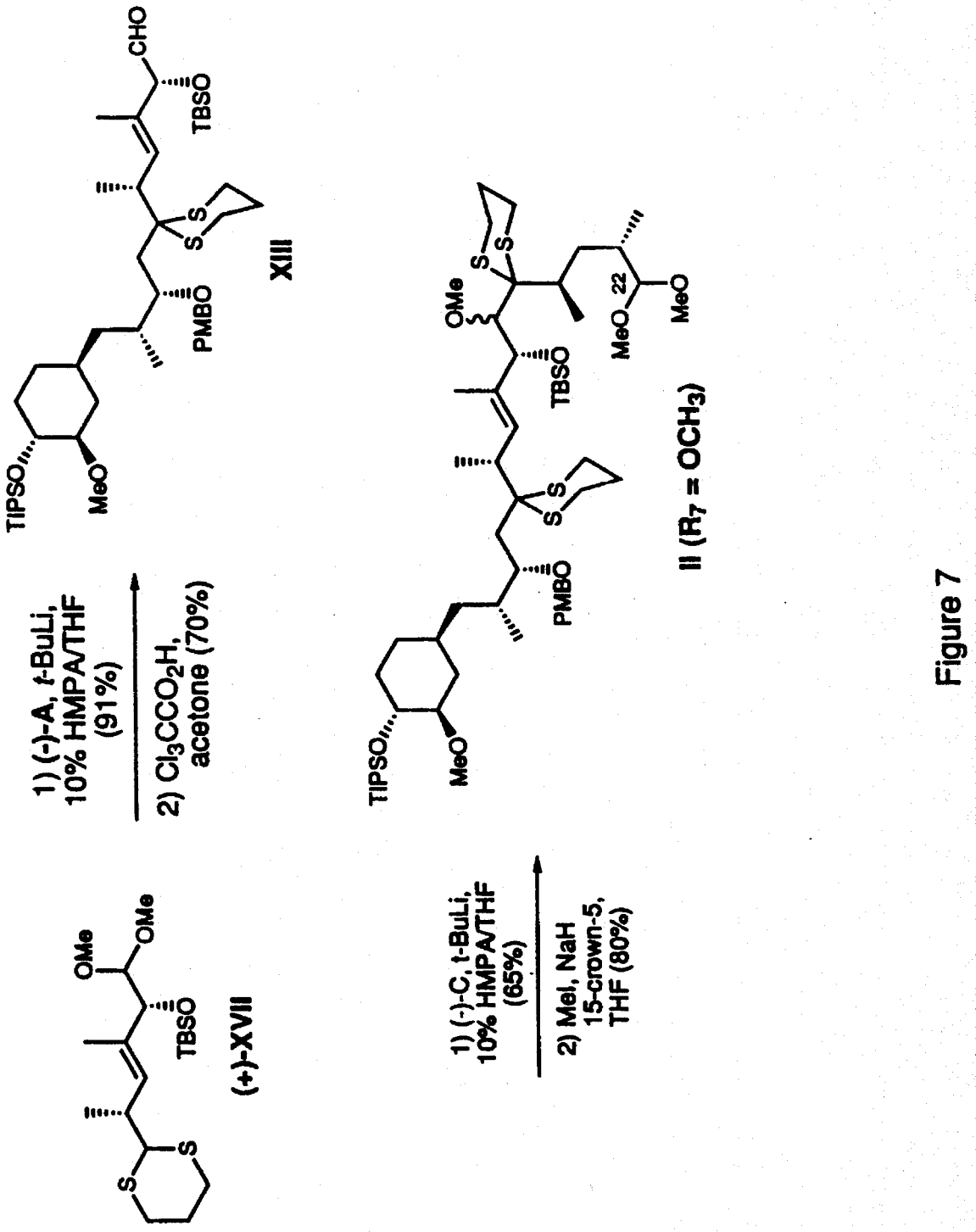

1) (-)-A, t-BuLi,
10% HMPA/THF
(91%)
2) Cl_3CCO_2H,
acetone (70%)
1) (-)-C, t-BuLi,
10% HMPA/THF
(65%)
2) MeI, NaH
15-crown-5,
THF (80%)
TIPSO
MeO
PMBO
TBSO
CHO
OMe
MeO
22
(+)-XVII
XIII
II (R_7 = OCH_3)

