Pergamon

Tetrahedron, Vol. 52, No. 44, pp. 13803-13835, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00822-8

TETRAHEDRON REPORT NUMBER 408

Trans-4-Hydroxy-L-Proline, a Useful and Versatile Chiral Starting Block

Philippe Remuzon

Bristol-Myers Squibb Pharmaceutical Research Institute
Chemical Process Research Lognes
BP 62, 77422 Marne-La-Vallée Cedex 2, France

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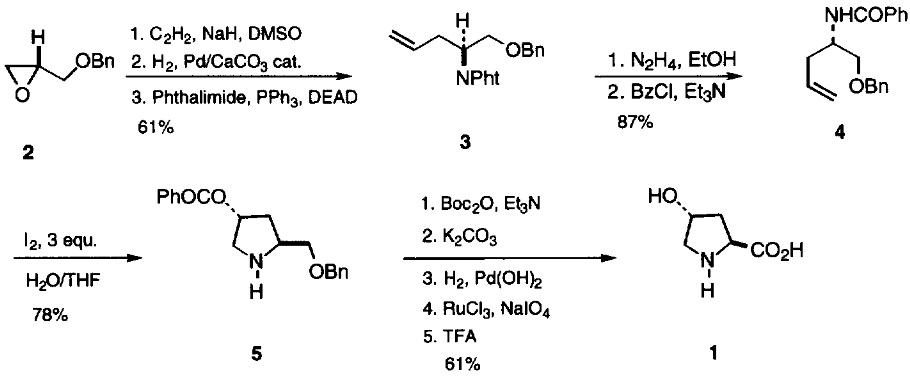
1. Introduction

Trans-(2*S*,4*R*)-4-hydroxy-L-proline **1** (L-Hyp) is present in both plants and animals. In plants hydroxyproline residues are bound to small lateral chains of polysaccharides to form glycoproteins.[1] In animals proline residues of protocollagen are hydroxylated to hydroxyproline. Hydrogen bonds between these hydroxylated residues are used to stabilize the triple helix of protocollagen.[2] L-Hyp is isolated from gelatin hydrolysates[3] together with proline. The (2*S*,4*R*) isomer is the most abundant of the three naturally occurring diastereomers. As a constituent of collagen, L-Hyp is a non-essential amino acid and is found in a number of secondary metabolites such as echinocandins,[4] etamycin, etc.

With its two chiral centers at C-2 and C-4, L-Hyp is a material of choice to access multifunctionalised pyrrolidine rings. Substitutions at all positions of the pyrrolidine ring are possible. Substitution at C-3 has been rendered possible thanks to the 4-hydroxy group by oxidation or olefin formation. Functionalisation at C-5 *via* oxidation reactions of this position has also been described. Inversion at C-2[5] and/or at C-4[6,7] was easily achieved leading to all four possible isomers of L-Hyp. Decarboxylation of L-Hyp was also found to be an easy way to access chiral 4-hydroxypyrrolidines.[8] L-Hyp allows access to a large variety of chiral molecules such as glutamic acids analogues, kainic acids, arginine analogues, carbapenems, natural products such as lycoperdic acid, bulgecins, echinochandins or didemnins, and also fully synthetic piperidines and pyrrolidines, benzodiazepins, puromycin analogues, baclofen, quinolones and naphthyridones, etc. We describe in this report the most recent papers[9] using L-Hyp as starting material.

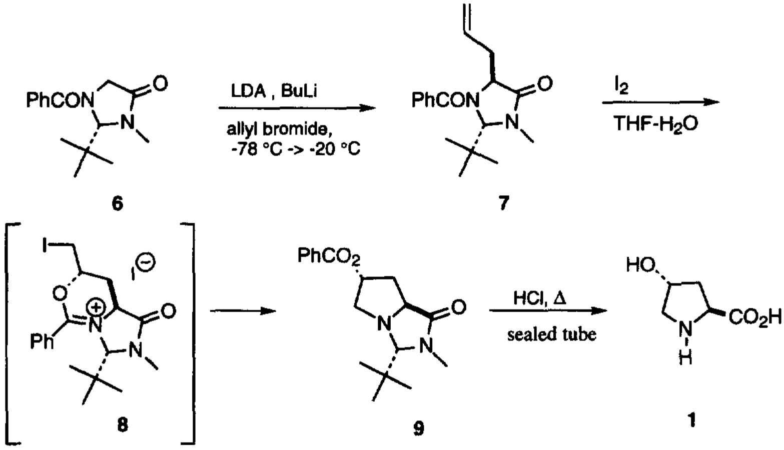
2. Synthesis of L-Hyp

Although L-Hyp **1** is commercially available and inexpensive, recently some authors reported an efficient synthesis. Takano[10] prepared L-Hyp **1** in a ten-step sequence (Scheme 1) using (*S*)-*O*-benzylglycidol **2** as starting material. After acetylene substitution of epoxide **2** and reduction of the resulting pentynol derivative, a Mitsunobu reaction with phthalimide furnished derivative **3**, which was reacted with hydrazine followed by benzoylation to afford **4**. Cyclisation occurred with **4** in the presence of iodine to obtain 4-benzoate-2-prolinol **5** which was protected with a Boc group, oxidized, and further deprotected to give **1**. The overall yield from **2** was 25%.



Scheme 1

Using a similar methodology, Thirring *et al.* [11] developed an enantioselective three-step synthesis starting with Seebach's compound **6** in 67.5% overall yield (Scheme 2). Diastereoselective introduction of an allyl group,



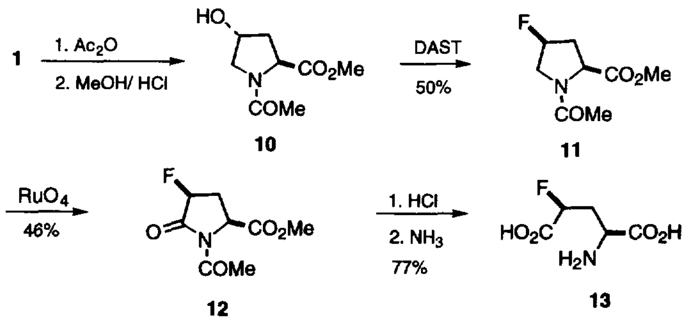
Scheme 2

followed by a cyclisation with iodine *via* intermediate **8** furnished bicyclo derivative **9** after rearrangement. Finally acidic hydrolysis of **9** in a sealed tube led to L-Hyp **1**.

3. Proline derivatives

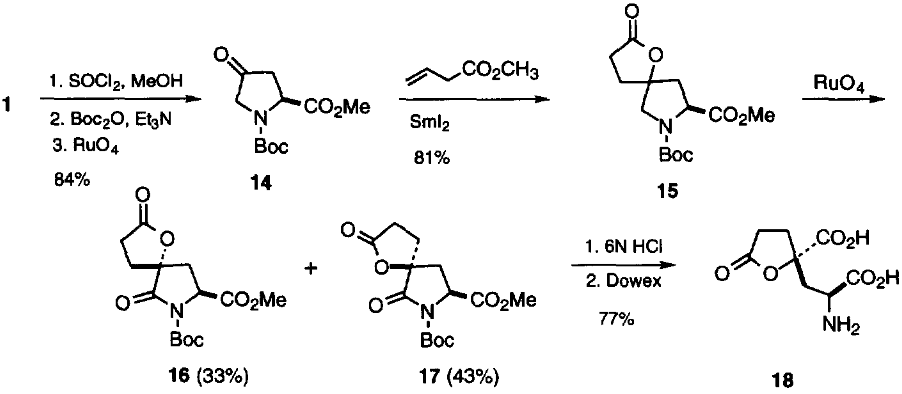
3.1. Fluoroprolines and mimetics of glutamic acid

Fluorinated proline **11** was prepared by Hudlicky[12] from L-Hyp by acetylation, esterification, and fluorination with DAST, with inversion of stereochemistry, as described by Young[13] in 50% yield (Scheme 3). After oxidation of **11** with RuO_4 and acidic hydrolysis, L-*threo*-4-fluoroglutamic acid **13** was obtained in 77% yield. Hydrolysis of **11** also led to *cis*-4-fluoro-L-proline as reported by the same author[14].



