AN ABSTRACT OF THE THESIS OF

Steven G. Toske for the degree of Doctor of Philosophy in Chemistry presented on June 10, 1993.

Title: Part I: Synthesis of Azetidin-2-ones from Pyrazolidin-3-ones.

Part II: Synthesis of a Subunit of the Immunosuppressant FK-506.

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Abstract approved: _____
James D. White

**Part I.** A new route for the preparation of azetidin-2-ones was studied using a tandem photochemical deprotection and ring contraction of pyrazolidin-3-ones as the key step. Pyrazolidin-3-ones **112-116** were first protected at the N-1 position with *o*-nitrobenzyl chloride yielding derivatives **117-121** which were acylated with 2-(trimethylsilyl)ethyl azidoformate to give the fully protected pyrazolidinones **125**, **126**, **131**, **132**, and **134** needed for photolysis. Irradiation of these compounds through a Pyrex filter removed the *o*-nitrobenzyl group, and subsequent photolysis using a Vycor filter effected ring contraction to afford N-(acylamino)azetidinones **137**, **138**, **141**, **142**, and **144**. These were converted to N-aminoazetidinones **161-165** with tetra-*n*-butylammonium fluoride. Completion of a general entry to the parent β-lactams **183-188** was accomplished by a nitrosative deamination with N,N-diphenylnitrosamine.

Synthesis of the known precursor **220** to the antibiotic PS-5 (**10**) was achieved using this methodology in ten steps from δ-valerolactone (**208**) and in an overall yield of 1.3%. Treatment of α,β-unsaturated-δ-lactone **211**, prepared from **208** in three steps, with hydrazine monohydrate furnished pyrazolidinone

**212**. Confirmation of the *cis* configuration was obtained by X-ray crystallographic analysis of the *o*-nitrobenzyl derivative **215**. Photolysis of the fully protected pyrazolidinone **217** gave N-(acylamino)azetidinone **218** in good yield. Removal of both silyl protecting groups in **218**, followed by nitrosative deamination of **219**, produced **220**.

**Part II.** Synthesis of the C20-C34 subunit **73** of the immunosuppressant drug FK-506 (**1**) was accomplished in fifteen steps in an overall yield of 2.8%. (-)-Quinic acid (**66**) was used as the starting material and was first converted to the bicyclic bromoimidazolide **79**. Simultaneous reduction of the alkyl bromide and imidazolide moieties in **79** with tri-*n*-butyltin hydride and α,α'-azobisisobutyronitrile gave **68** in good yield. Acid-catalyzed opening of lactone **68** with methanol, followed by formation of the methyl ether, provided ester **69** which was homologated to α,β-unsaturated aldehyde **75** in five steps. Condensation of **75** with the chiral enol borinate **88** afforded alcohols **89** and **90** in a 2.4:1 ratio, respectively. Conversion of the desired alcohol **89** to aldehyde **74** was accomplished by silylation and selective oxidative cleavage of the terminal olefin in **91**. Completion of the synthesis of **73** was achieved by stereoselective aldol condensation of the lithium enolate of ketone **100** with aldehyde **74**.

Part I: Synthesis of Azetidin-2-ones from Pyrazolidin-3-ones.

Part II: Synthesis of a Subunit of the Immunosuppressant FK-506.

By

Steven G. Toske

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Redacted for Privacy

Chairman of Department of Chemistry

Redacted for Privacy

Dean of Graduate School

Date thesis is presented June 10, 1993

Typed by Gabriela Toske for Steven G. Toske

*This work is dedicated to the memory of*
*my mother Carole A. Toske*

*She gave me love and courage*

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I would like to thank Professor James D. White for his support, guidance and patience throughout my graduate career. I would also like to thank Dr. John C. Amedio for showing a rather inexperienced chemist how to survive in the laboratory. Members of the White group including Kraig Yager, Mark Jensen, Scott Jeffrey, Hyunik Shin, Gary Bolton, Motoji Kawasaki, Warren Porter, Neal Green, Steve Perri, and Takayuki Yakura deserve mention for their freindship and helpful suggestions.

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My father Gerald has been a true friend through the highs and lows of my graduate career. He taught me at an early age to work hard and never quit until your goal has been achieved. In many ways, this degree is as much his as mine. Thanks goes out to Stephanie and Brenda for being great sisters and Sharon for being an admirable step mother.

Finally, I thank my wife Gabriela and daughter Suzanna for their love and support.

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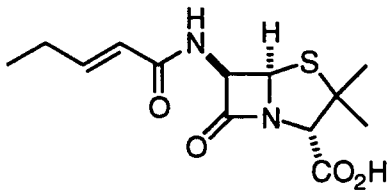
Part I: The Synthesis of Azetidin-2-ones from Pyrazolidin-3-ones.

## I-A. Introduction

Sir Alexander Fleming's discovery in 1929[1] that penicillin was an effective antibiotic against different bacterial cultures started the era of research into penicillin antibiotics. It was not until 1940, when Florey found that penicillin F (**1**) could protect mice from otherwise fatal injections of bacteria, that penicillin was thought to have medicinal value. This started an intense research effort that eventually led, through the use of *Penicillium notatum*, to large scale production of penicillin G (**2**). The latter was used as an effective antibiotic for the treatment of infections in injured World War II soldiers.



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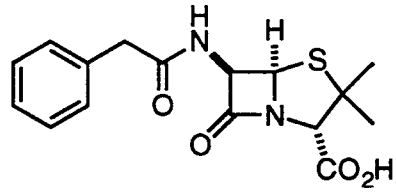


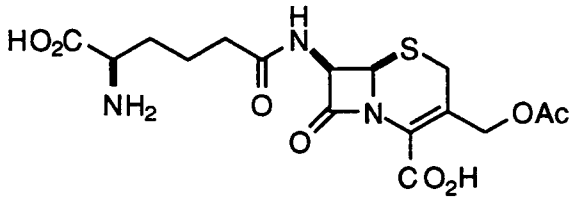
**2**

With the subsequent evolution of penicillinase-producing bacteria, in which the enzyme inhibits penicillin activity, the utility of penicillin G became limited. This unfortunate phenomenon motivated researchers to find alternative penicillin derivatives for medical use.

The structure of penicillin was studied intensively after 1943. This led to the extraordinary suggestion by Robinson that penicillin contained a β-lactam ring.[2] Later, in 1945, it was confirmed by X-ray crystallographic analysis that penicillin did indeed contain the β-lactam nucleus.[3]

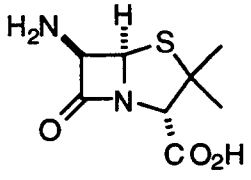
In the 1950's, two important discoveries contributed to the advancement of research on β-lactam antibiotics. The first, in 1953, was the isolation of

cephalosporin C (**3**) by Abraham from *Cephalosporium acremonium*.[4] This compound showed significant activity against Gram-positive and Gram-negative bacteria. Although **3** was hydrolyzed by the penicillinase enzyme it showed greater resistance to penicillinase-producing bacteria than penicillin G.



**3**

The second event, probably the most important development in this field, was the isolation of useful quantities of both 6-aminopenicillanic acid (**4**) from *Penicillium chrysogenium*,[5] and 7-aminocephalosporanic acid (**5**) by chemical removal of the side chain of **3**.[6]



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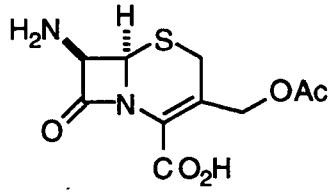
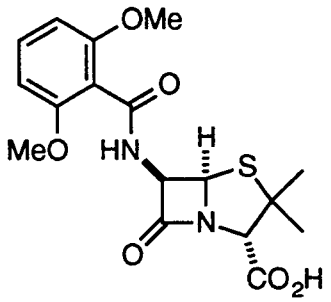
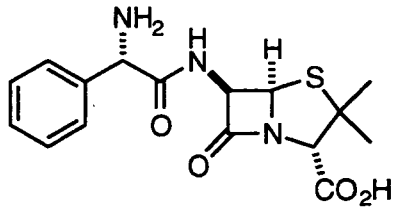


**5**

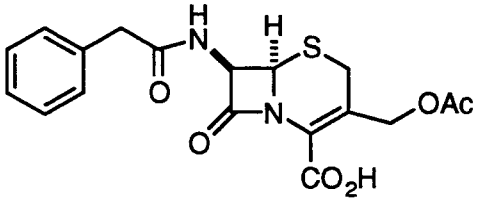
This led to the semisynthesis of large numbers of penicillins and cephalosporins which were evaluated for biological activity. Four of the most effective antibiotics synthesized commercially are illustrated below.



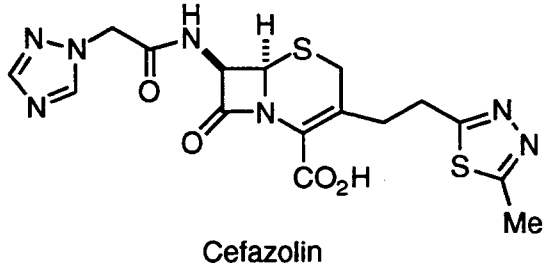
Methicillin



Ampicillin

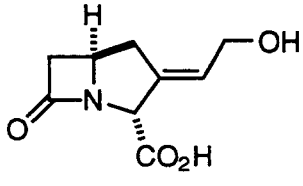


Cephalothin



Cefazolin

In the 1970's, as new screening procedures were developed, several new classes of β-lactam antibiotics emerged which were found to have therapeutic value.[7] These included β-lactamase inhibitors of *E. Coli* and *Penicillium aeruginosa* found in *Streptomyces* microorganisms such as clavulanic acid (**6**)[8] and the monocyclic β-lactam norcardicin A (**7**)[9].



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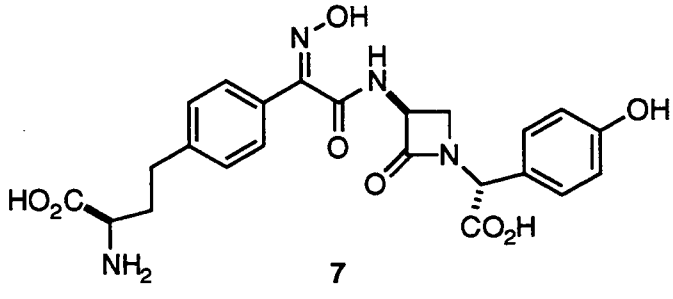
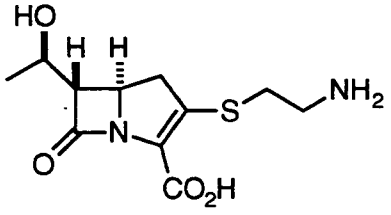


**7**

During this period and subsequently into the 1980's the carbapenem family and its relatives were discovered. Nearly forty different compounds were isolated from several different *Streptomyces* strains. Members of this family which showed powerful biological activity include thienamycin (**8**)[10], PS-5

(**10**)[11], PS-6 (**11**)[12], olivanic acid (**12**)[13], and carpetimycin A (**13**).[14] Interestingly, there were several *epi*-thienamycin structures reported such as **9**[15]; however, *epi*-compounds related to PS-5 (**10**), PS-6 (**11**), olivanic acid (**12**), and carpetimycin A (**13**) have yet to be isolated.

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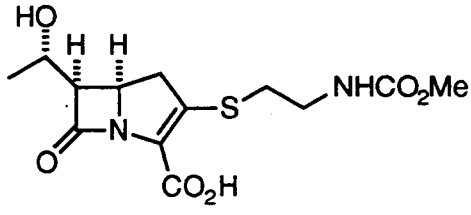


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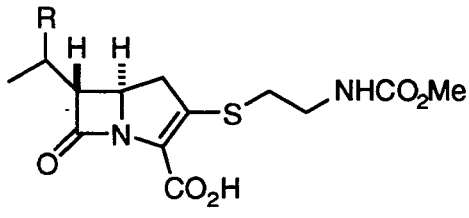
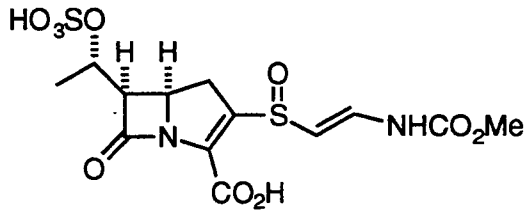
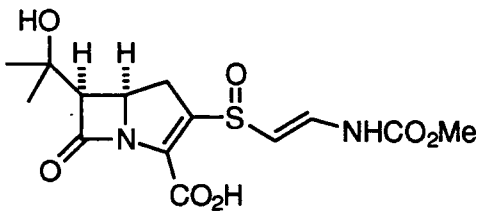



**10**, R = H
**11**, R = Me



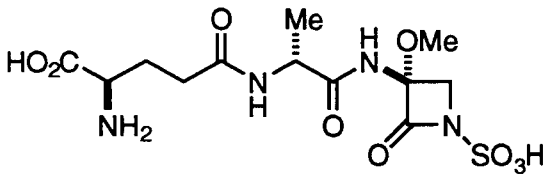

**12**



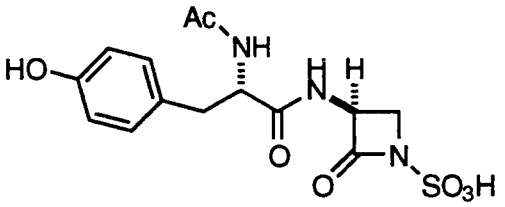

**13**

Concurrent with the emergence of the carbapenems was the discovery of the monobactams. These are monocyclic β-lactams containing a sulfonic acid moiety on the ring nitrogen. Sulfazecin (**14**), isolated from *Pseudomonas acidophila* in 1981,[16] is an example of a monobactam. This compound is active against strains of Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Escherica Coli*. Analogues of sulfazecin such as **15** were also isolated and tested for biological activity. It was found that the monobactams with methoxy

substitution at C-3 of the azetidinone ring, as in **14**, were the most resistant to β-lactamase-producing bacteria.[17]

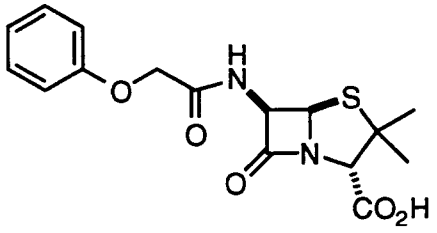


**14**



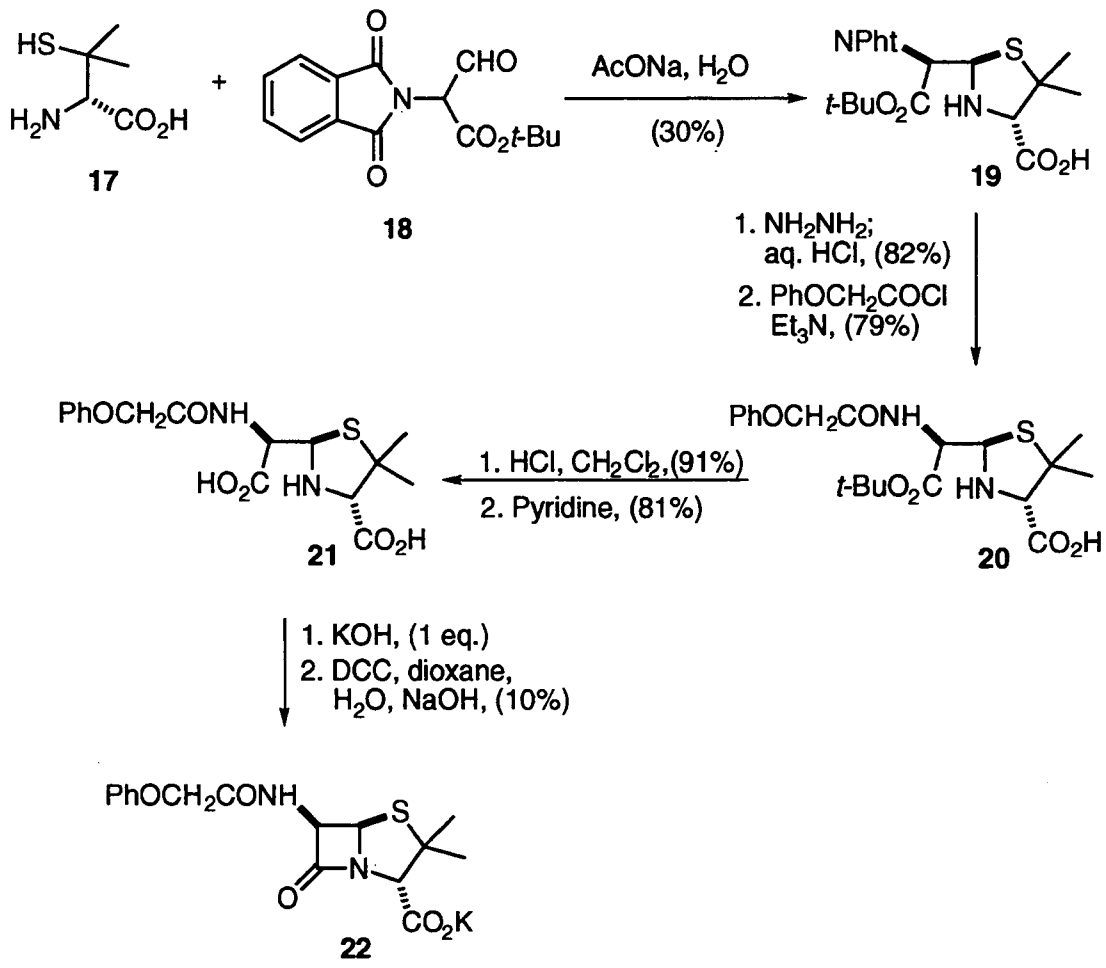
**15**

Although the synthesis of a β-lactam was accomplished by Staudinger as early as 1907,[18] it was not until the late 1950's, when interest in these compounds was increasing rapidly, that the first β-lactam antibiotic was synthesized. In 1959, Sheehan published a total synthesis of optically pure penicillin V (**16**).[19]



**16**

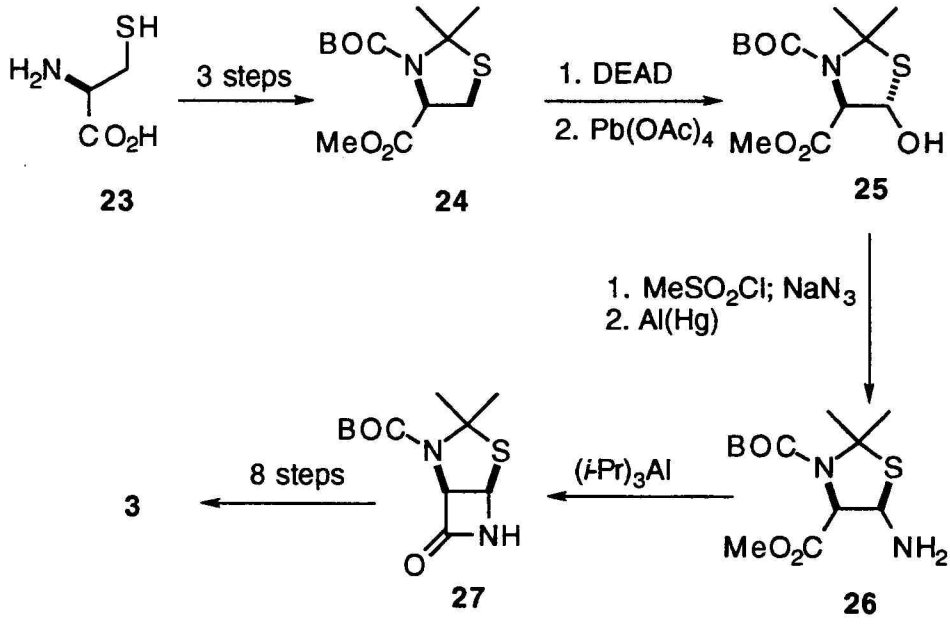
(*D*)-Penicillamine (**17**), a degradation product of the penicillins, was condensed with phthalimidomalonaldehyde **18** to afford, among other products, the thiazolidine **19** . After replacement of the phthalimido group with the phenoxymethyl side chain to yield **20**, hydrolysis of the *t*-butyl ester set the stage for ring closure. This was accomplished by treatment of the amino acid **21** with one equivalent of potassium hydroxide followed by dicyclohexylcarbodiimide, and provided the desired penicillin V potassium salt **22** in 10% yield (Scheme 1). The efficiency of this cyclization was later improved to 25% using diisopropylcarbodiimide.[20]




**Scheme 1**

In 1966, Woodward and co-workers completed an impressive total synthesis of cephalosporin C (**3**).[21] The starting material, (*L*)-cysteine (**23**), was converted to thiazolidine derivative **24** in three steps. Reaction of **24** with excess diethyl azodicarboxylate (DEAD) in the presence of lead tetraacetate resulted in stereospecific hydroxylation to give **25**. The hydroxyl group of **25** was then converted to the amino function of **26** with inversion of configuration. Cyclization of **26** was effected with triisobutylaluminum to yield the bicyclic β-lactam **27**. A further eight steps were needed for completion of this route to **3**. Unlike the Sheehan synthesis,[19] where the β-lactam ring was closed late in the synthesis, Woodward's construction of the β-lactam unit occured relatively early

in the sequence, a strategy which enabled intermediate **27** to be used for both penicillin and cephalosphorin syntheses (Scheme 2).[22]

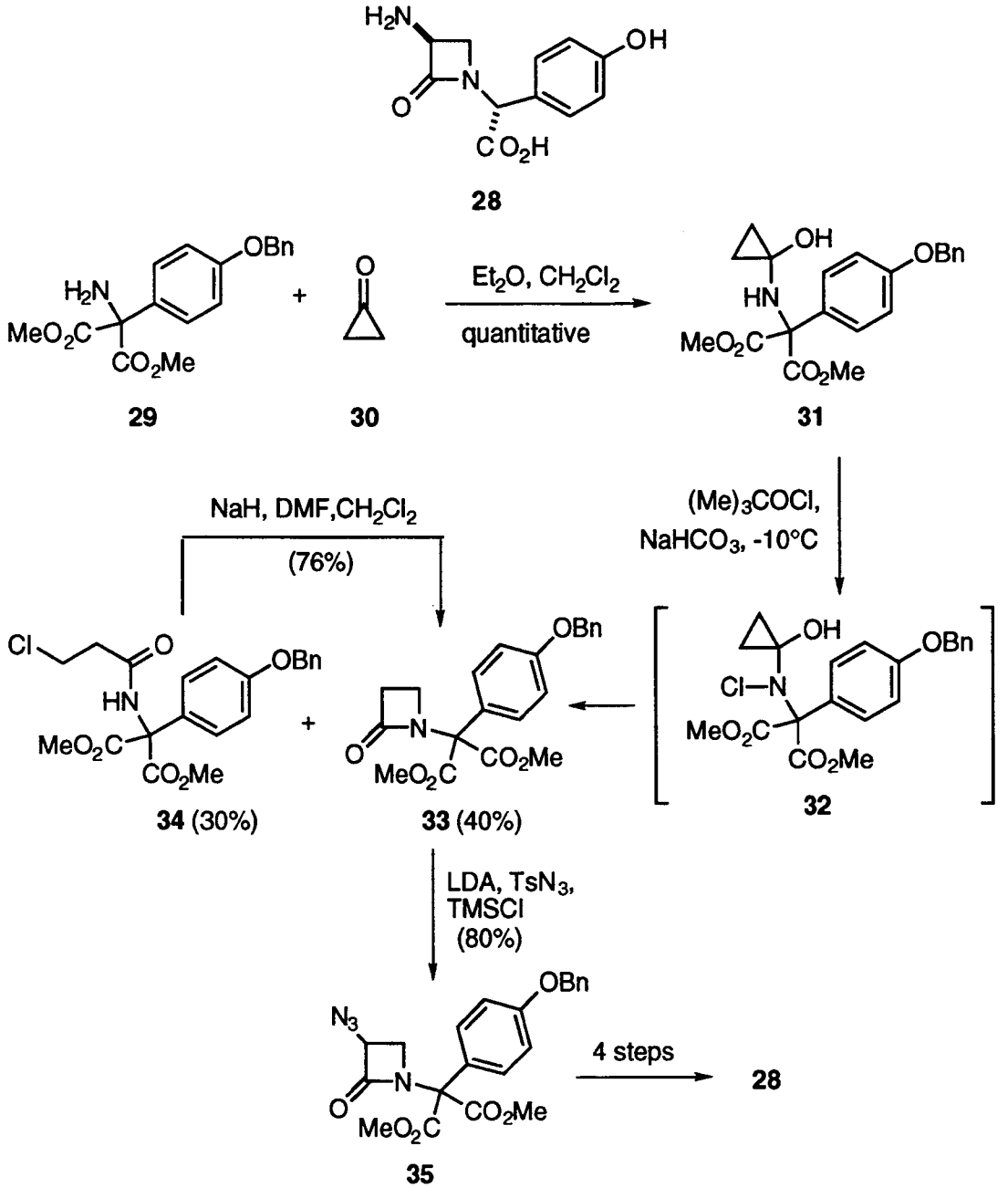



**Scheme 2**

There are many other syntheses of penicillins in the literature which form a body of work in the area of classical β-lactam antibiotics.[23] However, with the discovery of new structural classes of β-lactam antibiotics in the 1970's the synthetic chemist was forced to develop new strategies for their synthesis.

In 1978, Wasserman reported the synthesis of (±)-3-aminonocardicinic acid (**28**)[24], an attractive intermediate previously used in the synthesis of norcardicin A (**7**).[25] This synthesis illustrated a novel ring expansion which led to the β-lactam nucleus. Addition of the aminomalonate **29** to cyclopropanone **30** gave alkylaminocyclopropanol **31** in quantitative yield. Compound **31** was chlorinated to form the chloramine **32** which underwent ring expansion to form **33** in 40% yield, accompanied by chloroamide **34** in 30% yield. Chloroamide **34** was cyclized to the desired β-lactam **33** in good yield. The β-lactam **33** was

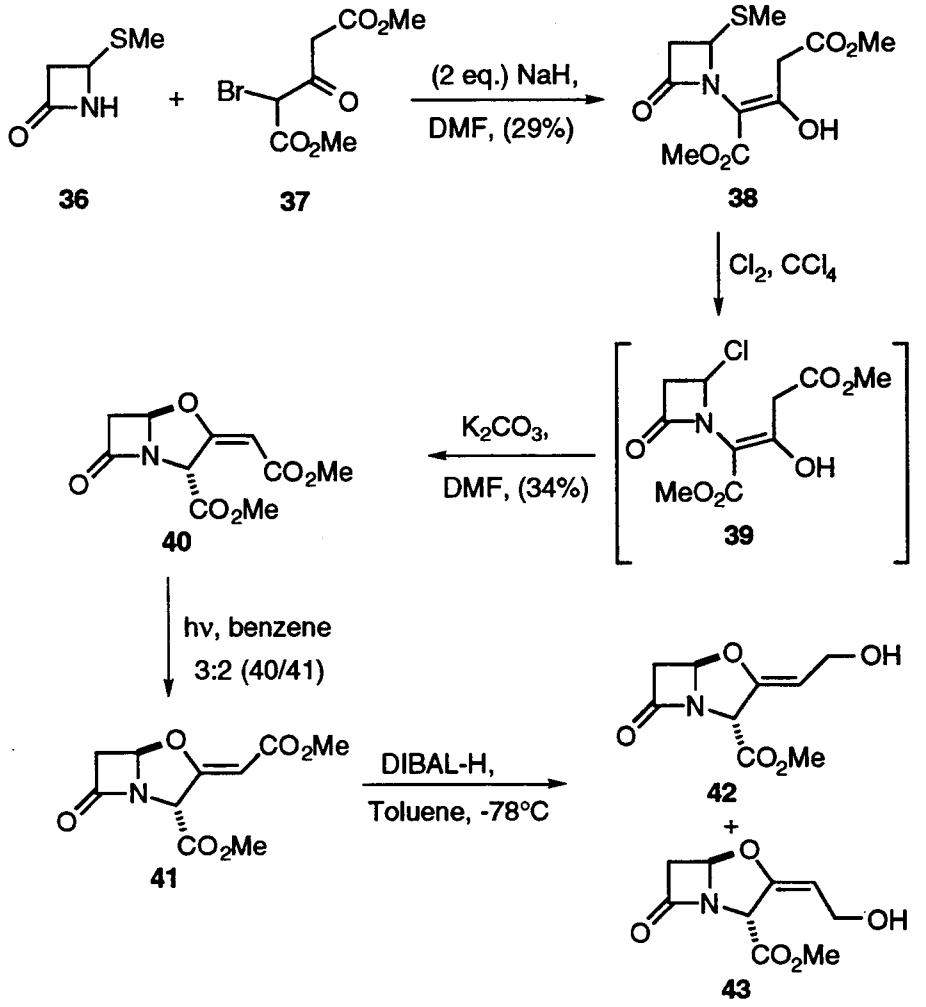
advanced to the 3-azido deriviative **35** using lithium diisopropylamide and *p*-toluenesulfonyl azide. A further four steps were needed for the preparation of racemic **28**.




**Scheme 3**

During the same period, Bentley and co-workers reported a synthesis of the oxapenem antibiotic (±)-clavulanic acid (**6**) (Scheme 4)[26]. Alkylation of

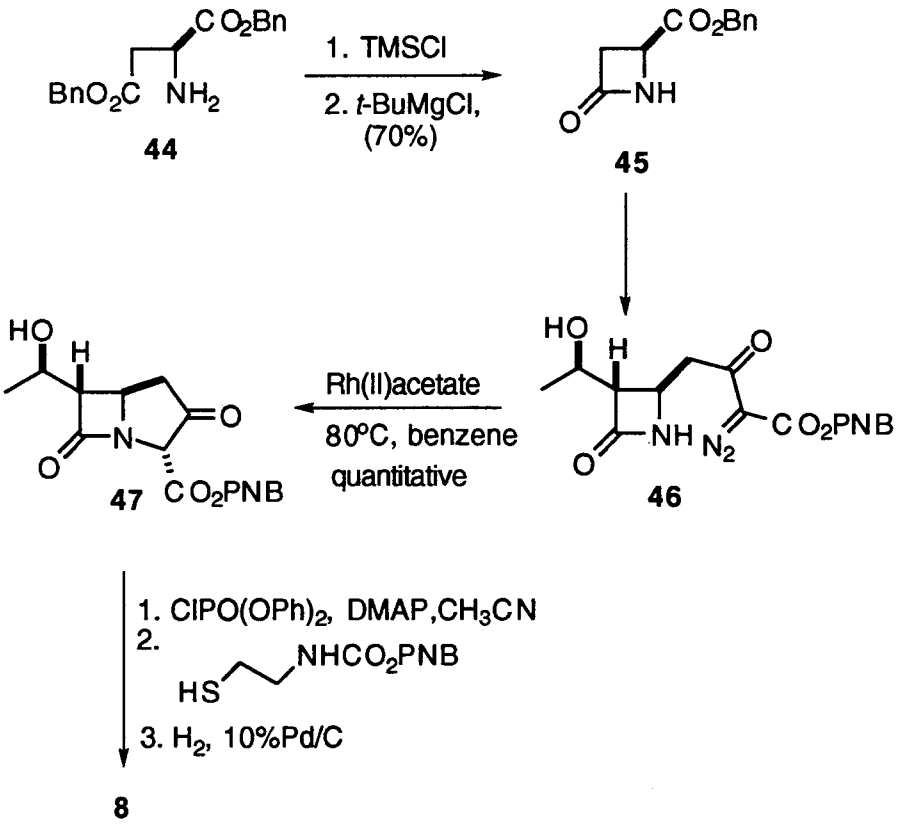
racemic 4-methylthioazetidin-2-one (**36**)[27] with methyl-γ-bromoacetate (**37**) provided the enolized β-keto ester **38** in low yield. This substance was treated with a small excess of chlorine in carbon tetrachloride to give **39** which was taken directly to the bicyclic oxapenem **40** without purification. Azetidinone **40**, which has the unnatural stereochemistry of the exocyclic double bond, was obtained as the sole stereoisomer. Isomerization of the double bond was accomplished by irradiation of **40** in benzene which gave **40** and **41** in a 3:2 ratio, respectively. Reduction of the mixture of **40** and **41** with diisobutylaluminum hydride afforded a separable mixture of racemic methyl clavulanate **42** and racemic methyl isoclavulanate **43** in low yield.




**Scheme 4**

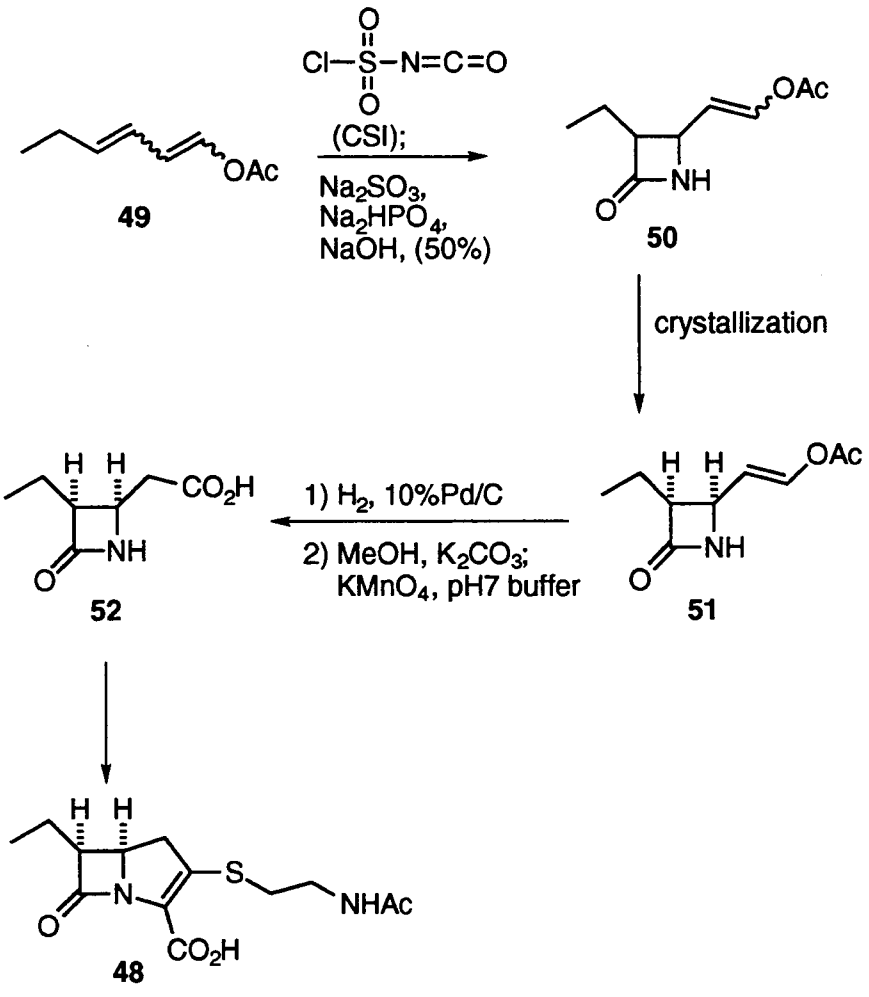
The synthesis of carbapenem-based antibiotics encompasses a large volume of work due to the many different structural variations that have been encountered.[28] The strategies which have been developed generally take into account the different C-6 alkyl side chains and the C-3 cysteaminyl side chains. The majority of these syntheses have employed construction of the β-lactam nucleus before elaboration to the [3.2.0]bicylic framework. These ring construction strategies include chiral amino acid cyclizations,[29] chlorosulfonylisocyanate-alkene cycloadditions,[32,33] acid chloride-imine cycloadditions,[34]and ester enolate-imine cyclizations.[36]

One of the most elegant approaches using a chiral amino acid cyclization for construction of the β-lactam ring is found in the synthesis of (+)-thienamycin (**8**) by Salzmann and co-workers at Merck.[29] The synthesis started from dibenzyl aspartate (**44**), available from (*L*)-aspartic acid.[30] The amino ester **44** was monosilylated and cyclized to azetidinone **45** upon treatment with *tert*-butylmagnesium chloride. After several more steps, this route culminated in the construction of **8** via a rhodium (II) acetate catalyzed carbenoid cyclization of diazoketone **46** to give the carbapenem nucleus of **47**.[29,31] The latter was then converted to **8** by straight forward means (Scheme 5). The carbenoid cyclization was a pivotal achievement and has been used in many formal syntheses of carbapenem antibiotics.[32,33,34,35]



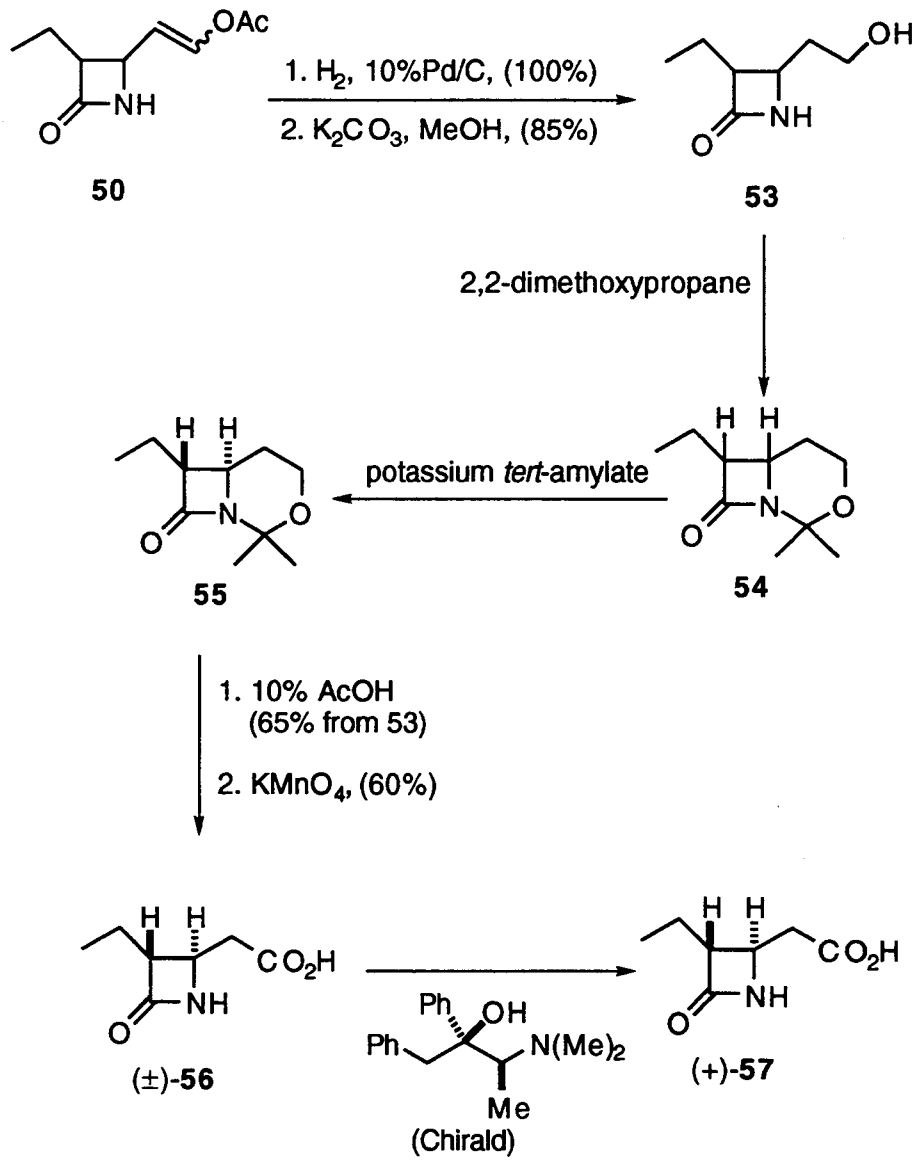

**Scheme 5**

An example of the utility of a chlorosulfonylisocyanate (CSI) cycloaddition to an alkene was published by Favara in his synthesis of 6-*epi*-PS-5 (**48**)[32] and (+)-PS-5 (**10**).[33] A [2+2] cycloaddition using excess CSI with conjugated diene **49,** followed by reductive hydrolysis, yielded a four-isomer mixture of β-lactams **50** in moderate yield (Scheme 6).[32] The *cis* isomer **51**, separated by crystallization from diisopropyl ether, was converted to the corresponding acid **52** in two steps. Completion of the synthesis of **48** was achieved using the method developed at Merck.[29,31]




