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Preparations of Two Pivotal Intermediates for the Synthesis of 1-β-Methyl Carbapenem Antibiotics

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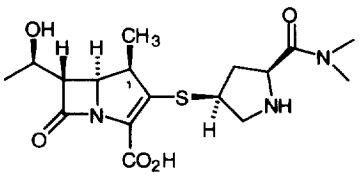
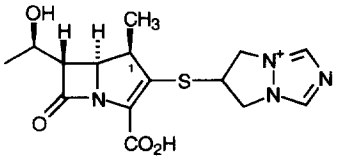
Contents

1. Introduction

The carbapenem class of antibiotics is an important group of drugs and the object of ongoing pharmaceutical development. In particular, carbapenems bearing a 1-β-methyl substituent, exemplified by meropenem[2] and biapenem,[3] have an excellent spectrum of activity and good resistance to renal dehydropeptidase I (DHP-I).[4]



MEROPENEM

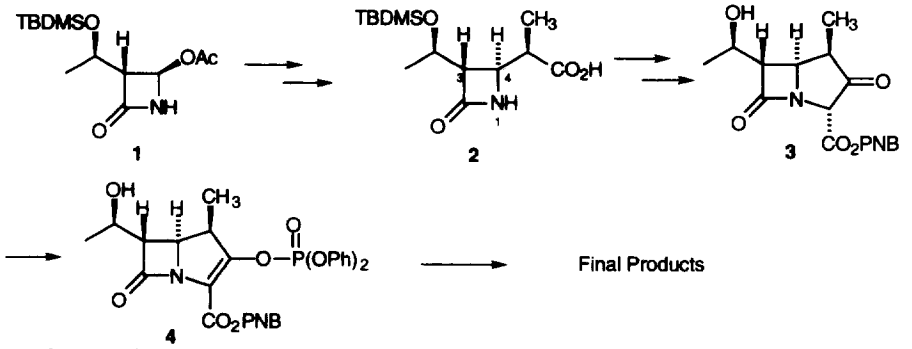


BIAPENEM

The most significant synthesis of this class of antibiotics was pioneered at Merck by Shih et al.,[5] who established **2** as a key intermediate for the synthesis of 1-β-methyl carbapenems. The Merck synthesis is depicted generically in Scheme 1. The starting point for this approach is **1**, (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1'-((*t*-butyldimethylsilyl)oxy)ethyl]-2-azetidinone, which is elaborated to **2**, (3*S*,4*S*)-[(*R*)-1'-((*t*-butyldimethylsilyl)-oxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone, containing the four contiguous stereogenic centers of the 1-β-methyl class of carbapenems. The C-4 isopropionate side chain is extended and subjected to an intramolecular cyclization to give **3**, and then carried forward to phosphate **4**, which can be reacted with thiols and deprotected to give the desired products. In addition its utility for 1-β-methyl carbapenems, **1** is also a common starting material for the synthesis of other carbapenems without the 1-β-methyl group and for penem and cephem antibiotics.

Despite a considerable body of literature describing synthetic routes to **1** and **2**, approaches to these

Scheme 1



azetidinones have not been well reviewed, and seem to be limited to a 1989 Japanese language paper and a subsequent 1993 chapter of approaches to **2**.[6] The present report deals comprehensively with the syntheses of these important structures.

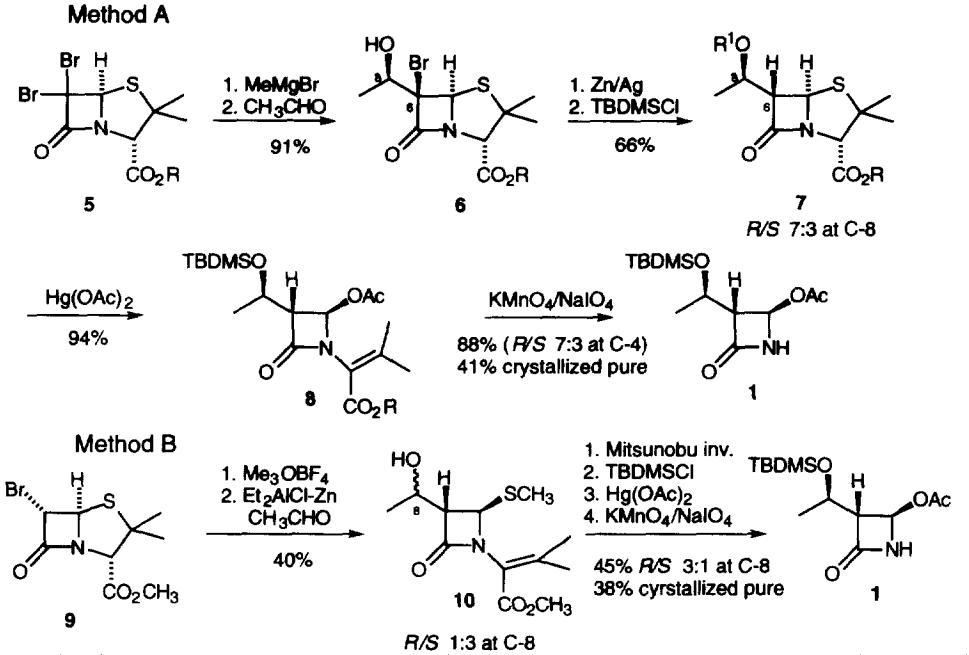
2. Routes to Acetoxy Azetidinone 1

The earliest references to azetidinone **1** are from the Sankyo Co., Ltd., and employed penicillanate esters as the chiral source, as shown in Scheme 2.[7] Two approaches were reported by this group. In method A, dibromopenicillanate **5** (R=benzyl), obtainable from the fermentation product 6-aminopenicillanic acid, was transmetallated with methyl Grignard reagent and treated with acetaldehyde, followed by zinc-silver couple, which reduced the second bromine, to give **7** (R^1 = H) as a 7:3 diastereomeric mixture. The major isomer was the 8-(*R*)-5,6-trans diastereomer as illustrated, with some of the undesired 8-(*S*)-5,6-trans diastereomer. The mixture was silylated to give penicillin **7** (R^1 = TBDMS), which was simultaneously cleaved and acetoxylated with mercuric acetate to furnish **8** enriched in the diastereomer shown. Dealkylation of the nitrogen was accomplished with permanganate and periodate to give **1**, which was obtained pure by crystallization (23% overall yield and five steps from **5**). The same Sankyo group also reported method B, starting with 6β-bromopenicillanate **9**, also obtained from 6-aminopenicillanic acid, which was cleaved with trimethyloxonium tetrafluoroborate and subjected to an aluminum mediated condensation with acetaldehyde to afford **10** as a 3:1 diastereomeric mixture, with the wrong diastereomer predominating. The diastereomeric mixture of **10** was inverted under Mitsunobu conditions (triphenyl phosphine and diethyl diazodicarboxylate in the presence of two equivalents of benzoic acid), and then was debenzoylated with methanolic sodium hydroxide, to give **10** with the desired 8-(*R*) configuration predominating. As in method A, the mixture was silylated, treated with mercuric acetate, and the nitrogen was deprotected with permanganate and periodate in buffer to afford pure crystalline **1** in 15% overall yield and five steps.[7b] This series of publications concluded that method B was superior despite the lower overall yield because the yield of starting material **9** (from 6-aminopenicillanic acid) was reported to be higher than the yield of starting material **5**, and also because the zinc-silver debromination step in method A was said to be troublesome.

Hirai of Sankyo later improved method A of Scheme 2 by using the methyl ester of compound **5** (R=CH_3).[8] This modification improved the diastereomeric ratio at C-6 to 5:1 after the condensation with acetaldehyde, and allowed a greatly improved debromination step, without the use of silver. They obtained **1** in about 23% overall yield. Work essentially identical to that of Hirai was reported by Leanza and DiNinno of Merck[9] and also by Goo at Seoul National University in South Korea.[10]

Martel of Bristol-Myers disclosed a variation on method A in Scheme 1, but employing **11**, obtained by known methods from 6-aminopencillanic acid, as a key intermediate (Scheme 3).[11] This method had a higher

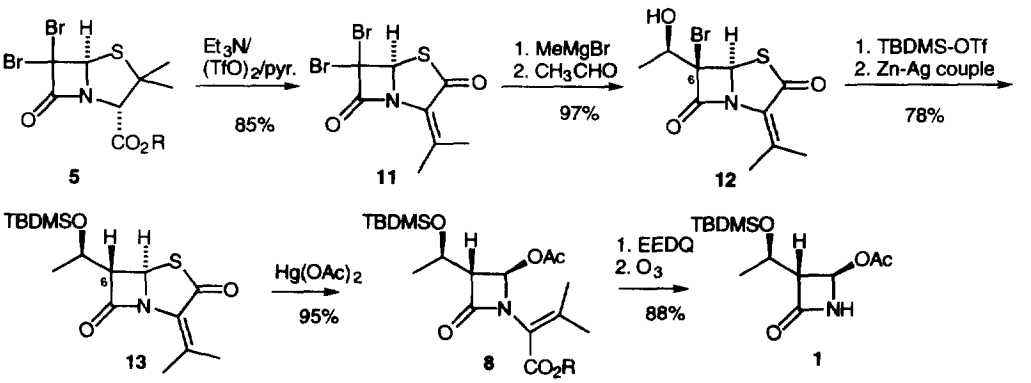
Scheme 2



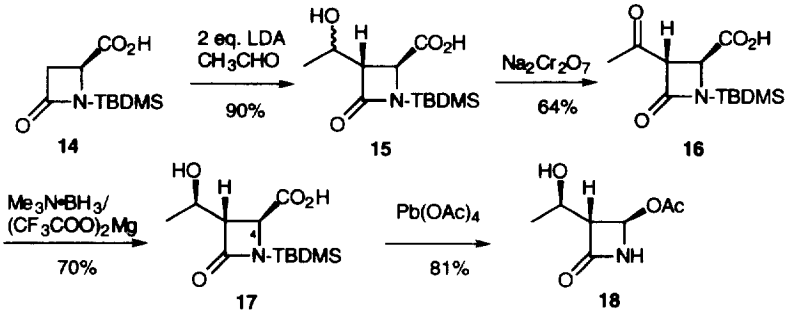
overall yield, 54%, and also gave a very good diastereomeric ratio of about 40:1 in the crucial acetaldehyde condensation. However, this sequence employed the less desirable zinc-silver couple bromide reduction. Dibromopenicillanic acid **5** (R=H), was rearranged to anhydrodibromopenicillin **11**, which was transmetallated with methyl Grignard reagent and then condensed with acetaldehyde to furnish **12**. Protection of the alcohol and reduction of the C-6 bromine gave **13**, which was manipulated to **1** by oxidative methods similar to those employed by the Sankyo group outlined in Scheme 2.

Another early approach to **1**, by Reider of Merck, started from the azetidinone without the C-3 hydroxyethyl side chain and relied on the C-4 configuration to control the stereochemistry of the assembly of the side chain (Scheme 4).[12] The *N*-protected azetidinone **14**, derived from L-aspartic acid, was treated with two equivalents of lithium diisopropylamide and then acetaldehyde to afford an epimeric mixture of alcohols

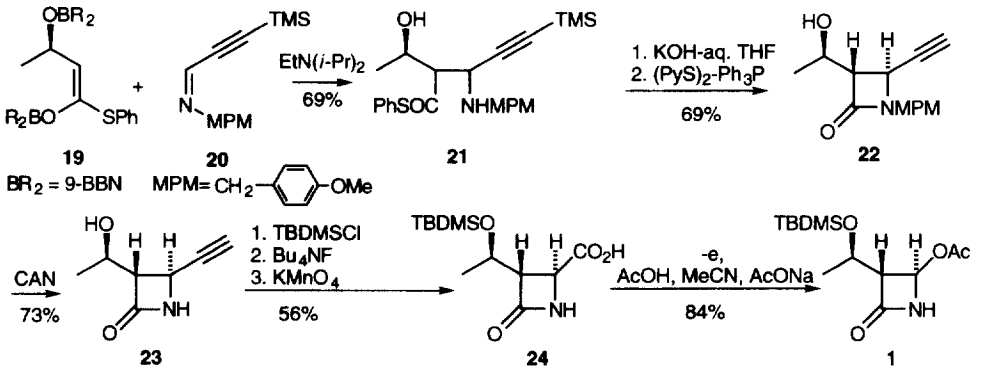
Scheme 3



Scheme 4



Scheme 5



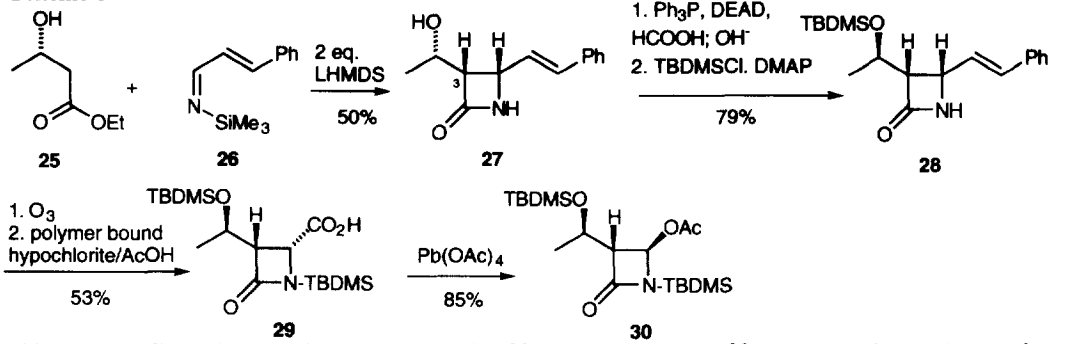
(**15**). Oxidation and stereospecific reduction furnished **17**,[13] which was oxidized with lead tetraacetate under conditions that simultaneously caused decarboxylation, installed the acetoxy group, and desilylated the nitrogen, to give **18**.

A significant alternative to the lead tetracetate transformation of C-4 acids, such as **17**, to the C-4 *O*-acetates, such as **18**, is an electochemical oxidation method developed by Mori and Shibasaki at Hokkaido University (Scheme 5).[14] The first part of this scheme is very similar to Scheme 31. The boron enolate **19** was combined with imine **20** in the presence of base to afford **21**, which was cyclized to **22**[63] and deprotected with ceric ammonium nitrate. A two-step procedure of silylation and selective *N*-desilylation with tetrabutyl ammonium fluoride, followed by oxidation of the alkyne, furnished acid **24**. Electrolysis of the acid in an acetate solution gave **1** with the desired stereochemistry, in 16% overall yield and seven steps.

A formal [2+2] cycloaddition involving Schiff bases, such as in Scheme 5, has been employed on several other occasions for constructing the azetidinone ring and has demonstrated excellent regio- and stereoselectivity. Cainelli and Panunzio, of the University of Bologna, employed the chirality of ethyl (*S*)-3-hydroxybutyrate as shown in Scheme 6 to stereospecifically obtain azetidinone **27**.[15] A condensation between the dianion of ester **25** and imine **26** gave azetidinone **27**, with the correct configuration at C-3. Inversion of the hydroxy group under Mitsunobu conditions and silyl protection of the alcohol afforded **28**. Ozonolysis of the styryl moiety and oxidation with a novel polymer bound hypochlorite reagent provided **29**, which was converted to **30** with lead tetracetate in a similar fashion to the last step of Scheme 4, although under milder conditions that preserved the nitrogen protecting group. Overall, the yield to **30** was 18% in six steps.

A virtually identical approach was reported by Georg of the University of Kansas, as shown in Scheme 7.[16] A 1:1 mixture of diastereomers of azetidinone **32**, formed analogously to **27** (cf. Scheme 6), was

Scheme 6

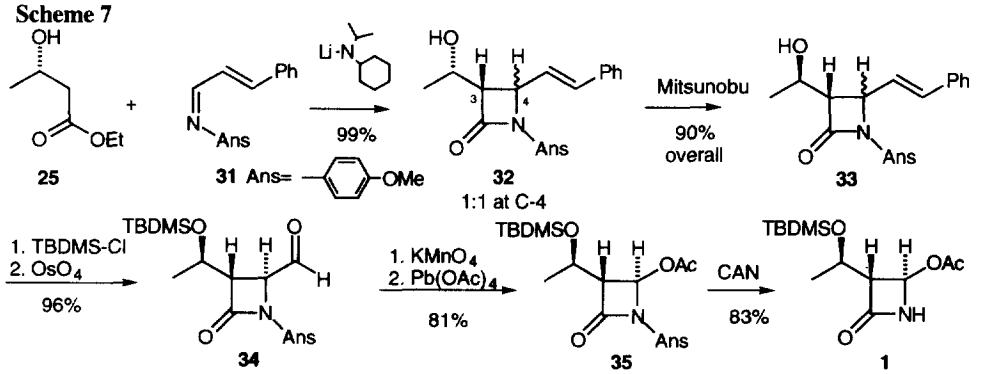


subjected to a Mitsunobu inversion sequence to give **33**. It is not clear why **32** was reported as a mixture of diastereomers when there is no mention of diastereomerism in **27**, which was formed under very similar circumstances. Silylation of the hydroxy group and osmolysis gave **34** as a single diastereomer, which was further oxidized to the corresponding acid and treated with lead tetraacetate to introduce the C-4 acetoxy group. Dealkylation of the nitrogen was accomplished with ceric ammonium nitrate to afford **1** in 58% overall yield and eight steps from the (*S*)-hydroxybutyrate.

