AN ABSTRACT OF THE THESIS OF

James B. LaMunyon for the degree of Master of Science in Chemistry presented on March 19, 1998. Title: Synthetic Approaches to the Tricarbonyl Subunit of Rapamycin.

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Abstract approved: _____
James D. White

Rapamycin (**5**) was isolated in 1975 from the soil bacteria *Streptomyces hygroscopicus* and its structure was determined from spectroscopic techniques and an x-ray crystallographic analysis. Although it was initially found to exhibit antibiotic activity, it was subsequently shown to possess potent immunosuppressive activity as well.

Three approaches to the synthesis of the tricarbonyl subunit (C1-C15) of **5** were investigated. The first plan for the synthesis of **127** envisioned a rearrangement of the α-acyloxy amide **135** to **136** followed by oxidation. The amide **135** was synthesized by coupling of the readily prepared chloroacetylpipecolate **131** with the carboxylic acid **134**.

The second approach was based on a model study in which the acetylenic ester **144** was oxidized to the α,β-diketoester **146**. However, synthesis of the requisite acetylenic amide precursor **150** was unsuccessful.

The third approach anticipated successful formation of **167** from the aldehyde **159** and bromoacetylpipecolate **166**, followed by Dess-Martin oxidation to afford the tricarbonyl subunit of rapamycin. The aldehyde was successfully prepared in ten steps from (*S*)-3-hydroxy-2-methylpropionate (**132**).

Synthetic Approaches to the Tricarbonyl Subunit of Rapamycin

by

James B. LaMunyon

A THESIS

submitted to

Oregon State University

in partial fulfillment of

the requirements for

the degree of

Master of Science

Completed March 19, 1998

Commencement June 1998

Master of Science thesis of James B. LaMunyon presented March 19, 1998

APPROVED:

Redacted for Privacy

Major Professor, Representing Chemistry

Redacted for Privacy

Chair of Department of Chemistry

Redacted for Privacy

Dean of Graduate School

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James B. LaMunyon, Author

Acknowledgments

I would like to express my gratitude and thanks to my advisor, Dr. James D. White, for his support and guidance during the course of my studies at Oregon State University.

I must also thank my colleagues, the many members of the White group, past and present, for their friendship and helpful discussions.

I would like to extend a special thanks to the faculty and staff of the Department of Chemistry at Oregon State University for the hard work and the educational opportunities they provided.

Finally, I must thank my lovely wife Nancy and our wonderful children for their support and encouragement.

Table of Contents

Synthetic Approaches to the Tricarbonyl Subunit of Rapamycin

Chapter I. Introduction and Review of the Literature

Immune systems respond to the presence of diseased cells, foreign matter and infectious organisms by a directed response that begins with the introduction of an antigen.[1] An antigen is a macromolecule that induces the formation of immunoglobulins (antibodies) and/or sensitized cells which react specifically with the antigen. The antigen may also be a cell which contains ligands (called epitopes) or small clusters of molecules on its surface that are not present on cells of the host organism. A more descriptive illustration is not possible since antigens are defined by the antibodies they produce and antibodies are defined by the antigens that produce them.[2]

Immune systems also vary in their levels of sophistication. Invertebrates (and some vertebrates) rely only on phagocytic cells that have general receptors for any foreign intruder. Most vertebrates have, in addition to such phagocytic cells, immune systems that can adapt to combat infectious organisms. In the adaptive immune system, cells can detect the presence of antigens via receptors which bind to specific epitopes of the antigen.

Innate immune systems primarily use neutrophils, eosinophils, and basophils which contain granular cytoplasm. In addition to these polymorphonuclear cells, innate systems utilize white blood cells (called monocytes) and other cells which are derived from monocytes (called macrophages). Of these immune cells, monocytes, macrophages, and neutrophils are the most active.

In adaptive immune systems two types of cells are the most important: B lymphocytes (B cells) and T lymphocytes (T cells). Both cell types originate

in bone marrow, but B cells mature in the bursa of Fabricus (birds) and T cells in the thymus. Mammals do not have a bursa of Fabricus and it is believed, although not certain, that gut-associated lymphoid tissue (GALT) is the mammalian equivalent. Both cell types exhibit similar morphology, but differ in many respects. The most important functional differences are that B cells are primarily associated with antibody production while T cells are primarily associated with directing the host's immune response.

The surface of B cells contain large numbers of specific receptors, and proliferation of B cells occurs when an antigen binds to a specific B cell. This causes the cell to multiply (along with other signals such as those induced by T helper cells) in a process known as clonal expansion. Some of these new cells (called plasma cells) are immunoglobulin (antibody) synthesizing cells. These antibodies can bind to specific epitopes in the antigen, either when the antibody is on the surface of the B cell, or when the antibody is excreted by the plasma cell. Occasionally, some of the B cells differentiate into "memory" cells that can remain in the body long after an infection has been repulsed. This is one reason why people who recover from most diseases are not likely to acquire them again.[3] High concentrations of B cells are found in the spleen, but B cells exhibit low blood concentrations.

The T cells are differentiated into several subsets with each subset regulating a different immune response.[4] Cytotoxic T cells (T_c cells) kill the host's cells when they become infected, and suppresser T cells (T_s cells) prevent the activation of other immune cells. Helper T cells (T_h cells) produce and secrete molecules that activate B cells which regulate the host's responses. The secreted molecules are called lymphokines and include

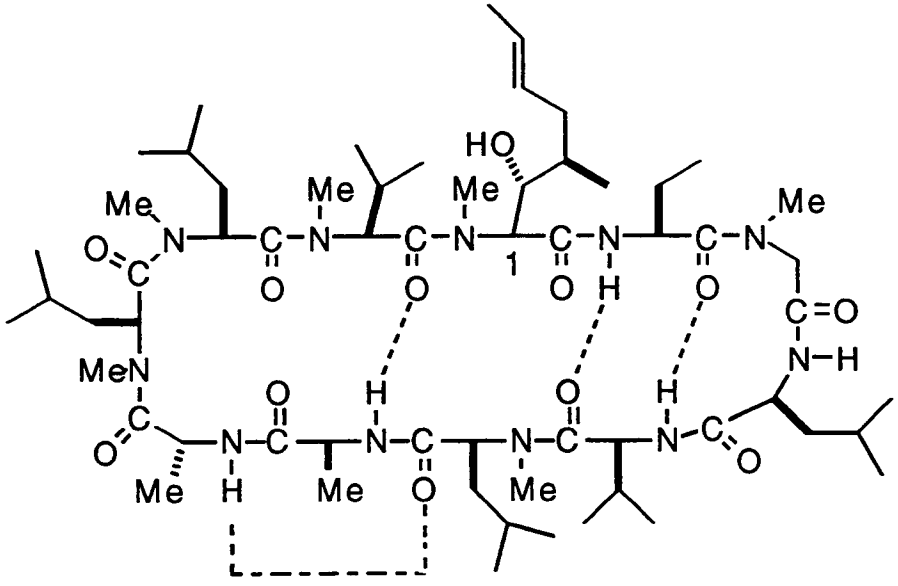
interleukins 2,3,4 (Il-2, Il-3, Il-4) and γ-interferon. Unlike B cells, T cells have relatively high blood concentrations and concentrate in thoracic lymph nodes.

Another difference exhibited between T cells and B cells is the mode of antigen recognition.[5] T cells, unlike B cells, do not bind independently with an antigen. The T cell receptor (TCR) must bind simultaneously to the antigen and a specific cluster of molecules called the major histocompatibility complex (MHC) that occurs on the surface of the host's cells. This permits T cells to identify infected cells and interact only with immune cells of the same antigen receptor. The host is thus able to mount an immune response against infected tissues only.

This mode of action has significant consequences with respect to organ and tissue in the role of T cells in transplant rejection. Such rejection usually occurs when tissues are transplanted between people with markedly different genes in the MHC region. The MHC region in these transplanted cells present foreign epitopes to T_c and T_h cells leading to the host's immune system responding to irradicate the foreign cells. Graft rejection occurs when antibodies form in response to surface MHC molecules of the transplanted organ. If this process proceeds unimpeded, the host's immune response will ultimately lead to cellular death and organ rejection. Prior to the introduction of immunosuppressive compounds, only grafts from closely matched siblings or highly inbred animal strains avoided rejection by the host. With the use of selective immunosuppressive compounds, more general methods of host-graft transplantation have become available.[6,7]

It has been known for decades that certain compounds, such as 6-mercaptopurine, suppress the body's ability to mount an immune response.[8] Chief among today's therapeutic immunosuppressants is the macrocyclic

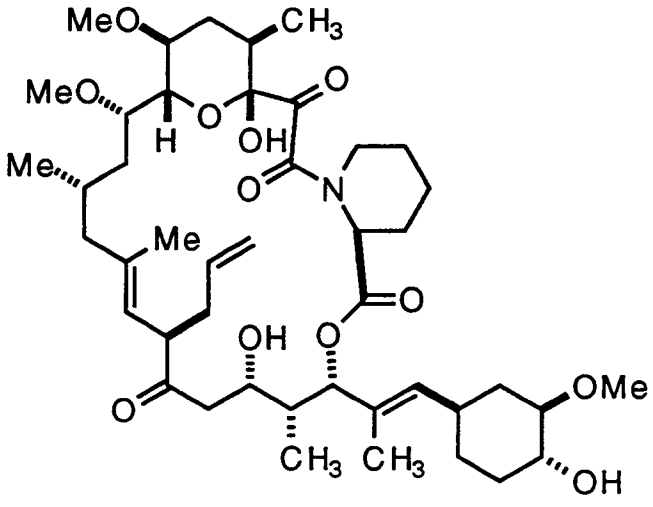
peptide cyclosporin A (**1**) (CsA). CsA, a fungal metabolite of *Tolypocladium*, was first isolated in 1971.[9] The *N*-methylbutenylthreonine moiety (attached to C-1) was unknown before the elucidation of CsA's structure. CsA is in fact routinely used in heart, liver, kidney and lung transplants and has led to a high success rate for transplantation in humans. It has become the drug of choice to prevent organ rejection and has significantly increased long-term survival rates of individuals who have received these transplants.



1

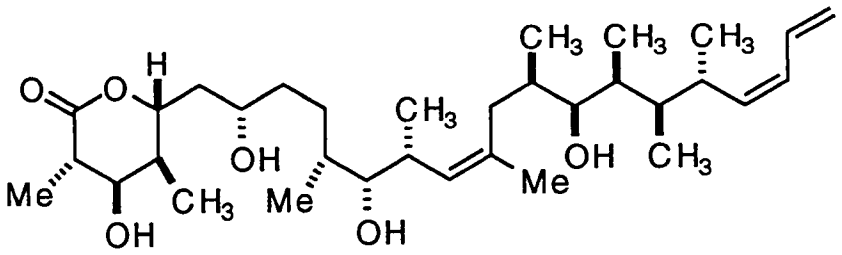
CsA is a strong immunosuppressant that is absorbed by T cells during the initial stages of mitosis and selectively prohibits T cell proliferation. Interference by CsA with T_h cells inhibits production of interleukins and γ-interferon.[10] One of the more undesirable side effects of CsA is its potential for kidney damage, leading to kidney failure in extreme cases.[11]

FK506 (2), another promising immunosuppressive agent, was isolated from the bacteria *Streptomyces tsukukaenis* in 1987.[12] This 23-membered macrolide was also found to be immunosuppressive with bioactivity similar to CsA, and is currently undergoing clinical trials for use in humans.[13] Importantly, FK506 has been shown to be 10-100 times more effective than CsA. However, in relatively high concentrations FK506 has been shown to be toxic in animals. This undesirable trait is circumvented by the lower concentrations required for therapeutic efficacy.

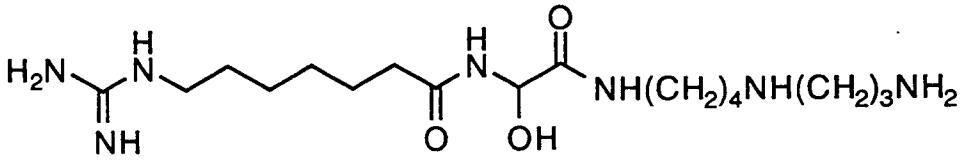


2

Recently it was discovered that discodermolide (3) and deoxyspergualin (4) also show immunosuppressive activity.[13] Presently, work is under way to determine the signaling mechanisms by which these compounds operate, but it is not yet known by what mechanism they inhibit T cell activation.[13]



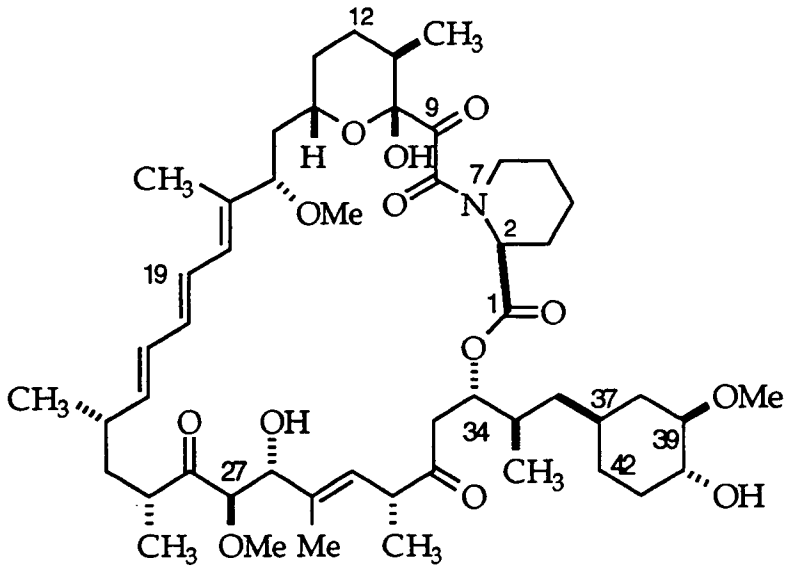
3



4

Rapamycin (5) is a metabolite of *Streptomyces hygroscopicus* and was isolated in 1975.[14] Although it was first described as a potent antibiotic, subsequent studies have shown it also affects the histology of lymphoid tissues. Rapamycin was later discovered to be a powerful immunosuppressant as well.[15a-c] Although CsA (1) and FK506 (2) both inhibit the production of interleukins and γ-interferon, rapamycin does not. Instead, rapamycin inhibits the response of immune cells to these lymphokines[13,16] and is effective at concentrations similar to those associated with FK506. When used jointly, rapamycin and FK506 inhibit each other's activity. However, when FK506 is administered simultaneously with CsA an increase in effectiveness has been observed. Rapamycin has recently been used successfully in animal models to suppress graft rejection,[17,18] and like FK506, rapamycin can also exhibit adverse side effects at high dosage levels.[18] Rapamycin inhibits T and B cell proliferation at a later stage in the immune response than does FK506 and can operate on immune response pathways

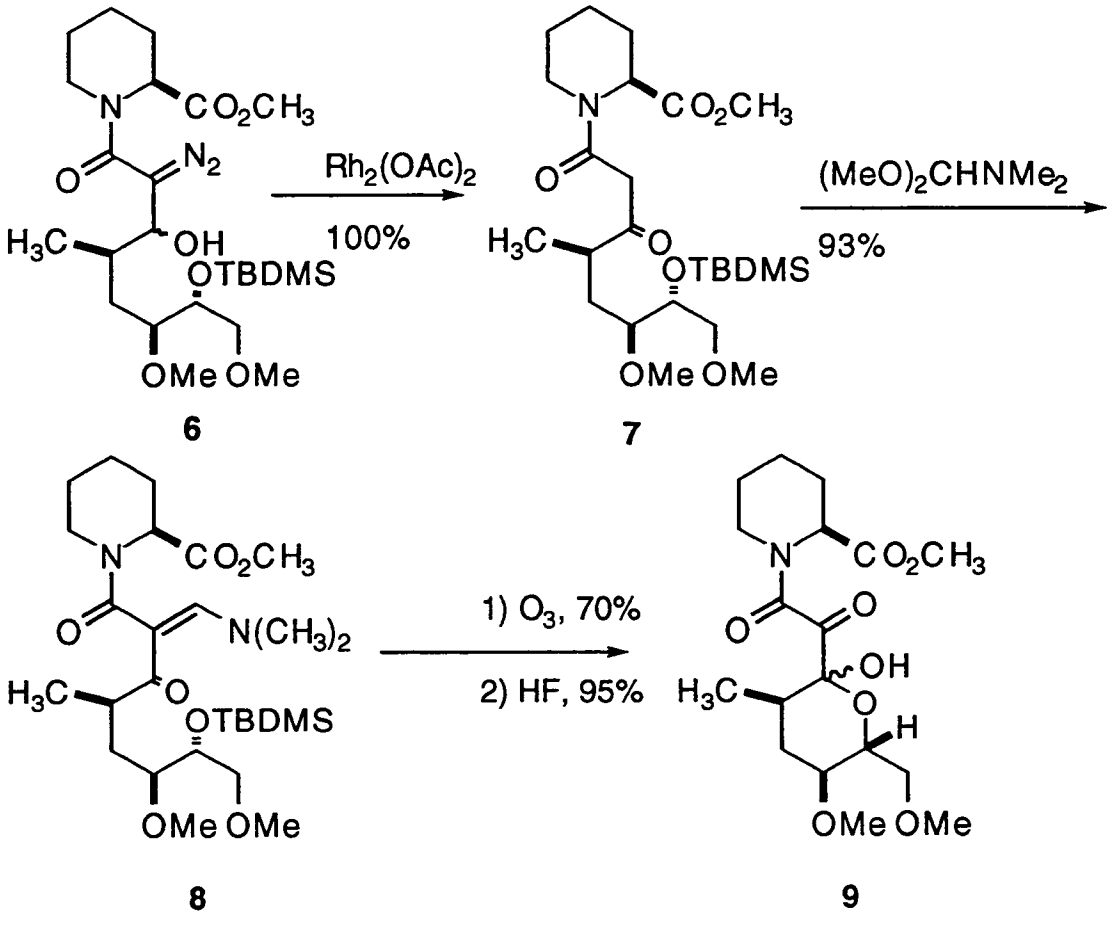
insensitive to FK506 such as Il-2 mediated T cell response. It inhibits activation of T cells by phorbol ester and B cells by bacterial lipopolysaccharide.[19]



5

Much effort has been directed to the synthesis of rapamycin (**5**) and the structurally similar FK506 (**2**) due to their potent activity[20a-k,21a-l] and in particular to the construction of the "tricarbonyl" moiety of both these two macrolides.[22a-m] The tricarbonyl region (C8-C10) has been shown to be crucial to the immunosuppressive activity of rapamycin.[23] All current synthetic studies culminate in an oxidation step at or near the final stages of the synthesis, for which the oxidative methods employed varied considerably. One of the earliest studies[22a] by Kocienski and co-workers made use of the β-ketoamide **7** obtained from the α-diazo-β-hydroxyamide **6** (Scheme I). The amide **7** was treated with dimethylformamide dimethylacetal, giving the desired enamine **8**, and ozonolysis of **8** afforded the desired tricarbonyl

intermediate. Desilylation followed by formation of the lactal was accomplished by in situ reaction with hydrofluoric acid to furnish the FK506 tricarbonyl segment **9**.

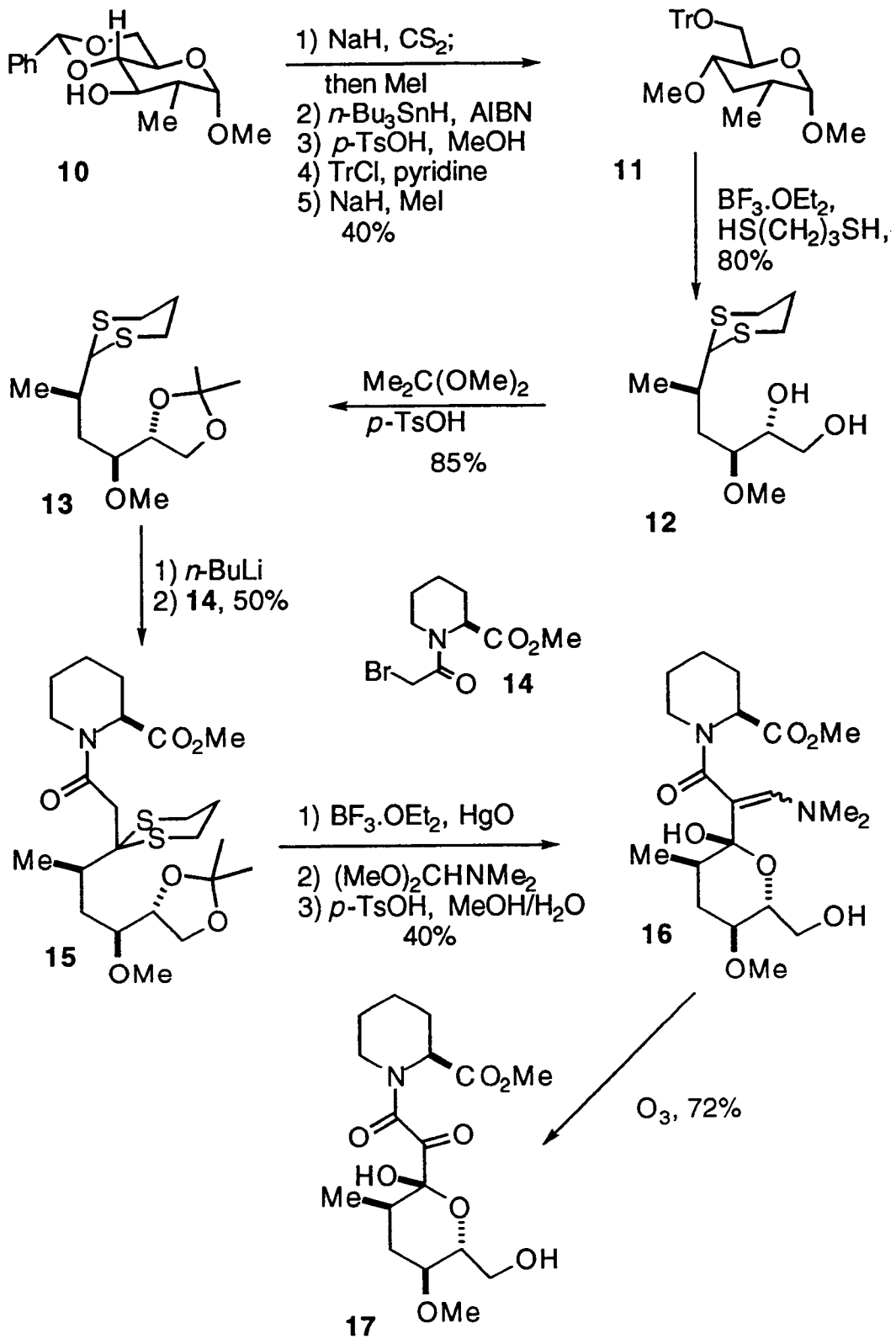


Scheme I

Rao and co-workers[22b] synthesized the tricarbonyl subunit of FK506 by ozonolysis of a similar enamine intermediate in the final step (Scheme II). This synthesis began with the previously described[24] methyl 4,6-*O*-benzylidene-2-deoxy-2-methyl-α-D-glucopyranoside (**10**) obtained from methyl α-D-glucopyranoside. The C-3 hydroxy group was removed by reduction of the xanthate with tri-*n*-butyltin hydride. The benzylidene acetal was readily cleaved with acid and the product was treated with trityl chloride

to protect the primary alcohol. Methylation of the secondary alcohol at C-4 gave the ether **11**. This pyranoside was ring-opened and the trityl group was removed with acid in the presence of 1,3-propanedithiol to give the thioacetal **12**. The diol moiety of **12** was converted to the acetonide **13** with 2,2-dimethoxypropane in the presence of an acid catalyst, and when **13** was treated with *n*-butyllithium and then with methyl *N*-bromoacetylpipecolate (**14**) the ester **15** was obtained. The enamine **16** was prepared by converting the thioacetal to a ketone, reacting the resultant β-diketone with dimethylformamide dimethylacetal, and hydrolyzing the acetonide to give **16** in low overall yield. The final step was accomplished by ozonolysis of **16** which gave the FK506 tricarbonyl subunit **17**.