**Scheme 6**

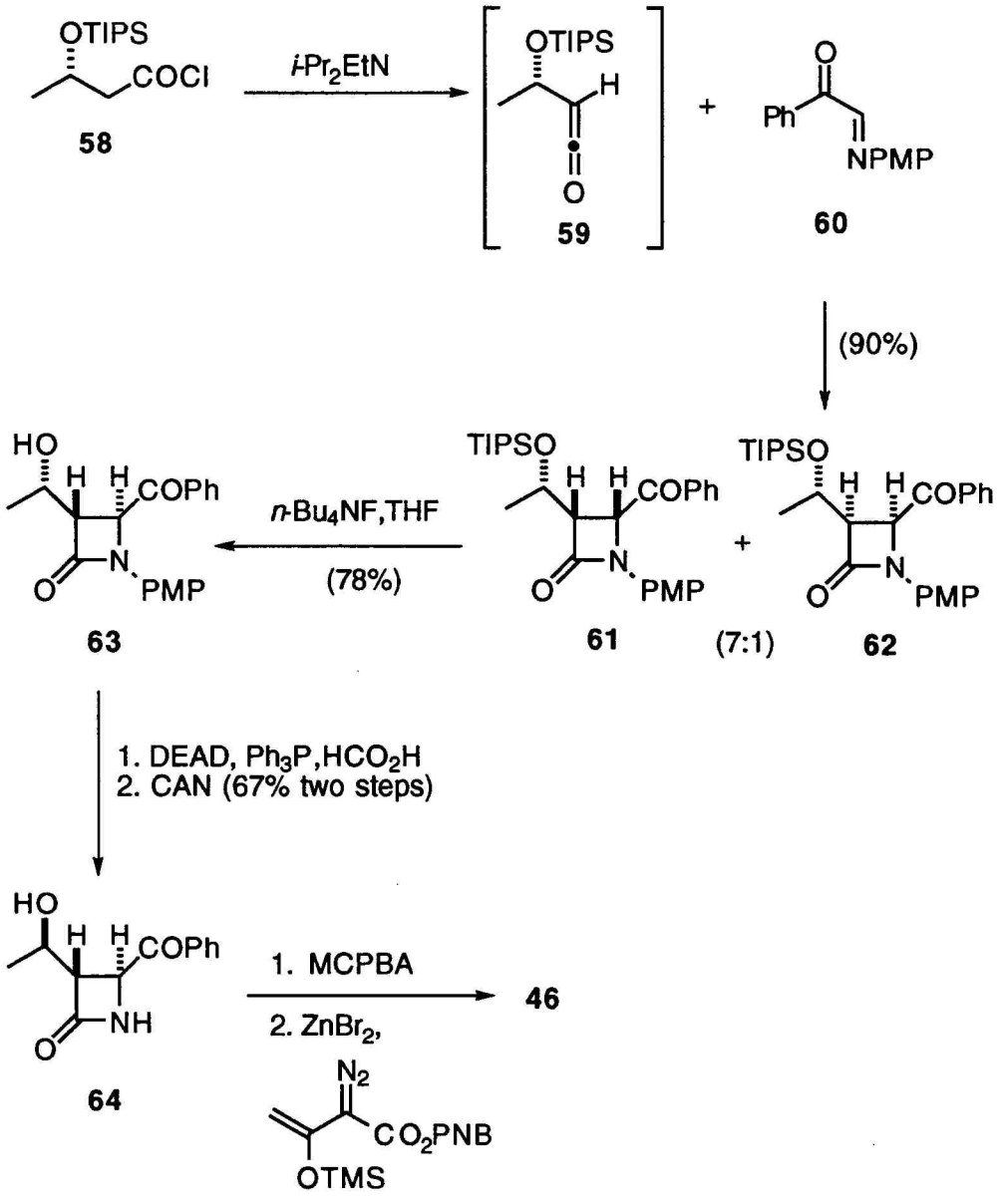
The synthesis of (+)-PS-5 was accomplished using the mixture of isomers **50** without purification (Scheme 7).[33] Catalytic hydrogenation of **50**, followed by methanolysis provided alcohol **53**. Simultaneous protection of the alcohol and lactam yielded acetonide **54**, which was epimerized with 1N potassium *tert*-amylate to afford the *trans* isomer **55**. Removal of the protecting group gave the *trans* alcohol which was oxidized to the corresponding acid **56** with potassium permanganate. Optical resolution of **56** using Chirald furnished **57** which was converted to (+)-PS-5 again using the Merck methodology.[29,31]




**Scheme 7**

Shinkai and co-workers reported the use of an acyl chloride-imine cycloaddition in their synthesis of (+)-thienamycin (**8**).[34] Acid chloride **58** was treated with diisopropylethylamine to generate ketene **59**, which underwent [2+2]-cycloaddition with imine **60** to afford β-lactams **61** and **62** in a 7:1 ratio respectively (Scheme 8). Desilylation of **61** resulted in epimerization at C-4 forming the desired *trans*-β-lactam **63**. Inversion of stereochemistry at the hydroxylethyl side chain utilizing the Mitsunobu protocol,[35] followed by removal

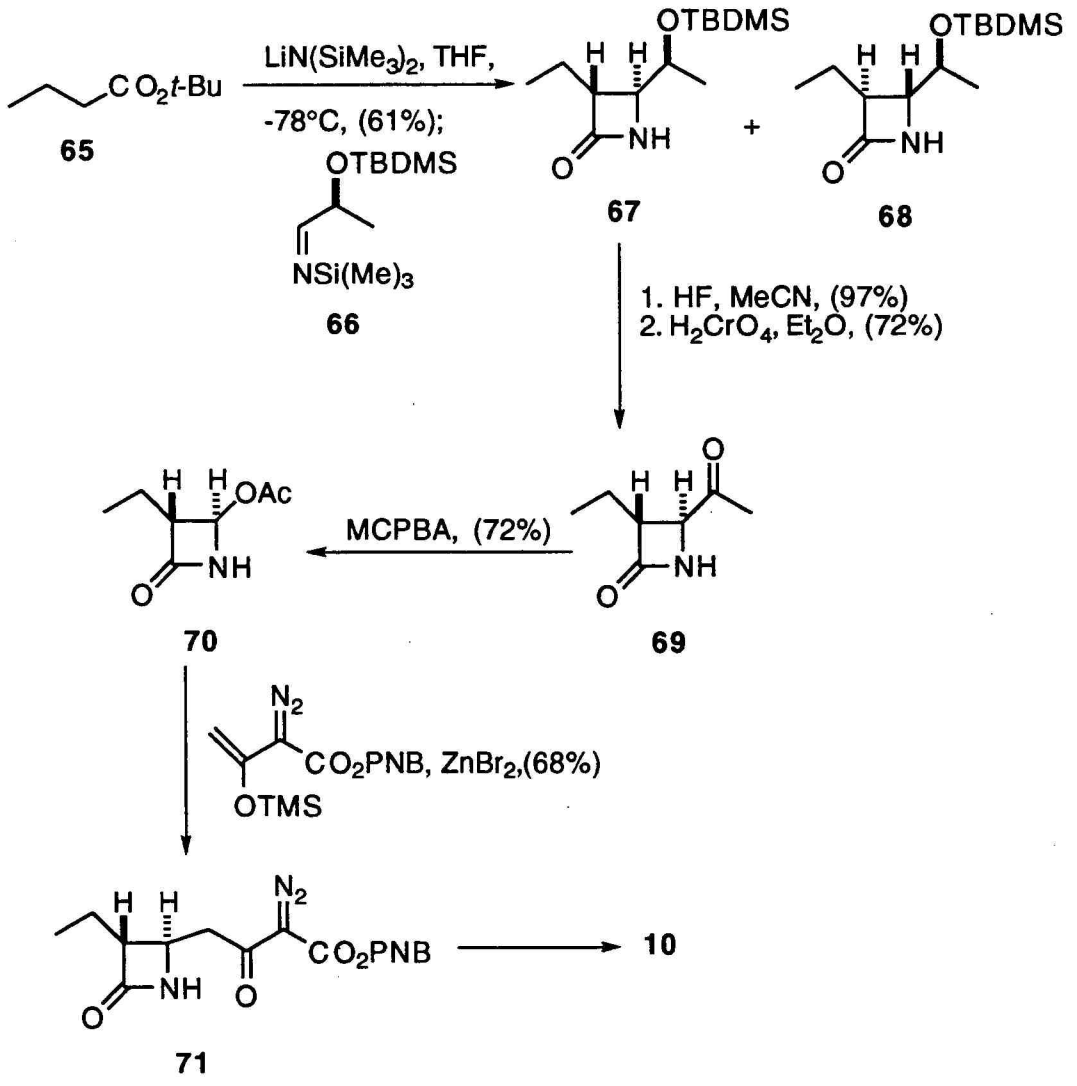
of the *p*-methoxyphenyl (PMP) group, provided β-lactam **64** which was converted to the known thienamycin intermediate **46** in two steps.




**Scheme 8**

Preparation of the β-lactam nucleus using the enolate-imine approach was first reported by Cainelli.[36] *Tert*-butyl butanoate **65** was treated with lithium bis(trimethylsilyl)amide, followed by silylimine **66**, yielding a 96:4 mixture of β-lactams **67** and **68**, respectively (Scheme 9). After deprotection of **67**, the

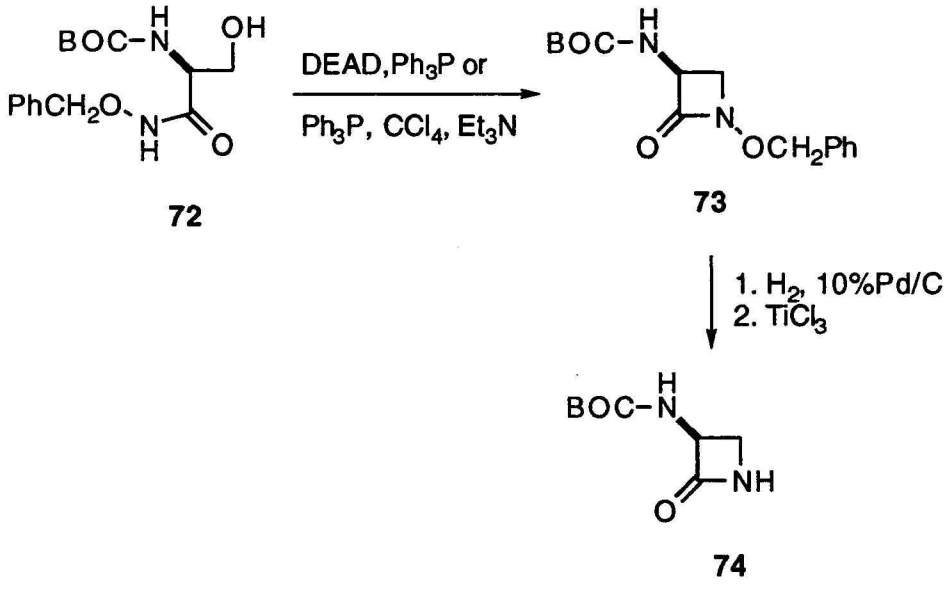
resulting alcohol was oxidized with chromic acid to ketone **69** which was then converted to acetate **70** by Baeyer-Villiger oxidation. β-Lactam **70** was converted via diazoketone **71** to **10**.[29,31]




**Scheme 9**

The syntheses of monobactams closely parallel the synthetic routes illustrated in the construction of carbapenem antibiotics. The strategies employed include chiral amino acid cyclizations, [2+2]-cycloadditions, and enolate-imine condensations.[37]

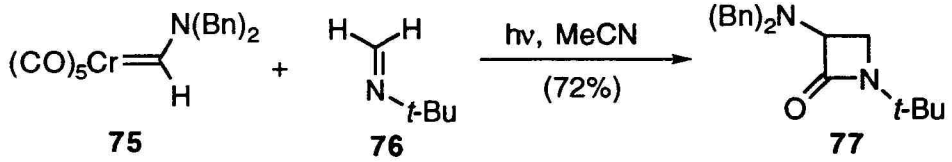
Foremost among the syntheses involving a chiral amino acid cyclization are those developed by Miller.[38] Hydroxamate **72** was closed to N-benzyloxyazetidinone **73** using two different methods (Scheme 10). Sequential reductive debenzylation and N-O bond cleavage with titanium (III) chloride gave the desired β-lactam **74**.




**72** **73** **74**

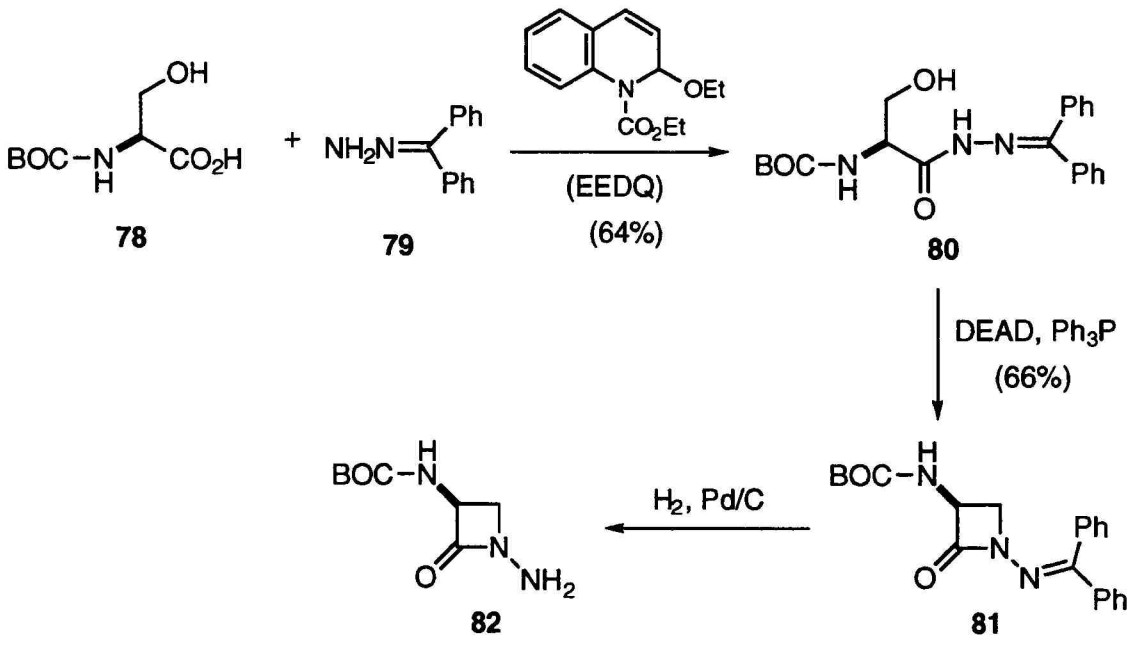
**Scheme 10**

Important new methodology for constructing the monobactam nucleus by means of a transition metal-mediated cycloaddition was reported by Hegedus.[39] This approach is similar to previously reported [2+2]-cycloadditions of an imine with a photogenerated ketene intermediate. β-Lactam **77** was produced cleanly and in good yield upon irradiation of the chromium carbene complex **75** in the presence of imine **76** (eq. 1).



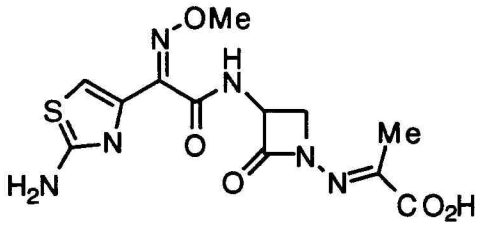

**75** **76** **77** (1)

The synthesis of N-amino-β-lactams as potential precursors of monobactam analogues was examined by Curran.[40] He found that N-Boc-protected (*L*)-serine **78** could be coupled to hydrazone **79** to afford hydrazide **80** (Scheme 11). Cyclization of **80** was accomplished using Mitsunobu conditions[35] to yield β-lactam **81**. Hydrogenation of **81** gave N-amino-β-lactam **82** needed for production of N-azamonobactam analogues.




**Scheme 11**

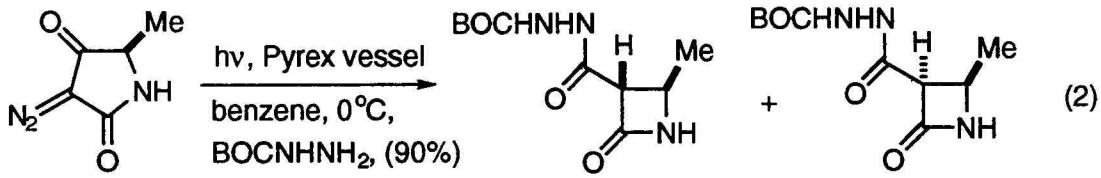
N-Aza-β-lactam **83** was synthesized from **82** and was found to have good biological activity against Gram-negative bacteria.[41]




**83**

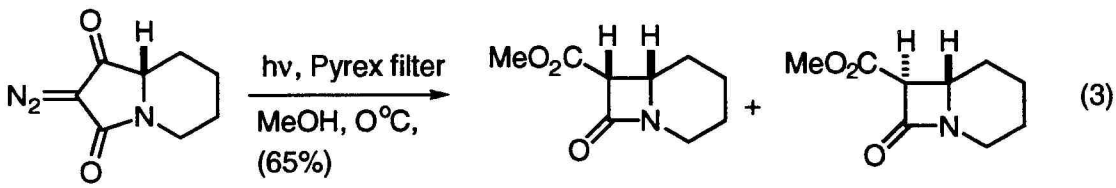
Many studies of photochemical ring contractions as routes to β-lactams have been reported.[42] All except one have involved five-membered ring contractions to the β-lactam nucleus. Several of these are outlined below.

Lowe has described the synthesis of β-lactams using a photolytic Wolff rearrangement.[43] He found that 3-diazo-5-methylpyrrolidine-2,4-dione (**84**) underwent a ring contraction which gave a 8:5 mixture of β-lactams **85** and **86**, respectively, in excellent yield (eq. 2).



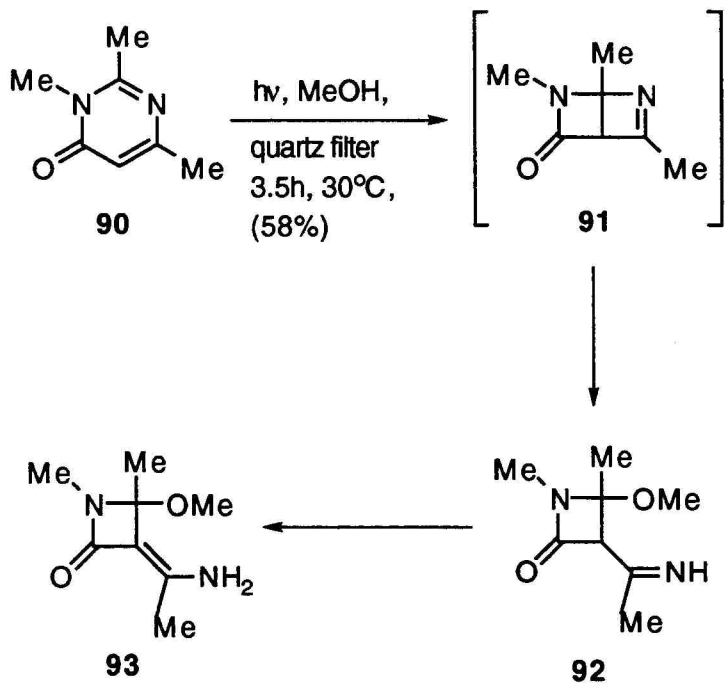

**84** **85** **86**

Stork also used the Wolff rearrangement to prepare bicyclic β-lactams.[44] Diazotetramic acid **87** was photolyzed in good yield and gave a 2:5 mixture of easily separated β-lactams **88** and **89**, respectively. Compound **88** was epimerized to **89** with great ease, thus leaving the ratio of initially formed products open to question (eq. 3).



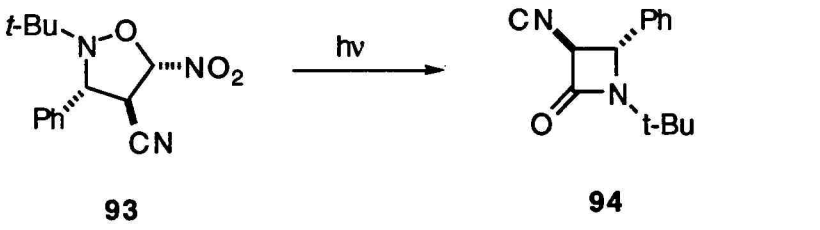

**87** **88** **89**

Nagata found that 4-pyrimidones undergo photolytic ring contraction forming β-lactam products.[45] For example, pyrimidone **90** was irradiated in methanol to give the corresponding azetidinone **93** in 58% yield. It was suggested that bicyclic intermediate **91** and β-lactam **92** were involved in the formation of **93** (Scheme 12).



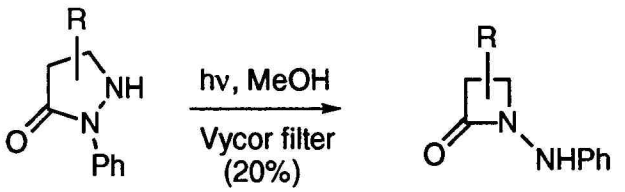

**Scheme 12**

Padwa devised a new approach to the β-lactam nucleus, in which he found that isoxazolidines, formed from nitrone cycloadditions, contract when subjected to irradiation.[46] Isoxazolidine **94** was subjected to ultraviolet irradiation and produced only the *trans*-β-lactam **95** (eq. 4).




(4)

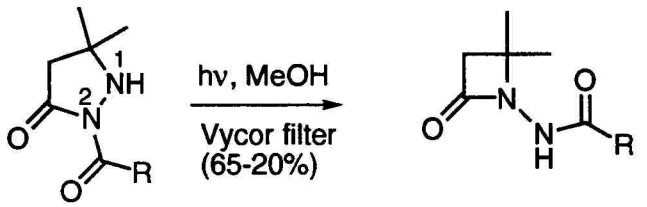
Among the known photolytic ring contractions which lead to a β-lactam, one reported by Ege,[47] in which the pyrazolidin-3-one **95** was shown to afford N-aminoazetidinone **96** upon irradiation, seemed especially well suited for further development (eq. 5).




(5)

**95** **96**

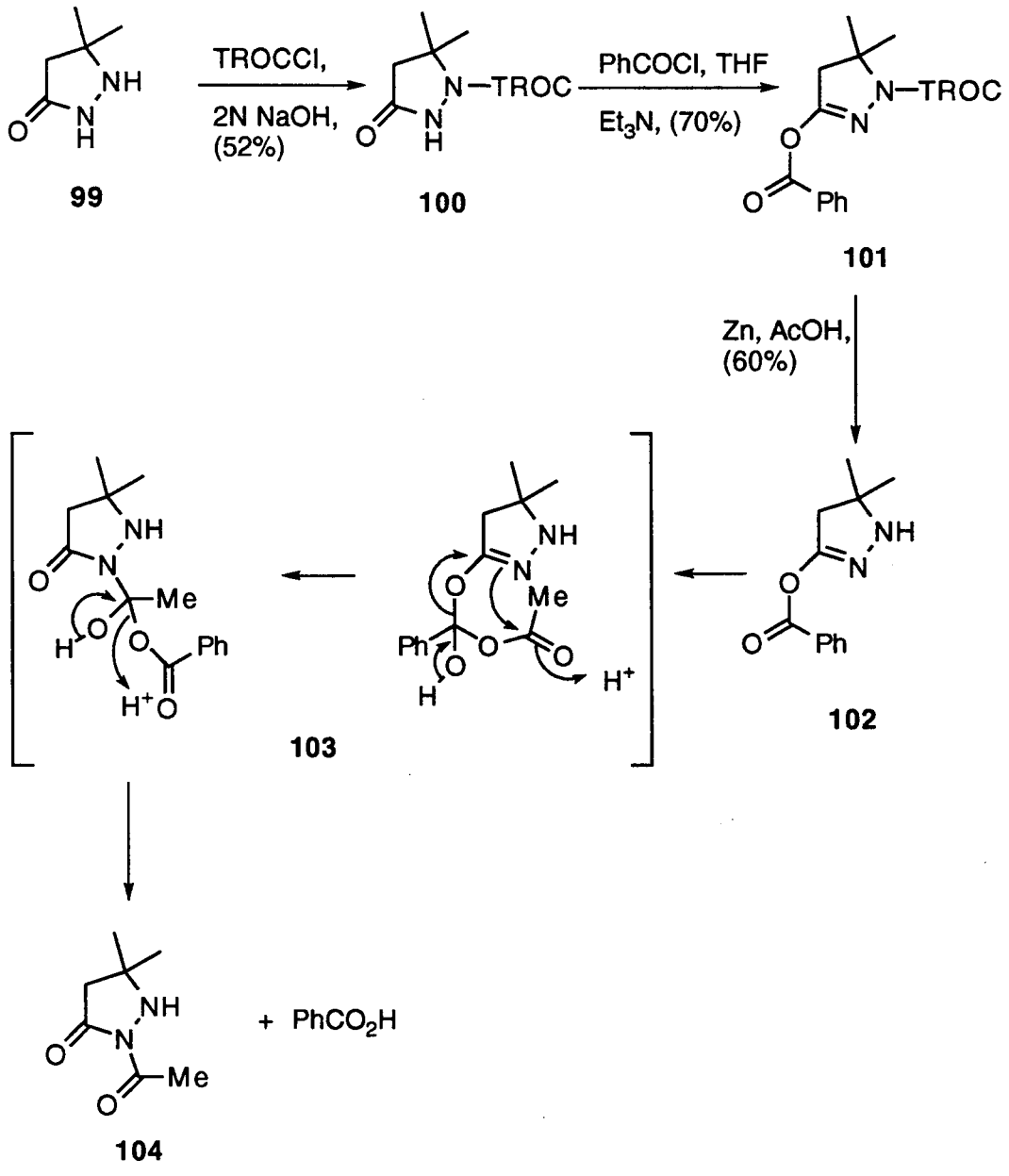
This reaction was further investigated by Johnson,[48] who found that the overall efficiency of the reaction was increased when an electron-withdrawing group was present at N2 of the pyrazolidinone ring (eq. 6). Pyrazolidinones **97** were photolyzed to the N-acylazetidinones **98** in a wide range of yields dependent on the R group.



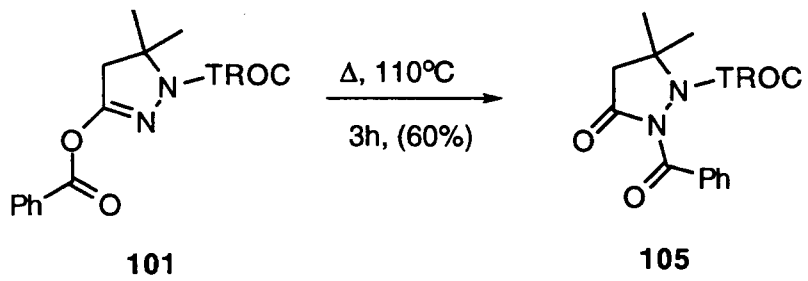

(6)

**97** **98**

In order for acylation at N2 to be accomplished, it was necessary to protect the more nucleophilic N1 nitrogen of the pyrazolidinone ring. This was carried out using an interesting rearrangement reaction (Scheme13).[48] The protected pyrazolidinone **100** was prepared from **99** using 2,2,2-trichloroethoxycarbonyl (TROC) chloride. Reaction of **100** with benzoyl chloride and triethylamine gave exclusively **101** which, upon treatment with zinc in acetic acid, yielded **102**. The latter underwent rearrangement as shown in **103** to **104**, the desired precursor for ring contraction. It was also found that pyrazolidinones such as **101** undergo thermal rearrangement to produce the desired N-acyl products like **105** in good yield (eq. 7).


TROCCl,
2N NaOH,
(52%)
PhCOCl, THF
Et3N, (70%)
Zn, AcOH,
(60%)
99
100
101
102
103
104
+ PhCO2H

**Scheme 13**


Δ, 110°C
3h, (60%)
101
105

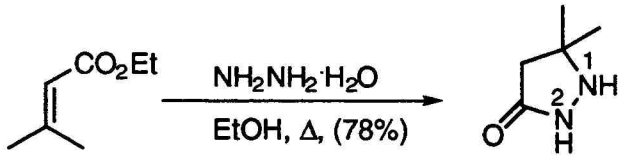
(7)

The foregoing work demonstrates that a photochemical ring contraction of pyrazolidin-3-ones offers a feasible route to N-substituted β-lactams. However, there are several limitations to this approach, including the difficulty of selective acylation at N2 to obtain the starting materials, the low yield of the ring contraction, the necessity for removing an N-amino function from the product azetidinone, and, finally, the lack of functional group variability needed to complete a useful β-lactam synthesis.

## I-B. Results and Discussion

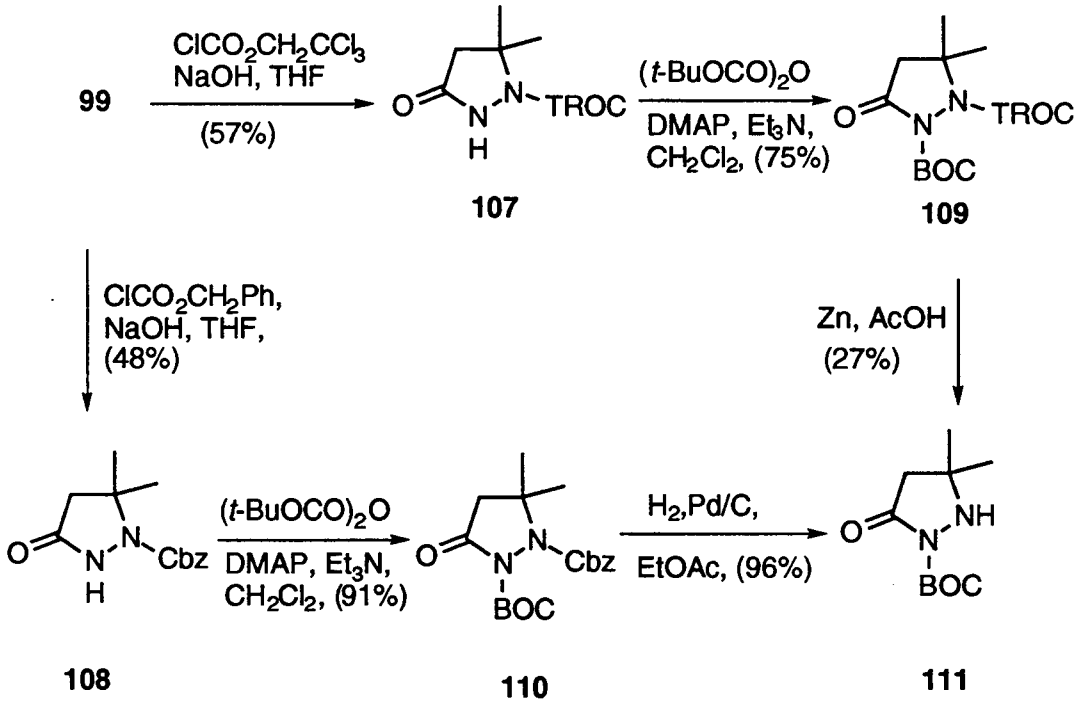
The objectives of this work were to develop an efficient synthesis of β–lactams using the photochemical ring contraction of pyrazolidin-3-ones discovered by Ege and to extend this methodology toward applications aimed at producing useful intermediates for carbapenem or monobactam antibiotics.

Attempts to improve the Ege-Johnson methodology in the hope of producing new N-substituted β–lactams was first undertaken in these laboratories by Slater.[49] He showed that the pyrazolidin-3-one starting materials could be readily prepared by condensation of hydrazine monohydrate with either an α,β–unsaturated ester or the corresponding acid. For example, ester **106** was converted to pyrazolidinone **99** using hydrazine monohydrate in refluxing ethanol in good yield (eq.8).



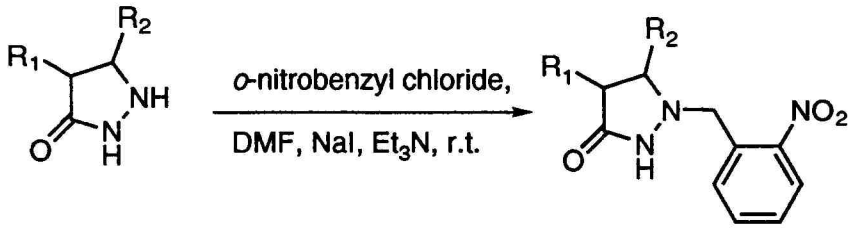

**106** **99** (8)

Unfortunately, selective acylation at N2 of these pyrazolidinones, to provide the precursor for ring contraction, necessitated a lengthy protection-acylation-deprotection sequence as outlined below (Scheme14). Protection of **99** as either the TROC derviative **107** or the carbobenzyloxy (Cbz) analogue **108** was followed by acylation to their corresponding N-*tert*-butoxycarbonyl (BOC) pyrazolidinones **109** and **110** which, upon deprotection, afforded **111**.




**Scheme 14**

An attractive alternative to this cumbersome procedure involved the use of a photolabile protecting group at N1 which would enable the ring contraction to be carried out in tandem with deprotection. The *o*-nitrobenzyl protecting group[50] appeared to meet the specifications of a photolabile group which would not interfere with azetidinone formation, and Perri found that N1-substituted derivatives **117-121** were easily prepared from their corresponding pyrazolidinone precursors **112-116** with *o*-nitrobenzyl chloride and dimethylformamide in the presence of sodium iodide and triethylamine (Table1).[49]




| Starting materials | $R_1$ | $R_2$ | Products | yield, (%) |
|---|---|---|---|---|
| **112** | Me | H | **117** | 63 |
| **113** | H | Me | **118** | 56 |
| **114** | Me | Me | **119** | 71 |
| **115** | H | H | **120** | 65 |
| **116** | H | $CH_2CO_2Et$ | **121** | 32 |

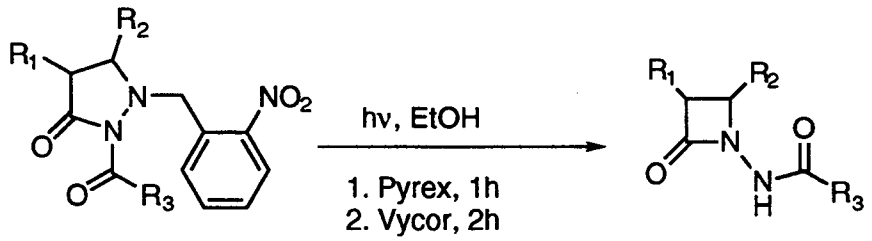
**Table 1. Preparation of 1-(*o*-Nitrobenzyl) pyrazolidin-3-ones.**

Several different acyl groups were used in combination with **117-121** to effect activation at N1 (Table 2). Acetyl derivatives **122** and **128** were obtained using Johnson's procedure outlined previously. Benzyl and ethyl carbamates **124** and **127** were prepared from their corresponding chloroformate esters. The BOC derivatives **123**, **129**, **130** and **133** were synthesized using *tert*-butoxycarbonic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP).[51] [2-(Trimethylsilyl)ethoxy] carbonyl (TEOC) derivatives **125**, **126**, **131**, **132**, and **134** were prepared by the method of Carpino using 2-(trimethylsilyl)ethyl azidoformate.[52]

| Starting Materials | $R_1$ | $R_2$ | $R_3$ | Products | yield (%) |
|---|---|---|---|---|---|
| **117** | Me | H | Me | **122** | 77 |
| **117** | Me | H | O-*t*-$C_4H_9$ | **123** | 98 |
| **117** | Me | H | $OCH_2C_6H_5$ | **124** | 73 |
| **117** | Me | H | $OCH_2CH_2SiMe_3$ | **125** | 73 |
| **118** | H | Me | $OCH_2CH_2SiMe_3$ | **126** | 81 |
| **118** | H | Me | OEt | **127** | 73 |
| **118** | H | Me | Me | **128** | 82 |
| **118** | H | Me | O-*t*-$C_4H_9$ | **129** | 96 |
| **119** | Me | Me | O-*t*-$C_4H_9$ | **130** | 99 |
| **119** | Me | Me | $OCH_2CH_2SiMe_3$ | **131** | 59 |
| **120** | H | H | $OCH_2CH_2SiMe_3$ | **132** | 90 |
| **121** | H | $CH_2CO_2Et$ | O-*t*-$C_4H_9$ | **133** | 94 |
| **121** | H | $CH_2CO_2Et$ | $OCH_2CH_2SiMe_3$ | **134** | 90 |

**Table 2. Preparation of 1-(*o*-Nitrobenzyl)-2-acylpyrazolidin-3-ones.**

Irradiation of pyrazoldinones **123-134** was carried out with a 450-W medium pressure Hanovia lamp using a Pyrex filter for 1h and then a Vycor filter for 2h producing azetidinones **135-144** (Table 3).

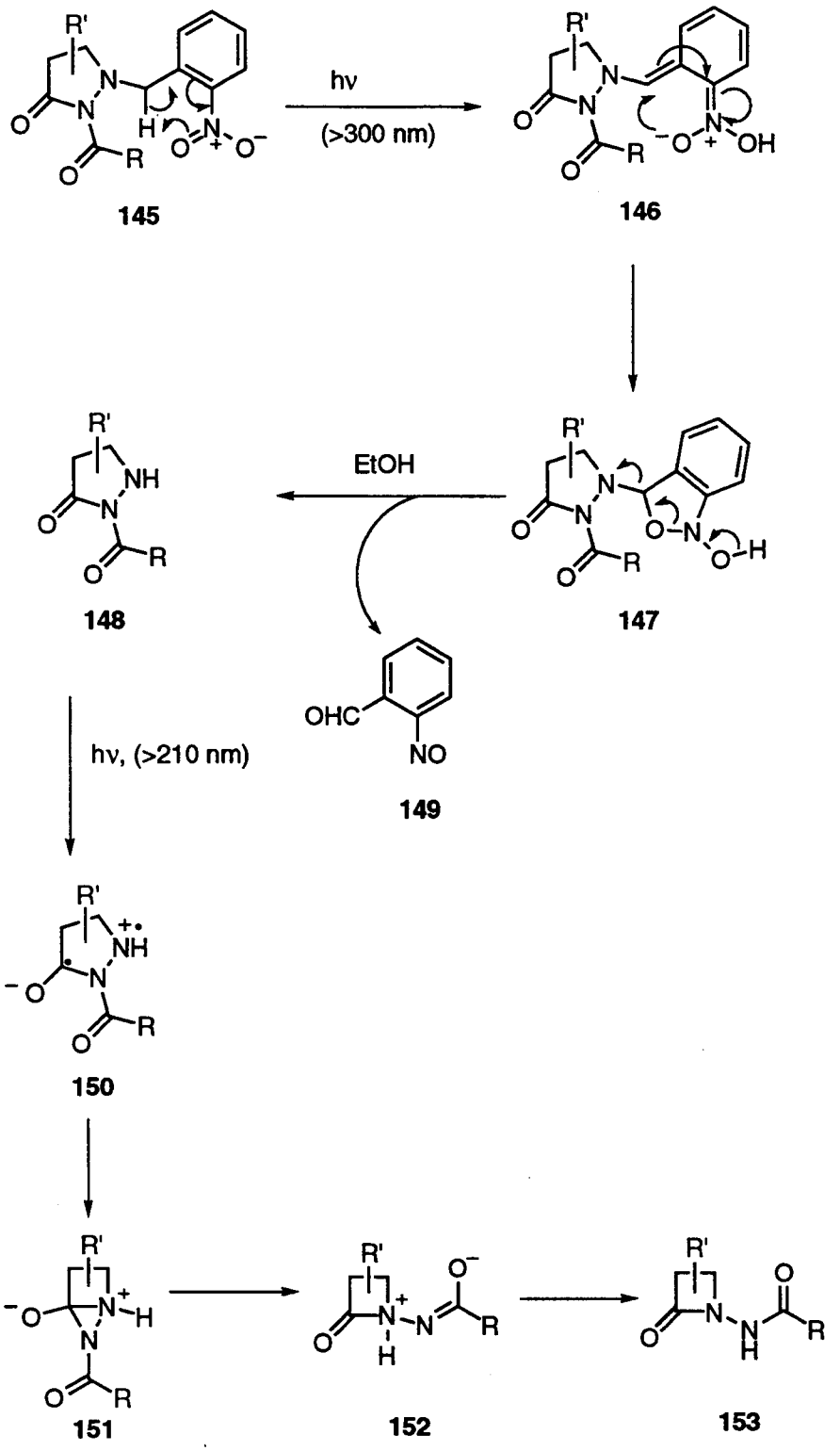



| Starting Materials | $R_1$ | $R_2$ | $R_3$ | Products | yield, (%) |
|---|---|---|---|---|---|
| **123** | Me | H | O-*t*-$C_4H_9$ | **135** | 84 |
| **124** | Me | H | $OCH_2C_6H_5$ | **136** | 17 |
| **125** | Me | H | $OCH_2CH_2SiMe_3$ | **137** | 60 |
| **126** | H | Me | $OCH_2CH_2SiMe_3$ | **138** | 44 |
| **129** | H | Me | O-*t*-$C_4H_9$ | **139** | 65 |
| **130** | Me | Me | O-*t*-$C_4H_9$ | **140** | 79 |
| **131** | Me | Me | $OCH_2CH_2SiMe_3$ | **141** | 55 |
| **132** | H | H | $OCH_2CH_2SiMe_3$ | **142** | 34 |
| **133** | H | $CH_2CO_2Et$ | O-*t*-$C_4H_9$ | **143** | 58 |
| **134** | H | $CH_2CO_2Et$ | $OCH_2CH_2SiMe_3$ | **144** | 41 |

**Table 3. Tandem Photochemical Conversion of Pyrazolidin-3-ones to 1-(Acylamino)azetidin-2-ones.**

The BOC derivatives **135**, **139**, **140**, and **143** were generally isolated in the best yields from (58%-84%), while the TEOC derivatives **137**, **138**, **141**, **142**, and **144** were isolated in yields varying from 34% to 60%. The one reaction leading to a Cbz-substituted azetidinone derivative (**136**) gave only a 17% yield.