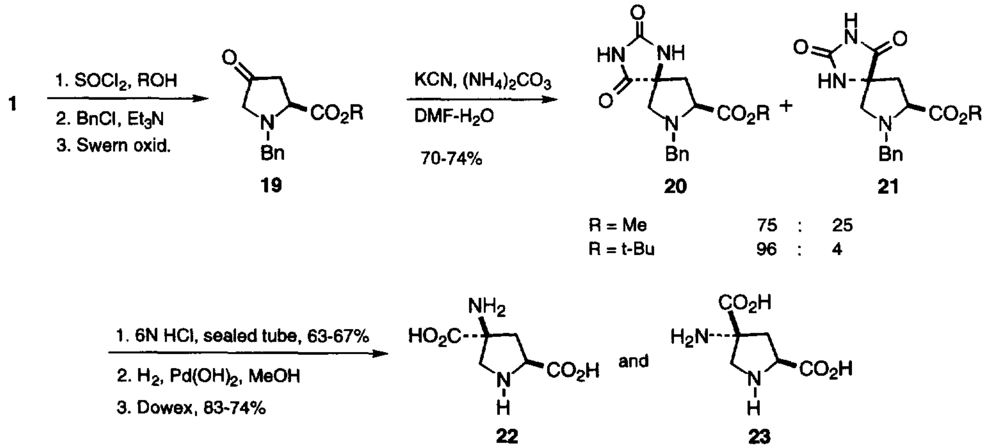
Scheme 3

Lycoperdic acid **18** was prepared according to Yoshifuji[15] by reductive cross coupling of **14** with methyl acrylate to afford **15** which on oxidation (with RuO_4) gave a mixture of two diastereomeric spirolactones **16** and **17** (Scheme 4).



Scheme 4

Separation of the pyroglutamic acid derivatives **16** and **17**, followed by acidic hydrolysis led to the non-proteinogenic α-amino acid **18** in 23% overall yield from **1**. Asymmetric syntheses of all four isomers of 4-amino-4-carboxyprolines as conformationally restricted analogues of glutamic acid were performed recently by Tanaka[16] (Scheme 5).

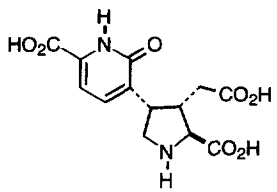


Scheme 5

The key step employed a Bucherer-Bergs reaction, in which the diastereoselectivity was strongly influenced by the ester at C-2 of the proline ring. After separation of both C-4 isomers, hydrolysis of hydantoins **20** and **21** and hydrogenation afforded the diastereomers **22** and **23** respectively. The corresponding enantiomers were obtained after inversion at C-2 of **19**.

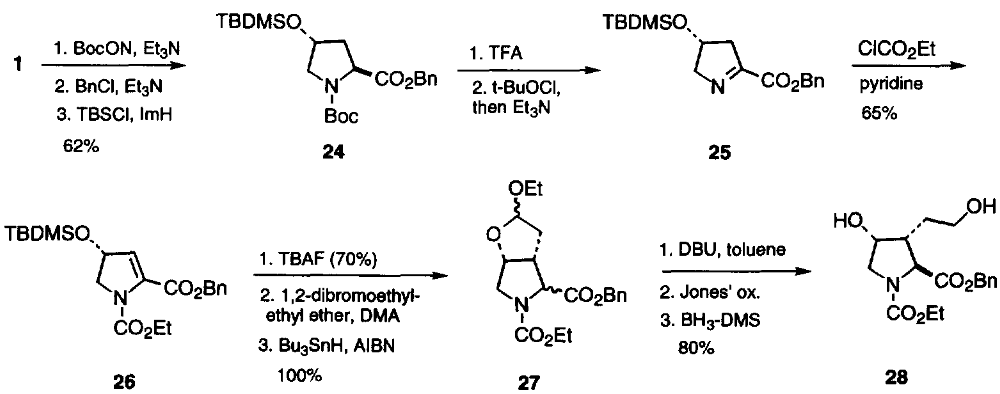
3.2. Kainoid analogues

The kainoid amino acids and in particular the acromelates (which include acromelic acid A) were found to be more highly neuroexcitatory than any known glutamate related derivatives.[17] Synthetic pathways to generate these type of compounds have been intensively studied.[18]



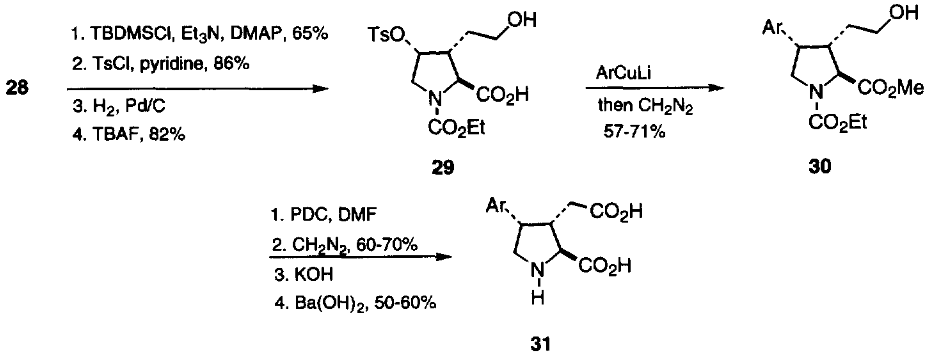
acromelic acid A

A general method for the preparation of acromelic congeners was disclosed by Shirahama[19] which introduced enantioselectively an aromatic ring at C-4 and a 2-acetic acid function at C-3. The first key step was radical ring closure of a 2,3-dehydro amino acid benzyl ester **26** to give bicyclo derivative **27** as a mixture of four diastereomers due to the two asymmetric centers at C-2 and the acetal carbon (Scheme 6). The substituent at C-2 was epimerized to the β-configuration by means of DBU. Jones oxidation of the acetal function of the 2β-epimer of **27** to a lactone followed by selective reduction by BH_3-DMS afforded diol **28** in 32% overall yield from **1**.



Scheme 6

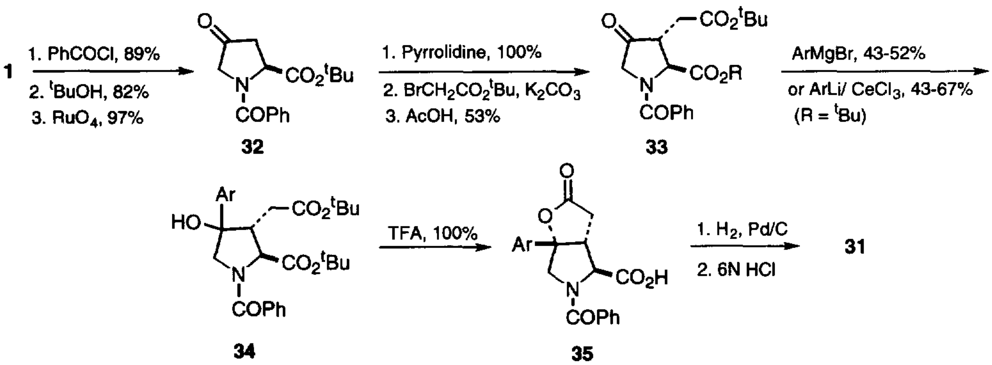
One other key step in the sequence[19] was introduction of an aromatic moiety at C-4 of tosylate **29** by the known reaction[20,21] of lithium diarylcuprates with a 4-tosyloxyproline with retention of configuration (Scheme 7). The resulting methyl esters were obtained in the following yields: Ar = Ph, 57%; Ar = *o*-anisyl, 58%; Ar = *p*-anisyl, 59%; Ar = *o,p*-diMeOPh, 71%.



Scheme 7

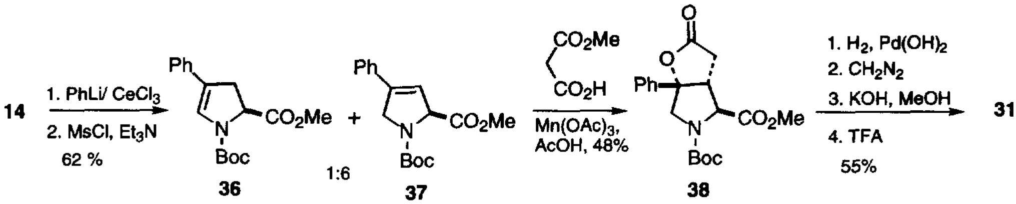
Finally oxidation of the primary alcohol of **30**, methylation of the resulting diacid, and basic hydrolysis furnished acromelic acid analogue **31** (Scheme 7).

Baldwin[22] disclosed other approaches by stereoselective alkylation with *t*-butyl bromoacetate at C-3 of a 4-ketoproline derivative **32** after enamine formation with pyrrolidine (Scheme 8). Aryl groups were introduced stereoselectively through Grignard reagents in Et_2O to obtain carbinols **34** in 43-52% yield. Fused enantiomerically pure bicyclic lactone **35**, arising from trifluoroacetic acid treatment, afforded, after smooth hydrogenation with inversion of configuration at C-4, diacids **31**.