Figure 7

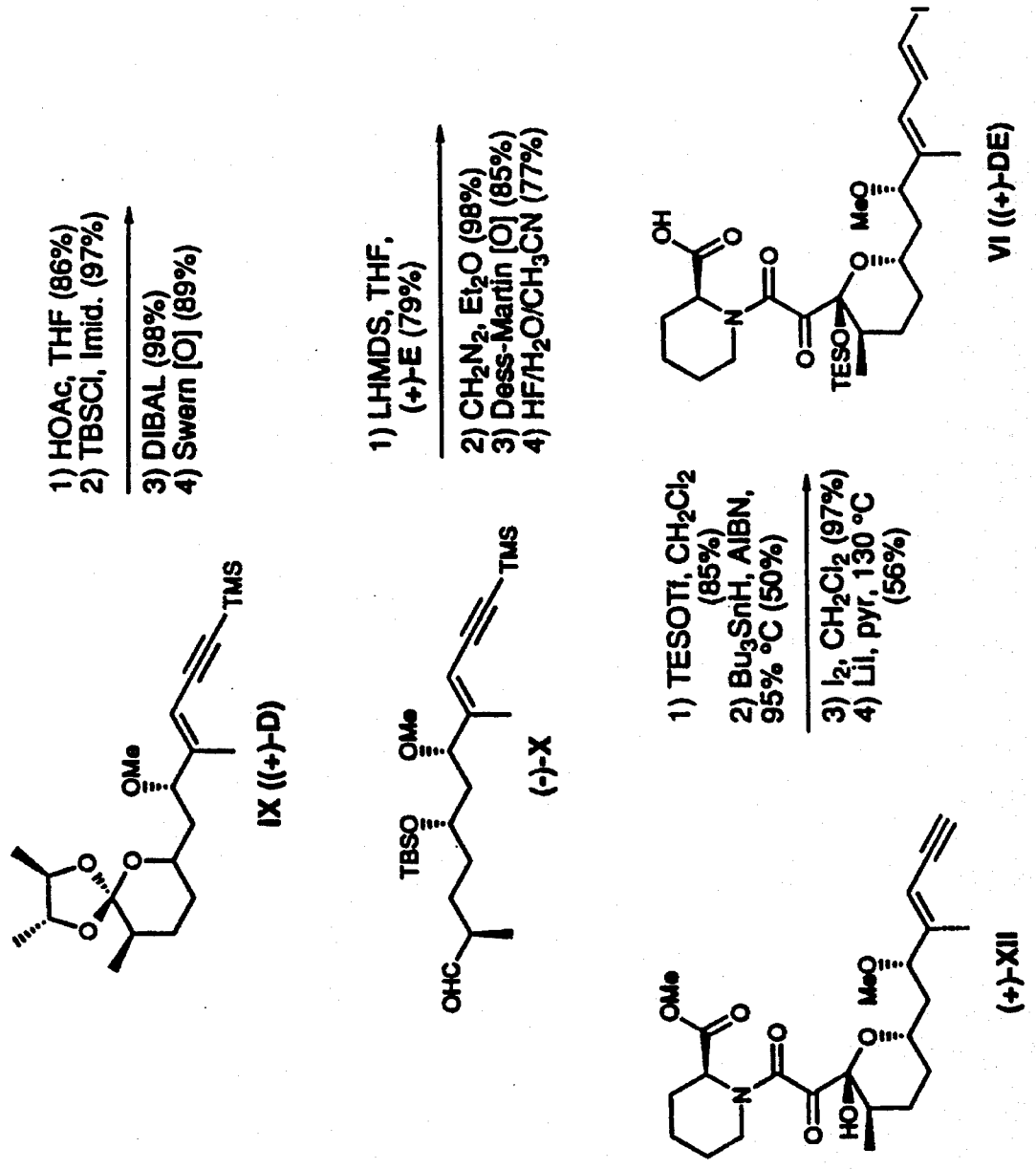

1) HOAc, THF (86%)
2) TBSCl, Imid. (97%)
3) DIBAL (98%)
4) Swern [O] (89%)
IX ((+)-D)
1) LHMDS, THF, (+)-E (79%)
2) CH_2N_2, Et_2O (98%)
3) Dess-Martin [O] (85%)
4) $HF/H_2O/CH_3CN$ (77%)
(-)-X
1) TESOTf, CH_2Cl_2 (85%)
2) Bu_3SnH, AIBN, 95% °C (50%)
3) I_2, CH_2Cl_2 (97%)
4) LiI, pyr, 130 °C (56%)
VI ((+)-DE)
(+)-XII