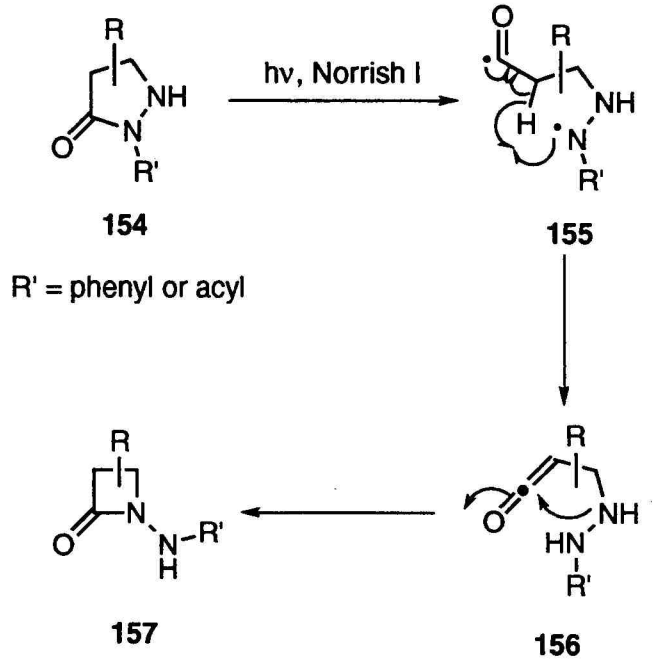
A mechanism which accounts for the sequence of steps that leads from (1-*o*-nitrobenzyl)-2-acylpyrazolidin-3-one **145** to N-(acylamino)azetidin-2-one **153** is shown in Scheme 15.




**Scheme 15**

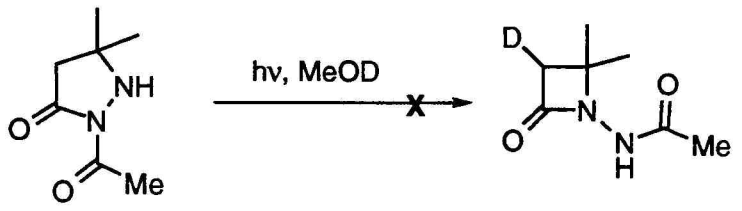
The initial excitation of **145** with a Pyrex filter occurs at wavelengths > 300 nm[50] causing the *o*-nitrobenzyl substituent to undergo a Norrish type II rearrangement to **146**. A facile electrocyclic cyclization of **146** generates **147** which fragments to give the N1-unsubstituted pyrazolidinone **148** and *o*-nitrosobenzaldehyde **149**.[53] Irradiation of pyrazolidinone **148** at a wavelength > 210 nm through a Vycor filter results in formation of a radical anion-radical cation species **150** via an intramolecular electron transfer from the excited state of **148**. Bond closure of **150** leads to the bicyclic intermediate **151**[48] which then undergoes bond reorganization to **152**. The latter yields **153** following proton transfer from **152**.

The possibility of an alternative mechanism for the ring contraction was proposed and examined by Ege[54] and Johnson.[48] A Norrish type I ring opening of pyrazolidinone **154** to intermediate **155** was considered. This would be followed by intramolecular hydrogen atom abstraction to give ketene **156** which would then cyclize to azetidin-2-one **157** (Scheme 16).




**Scheme 16**

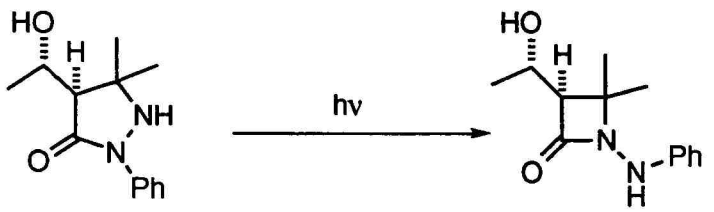
Johnson ruled out this mechanism by performing the photolysis of **105** in deuteriated methanol.[48] If the ketene mechanism was operative, then **158** should show incorporation of a deuterium atom at the 3-position of the β–lactam ring (eq. 9). Mass spectral analysis of the product revealed no incorporation of deuterium in the product from **105**.




(9)

**105** **158**

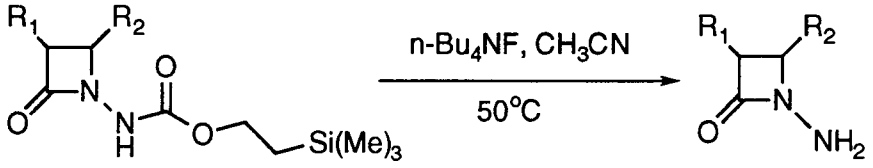
Ege also showed that the ring contraction cannot be occurring through a ketene intermediate in the photolysis of **159** to give **160** (eq. 10). X-ray crystal structures of both the starting material and product proved that the reaction proceeded with complete retention of configuration, a result which would not have been expected if a ketene were involved.[54]




(10)

**159** **160**

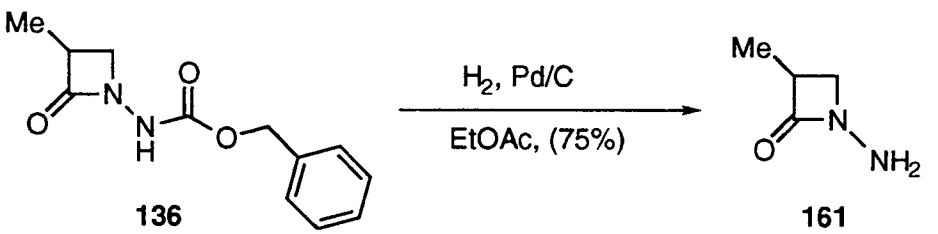
A practical route to N-aminoazetidinones was found through cleavage of the TEOC derivatives.[49] Azetidinones **137**, **138**, **141**, **142**, and **144**,when treated with tetra-*n*-butylammonium fluoride in acetonitrile, afforded the desired N-aminoazetidinones **161-165** in good yield (Table 4).




| Compound | $R_1$ | $R_2$ | Products | Yield, (%) |
|---|---|---|---|---|
| **137** | Me | H | **161** | 73 |
| **138** | H | Me | **162** | 58 |
| **141** | Me | Me | **163** | 73 |
| **142** | H | H | **164** | 88 |
| **144** | H | $CH_2CO_2Et$ | **165** | 33 |

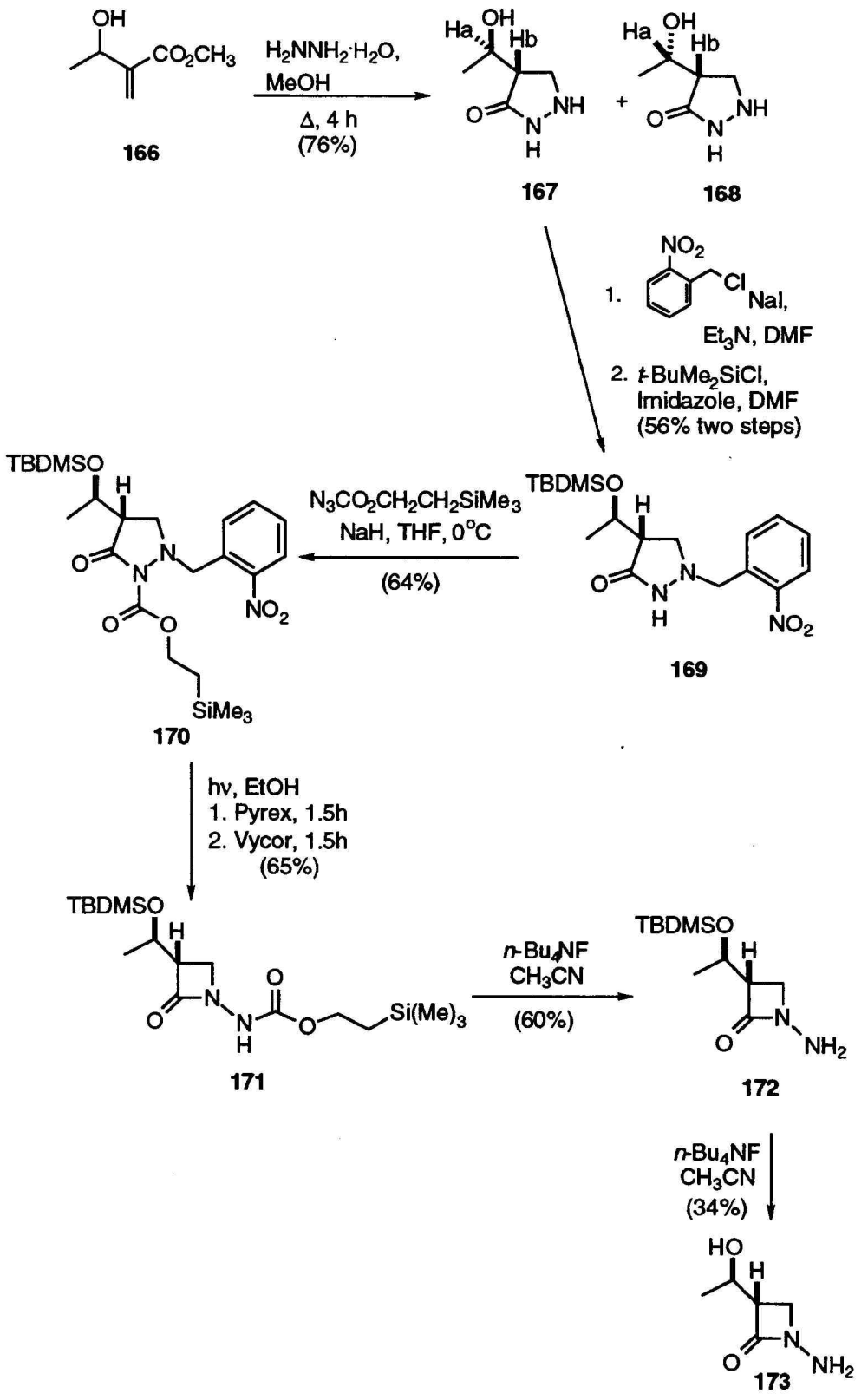
**Table 4. Preparation of 1-Aminoazetidin-2-ones.**

The BOC derivatives **139**, **140**, and **143** were eliminated as N-aminoazetidinone precursors when attempts to remove the BOC group with trifluoroacetic acid resulted in clean rearrangement of the azetidinone to the pyrazolidinone nucleus.[49,55] The Cbz derivative **136** was hydrogenated to afford N-aminoazetidinone **161** in good yield (eq. 11); however, the use of Cbz derivatives was made impractical by their low isolated yield in the photolysis step.



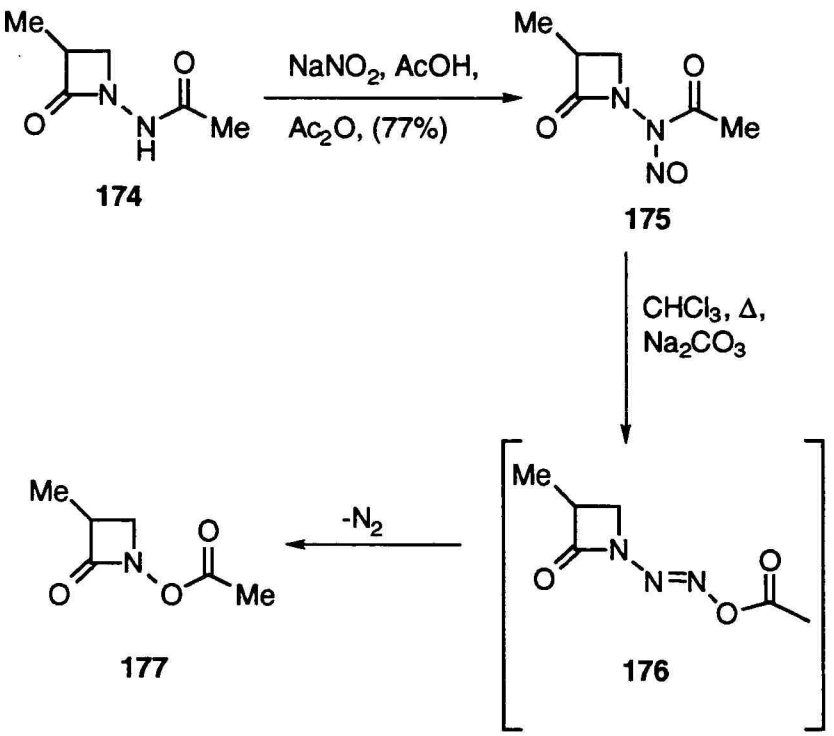

(11)

This tandem photochemical ring contraction was extended to include a β-lactam bearing the hydroxyethyl side chain characteristic of thienamycin. Treatment of hydroxy ester **166**[56] with hydrazine monohydrate gave the known pyrazolidinones **167** and **168**[57] as a 1:1 mixture of diastereomers which were readily separated by silica gel column chromatography (Scheme 17). Stereochemical assignments were made on the basis of the $H_a$-$H_b$ coupling constants. The more polar isomer **167** ($J_{ab}$ = 2.5 Hz) was assigned the thienamycin relative stereochemistry based on the empirical rule that $J_{ab}$ (*erythro*) < $J_{ab}$ (*threo*).[58] The $H_a$-$H_b$ proton pair of diastereoisomer **168** exhibited a larger coupling constant ($J_{ab}$ = 8.9 Hz) and was therefore assigned the *threo* configuration. Treatment of **167** with *o*-nitrobenzyl chloride afforded the expected N1-alkylated pyrazolidinone which, without purification, was converted directly to its *tert*-butyldimethylsilyl ether **169.** Acylation at N2 was accomplished using 2-(trimethylsilyl)ethyl azidoformate and yielded pyrazolidinone **170**. Photolysis of **170** through Pyrex and then through Vycor produced azetidinone **171** in good yield. Selective deprotection of **171** by brief contact with one equivalent of *tetra-n*-butylammonium fluoride afforded **172** in 60% yield. Further deprotection of **172** with one equivalent of tetra-*n*-butylammonium fluoride provided the desired N-amino alcohol **173** in 34% yield.


OH
CO2CH3
166
H2NNH2·H2O,
MeOH
Δ, 4 h
(76%)
Ha
OH
Hb
NH
O
N
H
167
168
NO2
Cl
1. NaI,
Et3N, DMF
2. t-BuMe2SiCl,
Imidazole, DMF
(56% two steps)
TBDMSO
H
169
N3CO2CH2CH2SiMe3
NaH, THF, 0°C
(64%)
SiMe3
170
hv, EtOH
1. Pyrex, 1.5h
2. Vycor, 1.5h
(65%)
Si(Me)3
171
n-Bu4NF
CH3CN
(60%)
NH2
172
n-Bu4NF
CH3CN
(34%)
HO
173

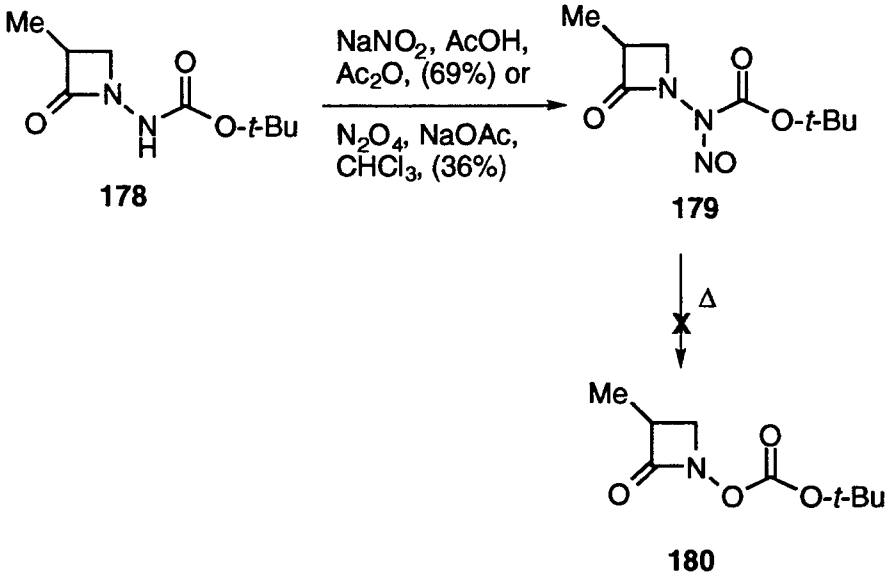
**Scheme 17**

Cleavage of the N-N bond in N-(acylamino)azetidinones is a necessary transformation for a general entry into the N-unsubstituted β-lactam system. This transformation was initially investigated by Perri who showed that N-acetylamino derivatives such as **174** were inert to hydrogenolysis with Raney nickel. He also found that they underwent decomposition with electron transfer reducing agents such as samarium diiodide.[59] Perri demonstrated that nitrosation of **174** proceeded in good yield to give nitrosohydrazide **175** which was converted to the N-acyloxyazetidinone **177** together with **174** in basic refluxing chloroform (Scheme 18). The formation of **177** can be explained by an intramolecular N-O acyl rearrangement followed by extrusion of nitrogen from diazo ester **176**, a documented deamination process.[60]




**Scheme 18**

Perri further examined this deamination protocol using N-BOC derivatives. He showed that urethane **178** could be nitrosated with either sodium nitrite and acetic acid or with dinitrogen tetroxide gas to give **179** (Scheme 19). Unfortunately,**179** failed to undergo acyl transfer to **180** in analogy to **175**. The principal outcome was denitrosation to **178**.

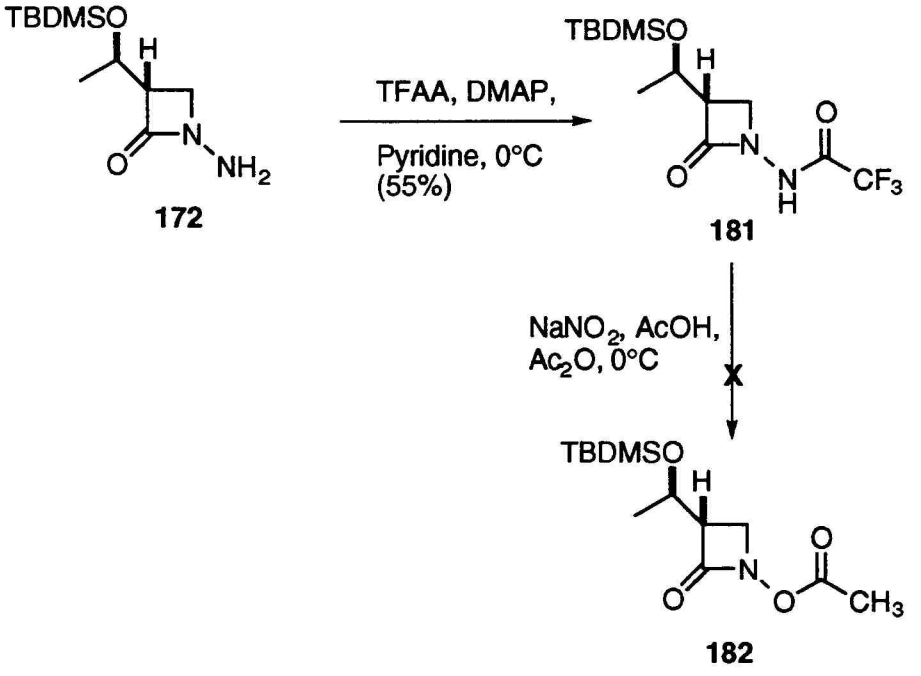



**Scheme 19**

The difficulty of removing the nitrogen substituent from the N-acylazetidinones prompted the search for an alternative approach. Although it appeared attractive at first glance, adaption of Miller's conditions for reductive cleavage of N-hydroxy β–lactams,[38] using an acidic solution of titanium (III) chloride, had to be ruled out since N-aminoazetidinones undergo ring expansion to pyrazolidinones under acidic conditions.

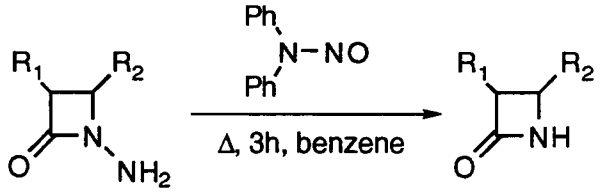
Ganem showed that simple trifluoroacetamides undergo smooth nitrosation and rearrangement to deaminated products,[61] and an extension of this procedure to our more complex β–lactam system was next investigated. Treatment of N-aminoazetidinone **172** with trifluoroacetic anhydride (TFAA)

produced the N-trifluoroacetylaminoazetidinone **181** in good yield. However, nitrosation of **181** under Ganem's conditions failed to produce the desired rearrangement product **182** and resulted only in decomposition (Scheme 20). Attempts to nitrosate **181** with nitrogen tetroxide were also unsuccessful.




**Scheme 20**

A solution to the problem of removing the N-amino substituent from the azetidinones was finally found in a report by Rees and Storr.[62] They showed that deamination of a 1-aminotriazine could be accomplished with diphenylnitrosamine.[63] When N-aminoazetidinones **161-165** were exposed to this reagent, β–lactams **183-188** were obtained in good yield (Table 5).[59] The azetidinone **188** has been used as an intermediate in the synthesis of several carbapenem antibiotics, including PS-5, PS-6, and thienamycin.[64]

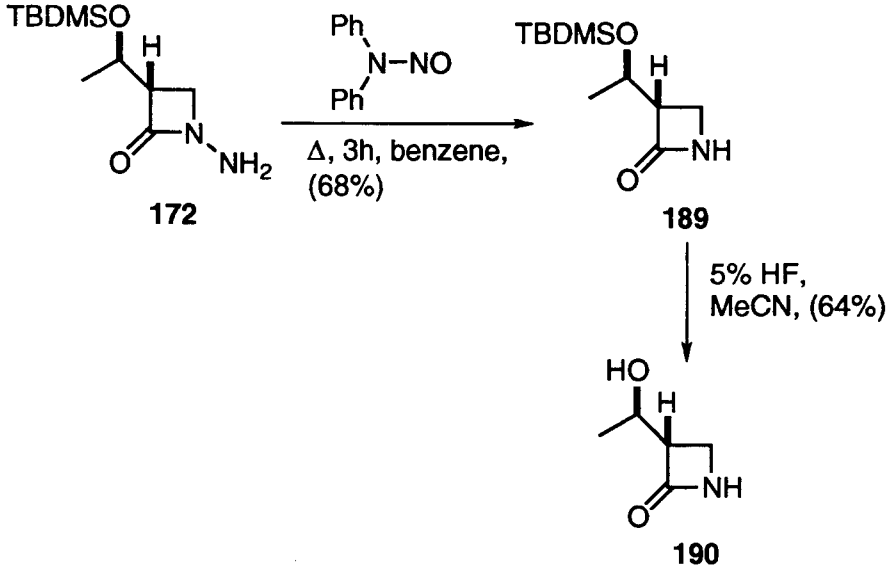



| Compound | $R_1$ | $R_2$ | Product | Yield (%) |
|---|---|---|---|---|
| **161** | Me | H | **183** | 55 |
| **162** | H | Me | **184** | 51 |
| **163**[a] | Me | Me | **185,186** | 67 |
| **164** | H | H | **187** | 61 |
| **165** | H | $CH_2CO_2Et$ | **188** | 65 |

a *cis: trans* mixture (3.5:1) of 185 and 186 was obtained and separated by chromatography.

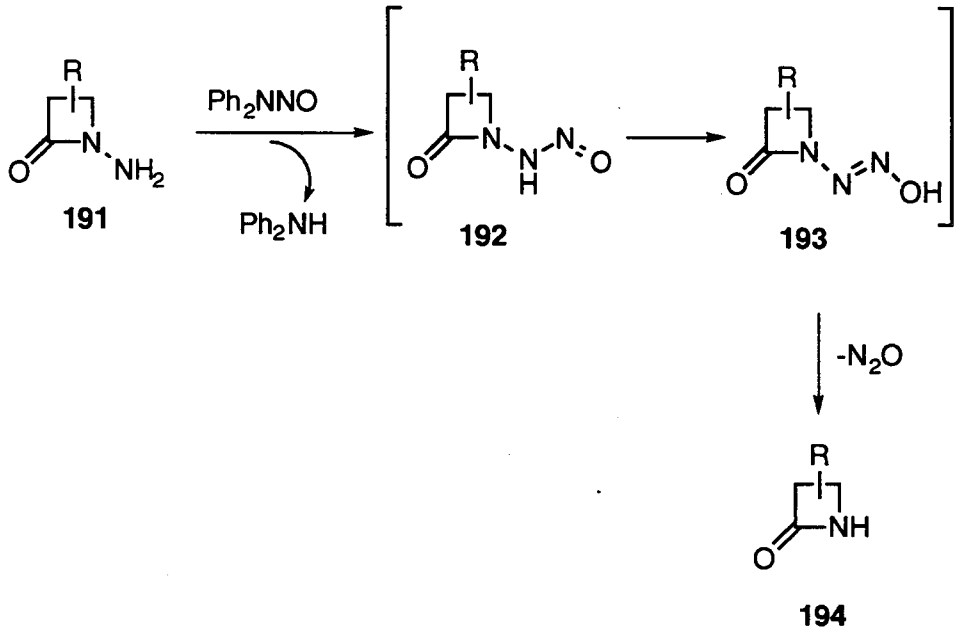
**Table 5. Nitrosative Deamination of 1-Aminoazetidin-2-ones.**

The aminoazetidinone **172** was deaminated to give **189** in good yield. The latter was deprotected with hydrofluoric acid in acetonitrile to afford **190**, a β–lactam possessing the thienamycin side-chain configurations (Scheme 21).



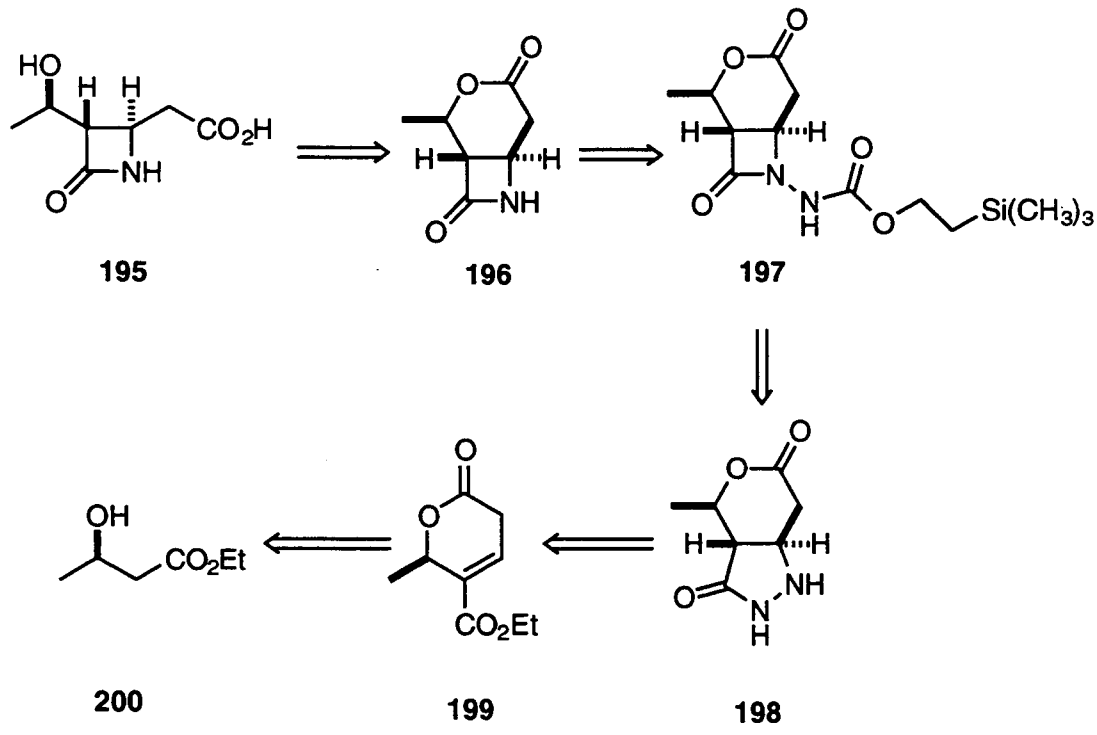

**Scheme 21**

A probable mechanism for this deamination involves transnitrosation of **191** to yield **192** and diphenylamine. The diazotate tautomer **193** would undergo elimination of $N_2O$ to give the parent β–lactam **194** (Scheme 22).




**Scheme 22**

With a complete route to N-unsubstituted β-lactams completed, our interest next turned to extending this methodology to the synthesis of more complex carbapenem antibiotics. Our target was the known intermediate **195**[29] which could be accessed via azetidinones **196** and **197**. Construction of the bicyclic pyrazolidinone precursor **198** was envisioned by stereoselective conjugate addition of hydrazine-monohydrate to α,β–unsaturated δ–lactone **199** followed by cyclization. Lactone **199** would be available from ethyl (*3R*)-hydroxybutyrate **200**. (Scheme 23).

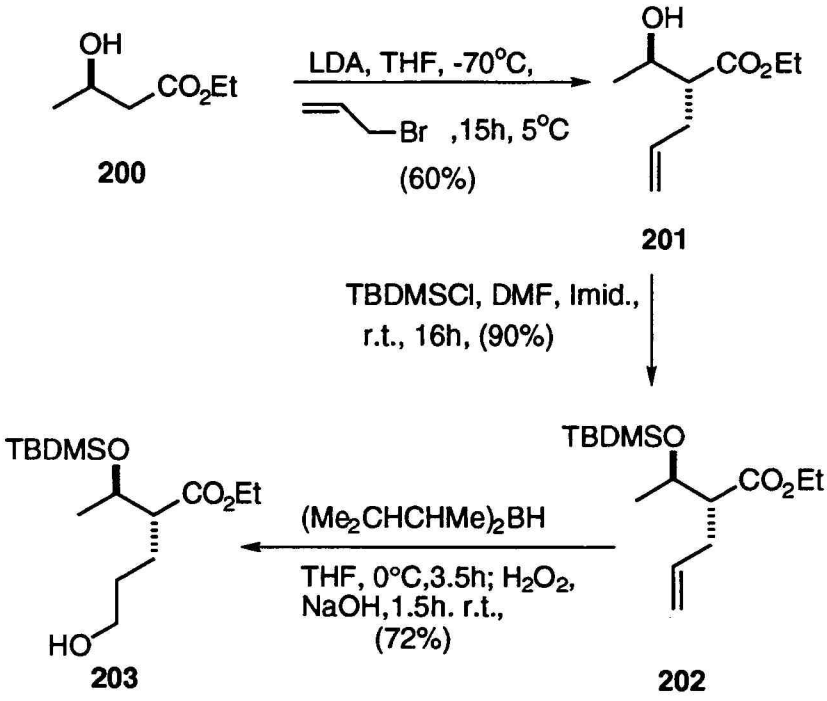



**195** **196** **197**

**200** **199** **198**

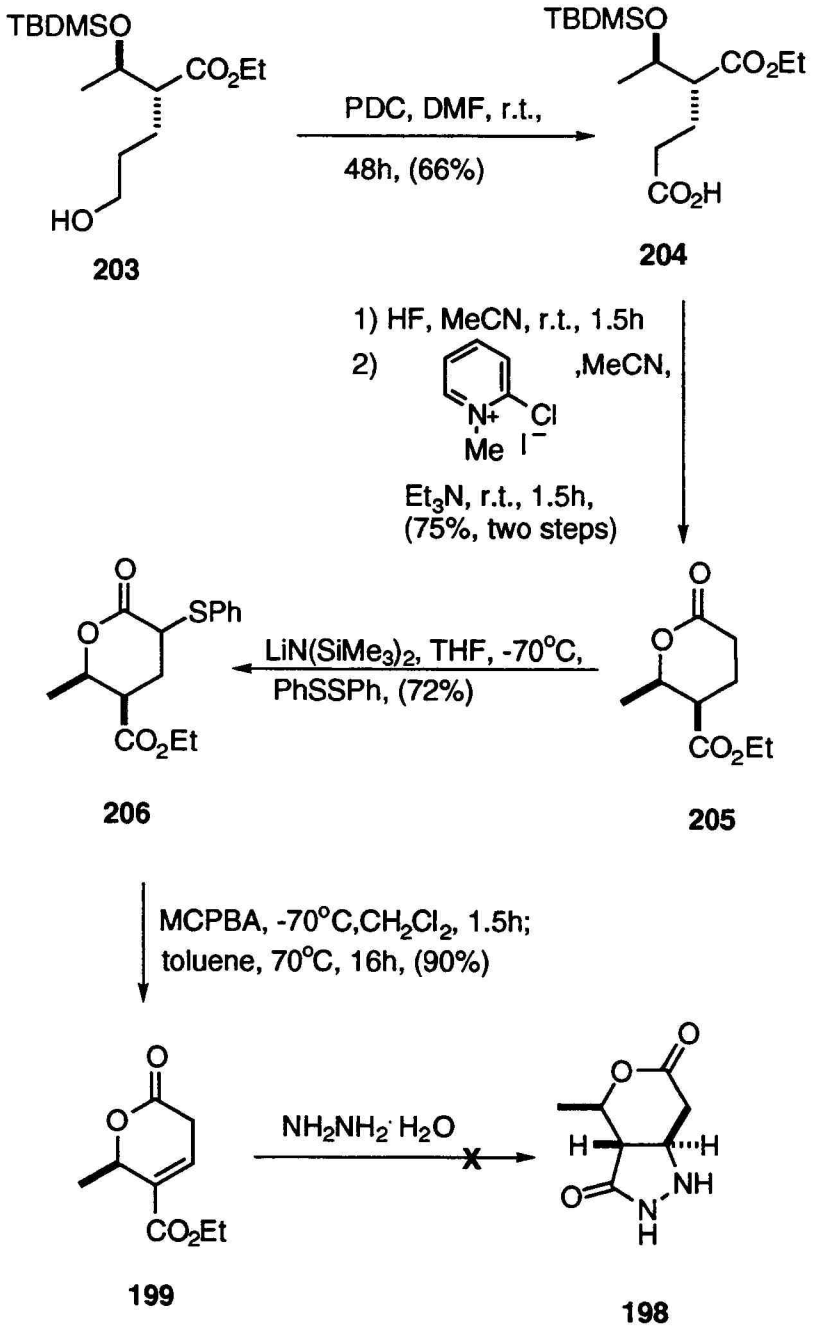
**Scheme 23**

The dianion of ethyl (*3R*)-hydroxybutyrate **200** was alkylated with allyl bromide producing **201**[65] which was protected as its silyl ether **202** using standard conditions.[66] Hydroboration-oxidation[67] of **202** with disiamylborane proceeded smoothly to alcohol **203** (Scheme 24).




**Scheme 24**

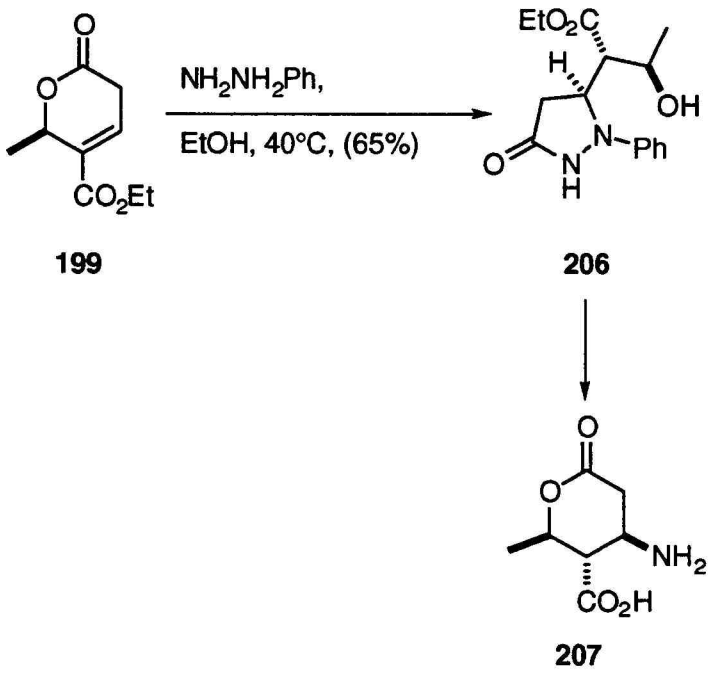
Hydroxy ester **203** was oxidized to the corresponding carboxylic acid **204** with pyridinium dichromate.[68] Deprotection of **204** with hydrofluoric acid resulted in an approximately 1:1 mixture of lactone **205** and the corresponding acyclic hydroxy acid. The crude mixture was converted entirely to **205** using Mukaiyama's lactonization conditions.[69] The enolate of lactone **205** was treated with diphenyldisulfide to give the α-sulfenyl lactone **206** which, on oxidation with *meta*-chloroperbenzoic acid, produced an intermediate sulfoxide.[70] Without purification, the sulfoxide was exposed to refluxing toluene causing elimination and isomerization of the resultant olefin to lactone **199**. Several attempts to form the desired bicyclic pyrazolidinone **198** from **199** were unsuccessful, the addition of hydrazine-monohydrate to **199** generally giving rise to polymeric products (Scheme 25).