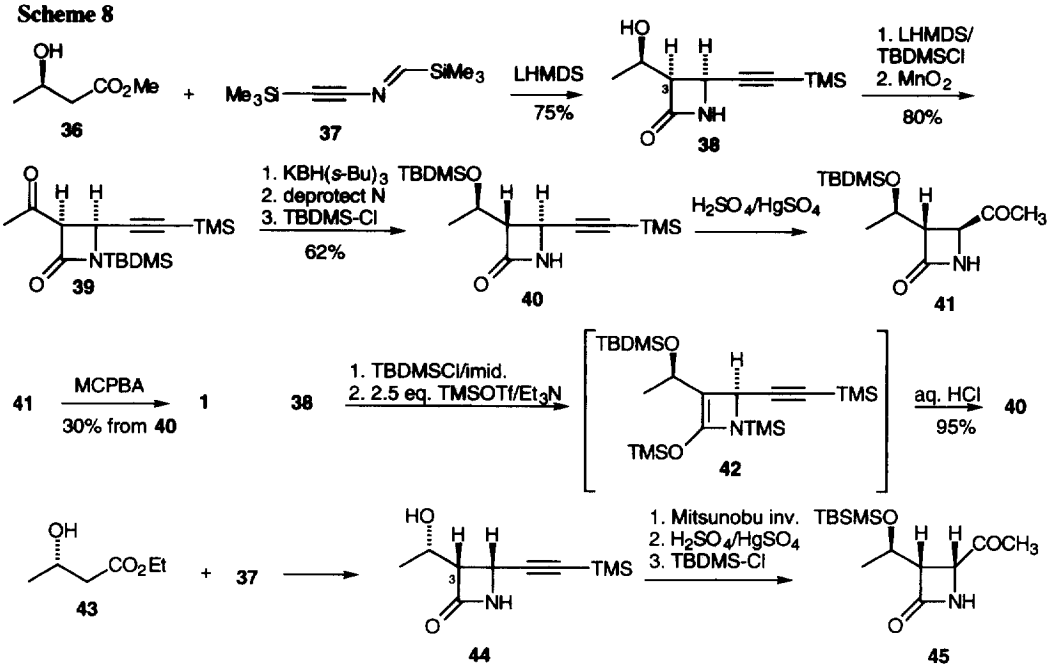
In a similar vein, Nakai of the Tokyo Institute of Technology, and in collaboration with Fujisawa, published an approach to **1** that started from methyl (*R*)-3-hydroxybutyrate (Scheme 8).[17] Ester **36** was condensed with alkynyl imine **37** in the presence of lithium hexamethyldisilazide to give azetidinone **38** with the undesired configuration at C-3.[17a] This problem was rectified by sequential protection of the lactam nitrogen, oxidation of the alcohol to the ketone, which concomitantly isomerized C-3 to the correct epimer, and selective reduction of the C-3 side chain with K-Selectride®.[13] After two functional group manipulations the silyl alkynyl group was hydrolyzed to ketone **41**, which was carried forward to **1** with a Baeyer-Villiger oxidation.[18] Subsequently, a superior epimerization of C-3 was reported, involving the lactam silyl enol ether **42**.[17c,d] Silylation of alcohol **38** with TBDMSCl and imidazole, followed by treatment with trimethylsilyltriflate and triethylamine, furnished an excellent yield of alkyne **40** after acidic hydrolysis in situ. An alternative procedure started with ethyl (*S*)-3-hydroxybutyrate (**43**),[17b] which was condensed as before with **37** to furnished the correct (*R*) configuration at C-3 of the azetidinone **44**. A Mitsunobu inversion of the hydroxy, and then hydrolysis of the ethynyl group and silyl protection of the alcohol resulted in **45**, which is potentially useful but has the wrong configuration at C-4 of the azetidinone. The Baeyer-Villiger oxidation product of **45**, acetate **105** (see Scheme 16 and eq. 2, infra), has been isomerized to **1**.[28]

Terashima, from the Sagami Chemical Research Center, derived the azetidinone C-3 configuration from

Scheme 7



Scheme 8

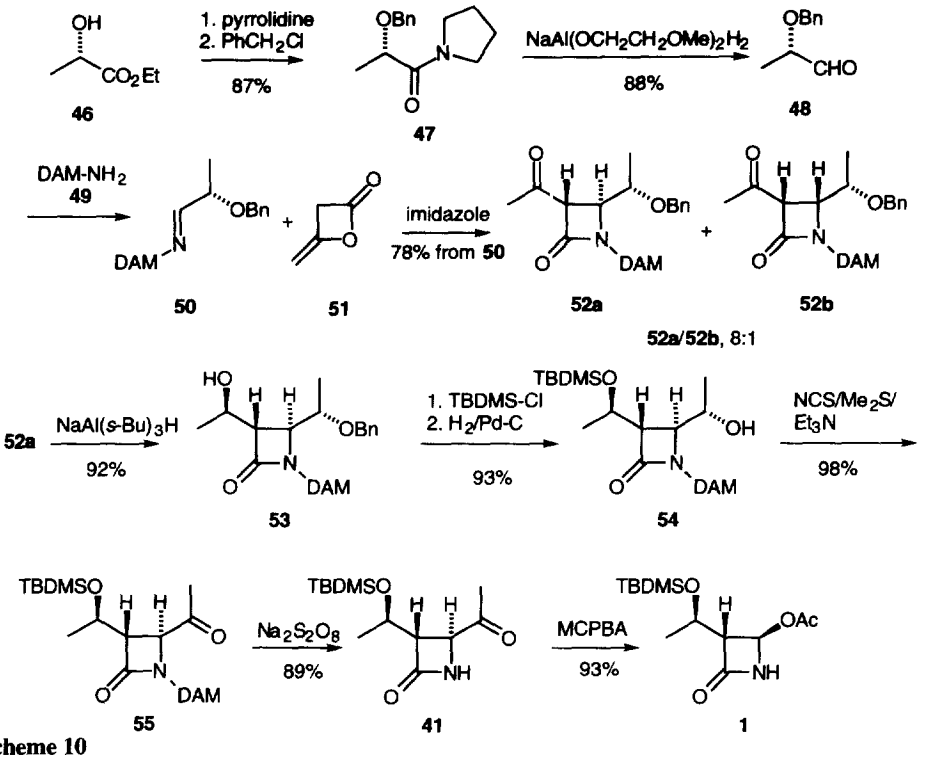


(*S*)-ethyl lactate and utilized a [2+2] cyclization with diketene to form the azetidinone ring (Scheme 9).[19] (*S*)-Ethyl lactate **46** was condensed with pyrollidine, followed by benzyl chloride, to afford amide **47**, which was then reduced to aldehyde **48**. The condensation of **48** with di-*p*-anisylmethylamine (DAM-NH_2, **49**) gave **50**, which was not isolated, but was immediately combined with diketene (**51**) giving **52a** and **52b** as an 8:1 mixture separated by chromatography. The major diastereomer **52a** was stereoselectively reduced to a single alcohol, **53**.[13] Protection of the alcohol, hydrogenation, and oxidation of the resulting secondary alcohol gave ketone **55**, which was then subjected to oxidative removal of the DAM protecting group. Baeyer-Villiger oxidation of **41**[18] furnished **1** in 41% overall yield in 11 steps.

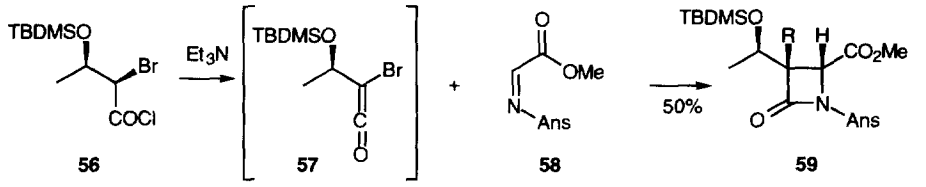
A group from Farmitalia S.p.A. published an approach involving the opposite synthetic analysis to that in Scheme 9, by generating a chiral ketene and reacting it with an achiral Schiff base (Scheme 10).[20] Acid chloride **56**, which was derived from D-*allo*-threonine, was treated with base to generate ketene **57** in situ, and subsequent alkylation with the achiral imine **58** afforded azetidinone **59** (R=Br). Known procedures can be employed to carry **59** forward to **1**, involving dehalogenation, nitrogen deprotection, and transformation of the ester to the acetoxy with the correct C-4 configuration.

Terashima developed another preparation of **1** relying on the [2+2] addition of chlorosulfonyl isocyanate, which gave **64** with very good selectivity. Unfortunately, the yields for the overall method, depicted in Scheme 11, were disappointing.[21] (*R*)-3-Hydroxybutyric acid (**60**) was condensed with (*S*)-benzyloxypropanal (**61**) to furnish dioxanone **62**, which was transformed to dioxin **63** and treated with chlorosulfonyl isocyanate to give **64** in moderate yield but with excellent stereoselectivity; other isomers comprised no more than 2% of the product mixture. Hydrogenation and oxidation provided ketone **65**. At this point, two methods were explored to oxidatively open the dioxane ring. Treatment of **65** with a peroxyacetic acid under protic conditions afforded formyl ester **66** in very good yield, whereas aprotic conditions furnished dioxanone **67** in rather poor yield. Unfortunately, hydrolysis of **66** under basic conditions resulted in decomposition of the azetidinone ring. Under acidic conditions, the yield of **68** from **66**

Scheme 9



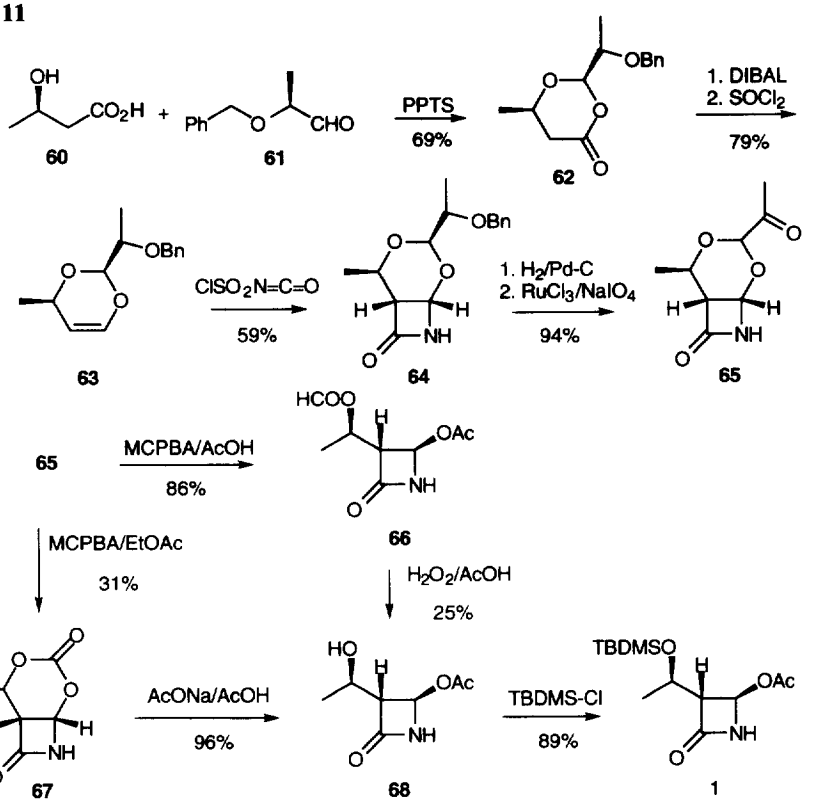
Scheme 10



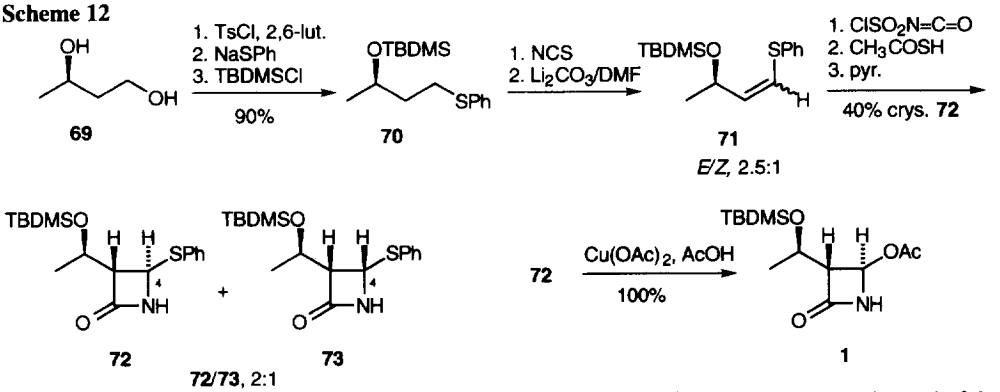
was a disappointing 25%. Conversely, **68** was available from **67** in excellent yield, but as just noted, **67** was only obtained in poor yields. This dilemma was not resolved in this study; however, both **66** and **67** could be converted to **2** in good yield via a Reformatsky condensation (see eq. 4, infra).[44] The overall yield to **1** was 8.0% in nine steps.

Ishiguro of Suntory, Ltd., reported the method shown in Scheme 12,[22] which had significant similarities to the Terashima method of Scheme 11, relying on essentially the same chiral source, and also utilizing a formal [2+2] cycloaddition of chlorosulfonyl isocyanate. Starting from 1,3-(*R*)-butanediol **69**, readily available by microbial transformation, the Suntory team prepared thioether **70** in three steps. Treatment with *N*-chlorosuccinamide followed by lithium carbonate furnished vinyl sulfide **71** as a 2.5:1 *E*/*Z* mixture. Cycloaddition of chlorosulfonyl isocyanate in ether and removal of the chlorosulfonyl group afforded a 2:1 ratio of thioazetidinones **72** and **73**, from which the desired **72** was isolated in crystalline form. Both pure isomers of **71** gave **72** as the major cyclization product in this reaction, so there was no advantage to isolation

Scheme 11

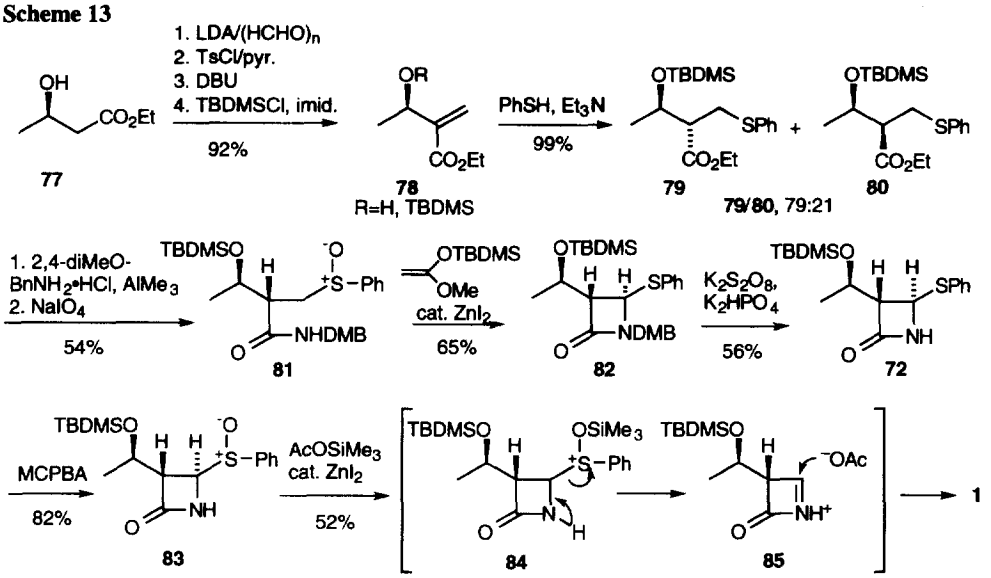


Scheme 12



of the pure diasteromers of **71**. Solvolysis of **72** through the agency of copper (II) acetate, instead of the mercury (II) salts previously employed for the transformation of C-4 sulfides to the acetate (cf. Schemes 2 and 3), was a significant advance in the industrial utility of these types of sulfide intermediates. Azetidinone **1** was obtained in six steps and 31% overall yield. In the Japanese patent literature this approach from Suntory also discloses the use of other copper compounds having an affinity for sulfur, such as copper oxide,[23a] cupric oxide,[23a] or copper bromide dimethyl sulfide complex,[23b] to displace phenyl sulfides, such as **72**, with alkoxy or acyloxy groups.

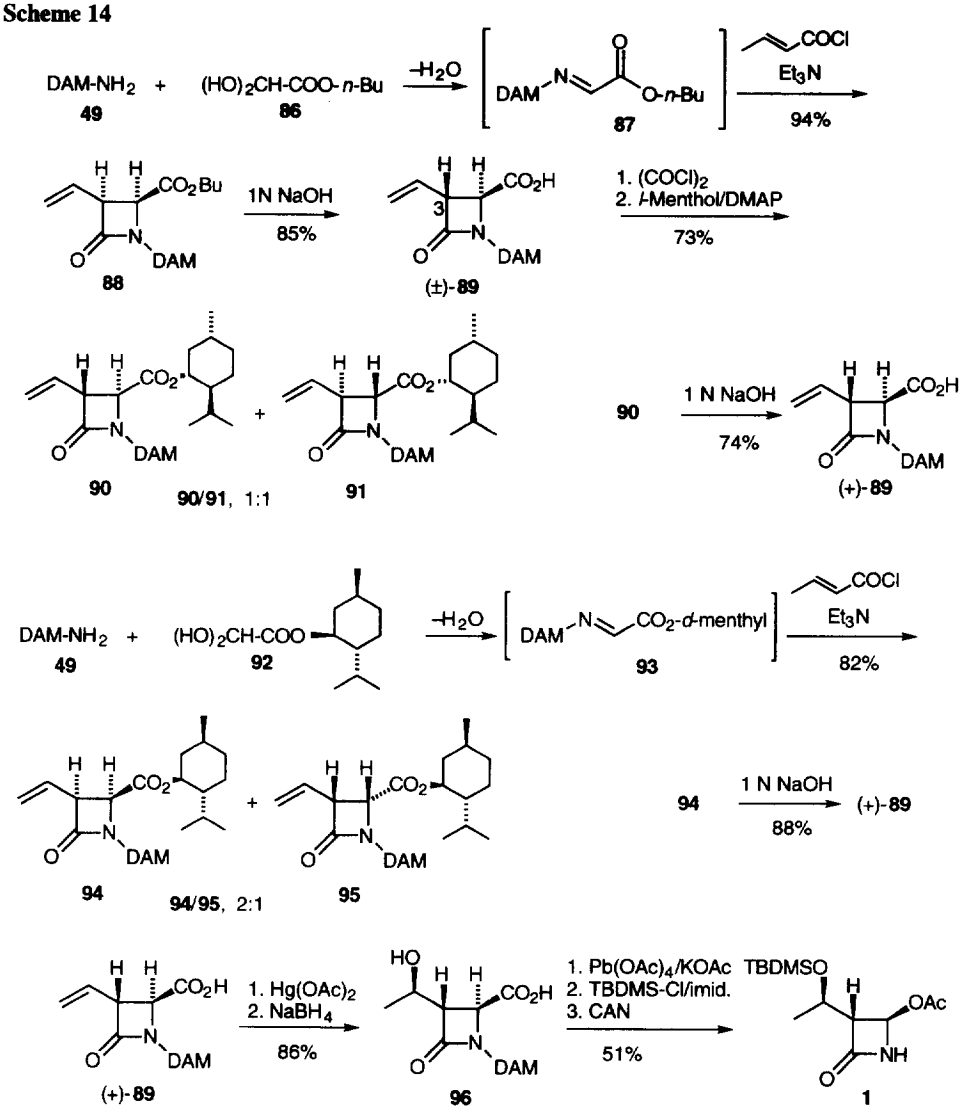
Scheme 13



An alternative synthesis of phenylthioazetidinone **72** was reported by Kita of Osaka University and carried forward to **1** by oxidation to the sulfoxide and a silyl transfer reaction (Scheme 13).[24] Ethyl (*R*)-3-hydroxybutyrate **77** was transformed into olefin **78**, which was protected and combined with thiophenol in Michael addition fashion to provide the mixture of diastereomers **79** and **80**.[24a] This mixture was amidated with 2,4-dimethoxybenzylamine hydrochloride and was oxidized with $NaIO_4$ to sulfoxide **81**. A silicon induced Pummerer type reaction effected the cyclization to azetidinone **82**. Oxidative deprotection furnished thioether **72**, which was oxidized to sulfoxide **83** and treated with trimethylsilyl acetate and catalytic zinc iodide in acetonitrile to give **1**.[24b] The overall yield to **1** was 7.6% in 11 steps, but the yield does not include the removal of the undesired isomer arising from **80**, which was not explicitly discussed.

Sasaki of Sumitomo Pharmaceuticals developed a synthesis of **1** proceeding through the key intermediate **89**, and stereospecifically introducing the 1'-hydroxy group via hydroxy mercuration (Scheme 14).[25] Two routes were investigated for obtaining (+)-**89**: resolution of chiral esters (**90** and **91**), and an asymmetric [2+2] cycloaddition, employing *d*-menthol esters **94** and **95**. Di-*p*-anisylmethylamine (DAM-NH_2, **49**) was condensed with *n*-butyl glyoxalate (**86**), and the resulting imine **87** was combined with crotonyl chloride to give the [2+2] cycloadduct **88**, in 94% yield based on the DAM-NH_2. Saponification concomitantly epimerized C-3 of the azetidinone to furnish racemic **89**, which was esterified with *l*-menthol to give a 1:1 mixture of crystalline esters **90** and **91**. Pure **90** was obtained by recrystallization from methanol, although in just 18% yield from **89**. No mention was made of recovery of additional **90**. Enantiomerically pure (+)-**89** was regenerated by saponification of the desired ester **90**. Alternatively, di-*p*-anisylmethylamine was condensed with *d*-menthyl glyoxalate **92** and the resulting Schiff base was treated with crotonyl chloride as before to give cycloadducts **94** and **95** in a 2:1 ratio. After chromatographic separation of these menthyl esters, the desired **94** was obtained pure by recrystallization from methanol, although the yield of pure **94** was not provided. Saponification of **94** epimerized C-3 of the azetidinone as before to furnish (+)-**89**, as above. With pure (+)-**89** available, four transformations were required to obtain **1**, and the authors stated that the sequence at this stage was not critical, however the one shown was explicitly discussed. The oxymercuration reaction leading to **96** was studied in detail, and the transformation shown was found to proceed with 80:1 stereoselectivity. Oxidative decarboxylation, protection of the hydroxy group, and oxidative deprotection of

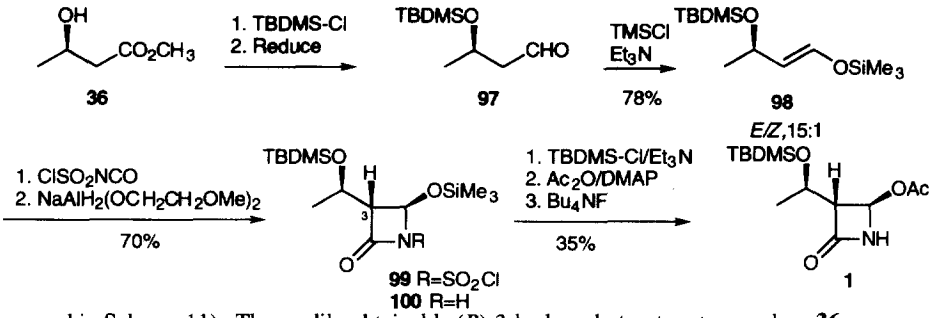
Scheme 14



the nitrogen afforded the final product. By the resolution method via **90**, the sequence employed eight steps and provided **1** in 4.67% yield overall. This yield includes the low 18% recovery of pure **90**. For the asymmetric synthesis route via **94**, a comparable yield cannot be given with the data provided. Assuming 100% recovery of **90** or **94**, respectively, the yields would be 9.47% and nine steps via the resolution method and 18.9% in eight steps via the assymetric synthesis. A favorable feature of this work is the potential for recovery of the chiral auxiliary, by either route studied. However, the chiral induction leading to **94** was minimal.