Figure 8

1) TsOH, acetone
R = OMe (84%)
R = H (92%)
2) CBr_4, HMPT, THF
3) n-BuLi, THF
R_7 = OMe (70%, 2 steps)
R_7 = H (75%, 2 steps)
1) DDQ, CH_2Cl_2, H_2O
R_7 = OMe (74%)
R_7 = H (90%)
2) MeI, $CaCO_3$
R_7 = OMe (60%)
R_7 = H (64%)
3) Bu_3SnH, $(Ph_3P)_2PdCl_2$
R_7 = OMe (88%)
R_7 = H (90%)
(-)-IVa
(+)-IIa R_7 = OMe
(+)-IIb R_7 = H
(+)-IIIa R = OMe
(+)-IIIb R = H
TIPSO
MeO
PMBO
TBSO
S
R_7

Figure 9A

(+)-DE,
EDAC·HCl, DMAP,
DMAP·HCl,
CH_2Cl_2, RT
R_7 = OMe (50%)
R_7 = H (67%)
(-)-IVa R_7 = OMe
(-)-IVb R_7 = H
(-)-VIIa R_7 = OMe
(-)-VIIb R_7 = H
1) (2-furyl$_3$P)$_2$PdCl$_2$,
DIPEA, DMF/THF, RT
R_7 = OMe (67%)
R_7 = H (48%)
2) TBAF/AcOH, 0 °C
3) HF·pyr, pyr, THF, RT
R_7 = OMe (64%, 2 steps)
R_7 = H
Rapamycin
Demethoxyrapamycin

Figure 9B

PROCESSES AND INTERMEDIATES FOR PREPARING MACROCYCLES

GOVERNMENT SUPPORT

Certain of the inventors were supported by National Institutes of Health Grant GM29028.

FIELD OF THE INVENTION

This invention relates to methods for the preparation of lactam- and lactone-containing macrocycles such as rapamycin and demethoxyrapamycin, and to intermediates useful in their preparation.

BACKGROUND OF THE INVENTION

Rapamycin and demethoxyrapamycin are two members of a growing class of macrolide natural products possessing marked immunosuppressive properties. Recently, several groups have focused on the preparation of both modest and advanced fragments of the polyketide skeleton, culminating in three total syntheses of rapamycin. In addition, several groups have prepared semi-synthetic analogs of rapamycin to improve upon its impressive therapeutic profile as well as to gain insight into the as-yet-unresolved mechanism of action.

To date, four research groups have reported the discovery and isolation of a 220 kDa protein which is thought to be the direct intracellular target of the rapamycin-FKBP complex. This protein shares structural homology with a number of known lipid kinases although its specific role in signal transduction and immunosuppression remains unclear. It has, however, been established that rapamycin interferes with a Ca^{2+}-independent signaling pathway emanating from the IL-2 receptor, thus prohibiting the progression of activated T cells from the G1 to the S phase of the cell cycle, perhaps via indirect inhibition of a cyclin dependent kinase specifically required for this transition.

There is a need for improved synthetic methods for the preparation of rapamycins. This invention is directed to this important end.

OBJECTS OF THE INVENTION

It is one object of the present invention to provide lactam- and/or lactone-containing macrocycles;

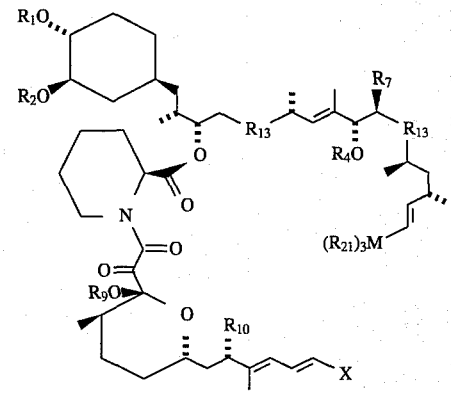
It is a further object to provide processes for the preparation of rapamycin, demethoxyrapamycin, and C-27 epirapamycin.

It is another object of this invention to provide intermediates useful in the processes.

SUMMARY OF THE INVENTION

These and other objects are satisfied by the present invention, which provides synthetic methods for the preparation of macrocycles, and novel compounds useful in the syntheses.