**Scheme 25**

A rationale for the failure to form **199** was apparent by comparison to the results of Saito and co-workers.[71] They found that treatment of lactone **199** with phenylhydrazine produced pyrazolidinone **206** in 65% yield (Scheme 26). This shows that the terminal nitrogen of phenylhydrazine reacts selectively at

the lactone carbonyl and is followed by cyclization. Pyrazolidinone **206** was converted to lactone **207**, a known intermediate in route to thienamycin.[72]

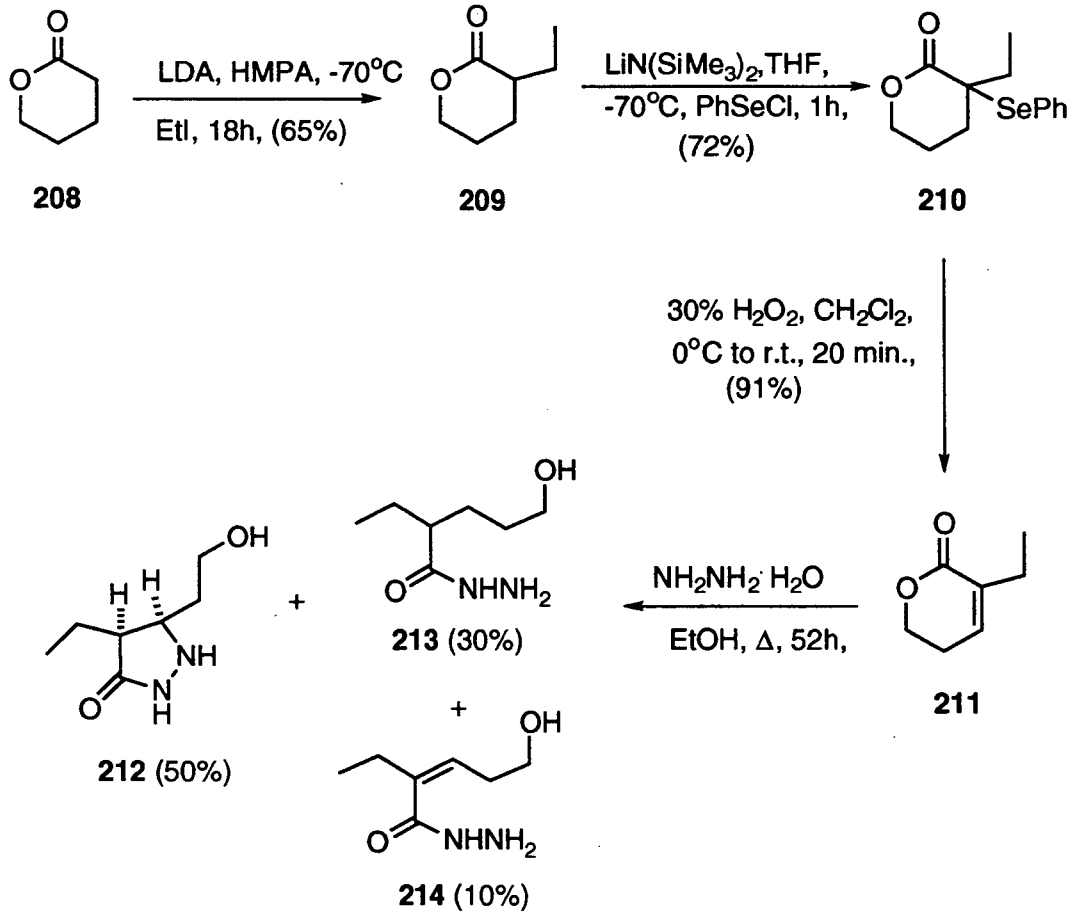



**Scheme 26**

Attempts to reduce the lactone carbonyl of **199** with diisobutylaluminum hydride in toluene at -70°C produced the corresponding lactol in a disappointing 25% yield. Allternatively, acidic or basic hydrolysis of **199** in an attempt to obtain the α,β-unsaturated carboxylic acid resulted in elimination to diene products.

The unfavorable reactivity of lactone **199** led to a reevaluation of our strategy as an approach to β-lactam antibiotics. An alternative plan was developed which led eventually to the formal synthesis of PS-5 (**10**).[73] This strategy was based on the earlier observation that α,β–unsaturated δ–lactones undergo hydrazinolysis to form pyrazolidinones via intramolecular cyclization at the lactone carbonyl.

This approach to the required α,β–unsaturated δ–lactone **211** with the ethyl side-chain necessary for constructing PS-5 utilized δ–valerolactone (**208**) as a starting material. The lithium anion of **208** was akylated with ethyl iodide to afford **209**.[74] Selenation[75] gave **210** which upon oxidation followed by elimination provided exclusively the *endo*cyclic α,β–unsaturated lactone **211**. Treatment of **211** with hydrazine monohydrate in refluxing ethanol gave the desired *cis*-3,4-dialkylpyrazolidinone **212**, accompanied by saturated hydrazide **213** and unsaturated hydrazide **214** in a 5:3:1 ratio, respectively (Scheme 27).

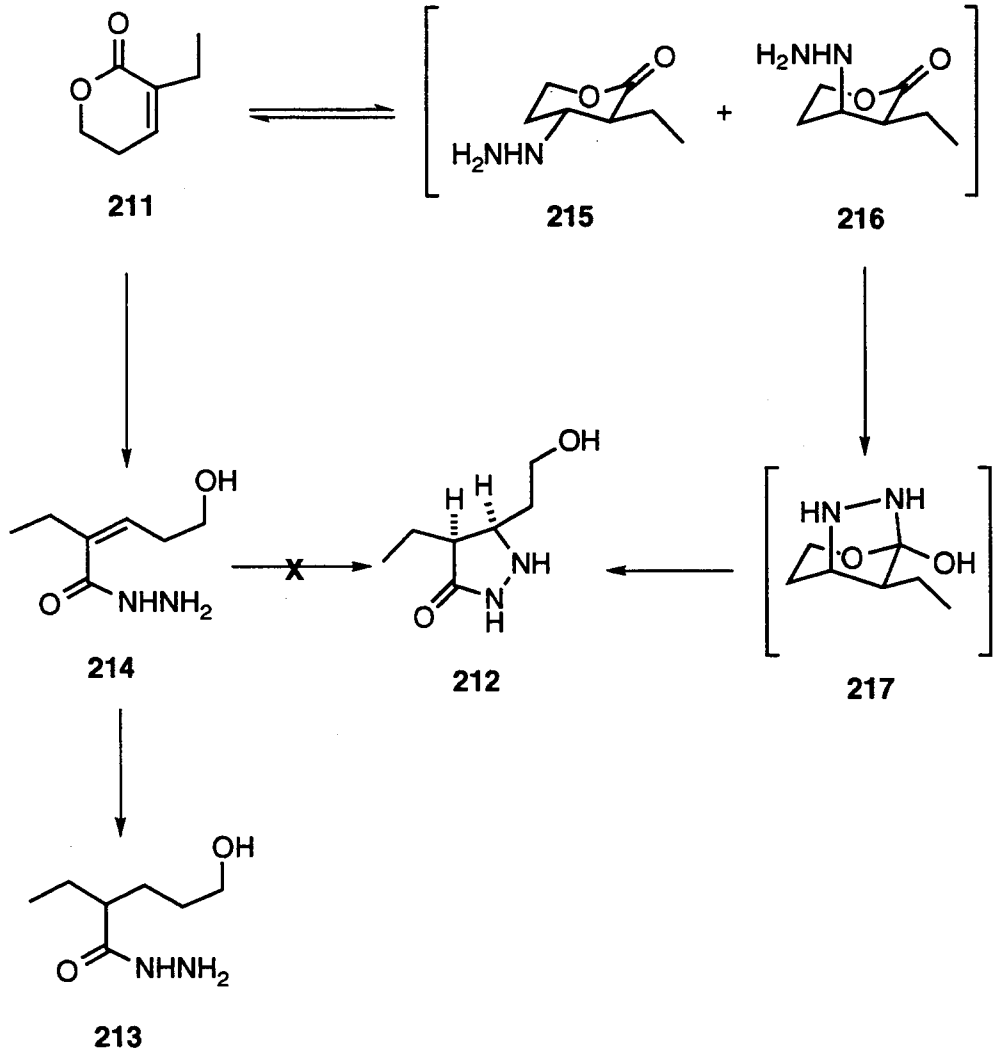



**208** **209** **210** **211**

**212** (50%) **213** (30%) **214** (10%)

**Scheme 27**

To rationalize this result, it was proposed that the reaction of **211** with hydrazine leads initially to *cis* and *trans* addition products **215** and **216** (Scheme 28). Only **216** is capable of undergoing transformation to the bicyclic intermediate **217** leading to pyrazolidinone **212** which, as a result, possesses *cis* configuration.

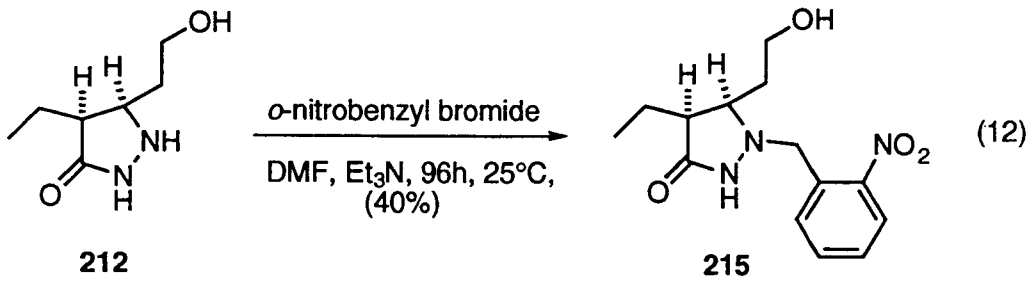



**Scheme 28**

Apparently, **214** does not undergo cyclization using these reaction conditions since its exposure to refluxing ethanol for 24 hours failed to produce

any *cis* or *trans* pyrazolidinone. Instead **214** is reduced in low yield with hydrazine to the saturated hydrazide **213**.

The structure of **212** was determined by *o*-nitrobenzylation which provided the monobenzylated pyrazolidinone **215** in modest yield (eq. 12). Confirmation of *cis* stereochemistry of this substance was obtained by X-ray crystallographic analysis (Figure 1).[76]




**212** **215** (12)

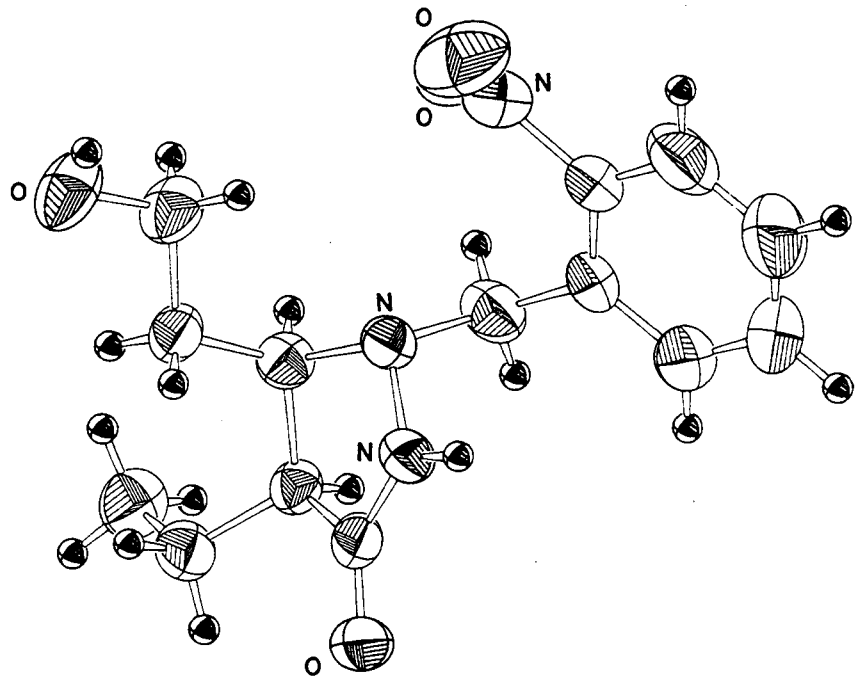
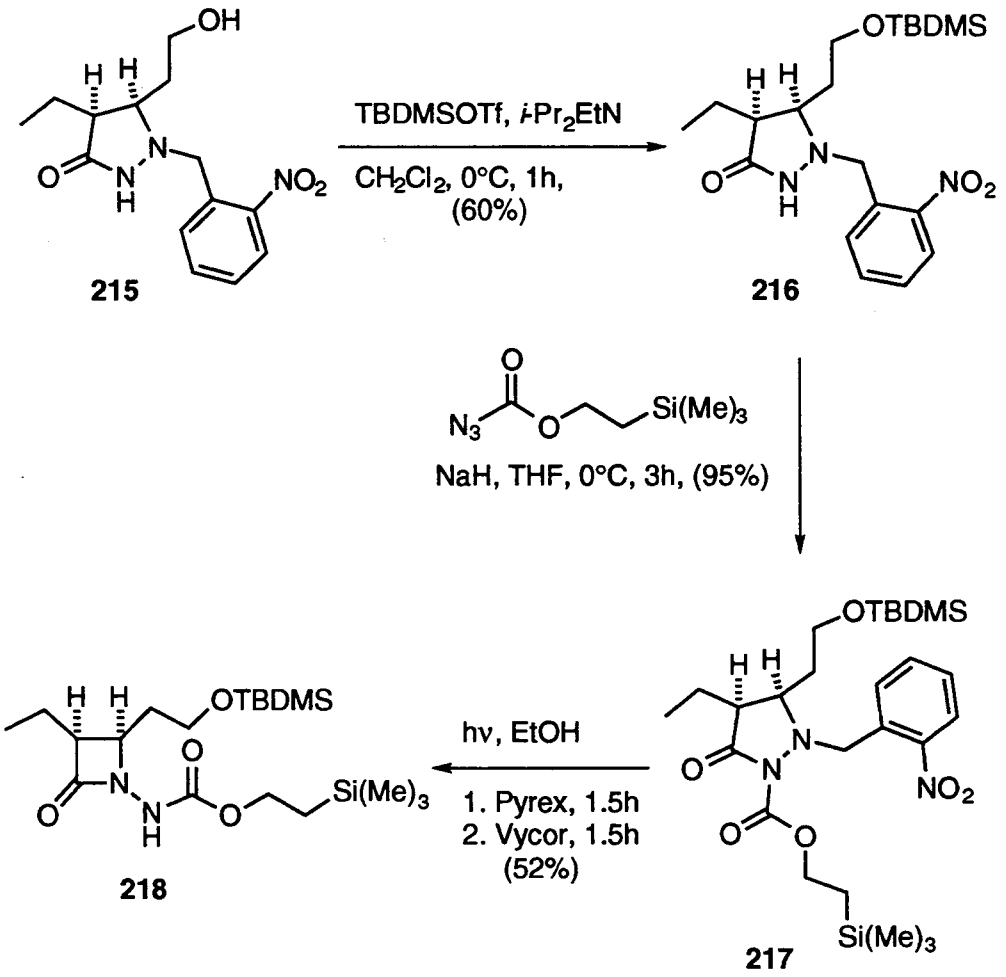



**Figure 1.** X-ray Crystal Structure of Pyrazolidinone **215.**

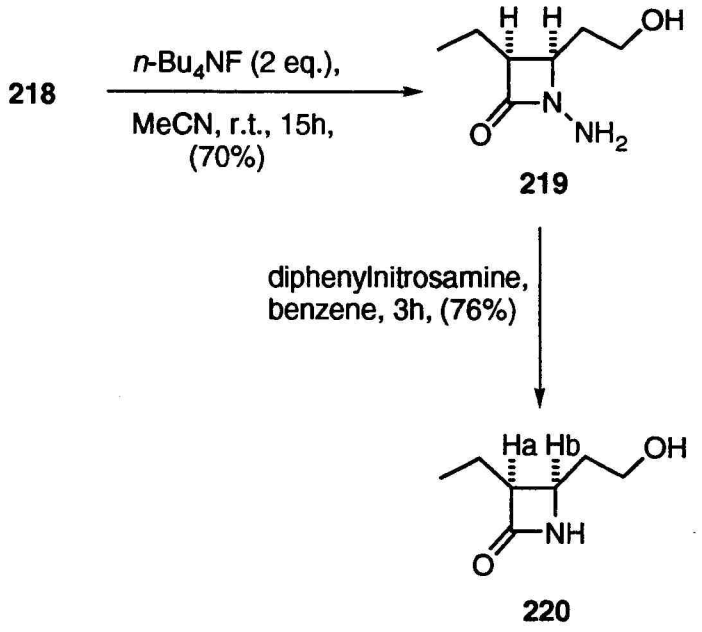
Continuation of the route from **215** required protection of the primary alcohol, and this was effected with *tert*-butyldimethylsilyl trifluoromethanesulfonate to give **216**. N2-Acylation of **216** with 2-(trimethylsilyl)ethyl azidoformate produced the fully activated pyrazolidinone **217** needed for photolysis. Irradiation of **217** in ethanol, first through Pyrex and then through a Vycor filter, resulted in smooth conversion to *cis* azetidinone **218** (Scheme 29).




**Scheme 29**

Treatment of **218** with two equivalents of tetra-*n*-butylammonium fluoride resulted in removal of both silyl protecting groups to give **219** in good yield

(Scheme 30). Nitrosative deamination of **219** finally gave the desired β–lactam **220**, a known intermediate in the synthesis of (+)-PS-5.[33] The Ha-Hb coupling constant in **220** (*J*ab = 5.4 Hz) compared well with that of *cis*-substituted β–lactams reported by Miller.[77]




**Scheme 30**

It is evident from these results that this ring contraction methodology can provide entry to useful carbapenem intermediates. The opportunity to create hybrid structures , such as β–lactam **190**, or analogues, such as **220** containing the unnatural *cis* stereochemistry, is a particularly valuable asset of this chemistry.

## I-C. Experimental

### General

Starting materials and reagents purchased from commercial suppliers were generally used without further purification. Solvents were dried by distillation from the appropriate drying agent immediately prior to use. Toluene, tetrahydrofuran, and ether were distilled from potassium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, diisopropylethylamine, dimethylformamide, acetonitrile, pyridine and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Moisture and air sensitive reactions were carried out under an atmosphere of argon.

Concentration *in vacuo* refers to the use of a rotary evaporator at water aspirator pressures. Residual solvent was removed by vacuum pump at pressures less than 2 torr. Reaction flasks were flame dried under a stream of argon. Syringes were oven dried at 200°C and cooled to room temperature in a desiccator over anhydrous calcium sulfate.

Analytical thin layer chromatography (TLC) was conducted using 1.5 x 5.0 cm precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Spots were visualized by ultraviolet light, or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, 10% ammonium molybdate, or a 1% solution of vanillin in 0.1M $H_2SO_4$ in methanol. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM).

Melting points were measured using a Büchi melting point apparatus. Optical rotations were measured on a Perkin-Elmer 243 polarimeter at ambient temperature using a 1 decimeter cell of 1 mL capacity. Infared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300, or Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. $^1$H NMR spectral data are reported in the order of: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad), coupling constant (*J*) in Hertz, and number of protons. Mass spectra MS(CI) were obtained using the Finnigan 4023 quadrapole GC-MS spectrometer with a 4500 source at 140°C and a vacuum of 0.7 torr. Mass spectra MS(EI) were obtained using the varian MAT311 with an ionization potential of 70 eV. High resolution mass spectra were obtained using the Kratos MS-50 RF spectrometer. X-ray crystallographic data was collected using the Rigaku AFC6R instrument. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

**4-[(1'-Hydroxy)ethyl]pyrazolidin-3-one (167).** To a solution of **166**[56] (825 mg, 6.42 mmol) in 15 mL of absolute methanol was added hydrazine hydrate (0.34 mL, 1.06 mmol) using a syringe. The resulting solution was heated at reflux for 4 h then concentrated *in vacuo* to a viscous oil. Purification by column chromatography on silica gel with 15% methanol-chloroform as the elutant provided (634 mg, 76%) of a 1:1 mixture of diastereomeric pyrazolidin-3-ones. Compound **167** eluted from the column after its stereoisomer: IR (neat) 3500-3000 (br), 1681 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 5.65 (bs, 2H), 4.30 (dq, *J* = 6.5, 2.5, 1H), 3.7-3.4 (m, 2H), 3.48

(s, 1H), 2.58-2.50 (m, 1H) 1.20 ( d, $J$ = 6.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 177.3, 64.9, 49.6, 45.9, 21.3; MS (EI) *m/z* (rel. intensity) 130 ($M^+$,20), 112 (29), 85 (100), 69 (50); HRMS, *m/z* calcd. for $C_5H_{10}N_2O_2(M^+)$: 130.0742. Found: 130.0741.

**4-[(1'-(*Tert*-Butyldimethylsilyloxy)ethyl]-1-(*o*-nitrobenzyl)pyrazolidin-3-one (169).** To a solution of **167** (1.57 g, 12.1 mmol) in dimethylformamide (30 mL) was added *o*-nitrobenzyl chloride (2.07g, 12.1 mmol), triethylamine (1.68 mL, 12.1 mmol), and sodium iodide (903 mg, 6.05 mmol). The reaction mixture was stirred under argon for 36 h at room temperature, and the dimethylformamide was removed *in vacuo* . The crude material was taken up in methylene chloride (20 mL) and washed with water (2 x 20 mL), saturated sodium chloride (2 x 20 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*.

The crude product (3.50 g) was diluted with dimethylformamide (75 mL) and *tert*-butyldimethylsilyl chloride (2.00 g, 13.3 mmol) was added along with imidazole (1.36 g, 19.9 mmol). The mixture was stirred under argon at room temperature for 24 h and then partitioned between water (30 mL) and ether (30 mL). The aqueous layer was washed with ether (2 x 30 mL) and the organic layers combined, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography on silica gel with 1:1 ethyl acetate-hexane as elutant afforded **169** (2.59 g, 56% based on **167**) as a yellow solid: mp 138-141°C; IR (thin film) 2955, 2929, 1696, 1528, 836, 668 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 1H), 7.61-7.58 (m, 2H), 7.51-7.45 (m, 1H), 6.67 (s, 1H), 4.35-4.31 (m, 1H), 4.21 (s, 2H), 3.54-3.52 (m, 1H), 3.39-3.33 (m, 1H), 2.77-2.70 (m, 1H), 1.17 (d, $J$ = 6.3 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 174.1, 149.3, 133.2, 131,5,

130.9, 128.9, 125.0, 66.4, 61.1, 53.4, 47.6, 25.7 (x3), 18.9, 17.9, -4.6, -4.9; MS (CI) *m/z* (rel. intensity) 380 (M + 1,100), 364 (26), 322 (39), 248 (15), 159 (18), 120 (19), 75 (14); HRMS, *m/z* calcd. for $C_{18}H_{30}N_3O_4Si$ (M + 1): 380.2006. Found: 380.2006. Anal. Calcd. for $C_{18}H_{29}N_3O_4Si$: C, 56.96, H, 7.71, N, 11.08. Found: C, 57.20, H, 7.80, N, 11.13.

**2-[(2-(Trimethylsilyl)ethoxycarbonyl]-1-(*o*-nitrobenzyl)-4-[(1'-(*tert*-butyldimethysilyloxy)ethyl]pyrazolidin-3-one (170).** To a solution of **169** (2.59 g, 6.82 mmol) and (trimethylsilyl)ethyl azidoformate (0.40 g, 7.51 mmol) in dry tetrahydofuran (100 mL).was added slowly sodium hydride (0.33g, 8.18 mmol, 60% in mineral oil) at 0°C. After all the sodium hydride was added, the reaction was stirred for 30 min at 0°C and 2 h at room temperature. The reaction mixture was partitioned between water (30 mL) and ether (30 mL), and the aqueous layer was separated and washed with ether (2 x 30 mL). The combined ether layers were dried over anhydrous magnesium sulfate then concentrated *in vacuo.* Purification by column chromatography on silica gel using 30% ethyl acetate-hexane as elutant provided **170** (2.28 g, 64%) as a colorless solid: mp 85-88°C (ether-hexane); IR (neat) 2955, 1788, 1734, 1528, 1347, 1288, 1252, 859, 838, 779 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$ ) δ 7.95-7.92 (m, 2H), 7.67-7.63 (m, 1H), 7.48-7.45 (m, 1H), 4.44-4.24 (m, 5H), 3.14 (dd, *J* = 11.9, 12.0 Hz, 1H), 3.00-2.97 (m, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.10-1.05 (m, 2H), 0.80 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H), 0.03 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 172.0, 149.9. 149.1, 133.3, 131.9, 131.4, 128.6, 124.5, 65.7, 65.6, 56.9, 48.0 (x2), 25.7 (x3), 22.3, 17.8, 17.6, -1.6 (x3), -4.5, 5.2; MS (CI) *m/z* (rel. intensity) 524 (M + 1,13), 496 (100), 480 (57), 452 (56), 73 (38), 41 (49); HRMS, *m/z* calcd. for $C_{24}H_{42}N_3O_6Si_2$ (M + 1): 524.2612. Found: 524.2612.

**3-[(1'-*Tert*-Butyldimethylsilyloxy)ethyl]-1-[(2-(trimethylsilyl)ethoxycarbonyl)amino]azetidin-2-one (171).** A sample of **170** (1.10 g, 2.09 mmol) in absolute ethanol (100 mL) was degassed for 1 hr in a quartz photochemical immersion well. The solution was irradiated through a pyrex filler with a 450-Watt Hanovia lamp for 2 h at 0°C. The filter was changed to Vycor, and the solution was irradiated for another 5.5 h at 0°C. The resulting solution was concentrated *in vacuo* to provide a dark brown oil. Purification by column chromatography on silica gel using 30% ethyl acetate-hexane as elutant afforded **171** (0.49 g, 60%) as a colorless oil: IR (neat) 3275, 2955, 2930, 1786, 1781, 1733, 1515, 1472, 1179, 1062, 1046, 836 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.66 (bs, 1H), 4.26.-4.17 (m, 3H), 3.63-3.61 (m, 1H), 3.53-3.51 (m, 1H), 3.11-3.08 (m, 1H), 1.23 (d, $J$ = 6.1 Hz, 3H), 1.04-0.98 (m, 2H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 9 H); $^{13}C$ NMR (75 MHz, $CDCl_3$ ) δ 168.8, 154.9, 65.7, 64.9, 55.3, 47.3, 25.6 (x3), 22.8, 17.9, 17.7, -1.2 (x3), -4.3, -5.0; MS (CI) *m/z* (rel. intensity) 389 (M + 1,17), 361 (78), 345 (100), 331 (22), 317 (69), 185 (26), 73 (66); HRMS, *m/z* calcd. for $C_{17}H_{37}N_2O_4Si_2$ (M + 1): 389.2292. Found: 389.2292.

**1-Amino-3-[(1'-*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (172).** To a solution of **171** (160 mg, 0.41 mmol) in acetonitrile (5 mL) was added 1.0 M tetra-*n*-butylammonium fluoride solution (0.41 mL, 0.41 mmol) in tetrahydrofuran. The mixture was heated at 45°C for 4.5 h and concentrated *in vacuo* to provide an oil. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **172** (63.0 mg, 60%) as a clear oil: IR (neat) 3332 (br), 2959, 2932, 2858, 1760, 1468, 1369, 1137, 1106, 1078, 1018, 985, 838, 778 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.19-4.13 (m, 1H), 3.96 (s,2H), 3.47-3.44 (m, 1H),

3.40-3.37 (m, 1H), 2.99-2.95 (m, 1H), 1.18 (d, $J$ = 6.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.7, 65.0, 54.6, 47.3, 25.7, 22.8, 17.9,-4.24, -5.05; MS (CI) *m/z* (rel. intensity) 245 (M + 1,51), 229 (69), 187 (85), 83 (30), 49 (40); HRMS, *m/z* calcd. for $C_{11}H_{25}N_2O_2$ (M + 1): 245.1685. Found: 245.1685. Anal. Calcd. for $C_{11}H_{24}N_2O_2Si$: C, 54.06, H, 9.91, N, 11.47. Found: C, 53.89, H, 10.02, N, 11.26.

**1-Amino-3-[(1'-hydroxy)ethyl]azetidin-2-one (173).** To a solution of **172** (33.7 mg ,0.14 mmol) in acetonitrile (5 mL), was added 1.0 M tetra-*n*-butylammonium fluoride solution (0.15 mL, 0.15 mmol) in tetrahydrofuran. The mixture was stirred under argon atmosphere for 24 h at room temperature and concentrated *in vacuo* to provide an oil. Purification by column chromatography on silica gel provided **173** (6.0 mg, 34%). The purification of this compound was not trivial. Four silica columns were performed using 10% methanol-methylene chloride twice, followed by 5% methanol-methylene chloride the remaining times. The tri-*n*-butylamine by-product appears to elute at the same rate ($R_f$ = .15, 10% methanol-methylene chloride) as the desired compound: IR (neat) 3329-3205 (br), 2969, 1744, 1138, 1091, 1011, 795 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ ) δ 4.23-4.14 (m, 1H), 4.07 (bs, 2H), 3.46-3.45 (m, 2H), 3.07-3.03 (m, 1H), 2.22 (bs, 1H), 1.27 (d, $J$ = 6.5 Hz, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$ ) δ 168.7, 64.8, 54.0, 47.7, 21.7; MS (EI) *m/z* (rel. intensity) 130 ($M^+$,5), 112 (25), 85 (36), 69 (98), 55 (100), 45 (79); HRMS, *m/z* calcd. for $C_5H_{10}N_2O_2$ ($M^+$): 130.0742. Found: 130.0741.

**1-Trifluoroacetamido-3-[(1'-*tert*-butyldimethylsilyloxy)-ethyl]azetidin-2-one (181).** To a solution of **172** (31 mg, 0.13 mmol) in dry pyridine (1 mL) containing N,N-(dimethylamino)pyridine (2 mg) was

added trifluoroacetic anhydride (61.6 μL, 0.38 mmol) at 0°C. The reaction mixture was warmed to room temperature and stirred for 6 h. The pyridine was removed *in vacuo*. The residue was dissolved in water (5 mL), extracted with chloroform (3 x 5 mL), and the combined organic dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel using 30% ethyl acetate-hexane as elutant provided **181** (23.8 mg, 55%) as a yellow oil: IR (neat) 3210, 2958, 2859, 1783, 1742, 1209, 1164 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.22 (quint., $J$ = 5.7 Hz, 1H), 3.73-3.70 (m, 2H), 3.26-3.21 (m, 1H), 1.23 (d, $J$ = 6.2 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H); 0.06 (s, 3H).

**3-Methyl-azetidin-2-one (183).** To a solution of **161**[49] (33.7 mg, 0.33 mmol) in benzene (2 mL) was added N,N-diphenylnitrosamine[63] (72.6 mg, 0.37 mmol). The mixture was heated at reflux for 3 h and concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant gave **183** (15.7 mg, 55%) as a clear oil: IR (neat) 3259 (br), 2971, 2902, 1739, 1195 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.90 (bs, 1H), 3.43 (t, $J$ = 5.3, 1H), 3.29-3.18 (m, 1H), 1.30 (d, $J$ = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$), δ 172.5, 46.2, 43.4, 13.6; MS (CI) *m/z* (rel. intensity) 86 (M + 1, 99); HRMS, *m/z* calcd. for $C_4H_8NO$ (M + 1): 86.0606. Found 86.0606.

**4-Methyl-azetidin-2-one (184).** To a solution of **162**[49] (70.0 mg, 0.692 mmol) in benzene (5 mL) was added N,N-diphenylnitrosamine (151 mg, 0.76 mmol). The mixture was heated at reflux for 2 h and concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant gave **184** (30.0 mg, 51%) as a

clear oil: IR (neat) 3266 (br), 2968, 2931, 1737, 1416, 1378, 1194 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.30 (bs, 1H), 3.77-3.70 (m, 1H), 3.09-3.02 (m, 1H), 2.50 (dd, *J* = 11.0, 2.0 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.1, 44.9, 43.8, 21.2; MS (CI) *m/z* (rel. intensity) 86 ( M + 1, 95); HRMS, *m/z* Calcd. for $C_4H_8NO$ (M + 1): 86.0607. Found 86.0601.

***cis*-3,4-Dimethylazetidin-2-one (185) and *trans*-3,4-Dimethylazetidin-2-one (186).** To a solution of **163**[49] (59.7 mg, 0.52 mmol) in benzene (5 mL) was added N,N-diphenylnitrosamine (114 mg, 0.56 mmol). The mixture was heated at reflux for 3 h and concentrated *in vacuo* to a dark brown oil. Separation of the two diastereomers by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **185** (27.0 mg, 52%) and **186** (8.0 mg, 15%) for a total yield of (67%) both as clear oils: **(185)**: $R_f$ 0.10 (1:1 ethyl acetate-hexane), IR (neat) 3258 (br), 2975, 2936, 1743, 1382, 1356, 1203 $cm^{-1}$;$^1H$ NMR: (300 MHz, $CDCl_3$) δ 6.25 (bs, 1H), 3.80 (quint, *J* = 6.0 Hz, 1H), 3.25-3.20 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.13 (d, *J* = 7.6 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 172.3, 47.6, 47.4, 15.9, 8.7; MS (CI) *m/z* (rel. intensity) 100 (M + 1, 100); HRMS, *m/z* Calcd. for $C_5H_{10}NO$ (M + 1): 100.0762. Found: 100.0763. **(186)**: $R_f$ 0.15 (1:1 ethyl acetate-hexane) IR (neat) 3256 (br), 2968, 2931, 1745, 1381, 1354, 1192, 1061 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.00 (bs, 1H), 3.36 (dq, *J* = 6.1 Hz, 2.0 Hz, 1H), 2.72 (dq, *J* = 5.8 Hz, 1.2 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.5, 52.8, 52.5, 20.3, 12.7; MS (CI) *m/z* (rel. intensity) 100 (M + 1, 39), 59 (100); HRMS, *m/z* calcd. for $C_5H_{10}NO$ (M + 1): 100.0762. Found: 100.0763.

**Azetidin-2-one (187).** To a solution of **164**[49] (15.1 mg. 0.18 mmol) in benzene (2 mL) was added N,N-diphenylnitrosamine (38.2 mg, 0.19 mmol). The mixture was heated at reflux for 2 h and concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel using 5% methanol-chloroform as elutant gave **187** (7.5 mg, 61%) as a clear solid; mp 74°C; IR (neat) 3294 (br), 2984, 2917, 1717, 1382, 1281, 1197 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.73 (bs, 1H), 3.29 (t, $J$ = 4.2 Hz, 2H), 3.02-3.00 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.1, 38.3, 35.1; MS (CI) *m/z* (rel. intensity) 72 (M + 1, 100); HRMS, *m/z* calcd. for $C_3H_6NO$ (M + 1): 72.0449. Found: 72.0449.

**4-[(Ethoxycarbonyl)methyl]azetidin-2-one (188).** To a solution of **165**[49] (7.0 mg, 0.04 mmol) in benzene (1 mL) was added N,N-diphenylnitrosamine (9.3 mg, 0.05 mmol). The mixture was heated at reflux for 2.5 h and concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant gave 4.5 mg of product. A second column on silica gel to remove minor impurities using 1:1 ethyl acetate-hexane produced **188** (4.2 mg, 65%) as a clear oil: IR (neat) 3274 (br), 2983, 1761, 1733, 1380, 1189 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.09 (bs, 1H), 4.14 (q, $J$ = 7.2 Hz, 2H), 3.96-3.89 (m, 1H), 3.17-3.10 (m, 1H), 2.74-2.50 (m, 3H), 1.25 (t, $J$ = 7.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.0, 166.9, 60.9, 43.8, 43.4, 39.9, 14.2; MS (CI) *m/z* (rel. intensity) 158 (M + 1, 25), (116, 100); HRMS *m/z* calcd. for $C_7H_{12}NO_3$ (M + 1): 158.0817. Found: 158.0817. Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49, H, 7.05, N, 8.91. Found: C, 53.38, H, 6.94, N, 8.96.

**3-[1'-[(*Tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (189).** To a solution of **172** (20.7 mg, 0.09 mmol) in benzene (3 mL) was added N,N-diphenylnitrosamine (19.0 mg, 0.09 mmol). The mixture was heated at reflux for 2 h and concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant gave **189** (13.3 mg, 68%) as a white solid: mp 55-58°C; IR (neat) 3190 (br), 2955, 2932, 1747, 1467, 1252, 1196, 1144, 1078, 1031, 839 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.77 (bs, 1H), 4.22-4.15 (m, 1H), 3.26 (t, $J$ = 5.1 Hz, 1H), 3.34-3.31 (m, 1H) 3.22-3.17 (m, 1H), 1.16 (d, $J$ = 6.1 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.5, 65.2, 59.3, 37.6, 25.7 (x3), 22.5, 27.9, -4.3, -5.0; MS (CI) *m/z* (rel. intensity) 230 (M + 1, 60), 214 (50), 172 (60), 133 (40), 115 (20), 98 (20), 55 (100); HRMS, *m/z* calcd. for $C_{11}H_{23}NO_2Si$ (M + 1): 230.1576. Found 230.1577.

**3-[(1'-Hydroxy)ethyl]azetidin-2-one (190).** To a solution of **189** (11.0 mg, 0.048 mmol) in acetonitrite (1 mL) was added an excess amount of 5% hydrofluoric acid in acetonitrile. The mixture was stirred at room temperature for 3 h and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant gave **190** (3.50 mg, 64%) as a clear oil: IR (neat) 3346 (br), 2964, 1731, 1378, 1203, 1093, 898 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.87 (bs, 1H), 4.25-4.15 (m, 1H), 3.37-3.31 (m, 2H), 3.30-3.26 (m, 1H), 2.17 (bs, 1H), 1.27 (d, $J$ = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.4, 64.9, 58.7, 38.0, 21.3; MS (CI) *m/z* (rel. intensity) 116 (M + 1, 43), 59 (100); HRMS, *m/z* calcd. for $C_5H_{10}NO_2$ (M + 1): 116.0713. Found: 116.0711.

**(*2R,3R*)-Ethyl-2-allyl-3-hydroxybutyrate (201).** To a solution of diisopropylamine (6.37 mL, 45.3 mmol) in dry tetrahydrofuran (50 mL) was added *n*-butyllithium (28.3 mL, 45.3 mmol, 1.60 M in hexanes) at -78°C. The mixture was warmed to 0°C for 30 min and recooled to -78°C for a further 30 min. (*3R*)-Hydroxybutyrate **200** (2.85 g, 21.6 mmol) was added dropwise using a syringe. The mixture turned yellow and was stirred for 45 min at -70°C before neat allyl bromide (4.66 mL, 53.9 mmol) was added via syringe. The reaction was sealed under argon atmosphere and stirred for 16h at 5°C then recooled to -50°C and quenched with acetic acid (2 mL) and ether (5 mL). The reaction mixture was transfered to a separatory funnel filled with water (20 mL) and ether (25 mL) where the layers separated. The ether layer was washed with saturated sodium bicarbonate (6 mL), saturated sodium chloride (6 mL), and the aqueous layer washed with ether (2 x 20 mL). The combined ether layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:3.5 ethyl acetate-hexane as elutant gave **201** (2.16 g, 58%) as a light yellow oil: $[\alpha]_D$ -9.50° (c = 1.50, $CHCl_3$); IR (neat) 3675, 2973, 1733, 1610, 1181 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.79-5.72 (m, 1H), 5.08 (dd, *J* = 15.7 Hz, 1.3 Hz, 1H), 5.04 (dd, *J* = 10.2 Hz, 1.1 Hz, 1H), 4.17 (q, *J* = 7.5 Hz, 3H), 3.93 (quint., *J* = 6.3 Hz, 1H), 2.62 (d, *J* = 7.4 Hz, 1H), 2.49-2.40 (m, 3H), 1.28 (t, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 6.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.6, 134.8, 117.1, 67.8, 60.6, 52.1, 33.6, 21.4, 14.3; MS (CI) *m/z* (rel. intensity) 173 (M + 1, 100); HRMS, *m/z* calcd. for $C_9H_{17}O_3$ (M + 1): 173.1178. Found: 173.1177.

**(*2R,3R*)-Ethyl-2-allyl-3-*tert*-butyldimethylsilyloxybutyrate (202).** To a solution of **201** (2.16 g, 12.6 mmol) in dry dimethylformamide was added *tert*-butyldimethylsilyl chloride (2.65 g, 17.6 mmol) and imidazole

(1.70 g, 25.2 mmol). The mixture was stirred at room temperature for 16 h under argon atmosphere and quenched with water (10 mL) and ether (20 mL). The aqueous layer was washed with ether (3 x 30 mL), and the combined organic layers were dried over anhydrous magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 30% ethyl acetate-hexane as elutant gave **180** (3.50 g, 97%) as a clear oil: $[\alpha]_D$ -24.3° (c = 1.63, $CHCl_3$); IR (neat) 3083, 2933, 1738, 1643, 1467, 1254, 1182, 1095 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.73-5.67 (m, 1H), 5.02 (dd, *J* = 16.9 Hz, 1.4 Hz, 1H), 4.97 (dd, *J* = 10.4 Hz, 1.9 Hz, 1H), 4.08 (dq, *J* = 7.5 Hz, 1.1 Hz, 2H), 3.98 (quint., *J* = 6.1 Hz, 1H), 2.47-2.41 (m, 1H), 2.36-2.19 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.7, 135.7, 116.4, 69.4, 60.1, 54.2, 32.4, 25.7 (x3), 21.2, 17.9, 14.3, -4.3, -5.1; MS (CI) *m/z* (rel. intensity) 287 (M + 1, 100); HRMS, *m/z* calcd. for $C_{15}H_{31}O_3Si$ (M + 1): 287.2042. Found: 287.2041.