A relatively short route to azetidinone **1** was reported by Ohashi of Kanefaguchi Chemical Industries, starting from aldehyde **97**, which is derived from (*R*)-3-hydroxybutyrate **36** (Scheme 15),[26] and utilizing a condensation with chlorosulfonyl isocyanate in an azetidinone formation step similar to that of the Sagami

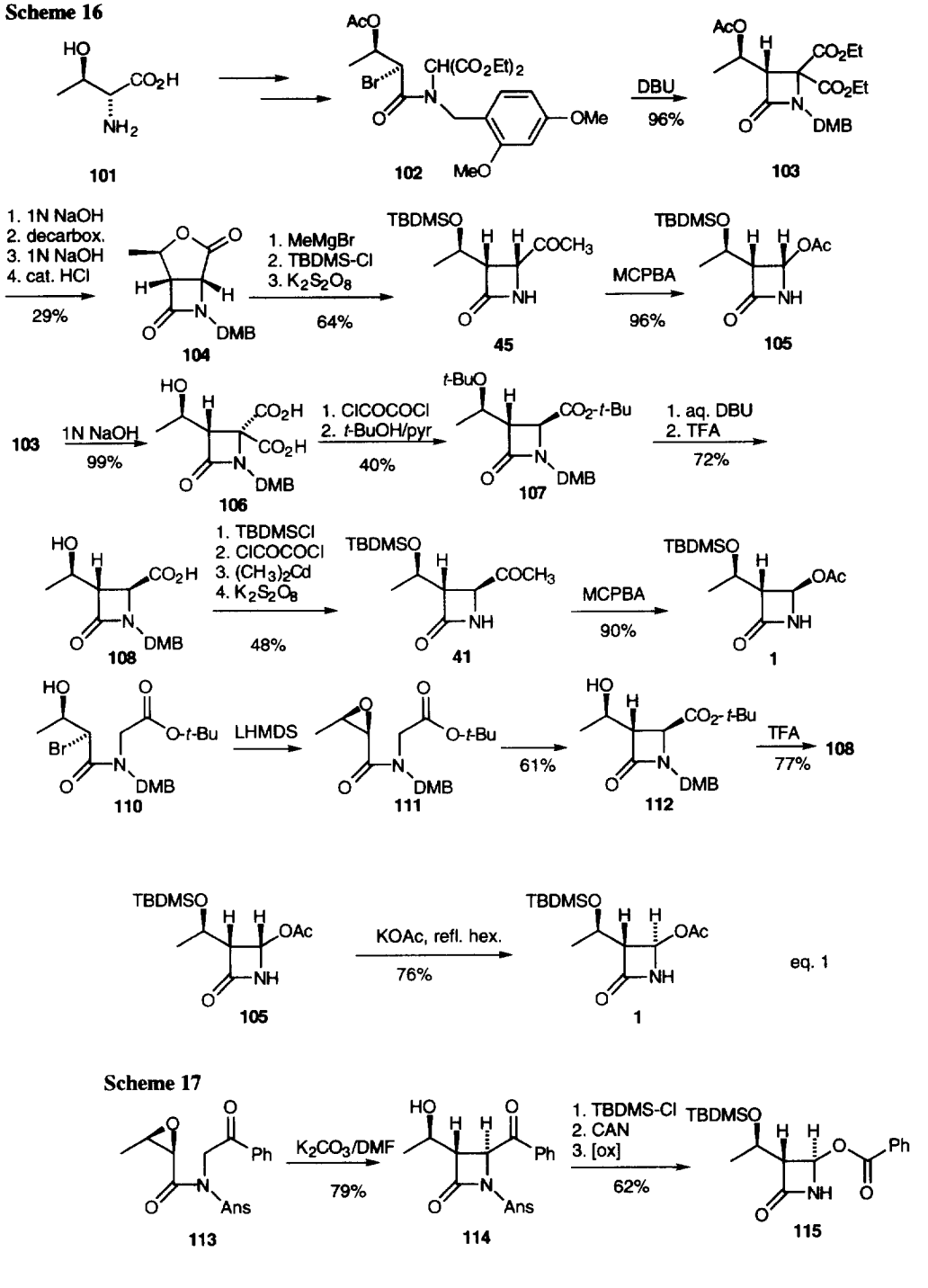
Scheme 15



group (discussed in Scheme 11). The readily obtainable (*R*)-3-hydroxybutyrate esters such as **36** were protected with a bulky silyl ether and partially reduced to aldehyde **97**. Silylation afforded the enol ether **98**. The *E/Z* ratio was important at this point, because the *Z* isomer leads in the next step to the undesired 3-*S* isomer of azetidinone **100**. There was no specific discussion of factors affecting the *E/Z* ratio of **98**, but several silyl enol ethers were reported in the examples, and the trimethyl silyl enol ether shown had the highest *E/Z* ratio of those indicated in the examples. A formal [2+2] cyclization of **98** with chlorosulfonyl isocyanate and reduction of the *N*-sulfonyl gave **100**. Of several reducing agents examined, sodium bis (2-methoxyethoxy)aluminum hydride afforded superior yields of **100** from **99**. Sequential protection of the nitrogen, displacement of the C-4 silyl ether with acetate, and deprotection furnished **1** in 19% overall yield from **97**. An alternative procedure for the transformation of **100** to **1** in 35% yield was reported using acetyl nitrate, prepared in situ from acetic anhydride and nitric acid.[26f] This scheme compensates for low yields with simplicity, requiring just three reaction vessels from **97**. A significant theme that is the subject of many patents on this scheme is the avoidance of heavy metal reagents (such as $Hg(OAc)_2$ or $Pb(OAc)_4$) in the introduction of the acetoxy group (i.e., the transformation of **100** to **1**).[26e-h]

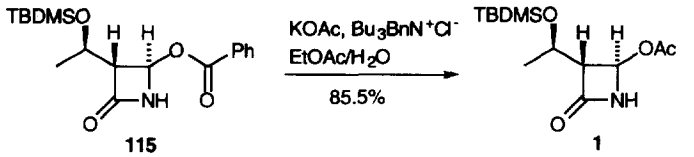
A significant tactic for construction of appropriate azetidinone systems leading to **1** is an intramolecular nucleophilic attack on an oxirane intermediate, e.g., **111**. This method was used by Shiozaki, of Sankyo, who synthesized **1** and its *cis* (1'*R*,3*R*,4*S*) diastereomer **105** starting with D-*allo*-threonine, and later, L-threonine (Scheme 16).[27] The intramolecular cyclization efficiently installs two (e.g., **103**) or three (e.g., **112**) of the asymmetric centers with the correct configuration. Amide **102**, derived from D-*allo*-threonine, **101**, was cyclized with DBU to give diester **103**.[27a] One of the ethyl esters in **103** was highly susceptible to saponification, and the resulting hydroxy acid was decarboxylated with collidine. Further saponification and treatment with catalytic acid furnished lactone **104**. This lactone was treated with methyl Grignard reagent, the resulting alcohol was protected, and the nitrogen was dealkylated with potassium peroxodisulfate to give the penultimate ketone **45**. Oxidation with MCPBA[18] gave **105** in 17% overall yield from **102**. Azetidinone **105** is potentially useful, but a method has been reported for epimerizing **105** to **1** (eq. 1).[28] Alternatively, **103** was completely saponified to **106**, which was decarboxylated and converted to **107**. Treatment with aqueous DBU cleaved the *t*-butyl ether, and trifluoroacetic acid hydrolyzed the *t*-butyl ester to afford acid **108**. Sequential alcohol protection, methylation via the acid chloride, and oxidative cleavage of the dimethoxybenzyl group furnished ketone **41**. Baeyer-Villiger oxidation[18] then provided **1** in 12% overall yield from **102**. This approach was optimized employing **110**,[29b,27c] obtained from L-threonine by straightforward chemistry. Exposure of **110** to two equivalents of lithium hexamethyldisilazide afforded **112** in 61% yield, via the optionally isolable epoxide **111**, and the action of TFA then gave **108**. This modification improved the yield of **1** from **110** to 16%.[29d]

Scheme 16



Scheme 17

A related tactic for assembly of the azetidinone was reported by Hanessian, in work very similar to that of Shiozaki's group at Sankyo but with fewer steps and superior yields (Scheme 17),[30] in a sequence that correctly constructed the three contiguous stereogenic centers in the cyclization step, leading to **114**. Epoxide **113**, which is very similar to **111** and derived from L-threonine in a two step process in 49% yield, was efficiently cyclized to azetidinone **114** on treatment with base. The hydroxy was then protected, the nitrogen was dealkylated with ceric ammonium nitrate, and the ketone oxidized[18] to the ester with monoperpthalic acid, to give **115** in 24% yield from L-threonine in just six steps. Hanessian carried **115** forward to a penem. A Japanese patent has disclosed the conversion of **115** to **1**, with retention of configuration, with acetate and a phase transfer catalyst in a two-phase solvent system (eq. 2).[31]

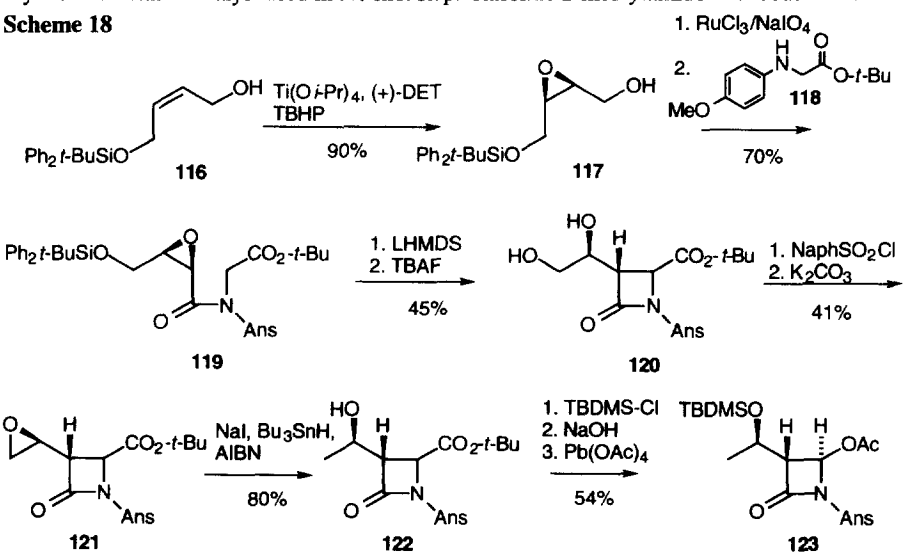


115 1 eq. 2

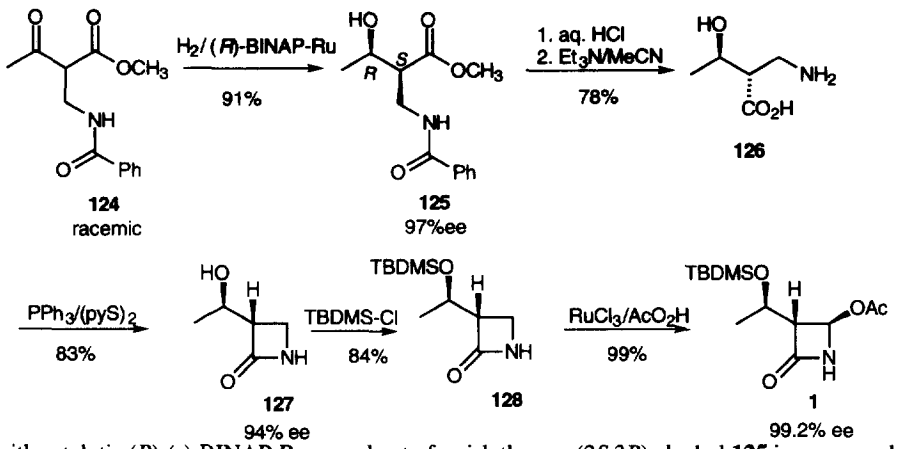
A similar azetidinone formation reaction was employed by Bonini (Scheme 18), but with a different approach to the epoxy intermediate, deriving chirality from the Sharpless method.[32] The monoprotected *E*-butendiol **116** was submitted to Sharpless chiral epoxidation conditions to give **117**, and oxidation of the free alcohol with ruthenium and periodate, followed by condensation with anisyl ester **118**, furnished epoxide **119**. Treatment with lithium hexamethyldisilazide and desilylation provided **120**. Selective sulfonylation of the primary alcohol and displacement of the napthylsulfonyl group furnished epoxide **121**, which was ring opened to **122** under novel free radical conditions. Sequential silylation of the free alcohol, hydrolysis of the *t*-butyl ester, and acetoxylation with lead tetraacetate gave **123** in 5.0% overall yield and 11 steps. *N*-Anisyl protected azetidinones like **123** have been converted to **1** with ceric ammonium nitrate (e.g., Scheme 17, above).

A significant motif for synthesizing **1** constructs **128**, the azetidinone with no substitution at C-4, and introducing the acetoxy in the last step. Noyori, of Nagoya University, and several others supported by the Japanese firm Takasago International Corp., reported the sequence in Scheme 19.[33] The chirality in **1** comes completely from the chiral catalyst used in the first step. Racemic 2-methylamido-3-oxobutanoate **124** was

Scheme 18



Scheme 19

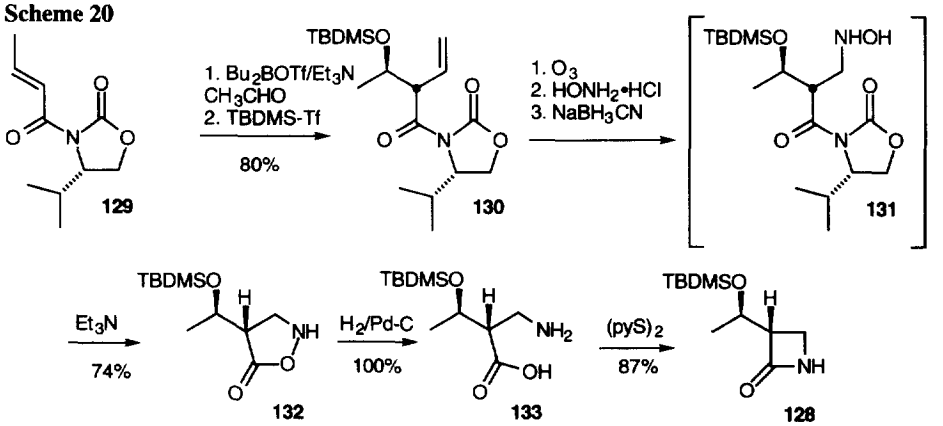


reduced with catalytic (*R*)-(-)-BINAP-Ru complex to furnish the *syn*-(2*S*,3*R*) alcohol **125** in very good yield and excellent enantioselectivity.[33a,c] Hydrolysis of the amide with aqueous hydrochloric acid and the ester with triethylamine in acetonitrile provided the β-amino acid **126**, which was cyclized to azetidinone **127** with triphenylphosphine and pyridyl disulfide. Protection of the alcohol gave **128**, which was then acetoxylated with peroxyacetic acid and catalytic ruthenium chloride,[33b,d,e] to give **1** in 50% overall yield and six steps. The Takasago group has also disclosed an oxidation of **128** to **1** with catalytic (2 mole%) osmium trichloride trihydrate, peroxyacetic acid, and sodium acetate, which proceeded in 92% yield.[33f]

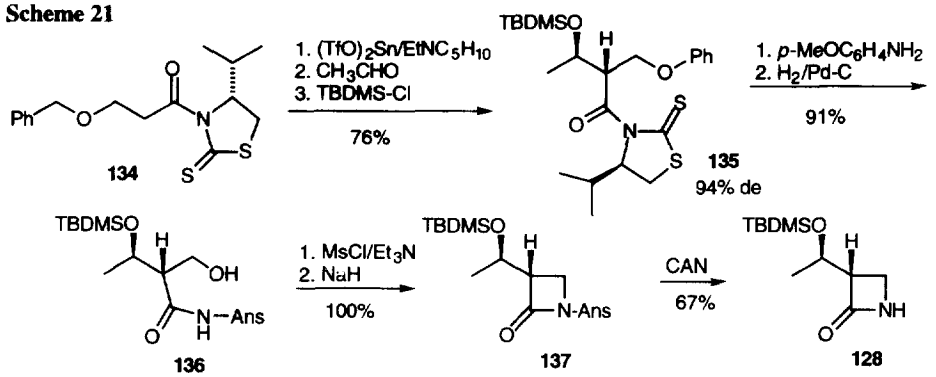
Evans also published a preparation of **128** (Scheme 20),[34] using the dibutylboryl enolate of oxazolidinone **129**. A highly selective condensation of **129**, derived from L-valine, with acetaldehyde and protection of the alcohol gave the silyl ether **130**. Ozonolysis, oxime formation, and reduction gave hydroxylamine **131** (not isolated) which was cyclized to the isoxazolidinone **132**. Hydrogenolysis and azetidinone formation with pyridyl disulfide furnished **128** in 52% overall yield and eight steps from **129**.

A similar route, employing thiazolidin-2-thiones rather than oxazolidinones, was reported by Nagao of the University of Tokushima and Lederle Japan (Scheme 21).[35] The (*R*)-thiazolidinethione **134**, obtained in 86% yield from 3-(benzyloxy)propionic acid and (4*R*)-isopropyl-1,3-thiazolidin-2-thione, was enolized with tin(II) triflate and *N*-ethylpiperidine and condensed with acetaldehyde to give **135** after silylation of the

Scheme 20



Scheme 21

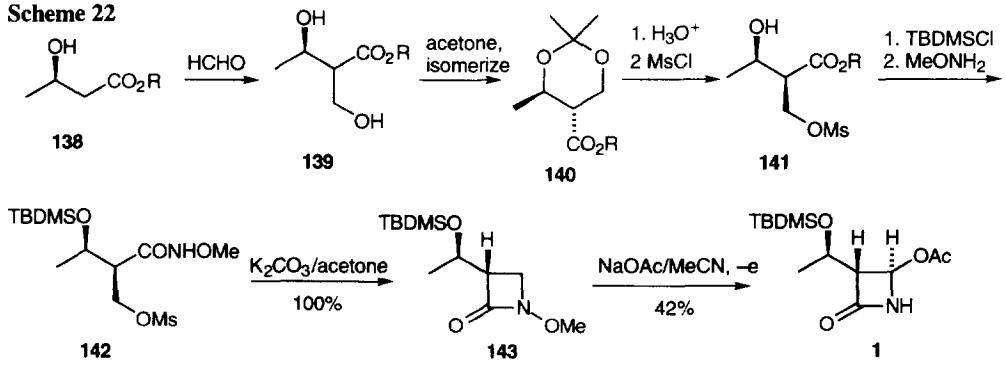


hydroxy group. The aldol condensation was rationalized to proceed via a chairlike transition state and a *Z*-enolate. The thiazolidinethione was cleaved with *p*-anisidine, and hydrogenated to furnish **136**. Mesylation of the primary alcohol and cyclization provided **137**, which was converted to **128** with ceric ammonium nitrate in 46% yield and seven steps. Note that the nitrogen of azetidinone comes from the chiral auxiliary, thus sacrificing the auxiliary group.