Scheme 8

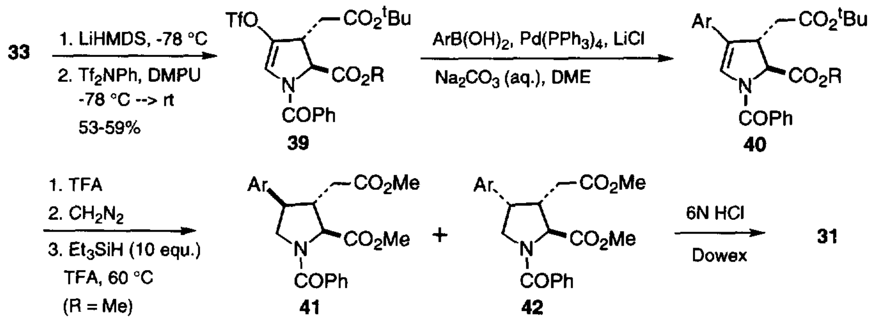
Shirahama[23a] very recently reported a related procedure to prepare **31** from **14** in eight steps (Scheme 9). After separation of the mixture of dehydroproline **36** and **37**, resulting from phenyl lithium-$CeCl_3$ addition[23b] to



Scheme 9

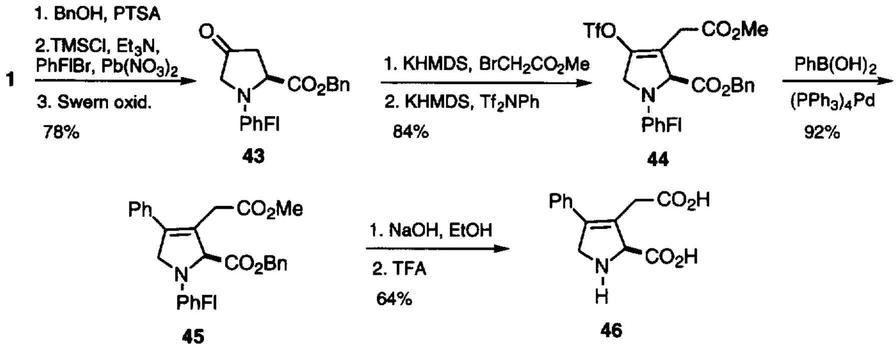
14 and elimination by means of triethylamine, the Δ^3-phenyldehydroproline **37** (Scheme 9) was treated with monomethyl malonate to give lactone **38** which after hydrolysis and deprotection afforded **31** (Ar = Ph).

A modified procedure was also described by Baldwin[24] using vinyl triflates **39** (Scheme 10). Phenylboronic and three anisylboronic acids were found to couple with both *tert*-butyl and methyl esters of **39** in 46-62% and 68-89% yields, respectively (R = Me, Ar = Ph, 73%; Ar = 2-MeOPh, 89%; R = *t*-Bu, Ar = Ph, 46%; Ar = 2-MeOPh, 52%). After hydrolysis of **40** and re-esterification with CH_2N_2, the resulting dimethyl esters were reduced with triethylsilane to give an approximately equal ratio of epimers **41** and **42** in 60% combined yield.



Scheme 10

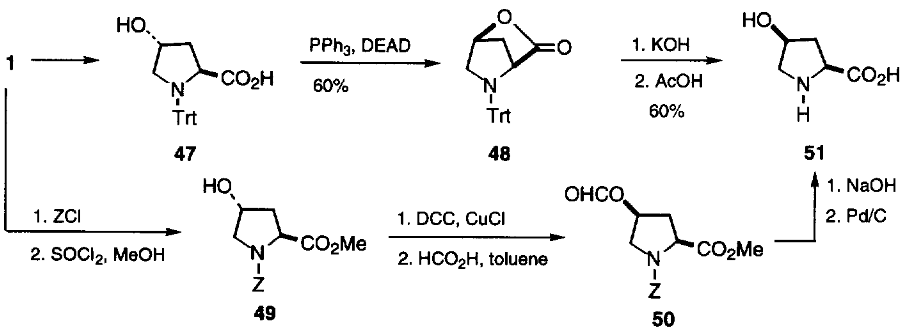
More recently, Lubell[25] disclosed the synthesis of (2*S*)-3,4-dehydro-4-phenylkainic acid **46** in eight steps and 39% overall yield (Scheme 11). After esterification of **1**, protection of the nitrogen of proline with a 9-(9-phenylfluorenyl) moiety (PhFl) and Swern oxidation, derivative **43** was converted to enol triflate **44** by means of *N*-phenyltrifluoromethanesulfonimide (Tf_2NPh). Alkylation at C-3 of this dehydroproline took place without racemization at the chiral C-2 center. Palladium-catalyzed cross-coupling of the resulting triflate **44** with phenylboronic acid gave styrene derivative **46** after deprotection of the two esters and the *N*-phenylfluorenyl groups in good yield.



Scheme 11

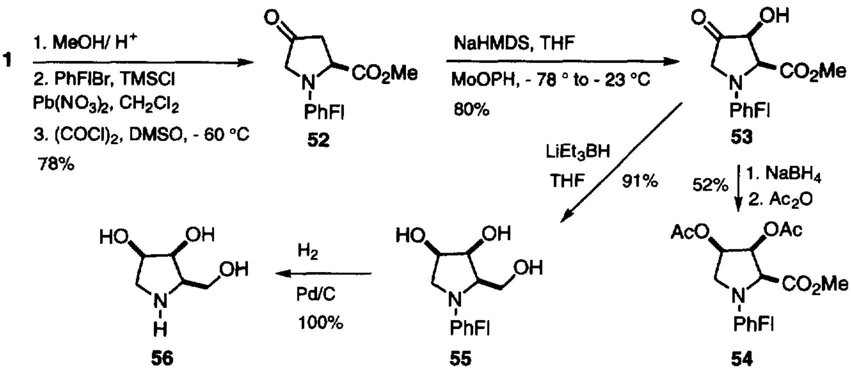
3.3. Hydroxyprolines

Papaioannou[6] reported the inversion of the hydroxyl group at C-4 in a Mitsunobu reaction *via* an intermediate lactone **48** (Scheme 12). More recently, Seki[7] described the preparation of (2*S*, 4*S*)-4-hydroxyproline **51** *via* a formate intermediate **50** in 5 steps and in 73% overall yield (Scheme 12).



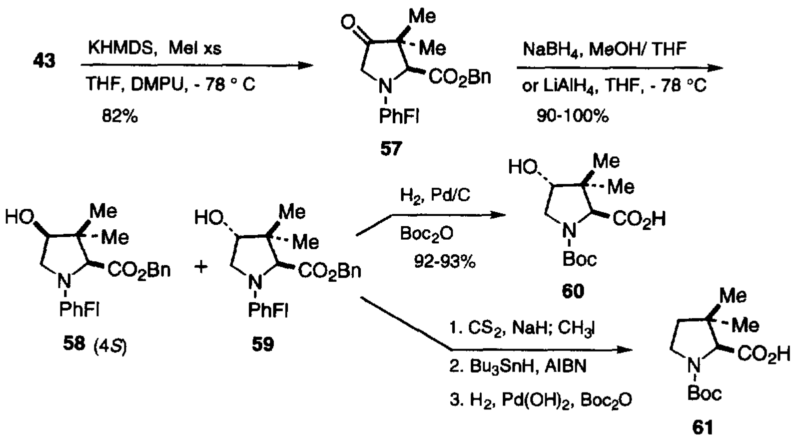
Scheme 12

Sardina[26] reported a stereoselective synthesis of **56**, a galactosidase inhibitor (Scheme 13). Regio- and stereoselective introduction of the hydroxyl group at C-3 was achieved by treatment of **52** with NaHMDS followed by oxidation of the corresponding enolate with MoOPH. Reduction of **53** with $LiEt_3BH$ led to triol **55** whereas with $NaBH_4$ reduction, followed by acetylation with Ac_2O diacetate **54** was obtained. Deprotection of proline **55** by hydrogenation to form prolinol **56** was quantitative. The overall yield from **1** to **56** was 57%.