**(*2R,3R*)-Ethyl-2-[3'-(hydroxy)propyl]-3-(*tert*-butyldimethylsilyloxy)butyrate (203).** To a solution of 1.0 M borane-tetrahydrofuran complex (12.5 mL, 12.5 mmol) was added 2-methyl-2-butene (2.73 mL, 25.75 mmol) and the reaction stirred for 1.5 h at -10°C (methanol-ice bath). Alkene **202** (2.38 g, 8.31 mmol) was added dropwise in tetrahydrofuran (5 mL). The reaction was stirred for 1.5 h at 0°C. A mixture of 30% hydrogen peroxide (5 mL), 1M sodium hydroxide (5 mL), and water (2 mL) was added slowly at 0°C. The mixture turned white and was allowed to stir for an addiltional 1.5 h at 0°C before extracting with ether (3 x 30 mL). The combined ether layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel

using 30% ethyl acetate-hexane as elutant gave **181** (1.82 g, 72%) as a clear oil: $[\alpha]_D$ IR (neat) 3436 (br), 2931, 1735, 1450, 1254, 1190, 1109, 1060, 834 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.11 (dq, *J* = 7.3 Hz, 2.1 Hz, 2H), 3.98 (quint., *J* = 6.7 Hz, 1H), 3.62-3.59 (m, 2H), 2.40-2.34 (m, 1H), 1.62-1.45 (m, 4H), 1.37 (t, *J* = 5.5 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.6, 69.8, 62.5, 60.2, 54.3, 30.7, 25.7 (x3), 24.1, 21.2, 17.9, 14.2, -4.3, -5.2; MS (CI) *m/z* (rel. intensity) 305 (M + 1, 100); HRMS, *m/z* calcd. for $C_{15}H_{33}O_4Si$ (M + 1): 305.2148. Found: 305.2148.

**(*4R,5R*)-4-Ethoxycarbonyl-5-(*tert*-butyldimethylsilyloxy) hexanoic acid (204).** To a solution of **203** (1.82 g, 5.98 mmol) in dry dimethylformamide (50 mL) was added pyridinium dichromate. The reaction was stirred for 48 h at room temperature then poured into water (50 mL). The phases were separated and the aqueous layer was extracted with ether (4 x 50 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **204** (1.25 g, 66%) as a light yellow oil: $[\alpha]_D$-5.3° (c = 1.81, $CHCl_3$); IR (neat) 3400-2900 (br), 2956, 2934, 1734, 1714, 1254, 835 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ (dq, *J* = 7.3 Hz, 2.0 Hz, 2H), 4.03 (quint., *J* = 6.5 Hz, 1H), 2.47-2.27 (m, 3H), 1.86 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), 0,04 (s, 3H), 0.02 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.9, 173.7, 69.5, 60.4, 53.3, 31.9, 25.7 (x3), 22.6, 20.9, 17.9, 14.2, -4.4, -5.2; MS (CI) *m/z* (rel. intensity) 319 (M + 1, 100); HRMS, *m/z* calcd. for $C_{15}H_{31}O_5Si$ (M + 1): 319.1941. Found: 319.1940. Anal. Calcd. for $C_{15}H_{30}O_5Si$: C, 56.57, H, 9.49, Si, 8.82. Found: C, 56.73, H, 9.45.

**(*6R,5R*)-5-Ethoxycarbonyl-6-methyl-pyran-2-one (205).** To a solution of **204** (1.25 g, 3.92 mmol) in acetonitrile (5 mL) was added excess 5% hydrofluoric acid in acetonitrile and the reaction stirred for 1.5 h at room temperature. Saturated ammonium chloride (5 mL) was added and a white precipitate appeared as the phases separated. The aqueous layer was extracted with ether (2 x 5 mL). The combined organic layers were washed with saturated sodium bicarbonate (2 x 5 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude material was used directly for the next reaction.

Mukaiyama's salt[69] (1.00 g, 3.92 mmol), and triethylamine (1.64 mL, 11.7 mmol) were stirred under argon atmosphere in acetonitrile (20 mL). The crude material was added by syringe as a solution in acetonitrile (5 mL). The reaction was stirred for 1.5 h at room temperature and the acetonitrile concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **205** (545 mg, 75%) as a clear oil: $[\alpha]_D$ + 73.4° (c = 1.26, $CHCl_3$); IR (neat) 2984, 1731, 1245, 1217, 1181, 1104, 1050, 1028 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 4.73-4.67 (m, 1H), 4.17 (dq, *J* = 6.7 Hz, 2.2 Hz, 2H), 2.89-2.85 (m, 1H), 2.77-2.69 (m, 1H), 2.56-2.48 (m, 1H), 2.22-2.03 (m, 2H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.25 (t, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 75.4, 61.2, 42.2, 27.2, 19.9, 18.1, 14.1; MS (CI) *m/z* (rel. intensity) 187 (M + 1, 100); HRMS, *m/z* calcd. for $C_9H_{15}O_4$ (M + 1): 187.0970. Found: 187.0970.

**(*6R*)-5-Ethoxycarbonyl-6-methyl-3-thiophenyl-pyran-2-one (206).** To a solution of **205** (530 mg, 2.85 mmol) in dry tetrahydrofuran (100 mL) was added lithium bis(trimethylsilyl) amide (4.26 mL, 4.26 mmol, 1 M solution in tetrahydrofuran) dropwise by syringe at -70°C. The mixture was

stirred for 45 min at -70°C. The reaction was quenched with saturated ammonium chloride (20 mL), extracted with ether (3 x 5 mL), the combined organic layers dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography on silica gel using 30% ethyl acetate-hexane as elutant provided **206** (606 mg, 72%) as a 1:1 mixture of diastereomers: IR (neat) 2985, 1729, 1448, 1387, 1248, 1191, 747, 695 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.58-7.50 (m, 4H), 7.36-7.28 (m, 6H), 4.77-4.70 (m, 2H), 4.17 (q, $J$ = 7.4 Hz, 4H), 4.13-4.03 (m, 1H), 3.88 (dd, $J$ = 8.3 Hz, 8.2 Hz, 1H), 3.01-2.92 (m, 2H), 2.65-2.56 (m, 1H), 2.48-2.41 (m, 1H), 2.28-2.10 (m, 2H), 1.36 (d, $J$ = 6.6 Hz, 6H), 1.27-1.21 (m, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.8, 170.3, 169.4, 168.6, 134.0 (x2), 133.6 (x2), 132.1, 129.2 (x2), 129.1 (x2), 128.7 (x2), 128.5, 75.0, 74.6, 61.4 (x2), 46.0, 43.8, 43.3, 41.7, 28.5, 27.4, 18.5, 17.4, 14.1 (x2); MS (CI) *m/z* (rel. intensity) 295 (M + 1, 100); HRMS, *m/z* calcd. for $C_{15}H_{19}O_4S$ (M + 1): 295.1004. Found: 295.1003. Anal. Calcd. for $C_{15}H_{18}O_4S$: C, 61.20, H, 6.16, S, 10.89. Found: C, 61.02, H, 5.98 S, 10.80.

**(*6R*)-5-Ethoxycarbonyl-6-methyl-4,5-dihydro-2H-pyran-2-one (199)**. To a solution of **206** (597 mg, 2.03 mmol) in methylene chloride was added 73% *m*-chloroperbenzoic acid at -78°C. The reaction was stirred for 30 min at -78°C, then the methylene chloride was removed *in vacuo*. The residue was taken up in ether (10 mL), washed with saturated sodium bicarbonate (2 x 5 mL), sodium sulfite (1 x 5 mL), and saturated sodium chloride (1 x 5 mL). The ether layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The sulfoxide product was taken on to the next reaction without purification.

A solution of the sulfoxide (630 mg, 2.03 mmol) in dry toluene (50 mL) and methylene chloride (3 mL) was heated for 15 h at 70°C. The reaction was

concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane provided **199** (319 mg, 85%) as a light yellow oil: $[\alpha]_D$ -35.5° (c = 2.02, $CHCl_3$); IR (neat) 2983, 2938, 1744, 1714, 1672, 1260, 1094, 1050, 1030, 801, 749 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.95-6.93 (m, 1H), 5.41-5.37 (m, 1H), 4.22 (dq, *J* = 7.2 Hz, 1.8 Hz, 2H), 3.27-3.20 (m, 2H), 1.49 (d, *J* = 6.7 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 167.6, 163.2, 132.0, 131.9, 75.7, 61.2, 30.0, 21.7, 14.0; MS (CI) *m/z* (rel. intensity) 185 (M + 1, 100); HRMS, *m/z* calcd. for $C_9H_{13}O_9$ (M + 1): 185.0814. Found: 185.0813.

**3-Ethyl-3-phenylselenyl-pyran-2-one (210).** To a solution of **209**[74] (298 mg, 2.33 mmol) in dry tetrahydrofuran (8 mL) at -70°C was added lithium bis(trimethylsilyl)amide (2.56 mL, 2.56 mmol, 1.0 M solution in tetrahydrofuran). The mixture was stirred for 20 min at -70°C when phenylselenyl chloride (490 mg, 2.56 mmol) in dry tetrahydrofuran (2 mL) was added *via* canula. The reaction was stirred for 1 h at -70°C then quenched with saturated ammonium chloride (5 mL) and extracted with ether (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:3 ethyl acetate-hexane as elutant provided **210** (477 mg, 72%) as a clear oil: IR (neat) 2970, 2938, 1719, 1253, 1158, 1123, 744 $cm^{-1}$; $^1H$ NMR (300 MHz, CDCl3) δ 7.60-7.55 (m, 2H), 7.45-7.36 (m, 1H), 7.34-7.27 (m, 2H), 4.58-4.50 (m, 1H), 4.32-4.25 (m, 1H), 2.24-1.65 (m, 6H), 0.92 (t, *J* = 7.0 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.1, 138.1 (x2), 129.7, 128.9 (x2), 126.9, 69.2, 50.7, 31.4, 30.4, 21.6, 9.4; MS (CI) *m/z* (rel. intensity) 285 (M + 1, 64), 255 (40), 99 (100); HRMS, *m/z* calcd. for $C_{13}H_{17}O_2Se$ (M + 1): 285.0393. Found: 285.0394.

**3-Ethyl-3,4-dihydro-2H-pyran-2-one (211).** To a solution of **210** (470 mg, 1.66 mmol) in methylene chloride (20 mL) at 0°C was added 30% hydrogen peroxide (0.30 mL, 2.49 mmol) and water (1 mL). The mixture was warmed to room temperature for 20 min then extracted with methylene chloride (3 x 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:3 ethyl acetate-hexane as elutant provided **211** (190 mg, 91%) as a clear oil: IR (neat) 2970, 2939, 1725, 1468, 1131, 1125, 980 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.55 (dd, $J$ = 5.4 Hz, 4.4 Hz, 1H), 4.31 (t, $J$ = 6.1 Hz, 2H), 2.40-2.32 (m, 2H), 2.30-2.24 (m, 2H), 1.03 (t, $J$ = 7.6 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 165.0, 137.7, 134.3, 66.3, 24.2, 23.8, 12.4; MS (CI) *m/z* (rel. intensity) 127 (M + 1, 100); HRMS, *m/z* calcd. for $C_7H_{11}O_2$ (M + 1): 127.0759. Found: 127.0759.

***cis*-4-Ethyl-5-[2'-(hydroxy)ethyl]pyrazolidin-3-one (212).** To a solution of **211** (1.01 g, 8.01 mmol) in 100% ethanol (75 mL) was added neat hydrazine-monohydrate (1.17 mL, 24.0 mmol). The mixture was refluxed for 62 h and the ethanol was removed *in vacuo*. Purification by column chromatography on silica gel using 5% methanol-chloroform, then 15% methanol-chloroform produced **212** (621 mg, 49%) as a white solid, **213** (380 mg, 30%), and **214** (98.0 mg, 8%) as clear oils. **(212)**: $R_f$ 0.15 (15% methanol-chloroform); mp 101-106°C; IR (neat) 3229 (br), 2963, 2938, 2878, 1679 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 1H), 3.88-3.79 (m, 3H), 3.5 (s, 1H), 2.55 (q, $J$ = 7.6 Hz, 1H), 1.81-1.68 (m, 3H), 1.53-1.50 (m, 1H), 1.41-1.31 (m, 1H), 1.01 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 178.9, 61.6, 61.5, 47.7, 28.4, 17.5, 12.3; MS (CI) *m/z* (rel. intensity) 159 (M + 1, 100); HRMS, *m/z* calcd. for $C_7H_{15}N_2O_2$ ( M + 1): 159.1133. Found: 159.1133. Anal.

Calcd. for $C_7H_{14}N_2O_2$: C, 53.15, H, 8.92, N, 17.71. Found: C, 53.16, H, 9.09, N, 17.44. **(213)**: $R_f$ 0.12 (15% methanol-chloroform); IR (neat) 3282 (br), 2926, 2871, 1650, 1530, 1457, 1383, 1057 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 3.75-3.51 (m, 2H), 2.08-1.95 (m,1H), 1.79-1.42 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 176.6, 62.6, 47.1, 30.3, 28.9, 25.9, 12.0. **(214)**: $R_f$ 0.20 (15% methanol-chloroform); IR (neat) 3286 (br), 2982, 2923, 1865, 1617, 1532, 1459, 1053 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.56 (t, *J* = 6.5 Hz, 1H), 3.75 (t, *J* = 6.4 Hz, 2H), 2.40-2.26 (m, 4H), 1.58 (bs, 2H), 1.02 (t, *J* = 7.3 Hz, 3H);

***cis*-4-Ethyl-5-[2'-(hydroxy)ethyl]-(*o*-nitrobenzyl)pyrazolidin-3-one (215).** To a solution of **212** (125 mg, 0.791 mmol) in dry dimethylformamide (10 mL) was added *o*-nitrobenzyl bromide and triethylamine (0.132 mL, 0.949 mmol). The reaction was stirred for 96 h at room temperature in the dark before removing the dimethylformamide *in vacuo*. Purification by column chromatography on silica gel using 5% methanol-chloroform as elutant provided **215** (91.4 mg, 40%) as a clear colorless glass: IR (neat) 3341 (br), 3109, 3076, 2965, 2939, 2878, 1692, 1528 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.49-7.45 (m, 2H), 7.00 (s, 1H), 4.48 (d, *J* = 12.9 Hz, 1H), 4.16 (d, *J* = 12.8 Hz, 1H), 3.72-3.61 (m, 3H), 3.00-2.94 (m, 1H), 2.54 (bs, 1H), 1.85-1.74 (m, 1H), 1.56-1.53 (m, 2H), 1.35-1.23 (m, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 177.3, 149.6, 133.1, 132.1, 131.3, 129.1, 125.0, 65.2, 60.1, 59.4, 42.6, 29.6, 17.3, 12.3; MS (CI) *m/z* (rel. intensity) 294 (M + 1,11), 60 (100); HRMS, *m/z* calcd. for $C_{14}H_{20}N_3O_4$ (M + 1): 294.1454. Found: 294.1454. Anal. Calcd. for $C_{14}H_{19}N_3O_4$: C, 57.33, H, 6.53, N, 14.33. Found: C, 57.20, H, 6.52, N, 14.36.

***cis*-4-Ethyl-5-[2'-*tert*-Butyldimethylsilyloxy)ethyl]-(*o*-nitrobenzyl)pyrazolidin-3-one (216).** To a solution of **215** (77.0 mg, 0.263 mmol) in dry methylene chloride (5 mL) was added N,N-diisopropylethylamine (91.0 μL, 0.525 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate. The mixture was stirred for 1 h at 0°C then quenched with water (1 mL) and extracted with methylene chloride (3 x 5 mL). The combined methylene chloride layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography using 1:1 ethyl acetate-hexane as elutant provided **216** (61.0 mg, 57%) as a white solid: mp 119-124°C; IR (KBr) 3159, 3067, 2957, 2930, 2857, 1697, 1528 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 7.59-7.41 (m, 3H), 6.6 (s, 1H), 4.37 (d, *J* = 13.4 Hz, 1H), 4.19 (d, *J* = 13.3 Hz, 1H), 3.65-3.50 (m, 3H), 2.99-2.91 (m, 1H), 1.82-1.75 (m, 1H), 1.57-1.23 (m, 3H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 177.2, 149.8, 132.8, 131.8, 131.5, 128.9, 124.9, 63.6, 59.6, 59.5, 42.5, 30.9, 25.9 (x3), 18.2, 17.7, 12.2, -5.4 (x2); MS (CI) *m/z* (rel. intensity) 408 (M + 1, 100); HRMS, *m/z* calcd. for $C_{20}H_{34}N_3O_4Si$ (M + 1): 408.2319. Found: 408.2316. Anal. Calcd. for $C_{20}H_{33}N_3O_4Si$: C, 58.94, H, 8.16, N, 10.31. Found: C, 58.02, H, 7.95, N, 10.38 (The total transferable sample was only 0.39 mg. Carbon accuracy at this quantity is ± 0.6-0.8%).

***cis*-4-Ethyl-5-[(2'-*tert*-butyldimethylsilyloxy)ethyl]-2-[2'-*tert*-butyldimethylsilyl)ethoxycarbonyl]-1-(*o*-nitrobenzyl)pyrazolidin-3-one (217).** To a solution of **216** (110 mg, 0.270 mmol) in dry tetrahydrofuran (10 mL) was added 2-(trimethylsilyl)-ethyl azidoformate and cooled to 0°C. Sodium hydride (13 mg, 0.324 mmol, 60% in mineral oil) was

added slowly, then the reaction was stirred for 3 h at 0°C which turned dark orange in color. The reaction was quenched with water (5 mL) and extracted with ether (5 x 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography using 15% ethyl acetate-hexane as elutant provided **217** (142 mg, 95%) as a clear glass: IR (neat) 2956, 2889, 2863, 1786, 1737, 1531, 1260, 1094, 843 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.83 (dt, *J* = 7.7 Hz, 1.2 Hz, 2H), 7.56 (dt, *J* = 8.3 Hz, 1.1 Hz, 1H), 7.42 (dt, *J* = 7.3 Hz, 1.1 Hz, 1H), 4.56 (d, *J* = 12.9 Hz, 1H), 4.27-4.15 (m, 2H), 4.07 (d, *J* = 13.1 Hz, 1H), 3.60-3.55 (m, 1H), 3.54-3.50 (m, 1H), 3.43-3.40 (m, 1H), 3.12-3.09 (m, 1H), 1.87-1.75 (m, 1H), 1.48-1.41 (m, 1H), 1.35-1.24 (m, 2H), 1.04-0.99 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.74 (s, 9H), 0.01 (s, 9H), -0.08 (s, 3H), -0.13 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.9, 150.6, 149.9, 133.0, 132.7, 131.1, 129.8, 124.2, 65.5, 59.6, 59.1, 55.4, 44.8, 30.8, 25.8 (x3), 18.1 (x2), 17.5, 11.7, -1.6 (x3), -5.5 (x2); MS (CI) *m/z* (rel. intensity) 552 (M + 1,19), 524 (100), 508 (63), 480 (42), 466 (28); HRMS, *m/z* calcd. for $C_{26}H_{46}N_3O_6Si_2$ (M + 1): 552.2925. Found: 552.2925.

***cis*-3-Ethyl-4-[(2'-*tert*-butyldimethylsiloxy)ethyl]-1-[2'-(trimethylsilyl)ethoxycarbonyl)amino]azetidin-2-one (218).** A solution of **217** (160 mg, 0.290 mmol) in abslolute ethanol (100 mL) was degassed with argon for 2 h in a photochemical immersion well. The solution was irradiated for 1.5 h at 0°C through a pyrex filter with a 450-W Hanovia medium-pressure photochemical lamp. The pyrex filter was then replaced by a vycor filter and the solution irradiated for a further 1.5h at 0°C. The mixture was concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel produced **218** (62.2 mg, 52%) as a pale yellow

oil: IR (neat) 3264, 2954, 2894, 2863, 1777, 1732, 1249, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.5 (s, 1H), 4.22 (dt, *J* = 7.4 Hz, 1.9 Hz, 2H), 4.04 (q, *J* = 6.3 Hz, 1H), 3.75-3.69 (m, 2H), 3.07-3.00 (m, 1H), 1.84 (q, *J* = 6.3 Hz, 1H), 1.08 (t, *J* = 7.4 Hz, 3H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H), 0.04 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 171.0, 155.2, 64.8, 60.7, 58.4, 51.5, 32.2, 25.9 (x3), 18.5, 18.3, 17.7, 12.5, -1.6 (x3), -5.4 (x2); MS (CI) *m/z* (rel. intensity) 417 (M + 1, 23), 389 (50), 133 (43), 51 (100); HRMS, *m/z* calcd. for $C_{19}H_{41}N_2O_4Si_2$ (M + 1): 417.2605. Found: 417.2606.

***cis*-1-Amino-3-ethyl-4-[2'-(hydroxy)ethyl]azetidin-2-one (219).** To a solution of **218** (52.0 mg, 0.13 mmol) in acetonitrile (2 mL) was added tetra-*n*-butylammonium fluoride (0.13 mL, 0.13 mmol, 1.0 M in tetrahydrofuran). The mixture was stirred at room temperature for 4 h; however, from thin layer chromatographic analysis, it was apparent that cleavage of both silyl groups was occurring. A further equivalent of tetra-*n*-butylammonium fluoride (0.13 mL, 0.13 mmol, 1.0 M in tetrahydrofuran) was added and the reaction stirred for an additional 2 h at room temperature before being concentrated *in vacuo*. Purification by column chromatography using 5% methanol-chloroform provided **219** (19.8 mg, 51%) as a clear oil: IR (neat) 3326 (br), 2961, 2928, 2880, 1740, 1048 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.20 (bs, 2H), 3.89-3.77 (m, 1H), 3.76-3.67 (m, 2H), 2.98-2.91 (m, 1H), 1.95-1.85 (m, 1H), 1.84-1.49 (m, 3H), 1.06 (t, *J* = 7.3 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$), δ 170.9, 60.9, 60.8, 51.4, 32.8, 18.5, 12.6.

***cis*-3-Ethyl-4-[2'-(hydroxy)ethyl]azetidin-2-one (220).** To a solution of **219** (6.0 mg, 0.038 mmol) in benzene (2 mL) was added N,N-diphenylnitrosamine[63] (11.3 mg, 0.057 mmol). The mixture was heated at

reflux for 3 h and concentrated *in vacuo* to a dark brown oil. Purification by column chromatography on silica gel twice using 5% methanol-chlorofom as elutant provided **220** (4.1 mg, 76%) as a clear oil: IR (neat) 3288 (br), 2960, 2931, 2880, 1734, 1384, 1058 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.2 (s, 1H), 3.86-3.70 (m, 3H), 3.10 (q, $J$ = 7.3 Hz, 1H), 1.85-1.64 (m, 3H), 1.62- 1.50 (m, 1H), 1.04 (t, $J$ = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.7, 61.2, 54.9, 50.4, 33.0, 18.2, 12.6; MS (CI) *m/z* (rel. intensity) 144 (M + 1, 100); HRMS, *m/z* calcd. for $C_7H_{14}N_2O$ (M + 1): 144.1025. Found: 144.1025.

## I-D. Bibliography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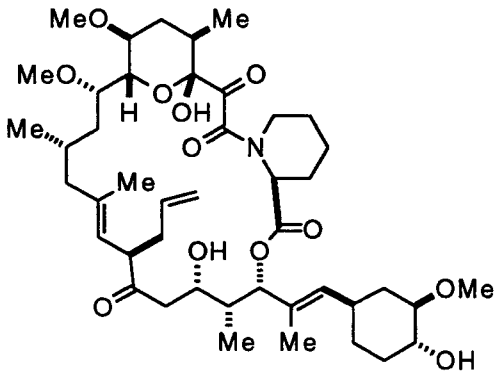
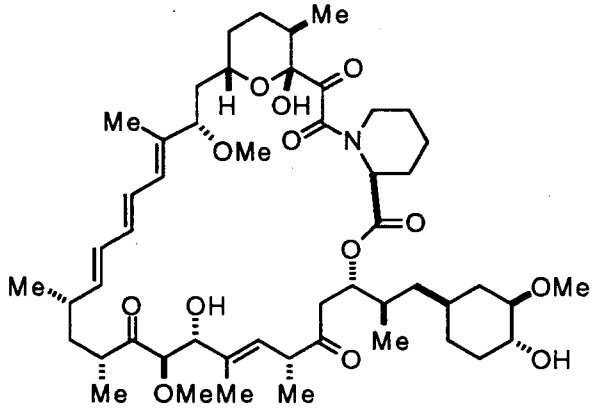
Part II: Synthesis of a Subunit of the Immunosuppressant FK-506.

## II-A. Introduction

The search for new metabolites from microorganisms for therapeutic purposes continues to be a major theme of natural products research. FK-506 (**1**), a 23-membered macrolide, was isolated in 1987 from the soil fungus *Streptomyces tsukubaenis*, and its structure was elucidated by chemical degradation and X-ray crystallographic analysis.[1] FK-506 and the related substance rapamycin (**2**), isolated in 1975 from *Streptomyces hygroscopicus*,[2] share many structural features and have been found to possess powerful immunosuppressant activity. Suppresion of the immune system to avoid rejection is a valuable adjunct to surgery in organ transplant operations. FK-506 has been used successfully in liver, kidney, and pancreas transplants with no serious side effects[3] and appears likely to replace cyclosporin A[4] as the drug of choice for this purpose.




1



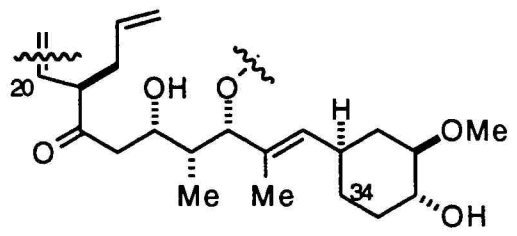

2

The mode of action of FK-506 involves inhibition of the adaptive immune system.[5] Specifically, it forms a complex with the FK-506 binding protein[6] which, through an undetermined mechanism,[7] causes deactivation of T cells[8]

necessary for regulating antibodies and other white blood cells used by the host to combat foreign antigens. Suppression of this immune mechanism is necessary for reducing the rejection of tissue obtained from the transplant.

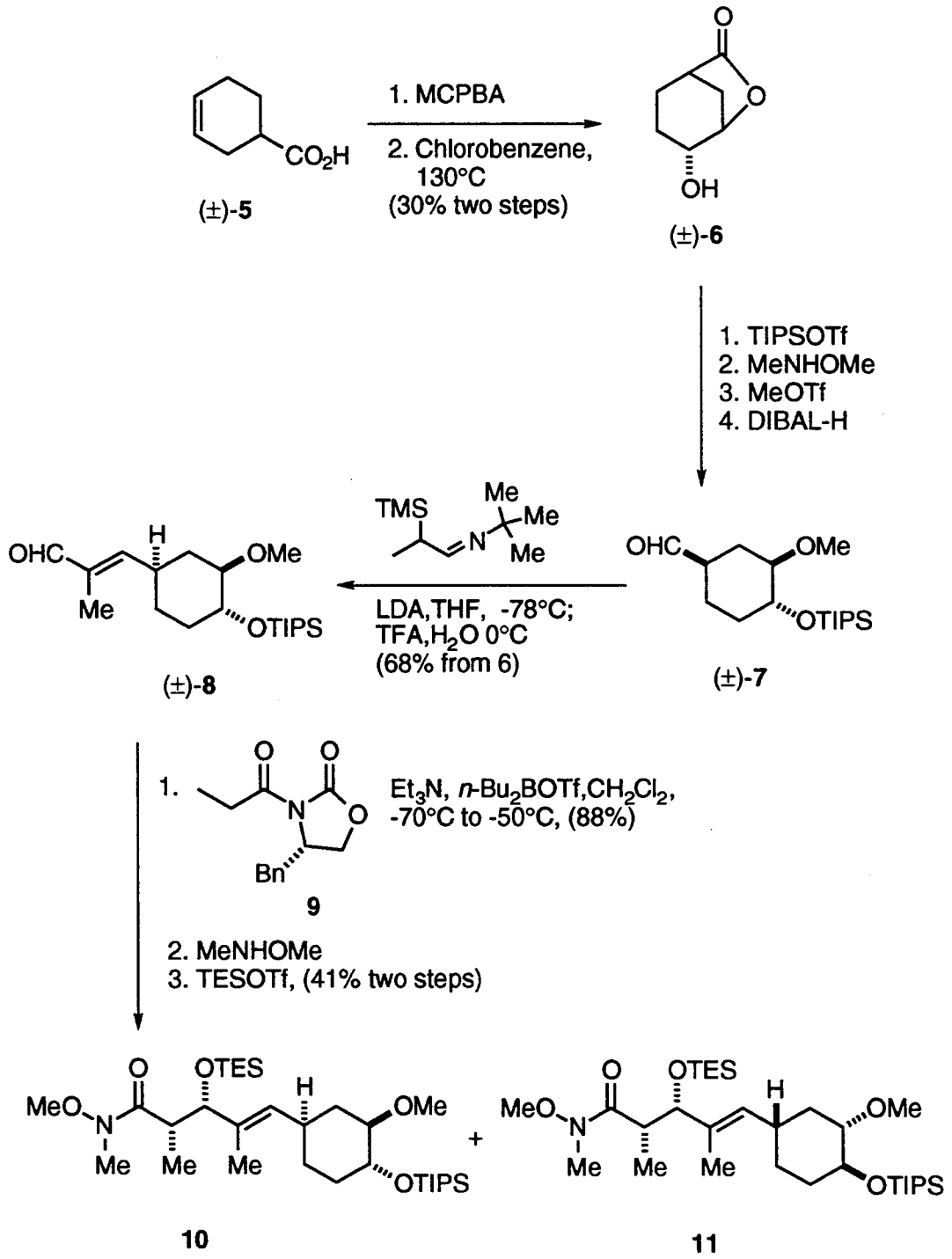
The exceptional biological activity of FK-506 has resulted in extensive work directed toward the synthesis of this material.[9] Two total syntheses[10,11] have been reported along with two formal syntheses.[12,13]

The C20-C34 fragment **3** of FK-506 represents a critically important portion of the molecule for which C20 is a logical synthetic disconnection point. This fragment has been constructed using several different strategies as outlined below.




**3**

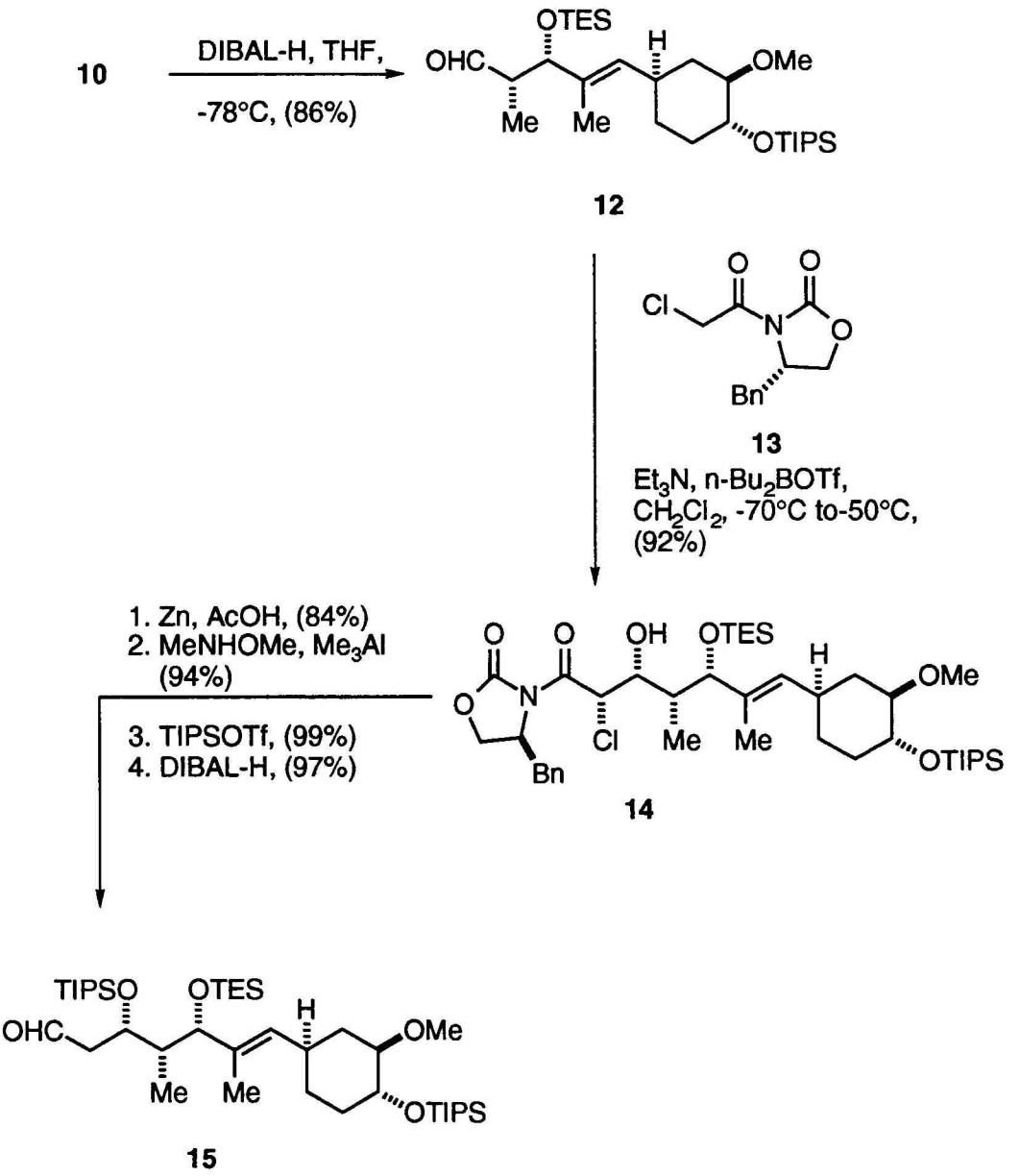
Jones and co-workers at Merck applied Evans' aldol technology utilizing a series of chiral condensations to build the desired fragment.[10] Hydroxy lactone **6**, available in two steps from (±)-3-cyclohexenecarboxylic acid **5**, was converted to aldehyde **7** in four steps (Scheme 1). Condensation of **6** with 2-lithio-2-triethylsilyl propanal *t*-butylimine[14] gave aldehyde **8**, the substrate for the first aldol condensation. Treatment of **8** with the enol borinate of oxazolidinone **9**[15] afforded, after transamination and silylation, a 1:1 mixture of diastereomers **10** and **11**,which were readily separated.

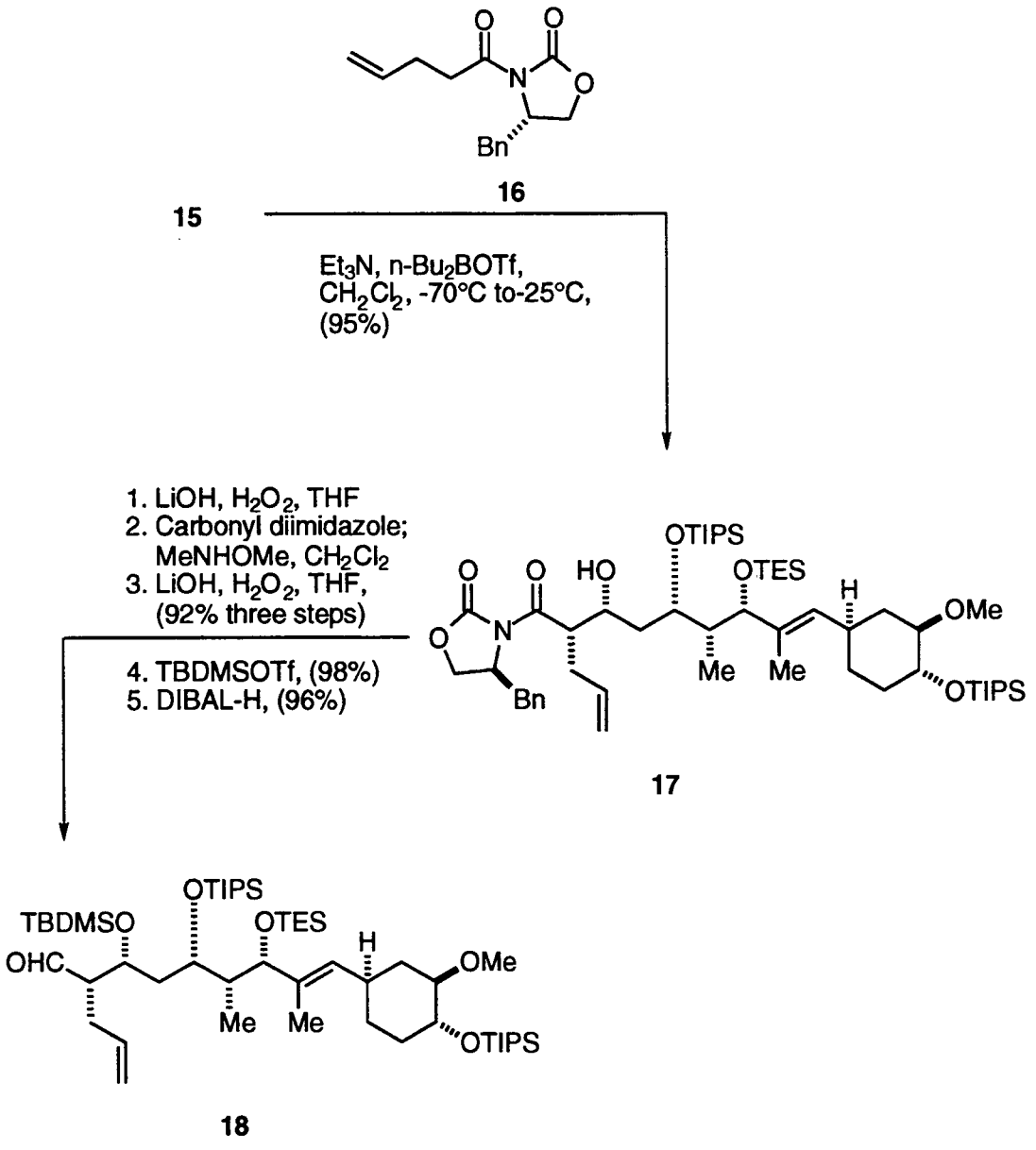



**Scheme 1**

Optically active amide **10** was reduced to aldehyde **12** which underwent aldol condensation with the enol borinate of **13**[15] to give **14** in excellent yield

(Scheme 2). Reductive dehalogenation followed by transamination, silylation, and reduction provided aldehyde **15**. A further condensation using oxazolidine **16**[15] gave the aldol product **17**. Five additional steps were needed to construct the desired aldehyde **18** used in the first total synthesis of FK-506.[10]

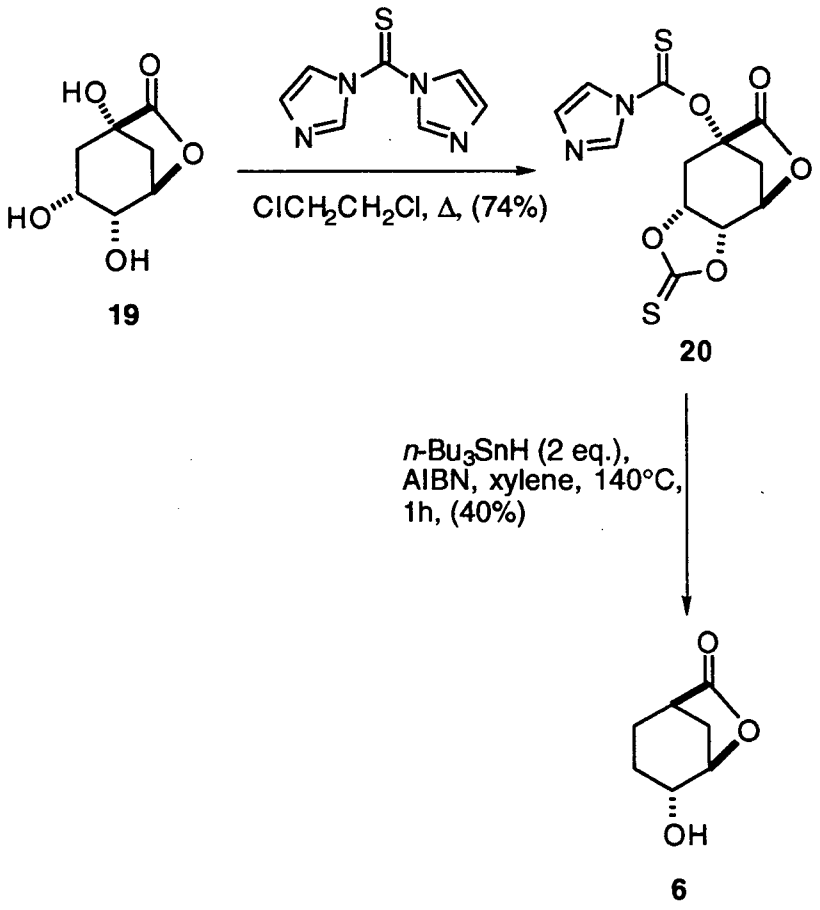





**Scheme 2**

The original plan devised by the Merck group involved an asymmetric synthesis of hydroxy lactone **6**[16] from bicyclic lactone **19**, readily available from (-)-quinic acid.[17] Lactone **19** was converted to *bis*-thiocarbonyl lactone **20** which, on reduction with two equivalents of *n*-tributyltin hydride in the presence of α,α'-azoisobutyronitrile (AIBN) gave **6** in moderate yield (Scheme 3). This

strategy was later abandoned in favor of the scheme previously outlined due to problems which arose with large scale synthesis of **6**.