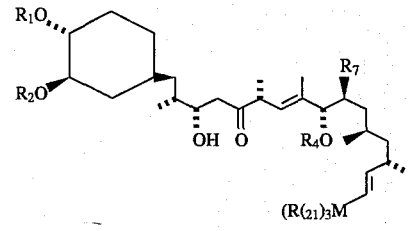
In certain embodiments, methods are provided for the preparation of a compound having formula (VII)



VII

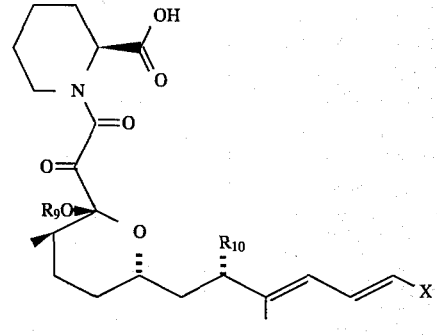
comprising the steps of:

providing a first compound of formula IV:



IV

and contacting said compound with a compound of formula (VI):



VI

for a time and under reaction conditions effective to form said compound of formula VII;

wherein:

R_1, R_4, and R_9 are, independently, hydrogen or a hydroxyl protecting group;

R_2 is alkyl having one to about six carbons;

R_7 is hydrogen or alkoxy having one to about six carbons;

R_{10} is H, OH, or alkoxy having one to about six carbons;

R_{21} is alkyl having one to about six carbons;

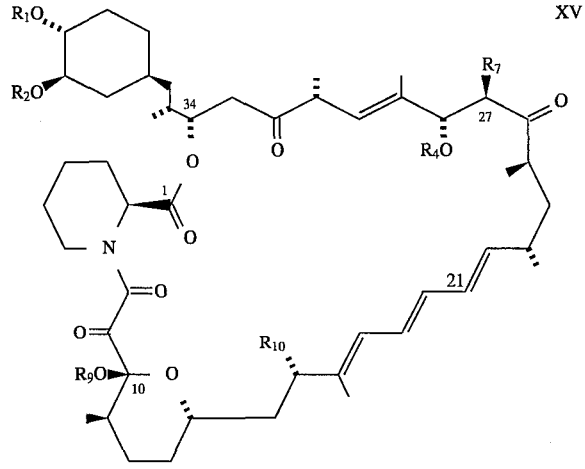
M is a metal atom; and

X is halogen.

In preferred embodiments R_7 is H or methoxy, and M is Sn.

Preferably the hydroxyl protecting groups are selected from the group consisting of TIPS, PMBO, TESO and TBS. More preferably, R_1 is TIPS; R_3 is H; R_4 is TBS; and R_9 is TES.

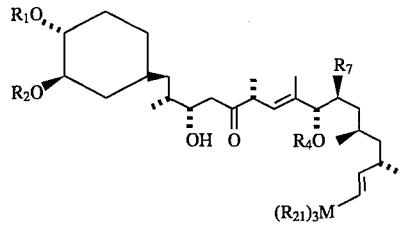
Preferred embodiments further comprise treating said compound of formula VII for a time and under reaction conditions effective to form a compound of formula XV:



XV

Preferably, the protecting groups are then removed.

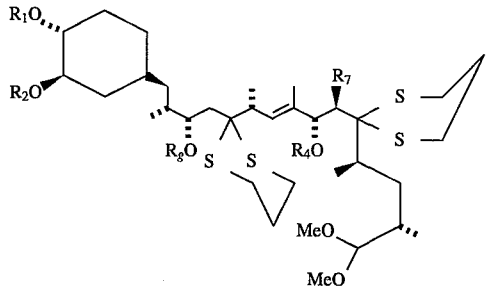
Also provided is a method for the preparation of a compound of formula IV:



IV

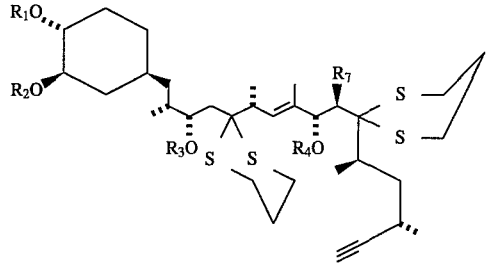
comprising the steps of:

providing a compound of formula II:



II

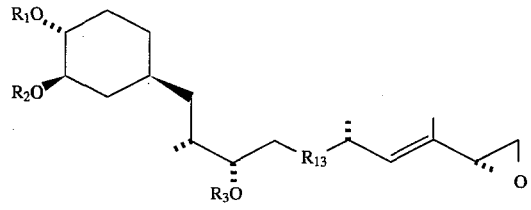
treating said compound of formula II for a time and under conditions effective to form a terminal acetylene of formula III:



III

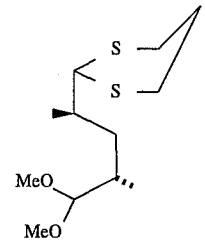
and treating said terminal acetylene for a time and under conditions effective to form said compound of formula IV.