Scheme 13

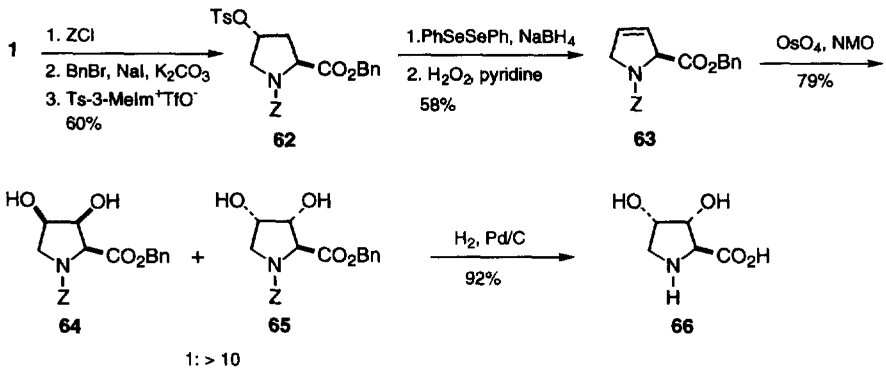
Very recently, Lubell[27] described the synthesis of the C-3 dimethylated proline derivative **57** by deprotonation of 4-oxoproline **43** with an excess of potassium hexamethyldisilazane (KHMDS) (Scheme 14). Reduction with $NaBH_4$ provided quantitatively a 3:2 mixture of 4-hydroxyprolines **58** and **59** whereas with $LiAlH_4$ a 1:2 ratio of **58** and **59** was encountered in favor of the (4*S*)-isomer.



Scheme 14

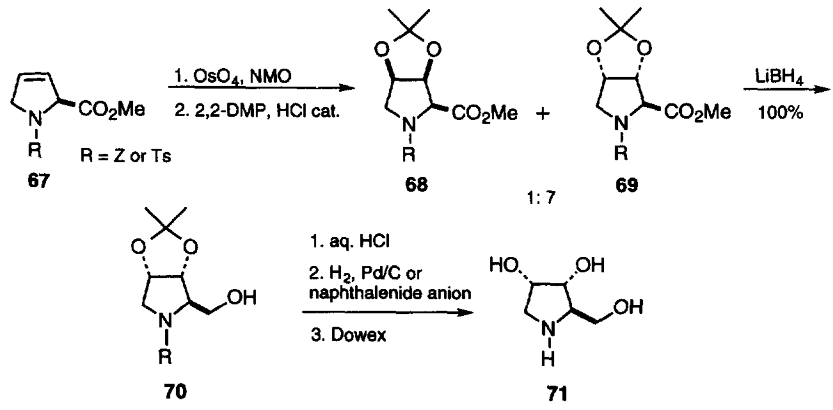
Hydrogenation of **59** in the presence of di-*tert*-butyldicarbonate (Boc_2O) afforded proline **60** in excellent yield (Scheme 14). Xanthate analogues of **58** and **59** were prepared in quantitative yield by thioacylation/alkylation of the hydroxy group. Reduction of the xanthate of **59** with tributylstannane (Bu_3SnH) and AIBN as radical initiator in refluxing xylene gave an excellent yield (91%) of the corresponding 3,3-dimethylproline. Hydrogenation of this proline in the presence of Boc_2O furnished **61** in 41% overall yield from **1**.

After tosylation of 2-benzyl ester proline analogue of **49** at C-4 with triflate of 1-methyl-3-tosylimidazole (Ts-3-MeIm$^+$ TfO$^-$), Baldwin[28] prepared 3,4-dehydroproline **63** according to Rüeger's[29] method *via* a phenylseleno derivative (Scheme 15). Derivative **63** was dihydroxylated with osmium tetraoxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO), to give predominantly **65**, by addition to the face opposite the ester group. Benzyl ester **65** gave 3,4-dihydroxyproline **66** after hydrogenolysis (Scheme 15).



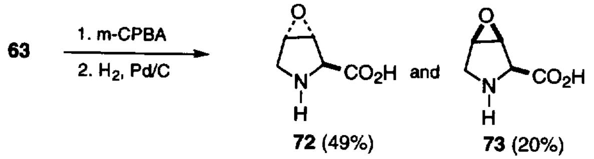
Scheme 15

Slama,[30] using the same methodology as above, performed OsO_4 dihydroxylation of 3,4-dehydroproline **67** in the presence of NMO in a 7:1 ratio to afford acetals **68** and **69** in 70% yield (Scheme 16). The protected diols **69** were quantitatively reduced to **70** while the *cis*-isomers **68** were found to be resistant to $LiBH_4$. The overall yield from **67** (R = Z) to **70** was 70%. Removal of the isopropylidene acetal followed by cleavage of the *N*-protecting group afforded the (2*R*,3*R*,4*S*)-prolinol **71** in 80-90% yield from **70**.



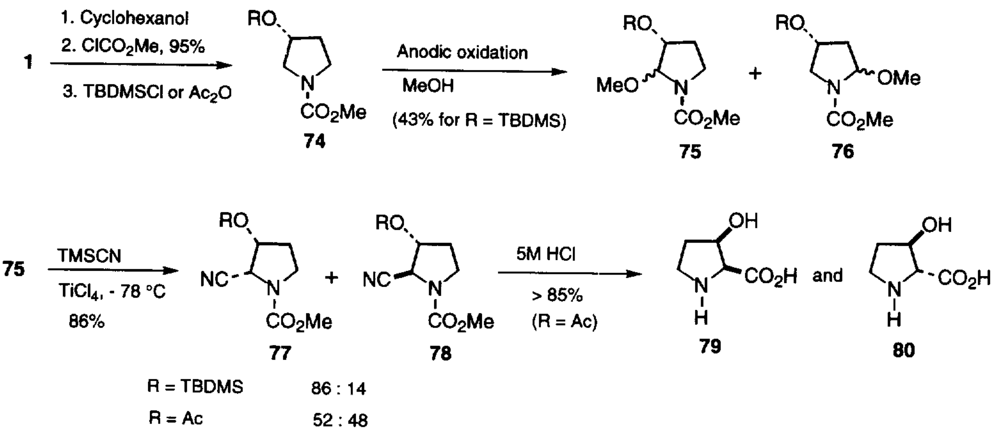
Scheme 16

Baldwin[28] obtained protected epoxides by known methods using *meta*-chloroperbenzoic acid (m-CPBA) which after hydrogenation afforded in good yield 3,4-epoxyprolines **72** and **73** (Scheme 17). It was demonstrated that epoxidation of 3,4-dehydro-L-proline was catalytically epoxidized in a *trans* fashion by proline-4-hydroxylase to furnish exclusively **72**.



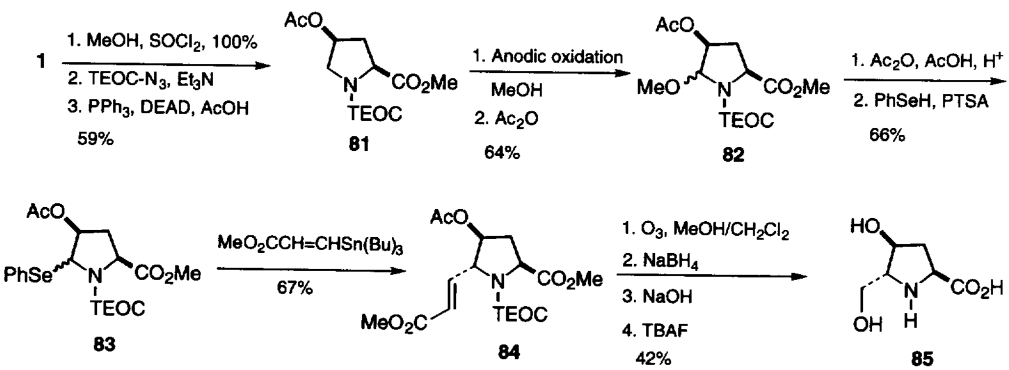
Scheme 17

Wistrand[31] disclosed anodic α-methoxylation of pyrrolidinol **74**, after decarboxylation at C-2 and *N*-protection with a methyl carbamate group (Scheme 18). No regioselectivity was found in the electrochemical methoxylation



Scheme 18

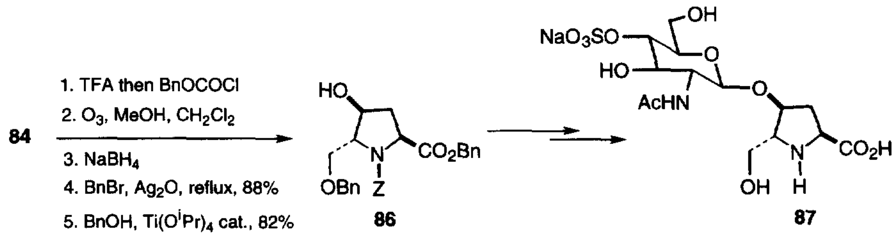
reaction, which gave an equal ratio of **75** and **76**. Substitution of the 2-methoxy group with a cyano group, *via* an



Scheme 19

iminium ion, was shown to occur predominantly in a *cis* fashion with a *t*-butyldimethylsilyloxy substituent at C-3 (Scheme 18). Under the same conditions, no diastereoselectivity was observed with a 3-acetoxy group. Hydrolysis of the resulting 3-acetoxycyano compounds **77** and **78** gave the *cis*-and *trans*-(3*R*)-3-hydroxyprolines **79** and **80** in good yield.