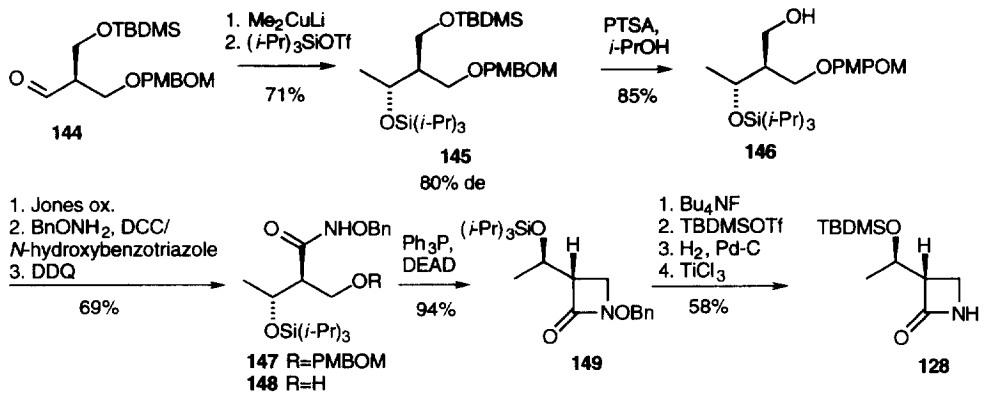
A sketchy route to **128** from (*R*)-3-hydroxybutyrates was disclosed by Fujisawa Pharmaceuticals with experimental detail provided only for the last two steps (Scheme 22).[36] The (*R*)-3-hydroxybutyrate **138** (R not specified) was condensed with formaldehyde and the resulting diol **139** was protected as the acetonide and isomerized to the desired stereoisomer shown (the isomerization method was unspecified, but likely was with base, which equilibrated **140** to the *trans* configuration). The acetonide was liberated with acid, and the primary alcohol was mesylated to give **141**. The secondary alcohol was protected, and the ester was converted to amide **142**, which was then cyclized to azetidinone **143** with potassium carbonate in acetone. Electrolysis of **143** furnished **1** with the desired stereochemistry. This reference provided both a novel route to **143**, which is a congener of **128**, and a potentially desirable alternative to the previously discussed oxidations of **128** involving ruthenium or osmium reagents, which are toxic.

An approach to **128** was published by Banfi at Genova University, starting from aldhyde **144**, derived from assymetric *bis*(hydroxymethyl)acetaldehyde ("BHYMA*"; Scheme 23).[37] The differentially protected diol **144** was alkylated with dimethyl lithium cuprate in good yield and diastereoselectivity, and the resulting secondary alcohol was protected with tri-*iso*-propylsilyl triflate to give **145**. Selective deprotection of the TBDMS ether was achieved with PTSA in isopropanol, and the resulting primary alcohol **146** was oxidized and converted to benzylhydroxamate **147**. Oxidative removal of the PMBOM group furnished **148**, which was cyclized to azetidinone **149** with triphenylphosphine and diethyl diazodicarboxylate. In two steps, the

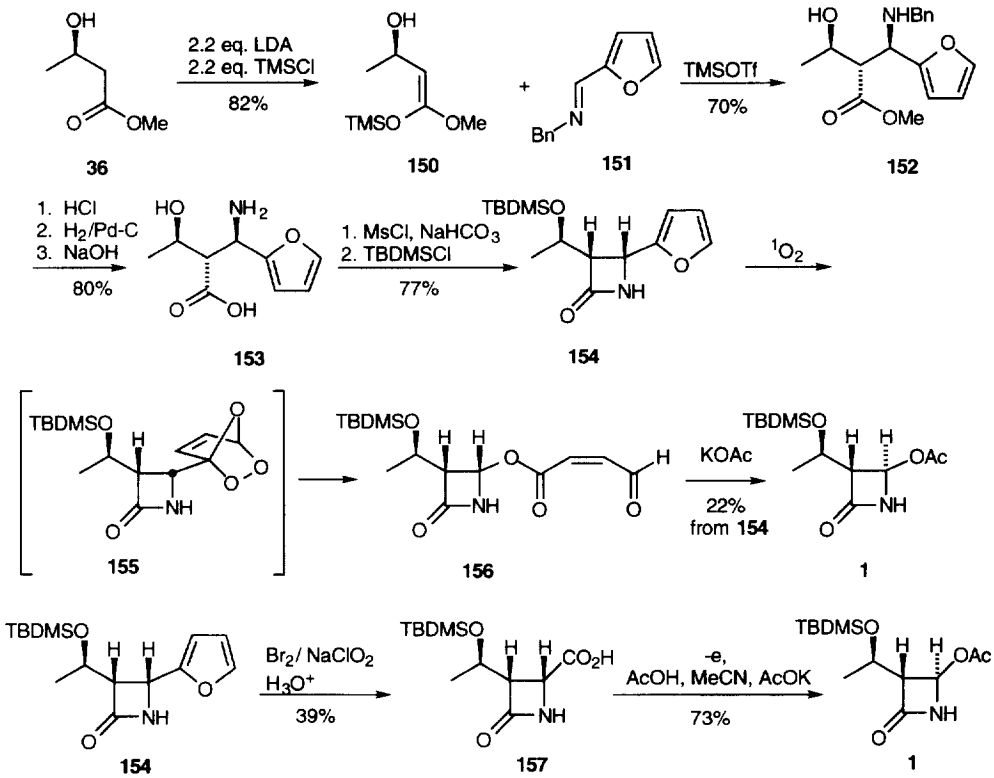
Scheme 22



Scheme 23



Scheme 24



silyl protecting group was converted to the TBDMS ether, and then hydrogenolytic debenzylation and dehydration of the intermediate *N*-hydroxy product with titanium trichloride afforded **128** in 23% overall yield and 11 steps.

Lynch of Merck reported a highly stereoselective approach (Scheme 24) to **1** starting from methyl (*R*)-3-

hydroxybutyrate and involving the key intermediate **154** bearing a furan moiety, which was elaborated to the required acetoxy with singlet oxygen,[38] or by an electrochemical reduction.[38e] The *Z*-silylketene acetal **150**, generated from **36** as a single isomer, was condensed with imine **151** with TMSOTf catalysis to give furan **152** as the only stereoisomer detected. The hydrochloride salt of **152** was hydrogenated and then saponified, both under carefully controlled conditions to prevent decomposition of the furan or epimerization, to furnish acid **153**, which was then cyclized and protected to give the key intermediate **154**. Treatment of **154** with singlet oxygen, generated photochemically with methylene blue as sensitizer, led to intermediates postulated to be diastereomers of endoperoxide **155**. This intermediate rearranged to the acyloxyazetidinone **156**, with retention of the C-4 configuration, consistent with a Baeyer-Villiger type of mechanism. Treatment of **156** with potassium acetate furnished **1**, but in a disappointing yield from **154**. Overall, this method gave **1** in 7.8% overall yield and eight steps.

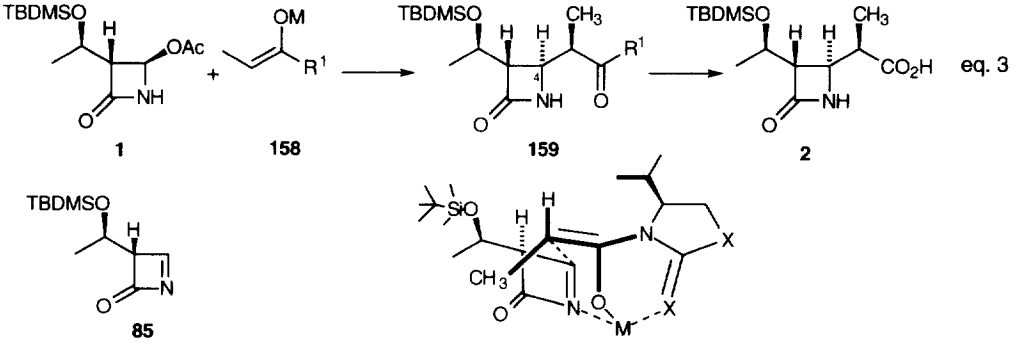
Alternatively, furan **154** was oxidized to acid **157** in a two-phase system, and converted to **1** electrochemically.[38e] Acid **157**, the epimer of **24** (Scheme 5), was obtained in crystalline form, and electrochemical displacement of the acid was accomplished under very similar conditions to that of Mori and Shibasaki (cf. Scheme 5). Note that both C-4 epimers of the azetidinone carboxylic acid (i.e., **24** and **157**) gave the same stereoisomer in the electrolysis, suggesting an S_N1 type of mechanism in the electrolytic displacement of the carboxylate with an acetoxy group. The overall yield of this transformation of **154** to **1** was 28%, which is only a minor improvement over the method proceeding via **156**. To date, the furan moiety of **154** has unfortunately proven unamenable to elaboration to **1** in high yields.

3. Routes to β-Methyl Azetidinone 2

Azetidinone **2** is the next key intermediate in the Merck carbapenem synthesis in Scheme 1. Although the orginal synthesis of **2** was rather crude (cf. Scheme 32), many elegant methods have since been developed. The majority of routes to **2** have involved an enolate addition to **1**. Another popular approach has been asymmetric hydrogenation of terminal olefinic precursors. Finally, a panoply of miscellaneous approaches to **2** will be discussed.

3.1. Enolate Addition to Azetidinone 1

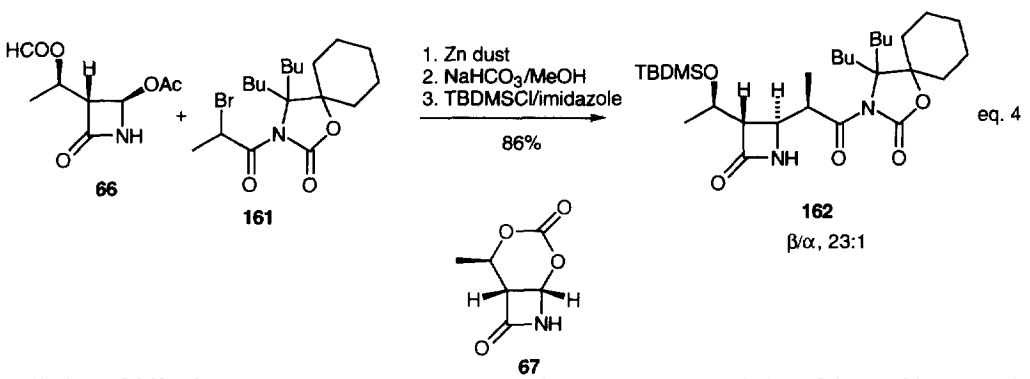
The enolate addition approaches to the synthesis of **2** can be drawn schematically as shown in eq. 3:



where an enolate **158** is added to **1** to produce **159** with the desired β-methyl stereochemistry shown. Alternatively, the corresponding Reformatsky type process has been employed. The results of this approach are summarized in Table 1 based on the nature of R^1, the metal or Lewis acid used in the enolization, and the stereochemical outcome in terms of the β:α ratio of the methyl group. A key feature of these reactions is that

the enolates **158** generally add to **1** to give the required *S* epimer at C-4 of the azetidinone ring with complete specificity. This outcome is presumably because **85** is the reactive intermediate.[48a,35,39] Because of the chirality of **1** and **85**, there is no absolute requirement that **158** also be chiral in order to achieve good selectivity in the adduct **159**. In some cases, **158** is chiral, but in other cases with excellent selectivity, it is not. Authors who have commented on transition states leading to a selective outcome suggest that the *Z* enolate **158** (shown) gives a Felkin chair type transition state which provides the observed stereochemistry. A generic transition state is shown as **160**.[40] This example shows an oxazolidinone type of auxiliary, and provides for a rigid system with the isopropyl and TBDMS groups in equatorial orientations to the pseudo [3.3.1] system at the core of **160**.

In Table 1, entry A is taken from a very recent report from the Tanabe Seiyaku Co.[41] The example shown is the only one for which experimental detail was provided. This group also examined replacement of the heterocyclic oxygen with sulfur or methylene, alternative substituents instead of the spiro cyclohexyl, and several substituents on the aromatic portion of the fused heterocycle. Entry B is a fragmentary reference from a Japanese patent.[42] No specific data were provided in the abstract. Entries C-F are taken from a study by Sagami Chemical Research also involving a Reformatsky-type condensation with substituted oxazolidinones, which were achiral, except for entry E which was an epimeric mixture.[43] It can be seen that the diastereoselectivity in the series increased with bulk on the oxazolidinone ring, consistent with a (*Z*)-enolate and a kinetically controlled chair type transition state, such as **160**. The Sagami group also reported a variation on the Reformatsky method, with 3'-formyloxy congeners of **1**, as shown in eq. 4.[44] Azetidinone **66**, discussed earlier in Scheme 11, was condensed with **161** (the same substrate as in entry F, Table 1; the α-bromo oxazolidinone of entry E was also studied but gave smaller β/α ratios with comparable yields) to give an



86% yield of **162**, after base catalyzed hydrolysis of the formate ester and silylation of the resulting secondary alcohol. In addition, the cyclic carbonate **67** was studied (also from Scheme 11), but the β/α ratio of the resulting **162** was only 3.3:1, and the yield was only 69%, further adding to the disappointment of **67** as an intermediate. In terms of yield and selectivity, there was no advantage to this route compared to the use of **1** as starting material.

Entries G-J employed 1,3-thiazolidin-2-thiones, and this study by Nagao (University of Tokushima) and Lederle Japan found that the chiral (4*S*)-ethyl and isopropyl thiazolidin-2-thiones gave superior diastereoselectivity in the aldol condensation.[45,47b] This condensation utilized tin(II) enolates, generated from tin(II) triflate and *N*-ethyl piperidine, which forms the desired (*Z*)-enolate preferentially. A very closely related study was reported by Déziel of Bristol-Myers (entries K-L),[46] who studied the thiazolidine and oxazolidine-2-thiones, with the 5,5-dimethyl substitution, and no substitution at the 5 position of the heterocycle (i.e., entries G and H were also studied). With entry K, Déziel obtained a somewhat higher diastereoselectivity than did Nagao. The results of Déziel for G and H were comparable to that of Nagao. Another example of the

Table 1. Stereospecific Enolate Additions to 1

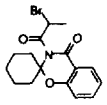
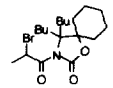
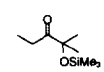
	Enolate or Precursor	Conditions	β:α ratio	Yield of **159**	Yield **159** → **2**	Ref.	Corporate Affiliation
A		Zn powder	92:8	75%	76%	41	Tanabe Seiyaku
B		†	†	†	†	42	Banyu Pharm
C		Zn dust	45:55	97%	53%	43	Sagami
D		Zn dust	79:21	94%	96%	43	Sagami
E		Zn dust	91:9	99%	66%	43	Sagami
F		Zn dust	23:1	95%	96%	43	Sagami
G		$Sn(OTf)_2$, 	4:1	73%	80%	45, 47b	Univ. Tokushima, Lederle Japan
H		$Sn(OTf)_2$, 	6.7:1	80%	80%	45	Univ. Tokushima, Lederle Japan
I		$Sn(OTf)_2$, 	9:1	80%	80%	45	Univ. Tokushima, Lederle Japan
J		$Sn(OTf)_2$, 	11:1	74%	80%	45	Univ. Tokushima, Lederle Japan
K		$Sn(OTf)_2$, 	24:1	79%	89%	46	Bristol-Myers
L		$Sn(OTf)_2$, 	9:1	75%	89%	46	Bristol-Myers
M		$Sn(OTf)_2$, 	20:1	90%	72%	47	Tokyo Inst. Tech. Fujisawa

Table 1. (continued)

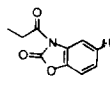
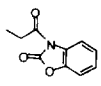
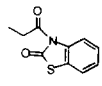
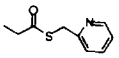
	Enolate or Precursor	Conditions	β:α ratio	Yield of **159**	Yield **159** →**2**	Ref.	Corporate Affiliation
N		TMSCl/LDA cat. ZnI_2	4:1	93%	†	48	Merck
O		$Sn(OTf)_2$, 	92:8	80%	†	48	Merck
P		Et_2BOTf, iPr_2NEt, $ZnBr_2$	≥99:1	†	73% (from 158)	48	Merck
Q		Et_2BOTf, iPr_2NEt, $BF_3{\bullet}OEt_2$	84:16	95%	94% (nmr)	48	Merck
R		Cp_2BOTf, iPr_2NEt, $ZnBr_2$	†	68%	†	49	Bayer
S		Et_2BOTf, iPr_2NEt, $ZnBr_2$	1.4:1	18%	†	50	Sankyo
T		Et_2BOTf, iPr_2NEt, $ZnBr_2$	10:1	81%	†	50	Sankyo
U		Et_2BOTf, iPr_2NEt, $ZnBr_2$	15:1	56%	83%	50	Sankyo
V		Et_2BOTf, iPr_2NEt, $ZnBr_2$	20:1	72%	†	50	Sankyo
W		Et_2BOTf, iPr_2NEt, $ZnBr_2$	60:1	75%	†	50	Sankyo
X		Et_3N, TBDMSOTf, $ZnCl_2$	10:90	91%	†	51	Bristol-Myers
Y		Et_3N, TBDMSOTf, $ZnCl_2$	8:92	37%	†	51	Bristol-Myers
Z		Et_3N, TBDMSOTf, $ZnCl_2$	40:60	58%	†	51	Bristol-Myers
AA		Et_3N, TBDMSOTf, $ZnCl_2$	87:13	80%	†	51	Bristol-Myers
BB		LHMDS, TBDMSOTf, $ZnCl_2$	>98:2	85-90%	†	51	Bristol-Myers

Table 1. (continued)

	Enolate or Precursor	Conditions	β:α ratio	Yield of **159**	Yield **159**→**2**	Ref.	Corporate Affiliation
CC		LDA-$Zr(Cp)_2Cl_2$	97:3	52%	†	52	Bristol-Myers
DD		LDA-$Zr(Cp)_2Cl_2$	87:15	47%	†	52	Bristol-Myers
EE		LDA-$Zr(Cp)_2Cl_2$	1:2	20%	†	53	Bristol-Myers
FF		LDA-$Zr(Cp)_2Cl_2$	94:6	15%	†	53	Bristol-Myers
GG		TMSOTf	1:2.6	94%	†	54	Sankyo
HH		TMSOTf	1.6:1	81%	†	54	Sankyo
II		ZnI_2	1:1	†	†	17b	Fujisawa/ Tokyo Inst. Tech.

† not given

Mukaiyama tin(II) enolate chemistry is shown in entry M,[47] employing an achiral and acyclic enolate, with results comparable to the best of the tin(II) enolates.