In some preferred embodiments said compound of formula II is formed by the reaction of an epoxide of formula V:



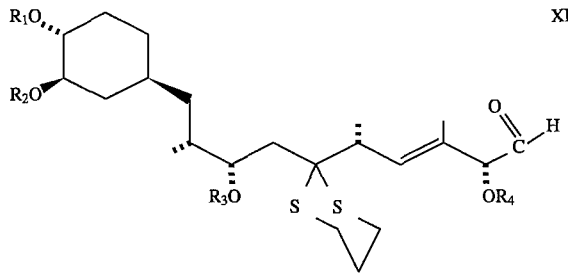
V

and a reagent of formula XVI:



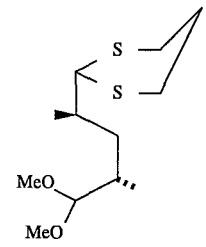
XVI

In other preferred embodiments said compound of formula II is formed by the reaction of an aldehyde of formula XIII:



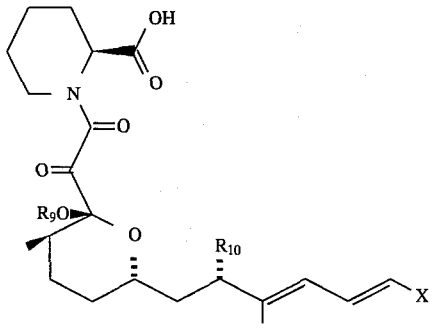
XIII

and a reagent of formula XVI:



XVI

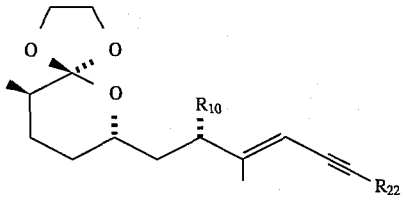
Also provided is a method for the preparation of a divinyl halide of formula VI:



VI

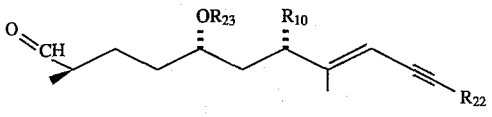
comprising the steps of:

providing an orthoester of formula IX;



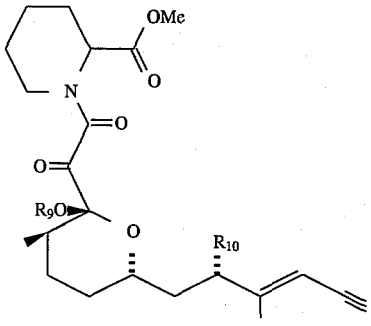
IX

treating said orthoester for a time and under conditions effective to form an aldehyde of formula X;



X

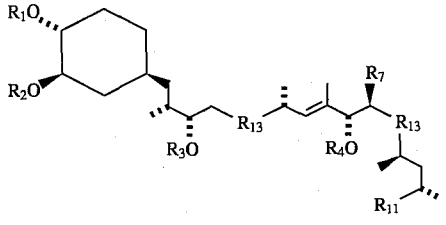
contacting said aldehyde with 2-carboxy-N-acetoylpiperidine for a time and under conditions effective to form a compound of formula XII;



XII

and treating said compound of formula XII for a time and under conditions effective to form said divinyl halide of formula VI.

Also provided according to the invention are novel intermediates, useful in the methods of the invention, having formula I:



I

wherein:

R_1, R_3 and R_4 are independently H or a hydroxyl protecting group;

R_2 is alkyl having from one to six carbons;

R_7 is H or alkoxy;

R_{13} is carbonyl group or protected derivative thereof;

R_{11} has the formula $—CH(OCH_3)_2$, $—C{\equiv}C—R_{12}$ or cis-$CH{=}CH\text{-}M(nC_4H_9)_3$;

wherein:

R_{12} is H or trimethylsilyl; and

M is a metal atom.

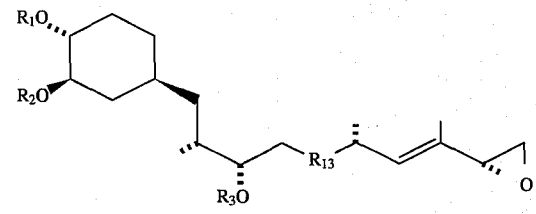
In certain preferred embodiments R_7 is H, and in other preferred embodiments R_7 is methoxy.