In their approach to the tricarbonyl subunit of FK506, Williams and co-workers[22c] used selenium dioxide to oxidize a β-ketoamide precursor as shown in Scheme III. The aldehyde **18**[25] was reacted with the freshly prepared Grignard reagent **19** derived from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate[26] to give **20** as the major stereoisomer. The secondary alcohol of **20** was first methylated, and this was followed by a dissolving metal cleavage of the benzyl ether to yield the primary alcohol **21** as a single isomer after column chromatography. Oxidation of **21** with Jones' reagent gave the carboxylic acid **22** without ketal hydrolysis, and conversion to the acid chloride **23** was accomplished by addition of excess oxalyl chloride to **22**. The pipecolic amide **24** was converted to its magnesium enolate with isopropylmagnesium chloride, and then **23** was added dropwise to give the acylated product **25** as a mixture of enolic isomers. Hydrogenolysis and decarboxylation of **25** resulted in the formation of the β-ketoamide. The carboxylic acid resulting from hydrogenolysis of the benzyl pipecolate was reprotected as methyl ester **26** by treatment with diazomethane. Oxidation of


1) NaH, CS2;
then MeI
2) n-Bu3SnH, AIBN
3) p-TsOH, MeOH
4) TrCl, pyridine
5) NaH, MeI
40%
10
11
BF3.OEt2,
HS(CH2)3SH,
80%
Me2C(OMe)2
p-TsOH
85%
13
12
1) n-BuLi
2) 14, 50%
14
1) BF3.OEt2, HgO
2) (MeO)2CHNMe2
3) p-TsOH, MeOH/H2O
40%
15
16
O3, 72%
17

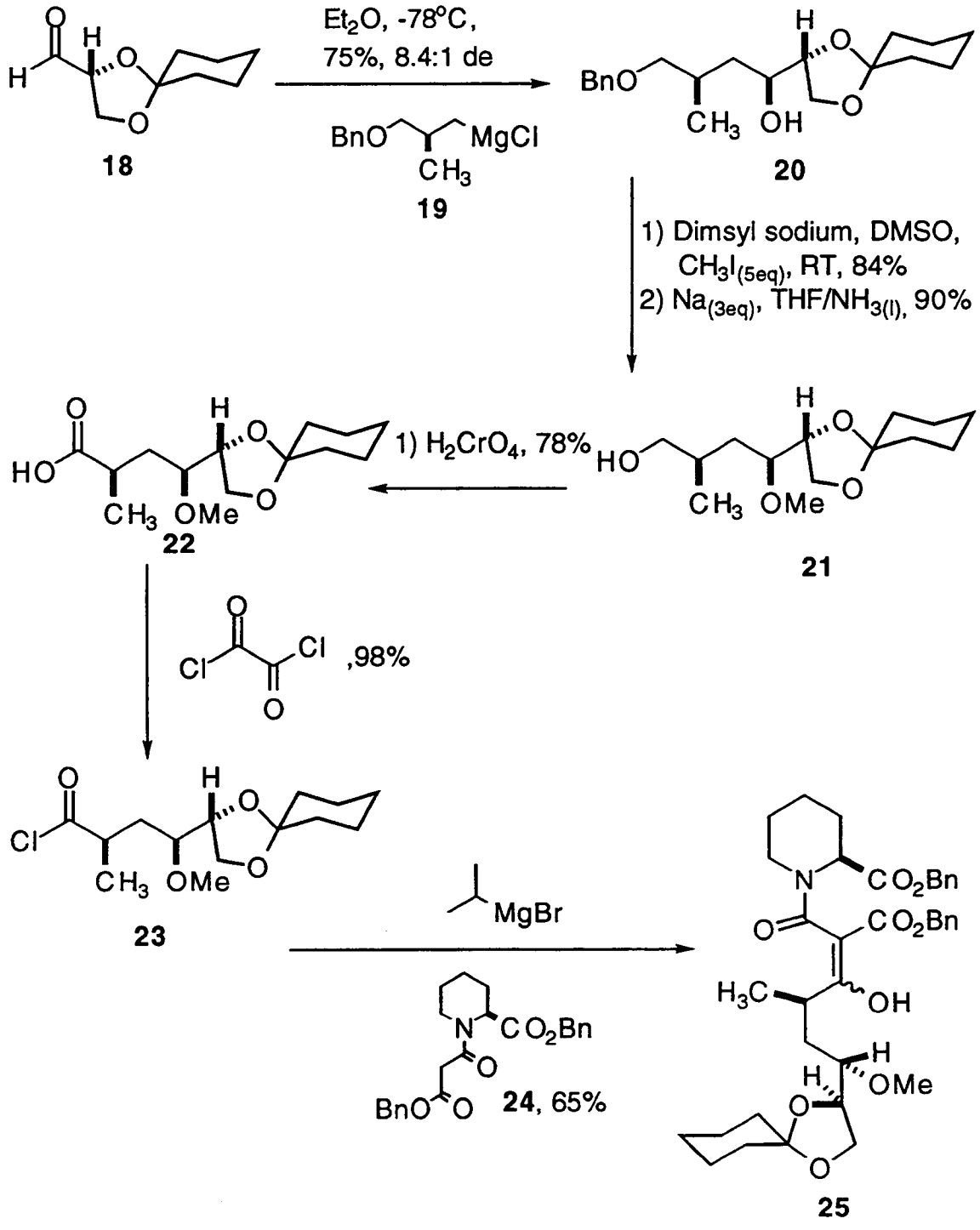
Scheme II

this β-ketoamide with selenium dioxide in refluxing dioxane gave the tricarbonyl precursor **27** as a partial hydrate (33% hydrated). Conversion of **27** to the FK506 subunit **17** was accomplished by ketal hydrolysis with hydrochloric acid in methanol.

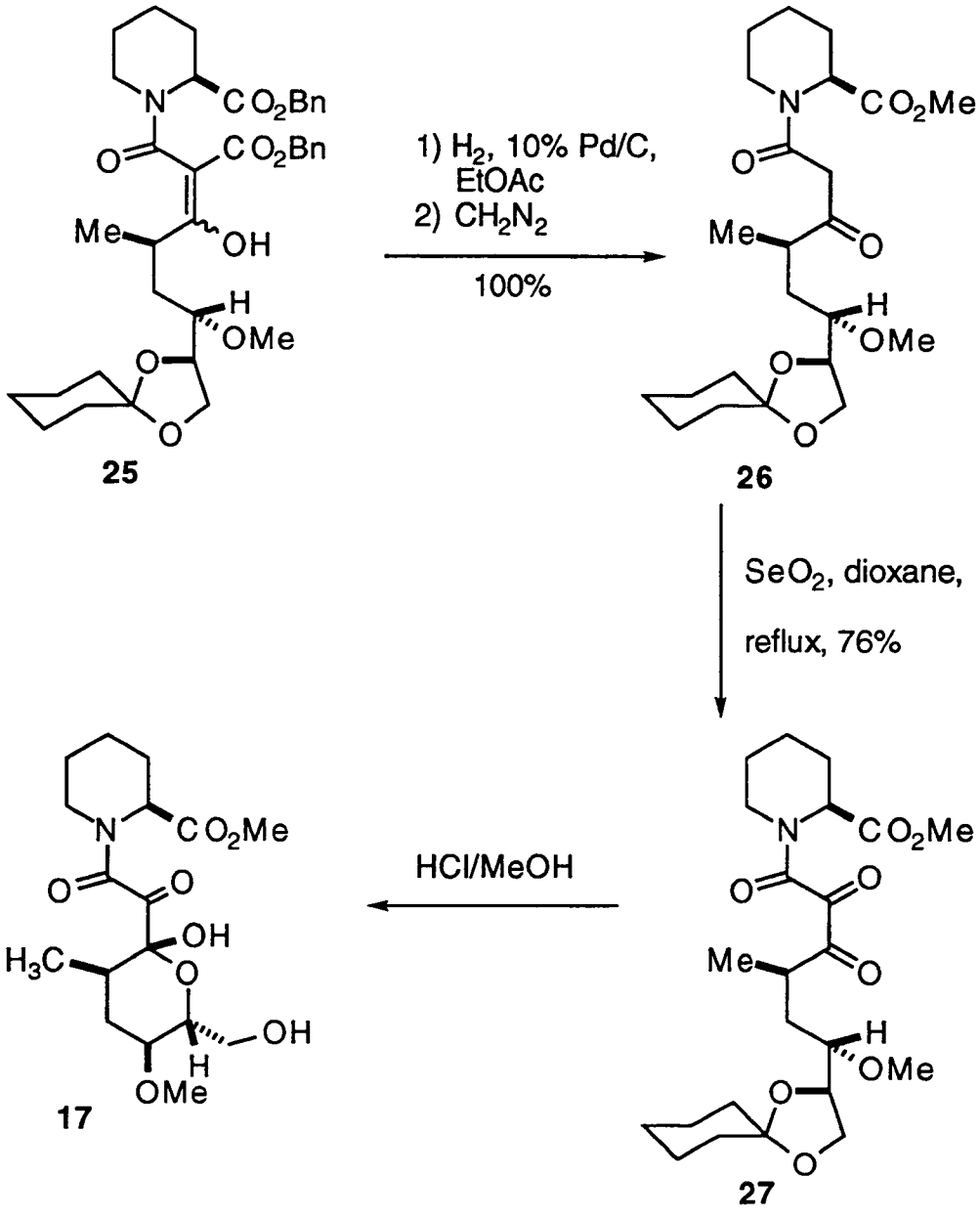
Synthetic strategies directed toward the FK506 tricarbonyl subunit have been the focus of much research in the Danishefsky group.[22d,e] Their first approach began with the conversion of the easily prepared *tert*-butyl pipecolate **28** into the oxalyl derivative **29** by treatment with methyloxalyl chloride (Scheme IV).

Treatment of thioacetal **30** with *n*-butyllithium followed by addition of the electrophile **29** gave the β-thioketal adduct, which was reacted with hydrogen fluoride in acetonitrile to give the alcohol **31**. Exposure of the thioketal to *N*-bromosuccinimide in acetone gave the diketoamide which cyclized spontaneously to the masked FK506 tricarbonyl subunit **32**.

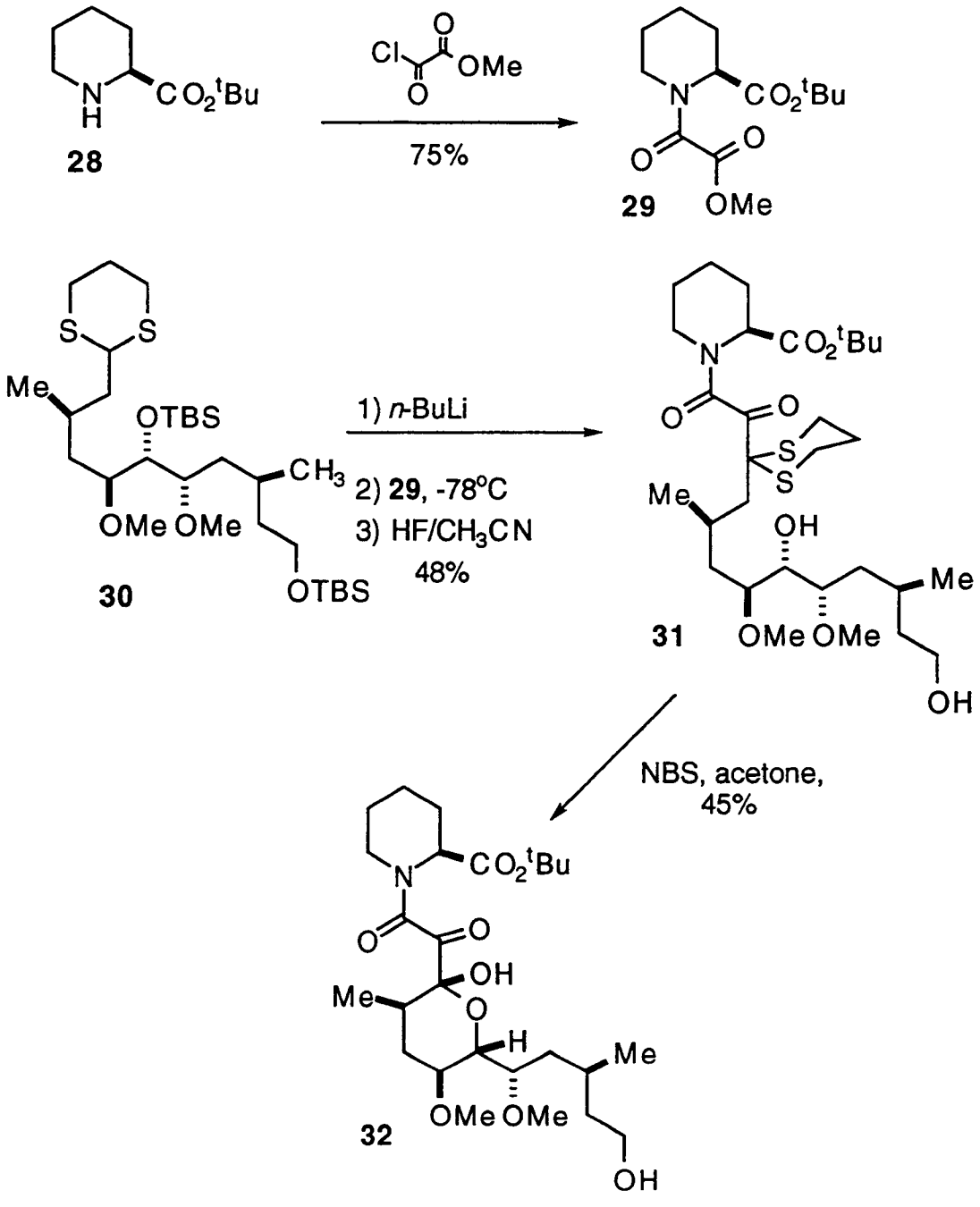
A different strategy[22e] by the Danishefsky group focused on the use of Dess-Martin periodinane for the oxidation of model systems similar to those found in rapamycin and FK506 (Scheme V). The enolate of racemic **33** reacted with benzaldehyde to give the alcohol **34** as a mixture of diastereoisomers which was oxidized with the Dess-Martin reagent to afford the tricarbonyl compound **35**. This approach was extended by coupling **33** with the racemic aldehyde **36**, giving the alcohol **37** as a mixture of diastereoisomers. Treatment of **37** with the Dess-Martin periodinane yielded the pipecolate **38**. Conversion to **39**, a structural unit common to both rapamycin and FK506, was accomplished by cleavage of the silyl ether, which was followed by spontaneous cyclization to give the desired hemiketal.


Et2O, -78°C,
75%, 8.4:1 de
BnO
MgCl
CH3
19
18
20
1) Dimsyl sodium, DMSO,
CH3I(5eq), RT, 84%
2) Na(3eq), THF/NH3(l), 90%
1) H2CrO4, 78%
22
21
Cl
,98%
23
MgBr
24, 65%
CO2Bn
OMe
OH
25

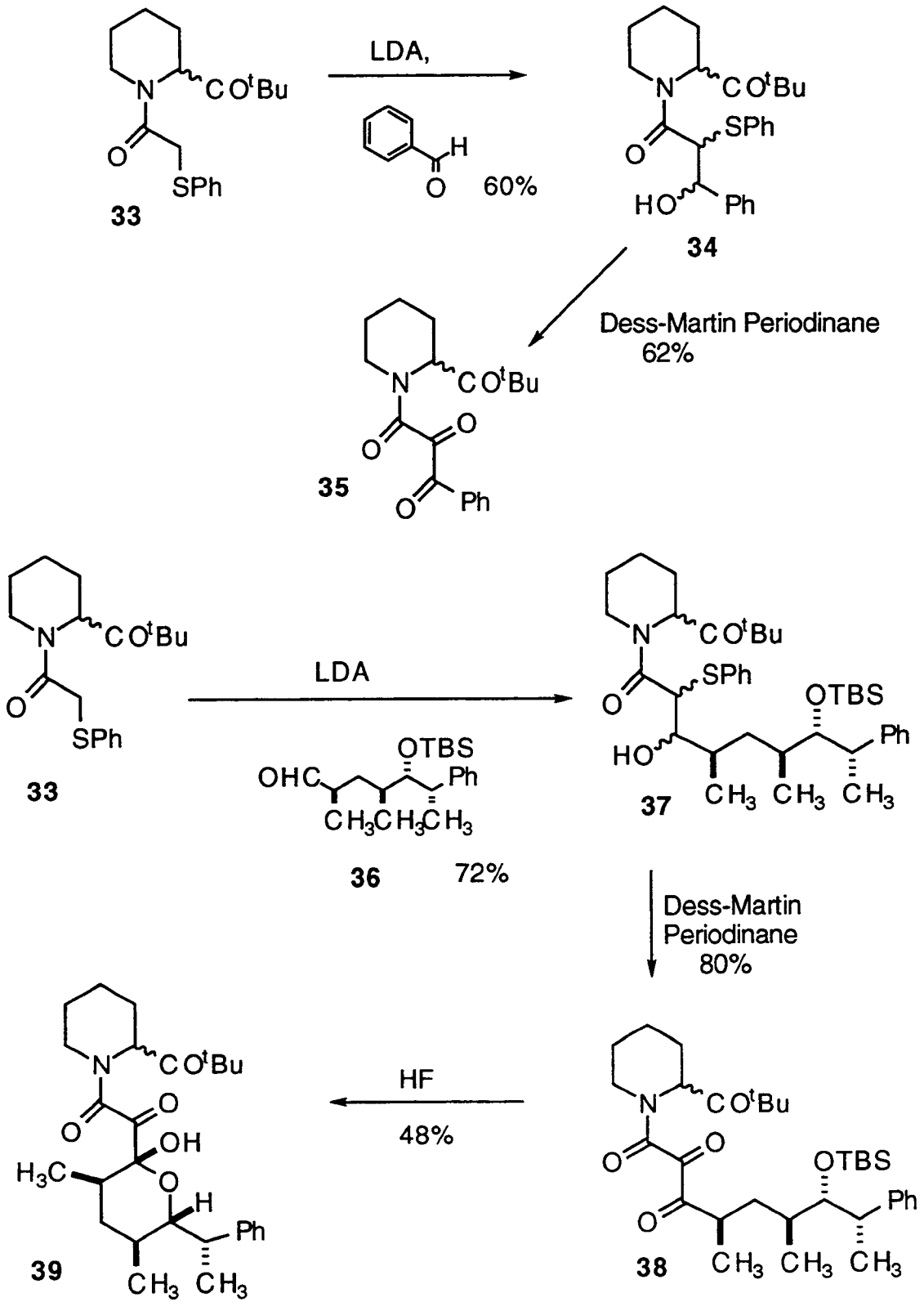
Scheme III



Scheme III, continued



Scheme IV


LDA,
60%
33
34
Dess-Martin Periodinane
62%
35
LDA
72%
36
37
Dess-Martin
Periodinane
80%
38
HF
48%
39

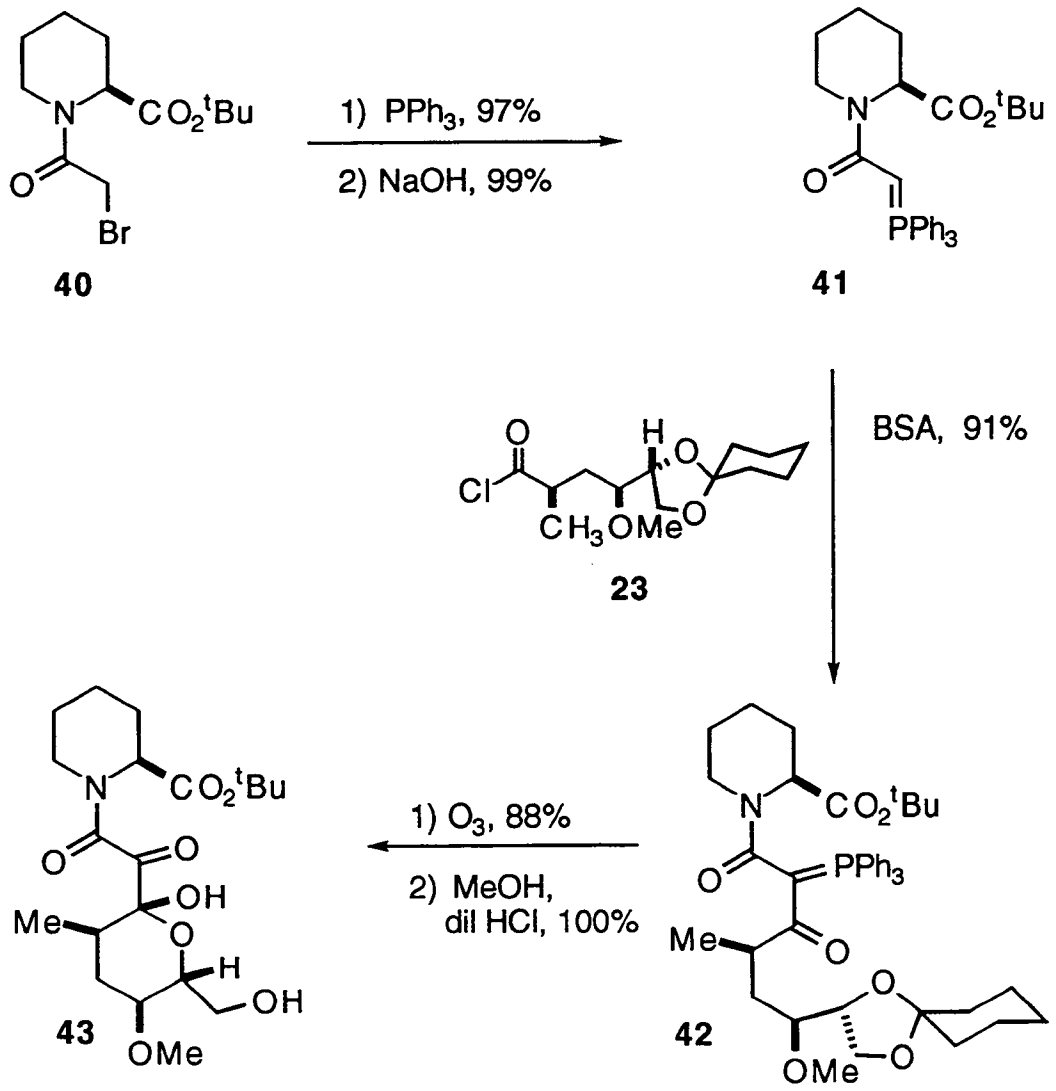
Scheme V

Wasserman and co-workers[22f] also utilized an ozonolysis to produce the tricarbonyl moiety of FK506 (Scheme VI). The *N*-bromoacetyl derivative **40**, prepared from the *t*-butyl ester of (-)-pipecolinic acid, was treated with triphenylphosphine to give a phosphonium salt, from which the ylide **41** was obtained by treatment with dilute sodium hydroxide. The ylide reacted with the acid chloride **23**[22c] in the presence of bis(trimethylsilyl)acetamide to give the keto ylide **42** which was ozonized to give a tricarbonyl compound. Quantitative hydrolysis of the ketal and cyclization to the FK506 tricarbonyl subunit **43** was accomplished with dilute hydrochloric acid in methanol.