The Fuentes group at Merck studied this reaction extensively, as summarized by entries N-Q,[48] with the silyl, tin(II), and boron enolates of the 1,3-oxazolidine-2-ones. Fuentes also studied the *Z*:*E* ratios of the silyl and boron enolates, and obtained ratios as high as 99:1 for the enolate generated with TMSCl and LDA in THF at -78°C, and 98:2 for the enolate made with Et_2BOTf and Hünigs base in methylene chloride at -78°C. The optimal conditions for production of **159** in entry P were claimed to have good reproducibility, with excellent diastereoselectivity and good isolated yields. In addition, the oxazolidinone auxilliary was recovered in 90% yield. A report from Bayer AG employed the same Evans auxiallary used by Fuentes (entry R).[49]

Sugimura of the Sankyo & Co. obtained excellent results with the planar boron enolates generated from the amides shown in entries S-W.[50] Although both the yield and selectivity were poor with the simple thiophenyl ester in entry S, the benzoxazolidinones and benzthiazolidinones in entries T-W gave very respectible yields and excellent diastereoselectivity in the aldol condensation, culminating in entry W. Only a representative example of the hydrolysis of the heterocyclic amide to furnish **2** was provided. For the adduct made with entry W, carbapenem **3** (Scheme 1) was obtained in one flask without the isolation of **2**; additionally, another alternative route to the carbapenem nucleus was provided not involving isolation of **2**.

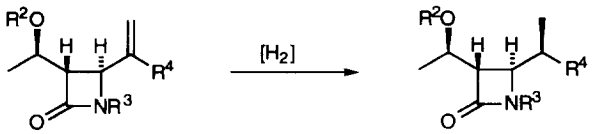
Another efficient approach again involving an achiral enolate was from Martel of Bristol-Myers,[51] who looked at a series of enolates generated from the thio esters represented by entries X-BB. Note that entry X employed the same substrate as entry S, but with the silyl enolate (entry X) the selectivity and yield was fairly good at providing the undesired α-methyl configuration. However, the use of a 2-pyridyl moiety (entry AA) turned the selectivity around in the direction of the desired β-methyl. The process was optimized with the 3-methyl-2-picolylthiopropionate in entry BB, giving >98% diastereoselectivity and very good yields. An earlier process by Kim of Bristol-Myers employed similar substrates (entries CC-DD),[52] but used a zirconium enolate rather than a silyl enolate and a Lewis acid catalyst. Comparing entries X and CC, the use of zirconium completely turns around the stereochemical outcome of the reaction. However, the yields were relatively low, and in the case of the 2-pyridyl ester from entries AA and DD, the zirconium enolate employed in DD had no effect on the diastereoselectivity, but did had a deleterious effect on the yield relative to the silyl enolate used in

entry AA. Another study by Endo of Bristol-Myers,[53] studied the condensation of enolates of the two esters shown in EE and FF with seven Lewis acids. Most permutations examined by Endo gave diastereomeric mixtures of **159** with predominantly the α-methyl configuration, with the notable exception of entry FF, which gave moderate selectivity but very poor yield. Endo speculated that ketene formation following treatment of the esters with base led to the poor yields.

Finally, the oldest references in Table 1 are to work by groups at Sankyo & Co.[54] and Fujisawa Pharmaceuticals[17b] published in 1985 (entries GG-II). These teams looked at simple enolates under conventional aldol conditions, and obtained poor selectivity.

3.2. **Asymmetric Hydrogenation of Olefinic Azetidinone Derivatives**

Another popular route to 1 and its congeners is asymmetric hydrogenation of the terminal olefin compound, **163** (eq. 5). In this family of reactions, summarized in Table 2, the carbon framework of **2** is



eq. 5

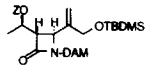
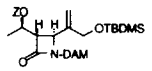
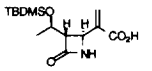
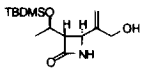
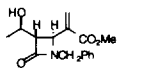
163 **164**

assembled in **163** with a prostereogenic center that is elaborated to **164** with four contiguous stereogenic centers by hydrogenation or hydride reduction. As in the enolate addition introduction of the β-methyl moiety, both chiral and achiral reactants have been successfully employed. A significant challenge is the relative difficulty of obtaining the olefinic precursors (i.e., **163**) for each example. Most cases in Table 2 already have three of the four chiral centers required in **2**, so the preparation of the substrates in Table 2 was not trivial.

The work in Table 2, entries A and B, is from Sunagawa of Sumitomo Pharmaceuticals, and is shown in greater detail in Scheme 25.[55] Azetidinone (+)-**89** (cf. Scheme 14) was esterified and treated with methyl Grignard reagent to give **165**, which was protected with the benzyloxycarbonyl (Z) group, and dehydrated to furnish **166**. Allylic chlorination followed by cuprous oxide and *p*-toluenesulfonic acid provided the allylic acohol. Silyl protection of the alcohol furnished the key intermediate **168** in 59% overall yield and seven steps from **89**. The optimized hydrogenation conditions shown (**168**→**169**) gave an 84.5% yield and a 13.1:1 ratio of **169** to the α-methyl isomer. Nearly pure **169** was obtained after recrystallization. Treatment of **169** with boron trifluoride etherate in the presence of 1,3-dimethoxybenzene cleaved both the silyl protection and the di-*p*-anisylmethyl (DAM) groups. Jones oxidation furnished **171**, and hydrogenation of the benzyloxycarbonyl and silylation afforded **2**, in 29% overall yield (not counting the recrystallization of **169**) and 13 steps.

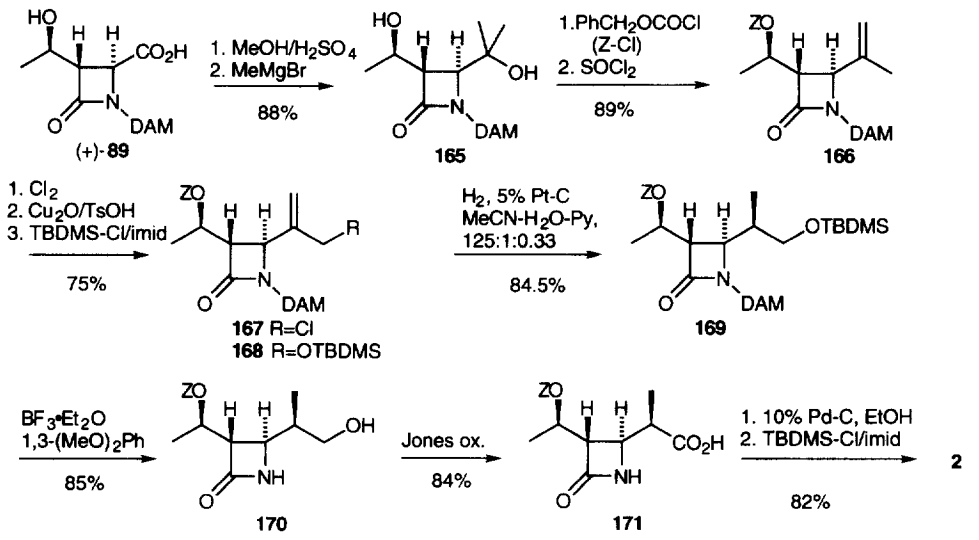
Another significant study in this area was from Merck (Table 2, entry C), and is shown in detail in Scheme 26.[56] Azetidinone **172**, from earlier studies by Merck, was alkylated to give **173** as a mixture of epimers that was phenylselenated, oxidatively eliminated, and treated with di-*iso*-butyl aluminum hydride to reduce the ester and provide **175**. This allylic alcohol was acetonated and desilylated, to furnish the key intermediate **177** in six steps from **172** and 48% overall yield. Hydrogenation of **176** gave predominantly the undesired α-methyl isomer, necessitating the desilylation step. The optimized conditions for the reduction of **177** employed Raney nickel in methanol as solvent, which was speculated to disrupt disadvantageous intramolecular hydrogen bonding between the hydroxyl group and the β-lactam carbonyl, thus enhancing the selectivity. Reintroduction of the silyl protecting group and oxidation afforded **2** in 37% yield and nine steps overall. Separation of the small amount of the α isomer of **178** was not necessary, because later steps of the carbapenem synthesis proceeded more efficiently with the β isomer.[57]

Table 2. Hydrogenation of Olefinic Azetidinones 163

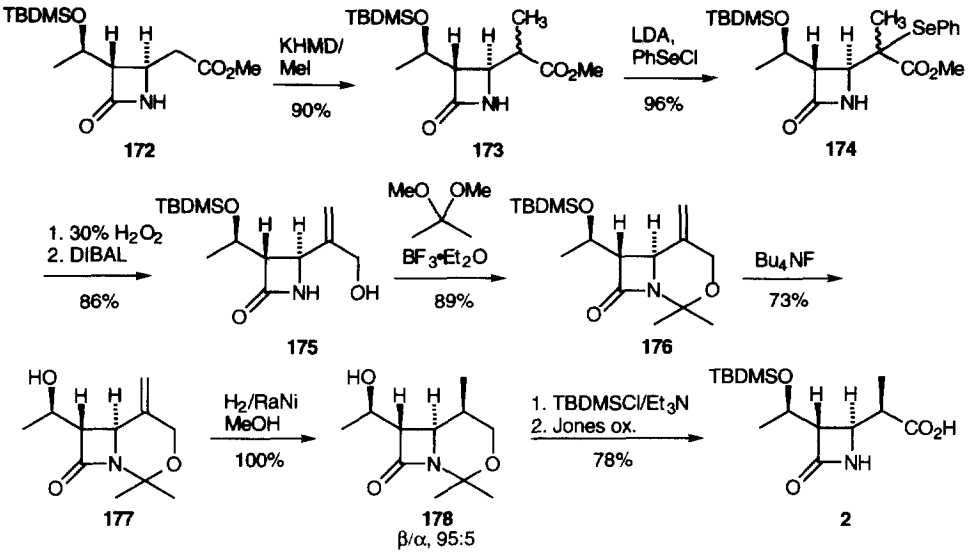
	Substrate **163**	Conditions	β:α ratio	Yield **164**	Yield **164**→**4**	Reference	Corporate Affiliation
A		H_2, 5% Pt-C, MeCN-H_2O-Py	13.1:1	85%	56%	55	Sumitomo
B		PtO_2/MeCN	7.8:1	92%	†	58	Sumitomo
C		H_2/ Raney Ni	20:1	100%	78%	56	Merck
D		PtO_2/ EtOH	2.82:1	†	†	58	Sumitomo
E		H_2/ Raney Ni	†	90%	†	60	Indian Inst. Chem. Tech
F		H_2/(*R*)-BINAP-Ru	87:13	100%	†	61	Nagoya Univ./Sankyo
G		H_2/(*R*)-BINAP-Ru	99.9:0.1	100%	†	62	Nagoya Univ.
H		LiBH(*s*-Bu)$_3$	8:1	77%	56%	63	Sagami

† not given

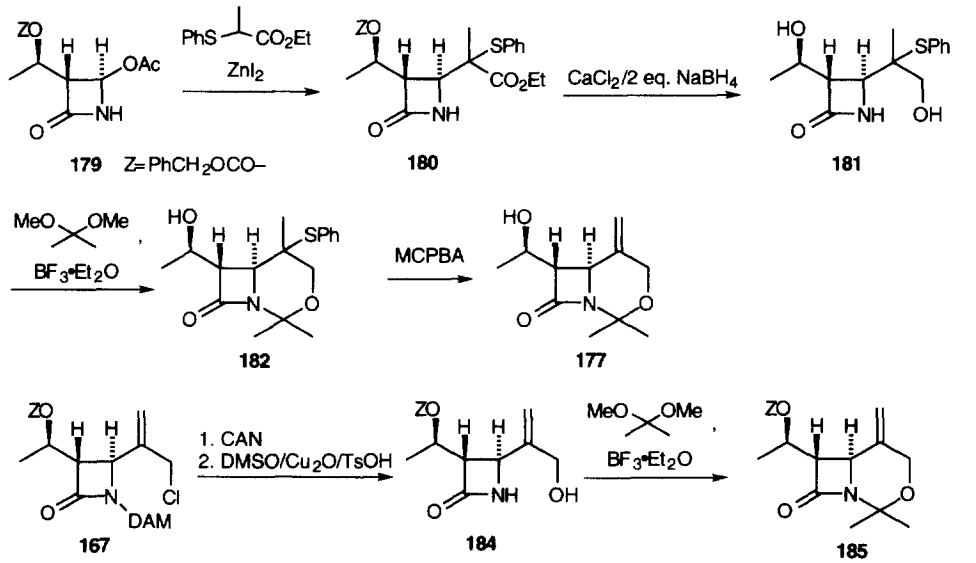
Scheme 25



Scheme 26

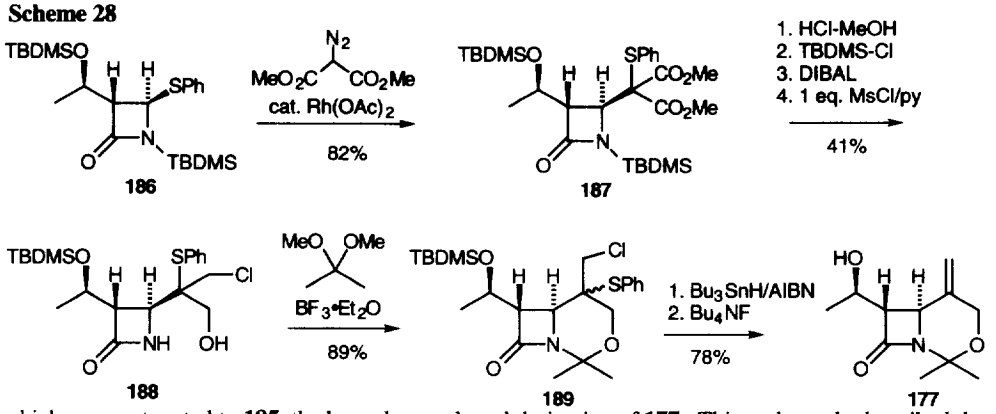


Scheme 27



Two alternative preparations of **177** were described by Sunagawa of Sumitomo, as shown in Scheme 27,[58] in the study that also included the work described in Scheme 25.[55] Azetidinone **179**, the benzyloxycarbonyl (Z) analogue of **1**, was condensed with ethyl 2-thiophenylpropionate under the influence of zinc iodide to provide ester **180** (no yields were provided for any of the transformations shown in Scheme 27). Both ester moieties in **180** were reduced with calcium borohydride generated in situ, and the resulting primary alcohol **181** was acetonated and the thioether was oxidatively eliminated to provide **177**. Alternatively, allyl chloride **167** (cf. Scheme 25) was deprotected and oxidized to the primary alcohol **184**,

Scheme 28

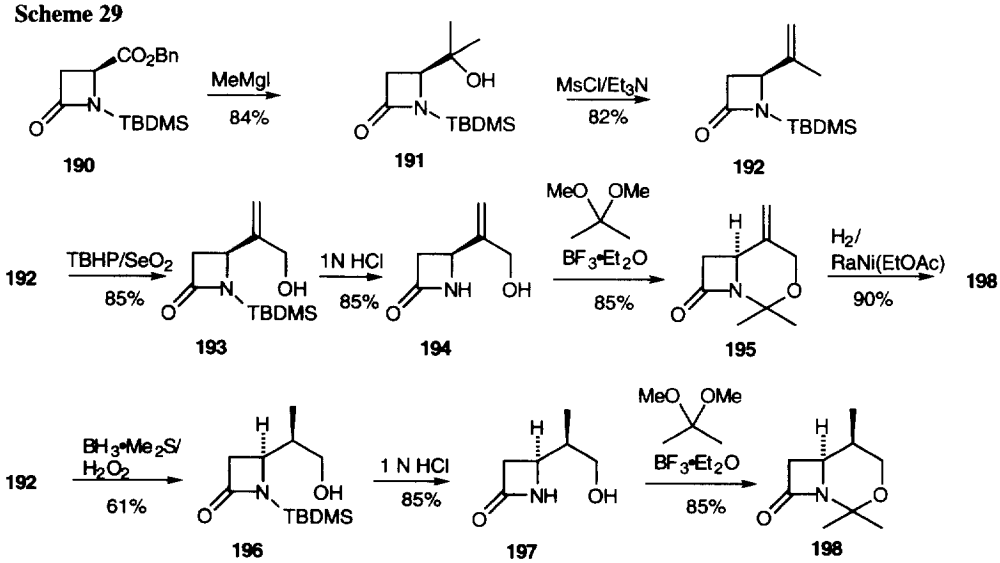


which was acetonated to **185**, the benzyloxycarbonyl derivative of **177**. This early study described the reduction of the olefins **177**, **185**, **168**, and related analogues by hydrogenation with conventional palladium and platinum catalysis and did not achieve β/α selectivities greater than 8:1 (Table 2, entry D). The thrust of this work was the synthesis of olefinic precursors rather than finesse in the hydrogenation conditions.

Another preparation of **177** was reported by Honda of Hoshi University (Scheme 28).[59] Azetidinone **186** was homologated with diazomalonate and catalytic rhodium acetate to furnish **187**, which was sequentially desilylated, selectively silylated at the hydroxy only, reduced, and partially chlorinated. Acetonide **189** was obtained, and the exocyclic olefin was formed with free radical elimination conditions. Desilylation afforded **177** in 23% overall yield and eight steps.

A related approach (Table 2, entry E) employing acetonides was reported by Rao of the Indian Institute of Chemical Technology in Hyderabad (Scheme 29).[60] Azetidinone **190**, derived from L-aspartic acid via known procedures, was treated with methyl Grignard reagent followed by mesylation and elimination to give olefin **192**. Two methods were developed to prepare the key intermediate **198** from **192**. Initially, **192** was hydroxylated at the allylic position, deprotected, and acetonated to furnish **195**, which was hydrogenated in

Scheme 29

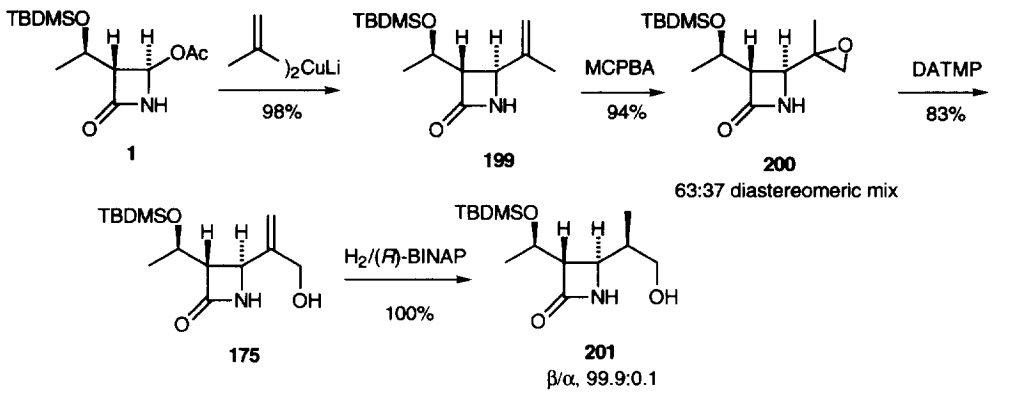


the presence of Raney nickel to afford **198**, in 38% isolated yield from **190** and six steps. No attempt was mentioned to quantify any α-methyl impurity from this reaction. Alternatively, **192** was hydroborated with borane followed by hydrogen peroxide, which both stereospecifically reduced the prochiral olefin to the desired configuration and oxidized the allylic position to provide **196** in one flask. Deprotection and acetonation gave **198** in 30% yield and 5 steps from **190**. The hydroxyethyl sidechain can be introduced via known chemistry (cf. Scheme 4[377] and also Scheme 4[412]).