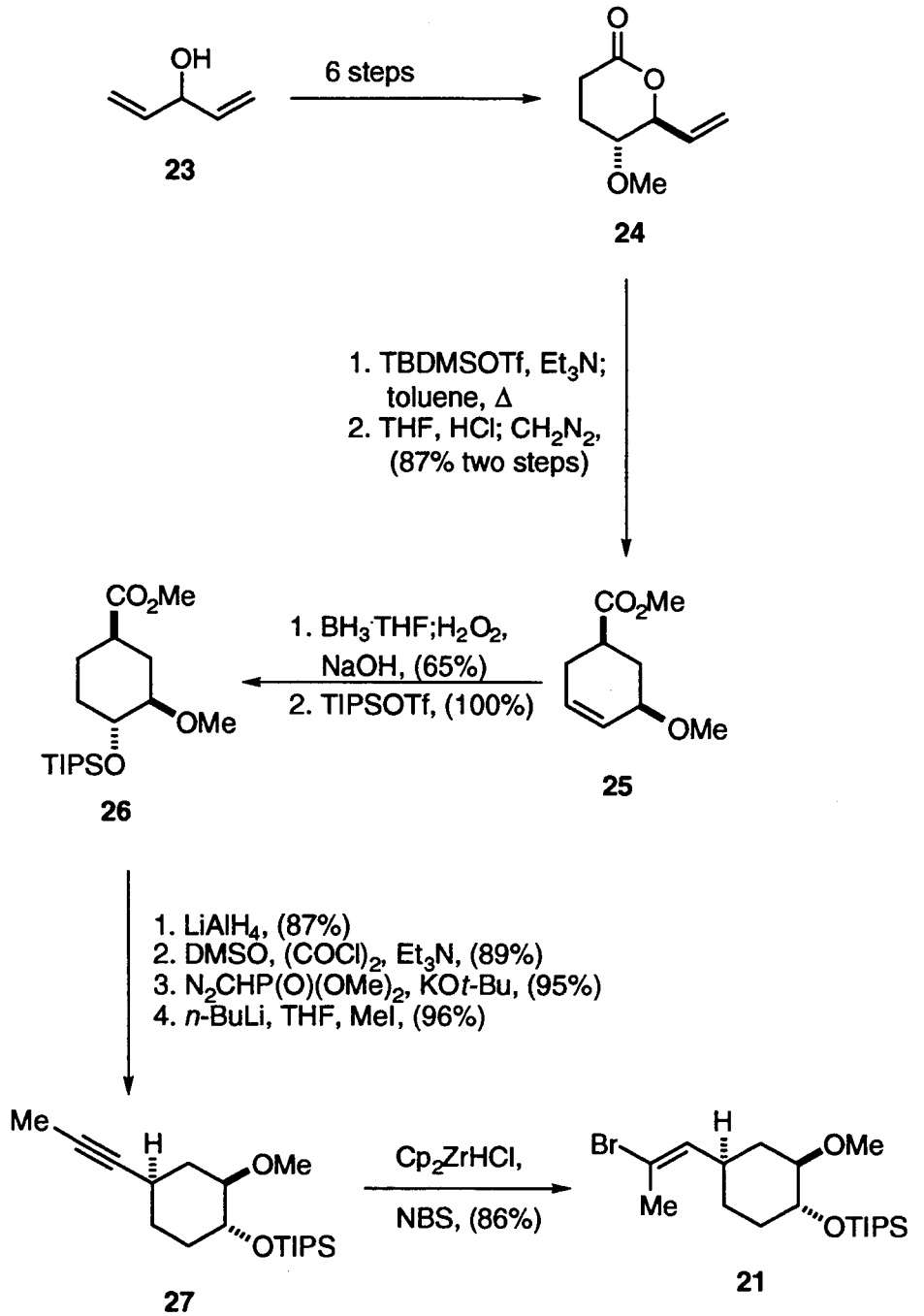



**19** **20** **6**

**Scheme 3**

In a different approach, Schreiber and co-workers synthesized the C20-C34 fragment utilizing a convergent strategy which entailed coupling at C26-C27.[11] This assembly was accomplished using optically active intermediates **21** and **22**. The construction of **21** was completed utilizing lactone **24** (Scheme 4), available in six steps from the divinyl carbinol **23**. Claisen rearrangement of the silyl enol ether of **24**, followed by transesterification, provided ester **25**. Regio- and stereoselective hydroboration followed by silylation afforded

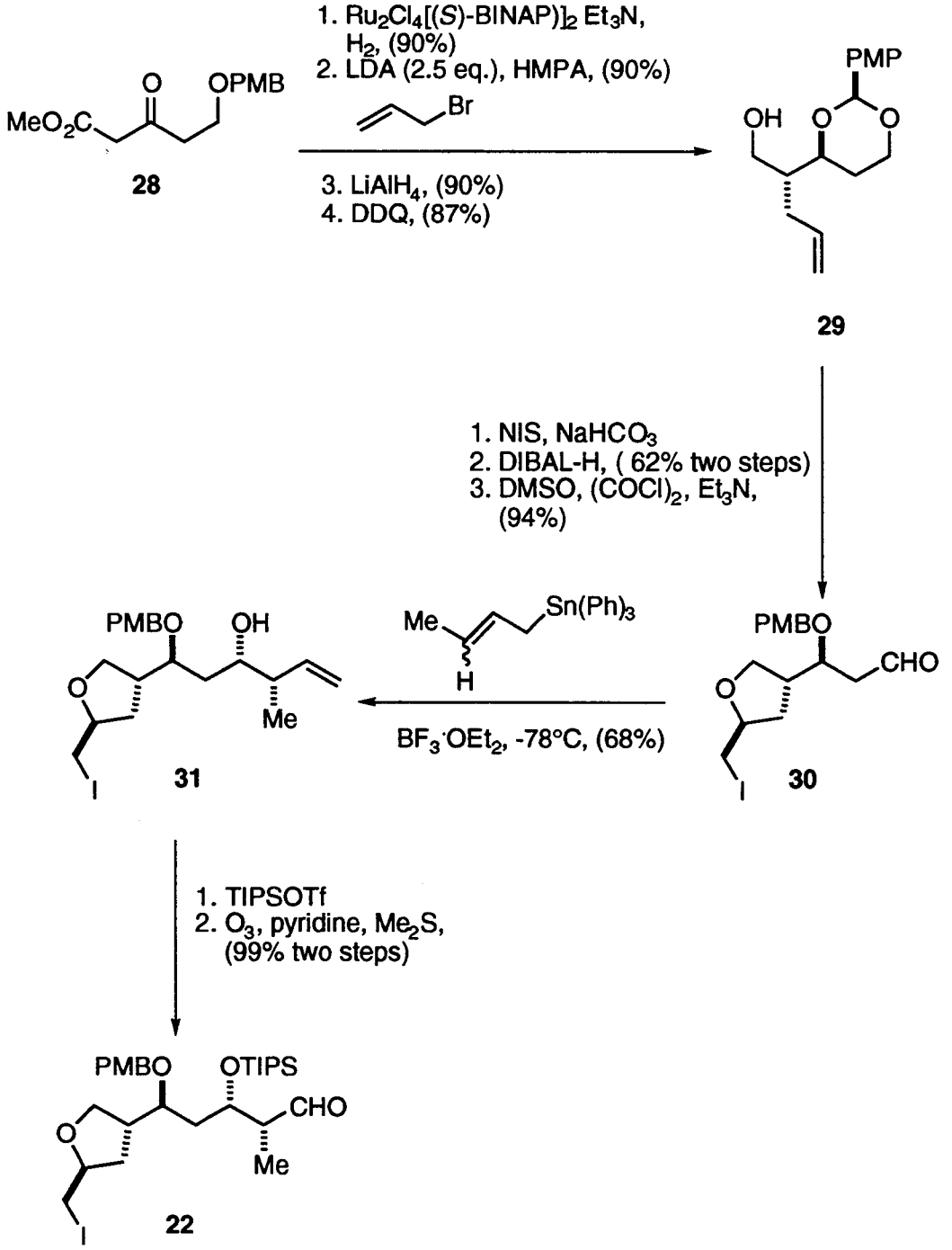
cyclohexane **26** which was homologated to alkyne **27** in four steps. Hydrozirconation and bromination of **27** furnished the desired vinyl bromide **21**.




**Scheme 4**

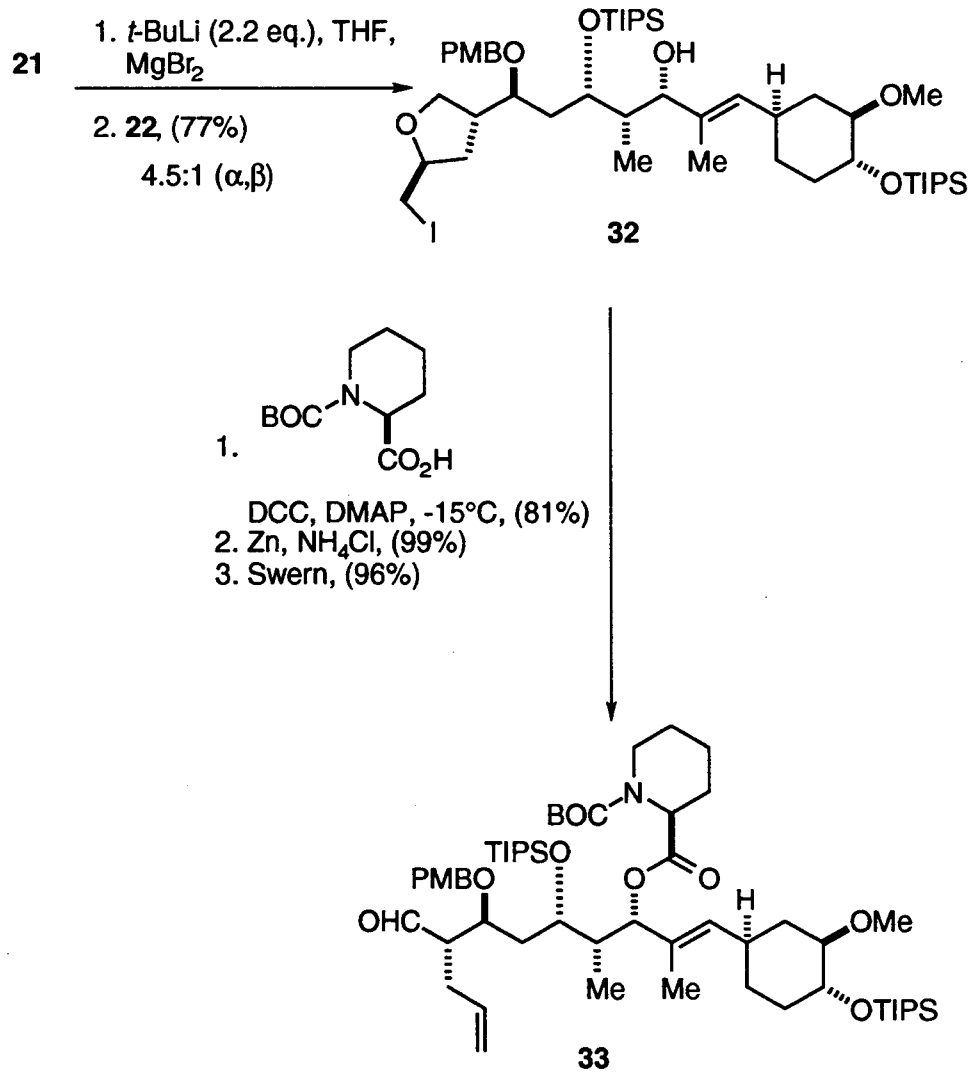
The synthesis of aldehyde **22** started with the conversion of β-keto ester **28** into acetal **29** in four steps using an asymmetric reduction and a

stereoselective alkylation (Scheme 5). The allyl group was cleverly protected as a cyclic iodoether, and the *p*-methoxybenzylidene acetal was smoothly converted to aldehyde **30**. Chelation-controlled crotylation of **30** afforded homoallylic alcohol **31** which was converted to **22** in two steps.




**Scheme 5**

The coupling of **21** with **22** proceeded via halogen metal exchange of **21** with *t*-butyl lithium, followed by subsequent addition to **22**, to give predominantly the desired adduct **32**. A further three steps were needed to secure the C20-C34 fragment **33** used in the total synthesis of FK-506[10] (Scheme 6).

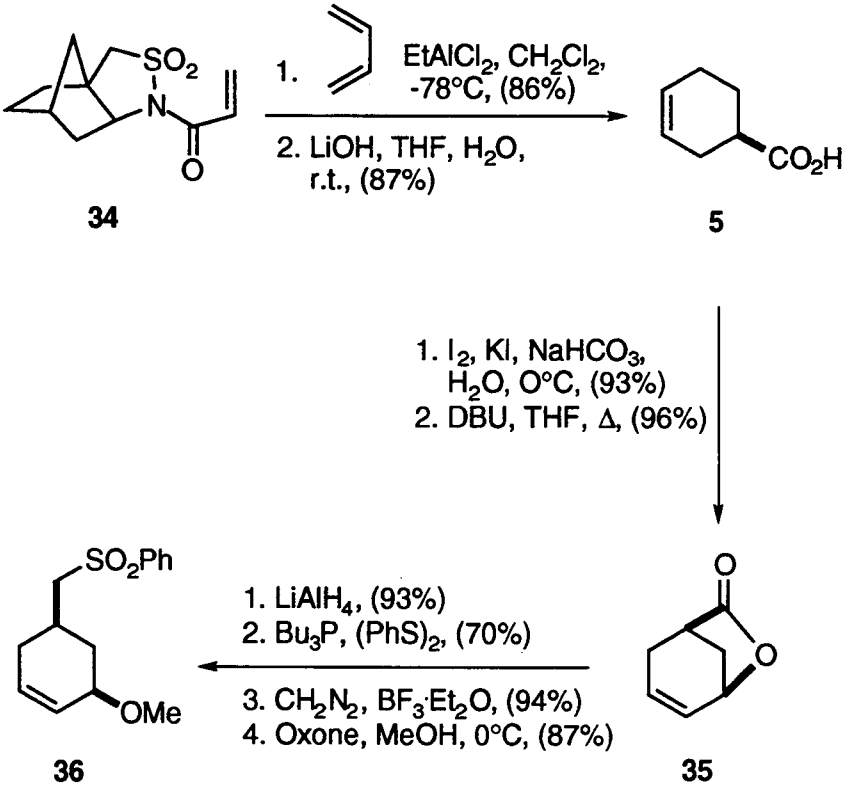


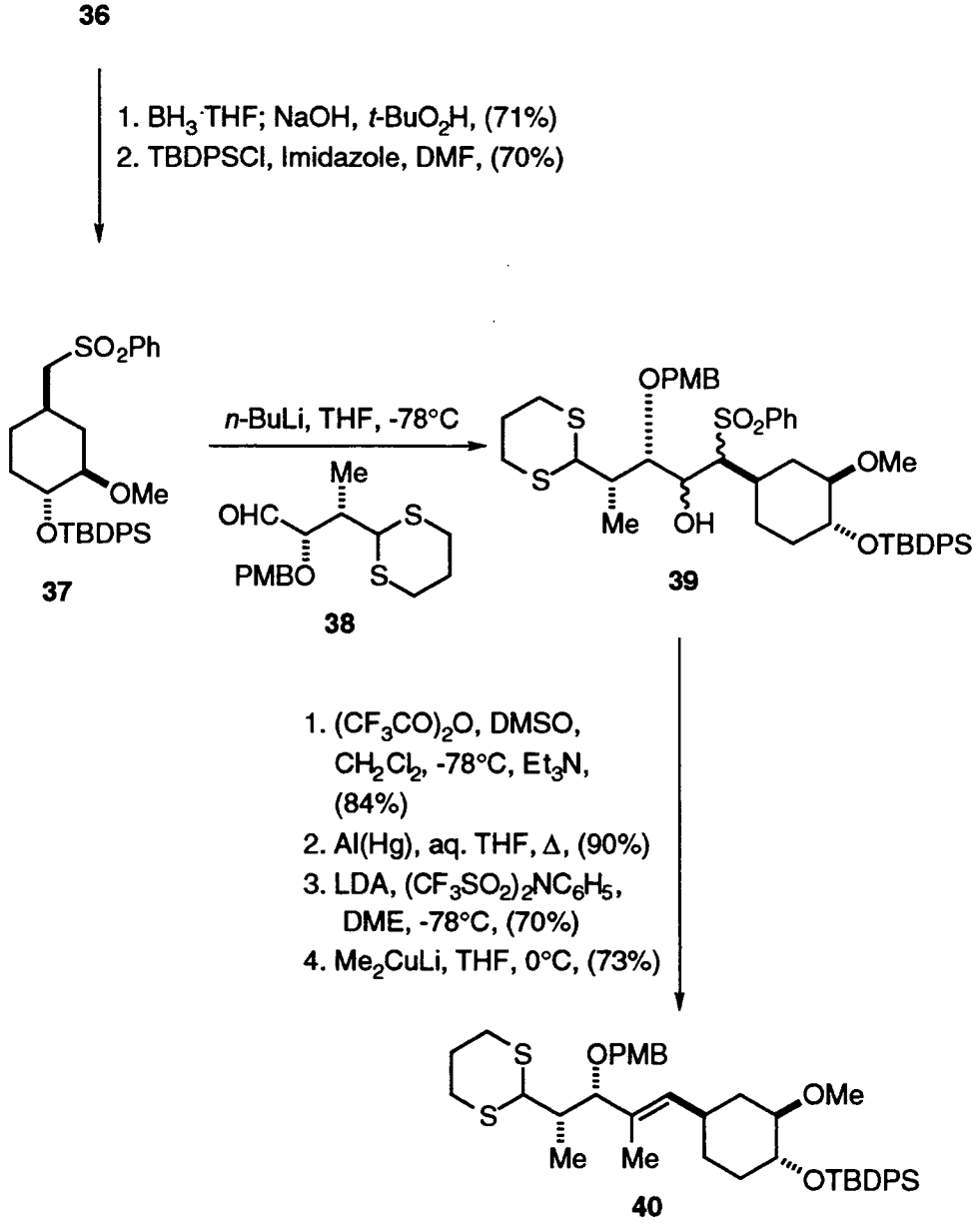

**Scheme 6**

Several research groups have used optically active 3-cyclohexenecarboxylic acid **5** as the starting material for a route to FK-

506.[12,18,19] Asymmetric Diels-Alder methodology was used to gain access to the cyclohexene moiety.

Smith and co-workers showed that the chiral sultam **34**[20] and butadiene underwent a Lewis acid-catalyzed Diels-Alder reaction which, after hydrolysis of the chiral auxilliary, provided **5** in good yield with 93% enantiomeric excess (Scheme 7).[18] Iodolactonization followed by elimination gave bicyclic lactone **35** which was converted to sulfone **36** in four steps. Regio- and stereoselective hydroboration with subsequent silylation afforded **37**. This was coupled with aldehyde **38**, available in six steps from crotyl alcohol, to give adduct **39**. A further four steps were needed for completion of the C24-C34 fragment **40**.

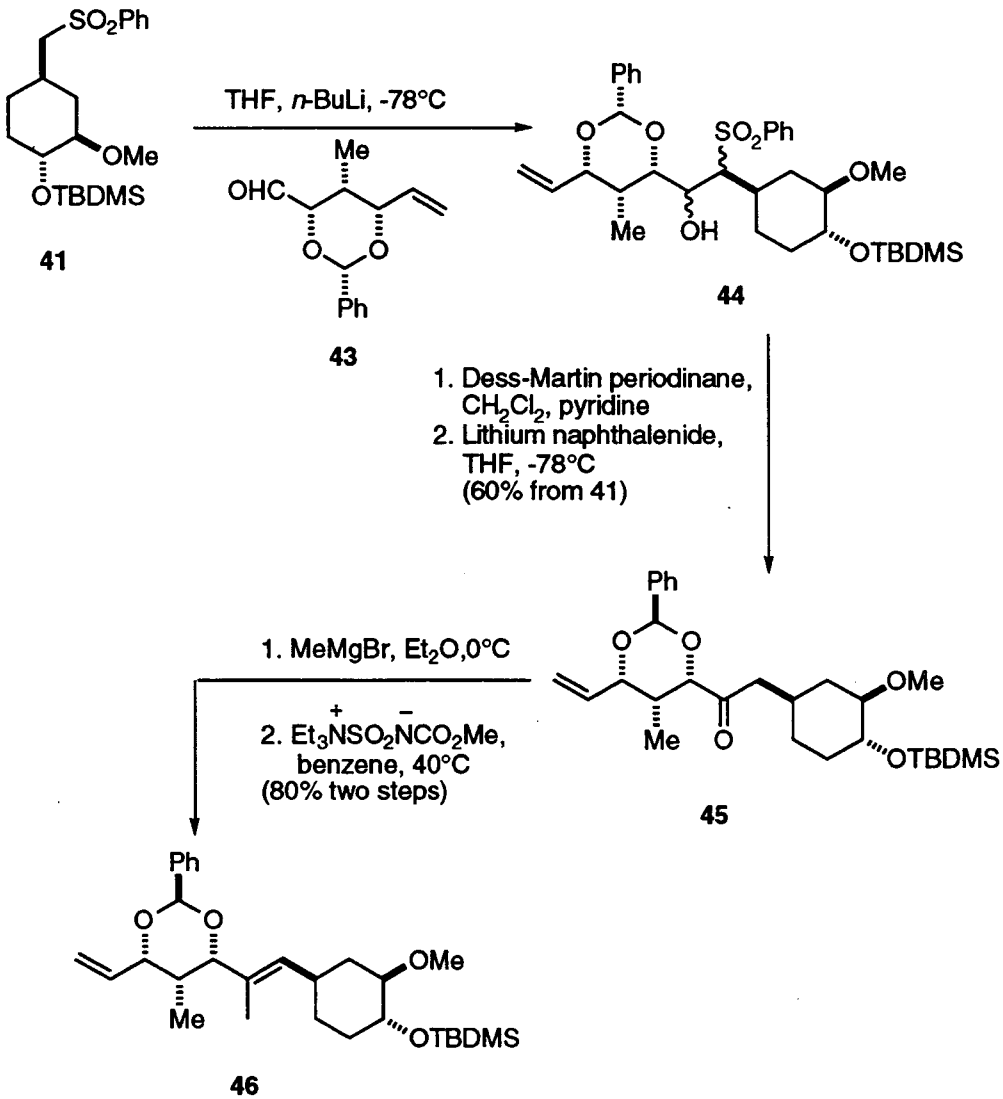




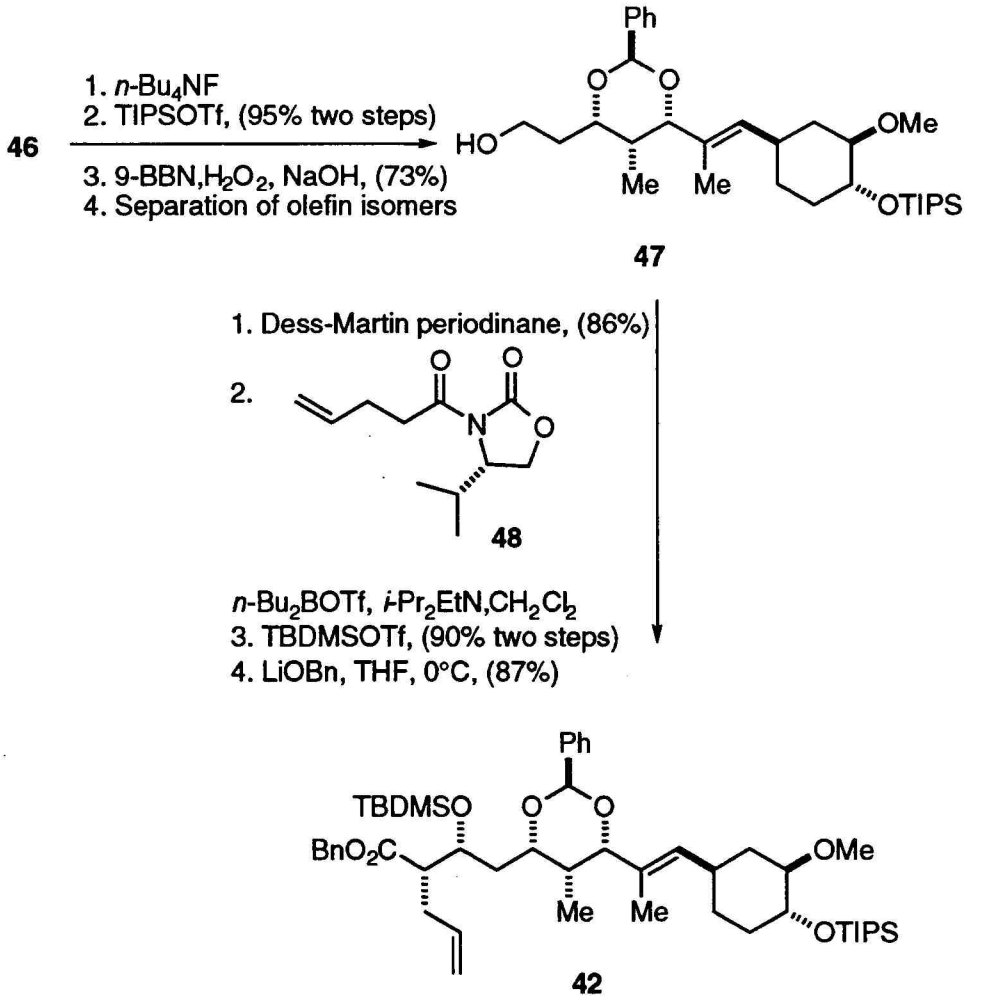

**Scheme 7**

Danishefsky and co-workers synthesized 3-cyclohexenecarboxylic acid **5** by the same procedure as Smith's[18] and converted it to sulfone **41** using again a strategy similar to that of the Smith route. This intermediate was used in the construction of fragment **42** to complete a formal synthesis of FK-506 (Scheme 8).[12] Thus, sulfone **41** was coupled to aldehyde **43**, and the resulting alcohol **44** was converted to ketone **45** in two steps. Treatment of **45** with

methylmagnesium bromide provided an intermediate carbinol which was dehydrated with Burgess' reagent to an inseparable (6:1.5:1) mixture of the three possible olefin isomers, the major product being the desired in-chain *E* isomer **46**. The isomer mixture, after exchanging the silyl protecting group, was converted by hydroboration-oxidation to their corresponding alcohols which were separated to yield **47** as the major product. Oxidation of **47** to its aldehyde and condensation with oxazolidinone **48** gave **42** after silylation and removal of the chiral auxilliary.

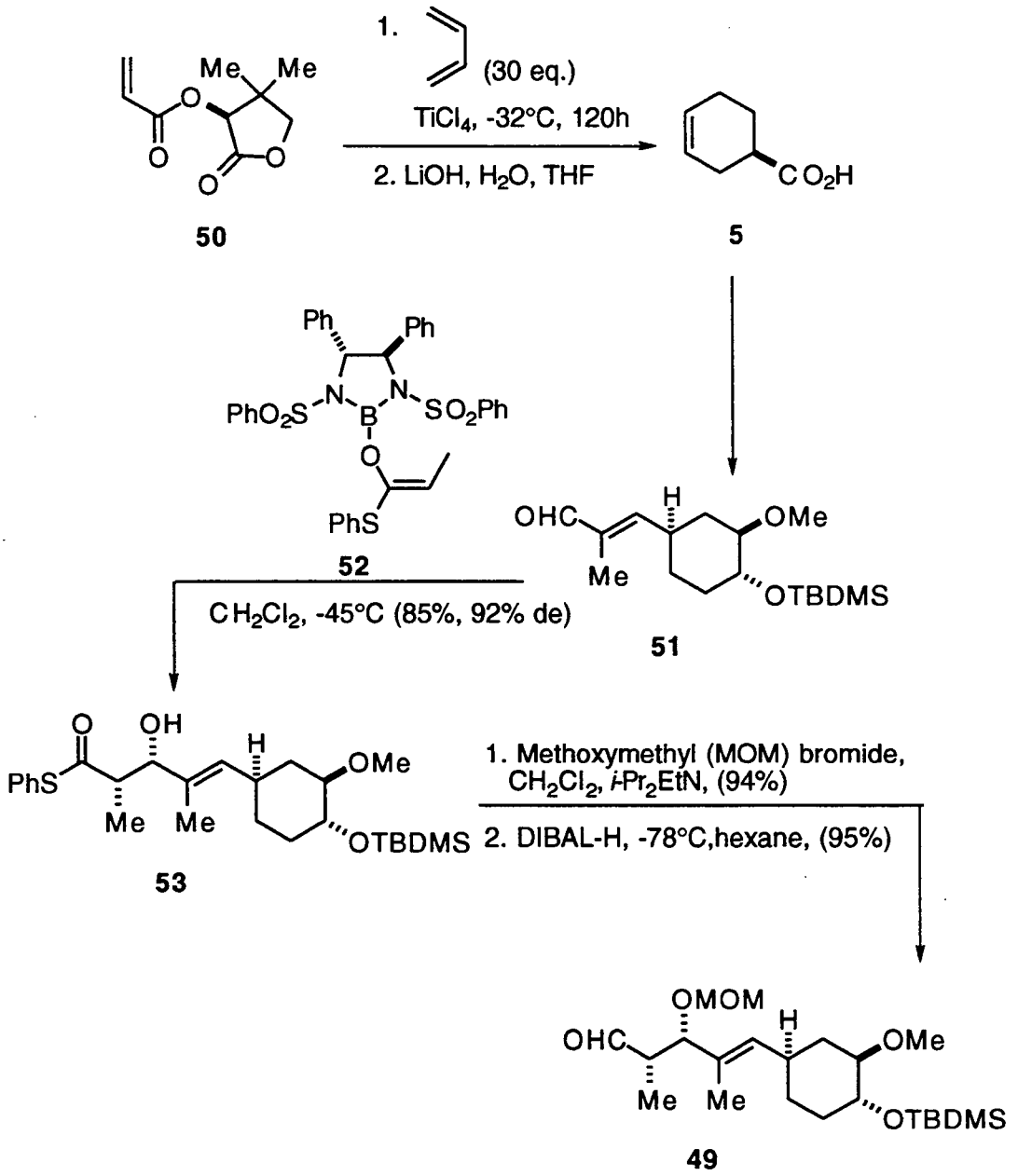



(6:1.5: 1, mixture of three olefin isomers)




**Scheme 8**

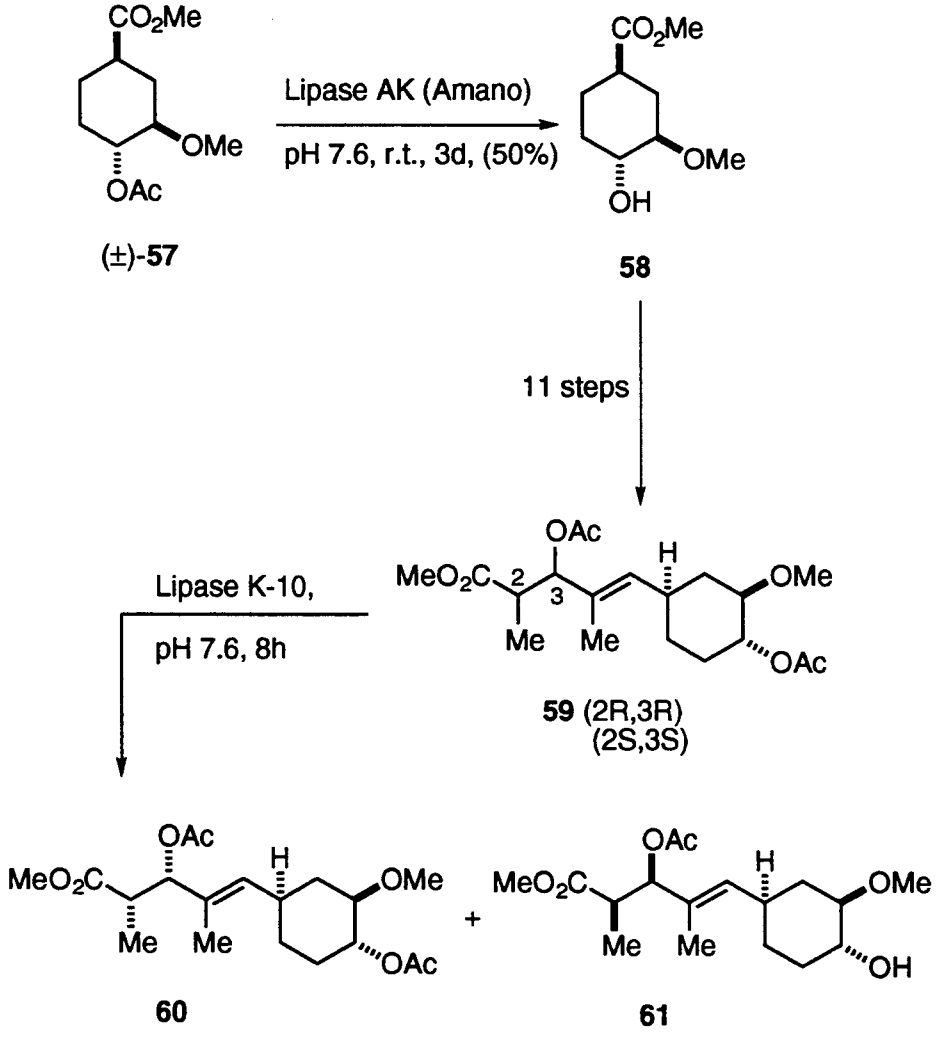
Corey and Huang also used an asymmetric Diels-Alder strategy for entry into the C24-C35 fragment **49**.[19] A titanium-catalyzed Diels-Alder addition of butadiene to chiral acrylate **50**, followed by hydrolysis, gave **5** which was converted to aldehyde **51** using a method analogous to that of Jones[8] (Scheme 9). Diastereoselective aldol condensation of **51** with **52** afforded thioester **53** in excellent yield. Protection of the resulting alcohol, followed by reduction, gave aldehyde **49**. The latter is a variant of the intermediate prepared by Jones.[10]

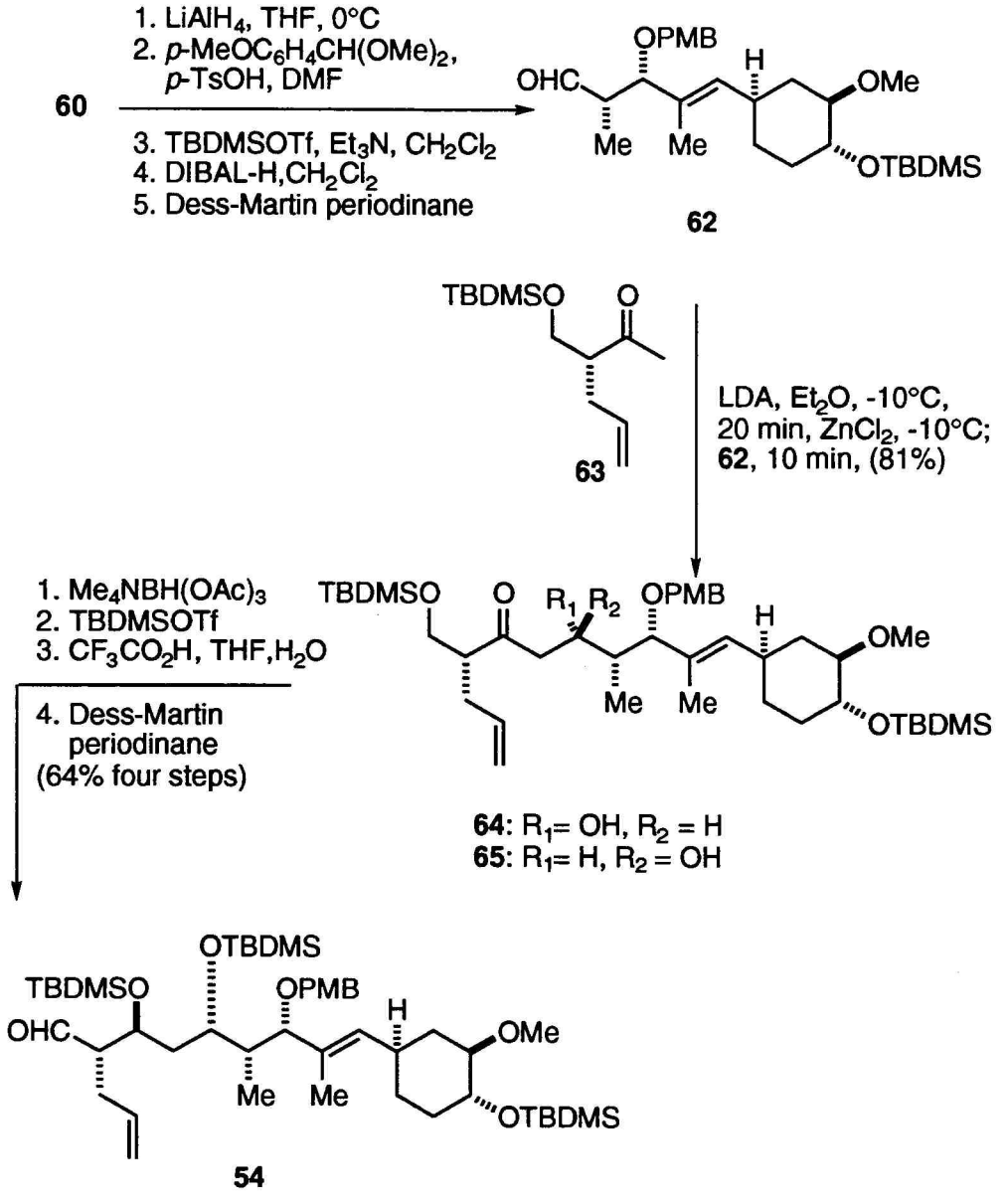



**Scheme 9**

Sih and Gu reported a formal synthesis of FK-506 which entailed construction of the C20-C34 segment **55** via a coupling reaction of aldehyde **62** and ketone **63**[13] (Scheme 10). Enantioselective lipase hydrolysis of racemic **57** provided optically active **58**, which was converted in several steps to a mixture of diastereomers **59**. Diastereoselective lipase hydrolysis of the cyclohexyl

acetate of **59** gave **60** and the alcohol **61**. Ester **60** was converted to the desired aldehyde **62** via a five-step reaction sequence. Coupling of aldehyde **62** with **63**, available in six steps from ethyl(*3S*)-hydroxybutyrate, afforded **64** and **65** in a ratio of 4:6, respectively. The desired isomer **64** was converted to **54** using a four-step procedure.