Preferably, R_{11} has the formula $—CH(OCH_3)_2$, $—C{\equiv}C—R_{12}$ or cis-$CH{=}CH\text{-}M(nC_4H_9)_3$; and M is Sn.

The compound of claim **6** wherein R_3 is H. In certain preferred embodiments R_{11} is $—CH(OCH_3)_2$ or $—C{\equiv}C—R_{12}$, and said protected derivative of said carbonyl group of said group R_{13} is a 1,3-dithiane.

Preferably, R_2 is methyl; and said hydroxyl protecting groups are selected from the group consisting of TIPS, PMBO, TES and TBS. In particularly preferred embodiments R_1 is TIPS, R_3 is PMB and R_4 is TBS.

Also provided are compounds of formula V:

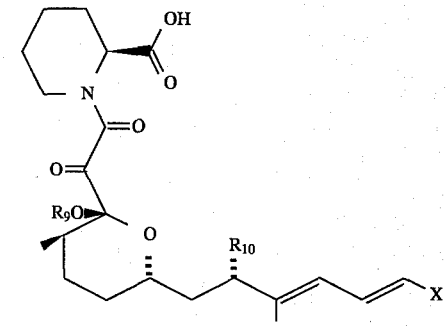


V

wherein

R_1, R_2, R_3 and are as defined above.

Compound are also provided having formula VI:



VI

wherein:

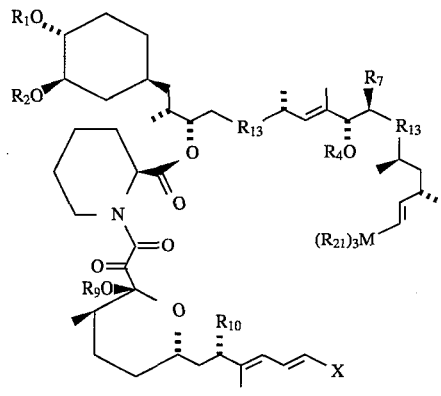
R_9 is H or a hydroxyl protecting group;

R_{10} is H, OH or alkoxy having one to about six carbon atoms; and

X is halogen, preferably iodine.

In certain embodiments R_8 is H, and R_{10} is methoxy.

Also provided are compounds having formula VII:



wherein

R_1, R_2, R_4, R_7, R_9, R_{10}, R_{21} and M are as defined above.

BRIEF DESCRIPTION OF THE DRAWINGS

The numerous objects and advantages of the present invention may be better understood by those skilled in the art by reference to the accompanying figures, in which:

FIG. **1** shows an overview of a synthesis of the invention as applied to rapamycin and demethoxyrapamycin.

FIG. **2** shows the preparation of compounds XV and VII from compounds IV and VI.

FIG. **3** shows the preparation of fragment IV from precursor compound II.

FIG. **4** shows exemplary synthetic routes for the derivation of compound II where R_7 is H or alkoxy.

FIG. **5** shows the preparation of compound VI from fragment D.

FIG. **6** shows the formation of compound II in the synthesis of demethoxyrapamycin.

FIG. **7** shows the formation of compound II in the synthesis of rapamycin.

FIG. **8** shows the synthesis of compound VI (fragment DE) from fragment D.

FIG. **9** shows the completion of the synthetic routes to rapamycin and demethoxyrapamycin from compounds IIa and IIb.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has been found in accordance with the invention that the synthesis of macrocycles such as rapamycin and/or derivatives can be achieved by highly convergent synthetic procedures wherein fully functionalized fragments corresponding to carbons 21–34 of the rapamycin skeleton are coupled with pinecolinate-tricarbonyl fragments corresponding to carbons 1–20, each fragment being available from building blocks A through E as outlined in FIG. **1**.

In preferred embodiments rapamycin or demethoxyrapamycin are prepared from compound VII, which is in turn prepared from precursor fragments IV and VI according to FIG. **2**. Preferably, compound IV is first coupled to compound VI by an intermolecular acylation to form compound VII. A preferred condensation agent for the acylation is ethyl-3-(3-dimethylamino)-propyl carbodiimide.HCl (EDAC.HCl), dimethylamino pyridine (DMAP). Closure of the ring in compound VII is preferably achieved by a Pd(0)-catalyzed Stille coupling. A preferred reagent for the coupling is $(2\text{-furyl}_3P)_2PdCl_2$, diisopropylethylamine (DIPEA) in DMF/THF. After ring closure, the protecting groups are preferably removed by any of several reagents known in the art to be suitable, for example tetrabutylammonium fluoride/acetic acid (TBAF/AcOH) followed by HF.pyridine, pyridine in THF.