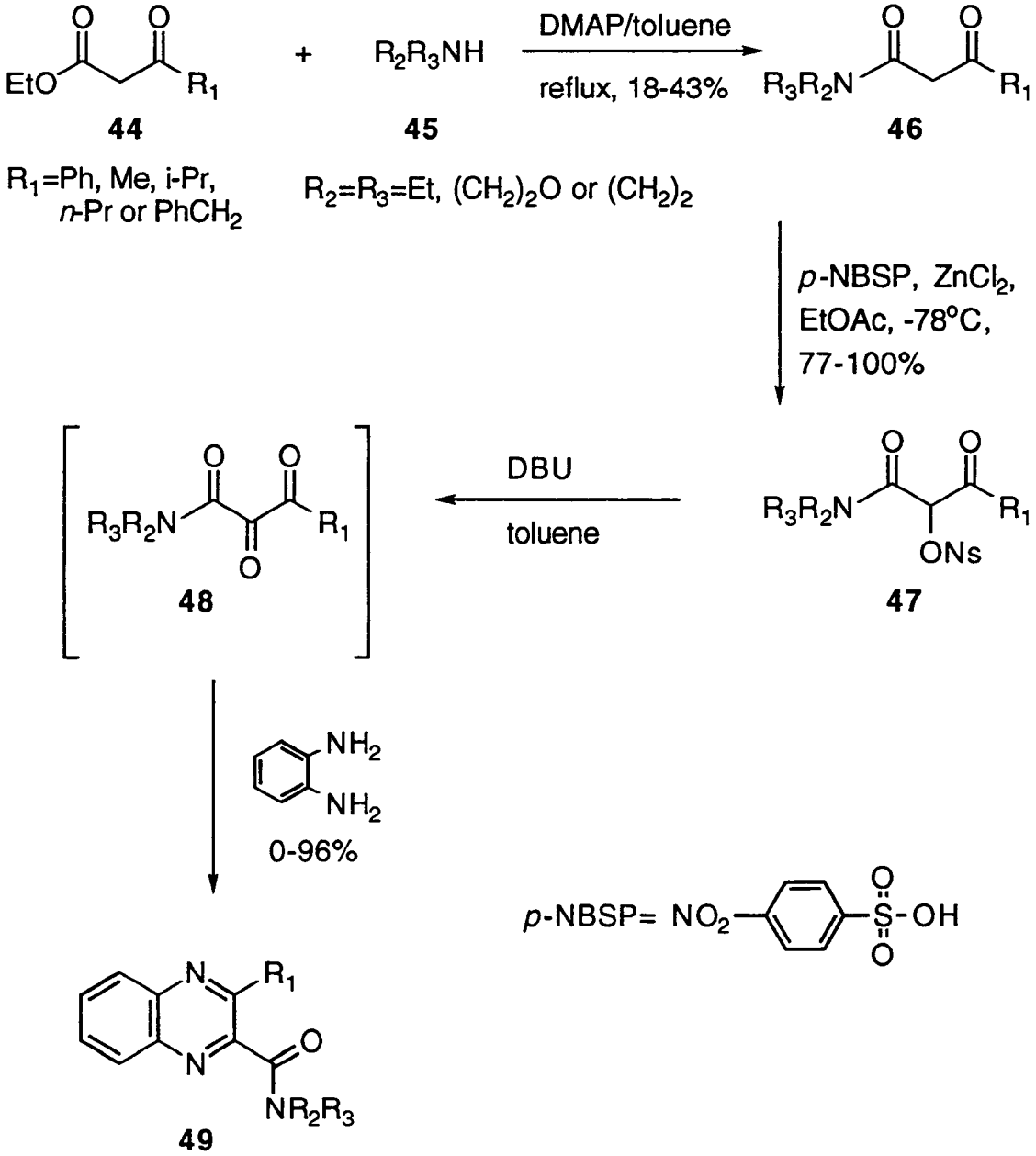
The Hoffman group[22g] carried out a model study on tricarbonyl systems similar to those found in rapamycin and FK506 in which a two-step oxidation of a β-keto amide **46** was used (Scheme VII). β-keto amides **46** were prepared from the corresponding β-keto esters **44** and a secondary amine **45** in the presence of 4-dimethylaminopyridine in refluxing toluene. The yields of the β-keto amides were low, ranging from 14% to 46%. These β-keto amides were readily converted to the 2-(nosyloxy)-3-keto amides **47** by treatment with *p*-nitrobenzenesulfonyl peroxide and zinc chloride. Reaction of **47** with 1,8-diazobicyclo[5.4.0]undec-7-ene gave the crude tricarbonyl compound **48**. Since this compound could be purified, the crude mixture was treated with *o*-phenylenediamine in order to trap the tricarbonyl compound as its quinoxaline derivative **49**.

A similar study by Golec and co-workers[22h] also made use of β-keto amides as well as β-hydroxy amides for the preparation of model tricarbonyl systems. In their work, Dess-Martin periodinane was used to obtain the tricarbonyl compound (Scheme VIII). Thus, β-hydroxy amides **50** and **52** were

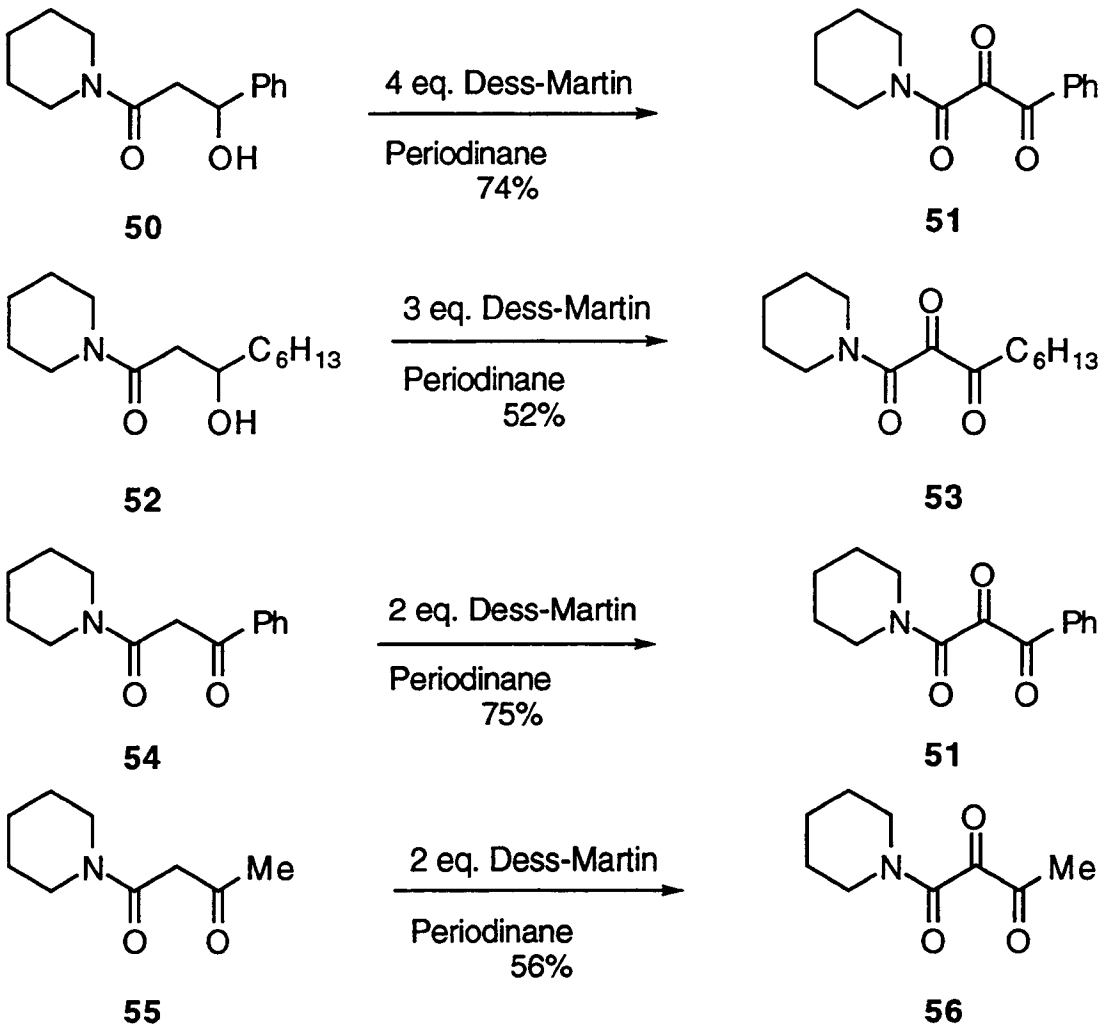
oxidized with Dess-Martin reagent to give tricarbonyl compounds **51** and **53** respectively. When the β-keto amides **54** and **55** were oxidized under the same conditions, the tricarbonyl products **51** and **56** were produced.



Scheme VI


EtO
R1
44
+
R2R3NH
45
DMAP/toluene
reflux, 18-43%
R3R2N
R1
46
R1=Ph, Me, i-Pr, n-Pr or PhCH2
R2=R3=Et, (CH2)2O or (CH2)2
p-NBSP, ZnCl2, EtOAc, -78°C, 77-100%
ONs
47
DBU
toluene
48
NH2
NH2
0-96%
p-NBSP= NO2
S
OH
NR2R3
49

Scheme VII



50 **51** **52** **53** **54** **51** **55** **56**

SchemeVIII

In a quite different approach, Pattenden and co-workers[22i] utilized a catalytic ruthenium dioxide oxidation of an acetylenic amide to furnish the tricarbonyl portion of rapamycin **67** (Scheme IX). The synthesis began with the iodide **57**[27], which was treated with sodium borohydride and tributyltin hydride to initiate addition of the radical from **57** to methyl acrylate. The resultant ester **58** was converted to the corresponding aldehyde **59** by initial reduction to the alcohol with diisobutylaluminum hydride followed by oxidation with pyridinium chlorochromate and sodium acetate. Wittig

olefination of **59** gave the dibromide **60** which was converted to the terminal acetylene **61** with *n*-butyllithium. The acetonide of **61** was hydrolyzed and the resulting diol was protected as the bis(*t*-butyldimethylsilyl) ether **62**. Metallation of **62** followed by reaction with carbon dioxide gave the carboxylic acid **63**. Coupling of the piperidine **64** with **63** using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate gave the acetylenic amide **65**. Oxidation with a ruthenium dioxide sodium periodate mixture afforded the tricarbonyl system **66** in low yield. Quantitative deprotection with hydrogen fluoride in acetonitrile gave the tricarbonyl portion of rapamycin **67** as a 1:1 mixture of diastereoisomers which were cleanly separated by silica gel column chromatography.

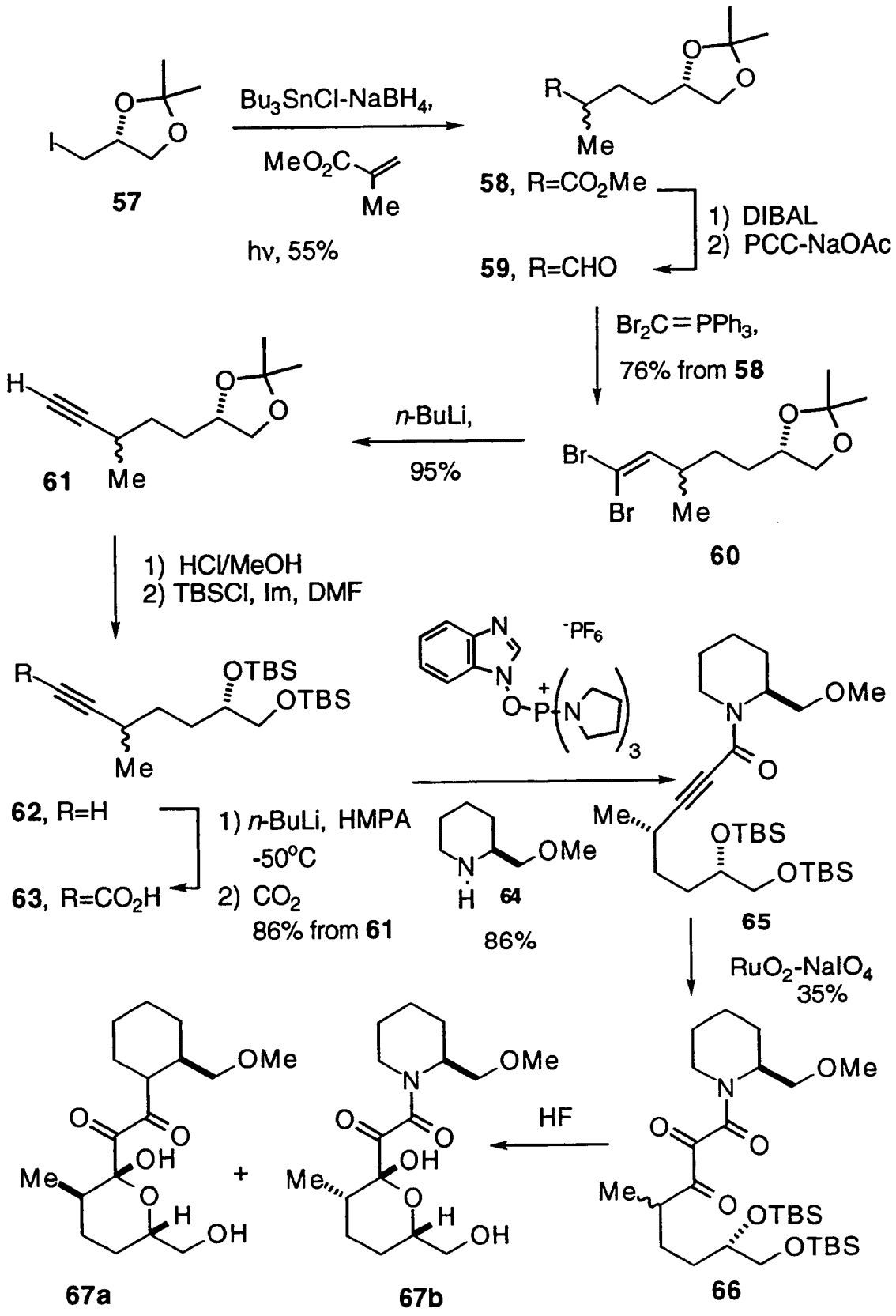
The Rao[22j] group also used Dess-Martin periodinane to effect oxidation to the rapamycin tricarbonyl subunit **83** near the end of their synthetic route. Their synthesis also utilized a double elimination following the coupling of the epoxy chloride **73** with the (*R*)-4-bromo-2-methylbutanolsilyl ether **72** to give the acetylenic compound **74**. Two Sharpless epoxidations were employed in the formation of **69** and **76** to impart the desired stereochemistry in the final product.

The Rao synthesis began with the Sharpless asymmetric epoxidation of alcohol **68** with (+)-diethyl tartrate as the chiral auxiliary to give **69** in 95% ee (Scheme X). The epoxide was regioselectively opened with trimethylaluminum to yield diol **70**. Periodate cleavage of **70** followed by treatment with sodium borohydride gave the terminal alcohol, and subsequent protection with *t*-butyldiphenylsilyl chloride in the presence of imidazole resulted in the silyl ether. The benzyl ether was cleaved by catalytic

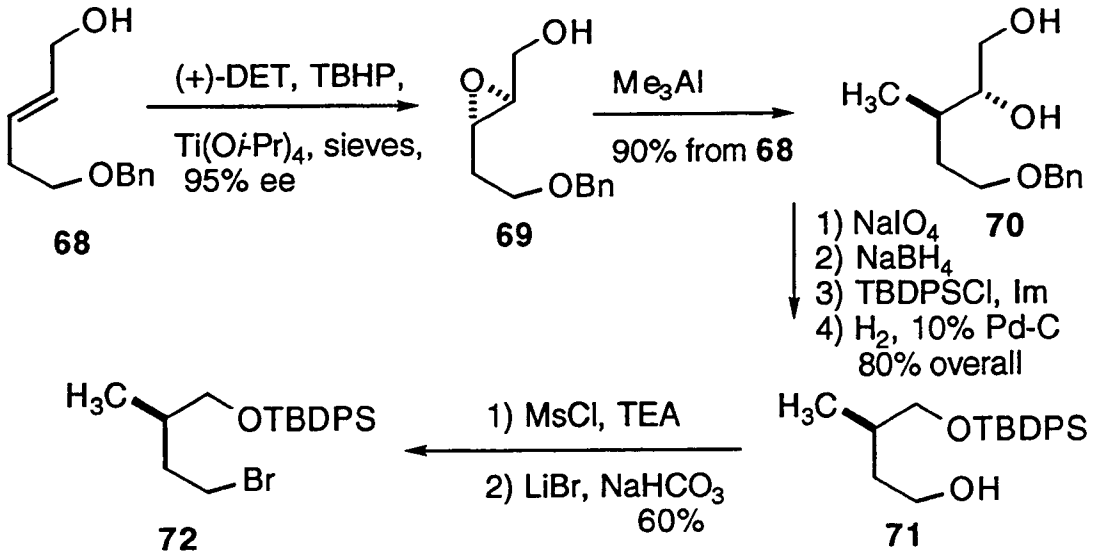
hydrogenolysis to give the alcohol **71**, and the alcohol was converted to the corresponding bromide **72** by formation of the mesylate followed by displacement with lithium bromide.

The chloroepoxide **73** was treated with lithium amide and then coupled with **72** to give the acetylene **74** (Scheme XI). The latter was hydrogenated to the cis olefin **75** over Lindlar's catalyst. Sharpless epoxidation of **75** gave the epoxy alcohol **76** (in 85% ee) which was reduced regioselectively to afford the diol **77**. Desilylation of **77** was followed by protection of the diol to furnish the acetonide **78**, which upon Swern oxidation yielded the aldehyde **79**. Conversion of **79** to a β-hydroxy ester was accomplished by a Reformatsky reaction with zinc and ethyl bromoacetate which gave the ester as a 1:1 mixture of diastereomers. Hydrolysis of the ester provided the corresponding acid **80** which was coupled with (*S*)-methyl pipecolate **81** by first activating the acid as its pentafluorophenyl ester. Treatment of the amide resulting from coupling **81** to this ester with Dess-Martin periodinane in situ gave the tricarbonyl compound **82**. Hydrolysis of this material furnished the desired rapamycin tricarbonyl subunit **83**.

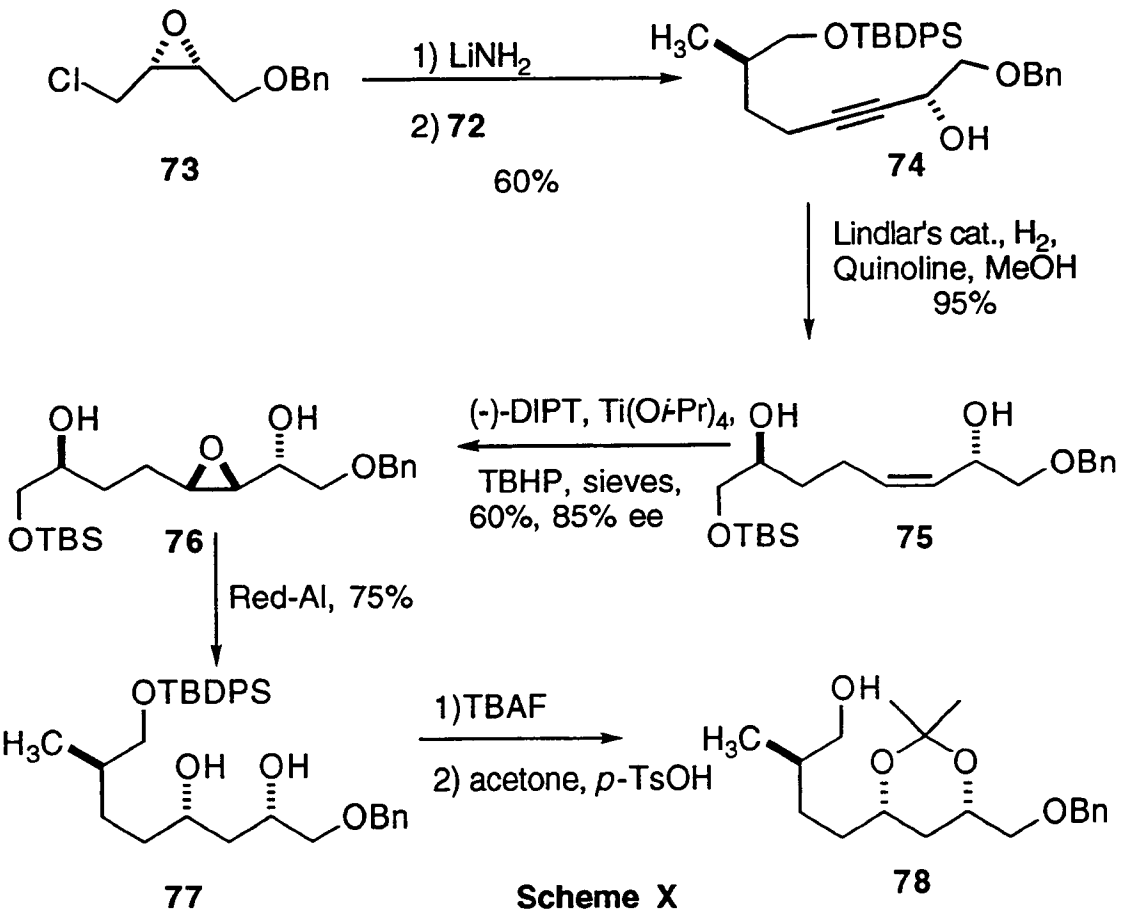
Mikami and co-workers[22k] prepared the C10-C15 segment **89** of rapamycin through an asymmetric carbonyl-ene reaction involving the (*S*)-binaphthol-titanium chiral complex **86** as catalyst (Scheme XII). The synthesis began with the previously prepared[28] homoallylic ether (*R*)-**84**, which when combined with the glyoxylate **85** in the presence of 10 mole % of (*S*)-**86** afforded hydroxy ester **87** with 97:3 diastereoselectivity. The exo methylene group was converted to the corresponding ketone **88** via ozonolysis, and the tosylhydrazone of **88** was reduced with catecholborane to give the C10-C15 rapamycin segment **89** after treatment with sodium acetate.