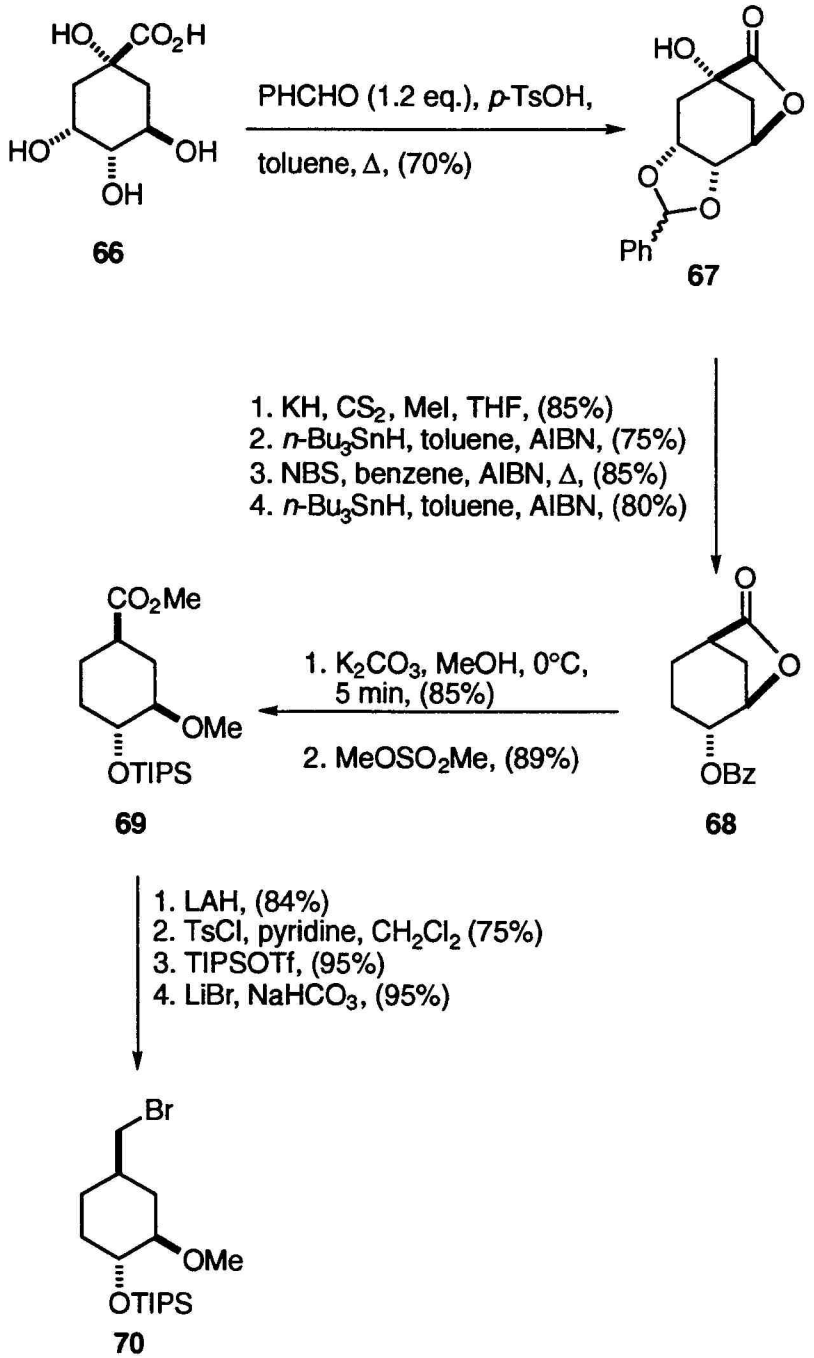




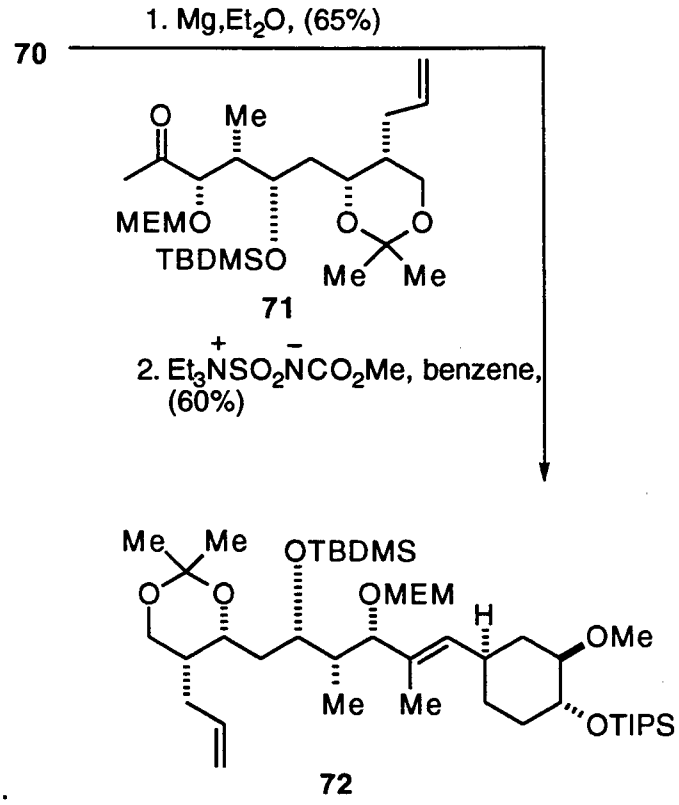

**Scheme 10**

A recent report by Rama Rao and co-workers showed that (-)-quinic acid (**66**) could be used as a practical starting material for the C20-C34 segment of FK-506.[21] Treatment of **66** with benzaldehyde led to the formation of tricyclic lactone **67** in good yield.[22] Deoxygenation of the tertiary alcohol via the xanthate, followed by regioselective ring opening of the benzylidene acetal[23] and a second reduction with *n*-tributyltin hydride, provided bicyclic lactone **68**.

Functional group manipulation led to ester **69** and then to the primary bromide **70** in a total of six steps (Scheme 11). The Grignard reagent derived from **70** was coupled to ketone **71** which was made using Evans' aldol methodology.[15] This sequence afforded **72** after dehydration (Scheme 12).




**Scheme 11**

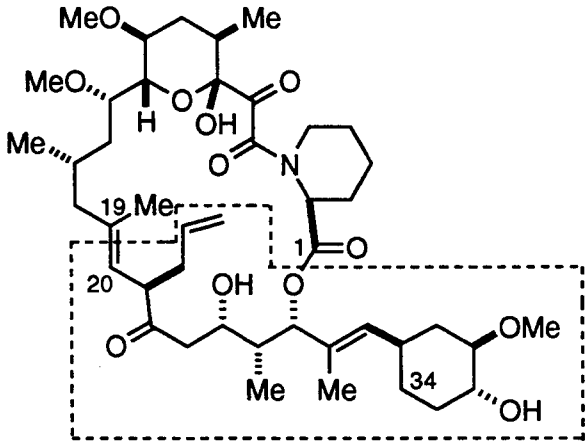



**Scheme 12**

The foregoing studies clearly indicate that the C20-C34 segment of FK-506 is a logical subunit to target for synthesis in the global plan. Access to this fragment using the trisubstituted olefin at C27-C28 to link the smaller segments has been a popular strategy. This has led to the use of 3-cyclohexenecarboxylic acid **5** as a frequent starting material.[10,12,18,19] Although the several routes to this portion of FK-506 share many features in common, each synthetic pathway has shown innovative use of contemporary methodology in the course of assembling this subunit.

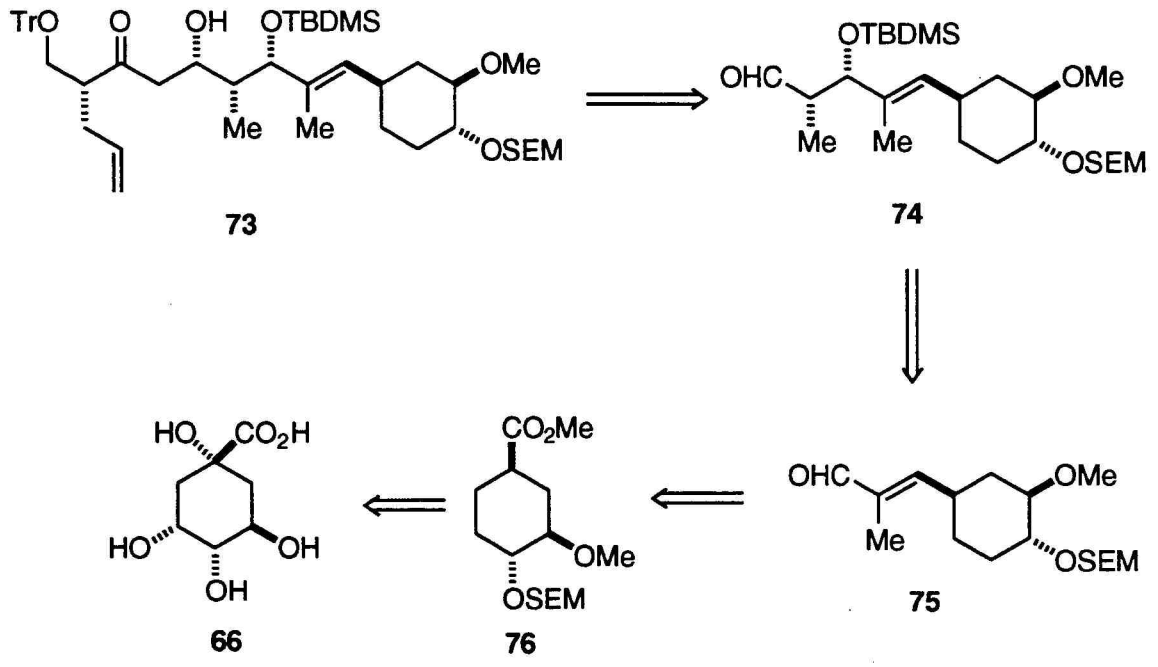
## II-B. Results and Discussion

The goal of this work was to develop an efficient entry to the total synthesis of the immunosuppressant FK-506 (**1**). This was envisioned by subdividing the macrolide into fragments which could later be assembled in a stepwise fashion. When planning the synthetic strategy, it was decided that the disconnection at C19-C20 and at C1 of the lactone moiety were the logical retrosynthetic choices. This resulted in the C20-C34 subunit being the initial target of interest.




**1**

The synthetic plan was based on the use of a suitably functionalized cyclohexane intermediate which would allow for systematic assembly of the required side chain (Scheme 13). It was envisioned that construction of the target molecule **73** would take place via a stereoselective aldol condensation of the protected aldehyde **74**. This aldehyde would be available from homologation of aldehyde **75** which, in turn, could be synthesized from ester **76**. An appropriate starting material for the synthesis of **76** would be (-)-quinic acid (**66**).

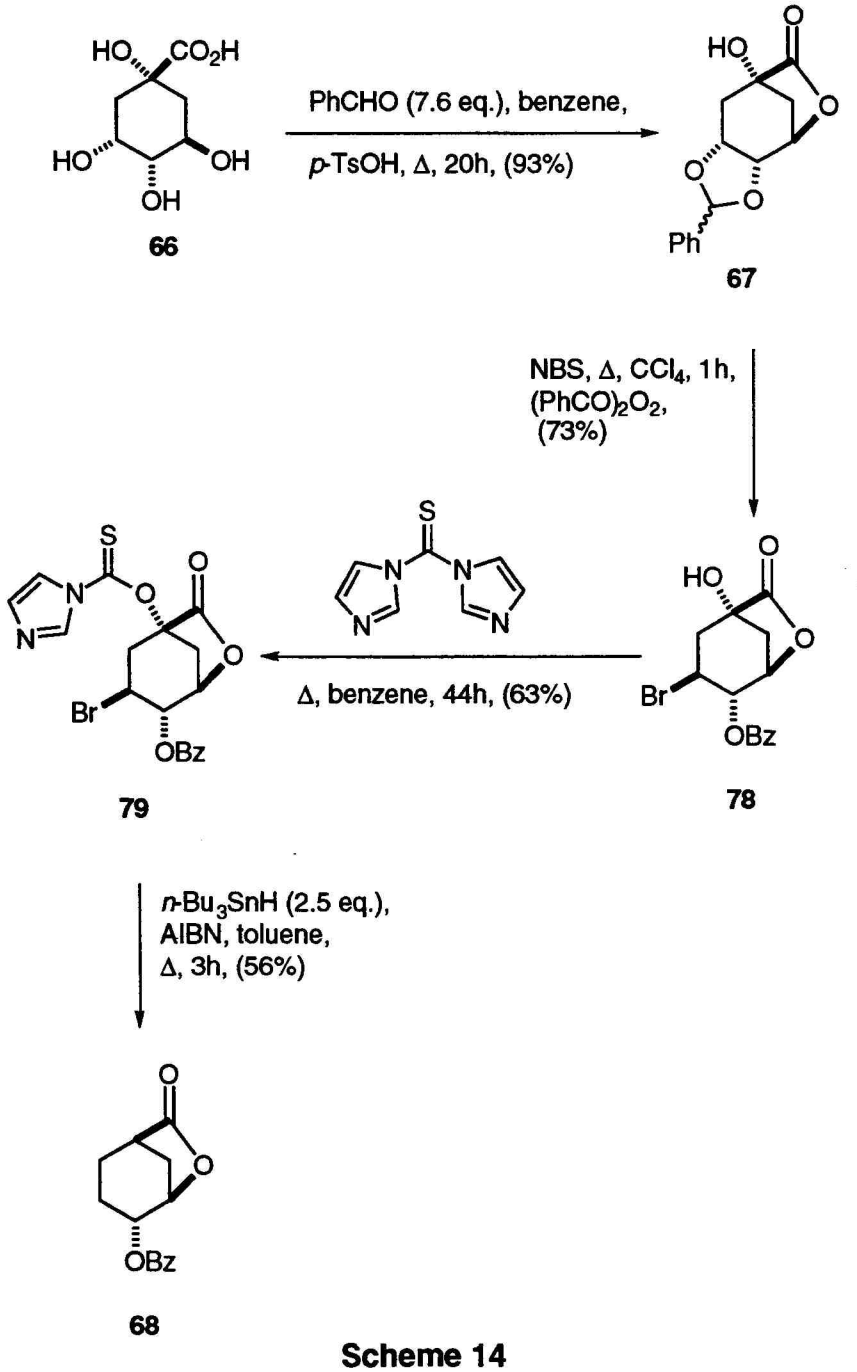



**Scheme 13**

The decision to use (-)-quinic acid (**66**) as the point of departure stems from the fact that it contains the required absolute stereochemistry and functionality needed for accessing the cyclohexane moiety of FK-506. (-)-Quinic acid is a relatively inexpensive starting material, and even though two unwanted hydroxyl groups must be removed, its use as a starting material is economically attractive.

(-)-Quinic acid (**66**) underwent acid-catalyzed acetalization with benzaldehyde and subsequent γ-lactonization to afford tricyclic lactone **67** as a 1:1 mixture of diastereomers in excellent yield[21, 22, 24] (Scheme 14). Although this initial step parallels that of Rama Rao,[21] our route immediately diverges after this reaction. Instead of deoxygenation at this point, regioselective ring opening of **67** with N-bromosuccinimide was used to provide bicyclic bromo benzoate **78**.[23,24] This was converted smoothly to imidazolide **79** with thiocarbonyl diimidazole.[25]

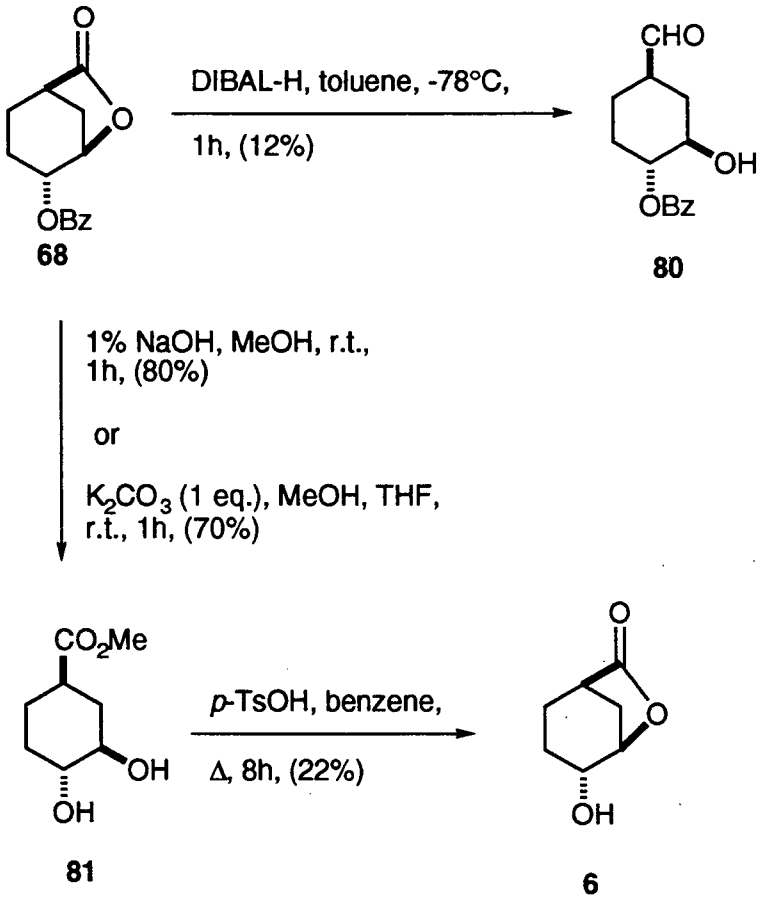
An important transformation at this stage was the simultaneous reduction of both the alkyl bromide and imidazolide moieties thereby improving the two-step methodology employed by Rama Rao.[21] Treatment of **79** with excess *n*-tributyltin hydride and α,α'-azobisisobutyronitrile in refluxing toluene afforded bicyclic lactone **68** in good yield.[25]




**Scheme 14**

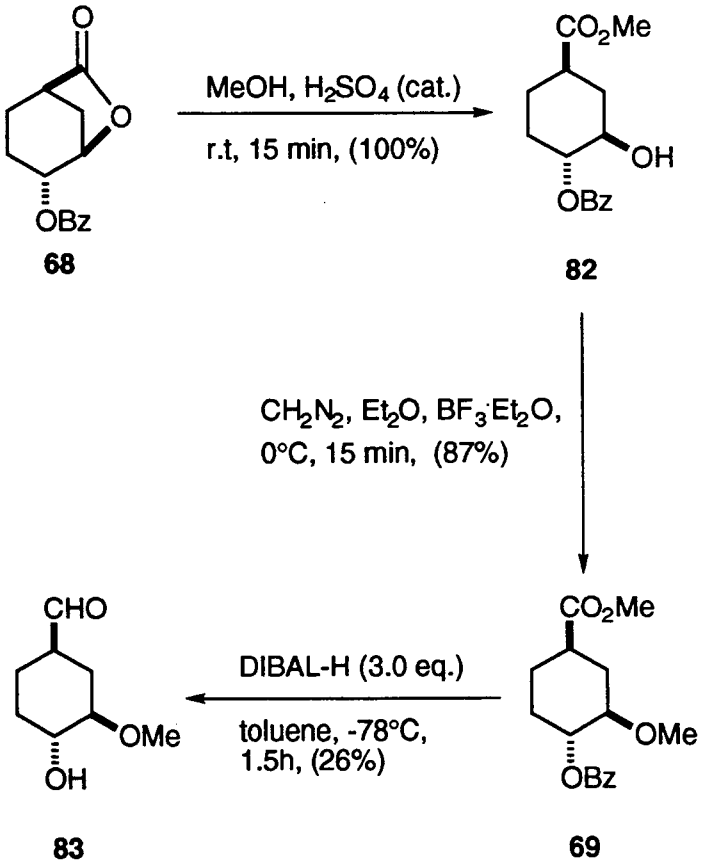
Initial attempts to selectively cleave the lactone moiety in **68** were unrewarding. Treatment of **68** with one equivalent of diisobutylaluminum hydride in toluene at -78°C gave aldehyde **80** in a disappointing 12% yield which could not be improved in spite of many attempts at optimization (Scheme 14).

A selective base-catalyzed transesterification was also attempted using 1% sodium hydroxide or potassium carbonate in methanol. In each case, no selectivity was observed, diol **81** being isolated as the major product. This diol could be relactonized in poor yield to hydroxylactone **6**, a previous intermediate in FK-506 synthesis[10,19] (Scheme 15).




**Scheme 15**

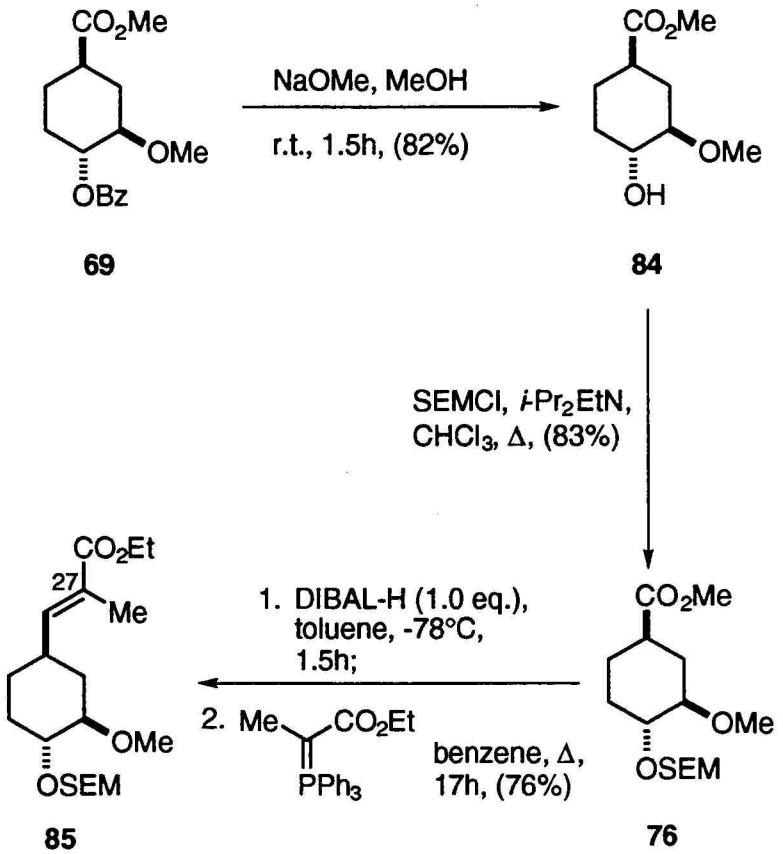
A straightforward solution to this problem proved to be a quantitative acid-catalyzed lactone opening of **68** which provided alcohol **82**. Treatment of **82** with diazomethane in the presence of a catalytic amount of boron trifluoride etherate afforded methyl ether **69**[26] (Scheme16). An attempt to simultaneously cleave the benzoyl group and reduce the ester group of **69** with two or three equivalents of diisobutylaluminum hydride (DIBAL-H) gave the desired aldehyde **83** in only 26% yield.




**Scheme 16**

At this point, it was found advantageous to replace the benzoyl group with a protecting group which could be used for the duration of the synthesis. Treatment of **69** with sodium methoxide yielded alcohol **84** which, upon protection with trimethylsilylethoxymethoxy (SEM) chloride,[27] afforded silyl

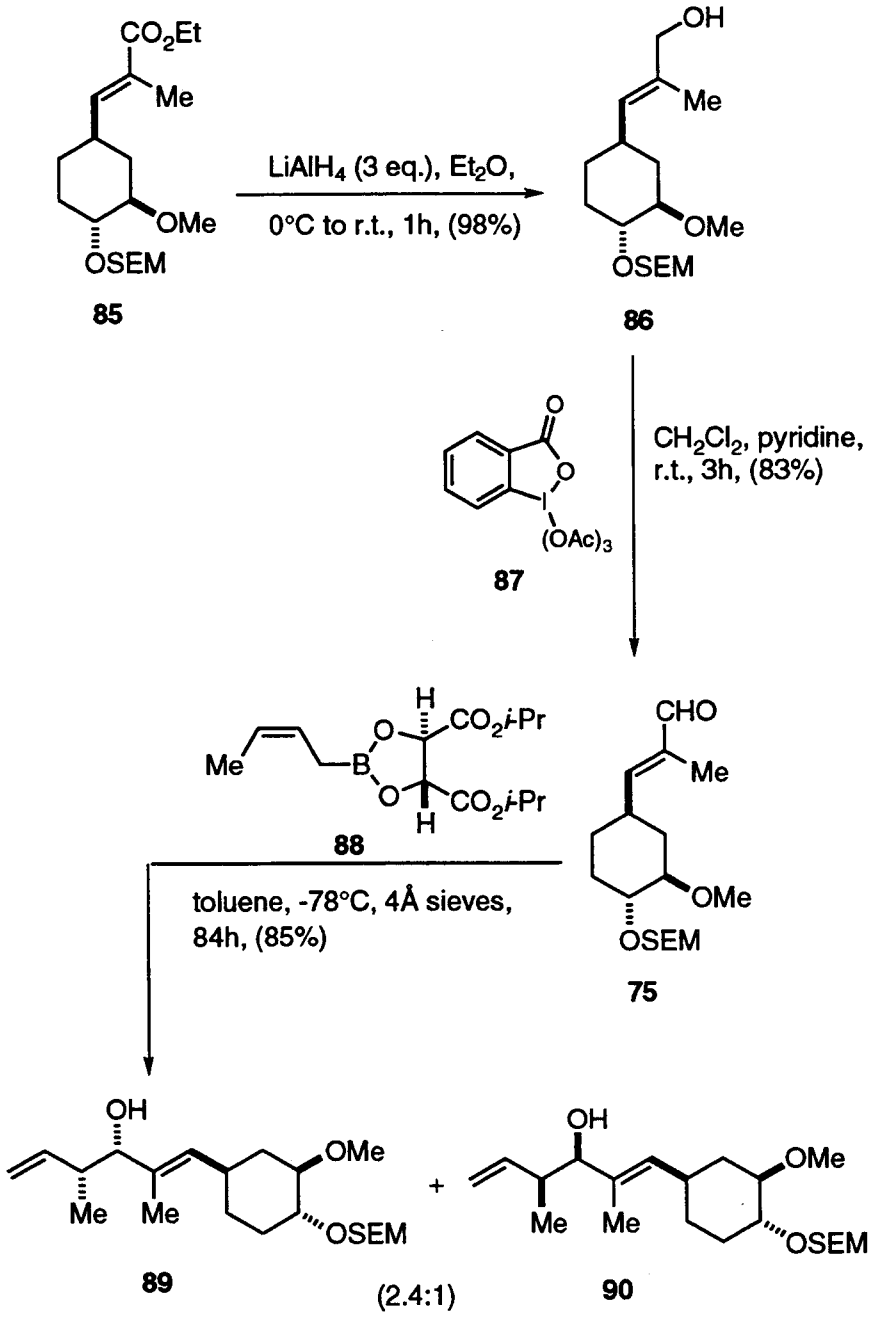
ether **76** (Scheme 17). Reduction of **76** with one equivalent of diisobutylaluminum hydride afforded the corresponding aldehyde, which, without purification, was converted exclusively to (*E*)-α,β-unsaturated ester **85** via Wittig olefination[28] using (carboethoxyethylidene)triphenylphosphorane. Evidence to support the (*E*)-olefin geometry came from analysis of the $^{13}C$ NMR spectrum of **85**. The C27 methyl signal is strongly shielded by the *cis*-cyclohexyl moiety and appears at 12.5 ppm. This observation correlates with a report by Smith, in which it is stated that the C27 methyl group resonates at 11.0 ppm for a related compound. This methyl group appears at 13.7 ppm in FK-506.[18]




**69** **84** **85** **76**

**Scheme 17**

Straightforward reduction of **85** afforded allylic alcohol **86**, which upon treatment with Dess-Martin periodinane **87**,[29] gave α,β-unsaturated aldehyde **75** (Scheme 18). Treatment of enal **75** with the (Z)-crotylboronate **88**,[30] derived from its corresponding diethanolamine complex and (*R,R*)-diisopropyl tartrate,[31] gave a 2.4 : 1 mixture of homoallylic alcohols **89** and **90**.




**Scheme 18**

The major product **89** was assigned the configuration shown based on the accepted transition state for this reaction (Figure 2).[32] The first step in the proposed mechanism is complexation of the aldehyde with the boronate to form a tetrahedral boron species. The chirality of this chelate is determined by the anti relationship between the aldehyde oxygen and the proximal carboisopropoxy moiety. This results in *si*-face addition by the crotyl group in a chair-like transition state with the R group of the aldehyde in a pseudo-equatorial position.

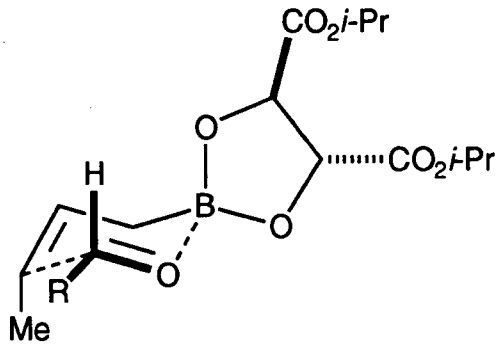
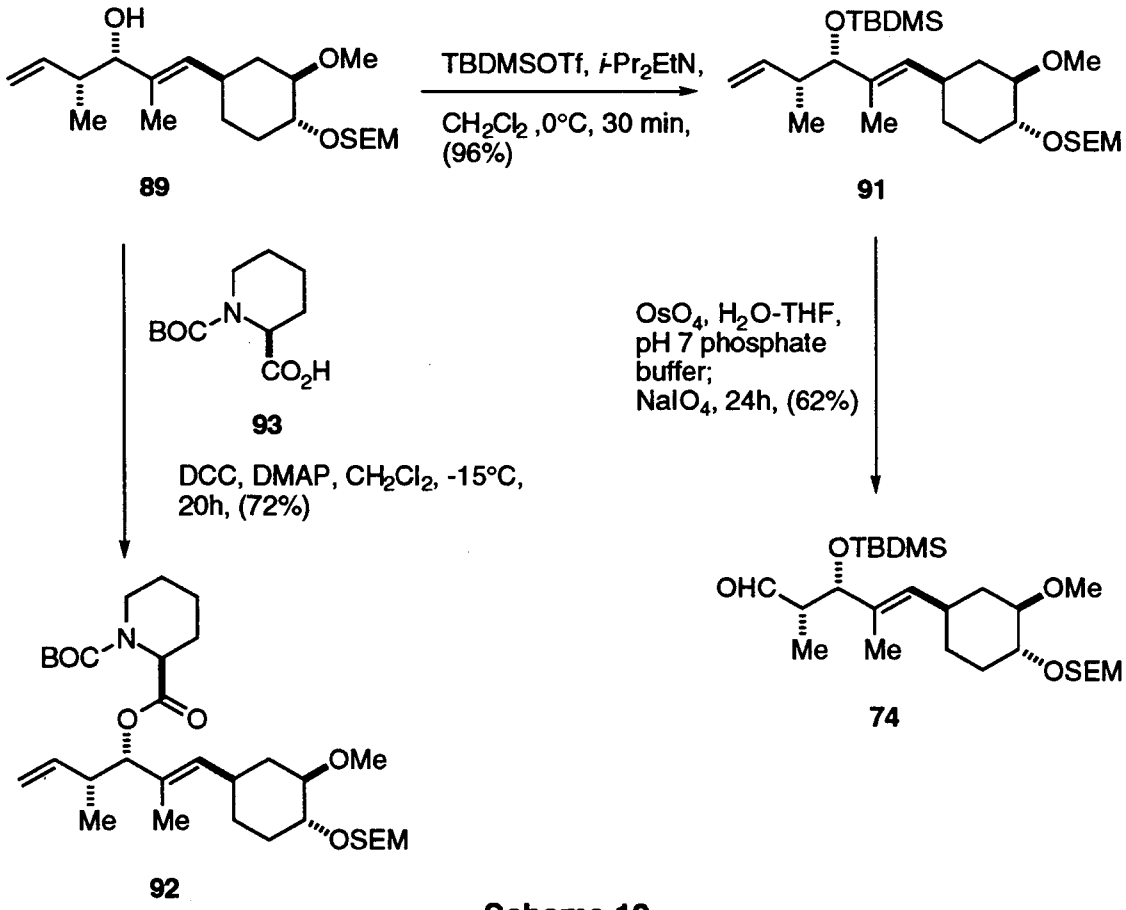



**Figure 2.** Transition State for the Crotylborinate Reaction.

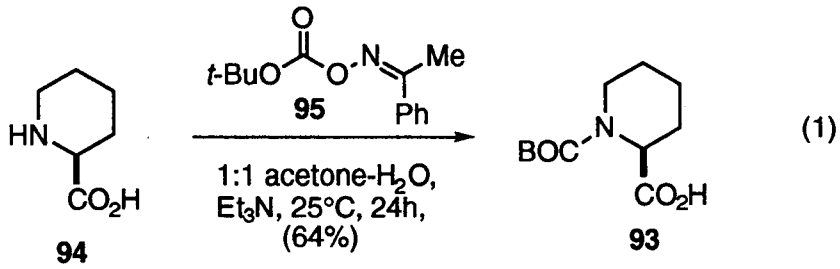
The alcohol **89** was protected using *t*-butyldimethylsilyl trifluoromethanesulfonate[33] to afford silyl ether **91** in excellent yield (Scheme 19). Selective oxidative cleavage[34] of the terminal olefin of **91** was accomplished using catalytic osmium tetroxide in the presence of sodium metaperiodate which gave the desired aldehyde **74**.

The alcohol **89** was also converted to ester **92** using (*S*)-pipecolinic acid protected as its *t*-butoxycarbonyl derivative **93**[35] in the presence of dicyclohexylcarbodiimide. The protected amino acid **93** was synthesized from commercially available (*S*)-pipecolinic acid **94** using 2-*tert*-butyloxycarbonyloxyimino-2-phenylacetonitrile **95**[36] (eq. 1). Attempts to

oxidatively cleave **92** under the same conditions as used for **91** resulted in decomposition of starting material with no evidence of product formation.

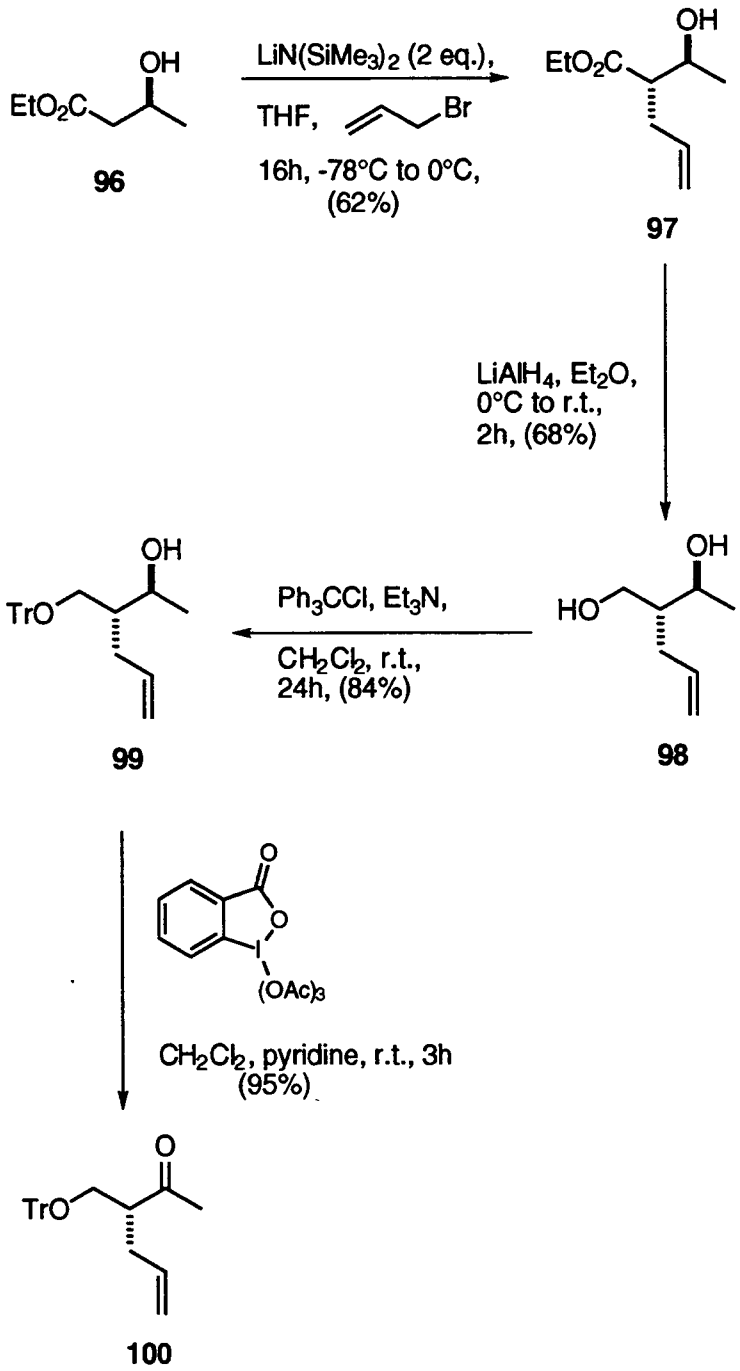



**Scheme 19**



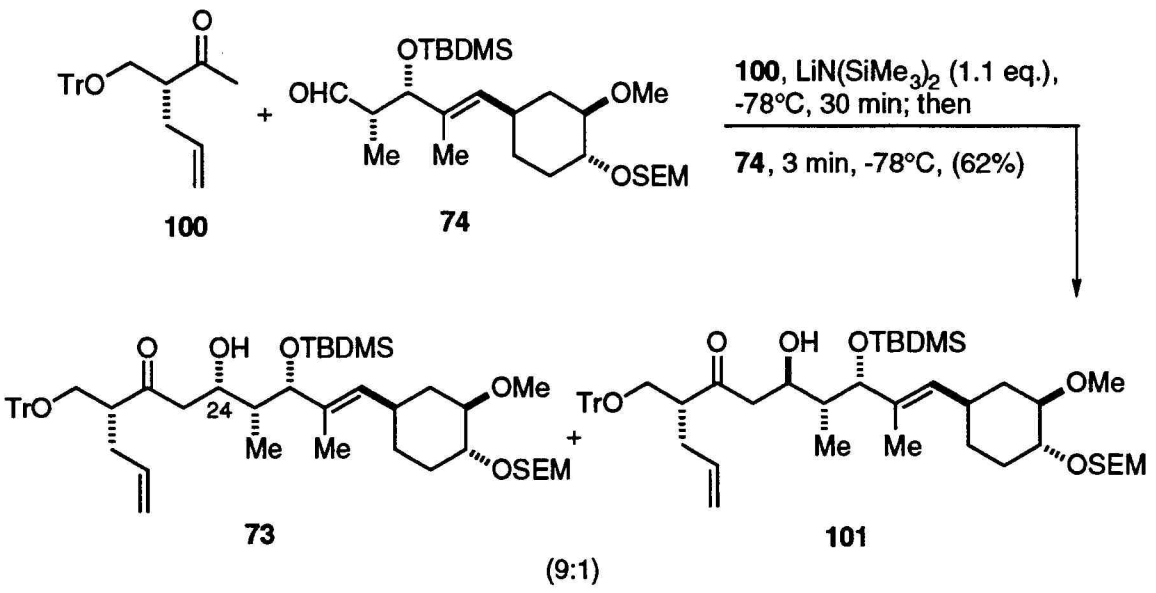

With the key aldehyde **74** in hand, attention now focused on the synthesis of the ketone **100** needed for the aldol reaction to give **73**. The ketone was synthesized in four steps from ethyl (*R*)-3-hydroxybutyrate (**96**) by the route shown in Scheme 20. The dianion of **96** was alkylated with allyl

bromide which provided ester **97**.[37] Reduction of **97** using lithium aluminum hydride resulted in diol **98**. Selective protection of the primary alcohol afforded trityl ether **99**[38] which, upon treatment with Dess-Martin periodinane,[29] gave ketone **100** in excellent yield.