The methods of the present invention allow flexibility in choice of substituents on the rapamycin skeleton. For example, R_7 can be varied to provide different rapamycin derivatives. In one preferred embodiment R_7 is hydrogen, and the resulting product is demethoxyrapamycin. Other similar substitutions may be made at other positions in the rapamycin skeleton, for example, at C-16.

The preparation of fragment IV from common precursor compound II is shown in FIG. **3**. Compound II is first treated to unmask the aldehyde group by reaction with, for example, TsOH in acetone, and then subjected to Corey-Fuchs homologation to yield the terminal acetylene compound III. See, Corey, E. J. and Fuchs, P. L., *Tetrahedron Lett.* 1972 13, 3769. Compound III is, in turn, treated to remove the protecting group at C-34. In preferred embodiments the protecting group at C-34 is PMBO (p-methoxybenzyloxy), which is preferably removed oxidatively by, for example, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in CH_2Cl_2. This is followed by hydrolysis of the dithiane group with, for example, MeI, $CaCO_3$, and palladium(0)-mediated hydrostannylation. See Zhang, H. X. et al., *J. Org. Chem.* 1990 55, 1857.

Compound II derives from two separate synthetic routes depending upon the nature of R_7. These synthetic routes are shown in FIG. **4**. In the synthetic route leading, for example, to demethoxyrapamycin, fragment B from FIG. **1** is coupled with the butyllithium derivative of fragment A of FIG. **1** to produce precursor acetonide VIII (fragment AB). Fragments A and B can be prepared according to the procedure of Smith, A. B. et al., *Tetrahedron Letters* 1994, 35(28), 4907–4910. Epoxide V is produced from compound VIII by standard techniques, such as, for example, unmasking with camphorsulfonic acid/methanol (CSA/MeOH), tosylation, and epoxidation with K_2CO_3/MeOH. Compound II (R_7=H) is formed from the coupling of terminal epoxide V and compound XVI. Preferably, the coupling is performed at low temperature (i.e., –78° C.) using an alkyllithium reagent, for example t-BuLi, in an appropriate solvent such as, for example, 10% (v/v) HMPA (hexamethylphosphoramide)/THF. In the synthetic route leading to, for example, rapamycin, aldehyde XIII is first produced by coupling fragment A from FIG. **1** with the lithium derivative of dithiane compound XVII. Fragment C from FIG. **1**, prepared according to the procedure of Smith, A. B. et al., *Tetrahedron Letters* 1994, 35(28), 4911–14 is metallated with t-butyllithium and added to aldehyde XIII, and the product is methylated to give compound II (R=OCH_3). The preparation of compound VI is shown in FIG. **5**. Fragment D from FIG. **1**, prepared according to the procedure in Smith, A. B. et al., *Tetrahedron Letters* 1994, 35(28), 4911–14, is hydrolyzed with, for example, AcOH/THF, and silated with, for example, 2 equivalents of TBSCl (t-butyldimethylsilyl chloride), imidazole, DMF. The ester is reduced by, for example DIBAL (diisobutylaluminum hydride) reduction, and aldehyde species X is formed by subsequent oxidation, for example with DMSO and oxalyl chloride by the method of Swern. See, March, J., *Advanced Organic Chemistry* Fourth Ed. Wiley & Sons New York, 1992 p. 1194.

Compound X is then condensed with the dianion of (L)-N-acetylpipecolinic acid in the presence of a condensing agent such as, for example, lithium hexamethyldisilazide (LHMDS). The products are treated with diazomethane followed by Des-Martin oxidation (5 equiv) to give the tricarbonyl species in accordance with the procedure developed by Golec, et al. See, Batchelor, M. J. et al., *Tetrahedron*

Lett., 1993, 34, 167; Dees, D. B. et al., *J. Org. Chem.* 1983 48 4155. Removal of the TBS group at C-14 yields the hemiketal compound XII, which is then protected at the free hydroxyl groups by, for example, reaction with triethylsilyltrifluoromethane sulfonate (TESOTf). Compound VI (fragment DE) is then formed from compound XII by free radical hydrostannylation according to the procedure of Nicolaou, et al., *Synthesis* 1986, 453, using, for example Bu_3SnH, 2,2'-azobisisobutrylonitrile (AIBN), tin-iodide exchange according to the procedure of Crisp, et al., *Tetrahedron Letters* 1992, 33(32), 4649, and subsequent conversion of the ester to the carboxylic acid by, for example, LiI in pyridine.