Bu3SnCl-NaBH4,
MeO2C
Me
hv, 55%
57
58, R=CO2Me
1) DIBAL
2) PCC-NaOAc
59, R=CHO
Br2C=PPh3,
76% from 58
n-BuLi,
95%
61
Me
60
1) HCl/MeOH
2) TBSCl, Im, DMF
OTBS
OTBS
62, R=H
1) n-BuLi, HMPA
-50°C
2) CO2
86% from 61
63, R=CO2H
-PF6
64
86%
OMe
65
RuO2-NaIO4
35%
66
HF
67a
67b

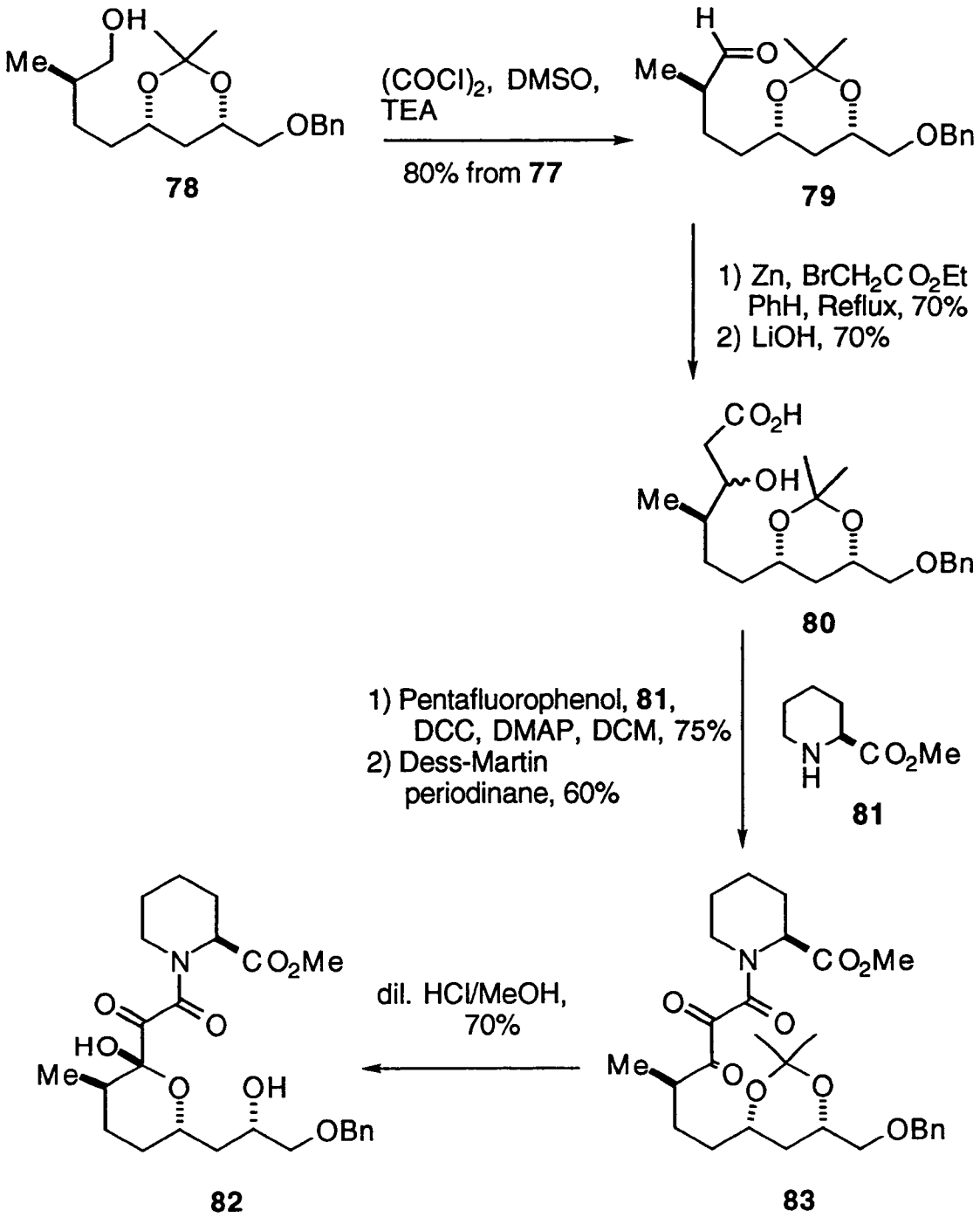
Scheme IX



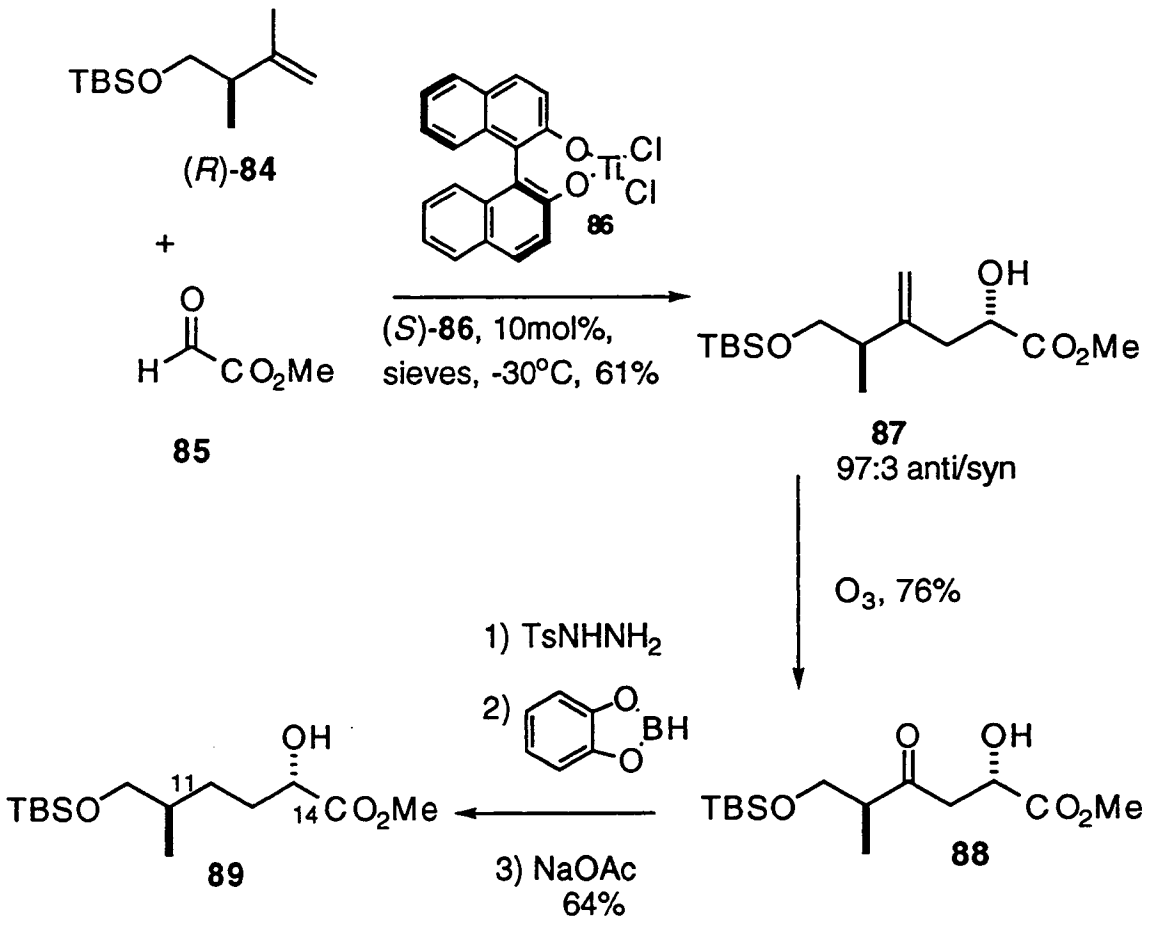
Scheme XII



Scheme X



Scheme XI, continued

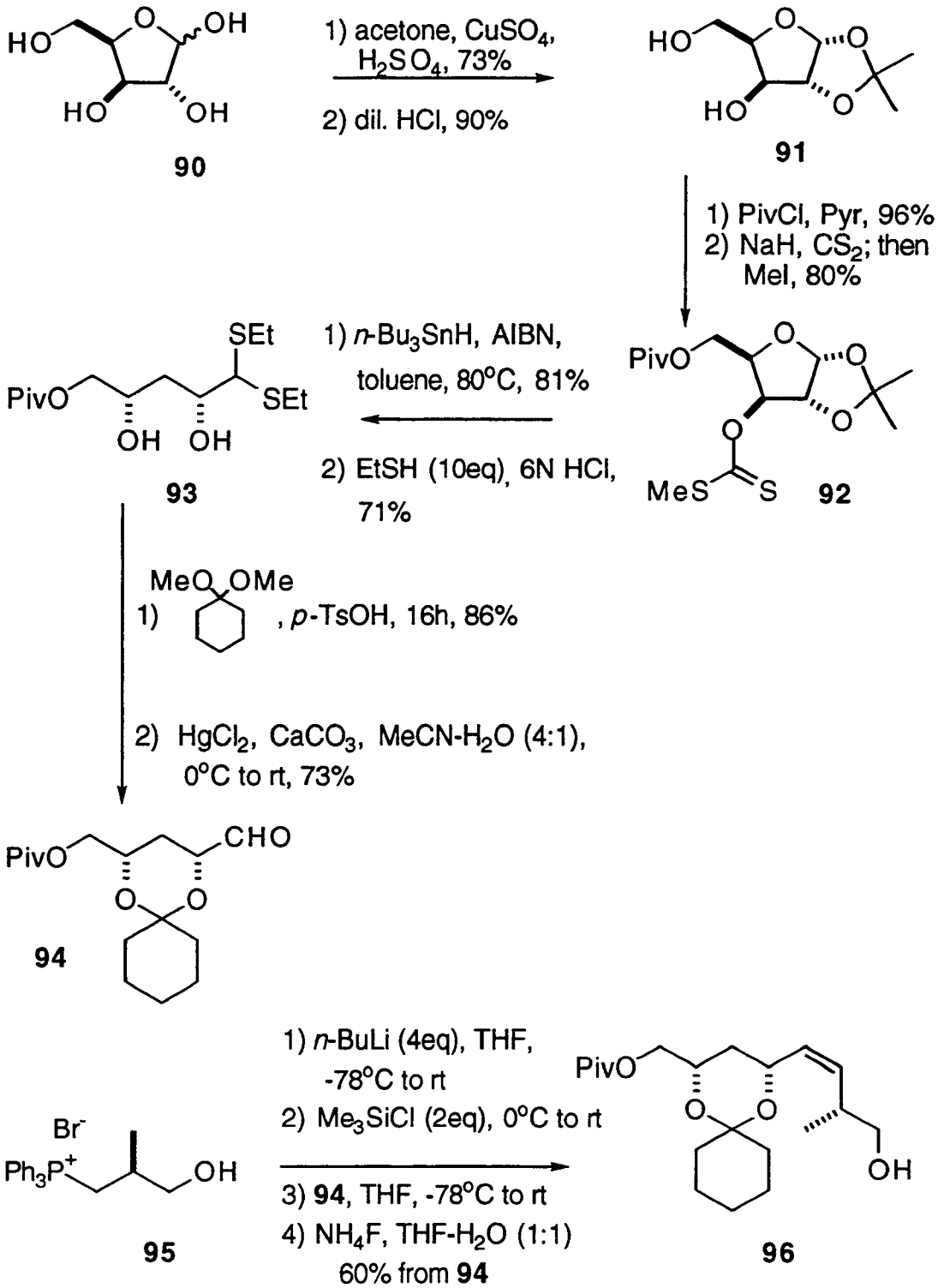


Scheme XII

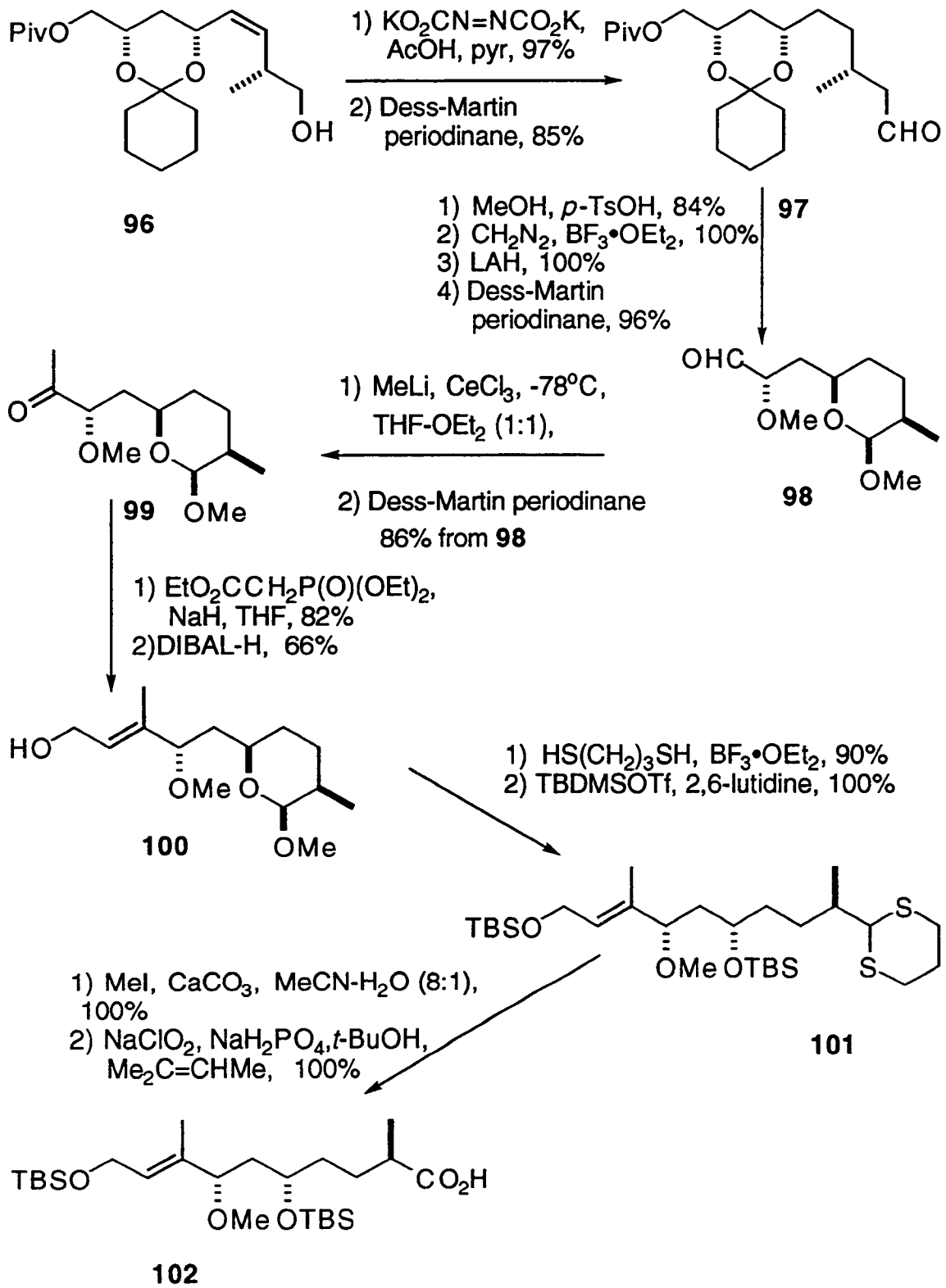
White and Jeffrey[221] made use of a Chan rearrangement[29] and oxidation with *m*-chloroperbenzoic acid in the later stage of their synthesis of the C8-C19 tricarbonyl segment of rapamycin (Scheme XIII). The synthesis started from D-(+)-xylose (**90**) which was converted to its acetonide **91** and the primary alcohol then protected as its pivalate. The remaining secondary alcohol was removed by conversion to its xanthate **92** followed by reduction of the xanthate with tri-*n*-butyltin hydride. Hydrolysis of the resulting acetal derivative in the presence of excess ethanthiol gave the thioacetal **93**. This was converted to the aldehyde **94** by first protecting the diol functionality as

its cyclohexylidene derivative and then by simultaneous hydrolysis of both the ketal and thioacetal in the presence mercurous chloride.

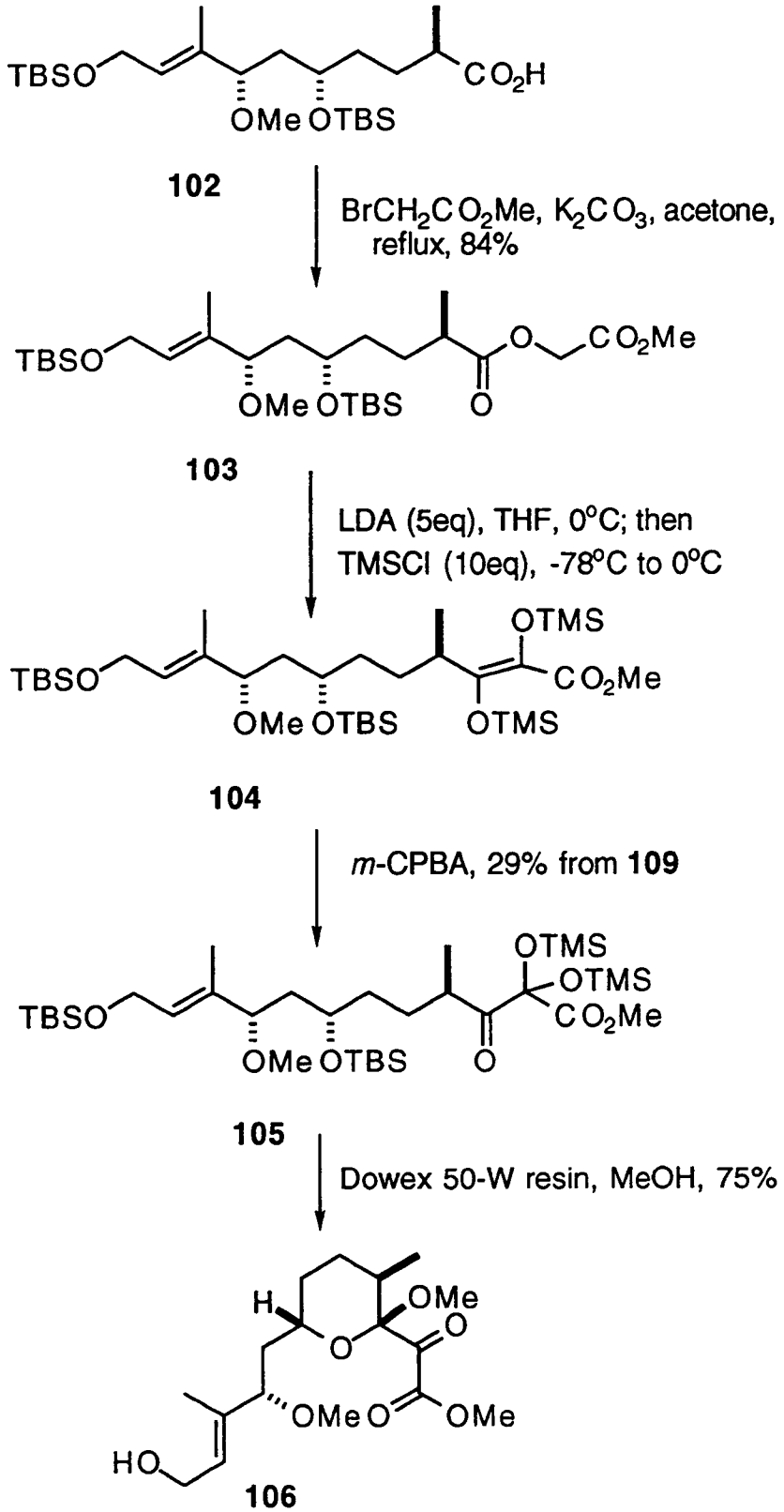
The phosphonium salt **95**[30] was treated with *n*-butyllithium, the primary alcohol was protected in situ as its trimethylsilyl ether and the silylated phosphorane was then coupled with **94**. The trimethylsilyl ether was immediately removed to give the alcohol **96**. The olefin of **96** was reduced with diimide and the primary alcohol was oxidized with Dess-Martin periodinane to give the aldehyde **97**. Cleavage of the cyclohexylidene protecting group by acidic methanolysis was accomplished in good yield and led to the cyclic acetal which was converted to its methyl ether with diazomethane. The pivalate was reduced to give a primary alcohol which was oxidized to the aldehyde **98** upon treatment with Dess-Martin periodinane. This aldehyde was transformed into methyl ketone **99** by treatment with methyllithium followed by oxidation of the resulting alcohol with Dess-Martin periodinane. Ketone **99** was condensed with the anion of triethyl phosphonoacetate to give an α,β-unsaturated ester which was reduced with diisobutylaluminum hydride to furnish the alcohol **100**. The methyl acetal of **100** was opened with 1,3-propandithiol in the presence of boron trifluoride etherate to give the corresponding dithiane. Both alcohol functionalities were then protected as *t*-butyldimethylsilyl ethers to give the bis silyl ether **101**. The dithiane of **101** was removed, and the resulting aldehyde was oxidized to yield the carboxylic acid **102** which was coupled with methyl bromoacetate to give the α-(acyloxy)acetate **103**. The ester **104** was formed by trapping the ene-diolate of **104** obtained under the conditions of the Chan rearrangement. Oxidation of **104** gave the β-keto ester **105** and the four silyl groups were removed in methanol over acidic resin to produce the tricarbonyl subunit **106** of rapamycin.