In similar fashion, Barrett[32,33] demonstrated the influence of structure on the efficiency of the electrochemical C-5 oxidation of (2*S*,4*S*)-4-hydroxyproline *N*-trimethylsilylethoxycarbonylcarbamate (TEOC) esters **81** (Scheme 19). The key step was the stereospecific free radical substitution reaction at C-5 to produce acrylate derivative **84** which after ozonolysis, $NaBH_4$ reduction, and deprotection furnished bulgecinine **85**, the aglycon of bulgecins.

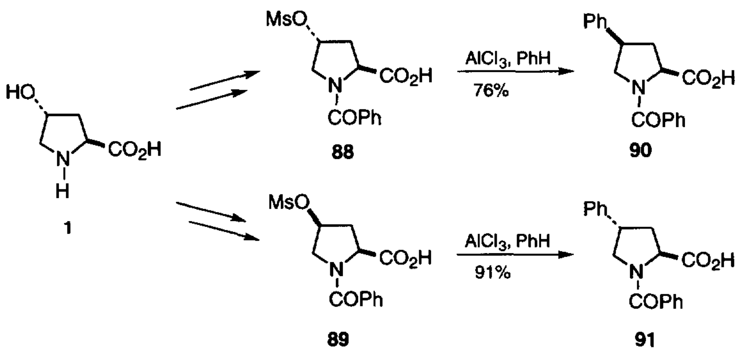


Scheme 20

After judicious protection of **84**, and after several additional steps, Barrett was able to synthesize bulgecin C **87** via a β-stereoselective glycosidation, regiospecific C-4' sulfation, and deprotection of benzyl groups using transfer hydrogenation with formic acid and palladium black (Scheme 20).

3.4. Other proline derivatives

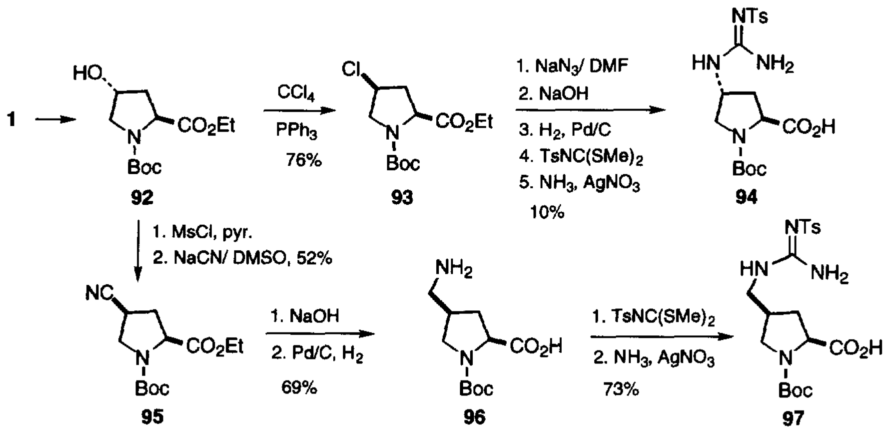
As indicated previously, displacement of 4-sulfonyloxyprolines with lithium diarylcuprates proceeds with retention of configuration.[19,21] Alternatively, Kronenthal[34] has demonstrated inversion of configuration



Scheme 21

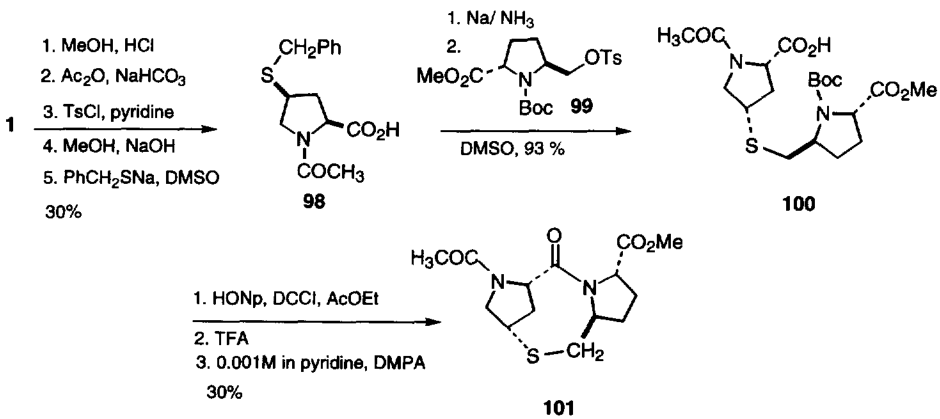
under Friedel-Crafts conditions. Thus, treatment of **88** and **89** (Scheme 21), both readily prepared from *trans*-L-Hyp **1**, gave **90** and **91**, respectively, with benzene-$AlCl_3$. The saturated congener of **91**, *trans*-4-cyclohexyl-L-proline, is the amino acid component of the antihypertensive agent Fosinopril.

Webb[35] reported the practical synthesis of conformationally constrained, protected arginine analogues which should be useful as probes for understanding protein-peptide interactions (Scheme 22). After chlorination of **92**



Scheme 22

at C-4 with inversion of configuration, azidonation, hydrolysis of the ethyl ester, and hydrogenation, an amino acid was isolated. When this amino acid was allowed to react with *S*,*S*-dimethyl-*N*-[(*p*-toluenesulfonyl)imino]di-

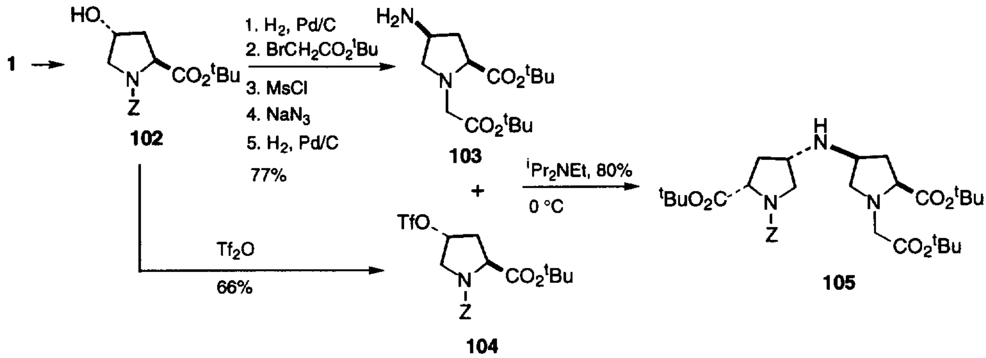


Scheme 23

thiocarboimidate, arginine analogue **94** was isolated after treatment with $AgNO_3$ (Scheme 22). The higher guanidino homologue **97** was prepared using a similar sequence[35] through cyano derivative **95.**

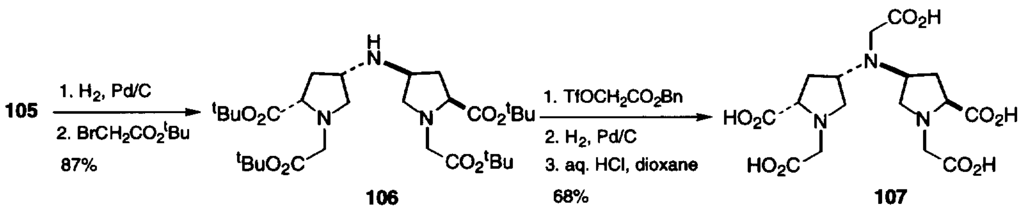
Kemp[36] described the preparation of the tricyclic derivative **101**, a conformationally restricted analogue of acetyl-L-prolyl-L-proline (Scheme 23). L-Hyp **1** furnished derivative **98** in 30% yield. Coupling of **98** and **99**, prepared from 2,5-dibromoadipate, afforded adduct **100** in excellent yield. Conversion of **100** to a *p*-nitrophenyl ester (ONp) was followed by high dilution cyclisation in pyridine to lead to the desired lactam **101**.

Rapoport[37] disclosed the synthesis of conformationally constrained diethylenetriaminepentaacetic acid (DTPA) analogues in an effort to probe the relationship between ligand structure and metal complex stability (Schemes 24 and 25).