**Scheme 20**

Synthesis of the C20-C34 segment **73** of FK-506 was completed by aldol condensation of ketone **100** with aldehyde **74** using kinetically controlled conditions[39] (Scheme 21). Treatment of the lithium enolate of **100**, prepared with lithium bis(trimethylsilyl)amide, with **74** at -78°C for three minutes gave aldol adducts **73** and **101** in a 9:1 ratio as determined by $^1$H NMR analysis. The selectivity observed in this condensation is a significant improvement on the 4:6 ratio of products reported for a similar aldol coupling by Sih.[13]




**Scheme 21**

The major product **73** is assigned 24(*S*) configuration based on a transition state analysis of the coupling. Aldol reactions normally proceed through a lithium-chelated, six-centered Zimmerman-Traxler transition state in which the hydrogen atom of the aldehyde occupies a pseudoaxial position.[40] The diastereofacial selectivity of attack at the aldehyde carbonyl can be rationalized in this transition state using the Felkin-Anh principle,[41] which predicts for the case at hand that the incoming enolate approaches the *si* face

of the aldehyde (Figure 3). This mode of attack would lead to (*S*) configuration at the new stereogenic center produced in the aldol condensation.

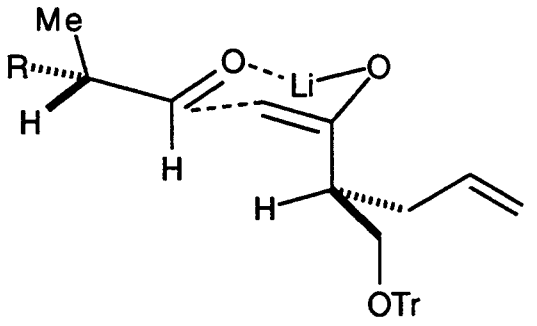



**Figure 3.** Transition State for the Stereoselective Aldol Reaction.

In conclusion, the synthesis of the C20-C34 subunit **73** of FK-506 (**1**) was accomplished in fifteen steps in an overall yield of 2.8%. Quinic acid (**66**) as starting material allowed for quick access to the key intermediate aldehydes **74** and **75**, and aldol condensation of **74** with the lithium enolate of **100** proved to be a remarkably stereoselective and efficient method for elaborating the desired fragment. The FK-506 segment **73** represents a strategic intermediate that will allow for future studies directed at the construction of the entire molecule.

## II-C. Experimental

### General

General experimental techniques and instrumentation used in this work are outlined in section IC.

**(*1R,3S,4S,5R*)-4-Benzoyloxy-3-bromo-1-*o*-imidazothiocarbonyl-6-oxabicyclo[3.2.1]octan-7-one (79).** To a solution of **78**[23,24] (7.06 g, 20.7 mmol) in benzene (300 mL) was added 1,1'-thiocarbonyldiimidazole (4.05 g, 22.8 mmol). The mixture was heated at reflux for 44 h then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **79** (5.92 g, 63%) as a white solid: mp 147-148.5°C; $[\alpha]_D$ +68.0° (c = 1.10, $CHCl_3$); IR (thin film) 1806, 1724, 1267, 1233, 1097, 1027, 714 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.96 (dd, *J* = 7.2 Hz, 1.3 Hz, 2H), 7.62-7.56 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 1.3 Hz, 1H), 5.59 (t, *J* = 2.6 Hz, 1H), 5.09-5.06 (m, 1H), 4.55 (d, *J* = 7.3 Hz, 1H), 3.47 (dd, *J* = 14.9 Hz, 11.9 Hz, 2H), 3.07 (d, *J* = 11.9 Hz, 1H), 2.67 (d, *J* = 14.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 179.0, 169.4, 164.2, 136.7, 134.0, 131.1, 129.7 (x2), 128.6 (x2), 128.1, 117.8, 81.8, 74.8, 71.3, 39.4, 37.9, 33.4; MS (CI) *m/z* (rel. intensity) 453 (M + 1, 29), 451 (M + 1, 32), 69 (100); HRMS, *m/z* calcd. for $C_{18}H_{16}{}^{79}BrN_2O_5S$ (M + 1): 450.9963. Found: 450.9963. Anal. Calcd. for $C_{18}H_{15}{}^{79}BrN_2O_5S$: C, 47.91, H, 3.35, N, 6.21, S, 7.10. Found: C, 47.86, H, 3.22, N, 6.04, S, 7.11.

**(*1R,4R,5R*)-4-Benzoyloxy-6-oxabicyclo[3.2.1]octan-7-one (68).** To a solution of tributyltin hydride (8.83 mL, 32.8 mmol) in refluxing toluene (200 mL) was added dropwise a mixture of **79** (5.92 g, 13.2 mmol) and α,α-azobisisobutyronitrile ( 108 mg, 0.66 mmol) in toluene (100 mL) over a 10 min period. The resulting mixture was stirred at reflux for 3 h, allowed to cool to room temperature, and the toluene removed *in vacuo*. Ether (300 mL) was added to the residue and washed with 2 M potassium fluoride (4 x 25 mL) and the phases separated. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:3 ethyl acetate-hexane as elutant provided **68** (1.80 g, 56%) as a white solid: mp 135-139°C; $[\alpha]_D$ -10.7° (c = 1.20, $CHCl_3$); IR (thin film) 3063, 3029, 2954, 1784, 1724, 1595, 1273, 1157, 1101, 757, 709 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.2, 1.6 Hz, 2H), 7.61-7.56 (m, 1H), 7.45 (dt, *J* = 7.8 Hz, 1.3 Hz, 2H), 5.35-5.31 (m, 1H), 4.91-4.88 (m, 1H), 2.70-2.68 (m, 1H), 2.33 (d, *J* = 2.8 Hz, 2H), 2.13-2.05 (m, 2H), 1.93-1.87 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 177.8, 165.3, 133.4, 129.6 (x3), 128.5 (x2), 76.2, 67.6, 37.9, 32.1, 24.3, 23.0; MS (CI) *m/z* (rel. intensity) 247 (M + 1, 38), 59 (100); HRMS, *m/z* calcd. for $C_{14}H_{15}O_4$ (M + 1): 247.0970. Found: 247.0970. Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28, H, 5.73. Found: C, 68.28, H, 5.54.

**(*1R,3R,4R*)-4-Benzoyloxy-3-hydroxy-cyclohexanal (80).** To a solution of **68** (26.0 mg, 0.11 mmol) in dry toluene (2 mL) was added diisobutylaluminum hydride (0.07 mL, 0.11 mmol, 1.5 M in toluene) at -78°C. The reaction was stirred for 1 h at -78°C then quenched with saturated ammonium chloride (1 mL) and warmed to room temperature. The two phases were partitioned and the aqueous layer was extracted with ethyl acetate (3 x 3

mL). The combined organic extracts were dried over magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **80** (3.00 mg, 12%) as a clear oil: IR (neat) 3474 (br), 2935, 1717, 1116, 713 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.05-8.03 (d, *J* = 7.2 Hz, 2H), 7.59-7.53 (t, *J* = 7.5Hz, 1H), 7.53-7.40 (t, *J* = 7.8Hz, 2H), 4.89-4.81 (m, 1H), 3.89-3.81 (m, 1H), 2.44-2.22 (m, 3H ), 2.08-1.98 (m, 1H), 1.66-1.51 (m, 3H).

***(1R,3R,4R)*-1-Methoxycarbonylcyclohexan-3,4-diol (81).** A solution of **68** (107 mg, 0.44 mmol) in 1% methanolic sodium hydroxide (5 mL) was stirred for 1 h at room temperature. The pH was adjusted by the addition of 10 drops of 1.5 M hydrochloric acid and the mixture extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **81** (60.2 mg, 80%) as a white solid: mp 93-96°C; $[\alpha]_D$ -12.2° (c = 1.20, $CHCl_3$); IR (thin film) 3385, 2946, 2870, 1729, 1061 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.45-3.35 (m, 2H), 2.48-2.40 (m, 1H), 2.27-2.16 (m, 3H), 2.10-1.94 (m, 2H), 1.68-1.25 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 174.9, 74.9, 74.5, 51.8, 41.4, 34.9, 31.3, 26.9; MS (CI) *m/z* (rel. intensity) 175 (M + 1, 48), 157 (68), 125 (66), 59 (100); HRMS, *m/z* calcd. for $C_8H_{15}O_4$ (M + 1): 175.0970. Found: 175.0971.

***(1R,4R,5R)*-4-Hydroxy-6-oxabicyclo[3.2.1]octan-7-one (6).** To a solution of **81** (50.0 mg. 0.29 mmol) in benzene (1 mL) was added *p*-toluenesulfonic acid monohydrate (27.4 mg, 0.14 mmol). The mixture was refluxed for 8 h, allowed to cool, and the benzene was removed *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-

hexane as elutant provided **6** (9.0 mg, 22%) as a clear glass: mp 159-162°C, [Lit.[19] m.p = 163.5-165°C]; $[\alpha]_D$ -18.8° (c = 1.69, $CHCl_3$), [Lit[19] $[\alpha]_D$ -21.5° (c = 2.00, $CHCl_3$)]; IR (thin film) 3421, 2961, 2903, 1751,1157, 971, 913 $cm^{-1}$; $^1H$ NMR (300 mHz, $CDCl_3$) δ 4.70-4.60 (m, 1H), 4.18 (s,1H), 2.39 (d, *J* = 14.5 Hz, 1H), 2.25-2.14 (m, 1H), 2.03-1.70 (m, 5H); $^{13}C$ NMR (75mHz,$CDCl_3$) δ 178.5, 78.9, 65.2, 38.4, 31.1, 27.3, 22.7; MS (CI) *m/z* (rel. intensity) 143 (M + 1, 100), 125 (72), 97 (28); HRMS, *m/z* calcd for $C_7H_{11}O_3$ (M + 1): 143.0708. Found: 143.0707.

**(*1R,3R,4R*)-4-Benzoyloxy-1-methoxycarbonylcyclohexan-3-ol (82).** To a solution of **68** (15.0 mg, 0.06 mmol) in methanol (1 mL) was added concentrated sulfuric acid (0.10 mL). The mixture was stirred at room temperature for 15 min then quenched with saturated sodium bicarbonate (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate then concentrated *in vacuo* to obtain **82** (16.9 mg, 100%) as a white solid: mp 101-102°C; $[\alpha]_D$ -35.8° (c = 1.30, $CHCl_3$); IR (thin film) 3489, 3066, 2950, 2872, 1782, 1721$cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 4.91-4.83 (m, 1H), 3.83-3.75 (m, 1H), 3.70 (s, 3H), 2.53-2.19 (m, 4H), 2.07-2.03 (m, 1H), 1.72-1.45 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 174.6, 166.7, 133.2, 130.0, 129.7 (x2), 128.4 (x2), 77.7, 71.8, 51.9, 40.9, 35.0, 28.5, 26.5; MS (CI) *m/z* (rel. intensity) 279 (M + 1, 100); HRMS, *m/z* calcd. for $C_{15}H_{19}O_5$ (M + 1): 279.1233. Found: 279.1230.

**(*1R,3R,4R*)-4-Benzoyloxy-3-methoxy-1-methoxycarbonyl-cyclohexane (69).** To compound **82** (15.7 mg, 0.06 mmol) in a solution of diazomethane in ether (1 mL) was added boron trifluoride etherate (0.10 mL) at

0°C. While stirring for 15 min at 0°C, the reaction decolorized yielding a white precipitate and evolved nitrogen gas. The mixture was filtered to remove the white solid, and the ether was removed *in vacuo*. Purification by column chromatography on silica gel using 1:3 ethyl acetate-hexane as elutant provided **69** (14.1 mg, 87%) as a clear oil: $[\alpha]_D$ -52.3° (c = 1.05, $CHCl_3$); IR (neat) 3065, 2948, 2874, 1786, 1724 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.1 Hz, 1.3 Hz, 2H), 7.58-7.52 (m, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 5.03-4.95 (m, 1H), 3.70 (s, 3H), 3.62-3.33 (m, 1H), 3.40 (s, 3H), 2.47-2.37 (m, 2H), 2.26-2.21 (m, 1H), 2.04-1.98 (m, 1H), 1.69-1.45 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 174.5, 165.9, 132.8, 130.5, 129.6 (x2), 128.3 (x2), 80.2, 75.4, 57.6, 51.8, 40.8, 32.0, 28.8, 26.1; MS (CI) *m/z* (rel. intensity) 293 (M + 1, 100); HRMS, *m/z* calcd. for $C_{16}H_{21}O_5$ (M + 1): 293.1389. Found: 239.1389. Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74, H, 6.90. Found: C, 65.88, H, 6.84.

***(1R,3R,4R)*-3-Methoxy-4-hydroxycyclohexanal (83)**. To a solution of **69** (33.3 mg, 0.11 mmol) in dry toluene (2 mL) was added diisobutylaluminum hydride (0.23 mL, 0.34 mmol, 1.5 M in toluene) at -78°C. The reaction was stirred for 1.5 h at -78°C then quenched with saturated ammonium chloride (1 mL) and warmed to room temperature. The two phases were partitioned, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined extracts were dried over magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **83** (4.7 mg, 26%) as a clear oil: IR (neat) 3424 (br), 2936, 2869, 2830, 1721, 1094.$cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 3.46-3.40 (m, 1H), 3.43 (s, 3H), 3.07-3.01 (m, 1H), 2.68 (s, 1H), 2.45-2.39 (m, 1H), 2.35-2.29 (m, 1H ), 2.17-2.10 (m, 1H), 2.06-2.00 (m, 1H), 1.57-1.11 ( m, 3H).

**(*1R,3R,4R*)-3-Methoxy-1-methoxycarbonylcyclohexan-4-ol (84).** To a solution of **69** (323 mg, 1.11 mmol) in methanol ( 3 mL) was added sodium methoxide (1.32 mL, 1.32 mmol, 1 M in methanol). The mixture was stirred at room temperature for 1.5 h, and the methanol was removed *in vacuo.* The residue was taken up in ether (10 mL) and acidified to pH = 3 with 1.5 M hydrochloric acid (1.5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic extracts were dried over magnesium sulfate then concentrated *in vacuo.* Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **84** (172 mg, 82%) as a clear oil: $[\alpha]_D$ -81.5° (c = 1.14, $CHCl_3$); IR (neat) 3445 (br), 2946, 2873, 2833, 1732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.45-3.39 (m, 1H), 3.39 (s, 3H), 2.99-2.94 (m, 1H), 2.37-2.29 (m, 2H), 2.06-1.93 ( m, 2H), 1.48-1.23 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.8, 83.8, 73.0, 56.6, 51.7, 41.3, 30.8, 30.7, 26.6; MS (CI) *m/z* (rel. intensity) 189 (M + 1, 100), 157 (80), 139 (30); HRMS, *m/z* calcd. for $C_9H_{17}O_4$ (M + 1): 189.1127. Found: 189.1127. Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43, H, 8.57. Found: C, 57.44, H, 8.72.

**(*1R,3R,4R*)-3-Methoxy-1-methoxycarbonyl-4-(trimethylsilylethoxy)methoxycyclohexane (76).** To a solution of **84** (127 mg, 0.68 mmol) in chloroform (5 mL) was added diisopropylethylamine (0.50 mL, 2.70 mmol) along with trimethylsilylethoxymethoxy chloride (0.358 mL, 2.03 mmol). The mixture was refluxed 3 h, turning a dark orange color, allowed to cool, and the chloroform removed *in vacuo.* Purification by silica gel column chromatography using 1:3 ethyl acetate-hexane provided **76** (178 mg, 83%) as a clear oil: $[\alpha]_D$ -12.3° (c = 1.41, $CHCl_3$); IR (neat) 2950, 2891, 1738 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.79 (s, 2H), 3.68-3.60 (m, 2H), 3.67 (s, 3H), 3.43-

3.40 (m, 1H), 3.40 (s, 3H), 3.10-3.08 (m, 1H), 2.36-2.32 (m, 2H), 2.15-2.07 (m, 1H), 1.99-1.91 (m, 1H), 1.64-1.57 (m, 1H), 1.45-1.34 (m, 3H), 0.93 (dt, $J$ = 9.6 Hz, $J$ = 7.3 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 174.9, 94.4, 82.1, 78.4, 64.9, 57.2, 51.7, 40.9, 32.0, 30.0, 26.5, 18.0, -1.5 (x3); MS (CI) *m/z* (rel. intensity) 319 (M + 1, 64), 261 (100), 171 (99); HRMS, *m/z* calcd. for $C_{15}H_{31}O_5Si$ (M + 1): 319.1941. Found: 319.1939. Anal. Calcd. for $C_{15}H_{30}O_5Si$: C, 56.57, H, 9.49, Si, 8.82. Found: C, 56.72, H, 9.60, Si, 8.36.

**Ester 85.** To a solution of **76** (94.5 mg, 0.30 mmol) in dry toluene (3 mL) was added diisobutylaluminum hydride (0.22 mL, 0.33 mmol, 1.5 M in toluene). The mixture was stirred for 1.5 h at -78°C, quenched with saturated ammonium chloride (1 mL), and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate then concentrated *in vacuo*.

A solution of the crude product from above and (carboethoxyethylidene)triphenylphosphorane (161 mg, 0.446 mmol) in dry benzene (5 mL) was refluxed for 17 h. The benzene was removed *in vacuo*, and the residue purified by column chromatography on silica gel, using 15% ethyl acetate-hexane as elutant, to yield **85** (83.6 mg, 76%) as a clear oil: $[\alpha]_D$ -1.5° (c = 1.47, $CHCl_3$); IR (neat) 2936, 2893, 2828, 1712 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.52 (dd, $J$ = 8.2 Hz, 1.2 Hz, 1H), 4.81 (s, 2H), 4.19 (q, $J$ = 7.1 Hz, 2H), 3.73-3.61 (m, 2H), 3.48-3.41 (m, 1H), 3.41 (s, 3H), 3.17-3.09 (m, 1H), 2.43-2.30 (m, 1H), 2.24-2.02 (m, 2H), 1.85 (d, $J$ = 1.4 Hz, 3H), 1.68-1.60 (m, 1H), 1.45-1.35 (m, 2H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.26-1.10 (m, 2H), 1.00-0.852 (m, 3H), 0.02 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.7, 127.1, 94.4, 82.5, 78.9, 64.9, 60.6, 57.3, 35.7, 30.6, 29.8, 18.0, 14.3, 12.5, -1.4 (x3); MS (CI) *m/z* (rel. intensity) 373 (M + 1, 27), 345 (53), 299 (73), 235 (100); HRMS, *m/z*

calcd. for $C_{19}H_{37}O_5Si$ (M + 1): 373.2410. Found: 373.2412. Anal. Calcd. for $C_{19}H_{36}O_5Si$: C, 61.25, H, 9.74. Found: C, 61.46, H, 9.74.

**Allylic alcohol 86.** To a solution of **85** (75.6 mg, 0.20 mmol) in dry ether (4 mL) was added lithium aluminum hydride (23.1 mg, 0.61 mmol) at 0°C. The reaction was warmed to room temperature over 1 h, recooled to 0°C, then quenched with water (1 mL) and 1.5 M hydrochloric acid (1 mL). The two phases were partitioned, and the aqueous layer was extracted with ether (3 x 5 mL). The combined ether extracts were dried over anhydrous magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **86** (65.7 mg, 98%) as a clear oil: $[\alpha]_D$ +5.0° (c = 1.43, $CHCl_3$); IR (neat) 3457 (br), 2933, 2893, 1052, 1030, 839 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.21 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H), 4.80 (s, 2H), 3.98 (d, *J* = 1.0 Hz, 2H), 3.70-3.60 (m, 2H), 3.43-3.37 (m, 1H), 3.40 (s, 3H), 3.15-3.07 (m, 1H), 2.75-2.25 (m, 1H), 2.10-2.00 (m, 2H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.63-1.59 (m, 1H), 1.37-1.30 (m, 3H), 1.20-0.88 (m, 3H), 0.02 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 134.0, 129.9, 94.4, 82.8, 79.2, 68.6, 64.8, 57.2, 36.4, 34.7, 30.9, 30.8, 18.0, 13.8, -1.5 (x3); MS (CI) *m/z* (rel. intensity) 331 (M + 1, 49), 213 (42), 117 (100); HRMS, *m/z* calcd. for $C_{17}H_{35}O_4Si$ (M + 1): 331.2305. Found: 331.2305. Anal. Calcd. for $C_{17}H_{34}O_4Si$: C, 61.77, H, 10.37. Found: C, 61.70, H, 10.25.

**Aldehyde 75.** To a soluton of **86** (270 mg, 0.08 mmol) in dry methylene chloride was added the Dess-Martin periodinane **87**[29] (27.2 mg, 0.11 mmol) and pyridine (13 µl, 0.16 mmol) at room temperature. After 2 h, thin layer chromatography indicated the presence of starting material, so a further equivalent of **87** was added, and the mixture was stirred for an additional hour.

The reaction was quenched by the addition of ether (3 mL) and 1 M sodium hydroxide (1 mL). The two phases were partitioned, and the organic layer was washed with water (2 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:3 ethyl acetate-hexane provided **75** (22.1 mg, 83%) as a clear oil: $[\alpha]_D$ +3.6° (c = 1.17, $CHCl_3$); IR (neat) 2934, 2894, 1690, 1643, 1054, 837 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 6.23 (dd, *J* = 9.4 Hz, 1.4 Hz, 1H), 4.80 (s, 2H), 3.71-3.61 (m, 2H), 3.50-3.42 (m, 1H), 3.41 (s, 3H), 3.20-3.13 (m, 1H), 2.63-2.52 (m, 1H), 2.15-2.05 (m, 2H), 1.75 (d, *J* = 1.0 Hz, 3H), 1.75-1.68 (m, 1H), 1.48-1.11 (m, 3H), 1.00-0.89 (m, 2H), 0.01 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 195.3, 156.7, 138.1, 94.4, 82.2, 78.7, 64.9, 57.5, 35.9, 35.0, 30.5, 29.5, 18.0, 9.3, -1.5 (x3); MS (CI) *m/z* (rel. intensity) 329 (M + 1, 20), 117 (100); HRMS, *m/z* calcd. for $C_{17}H_{33}O_4Si$ (M + 1): 329.2148. Found: 329.2148. Anal. Calcd. for $C_{17}H_{32}O_4Si$: C, 62.15, H, 9.82, Si, 8.55. Found: C, 62.07, H, 9.91, Si, 8.17.

**Homoallylic alcohol 89.** To a solution of **88** (122 mg, 0.41 mmol), dervived from the (*z*)-crotylboronate diethanolamine complex and *L*-(*R,R*)-diisopropyltartrate,[31] in dry toluene (1.5 mL) was added powdered 4 Å molecular sieves (150 mg) under argon atmosphere. The mixture was cooled to -78°C and **75** (53.8 mg, 0.16 mmol) in dry toluene (1.5 mL) was added dropwise over a 15 min period using a syringe pump. The reaction mixture was stirred for 84 h at -78°C, then warmed to 0°C, 1 M sodium hydroxide (1 mL) was added, and the mixture stirred for 20 min. The reaction was extracted with ether (3 x 15 mL), and the combined ether extracts dried over anhydrous magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 15% ethyl acetate-hexane as elutant

provided **89** (37.6 mg, 60%) and **90** (16.3 mg, 25%) both as clear oils: **89**: Rf 0.08 (15% ethyl acetate-hexane), $[\alpha]_D$ -3.3° (c = 3.60, $CHCl_3$); IR (neat) 3462 (br), 2934, 2891, 1107, 1049, 1031, 854, 840 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.77-5.61 (m, 1H), 5.17 (d, *J* = 8.9 Hz, 1H), 5.04-4.95 (m, 2H), 4.79 (s, 2H), 3.76 (d, *J* = 7.4 Hz, 1H), 3.69-3.58 (m, 2H), 3.44-3.35 (m, 1H), 3.39 (s, 3H), 3.14-3.04 (m, 1H), 2.35 (q, *J* = 7.0 Hz, 1H), 2.28-2.19 (m, 1H), 2.09-1.98 (m, 2H), 1.59 (d, *J* = 1.1 Hz, 3H), 1.40-1.22 (m, 1H), 1.15-0.86 (m, 5H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.00 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 141.0, 134.9, 131.1, 114.3, 94.4, 82.8, 80.5, 79.3, 64.8, 57.3, 41.1, 36.4, 34.7, 30.9, 30.7, 18.0, 14.7, 12.4, -1.4 (x3); MS (CI) *m/z* (rel. intensity) 385 (M + 1, 2.4), 205 (100). Anal. Calcd. for $C_{21}H_{40}O_4Si$: C, 65.58, H, 10.48. Found: C, 65.80, H, 10.23. **90**: Rf 0.10 (15% ethyl acetate-hexane) $[\alpha]_D$ +5.6° (c = 1.40, $CHCl_3$); **90** has identical spectra [IR, $^1H$ NMR, $^{13}C$ NMR] to that of compound **89**.

***tert*-Butyldimethylsilyl ether 91.** To a solution of **89** (35.0 mg, 0.09 mmol) in methylene chloride (3 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (52.0 μL, 0.23 mmol) and diisopropylethylamine (48.0 μL, 0.27 mmol) under argon atmosphere. The mixture was stirred for 30 min at 0°C, and the methylene chloride was removed *in vacuo*. Purification by column chromatography on silica gel using 5% ethyl acetate-hexane as elutant provided **91** (43.6 mg, 96%) as a clear oil: $[\alpha]_D$ -8.0° (c = 1.20, $CHCl_3$) IR (neat) 2933, 2891, 2862, 1252, 1109, 1056, 838, 774 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.64-5.55 (m, 1H), 5.01 (d, *J* = 8.9 Hz, 1H), 4.85 (dddd, *J* = 17.8 Hz, 10.5 Hz, 2.0 Hz, 1.2 Hz, 2H), 4.78 (s, 2H), 3.68-3.56 (m, 3H), 3.43-3.35 (m, 1H), 3.40 (s, 3H), 3.13-3.04 (m, 1H), 2.27-2.18 (m, 2H), 2.04-1.96 (m, 2H), 1.53 (d, *J* = 1.0 Hz, 3H), 1.33-1.23 (m, 1H), 1.08-0.84 (m, 5H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 9H), -0.01 (s, 3H), -0.07 (s, 3H); $^{13}C$ NMR (75 MHz,

$CDCl_3$) δ 141.6, 135.6, 130.9, 113.2, 94.3, 82.8, 82.4, 79.4, 64.8, 57.4, 42.4, 36.3, 34.7, 30.9, 30.8, 25.9 (x3), 18.2, 18.1, 16.0, 11.9, -1.4 (x3), -4.4, -5.0; MS (CI) *m/z* (rel. intensity) 499 (M + 1, 22), 443 (100); HRMS, *m/z* calcd. for $C_{27}H_{55}O_4Si_2$ (M + 1): 499.3639. Found: 499.3640.

**Aldehyde 74.** To a solution of **91** (31.7 mg, 0.06 mmol) in tetrahydrofuran (1 mL) and pH 7 phosphate buffer (1 mL, aqueous $KH_2PO_4$ and $Na_2HPO_4$) was added osmium tetroxide (9.7 mL, 0.002 mmol, 4% in water) along with one equivalent of sodium metaperiodate (15.0 mg, 0.06 mmol). The reaction mxture was stirred for 4 h before an additional three equivalents of sodium *meta*-periodate (40.7 mg, 0.18 mmol) were added. This mixture was stirred for 20 h at room temperature, quenched with $Na_2S_2O_3$ (1 mL), and stirred an additional 20 min before being extracted with ether (3 x 5 mL). The combined ether extracts were dried over magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 30% ethyl acetate-hexane as elutant provided **74** (19.8 mg, 62%), $[\alpha]_D$ -9.8° (c = 0.53, $CHCl_3$); IR (neat) 2931, 2893, 1727, 1460, 1054, 1034, 776 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.62 (d, *J* = 2.0 Hz, 1H), 5.17 (d, *J* = 9.3 Hz, 1H), 4.78 (s, 2H), 4.21 (d, *J* = 5.8 Hz, 1H), 3.68-3.58 (m, 2H), 3.43-3.35 (m, 1H), 3.41 (s, 3H), 3.13-3.05 (m, 1H), 2.49-2.44 (m, 1H), 2.25-2.20 (m, 1H), 2.06-1.94 (m, 2H), 1.58-1.52 (m, 1H), 1.57 (d, *J* = 1.0 Hz, 3H), 1.33-1.23 (m, 1H), 1.08-0.87 (m, 4H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H) 0.00 (s, 9H), -0.04 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 204.4, 134.0, 131.6, 94.3, 82.7, 79.3, 77.2, 64.8, 57.5, 50.8, 36.3, 34.8, 30.8, 30.7, 25.7 (x3), 18.1, 18.0, 12.6, 8.9, -1.4 (x3), -4.3, -5.2; MS (CI) *m/z* (rel. intensity) 501 (M + 1, 1.3), 391 (100); HRMS, *m/z* calcd. for $C_{26}H_{53}O_5Si_2$ (M + 1): 501.3432. Found: 501.3431.

**Ester 92.** To a solution of **89** (23.7 mg, 0.06 mmol) in methylene chloride (4 mL) was added dicyclohexylcarbodiimide (63.6 mg, 0.31 mmol) and N,N-dimethylaminopyridine (15.0 mg, 0.12 mmol) under argon atmosphere. The reaction mixture was stirred for 20 h at -15°C, quenched with saturated sodium bicarbonate (3 mL), and allowed to stir for an additional 15 min at room temperature. The organic layer was extracted with methylene chloride (3 x 10 mL), and the combined organic extracts were dried over magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:3 ethyl acetate-hexane as elutant provided **92** (26.4 mg, 72%) as a clear oil: IR (neat) 2935, 2868, 1741, 1700, 1157, 1044 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 333K) δ 5.66-5.57 (m, 1H), 5.25-5.18 (m, 1H), 5.03-4.80 (m, 2H),4.80-4.75 (m, 1H), 4.78 (s, 2H), 4.04-3.95 (m, 1H), 3.70-3.57 (m, 2H), 3.42-3.34 (m, 1H), 3.39 (s, 3H), 3.11-3.03 (m, 1H), 3.00-2.90 (m, 1H), 2.49 (d, $J$ = 6.9 Hz, 1H), 2.22-1.17 (m, 2H), 2.10-1.92 (m, 2H), 1.71-1.50 (m, 5H), 1.60 (s, 3H), 1.44 (s, 9H), 1.43-1.24 (m,5H),1.09-0.88 (m, 3H), 1.00 (d, $J$ = 6.7 Hz, 2H), 0.01 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 171.1, 155.8, 139.9, 133.3, 131.5, 131.4, 114.8, 94.6, 83.1, 82.9, 82.3, 79.8, 79.4, 64.9,40.2, 36.5, 35.1, 31.0, 30.7, 28.5 (x3), 26.9, 24.9, 24.7, 20.8, 18.2, 15.8, 13.1, -1.4 (x3).

**N-(*tert*-Butoxycarbonyl)-*L*-piperidine-2-carboxylic acid (93).** To a solution of **94** (100 mg, 0.78 mmol) and 2-*tert*-butyloxycarbonyloxyimino-2-phenylacetonitrile (BOC-ON) **95** (210 mg, 0.85 mmol) was added triethylamine (0.16 mL, 1.16 mmol). The reaction mixture was stirred for 24 h at 25°C and extracted with ether (3 x 5 mL) and the layers separated. The aqueous layer was acidified with 1.5 M hydrochloric acid (2 mL) and extracted with ethyl acetate (3 x 5 mL), and the combined organic extracts were dried over magnesium sulfate then concentrated *in vacuo* to provide a white solid.

Recrystallization using hexane (10 mL) provided **93** (114 mg, 64%) as a white solid: mp 120-123°C [Lit[42] mp 124°C]; $[\alpha]_D$ -42.4° (c = 1.00, MeOH), [Lit[42] $[\alpha]_D$ -45.1° (c = 1.0, MeOH)]; IR (thin film) 3431-2867 (br), 1738, 1699 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.95-4.62 (m, 1H), 4.10-3.88 (m, 1H), 3.00-2.80 (m, 1H), 2.23-2.15 (m, 1H), 1.75-1.60 (m, 2H), 1.43 (s, 9H), 1.50-1.22 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$, 323K) δ 177.2, 157.0, 79.9, 56.5, 42.2, 28.6 (x3), 27.3, 25.3, 21.1; MS (EI) *m/z* (rel. intensity) 84 (100), 128 (60).

**(*2S,3S*)-Ethyl-2-allyl-3-hydroxybutyrate (97).** Hydroxy ester **96**[36] was prepared in the same manner as described for the preparation of its enantiomer in part IC: 62% yield; colorless oil; $[\alpha]_D$ +7.8° (c = 0.55, $CHCl_3$), [Lit[36] $[\alpha]_D$ +14.5° (c = 0.37, $CHCl_3$)].

**(*2S,3R*)-2-Allyl-3-hydroxybutanol (98).** To a solution of **97** (777 mg, 4.52 mmol) in dry ether (100mL) at 0°C was added lithium aluminum hydride (514 mg, 13.6 mmol). The reaction mixture was allowed to warm to room temperature over 2 h then recooled to 0°C before being quenched with water (5 mL) and hydrochloric acid (2 mL). The two phases were partitioned, and the aqueous layer was washed with ethyl acetate (5 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate then concentrated *in vacuo*. Purification by column chromatography on silica gel using 1:1 ethyl acetate-hexane as elutant provided **98** (402 mg, 68%) as a clear oil: $[\alpha]_D$ +3.2° (c = 2.57, $CDCl_3$); IR (neat) 3353 (br), 3078, 2974, 2925, 2896, 1038, 912 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.86-5.74 (m, 1H), 5.11-5.01 (m, 2H), 3.94-3.86 (m, 2H), 3.66 (dd, *J* = 6.2 Hz, 6.3 Hz, 1H), 2.57 (s, 2H), 2.25-2.05 (m, 2H), 1.59-1.53 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 136.4, 116.6, 71.4, 64.2, 45.9, 33.2, 22.0; MS (CI) *m/z* (rel. intensity)

131 (M + 1, 44), 113 (43); HRMS, *m/z* calcd. for $C_{17}H_{15}O_2$ (M + 1): 131.1072. Found: 131.1072.

**(*2S,3R*)-2-Allyl-3-hydroxy-[1-(triphenyl)methyoxy]butane (99).** To a solution of **98** (208 mg, 1.60 mmol) in dry methylene chloride (20 mL) was added triphenylmethyl chloride (468 mg, 1.68 mmol) and triethylamine (0.25 mL, 1.76 mmol). The reaction mixture was stirred at room temperature for 24 h then concentrated *in vacuo.* Purification by column chromatography on silica gel using 15% ethyl acetate-hexane as elutant provided **99** (504 mg, 84%) as a clear oil: $[\alpha]_D$ +4.9° (c = 1.33. $CHCl_3$); IR (neat) 3438 (br), 3064, 2973, 2925, 2890, 1447, 1062, 703 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.44-7.40 (m,6H), 7.32-7.20 (m, 9H), 5.70-5.558 (m, 1H), 4.96 (ddd, *J* = 17.1 Hz, 10.5 Hz, 1.2 Hz, 2H), 3.80 (q, *J* = 6.1 Hz, 1H), 3.33 (dd, *J* = 9.5 Hz, 3.8 Hz, 1H), 3.20 (dd, *J* = 9.5 Hz, 6.0 Hz, 1H), 2.87 (d, *J* = 4.8 Hz, 1H), 2.30-2.08 (m, 2H), 1.66-1.60 (m, 1H), 1.06 (d, *J* = 6.4 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 143.7 (x3), 136.6, 128.6 (x6), 127.9 (x6), 127.1 (x3), 116.4, 84.8, 70.1, 64.2, 45.1, 33.2, 21.0; MS (CI) *m/z* (rel. intensity) 243 (100), 131 (M + 1-$C_{19}H_{15}$, 8.7).

**(*3R*)-3-Allyl-[4-(triphenyl)methyoxy]butan-2-one (100).** To a solution of **99** (483 mg, 1.29 mmol) in dry methylene chloride (20 mL) was added the Dess-Martin perodinane[29] (658 mg, 2.58 mmol) and pyridine (0.209 mL, 2.58 mmol). The reaction mixture was stirred at room temperature for 3 h then concentrated in vacuo. Purification by column chromatography on silica gel using 15% ethyl acetate-hexane provided **100** (456 mg, 95%) as a white solid: mp 40-44°C; $[\alpha]_D$ -14.5°C (c = 2.03,$CHCl_3$); IR (thin film) 3064, 3028, 2927, 1714, 1167, 704 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.39-7.35 (m, 6H), 7.30-7.18 (m, 9H), 5.64-5.52 (m, 1H), 4.98-4.91 (m, 2H), 3.32-3.22 (m, 2H), 2.76 (q,

$J$ = 6.4 Hz, 1H), 2.38-2.28 (m, 1H), 2.20-2.12 (m, 1H), 2.09 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 210.3, 143.7 (x3), 135.1, 128.6 (x6), 127.8 (x6), 127.0 (x3), 116.9, 86.7, 63.9, 52.8, 32.5, 29.8; neg. FABMS, *m/z* (rel. intensity) 369 [(M - 1)$^-$, 16], 243 (20). Anal. Calcd. for $C_{26}H_{26}O_2$: C, 84.29, H, 7.07. Found: C, 84.40, H, 6.92.

**Aldol adduct (73).** To a solution of **100** (12.3 mg, 0.04 mmol) in dry tetrahydrofuran (.5 mL) was added lithium bis(trimethylsilyl)amide (35 μL, 0.04 mmol, 1.0 M in THF) at -78°C, and the mixture was stirred for 30 min. Aldehyde **74** (11.1 mg, 0.02 mmol) was added via a canula as a solution in tetrahydrofuran (0.5 mL). The reaction was immediately quenched with saturated ammonium chloride (0.3 mL) after 3 min, warmed to room temperature, dried over magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography on silica gel using 15% ethyl acetate-hexane as elutant provided a 9:1 mixture of **73** and **101** (12.3 mg, 62%) as a clear oil: IR (neat) 3464 (br), 2934, 2891, 1706, 1450, 1033, 839 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 7.30-7.18 (m, 10H), 5.62-5.53 (m, 1H), 5.10 (d, $J$ = 9.0 Hz, 1H), 4.97-4.90 (m, 2H), 4.79 (s, 2H), 4.07 (d, $J$ = 4.2, 1H), 3.84-3.75 (m, 1H), 3.70-3.58 (m, 2H), 3.42-3.31 (m, 1H), 3.41 (s, 3H), 3.28-3.20 (m, 3H), 3.15-3.06 (m, 1H), 2.77-2.73 (m, 1H), 2.54-2.50 (m, 2H), 2.35-1.95 (m, 4H), 1.63-1.51 (m, 1H), 1.55 (s, 3H), 1.33-1.24 (m, 2H), 1.10-0.85 (m, 5H), 0.87 (s, 9H), 0.67 (d, $J$= 6.8 Hz, 3H), 0.01 (s, 3H), 0.00 (s, 9H), -0.07 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 213.9, 143.6, 135.2, 135.0 (x3), 130.1, 128 6 (x6), 127.9 (x6), 127.1 (x3) , 117.1, 94.4, 86.9, 82.9, 79.4, 77.2, 68.3, 64.8, 64.0, 57.6, 52.7, 46.4, 41.6, 36.6, 34.8, 32.4, 30.9, 30.8, 25.9 (x3), 18.2, 18.0, 13.3, 9.6, -1.4 (x3), -4.4, -5.1; neg. FABMS, *m/z* (rel. intensity) 869 [(M - 1)$^-$, 1.4], 243 (23), 131 (100).

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