1) acetone, CuSO4, H2SO4, 73%
2) dil. HCl, 90%
90
91
1) PivCl, Pyr, 96%
2) NaH, CS2; then MeI, 80%
92
1) n-Bu3SnH, AIBN, toluene, 80°C, 81%
2) EtSH (10eq), 6N HCl, 71%
93
1) , p-TsOH, 16h, 86%
2) HgCl2, CaCO3, MeCN-H2O (4:1), 0°C to rt, 73%
94
1) n-BuLi (4eq), THF, -78°C to rt
2) Me3SiCl (2eq), 0°C to rt
3) 94, THF, -78°C to rt
4) NH4F, THF-H2O (1:1)
60% from 94
95
96

Scheme XIII



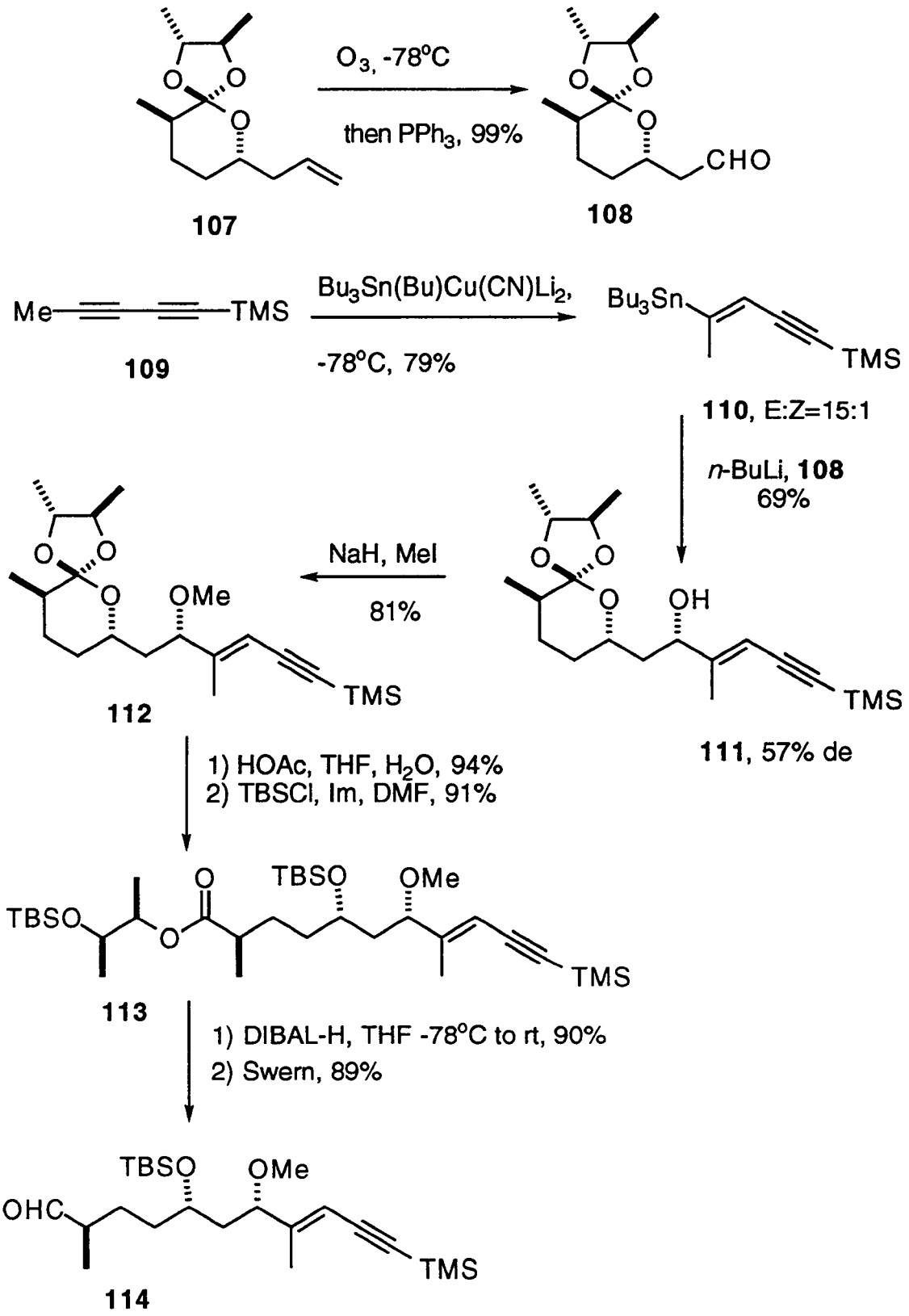
Scheme XIII, continued



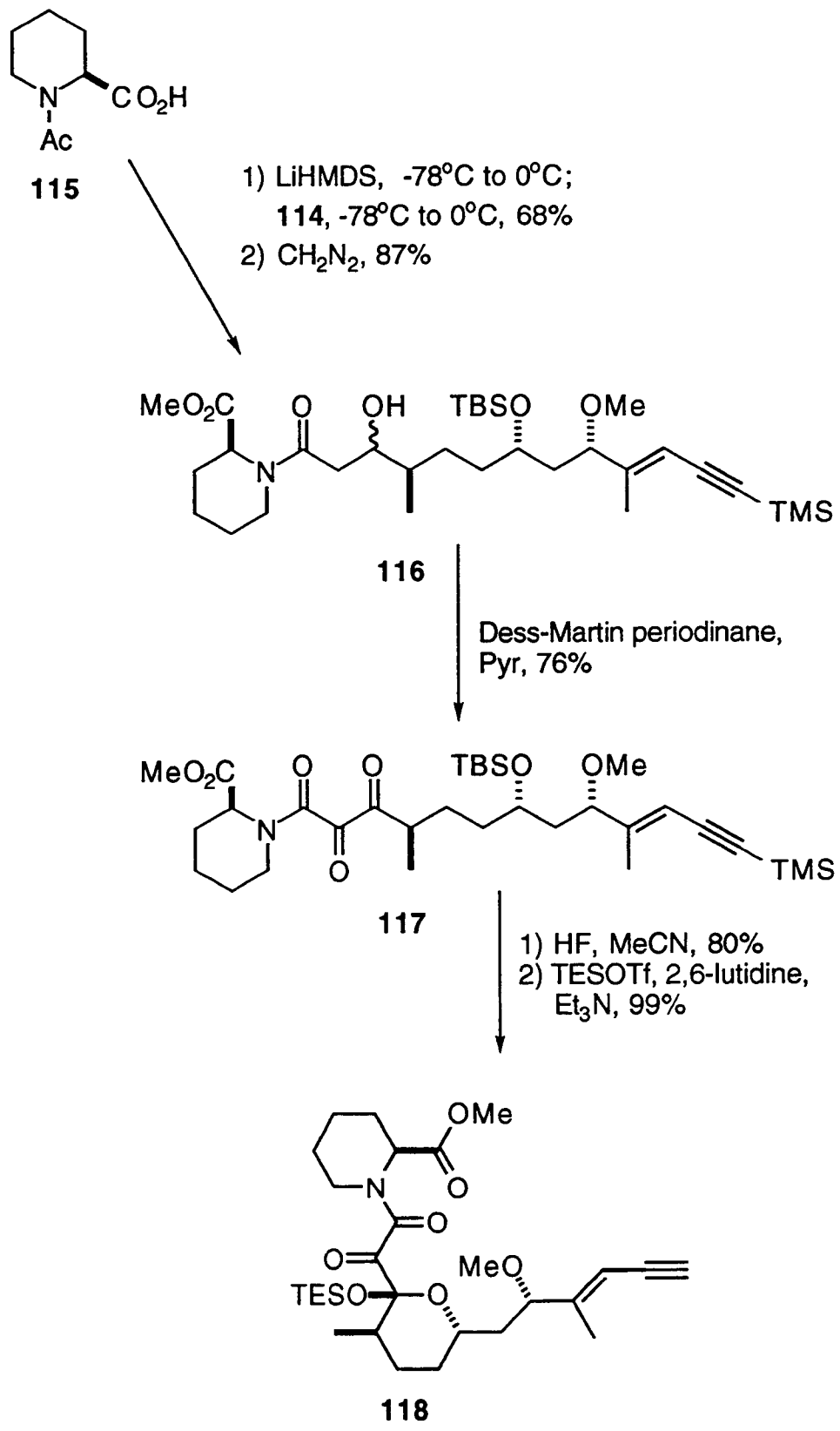
Scheme XIII, continued

Smith and co-workers[22m] used stannane chemistry along with Dess-Martin oxidation to produce the tricarbonyl functionality of rapamycin. Their synthesis began with the known alkene **107**[31] which underwent ozonolysis, giving the aldehyde **108** (Scheme XIV). The vinylstannane **110** resulting from hydrostannylation of the diyne **109** was reacted with **108** to afford alcohol **111** along with its diastereoisomer. The major alcohol **111** was converted to its methyl ether **112** and the ortho ester moiety of **112** was hydrolyzed, resulting in a dihydroxy ester which was silylated to give **113**. Reduction of **113** with diisobutylaluminum hydride gave an alcohol which upon Swern oxidation yielded the aldehyde **114**.

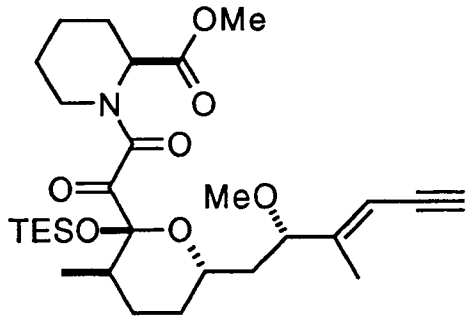
Coupling of *N*-acetyl-L-pipecolinic acid (**115**) with aldehyde **114** gave the carboxylic acid which was converted to methyl ester **116**. Treatment of **116** with Dess-Martin periodinane produced the tricarbonyl compound **117** after which the silyl ethers were cleaved to yield the hemiketal. The hemiketal was converted to the silylated ketal **118** and hydrostannylation of enyne **118** gave the dienyl stannane. Addition of iodine gave the iodide after which the methyl ester was cleaved with lithium iodide, resulting in the rapamycin tricarbonyl subunit **119**.


O3, -78°C
then PPh3, 99%
CHO
107
108
Me
TMS
109
Bu3Sn(Bu)Cu(CN)Li2,
-78°C, 79%
Bu3Sn
TMS
110, E:Z=15:1
n-BuLi, 108
69%
OH
TMS
111, 57% de
NaH, MeI
81%
OMe
TMS
112
1) HOAc, THF, H2O, 94%
2) TBSCl, Im, DMF, 91%
TBSO
O
TBSO
OMe
TMS
113
1) DIBAL-H, THF -78°C to rt, 90%
2) Swern, 89%
TBSO
OMe
OHC
TMS
114

Scheme XIV

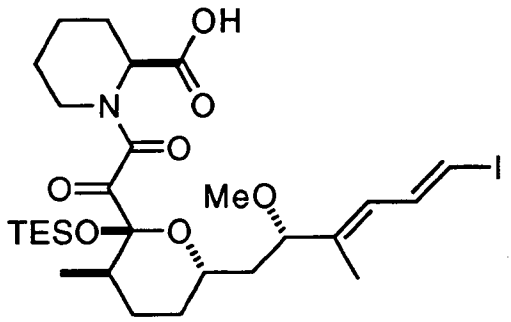


Scheme XIV, continued



118

1) Bu_3SnH, AIBN, 55%
2) I_2, 97%
3) LiI, pyr, reflux, 56%



119

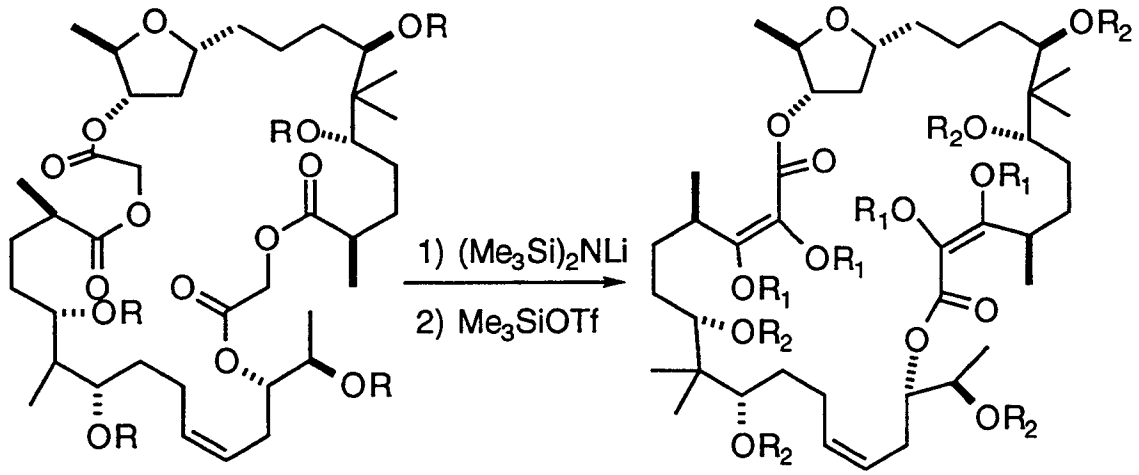
Scheme XIV, continued

Chapter II. Approaches to the Tricarbonyl Subunit of Rapamycin

The approach which we initially chose to introduce the tricarbonyl moiety of rapamycin was based on previous work done in the White group on the total synthesis of boromycin (**123**).[32] During the later stages of the synthesis of **123**, White and co-workers made use of a double Chan rearrangement[29] to contract a 34-membered ring and form the bis α,β-enediolate **121** from the bis α-acyloxyacetate **120** (Scheme XV). The deprotected α,β-enediolate **121** cyclized to the heptaol **122** upon treatment with tetra-n-butylammonium fluoride and then with hydrochloric acid.

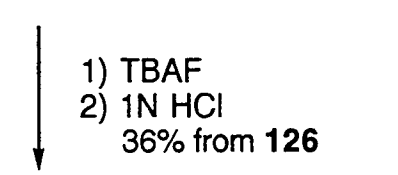
Following this precedent it was postulated that a simpler system (e.g. **124**) could be converted to the tricarbonyl precursor of rapamycin **127** by making use of an analogous Chan rearrangement (Scheme XVI). The resultant α,β-enediolamide **126** could, in principle, be deprotected and oxidized to give the desired rapamycin tricarbonyl subunit **127**.

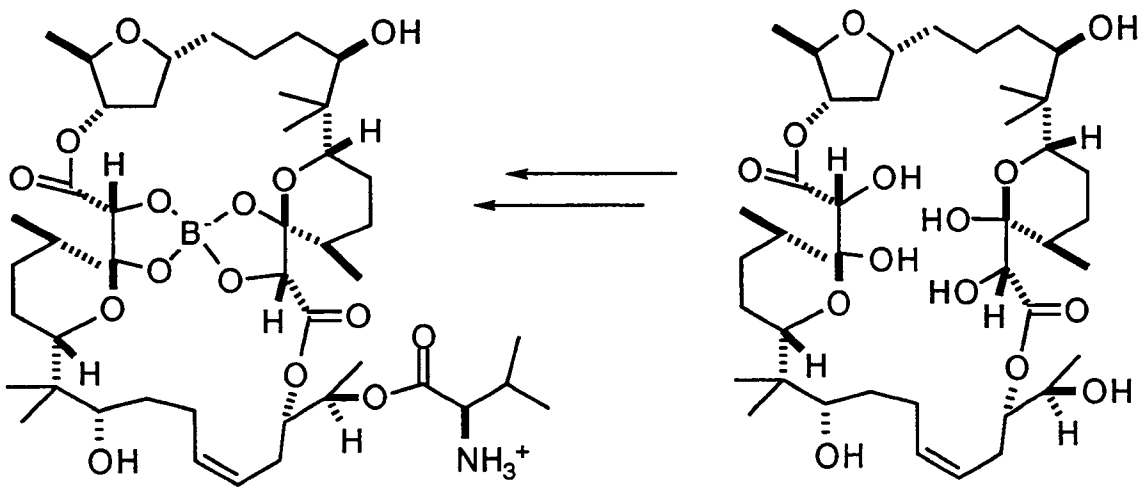
An approach along this line was initiated with the conversion of commercially available DL-pipecolinic acid (**128**) to methyl *N*-chloroacetylpipecolate (**131**). Two possible routes from **128** were examined for this purpose (Scheme XVII). The first path involved treatment of **128** with chloroacetyl chloride[35] to give chloroacetyl pipecolinic acid (**129**) which was esterified with diazomethane to yield the *N*-chloroacetylpipecolate **131**. The second route to **131** was accomplished by esterification of **128** with methanol and sulfuric acid to give methyl pipecolate **130**. By contrast, an attempt to convert **128** to **130** with diazomethane failed. Methyl *N*-chloroacetylpipecolate (**131**) was generated from **130** by addition of chloroacetyl chloride.



120, R=TBDMS

121, R_1=TMS, R_2=TBDMS

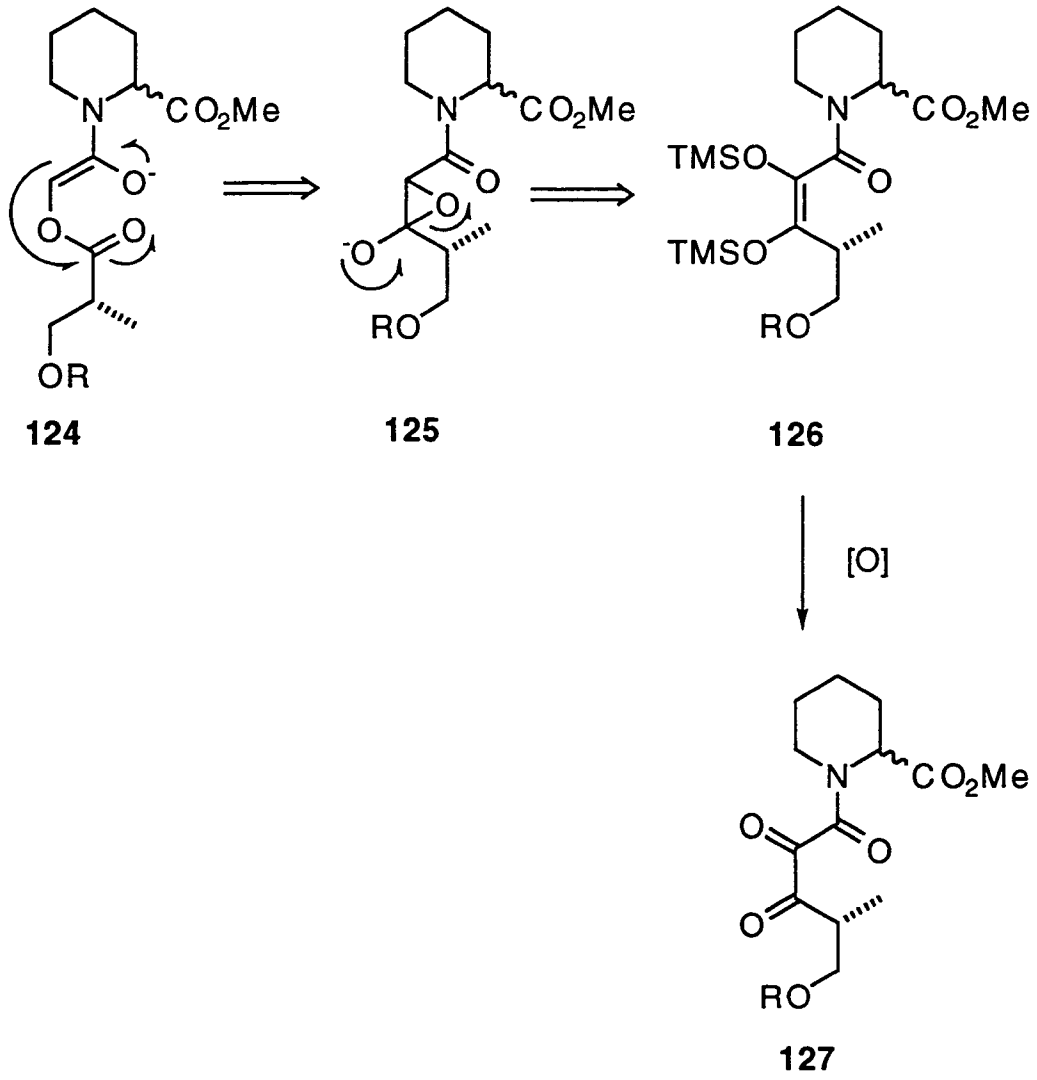




123

122

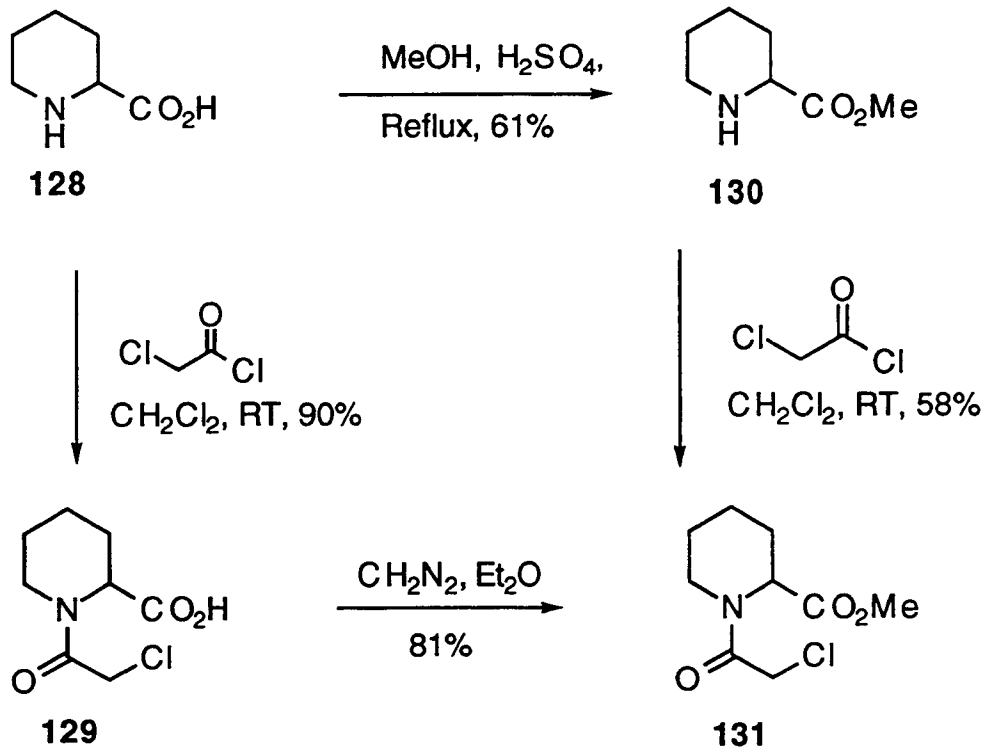
Scheme XV



124 **125** **126**

127

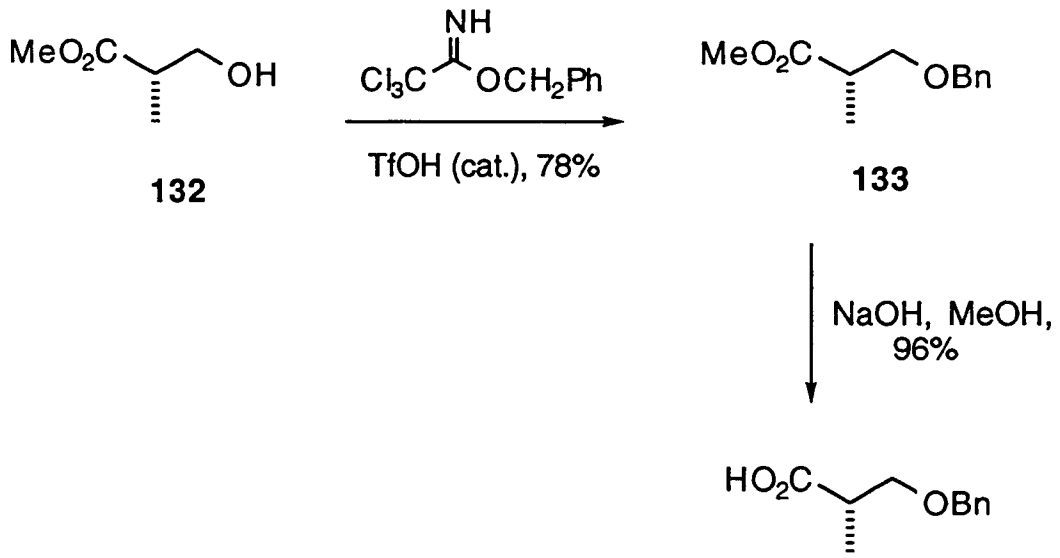
Scheme XVI



128 **130** **129** **131**

Scheme XVII

The carboxylic acid required for coupling with **134** was synthesized in two steps from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate (**132**) (Scheme XVIII). Thus, **132** in a mixture of cyclohexane and dichloromethane was treated with 1.5 equivalents of benzyl trichloroacetimidate and a catalytic amount of triflic acid[34,35] to give the 3-benzyloxy-2-methylpropionate **133**. Basic hydrolysis of **133** in methanol furnished the carboxylic acid **134**.