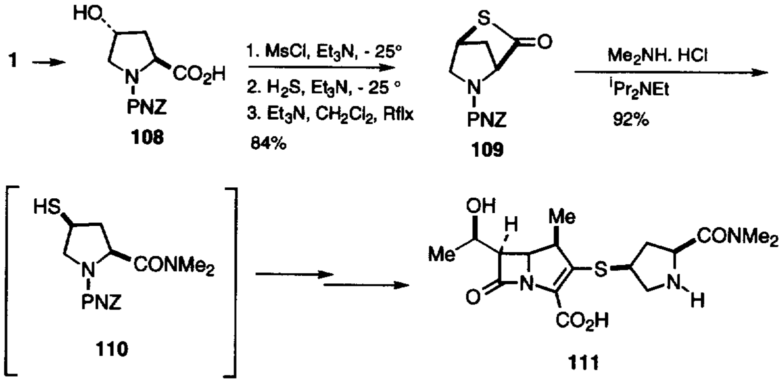
Scheme 24

The key step was the condensation of 4-aminoproline **103** with 4-*O*-triflate proline **104**, also obtained directly from **1** after *N*- and carboxylic protections and triflation of the 4-hydroxyl group (Scheme 24). The 4,4'-aminobispyrrolidine **105** was then hydrogenated and *N*-alkylated on the unsubstituted pyrrolidine. The exocyclic amino group was easily alkylated with the triflate of benzyl glycolate. After deprotection, the pentaacid **107** was isolated in 68% yield from **106** (Scheme 25).



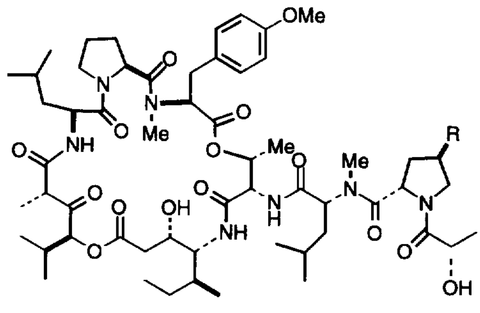
Scheme 25

A synthesis of the pyrrolidine part of meropenem **111** was recently described by Sunagawa.[38] Derivative **109**, a key intermediate, was prepared from *N*-[[(4-nitrobenzyl)oxy]carbonyl] derivative **108**, a *N*-PNZ-protected derivative of **1** through mesylation, thiol substitution of the resulting mesylate, and cyclisation with Et_3N (Scheme 26). Intermediate **109** was used in a one-pot amidation (compound **110**) and substitution of a 2-[(di-



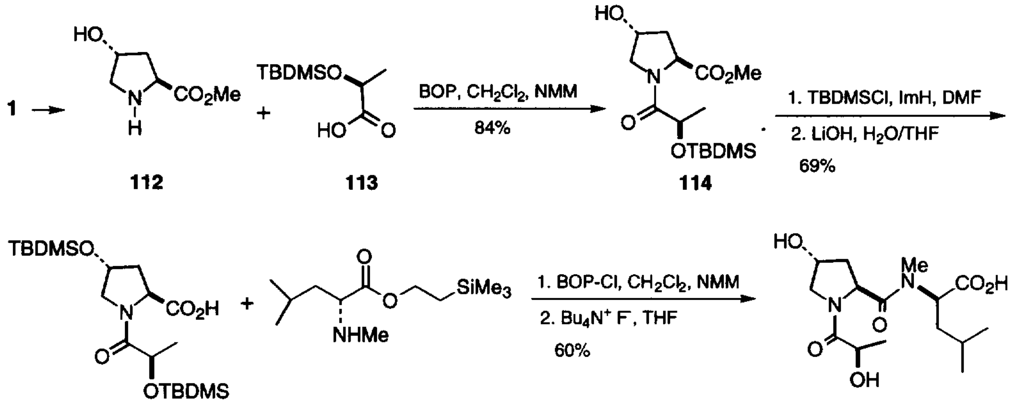
Scheme 26

phenylphosphono)oxy]-1-methylcarbapenem derivative. After deprotections of the *p*-nitrobenzyl ester group on carbapenem and the *N*-PNZ group of the 2-(4-thio-4-yl-prolinamide) side-chain, antibacterial agent meropenem **111** was obtained (Scheme 26).



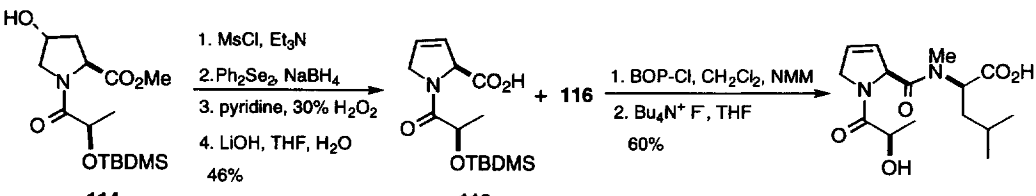
didemnin B (R = H)

The didemnins are a class of novel cyclodepsipeptides, with a common macrocycle and a variable side chain attached to the backbone *via* the amino group of a threonine residue. Joullié[39] introduced modifications of the R side chain of didemnin B. In particular, a hydroxy group at C-4 of the proline was thought to increase the polar nature of the molecule. Unsaturation at C-3-C-4 of the proline ring was also selected to increase rigidity of the ring.



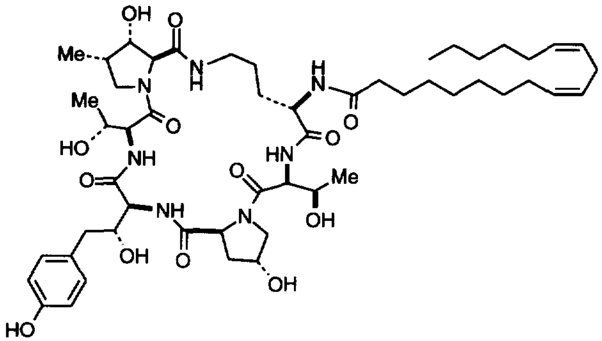
Scheme 27

The lactylhydroxyproline didemnin B side chain was prepared in good yield by coupling **112** with **113** using the (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate coupling reagent (BOP) (Scheme 27). The following step consisted in coupling of acid **115** using the *N,N*-bis(2-oxo-3-oxazolidinyl)phosphonic chloride coupling reagent (BOP-Cl) with amine **116**, obtained from D-leucine in 4 steps and 76% yield, which in turn furnished proline **117** after quantitative deprotection of the hydroxyl and carboxylic acid groups.



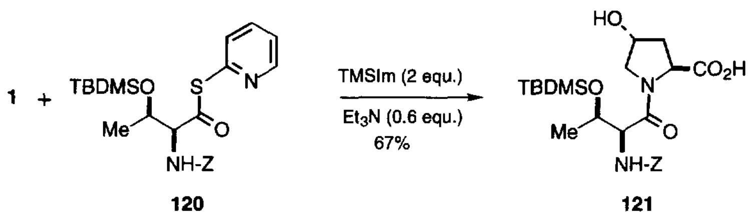
Scheme 28

A similar methodology[39] to synthesize derivative **119** was employed with formation of the internal double bond in the pyrrolidine ring by using the procedure described by Rüeger[29] (Scheme 28). The attachment of the carboxylic side chains **117** and **119** to the didemnin core was successfully accomplished with the help of the BOP coupling reagent in 65% and 84% yield respectively, including the final deprotection step.



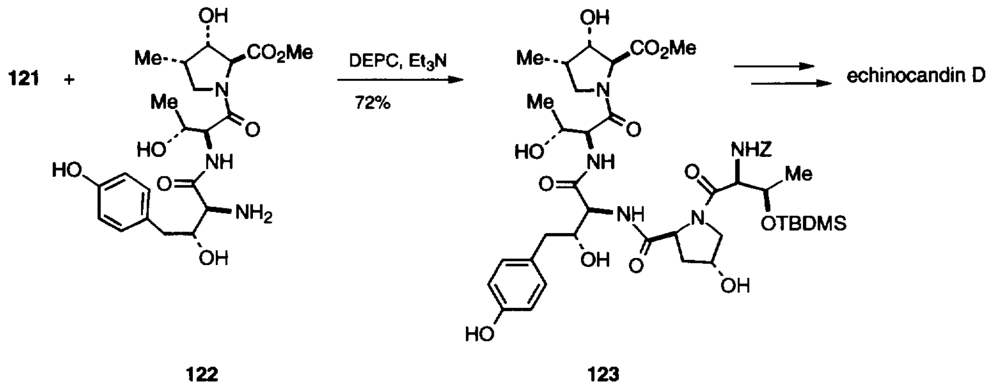
echinocandin D

Ohfune[40] studied the total synthesis of a new fungicidal molecule echinocandin D. The 2-pyridylthiol ester of *O*-protected-L-threonine **120** was coupled with unprotected **1** in the presence of trimethylsilylimidazole (TMSIm) to afford **121** (Scheme 29), which was in turn condensed in 72 % yield with **122** using diethylphosphorylcyanide (DEPC) as a coupling reagent (Scheme 30). Compound **122** was prepared by coupling a triprotected homotyrosine residue with the nitrogen of an *O*-silylated threonine residue followed by final addition of totally synthetic 3-hydroxy-4-methylproline methyl ester, prepared from a glycidic acid derivative. Addition of a N^{α}-