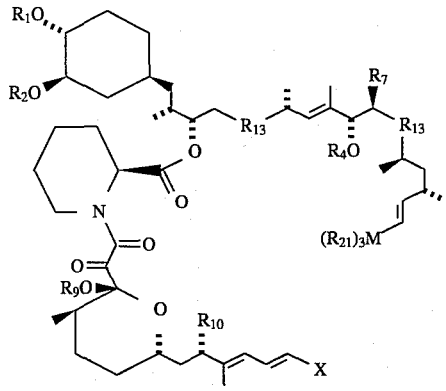
Compounds of the invention contain protecting groups. Protecting groups are known per se as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Some representative protecting groups useful for protecting the for carbonyl functionality are 1,3-dithiane groups and dimethoxyacetal groups. Some representative protecting groups useful for protecting the for hydroxyl functionality are TIPS (triisopropylsilyl), PMB methoxybenzyl), TBS (t-butyldimethylsilyl), TES/triethylsilyl) and lower alkyl groups such as methyl. Other representative groups may be found in Greene, T. W. and Wuts, P. G. M., *"Protective Groups in Organic Synthesis"* 2d. Ed., Wiley & Sons, 1991. In preferred embodiments R_1 is TIPS, R_3 is PMB, R_4 is TBS, and R_9 is TES.

R_2 is preferably hydrogen or alkyl having from one to about six carbons. Alkyl groups according to the invention include straight chain, branched, and cyclic hydrocarbons such as methyl, isopropyl, and cyclohexyl groups. Alkoxy groups are oxygen atoms having an alkyl group appended thereto. It will be recognized that a wide variety of compounds according to the invention can readily be prepared according to the methods of the invention.

Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all equivalent variations as fall within the true spirit and scope of the invention.

What is claimed is:

1. A compound of formula VII:



VII

wherein:

R_1, R_4, and R_9 are, independently, hydrogen or a hydroxyl protecting group;

R_2 is alkyl having from one to about six carbon atoms;

R_7 is hydrogen or alkoxy having one to about six carbon atoms;

R_{10} is H, OH, or alkoxy having one to about six carbon atoms;

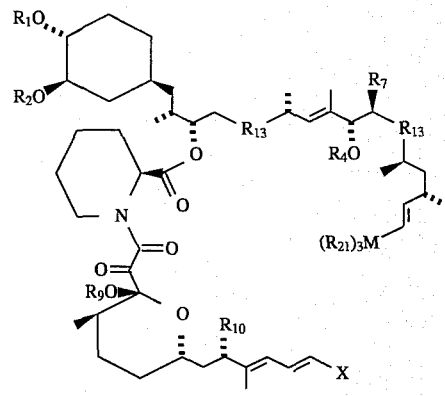
R_{13} is a carbonyl group or a protected derivative thereof;

R_{21} is alkyl having one to about six carbon atoms;

M is a tetravalent metal atom; and

X is halogen.

2. A compound of formula:



wherein:

R_1, R_4, and R_9 are, independently, hydrogen or a hydroxyl protecting group;

R_2 is alkyl having from one to about six carbon atoms;

R_7 is hydrogen or alkoxy having one to about six carbon atoms;

R_{10} is H, OH, or alkoxy having one to about six carbon atoms;

R_{13} is a carbonyl group or a protected derivative thereof;

R_{21} is alkyl having one to about six carbon atoms;

M is Sn; and

X is halogen.

3. The compound of claim **1** wherein R_7 is H.

4. The compound of claim **1** wherein R_7 is methoxy.

5. The compound of claim **1** wherein said protected derivative of said carbonyl group of said group R_{13} is a 1,3-dithiane.

6. The compound of claim **1** wherein R_2 is methyl.

7. The compound of claim **1** wherein said hydroxyl protecting groups are selected from the group consisting of TIPS, PMBO, TES and TBS.

8. The compound of claim **1** wherein R_1 is TIPS, R_4 is TBS, and R_9 is TES.

9. The compound of claim **1** wherein R_{21} is butyl.

10. The compound of claim **1** wherein X is iodine.

* * * * *