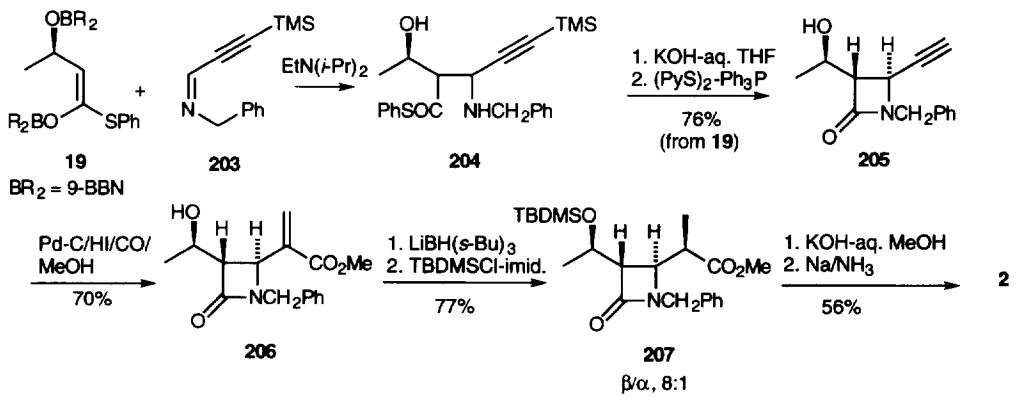
A very significant motif for the asymmetric reduction of olefins of the type of **163** is the ruthenium(II) BINAP complexes pioneered by Noyori. The initial attempt, with the acid shown in Table 2, entry F[61] was greatly improved as shown in entry G,[62] by the use of the corresponding allylic alcohol instead of the acid. The substrate in entry G, **175** (also made by Fuentes of Merck; see Scheme 26), was prepared by Noyori's group as shown in Scheme 30.[62] Azetidinone **1** was alkylated with a lithium di-2-propenylcuprate, epoxidized, and rearranged with *N*-diethylaluminum tetramethylpiperidide to give **175** in 76% overall yield and three steps. This compares with a 74% yield and four steps in the Merck synthesis of **175** (Scheme 26).[56] The very impressive selectivity on the reduction of **175** to **201** is not surprising in that both the substrate and the catalyst are chiral, and under certain conditions both the azetidinone substrates affected by an achiral reagent, and the BINAP catalyst acting on achiral substrates, have themselves given excellent stereoselectivity.

Shibasaki of the Sagami Chemical Research Center successfully employed L-Selectride® to reduce an

Scheme 30

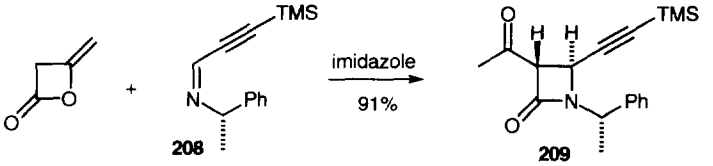


Scheme 31



isoprenyl azetidinone (Table 2, entry H and Scheme 31; the first part of this work is very similar to Scheme 5).[63] The boron enolate **19**, obtained in 55% yield from (*R*)-3-hydroxybutyric acid (**60**; see Scheme 11), was alkylated with imine **203** to give **204**, which was hydrolyzed and cyclized to furnish alkyne **205**.[63b] A novel palladium catalyzed methoxycarbonylation gave the key intermediate **206**.[63c] Attempts at this stage to effect the stereoselective reduction to the β-methyl side chain by hydrogenation with palladium on carbon, ruthenium triphenylphosphine chloride, and several cationic ruthenium complexes were unsuccessful, giving either low yields or diastereomeric product mixtures. It was found that L-Selectride® in THF with *sec*-butyl alcohol as cosolvent afforded **207** in 77% yield following protection of the alcohol. Hydrolysis of the methyl ester and debenzylation with sodium in ammonia afforded the desired acid **2** in 12.6% overall yield from **19** in eight steps.

A related alternative approach from the Sagami group is shown in eq. 6.[63d] In this fragmentary reference, diketene was condensed with (*S*)-1-phenylethyl imine **208** in the presence of imidazole to give **209**, in 91% yield, and "mainly" the stereoisomer shown. Stereospecific reduction of ketones such as the acetyl on azetidinone **209** are known,[13] and the rest of the chemistry in Scheme 31 is probably applicable to the synthesis of **2** from **209**.



eq. 6

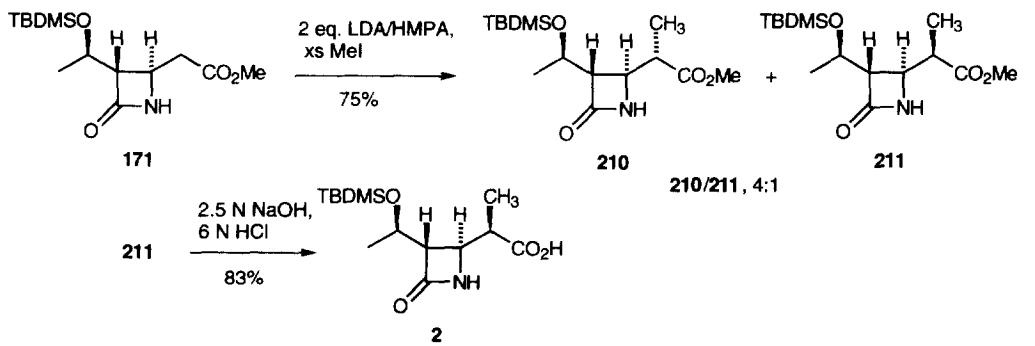
3.3. Other Routes to β-Methyl Azetidinone 2

This section summarizes a variety of additional methods reported for the synthesis of **2**.

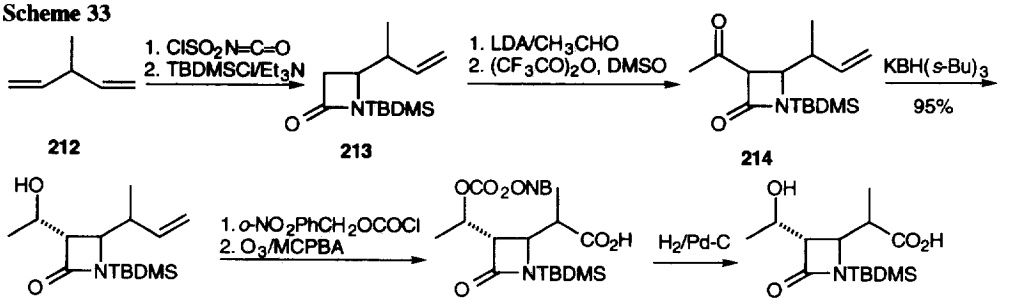
The original approach to **2**, and the early benchmark for these compounds, was the method reported by Shih et al. of Merck in 1984 (Scheme 32).[5] Treatment of methyl ester **171**, readily obtained from earlier work on carbapenems without the β-methyl substituent, with two equivalents of LDA containing one equivalent of HMPA, followed by excess methyl iodide, resulted in a 4:1 mixture of **210** and the desired **211**. The mixture was separated by preparative HPLC, and a recycling procedure was employed, epimerizing **210** with acetic acid, which allowed recovery of additional amounts of **211**. Hydrolysis of **211** to **2** was accomplished without racemization. The unfavorable isomeric ratio of this simple alkylation, and the use of preparative HPLC to seperate the products, were obviously big drawbacks to the large scale application of this method, and provided the impetus for the many thoughtful methods for the synthesis of **2** discussed in this review, including several highly selective and efficient techniques from teams at Merck.

Another early Merck report described a fairly crude method for the synthesis of **2**, and includes little

Scheme 32



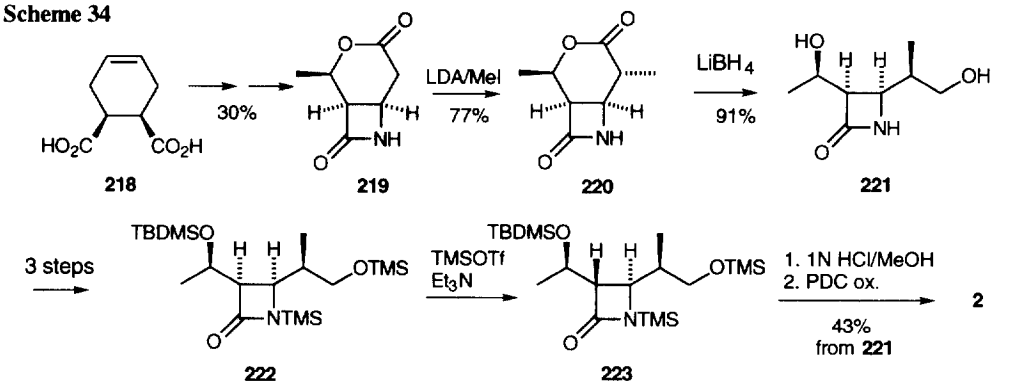
Scheme 33



mention of stereocontrol and only one reaction yield (Scheme 33).[64] The symmetric diene **212**, derived from 3-methylglutaric acid, was treated with chlorosulfonyl isocyanate and *N*-protected to furnish the [2+2] cycloadduct **213**. This azetidinone was subjected to an aldol condensation with acetaldehyde and oxidation with trifluoroacetic anhydride and DMSO to give ketone **214**. It is likely that **214** equilibrates at this stage to the *trans* configuration at C-3 and C-4 of the azetidinone, but no specific comment was made to that effect. Reduction with K-Selectride® provided **215**, which is drawn as shown by the inventors, although other publications discussed in this review have shown that ketones such as **214** are stereoselectively reduced by bulky borohydride reagents to give the configuration required in **1** or **2** for carbapenem syntheses.[13] Protection of the secondary alcohol with *ortho*-nitrobenzylchloroformate, ozonolysis, and hydrogenation gave **217**, which was carried forward to β-methyl carbapenems. Presumably, this effort hoped to compensate for the lack of selectivity in the side chain methyl with the fact that the β-methyl isomer cyclizes preferentially at a later stage of the carbapenem synthesis.[57]

Moving on to more controlled approaches to **2**, Ohno of the University of Tokyo published a highly stereocontrolled preparation of **2**, taking advantage of a rigid [4.2.0] bicyclic system (Scheme 34).[65] Known chemistry was used to prepare **219** in 30% yield from diacid **218**, and the key methylation step to form **220** occured exclusively from the convex face of the bicyclic system giving a single stereoisomer with the putative β-methyl geometry. Lithium borohydride lactone ring opening gave azetidinone **221**, however, the nature of the bicyclic system dictated a *cis* azetidinone, with the wrong configuration at C-3 of the azetidinone ring. A four-step sequence was employed to epimerize the C-3 of the azetidinone to the required configuration, involving some functional group manipulation leading to **222**, and epimerization with trimethylsilyl triflate and triethylamine to afford **223**, with the four contiguous stereocenters correctly configured. Detrimethylsilylation was accomplished with 1N HCl and oxidation with pyridinium dichromate furnished the desired acid **2** in 30%

Scheme 34

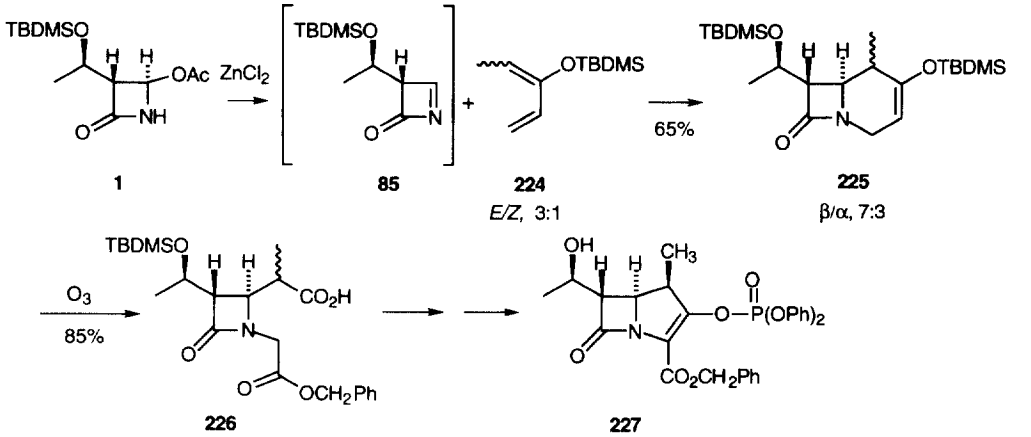


overall yield and eight steps from **219**.

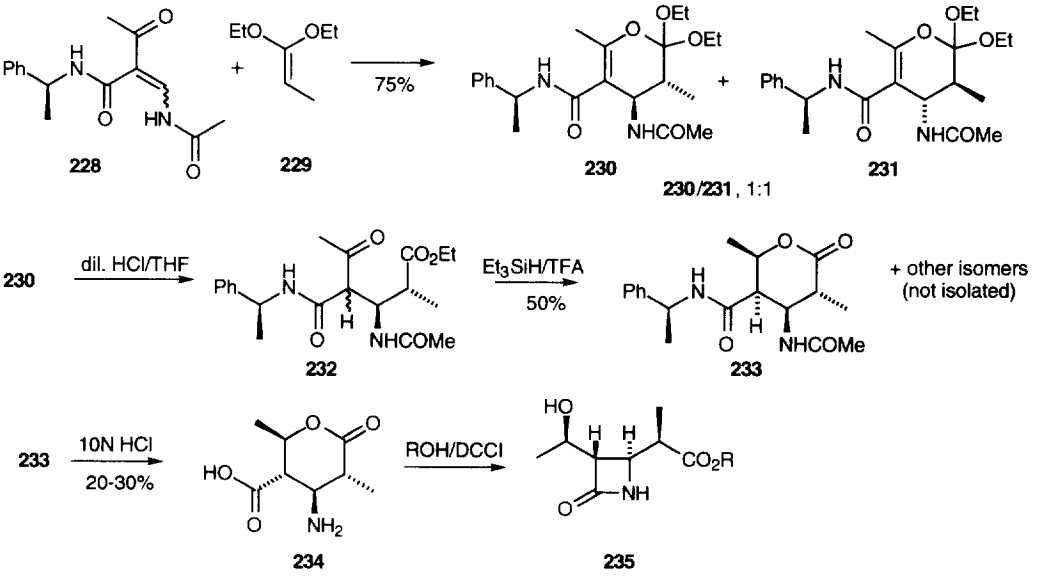
There have been several Diels-Alder type approaches to **2**. Meyers, of Colorado State, executed the method in Scheme 35,[66] in which azetidinone **1** was combined with diene **224**, in the presence of zinc chloride, to afford **225** as a 7:3 mixture of epimers in 65% yield. Efforts to improve the β:α ratio of **225**, by the use of pure (*E*)-or (*Z*)-diene **224**, were unsuccessful, and it was shown that **225** equilibrates to an epimeric mixture under the reaction conditions. Although compound **2** was not actually prepared in this study, ozonolysis produced the benzyl ester **226** in 85% yield. Two additional steps afforded the β-methyl carbapenem nucleus. It is noteworthy that only the desired β-methyl diasteromer of **227** is formed, because the α-methyl diastereomer is unreactive during the installation of the phosphonate.[57]

Lactone **234** has been a popular intermediate for the synthesis of **2**. This lactone has the four contiguous

Scheme 35



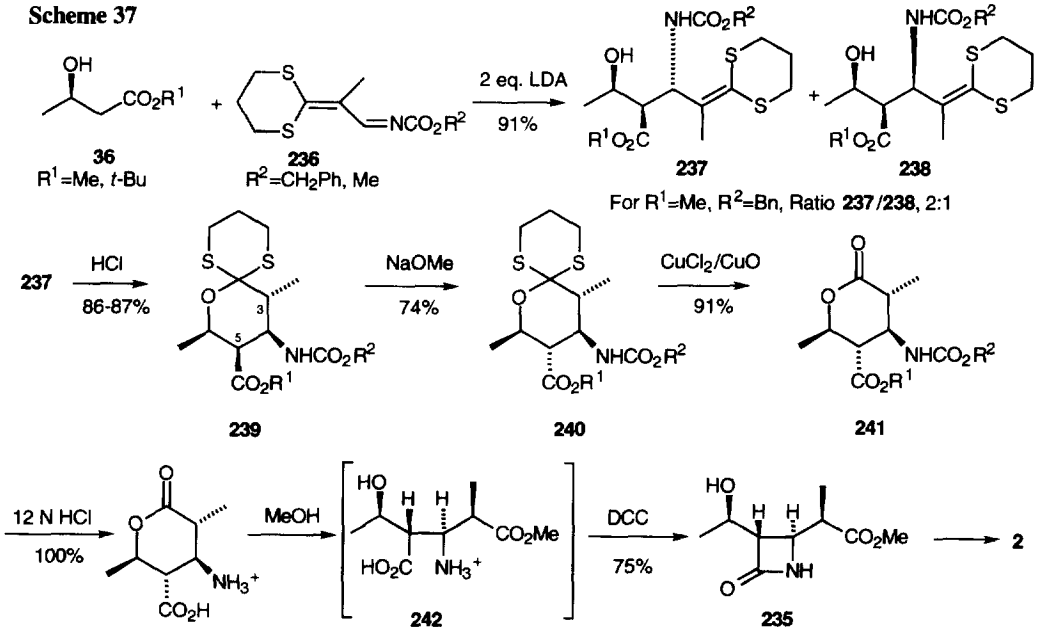
Scheme 36



chiral centers of **2**, can be easily transformed to **2**, and it has been amenable to preparation from several different strategies (Schemes 36, 37, 38, and 39). Flynn, Galt, and Turner, of ICI, prepared **235** via an inverse electron demand Diels-Alder cyclization leading to a stereocontrolled dihydropyran (Scheme 36).[67] The example illustrated in Scheme 36 is the nonracemic example from the ICI group. They also studied achiral congeners of **228** and obtained generally higher yields, but of racemic products. However, since the correct enantiomer of **2** is required for biological activity in the carbapenems, the nonracemic version of their method is illustrated here. The 4+2 cyclization of **228** and **229** led to a 1:1 mixture of the diasteromers **230** and **231** (i.e., no chiral induction was observed), along with a small amount of the corresponding *cis* isomers.[67a] These isomers were easily separated by crystallization, and the desired **230** was hydrolysed and reduced to **233**. Lactone **233** was isolated from a mixture of the four possible reduction products by crystallization in 50% yield from **230** (a direct reduction of **230** to **233** was not possible).[67b] Deprotection of **233** was troublesome and required harsh acidic conditions causing some racemization, but **234** was isolated pure in 20-30% yield by crystallization. Alcoholysis and DCC coupling gave **235** (no yield given; reference was made to Hatanaka, below).

Hatanaka, of Osaka University, also constructed lactone **234** but by a different approach, employing an acyclic precursor derived from (*R*)-hydroxybutyric acid, shown in Scheme 37.[68] The dianion of methyl (*R*)-3-hydroxybutyate **36** (R^1=Me) was condensed with *N*-benzyloxycarbonylimine **236** (R^2=benzyl), obtained in 71% yield in a two-flask sequence from 2-trimethylsilyl-1,3-dithiane, to furnish a 2:1 mixture of **237** (desired), and **238**. Dithiane **237** was cyclized to **239** with catalytic HCl in methylene chloride, with complete chiral induction at C-3. The C-5 center was epimerized under basic conditions to give **240**, and the lactone **241** was generated on treatment with cupric chloride and cupric oxide. Liberation of the protecting groups required harsh acidic conditions, as was the case with Flynn, et al. (Scheme 36), but the *N*-benzyloxycarbonyl was cleaved quantitatively in refluxing 12 N HCl, to furnish **234**. Methanolysis and dicyclohexylcarbodiimide coupling afforded azetidinone **235**. The overall yield to **235** was 26% in six steps.