Scheme 29

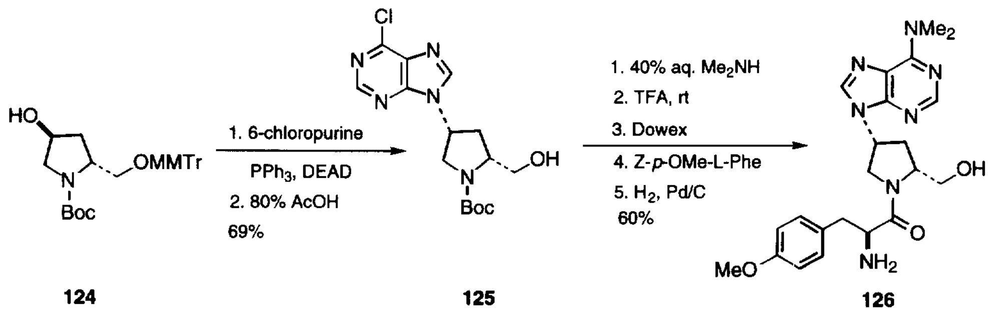
linoleyl-ornithine derivative to **123**, afforded a hexapeptide intermediate which on deprotection and cyclisation using diphenylphosphorylazide (DPPA) furnished echinocandin D in 27% yield from **123** (Scheme 30). Synthetic echinocandin D was reduced (H_2, Pd/C, 100%) and was found to be identical with a sample derived from natural compounds.



Scheme 30

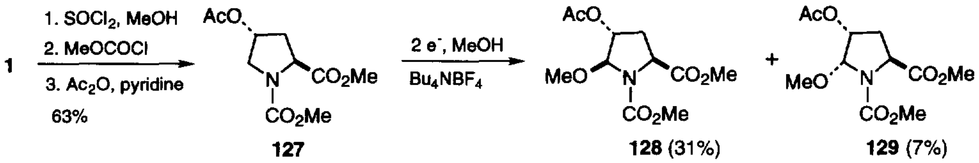
4. Pyrrolidine derivatives

Double inversion of **1**, *N*-Boc protection, reduction with $LiBH_4$, and protection with an *O*-*p*-methoxytriphenylmethyl group (MMTr) afforded **124**. Vince[41] described the condensation of **124** with 6-chloropurine to afford



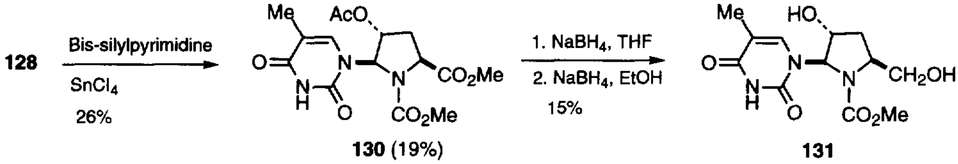
Scheme 31

intermediate **125**, which was substituted with dimethylamine, deprotected with trifluoroacetic acid, acylated with a phenylalanine derivative, to furnish the puromycin analogue **126** after a few steps (Scheme 31).



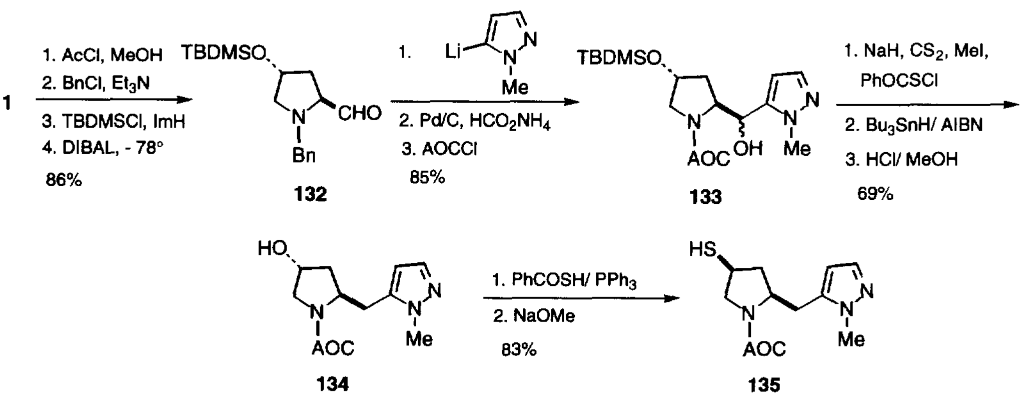
Scheme 32

Walker[42] disclosed the preparation of an azanucleoside analogue as a potential antiviral drug. Protected proline **127** was electrochemically oxidized to furnish a mixture of **128** and **129** (Scheme 32). Coupling of **128** with bis-silylpyrimidine in the presence of $SnCl_4$ afforded a mixture of isomer **130** and its C-5 enantiomer in 26% yield. Isomer **130** was further reduced with $NaBH_4$ to **131** (Scheme 33).



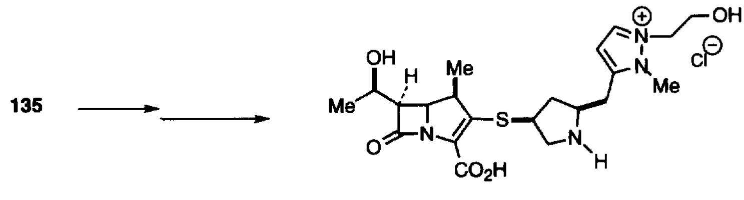
Scheme 33

Azami[43] prepared aldehyde **132** in high yield from **1** (Scheme 34). Aldehyde **132** was further reacted with 5-lithium pyrazole to afford **133** after deprotection and reprotection with an allyloxycarbonyl group (AOC). Reduction of the resulting hydroxyl function and thiol introduction in **134** *via* a Mitsunobu reaction was performed in high yield.



Scheme 34

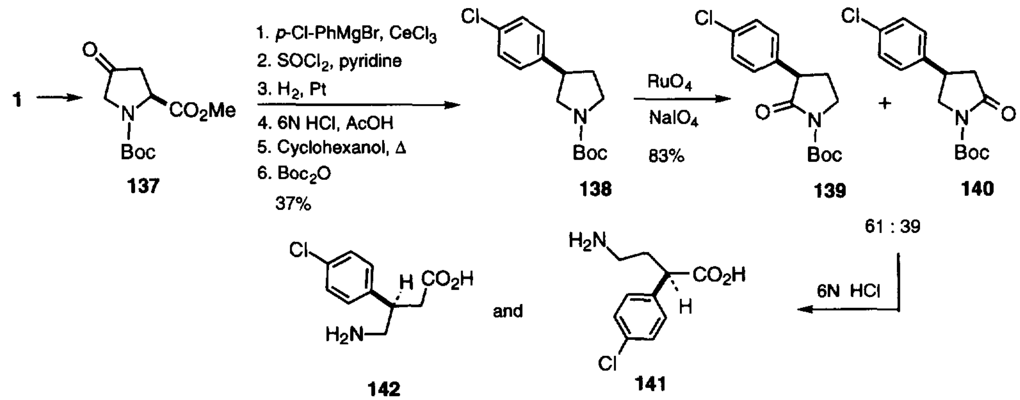
The key thiol **135** was coupled with a 2-[(diphenylphosphono)oxy]-1-methylcarbapenem in 73% yield (Scheme 35) and was successively alkylated with a monotriflate of ethyleneglycol to furnish after two additional steps the antibacterial carbapenem **136** (FR21818).



136

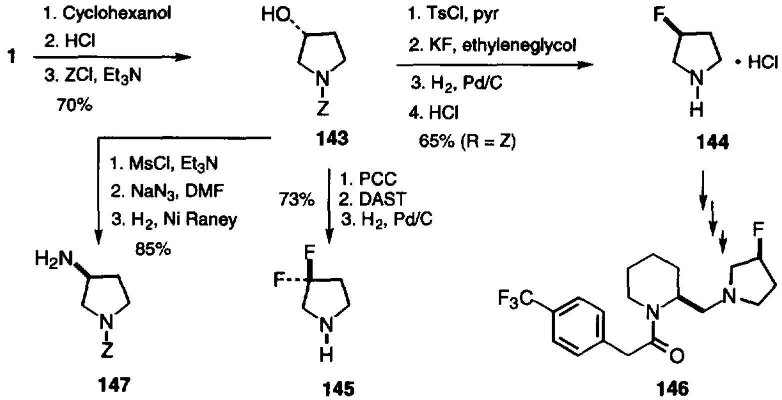
Scheme 35

Yoshifuji[44] demonstrated that the reaction of 4-chlorophenyl magnesium bromide with **137** proceeded stereoselectively to yield a single adduct in 78 % yield (Scheme 36). Chlorination, dehydrohalogenation, and H_2/ Pt reduction of this adduct followed by decarboxylation in cyclohexanol and protection of the pyrrolidine ring led to **138** (Scheme 36). Oxidation of **138** afforded a mixture of regioisomers **139** and **140** which were hydrolyzed to PCPGABA **141** and (*R*)-baclofen **142** respectively. Baclofen (racemic form of **142**) is a known antispastic agent.