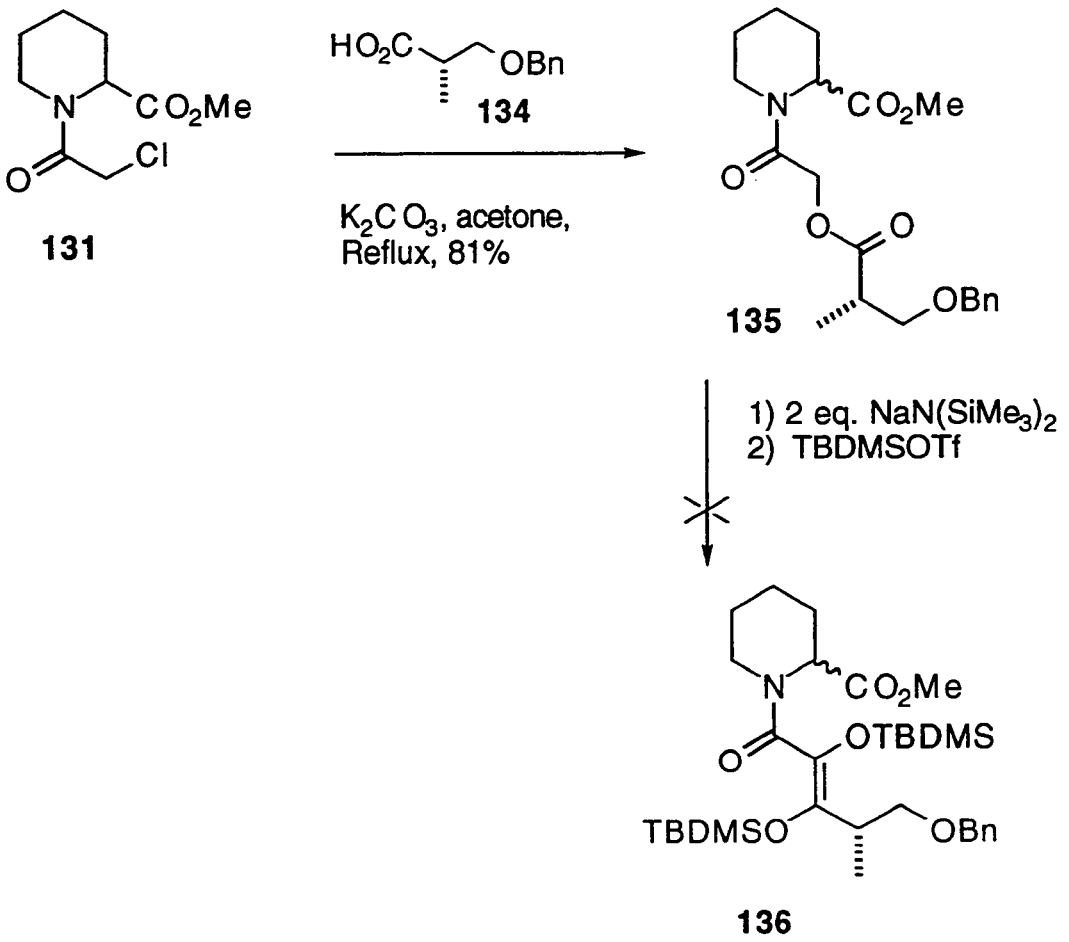
132 **133** **134**

Scheme XVIII

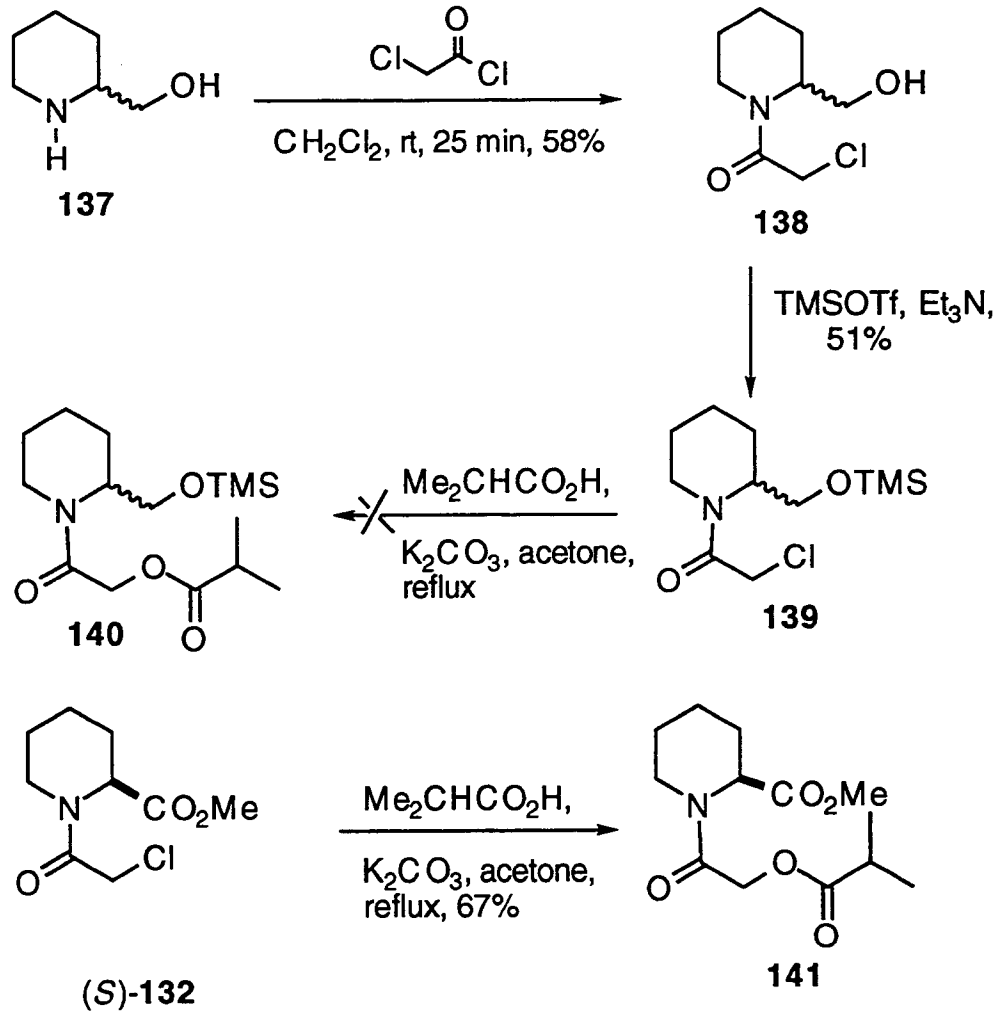
Coupling of **131** with **134** was effected with potassium carbonate in refluxing acetone and gave the α-acyloxy amide **135** as a mixture of two diastereoisomers in excellent yield (Scheme XIX). However, when Chan rearrangement of **135** was attempted by treatment with two equivalents of sodium bis(trimethylsilyl)amide followed by *t*-butyldimethylsilyl trifluoromethanesulfonate, an inseparable mixture of many products was obtained. When other bases, such as lithium diisopropylamide and lithium bis(trimethylsilyl)amide, or trapping agents such as trimethylsilyl chloride were used, complete substrate decomposition or multi-component mixtures were obtained. No trace of the protected α,β-enediolamide **136** could be found in the mixture.

In response to this disappointing result, a model study designed to synthesize the piperidine system **140** was investigated (Scheme XX). This study, which masks the pipecolate ester as a protected alcohol, began by acetylation of DL-2-piperidinemethanol (**137**) with chloroacetyl chloride to give **138**. The alcohol was converted to its trimethylsilyl ether **139**, but,

coupling of **139** with isobutanoic acid under the same conditions as used with **135** led only to decomposition of the starting materials. By contrast, *N*-chloroacetylpipecolate **132** underwent coupling with isobutanoic acid to give **141** in good yield. Unfortunately, the pipecolinic acid derivative **141** also gave inseparable multi-component mixtures under Chan rearrangement conditions.[29]



Scheme XIX

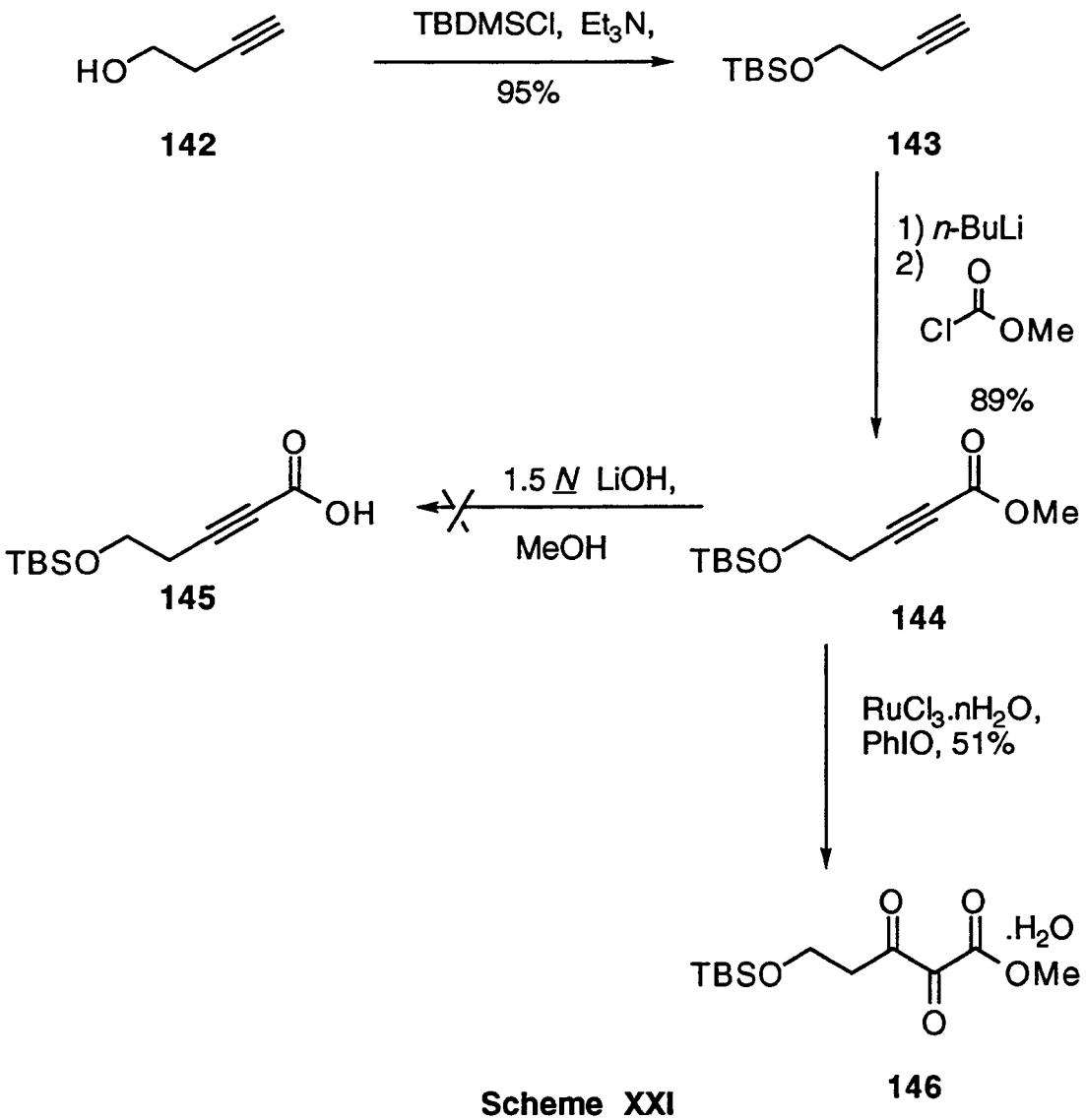


Scheme XX

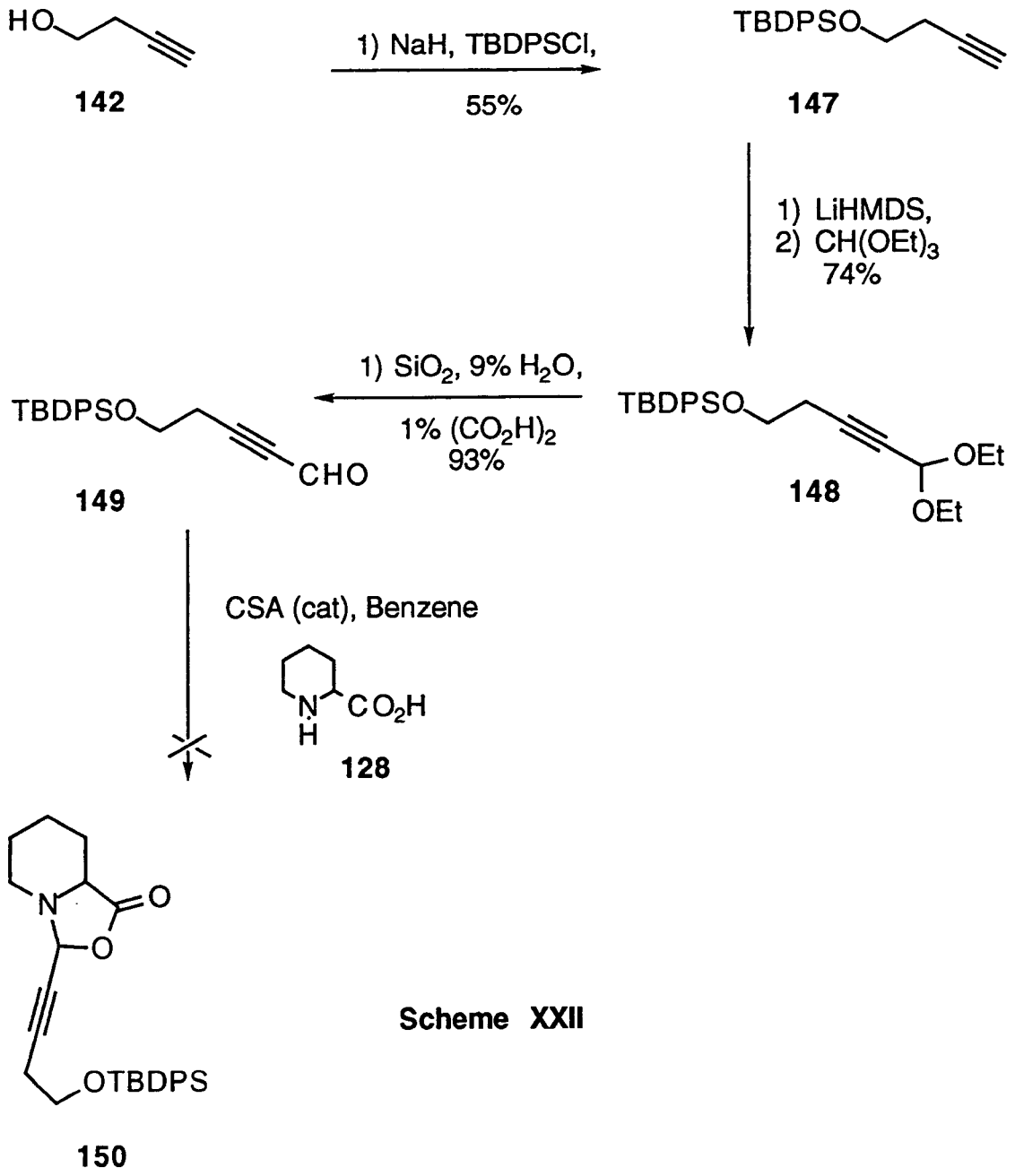
The failure to effect the rearrangement of **135** and **141** to an enediolate system prompted a search for an alternative method to secure the tricarbonyl moiety of rapamycin. The preparation of α-diketones by oxidation of acetylenes has been well studied[36a-e] and appeared to offer an attractive entry to the 1,2,3-tricarbonyl unit needed for rapamycin. A model system was constructed by first protecting the alcohol of 3-butyn-1-ol (**142**) with *t*-butyldimethylsilyl chloride to give the silyl ether **143** (Scheme XXI). Formation of the lithium acetylide by treatment of **143** with *n*-butyllithium followed by reaction with methyl chloroformate gave the acetylenic ester **144**

in excellent yield. However, when hydrolysis of **144** to the acetylenic acid **145** was attempted with lithium hydroxide or potassium hydroxide,[37] only decomposition of the starting material resulted. Even under mild hydrolysis conditions, for example with trimethylsilyl iodide in acetonitrile[38] or with aqueous sodium iodide and lutidine,[39] decomposition of **144** was still the principal result. Nevertheless, it was possible to oxidize the acetylenic ester **144** with catalytic ruthenium trichloride[36a] using freshly prepared iodosobenzene[40] as the stoichiometric oxidant to give the α,β-diketoester **146**. The latter was isolated as a hydrate, as was previously observed in a similar tricarbonyl system,[22c] and was evident from both IR and NMR spectroscopy.

As a consequence of this favorable result, it was hoped that it would be possible to construct an acetylene incorporating the requisite pipecolinic acid moiety (Scheme XXII). First, the butynol **142** was treated with sodium hydride in tetrahydrofuran and then with *t*-butyldiphenylsilyl chloride, to afford silyl ether **147**. When the acetylene was treated with zinc chloride and triethyl orthoformate[41] none of the desired diethyl acetal **148** was observed, but if **147** was initially deprotonated with lithium bis(trimethylsilyl)amide and then reacted with triethyl orthoformate, a good yield of **148** was isolated. An attempted hydrolysis of **148** using wet silica in dichloromethane gave no observable aldehyde, but addition of a small amount of oxalic acid[42] to the wet silica converted **148** to the aldehyde **149** in excellent yield. Unfortunately, all attempts to condense **149** with pipecolinic acid (**128**) to give **150** were unsuccessful, decomposition of the starting materials being the predominant outcome.


TBDMSCl, Et3N,
95%
HO
TBSO
142
143
1) n-BuLi
2)
Cl
OMe
89%
1.5 N LiOH,
MeOH
TBSO
OH
OMe
145
144
RuCl3.nH2O,
PhIO, 51%
.H2O
146

Scheme XXI



Scheme XXII

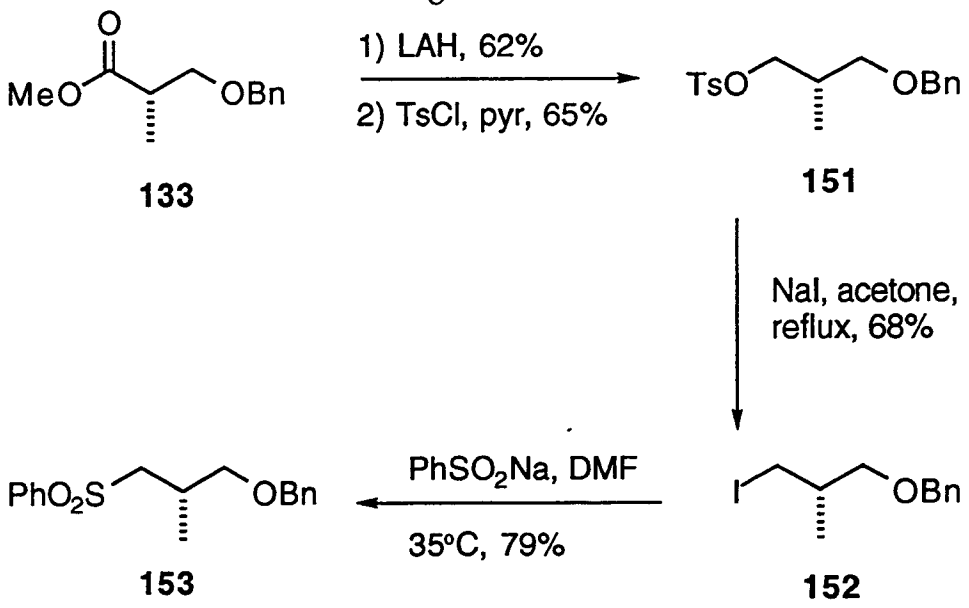
With the failure to prepare a suitable alkyne precursor to the 1,2,3-tricarbonyl segment of rapamycin, a new approach was initiated which envisioned raising the oxidation level of an α,β-unsaturated ester to that of a tricarbonyl system. This approach commenced from the benzyl ether of methyl (*S*)-3-hydroxy-2-methylpropionate (**132**). The ester **133** was reduced

with lithium aluminum hydride to give an alcohol which was converted to its tosylate **151** with tosyl chloride in pyridine (Scheme XXIII). Displacement of **151** with NaI gave the iodide **152** which underwent substitution of the iodine with benzenesulfinic acid sodium salt[35] to yield the sulfone **153**. In a separate sequence, epoxide **155** was obtained by reaction of (*R*)-glycidol (**154**) with *t*-butyldimethylsilyl chloride and imidazole.

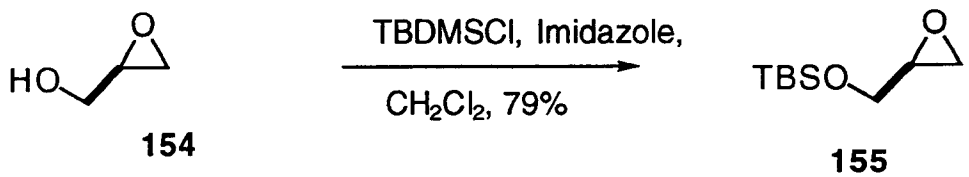
The sulfone **153** was converted to its anion with *n*-butyllithium in hexamethylphosphoramide, and addition of the epoxide **155** to this solution gave **156** in excellent yield. The sulfonyl group was cleaved from **156** with sodium-mercury amalgam to afford the alcohol **157** (Scheme XXIV). The secondary alcohol was protected as its *t*-butyldimethylsilyl ether and the benzyl ether was cleaved by catalytic hydrogenation to produce the primary alcohol **158**. Oxidation of **158** using freshly prepared Dess-Martin periodinane[43] furnished the desired aldehyde **159**. Wittig olefination of **159** with ethyl (triphenyphosphoranylidene)acetate gave the trans α,β-unsaturated ester **160**[44] in high yield, but all attempts at hydrolysis of this ester to the carboxylic acid **161** were unsuccessful. This unexpected outcome may have resulted from deprotonation of the γ-hydrogen of **160** to form a relatively stable conjugated anion, a hypothesis which is supported by the observed epimerization of **160**.

As an alternative to the Wittig approach via **160**, it was hoped[45] that aldehyde **159** could be coupled with the Wittig ylide **163** to give the pipecolamide **165**. Methyl (*S*)-*N*-chloroacetylpipecolate **131** was first treated with sodium iodide to yield methyl (*S*)-*N*-iodoacetylpipecolate **162** (Scheme XV). Reaction of **162** with triphenylphosphine gave the phosphonium salt **163**, which was deprotonated with a stoichiometric amount of sodium hydroxide[44] to yield the stable phosphonium ylide **164** quantitatively.

However, when coupling of aldehyde **159** and ylide **164** was attempted[45], no reaction was observed even under vigorous conditions, and the starting aldehyde **159** was recovered unchanged .