Scheme 37

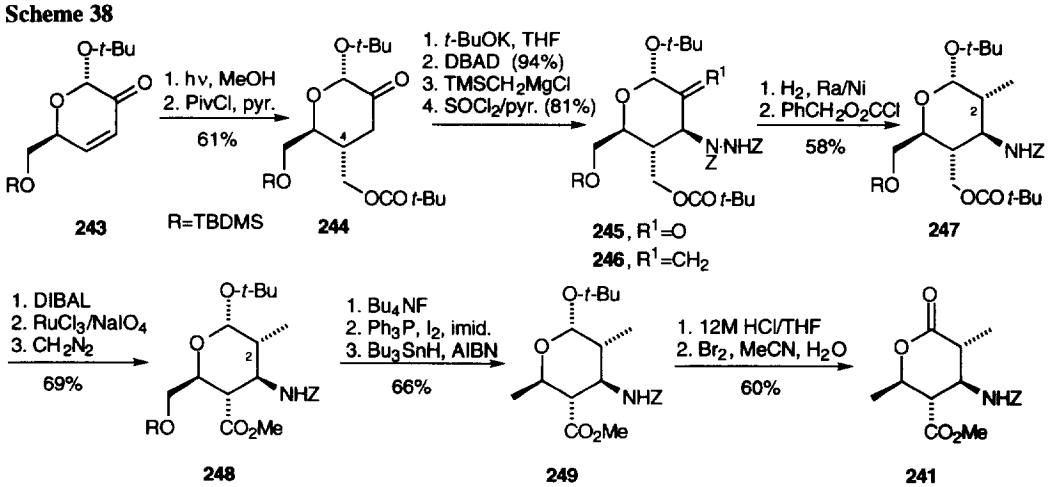


Hatanaka also studied the condensation of *t*-butyl (*R*)-3-hydroxybutyate **36** (R^1=*t*-Bu) with **236** (R^2=Bn), and obtained a 4:1 ratio of condensation products **237** and **238**, but did not pursue that investigation because of difficulty in synthesizing **36** with R^1=*t*-Bu; an inefficient transesterification from the methyl ester was employed, and it was not clear if other approaches to the *t*-butyl ester were explored. Additionally, Hatanaka investigated this sequence starting from the *N*-methyloxycarbonylimine **236** (R^2=Me), and obtained essentially identical yields and ratios to the benzyl carbamates illustrated, but the deprotection to furnish **234** could not be achieved without epimerization of the C-3 methyl group. The ICI approach (Scheme 36) had the same experience with racemization during hydrolysis of the methyl carbamate moiety.

Another route to **234** was published by Fraser-Reid of Duke University, and is shown in Scheme 38.[69] This scheme employed a stereospecific photoaddition of methanol and a stereospecific electrophilic amination as key steps. Starting from enone **243**, which was part of a study of the photoaddition of methanol to enones, the Duke researchers found that in the presence of light and a photosensitizer, the addition of methanol occurred stereoselectively, with the major product having the desired configuration for the synthesis of carbapenems (α/β ratio, 8:1 at C-4). Esterification with pivaloyl chloride, and then electrophilic amination with *t*-butoxide followed by dibenzyl azodicarboxylalate (DBAD), afforded pyranone **245**. Olefin **246** was obtained after addition of $TMSCH_2MgCl$ and subsequent elimination with thionyl chloride in pyridine. Hydrogenation and reintroduction of the benzyloxycarbonyl (Z) group furnished pyran **247**, as a 5:1 epimeric mixture at C-2, with the desired α isomer predominating. The ester was reduced, and the resulting alcohol was oxidized and esterified to give **248**. Deoxygenation of the silyl ether, hydrolysis of the *t*-butyl ether, and oxidation provided **241** (cf. Scheme 37; R^1=Me, R^2=Bn), an established intermediate for **234** and **2**. The overall yield to **241** in this sequence is 7.4% in 16 steps; based on Hatanaka's method (Scheme 37), the transformation to **2** would require two additional steps and an overall yield from **243** of 5.5%.

Another approach to **2** involving derivatives of **234** and **242** was reported by Sunagawa of Sumitomo Pharmaceuticals involving a selective reduction of the acyclic precursor **261** (Scheme 39).[70] Enamine **251**, obtained by the alkylation of **250**, a known precursor to thienamycin, was selectively reduced with catechol-borane and $NaBH_3CN$ to give a 98:2 mixture of **253** and **254**.[70a] The bicyclic chelation intermediate **252** was invoked to explain this stereoselective result, with addition of hydride *anti* to the methyl group. Lactonization to **255** was accomplished with anhydrous HCl, and the methyl ester was then exchanged for a benzyl ester to give **256**. Ring opening, esterification with methyl iodide, and debenzylation afforded **258**, which was cyclized with DCC to give azetidinone **259**, with the wrong configuration on the C-3

Scheme 38

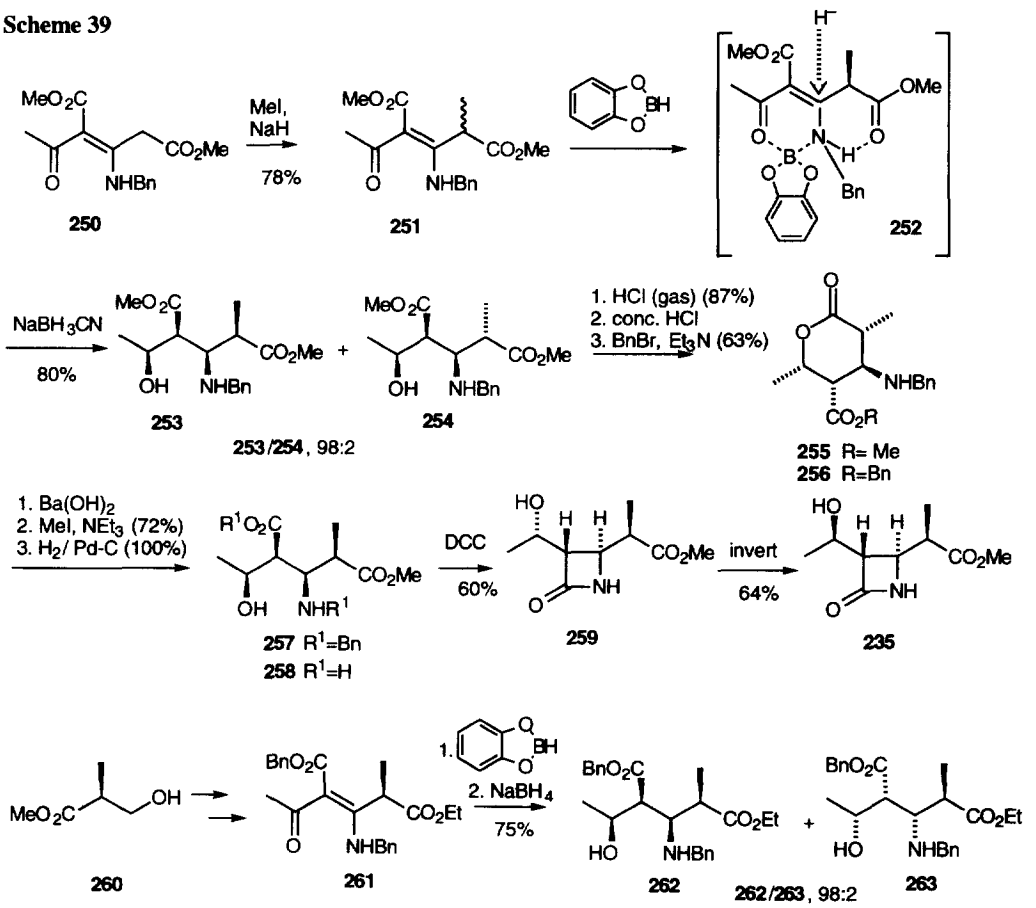


hydroxyethyl group. Mitsunobu inversion and saponification furnished the desired diasteromer **235** in racemic form. A nonracemic version of this methodology employed methyl (*S*)-(+)-3-hydroxy-2-methyl-propionate (**260**) as the chiral source.[70b] In several steps that were incompletely described, **261** was obtained from **260**, and the catecholborane mediated borohydride reduction gave **262**, a nonracemic analogue of **253**, with the same 98:2 selectivity seen in the racemic form of this reaction. A judicious selection of protecting groups in **262** allowed a simplified conversion to nonracemic **2**, without the ester exchange sequence.

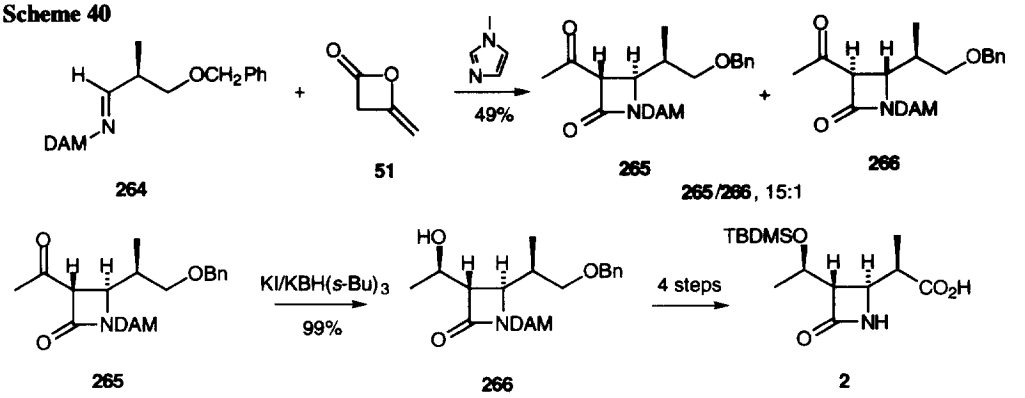
A [2+2] cyclization route to **2** has been elaborated by Terashima of the Sagami Chemical Research Center and Sumitomo Pharmaceuticals (Scheme 40),[71] in an approach closely related to the method illustrated in Scheme 9 for the synthesis of **1**.[19] Imine **264**, prepared in three steps in 87% yield from (*S*)-(+)-3-hydroxy-2-methyl-propionate (**260**, Scheme 39), was treated with diketene (**51**) in the presence of 4-methylimidazole to furnish a 15:1 mixture of diastereomeric ketones **265** and **266**, which were seperated by silica gel chromatography. The desired **265** was reduced with potassium *sec*-butyl borohydride to give **266** in a 16:1 ratio with the epimeric alcohol, seperated by silica gel chromatography.[13] Four additional functional group manipulations afforded **2** in 30% overall yield and nine steps from **260**.

Fukumoto, of Hoshi University,[72,73] and Terashima, of Sagami,[74] have reported cycloaddition routes to **2**, shown in Scheme 41, proceeding through the key intermediate isoxazolidine **272**, stereoselectively

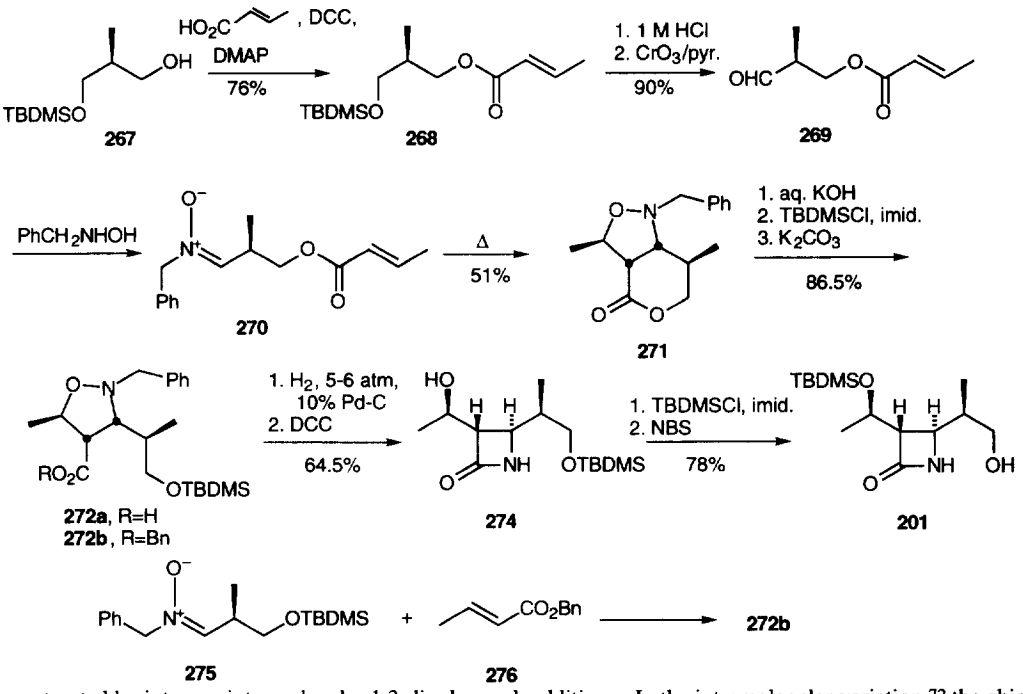
Scheme 39



Scheme 40



Scheme 41



constructed by intra- or intermolecular 1,3-dipolar cycloadditions. In the intramolecular variation,[72] the chiral alcohol **267**, obtained from (*R*)-methyl 3-hydroxy-2-methylpropionate in two steps and 86% yield, was condensed with crotonic acid to afford **268**. Deprotection and oxidation provided aldehyde **269**, which was transformed to nitrone **270** as a single isomer, on treatment with *N*-benzylhydroxylamine. When **270** was heated in refluxing *t*-amyl alcohol, cycloadduct **271** was formed as a single isomer. Saponification of the lactone followed by silylation and selective hydrolysis of the silyl ester furnished isoxazolidine **272a**. After hydrogenolytic ring cleavage, treatment with DCC induced cyclizaton to azetidinone **274**, and alcohol **201** was obtained following silyl functional group adjustments. Azetidinone **201** is known from several other studies and can be readily oxidized to **2** with PDC in 91% yield.[71b,5] Overall, this isomerically clean scheme

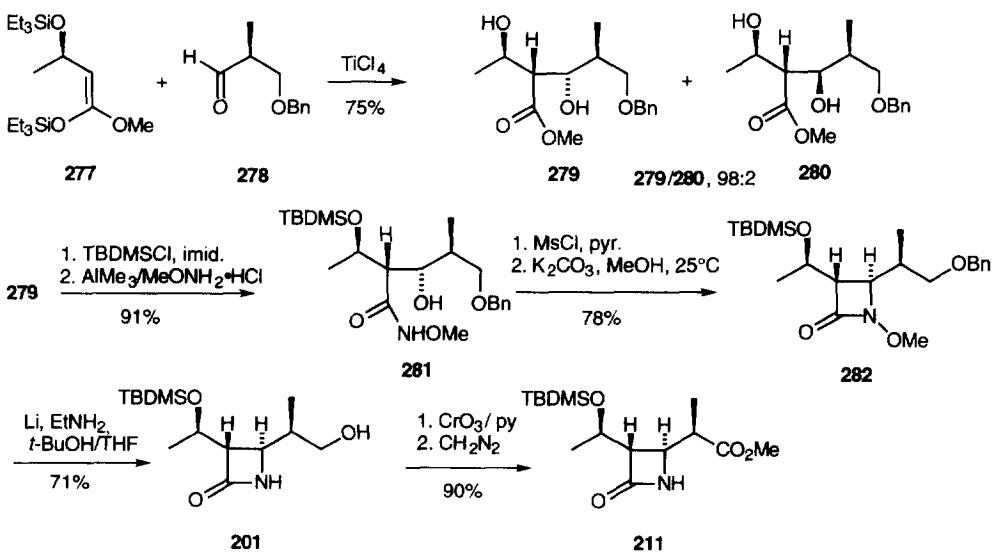
has 14 steps and gave an 11.9% yield from the inexpensive chiral starting material.

An earlier report by Fukumoto[73] and virtually identical chemistry by Terashima[74] describe the intermolecular variation of the reaction, by the cycloaddition of **275** with **276** in refluxing benzene to produce **272b**. However, this method gave **272b** as diastereomeric mixtures. Fukumoto isolated **272b** as one of several major isomers by HPLC, whereas Terashima stated in greater detail that four isomers of **272b** were formed in approximately equal amounts, indicating that the chiral center in **275** cannot control the facial selectivity of the cycloaddition. Both Fukumoto and Terashima carried **272b** forward to **201** under similar conditions to those in the Fukumoto intramolecular report.

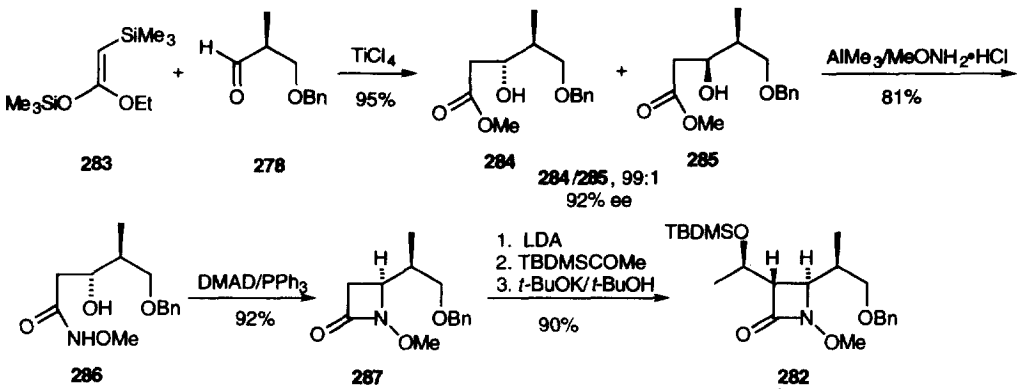
Nakai (of Fujisawa Pharmaceuticals and the Tokyo Institute of Technology) has demonstrated a double asymmetric aldol condensation route to **2**. This approach, shown in Scheme 42, provides highly stereoselective access to the acyclic intermediate **279**, which has the four contiguous stereocenters of **2**.[75] Ketene acetal **277**, derived from (*S*)-methyl 3-hydroxybutyrate, and aldehyde **278**, derived from (*S*)-methyl 3-hydroxy-2-methylpropionate, were condensed under chelation controlled aldol conditions to afford **279** in 75% yield and 50:1 diastereoselectivity. Cyclization was achieved via the hydroxamate **281**, obtained after selective silylation and a Lewis acid mediated hydroxylaminolysis. Mesylation and treatment with base produced azetidinone **282**. Birch reduction[76] concomitantly deprotected both the nitrogen and benzyl alcohol, and afforded the primary alcohol **201**, a well known intermediate.[71b,5] Oxidation and esterification gave **211**, the methyl ester of **2**, in 34% overall yield from **277**, and eight steps, making this one of the more efficient syntheses described in this review.

The same group also published a modified account that added the hydroxyethyl side chain at a later stage in the synthesis (Scheme 43).[77] Unfortunately, difficulties were encountered in the introduction of the side chain, and in an apparent loss of enantiomeric purity in the initial aldol reaction. The achiral silyl enol ether **283** was treated with **278** under the chelation controlled aldol conditions as described for the sequence in Scheme 42. Although and this substrate afforded a slightly higher yield and diastereoselectivity, the product **284** was found to be only 92% ee. The cause of the partial racemization was not determined, but obviously could be due to low ee in **278** or to racemization under the reaction conditions. Either case might have been masked in Scheme 42, because the second chiral center (i.e, in **277**) may exert some chiral induction that

Scheme 42



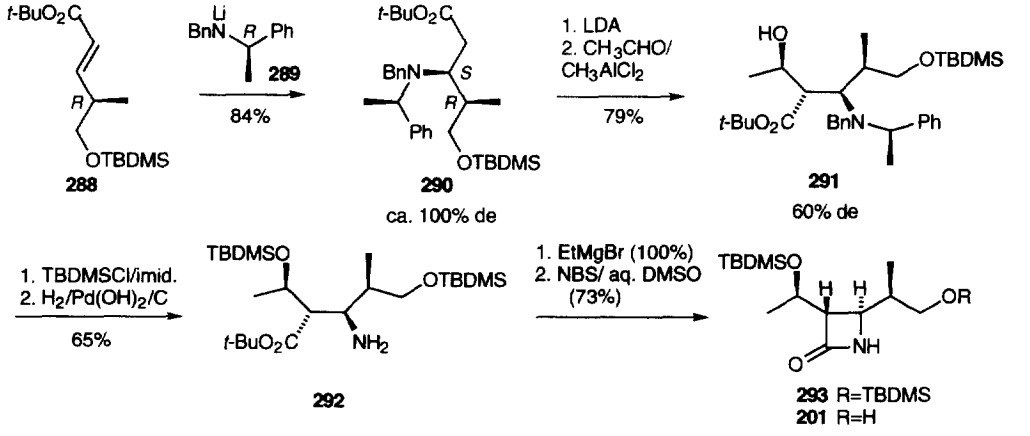
Scheme 43



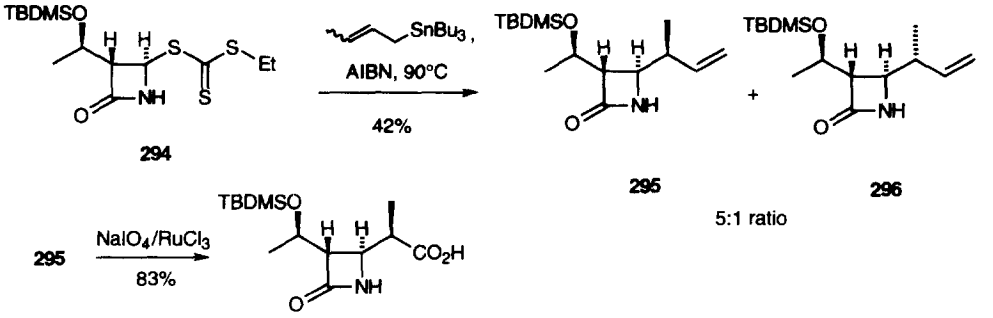
would be absent in Scheme 43. Ester **284** was converted to the hydroxamate **286** and cyclized with triphenyl phosphine and dimethyl azodicarboxylate (conditions that were unsuccessfully attempted in Scheme 42), to give azetidinone **287**. At this stage, introduction of the hydroxyethyl side chain was troublesome, and Nakai resorted to treating the enolate of **287** with *tert*-butyldimethylsilyl methyl ketone followed by a rearrangement, which afforded the desired **282** in 57% yield with 37% recovered **287** (the reaction could not be driven to completetion; the yield was 90% based on recovered **287**). More conventional aldol condensations with lithium or zirconium enolates gave inferior yields and diastereomeric product mixtures. Azetidinone **282** was carried through to **211** as shown in Scheme 42,[76] but the final product was only of 91% ee. Overall, this scheme gave a 46% yield (based on recovery of **287**) from **283** to **211** in nine steps, but given the loss of enantiomeric purity and the trouble with the late introduction of the side chain, this scheme seems to be inferior to the method described in Nakai's earlier report.