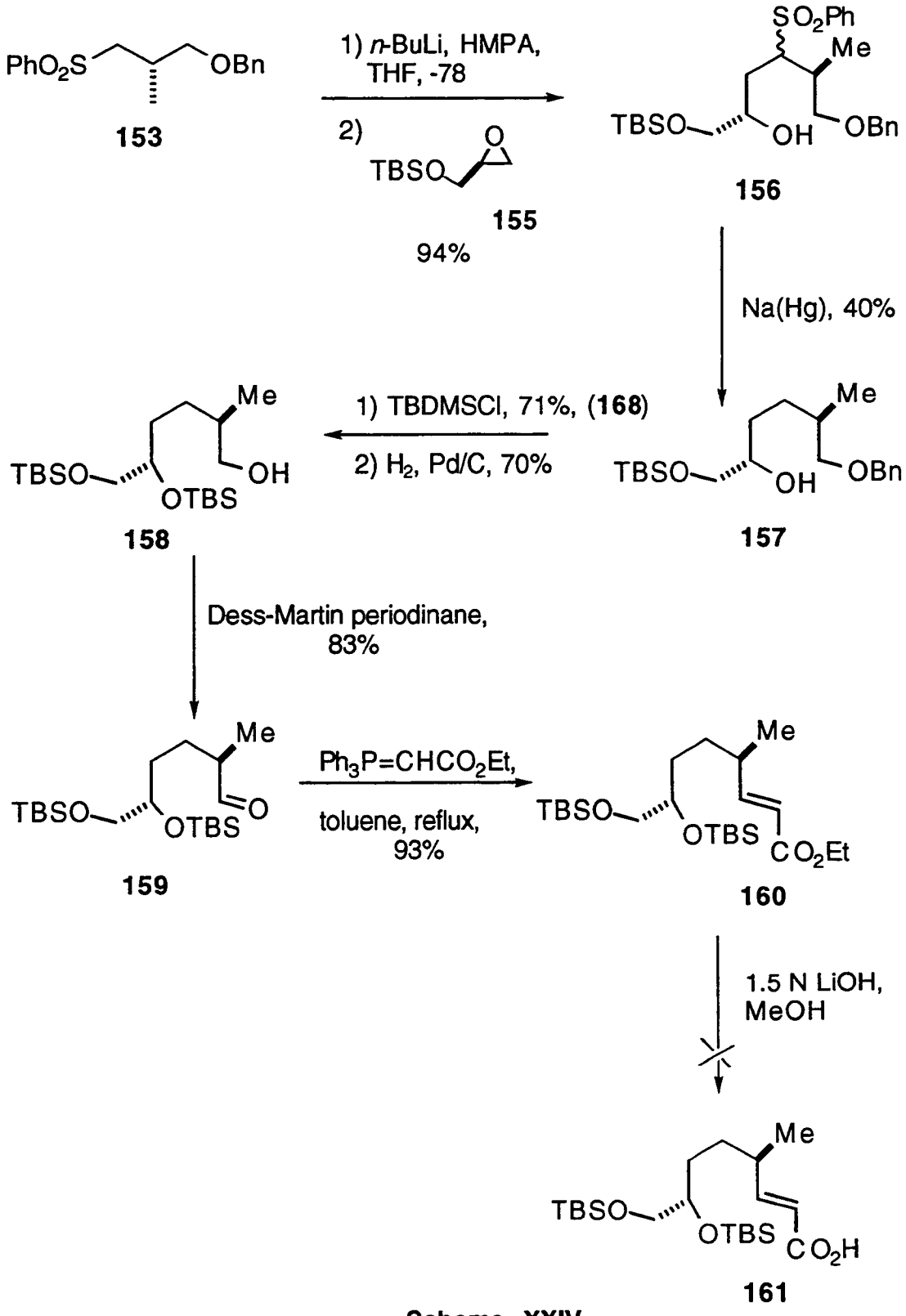


133 **151** **153** **152**

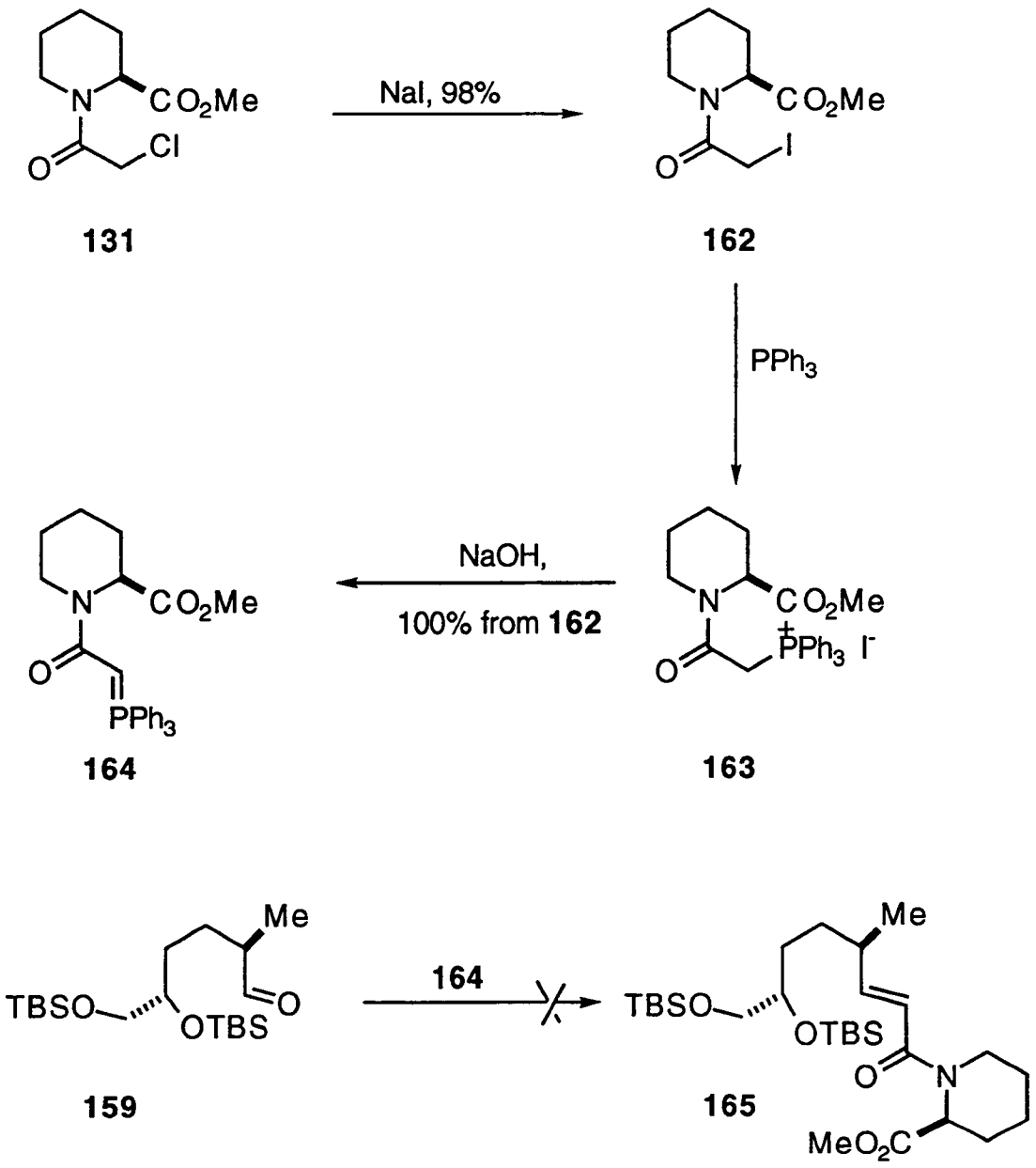


154 **155**

Scheme XXIII


PhO2S
OBn
153
1) n-BuLi, HMPA, THF, -78
2)
TBSO
O
155
94%
SO2Ph
Me
TBSO
OH
OBn
156
Na(Hg), 40%
Me
TBSO
OH
OBn
157
1) TBDMSCl, 71%, (168)
2) H2, Pd/C, 70%
Me
TBSO
OH
OTBS
158
Dess-Martin periodinane, 83%
Me
TBSO
O
OTBS
159
Ph3P=CHCO2Et,
toluene, reflux, 93%
Me
TBSO
OTBS
CO2Et
160
1.5 N LiOH, MeOH
Me
TBSO
OTBS
CO2H
161

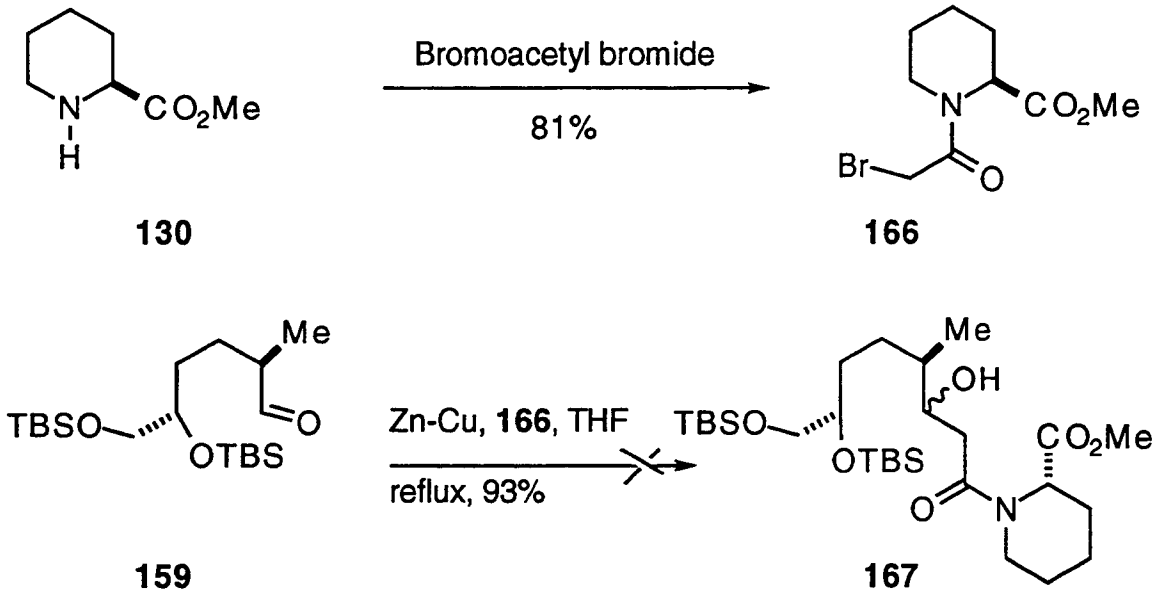
Scheme XXIV



Scheme XXV

As an alternative to the forgoing Wittig approach, it was surmised that the tricarbonyl region of rapamycin could be obtained with bromoacetyl pipecolate and aldehyde **159** using a Reformatski reaction[46]. Methyl pipecolate (**130**) was treated with bromoacetylbromide to give the (*S*)-methyl *N*-bromoacetylpipecolate (**166**), attempted coupling of the latter with aldehyde **159** in the presence of a zinc-copper couple failed to give the desired β-

hydroxyamide **167** (Scheme XXVI). With this failure, it was concluded that none of the strategies investigated in the course of this research would provide access to the tricarbonyl subunit of rapamycin.



130 **166**

159 **167**

Scheme XXVI

Chapter III. Conclusion

Much synthetic work has been directed by many research groups towards the synthesis of the tricarbonyl subunit of the potent immunosuppressants rapamycin and FK506. Several different strategies have been utilized by others to generate this tricarbonyl moiety. This project demonstrated that ruthenium trichloride and iodosobenzene is able to carry out oxidation of an alkyne to the hydrated tricarbonyl system **146** under mild conditions, but extension of this approach to the corresponding segment of rapamycin failed

Chan rearrangement of the pipecolinic acid containing derivative **135** was not successful. However, construction of the potential rapamycin tricarbonyl subunit precursor **167** via coupling of sulfone **153** and the epoxide **155** was accomplished in good yield and resulted in the alcohol **156**. This alcohol was converted to the aldehyde **159** with Dess-Martin periodinane. Unfortunately, all attempts to employ this aldehyde as a precursor to the desired tricarbonyl system were unsuccessful.

Chapter IV. Experimental

General Procedures. All anhydrous or air sensitive reactions were carried out in flame dried glassware under inert (argon or nitrogen) atmosphere. Stirring was accomplished with teflon coated magnetic stir bars. Starting materials and reagents were purchased from commercial suppliers and usually used without further purification. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from potassium and benzophenone. Dichloromethane (CH_2Cl_2), hexamethylphosphoramide (HMPA) and toluene were distilled from calcium hydride. Ethyl acetate (EtOAc), hexanes, and any other solvents used in reactions or for chromatographic purifications were reagent grade and distilled prior to use through glass.

Concentration of products from solutions was accomplished by use of a rotary evaporator under reduced pressure provided with a water aspirator, unless otherwise specified. Residual solvents were removed by vacuum at pressures less than 2 m m Hg. Syringes were oven dried at 160°C and cooled to room temperature in a desiccator over anhydrous calcium sulfate.

Neutral silica gel (E. Merck, 230-400 mesh ATM) was used for flash chromatography unless otherwise specified. All analytical thin layer chromatography was conducted with 2.5 x 7 cm precoated aluminum E. Merck TLC plates (0.2 mm of silica gel 60 F-254). Spots were visualized under ultraviolet light (uv), exposure to iodine vapor, or by heating with a heat gun after dipping or spraying with a 3% commercial solution of phosphomolybdic acid in ethanol or a solution prepared from 1 g of vanillin in 15 mL of 0.1 M H_2SO_4 and 85 mL of methanol.

Infrared (IR) spectra were measured with a Nicolet 5DXB FT-IR spectrometer. Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic

resonance (NMR) spectra were obtained with either a Bruker AM 400 or AC 300 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. The ^1H NMR spectral data are reported in order of chemical shift, number of protons, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad), and coupling constant (J) in Hertz (Hz). Mass spectra (MS) were obtained using ether a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High resolution mass spectra were recorded using a Kratos MS-50 TC spectrometer.

DL-*N*-Chloroacetyl-2-pipecolinic Acid (129). To a suspension of DL-pipecolinic acid (434 mg, 2.66 mmol) in 10 mL of CH_2Cl_2 was added dropwise a solution of chloroacetyl chloride (310 mg, 2.74 mmol) in 10 mL CH_2Cl_2 at room temperature. The reaction was stirred for 18 min and quenched with 15 mL of water. To the mixture was added 300 mg of potassium carbonate and the biphasic mixture was shaken. The layers were allowed to separate, and the aqueous layer was washed with diethyl ether (2 x 30 mL) and the organic layer was discarded. The aqueous layer was acidified to pH 2 with 1 N hydrochloric acid and was extracted with Ethyl acetate (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give 487 mg (90%) of chloroacetyl-2-pipecolinic acid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (2H, bs), 5.36 (1H, d, J=1.8 Hz), 4.71 and 4.59 (1H, ABX, J_{AB}=21, J_{AX}=1 Hz), 4.21-4.07 (4H, m), 3.84 (1H, d, J=6 Hz), 3.34 (2H, td, J=4, 1 Hz), 2.32 (3H, d, J=5 Hz), 1.80-1.64 (4H, m), 1.64-1.30 (3H, m), 1.30-1.19 (2H, m), 0.88 (1H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.1, 166.4, 56.5, 52.3, 44.0, 41.1,

26.3, 24.9, 20.6; IR (neat) 3200-3000 broad, 2951, 2361, 1736, 1617, 1455, 1208, 1169, 1142, 1026, 934, 898, 787, 725, 667 cm^{-1}; HRMS calcd for $C_8H_{12}ClNO_3$ 205.05057 (M^+). Found 205.1 (M^+), 170.1, 160.0, 126.1, 84.1

Methyl DL-Pipecolate (130). To a solution of DL-pipecolinic acid (3.014 g, 23.30 mmol) in 70 mL of absolute methanol was added 8.0 mL of fuming sulfuric acid dropwise at room temperature. The solution was heated to reflux and stirred overnight. The cooled solution was neutralized to pH 7 with 3 M sodium hydroxide followed by addition of 25 g of potassium carbonate. The resulting mixture was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated by short path distillation. Further Kugelrohr distillation gave 2.05 g (61.3%) of **130** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (3H, s), 3.36 (1H, dd, J=4, 1 Hz), 3.09 (1H, d, J=4 Hz), 2.66 (1H, td, J=2, 0.6 Hz), 1.98 (1H, m), 1.81 (1H, m), 1.61-1.37 (4H, m), 1.26 (1H, d, J=1 Hz), 0.88 (1H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.1, 58.7, 51.9, 45.8, 29.3, 25.9, 24.1; IR (neat) 3353, 2936, 2855, 2789, 2365, 1740, 1439, 1358, 1331, 1257, 1204, 1127, 1053, 991, 902, 864, 756, 649 cm^{-1}.

Methyl DL-*N*-Chloroacetyl-2-pipecolate (131). From **129**: To a stirred solution of **129** (85.6 mg, 0.416 mmol) in 2 mL of diethyl ether was added dropwise a 0.3 M solution of diazomethane in diethyl ether until a yellow color persisted for 5 min. The solution was warmed gently to remove the excess diazomethane. Removal of the residual ether by Kugelrohr distillation gave 74.4 mg (81%) of **131** as a clear oil.

From **130**: To a solution of **130** (347 mg, 2.42 mmol) in 10 mL CH_2Cl_2 was added dropwise a solution of chloroacetyl chloride (279 mg, 2.47 mmol)

in 4 mL of CH_2Cl_2 at room temperature. The solution was stirred for 10 min and quenched with 10 mL water. The aqueous phase was adjusted to pH 2 with 1 N hydrochloric acid. Diethyl ether (50 mL) was added and the biphasic mixture was shaken. The organic extract was washed with 15 mL of saturated sodium bicarbonate and 15 mL of brine. The organic extract was dried over magnesium sulfate, filtered and concentrated. The solvent was removed under high vacuum to give 307 mg (58%) of **131** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (2H, d, J=2 Hz), 4.57 (1H, ABX, J_{AB}=18, J_{BX}=4, J_{AX}=0.6 Hz), 4.22-4.08 (6H, m), 3.81-3.67 (10H, m), 3.34 (2H, td, J=4, 1 Hz), 2.23 (3H, d, J=5 Hz), 1.77-1.62 (8H, m), 1.62-1.49 (2H, m), 1.49-1.26 (3H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.1, 166.4, 56.5, 52.3, 44.0, 41.1, 26.9, 26.3, 24.9; IR (neat) 2951, 2862, 1744, 1653, 1433, 1358, 1342, 1327, 1283, 1242, 1211, 1165, 1144, 1111, 1080, 1028, 997, 955, 927, 870, 860, 821, 783, 659 cm^{-1}. HRMS calcd for $C_9H_{14}ClNO_3$ 219.06622 (M^+). Found 219.1 (M^+), 196.0, 184.1, 160.1, 142.1, 97.1, 84.1. For (*S*)-(L)-*N*-chloroacetyl 2-methyl pipecolate $[\alpha]_D^{21}$ = -67.7 (c=3.92, $CHCl_3$).

(2*S*)-Methyl 3-(Benzyloxy)-2-methylpropionate (133). To a solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (2.65 g, 22.5 mmol) in 45 mL of 2:1 cyclohexane-CH_2Cl_2 was added 6.24 mL of benzyltrichloroacetimidate (33.8 mmol) and catalytic triflic acid. The solution was stirred at room temperature for 24 h and then filtered to remove solids. The filtrate was washed with saturated sodium bicarbonate and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The crude mixture was purified by column chromatography on silica/hexane-EtOAc 4:1 to give 3.63 g (78%) of **133** as a pale oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (5H, m), 4.50 (2H, s), 3.50 (1H, dd, J=5.8 Hz and 5.8 Hz), 3.48 (1H, m), 2.78-2.73 (1H, m), 1.16 (3H, d, J=7.0 Hz). IR (neat) 3030, 2981, 2980,

2948, 2902, 2863, 1739, 1494, 1456, 1366, 1250, 1202, 1098, 1024, 994, 740, 699, 606 cm^{-1}. ^1H NMR and IR matched those from N. Reedy. LRMS calcd for $C_{12}H_{16}O_3$ 208.25 (M^+). Found 208 (M^+), 191, 177, 121, 107, 102, 91, 87, 77.

(2*S*)-3-(Benzyloxy)-2-methylpropionic Acid (134). To a stirred solution of **133** (1.64 g, 7.86 mmol) in 50 mL of absolute methanol was add 1.5 N lithium hydroxide (14.9 mL, 9.9 mmol) and the solution was stirred 24 h at room temperature. The methanol was removed by roto-evaporation and the basic aqueous layer was washed twice with CH_2Cl_2 (2 x 25 mL). The aqueous layer was acidified to pH 2 with 1 N hydrochloric acid then extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated to give 1.47 g (96%) of **134** as a pale oil. ^1H NMR (300 MHz, $CDCl_3$) δ 11.3 (1H, bs), 7.35-7.20 (5H, m), 4.55 (2H, s), 3.69-3.67 (2H, m), 2.80-2.75 (1H, m), 1.19 (3H, d, J=7 Hz); IR (neat) 3500-3063 broad, 3063, 3031, 2980, 2939, 2905, 2867, 2668, 2654, 1709, 1458, 1421, 1365, 1291, 1251, 1228, 1097, 944, 914, 740, 699 cm^{-1}. ^1H NMR and IR matched those from N. Reedy.

DL-Methyl *N*-12-(Benzyloxy)-(11*S*)-methylpropyloxoacetyl-2-pipecolate (135). To a solution of **131** (83.2 mg, 0.379 mmol) in 4 mL of dry acetone was added **134** (74 mg, 0.38 mmol) in 4 mL dry acetone followed by addition of 150 mg potassium carbonate. The reaction mixture was heated to reflux for 4.5 h. The cooled solution was filtered through florisil and diluted with diethyl ether. The filtrate was dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash column on silica/hexane-EtOAc 1:1 to give 115 mg (80.6%) of **135** as a oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (5H, m), 5.31 (2H, d, J=2 Hz), 4.92 (1H, dd, J=10, 5 Hz),

4.62 (1H, dd, J=10, 5 Hz), 4.53 (2H, d, J=0.3 Hz), 4.13 (2H, dd, J=8, 6 Hz), 3.80-3.72 (6H, m), 3.58-3.52 (2H, dd, J=4, 2 Hz), 3.38-3.23 (1H, m), 2.96-2.88 (1H, m), 2.27 (2H, m), 1.81-1.61 (4H, m), 1.57-1.31 (3H, m), 1.27 (3H, d, J=2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 171.4, 166.6, 138.3, 128.4, 127.6, 73.2, 71.9, 61.4, 52.3, 44.2, 42.5, 41.2, 40.2, 40.1, 27.1, 26.5, 25.1, 25.0, 24.4, 20.8, 14.0; IR (neat) 3032, 2947, 2861, 2017, 1734, 1684, 1670, 1663, 1559, 1541, 1507, 1497, 1456, 1437, 1362, 1339, 1325, 1206, 1181, 1163, 1143, 1100, 1019, 742, 700 cm^{-1}.

DL-*N*-Chloroacetyl-2-piperdene Methanol (138). To a solution of 2-piperdine methanol (299 mg, 2.60 mmol) in 20 mL CH_2Cl_2 was added a solution of chloroacetyl chloride (0.21 mL, 2.6 mmol) at room temperature. The reaction was stirred for 25 min and quenched with saturated sodium bicarbonate followed by extraction with ether (3 x 20 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. Flash column on silica/ hexane-EtOAc-MeOH 4.5:4.5:1 gave 287 mg (58%) of **138** as a oil. ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (1H, m), 4.39 (1H, ABX, J_{AB}=11, J_{AX}=4 Hz), 4.10 (3H, m), 3.84 (1H, t, J=3 Hz), 3.71 (1H, m), 2.05 (1H, s), 1.73-1.47 (10H, m), 1.31-1.26 (5H, m), .91-.83 (4H, m). IR (neat) 3403-3390, 2941, 2870, 1716, 1634, 1447, 1375, 1361, 1324, 1280, 1255, 1171, 1140, 1121, 1052, 1028, 994, 788, 662 cm^{-1}.

(*S*)-Methy *N*-(Isobutyrloxoacetyl-2-pipecolate (141). To a solution of **132** (57 mg, 0.26 mmol) in 8 mL of acetone was added 150 mg potassium carbonate and 0.024 mL isobutyric acid (0.26 mmol). The solution was warmed to reflux for 4.5 h, then the cooled was filtered through florisil. The florisil was rinsed with a small portion of ether and the combined filtrate was concentrated. The crude mixture was purified by flash column on silica/hexane-EtOAc 1:1 to

give 47 mg (67%) of **141** as a oil. $[\alpha]_D^{21}$= -50.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (1H, d, J=2 Hz), 4.81 (2H, dd, J=30, 5 Hz), 4.14 (0.3H, dd, J=10, 4 Hz), 3.76 (0.7H, d, J=4 Hz), 3.73 (1H, s), 3.65 (1H, d, J=16 Hz), 3.32 (1H, td, J=3, 4 Hz), 2.70 (1H, m), 2.28-1.27 (6H, m), 1.24 (6H, dd, J=2, 1 Hz), 1.05-.86 (1H, m); IR (neat) 3623-3613, 3474, 2947, 2866, 1750, 1734, 1679, 1448, 1384, 1354, 1327, 1249, 1209, 1192, 1159, 1149, 1098, 1017, 995, 950, 926, 901, 965, 824, 795, 779, 661 cm^{-1}.

4-*tert*-Butyldimethylsilyloxy-1-butyne (143). To a solution of 3-butyn-1-ol (1.19 g, 17.0 mmol) in 75 mL of dry THF under argon was added 3.8 g (34 mmol) of triethylamine followed by 3.8g (25 mmol) of *tert*-butyldimethylsilyl chloride. The solution was stirred two days at room temperature. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (2x40 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 95:5 gave 3.91g (95%) of **143** as a pale oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (2H, t, J=2 Hz), 2.39 (2H, td, J=2, 1 Hz), 1.96 (1H, t, J=1 Hz), 0.90 (9H, s), 0.86 (6H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 77.1, 69.2, 61.6, 25.8, 22.8, 18.2, -5.4; IR (neat) 3316, 2956, 2930, 2885, 2858, 1734, 1472, 1464, 1362, 1256, 1107, 838, 778 cm^{-1}. LRMS calcd for $C_{10}H_{20}OSi$ 184.1284 (M^+). Found 157, 145, 127, 109, 97, 73.

Methyl 5-*tert*-Butyldimethylsilyloxy-2-pentynoate (144). To a solution of **143** (286 mg, 1.55 mmol) in 2 mL dry THF under argon was added 1.16 mL (1.86 mmol) of 1.6 N n-butyllithium in hexanes at -78°C and the reaction was stirred for 1 h. To the reaction was added 0.72 mL (9.3 mmol) of methyl chloroformate and the reaction was stirred for 30 minutes then allowed to warm to 0°C for 1 hour. The reaction was quenched with 7 mL of saturated

sodium bicarbonate then diluted with ether. The phases were separated and the aqueous was extracted with ether (3x25 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 19:1 gave 334 mg (89%) of **144** as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (2H, t, J=2 Hz), 3.75 (3H, s), 2.55 (2H, t, J=2 Hz), 0.90 (9H, s), 0.08 (6H, s); IR (neat) 2955, 2933, 2860, 2243, 1720, 1468, 1437, 1412, 1388, 1256, 1112, 1078, 839, 779, 753 cm^{-1}.

α,β-Diketo Ester 146. To a solution of **144** (134 mg, 0.551 mmol) in 4.2 mL acetone was added freshly prepared iodosobenzene[43] (369 mg, 1.65 mmol) and 3 mg of $RuCl_3.nH_2O$. The reaction was stirred 27 h, then concentrated. Flash column on silica/hexane-EtOAc 1:1 gave 78.3 mg (51%) of **146** as a hydrated oil. ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (2H, s, shifts to 4.71 with D_2O), 3.94 (2H, t, J=2 Hz), 3.85 (3H, s), 2.86 (2H, t, J=2. Hz), 0.88 (9H, s), 0.075 (6H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.0, 169.5, 92.8, 58.5, 53.7, 39.5, 25.8, 18.2, -5.6; HRMS calcd for $C_{12}H_{24}O_5Si$ 276.4053 (M^+). Found 257, 229, 217, 187, 159, 145, 102, 89, 73; IR (neat) 3360 (broad), 2956, 2933, 2890, 2860, 1748, 1719, 1468, 1439, 1284, 1260, 1198, 1105, 940, 836 cm^{-1}.

***tert*-Butyldiphenylsilyl 3-Butynyl Ether (147).** To a solution of 3-butyn-1-ol (752 mg, 10.7 mmol) in 50 mL of THF was added 449 mg (11.2 mmol) of a 60% dispersion of sodium hydride in mineral oil at 0°C. The solution was stirred 1 hour at 0°C then 2.10 mL (12 mmol) of *tert*-butyldiphenylsilyl chloride was added. The reaction was warmed to room temperature and stirred for 2 days. The reaction was quenched with saturated sodium bicarbonate and extracted with ether (2x40 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and

concentrated. Flash column on silica/hexane-EtOAc 4:1 gave 1.808g (55%) of **147** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.66 (5H, m), 7.43-7.38 (5H, m), 3.78 (2H, t, J=2 Hz), 2.45 (2H, td, J=2, 1 Hz), 1.94 (1H, t, J=1 Hz), 1.05 (9H, t, J=1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 135.5, 133.5, 129.6, 127.6, 81.4, 69.1, 62.0, 26.7, 22.5, 19.1, 16.0; IR (neat) 3306, 3071, 3050, 3019, 3000, 2883, 2850, 1590, 1469, 1445, 1427, 1388, 1221, 1111, 1080, 1033, 1005, 937, 829, 738, 705, 639, 615 cm^{-1}.

5-(*tert*-Butyldimethylsilyloxy)pent-2-yne Diethyl Acetal (148). To a solution of **147** (39 mg, 0.1 mmol) in 25 mL of dry ether at -78°C was added 0.13 mL (0.13 mmol) of 1 M lithium bis(trimethylsilyl)amide in THF under argon. The solution was stirred for 5 minutes then warmed to 0°C for 30 minutes. To the reaction was added 0.022 mL (0.13 mmol) of freshly distilled triethylorthoformate and the reaction was slowly warmed to room temperature and stirred 8 hours. The reaction was quenched with saturated sodium bicarbonate, extracted with ether (3x30 mL) and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 4:1 gave 39 mg (74%) of **148** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (5H, m), 7.42-7.35 (5H, m), 5.23 (1H, t, J=0.5 Hz), 3.8-3.67 (4H, m), 3.60-3.52 (2H, m), 2.51 (2H, td, J=3, 0.4 Hz), 1.21 (6H, t, J=2 Hz), 1.05 (9H, t, J=1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 135.5, 133.4, 133.1, 129.8, 129.6, 129.3, 127.7, 127.6, 91.3, 83.2, 62.0, 61.1, 60.5, 58.4, 27.4, 26.7, 23.2, 22.7, 19.1, 18.4, 15.9, 15.0, 3.3; IR (neat) 3071, 3050, 2959, 2933, 2885, 2860, 2205, 1670, 1470, 1428, 1388, 1361, 1331, 1151, 1110, 1054, 1007, 822, 738, 705, 613 cm^{-1}.

5-*tert*-Butyldimethylsilyloxypent-2-ynal (149). To a suspension of silica gel (70-230 mesh) in 2.5 mL of CH_2Cl_2 at room temperature was added 0.30 mL

of 10 % aqueous oxalic acid solution. The suspension was stirred for 2 min. To the suspension was added 98 mg (0.24 mmol) of **148** in 0.5 mL of CH_2Cl_2. The reaction mixture was stirred for 4.5 h then 100 mg of solid sodium bicarbonate was added. The mixture was stirred for an additional 10 min then filtered. The solids were washed repeatedly with ethyl acetate and finally with a small (8 mL) portion of methanol. The combined organic filtrate was dried over magnesium sulfate, filtered and concentrated. Plate (chromatatron) chromatography with pentane-ether 9:1 gave 75 mg (93%) of **149** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (1H, d, J=0.3 Hz), 7.69-7.65 (5H, m), 7.44-7.36 (5H, m), 3.83 (2H, t, J=2 Hz), 2.65 (2H, t, J=2 Hz), 1.06 (9H, t, J=1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.9, 135.5, 133.1, 129.8, 127.7, 96.1, 88.3, 61.1, 26.7, 23.2, 19.1, 15.9, 3.3; IR (neat) 3071, 3050, 3020, 2999, 2957, 2933, 2858, 2280, 2205, 1669, 1468, 1428, 1387, 1137, 1110, 823, 738, 704, 614 cm^{-1}.

(2*R*)-3-(Benzyloxy)-2-methylpropanol. To a solution of **133** (5.29 g, 20.4 mmol) in 20 mL of dry ether under argon at 0°C was added a suspension of lithium aluminum hydride (773 mg, 20.4 mmol) in 50 mL of ether over 30 min. The reaction was warmed to room temperature and stirred for 30 min. The reaction was quenched with 2 mL of saturated sodium bicarbonate then 4 mL of water. The slurry was stirred for 15 min. Magnesium sulfate was added, and the resulting solids were filtered and washed with 200 mL of ether. The filtrate was concentrated and flash column on silica/hexane-EtOAc 2:1 gave 2.34 g (64%) of (2*R*)-3-(benzyloxy)-2-methylpropanol as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m), 4.52 (2H, s), 3.62 (2H, m), 3.55 (1H, t, J=2 Hz), 3.43 (1H, t, J=3 Hz), 2.50 (1H, b), 2.09 (1H, m), 0.88 (3H, d, J=2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.9, 128.4, 127.6, 127.5, 73.3, 67.7, 35.5, 13.4; IR

(neat) 3409 (broad), 3109, 3030, 2959, 2923, 2870, 1492, 1455, 1364, 1257, 1209, 1096, 1038, 994, 739, 699, 605 cm^{-1}. HRMS calcd for $C_{11}H_{16}O_2$ 180.1151 (M^+). Found 180 (M^+), 165, 107, 91, 79.

(2*S*)-1-(Benzyloxy)-2-methyl-3-(*p*-toluenesulfonyloxy)propane (151). To a solution of (2*R*)-3-(benzyloxy)-2-methylpropanol (2.34 g, 13.0 mmol) in 50 mL of pyridine was added *p*-toluenesulfonyl chloride (3.34 g, 17.6 mmol). The reaction was stirred for 2 days at room temperature. The reaction solution was poured into 10 N hydrochloric acid and ice. The aqueous layer was extracted with ether (3x50 mL). The combined extracts were washed with water, saturated copper sulfate, and brine. The combined extracts were dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 3:1 gave 2.88 g (66%) of **151** as an oil. $[\alpha]_D^{21}$ = +4.8 (c=2.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, J=1 Hz), 7.30 (7H, m), 4.40 (2H, s), 4.02 (2H, m), 3.33 (2H, m), 2.42 (3H, s), 2.10 (1H, m), 0.94 (3H, d, J=2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.5, 138.1, 132.9, 129.7, 128.2, 127.8, 127.5, 127.3, 73.0, 72.1, 71.0, 33.6, 21.5, 13.5, 4.6; IR (neat) 2968, 2925, 2862, 1456, 1361, 1181, 1098, 975, 944, 836, 816, 741, 698, 667 cm^{-1}; LRMS calcd for $C_{18}H_{22}O_4S$ 454.45 (M^+). Found 334, 173, 155, 107, 91.

(2*S*)-1-(Benzyloxy)-2-methyl-3-iodopropane (152). To a solution of **151** (2.88 g, 8.60 mmol) in 20 mL of acetone was added 2.58 g (17.2 mmol) of sodium iodide. The solution was heated to reflux for 4 h. The cooled reaction was poured into 25 mL of water. The mixture was extracted with 100 mL of ether. The ether extract was washed with saturated sodium bicarbonate, saturated sodium thiosulfate, and brine. The extract was dried over magnesium sulfate, filtered and concentrated. Flash column on

silica/hexane-EtOAc 6:1 gave 1.91 g (77%) of **152** as a colorless oil. $[\alpha]_D^{21}$= +9.95 (c=3.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (5H, m), 4.5 (2H, s), 3.32 (4H, m), 1.81 (1H, m), 0.99 (3H, d, J=2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.2, 128.7, 128.3, 127.5, 74.0, 73.1, 35.1, 17.6, 13.9; IR (neat) 3062, 3028, 2962, 2927, 2859, 1494, 1454, 1424, 1365, 1326, 1250, 1200, 1100, 1027, 739, 698, 605 cm^{-1}; LRMS calcd for $C_{11}H_{15}OI$ 290.14 (M^+). Found 270, 180, 107, 91, 71.

(2*S*)-1-(Benzyloxy)-2-methylpropyl Phenylsulfone (153). To a solution of **152** (1.70 g, 5.86 mmol) in 15 mL dimethylformamide was added benzene sulfinic acid sodium salt (1.44 g, 8.79 mmol) and the reaction was warmed to 35°C overnight. The reaction was poured into saturated sodium bicarbonate and extracted with ether. The organic extract was washed with brine, dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 4:1 gave 79% of **153** as an oil. $[\alpha]_D^{21}$ = +4.2 (c=2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (2H, m), 7.63 (3H, m), 7.33 (5H, m), 4.41 (2H, d, J=1 Hz), 3.40 (2H, m), 3.38 (1H, q, J=1 Hz), 2.93 (1H, q, J=3 Hz), 2.38 (1H, m), 1.11 (3H, d, J=2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.0, 138.0, 133.4, 129.1, 128.2, 127.7, 127.5, 127.4, 73.5, 72.8, 59.2, 29.3, 17.1; IR (neat) 3064, 3030, 2967, 2927, 2862, 1451, 1361, 1306, 1148, 1086, 743, 694 cm^{-1}.

(2*R*)-1-*tert*-Butyldimethylsilyloxy-2-propylene Oxide (155). To a solution of (*R*)-glycidol (50 mg, 0.67 mmol) in 2 mL dry CH_2Cl_2 under argon was added imidazol (64 mg, 0.95 mmol) and 111 mg of *tert*-butyldimethylsilyl chloride (0.74 mmol). The reaction was stirred at room temperature for 3 days then poured into saturated sodium carbonate. The aqueous layer was extracted with CH_2Cl_2 and the extract was washed with brine. The extract was dried over magnesium sulfate, filtered and concentrated. Flash column on

silica/pentane-ether 6:1 followed by vacuum distillation gave 63.5 mg of **155** as a colorless oil. $[\alpha]_D^{21}$= +2.35 (c=3.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (1H, m), 3.70 (2H, m), 3.58 (2H, m), 0.95 (6H, s), 0.89 (9H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 71.3, 63.3, 45.2, 25.7, -5.6; IR (neat) 2956, 2932, 2894, 2860, 1467, 1255, 1132, 1098, 840, 778 cm^{-1}.

(2*S*,5*S*)-6-Benzyloxy-2-hydroxy-5-methyl-4-(phenylsulfonyl)hexyl *tert*-Butyldimethylsilyl Ether (156). To a solution of the **153** (300 mg, 0.990 mmol) in 3 mL of THF at -78°C under argon was added 0.63 mL of *n*-butyllithium (1.0 mmol) in hexanes. The reaction was stirred for 20 min then 0.21 mL of hexamethylphosphoramide (1.2 mmol) in 2 mL of THF was added to the reaction. The reaction was stirred for 10 min then 131 mg (0.70 mmol) of **155** in 2 mL THF was added. The reaction was warmed to 0°C and stirred 2.25 h. The reaction was quenched with saturated ammonium chloride and extracted with ether (2x50 mL). The organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 4:1 gave 326 mg (94%) of **156** as a oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (2H, m), 7.57 (3H, m), 7.33 (5H, m), 4.41 (2H, dd, J=5, 6 Hz), 4.13 (0.5H, q, J=2 Hz), 3.64 (1H, td, J=2, 0.5 Hz), 3.39 (2H, m), 3.33 (2H, m), 2.93 (0.5H, q, J=2 Hz), 2.64 (1H, m), 2.37 (1H, m), 2.04 (1H, s), 1.81 (0.5H, m), 1.26 (0.5H, t, J=2 Hz), 1.13 (2H, dd, J=1, 1 Hz), 1.01 (1H, d, J=4 Hz), 0.87 (9H, d, J=2 Hz), 0.04 (6H, t, J=2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.1, 138.1, 133.5, 129.2, 129.2, 128.9, 128.7, 128.5, 128.4, 127.8, 127.6, 127.5, 127.5, 127.2, 127.2, 73.5, 72.9, 70.6, 59.2, 43.4, 29.4, 25.8, 25.6, 19.7, 17.2, 6.1; IR (neat) 3505 (broad), 2955, 2930, 2883, 2858, 1451, 1363, 1306, 1256, 1146, 1087, 840, 779, 740, 695 cm^{-1}; LRMS calcd for $C_{26}H_{40}O_5SSi$ 492.75 (M^+). Found 493 (M^+), 475, 435, 419, 385, 327, 305, 271, 197, 181, 143, 118, 107, 91.

(2*S*,5*S*)-6-Benzyloxy-2-hydroxy-5-methylhexyl *tert*-Butyldimethylsilyl Ether (157). To a solution of **156** (727 mg, 1.48 mmol) in 35 mL absolute ethanol was added 27.3 g of 2.5 % Na/Hg amalgam (2.97 mmol). The reaction was stirred overnight at room temperature then quenched with saturated NH_4Cl. The mixture was extracted with ether (3 x 100 mL). The combined extracts were dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 4:1 gave 246 mg (47%) of **157** as a oil. $[\alpha]_D^{21}$ = +4.1 (c=1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (5H, m), 4.49 (2H, s), 3.61 (2H, m), 3.33 (2H, m), 2.4 (1H, bs), 1.77 (1H, m), 1.61 (1H, m), 1.46 (2H, m), 1.15 (1H, m), 0.94 (3H, d, J=2 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 138.8, 128.7, 128.2, 127.4, 127.3, 75.8, 73.3, 72.9, 67.2, 33.6, 31.6, 29.0, 25.9, 18.3, 17.4, -4.3, -4.8, -5.3; IR (neat) 3458 (broad), 2954, 2930, 2858, 1458, 1255, 1101, 838, 778, 736, 698 cm^{-1}; LRMS calcd for $C_{20}H_{36}O_3Si$ 352.59 (M^+). Found 352 (M^+), 187, 131, 117, 105, 91, 75.

(2*S*,5*S*)-5,6-Di(*tert*-butyldimethylsilyloxy)-2-methylhexan-1-ol (159). To a solution of (2*S*,5*S*)-1-benzyloxy-5,6-di(tert-butyldimethylsiloxy)-2-methylhexane (303 mg, 0.649 mmol) in 5 mL of ethyl acetate was added 50 mg of 10 % Pd/C then 5 μL of 10% hydrochloric acid. The reaction was stirred for 12 hours under hydrogen at room temperature then 20 μL of triethylamine was added followed by the magnesium sulfate. The mixture was filtered through celite and washed with 30 mL of ethyl acetate. The filtrate was concentrated. Flash column on silica/hexanes-EtOAc 4:1 gave 215 mg (88%) of **159** as an oil. $[\alpha]_D^{21}$ = -8.25 (c=1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (1H, m), 3.51 (2H, dd, J=2, 6 Hz), 3.43 (2H, m), 1-65-1.35 (6H, m), 0.93 (3H, d, J=2

Hz), 0.89 (9H, s), 0.88 (9H, s), 0.06 (6H, s), 0.05 (6H, d, J=1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 76.2, 68.1, 67.1, 35.8, 31.4, 28.2, 25.9, 25.8, 18.1, 16.6, 5.3, -4.46, -4.8, -5.4.

(2*S*,5*S*)-5,6-Di(*tert*-butyldimethylsilyloxy)-2-methylhexanal (160). To a solution of **159** (110 mg, 0.268 mmol) in 10 mL CH_2Cl_2 was added 190 mg (0.43 mmol) of Dess-Martin periodinane. The reaction was stirred at room temperature for 45 min then poured into 45 mL of saturated sodium bicarbonate. The mixture was diluted with 75 mL of ether and 3g of $Na_2S_2O_3$ the was added to the biphasic mixture. The phases were shaken together and allowed to separate. The organic phase was washed with 20 mL of saturated sodium bicarbonate then 20 mL of brine. The organic phase was dried over magnesium sulfate, filtered and concentrated. Flash column on silica/hexane-EtOAc 4:1 gave 91 mg (83%) of **160** as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (1H, s), 3.66 (1H, m), 3.52 (1H, m), 2.34 (1H, m), 1.42 (2H, m), 1.25 (2H, m), 1.09 (3H, d, J=2 Hz), 0.92 (9H, d, J=1 Hz), 0.88 (9H, d, J=0.4 Hz), 0.58 (12H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.2, 72.8, 67.0, 46.4, 31.5, 25.9, 23.1, 18.3, 12.3, 6.0, -4.3, -4.8, -5.3; IR (neat) 2956, 2932, 2899, 2889, 2859, 2805, 2709, 1730, 1467, 1389, 1363, 1254, 1216, 1189, 1114, 1069, 1005, 983, 939, 920, 835, 813, 777, 721, 666 cm^{-1}.

(*S*)-Methyl N-Iodoacetylpipecolate (163). To a solution of **131** (115 mg, 0.576 mmol) in 3 mL of acetone was added 86 mg (0.58 mmol) of sodium iodide. The reaction was stirred overnight at room temperature. The reaction was treated with 20 mL of water to dissolve solid sodium chloride and the resulting mixture was extracted with ether (3 x 30 mL). The combined extracts were washed with saturated $Na_2S_2O_3$ and then brine. The combined

extracts were dried over magnesium sulfate, filtered and concentrated. Plate chromatography on silica/EtOAc gave 162 mg (98%) of **163** as a pale yellow oil. $[\alpha]_D^{21}$ = -31.3 (c=1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (0.7H, d, J=2 Hz), 4.55 (0.3H, m), 3.78 (2H, m), 3.74 (3H, s), 3.26 (1H, dt, J=2, 5 Hz), 2.24 (1H, d, J=4 Hz), 1.72 (5H, m), 1.37 (1H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 167.8, 57.48, 52.2, 45.15, 39.91, 26.36, 24.71, 20.63, -3.96; IR (neat) 2945, 2860, 1739, 1643, 1441, 1415, 1341, 1275, 1210, 1164, 1144, 1021 cm^{-1}; LRMS calcd for $C_9H_{14}O_3IN$ 311.12 (M^+). Found 312 (M^+), 280, 252, 184, 154, 144, 89.

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