Another synthesis of **201** was reported by Yamamoto of Tohuku University, as shown in Scheme 44.[78] The α,β–unsaturated ester **288**, derived from methyl (*R*)-3-hydroxy-2-methylpropionate, was treated with the lithium salt of (*R*)-(*N*)-benzyl-(*N*)-phenylethylamine (**289**), to give the conjugate addition product **290** in essentially 100% diastereomeric purity. The lithium enolate of **290** was condensed with acetaldehyde in the presence of methyl aluminum chloride to furnish alcohol **291**, with the four contigous chiral centers required

Scheme 44

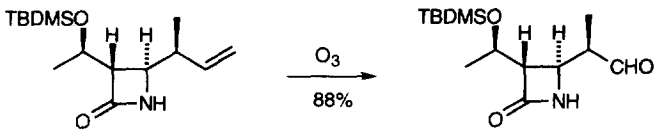


Scheme 45



in **2**, in 80% diastereomeric purity. Silica gel chromatography afforded pure **291**, and after two funtional group manipulations, treatment of **292** with ethyl Grignard reagent provided azetidinone **293**. Selective desilyation afforded primary alcohol **201** in 31% overall yield and seven steps from **288**.

Olefin **295** has been prepared as a key intermediate by several groups (Schemes 45, 46, 47, and 48). Fliri and Mak (Sandoz) approached the problem by stanyl allylation of derivatives of **1**, as shown in Scheme 45.[79] Thiocarbonate **294**, obtained quantitatively from azetidinone **1**, was treated with tri-*n*-butyl crotylstannane to give a 5:1 mixture of diastereomers with the desired **295** predominating. After chromatographic separation, **295** was converted to **2** via oxidation with sodium metaperiodiate and catalytic ruthenium chloride in 83% yield.[80] Overall, in terms of length and yield, three steps from **1** and a 35% yield, this is a very competitive scheme. A closely related reaction was reported in a patent by Fujisawa Pharmaceuticals, involving similar allyltins or allylsilyls that were reacted with **1** and its congeners.[81] A patent from Kaneka Chemical Industries described the transformation of **295** to aldehyde **297** via ozonolysis (eq. 7).[82]



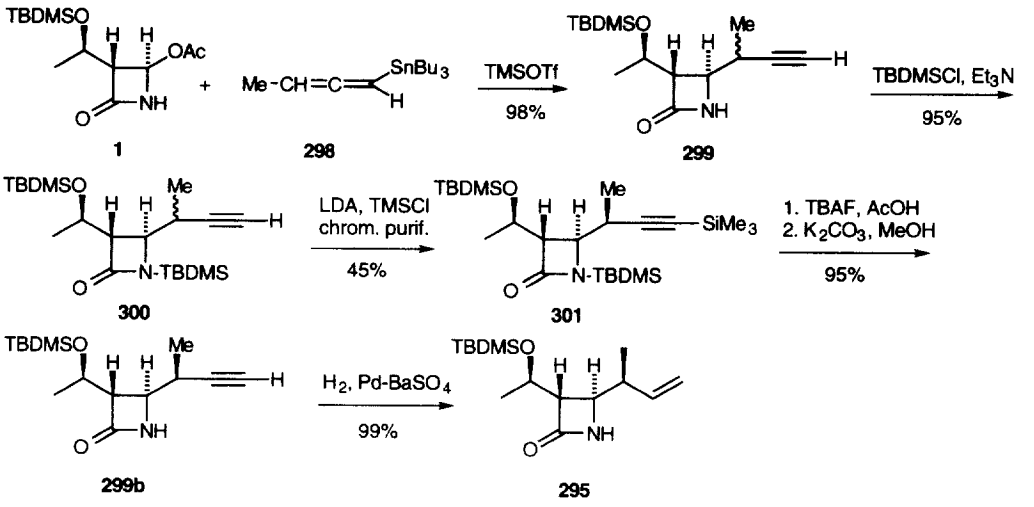
eq. 7

Haruta and Kita of Osaka University described another alkyltin approach to **295** (Scheme 46).[83] Azetidinone **1** was propargylated with 3-methyl-1-tributylstannlyallene to give **299** as a 1:1 epimeric mixture. Silylation of the nitrogen and the terminal alkynyl position permitted resolution on silica gel chromatography, and **301** was obtained after chromatographic separation of the α-methyl diastereomer. *N*-desilylation with TBAF followed by alkyl desilylation with potassium carbonate in methanol provided the β-methyl epimer **299b**, which was reduced via Lindlar reduction to **295**.

Uyeo of Shionogi & Co. also prepared **295** from **1** via an intramolecular Sakurai-type reaction, as shown in Scheme 47.[84] Azetidinone **1** was treated with (*Z*)-2-butenylchlorodimethylsilane **302** in the presence of triethylamine to give azetidinone **303**. Exposure of **303** to trimethylsilyltriflate furnished **295** in 84% overall yield from **1** after crystallization. The presumed intermediate was azetidinium ion **304**, which undergoes a sterocontrolled rearrangement. An attractive feature of this reaction is that only a single isomer of **295** was formed, and in excellent overall yield.

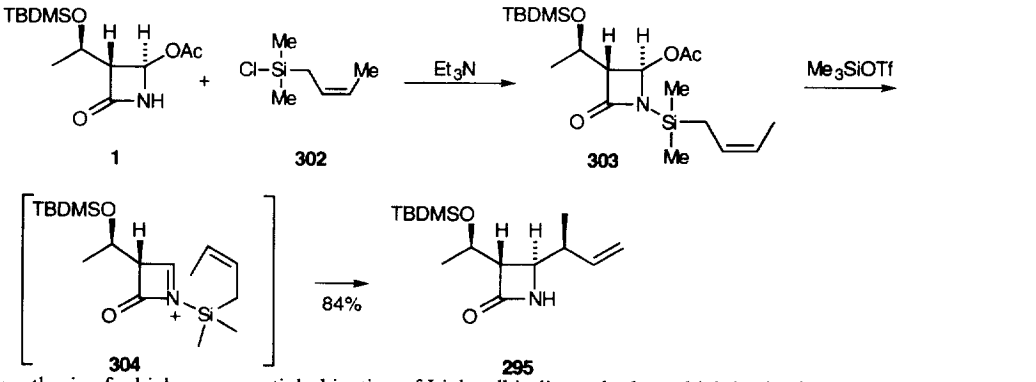
Liebeskind, of Emory University (and with support from Bristol-Myers), employed a propargyl-cobalt complex to achieve a high degree of selectivity in the formation of **2** (Scheme 48).[85] Ketone **305**, the

Scheme 46



1 298 299 300 301 299b 295

Scheme 47

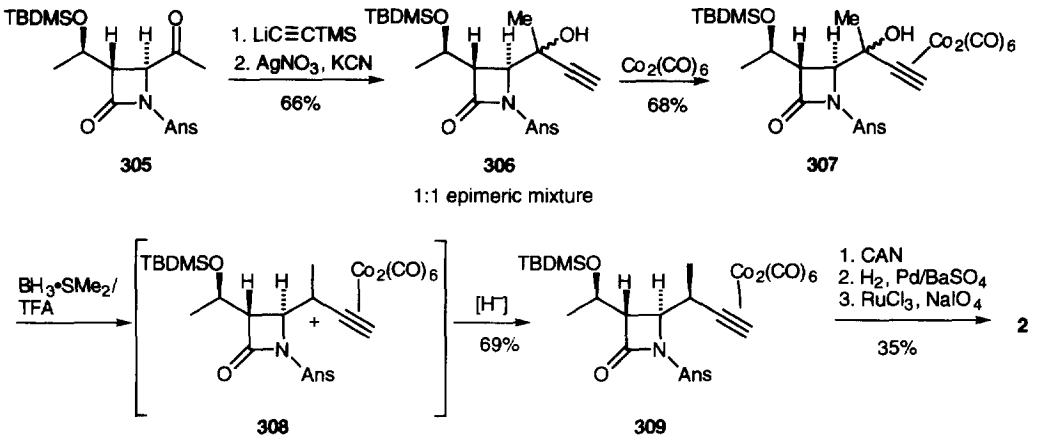


1 302 303 304 295

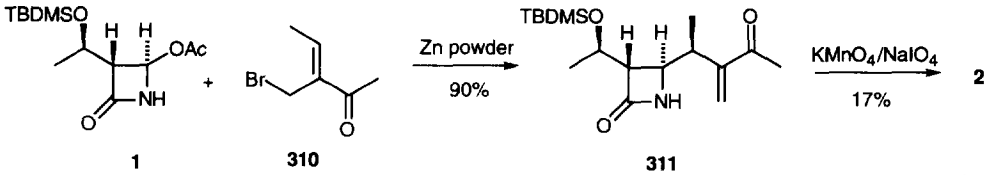
synthesis of which was a partial objective of Liebesdkind's study, but which is also known from other work discussed in this review relating to preparations of **1**,[86] was propargylated and selectively desilylated with silver nitrate to afford **306**, as a 1:1 mixture of epimeric alcohols. Propargylate **306** was complexed to hexacarbonyldicobalt, and subsequent reduction with borane gave **309** as a single epimer, via the intermediacy of the propargyl cation **308**, which was believed to be stabilized by the cobalt complexation, and allowed a stereocontrolled approach of the hydride. Treatment with ceric ammonium nitrate effected cobalt decomplexation and nitrogen deprotection in 50% yield (intermediate **299b** is not shown), and then Lindlar reduction to the olefin (i.e., **295**) and oxidative cleavage[80] furnished **2**.

Workers at Sankyo & Co. reported a very brief synthesis of **2** from **1** involving a permanganate oxidation of **311** to **2** (Scheme 49).[80b] Azetidinone **1** was condensed with (*Z*)-3-bromomethyl-3-penten-2-one (**310**) and the resultant olefin was oxidatively cleaved to **2**, although in rather poor yield. It is noteworthy that the condensation proceeds with apparently complete chiral induction to give only the β-methyl in **311**. Overall, this scheme provides a 15.3% yield, but given that just two steps are involved, it is potentially an attractive method.

Scheme 48

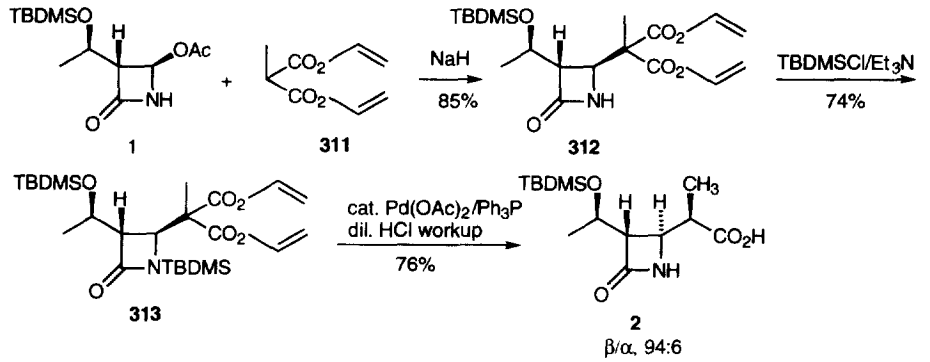


Scheme 49



Researchers at Takasago International Corp. have developed several notably efficient routes to **2**. In the method shown in Scheme 50, malonic diesters were prepared from azetidinone **1** and efficiently decarboxylated, providing a very rapid approach.[87] In the first step, **1** was alkylated with the enolate of diallyl methylmalonate generated from sodium hydride in DMF. The resulting diester **312** was *N*-protected, and then decarboxylated with catalytic palladium(0) and deprotected on dilute acidic workup to give **2** in 88% diastereomeric excess and 48% overall yield. There were several other methylmalonate esters disclosed in the specification, including ethyl, benzyl, and mixed *t*-butyl-ethyl malonated, but the allyl malonate **311** gave the best yields and diastereoselectivity in the last step. Likewise, other *N*-protecting groups studied included benzyl, *para*-anisyl, dimethylphenylsilyl, and triethylsilyl, but again in the Pd(0) dealkylation, the *N*-TBDMS function gave the best diastereoselectivity and yields. Attempts to perform the dealkylation, under a variety of

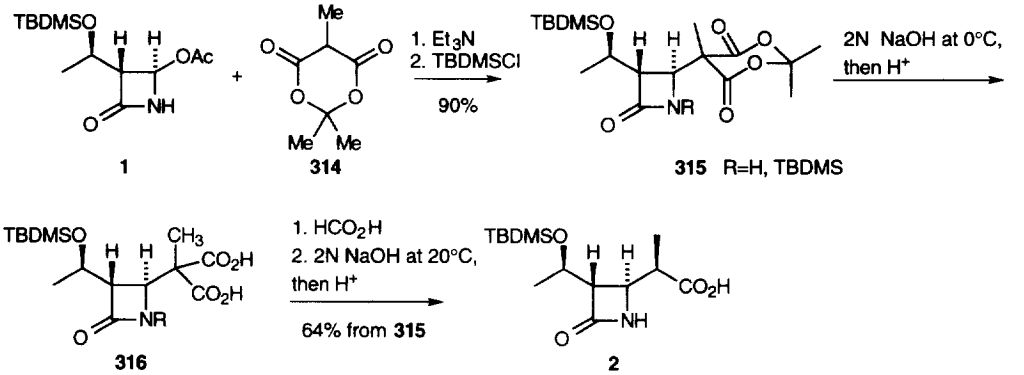
Scheme 50



conditions, on **312** or its corresponding alternative esters or the diacid gave, in each case reported, a predominance of the α-methyl isomer of **2**.

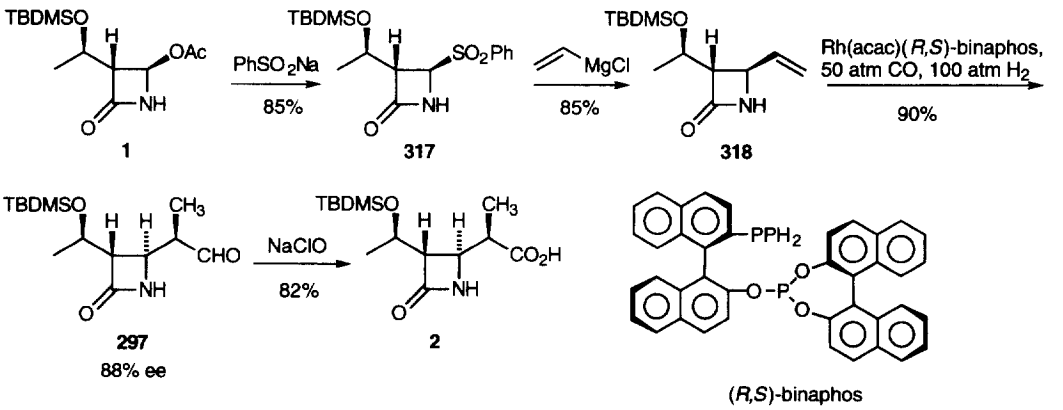
A group at Merck has published a conceptually related approach to **2** illustrated in Scheme 51.[88] Azetidinone **1** was coupled to 2,2,5-trimethyl-1,3-dioxan-4,6-dione **314** and *N*-protected with TBDMSCl, to furnish **315** (R=TBDMS). Hydrolytic ring opening of **315** afforded diacid **316** (R=TBDMS). The key decarboxylation step was accomplished with catalytic formic acid in refluxing ethyl acetate. The crude yield had a 94:6 ratio of β:α isomers. Selective removal of the *N*-silyl group was accomplished by treatment with aqueous sodium hydroxide. After crystallization, **2** was obtained in >99% diastereomeric purity in 58% overall yield and five steps. Attempts to decarboxylate **316** with R=H gave predominantly an undesired ring opened byproduct, presumably because the transition state has a different conformation than the case with a bulky protecting group on the lactam nitrogen.

Scheme 51



Another process from Takasago employed an asymmetric hydroformylation with chiral binapthyl rhodium complexes (Scheme 52).[89] Azetidinone **1** was sulfinylated to furnish **317** and alkylated with vinyl magnesium chloride to provide **318**. The key step was a rhodium catalyzed hydroformylation, with 2 mole % (*R,S*)-binaphos/rhodium catalyst and high pressures of carbon monoxide and hydrogen, to give **297**, which was easily oxidized to the desired product **2** with hypochlorite. A number of binaphthyl type catalysts were disclosed in the patent, but experimental data were provided only for the (*R,S*)-binaphos ligand shown. The overall yield for this method is 53% with four steps, all of which seem suitable for industrial scale application.

Scheme 52



4. Conclusions

Several of the methods described in this review demonstrate high efficiency and selectivity for the synthesis of azetidininones **1** and **2**. Attractive routes deriving chirality from inexpensive chiral starting materials, as well as efficient chiral induction methods from chiral catalysts, have been reported. Given the potential importance of second generation carbapenems with the 1-β-methyl substituent in the arsenal of antibacterial drugs, inexpensive approaches to **1** and **2** are imperative. Hopefully this review has put the substantial literature on the synthesis of **1** and **2** into perspective.

Acknowledgement: Dr. Martin (Mike) J. Weiss of the American Cyanamid Medical Research Division insightfully initiated this study. The support of family, colleagues, the American Cyanamid Company, and Wyeth-Ayerst Research is gratefully acknowledged in allowing this project to come to fruition.

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7. (a) Earliest Literature Ref: Oida, S. *Recent Advances in Beta Lactam Antibiotics*; Royal Society of Chemistry: London, 1981; pp 330-348. (b) This same work is presented in Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1981**, *29*, 2899-2909. (c) Method B is disclosed in Ohki, E.; Oida, S.; Yoshida, A.; Hayashi, T.; Sugawara, S. U.S. Patent US 4395418, Jul. 26, 1983 (Derwent WPI 81-95037D).
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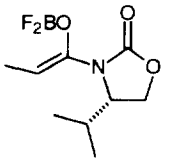

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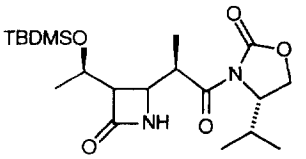

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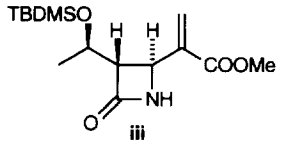

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