Scheme 36

Giardina[45] prepared 3-fluoro- and 3,3-difluoropyrrolidines in high yield and high enantioselectivity *via* decarboxylated proline **143** (Scheme 37). Nucleophilic displacement of the tosylate of **143** with KF afforded, after



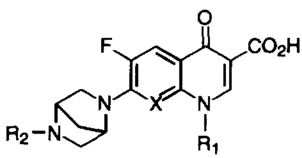
Scheme 37

hydrogenation, 3-fluoropyrrolidine **144**. Oxidation of **143** with pyridinium chlorochromate (PCC) followed by difluorination with diethylaminosulfur trifluoride (DAST) furnished **145** in good yield after hydrogenation. Fluoropyrrolidines such as **144** and **145** led to potential analgesics of type **146**.[45]

Sanchez[46] described the preparation of protected (3*S*)-3-aminopyrrolidine **147** from intermediate **143** by successive mesylation, inversion with sodium azide, and finally reduction with Raney nickel in good overall yield (Scheme 37). Aminopyrrolidine **147** after deprotection was condensed with 7-halogeno-6-fluoroquinolones and -naphthyridones.

5. Bridged piperazines and piperidines

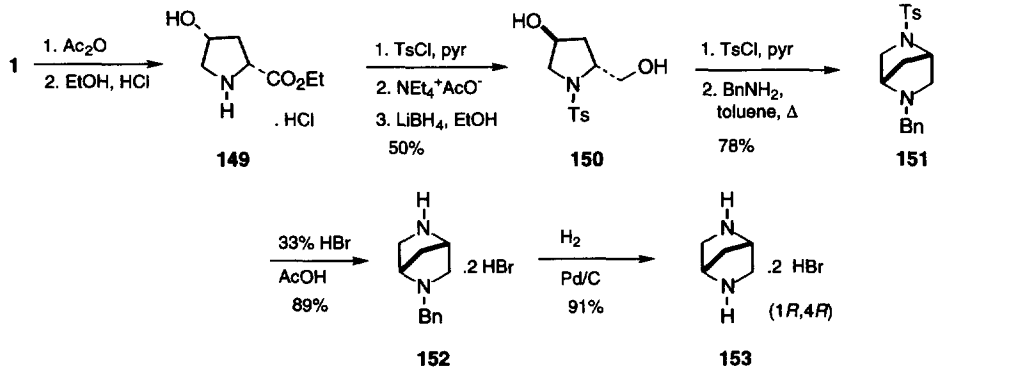
A large number of new synthetic antibacterials such as **148**, belonging to the class of fluoroquinolones, are characterized by a 2,5-diazabicyclo[2.2.1] heptane moiety at C-7.[47]



148

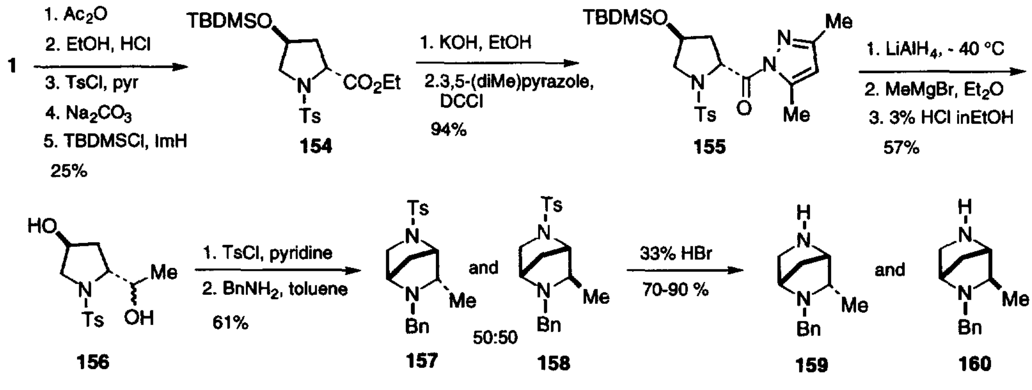
R_1 = Et, c-C_3H_5, ^{t}Bu;
R_2 = H, Me;
X = CH, N

The synthesis of the (1*S*,4*S*) and (1*R*,4*R*) bridged piperazines were simultaneously reported by Bouzard,[48] (Scheme 38), Braish[49] (*N*-methylated derivatives) and Sauter;[50] all started with L-Hyp **1**, using similar pathways by a method described previously.[51]



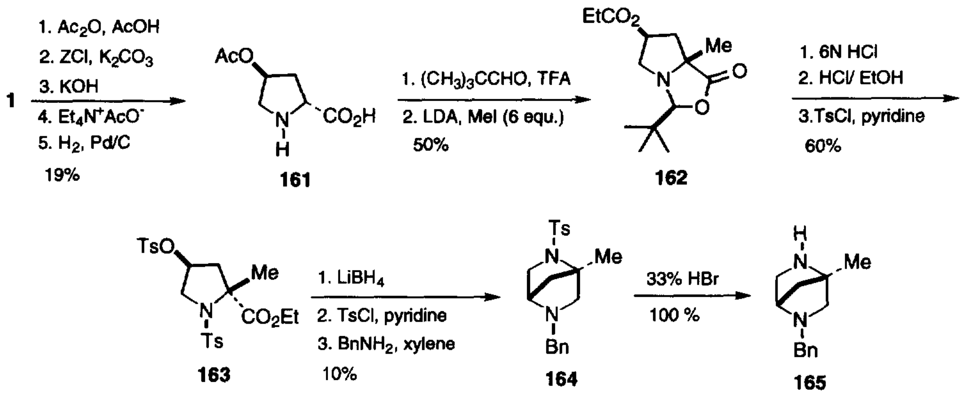
Scheme 38

Inversion at C-2[5] of **1** was made possible by acetylation followed by esterification with ethanolic HCl to give **149**. Inversion at C-4 was carried out by nucleophilic displacement[5] of a 4-tosylate with tetraethylammonium acetate followed by mild reduction with $LiBH_4$ to give the free diol **150**. Tosylation of the diol followed by condensation with benzylamine afforded derivative **151**. Deprotection with HBr in AcOH and then hydrogenation led to the bridged piperazine **153** which was condensed with 7-halogeno-4-oxoquinolone or -naphthyridone in the presence of bases such as DBU to afford derivatives of type **148**.



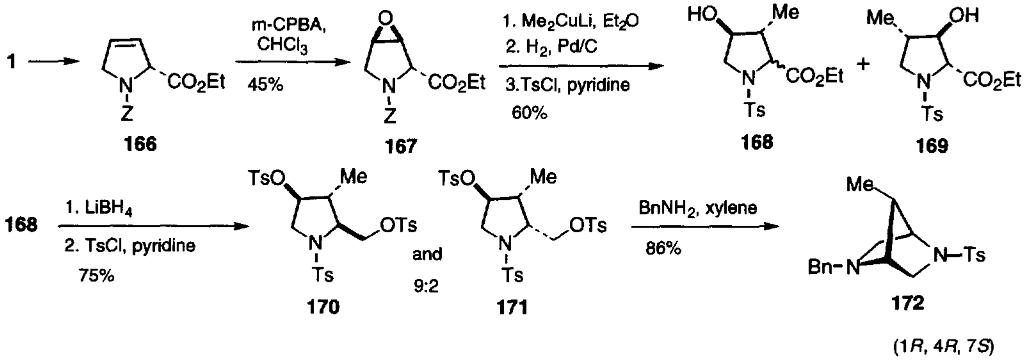
Scheme 39

Remuzon[52] reported the preparation of 7-(6-methylated 2,5-diazabicyclo[2.2.1]heptan-2-yl)-1,8-naphthyridone derivatives for the synthesis of antibacterials[53] (Scheme 39). The key step was the formation of an aldehyde by reduction of amide **155**, followed by addition of a Grignard reagent to provide a 50:50 ratio of alcohols **156**. Further cyclisation of the ditosylate of **156** with benzylamine furnished (3*R*)- and (3*S*)-3-methylpiperazines **159** and **160** after cleavage of the tosyl groups of **157** and **158** respectively.



Scheme 40

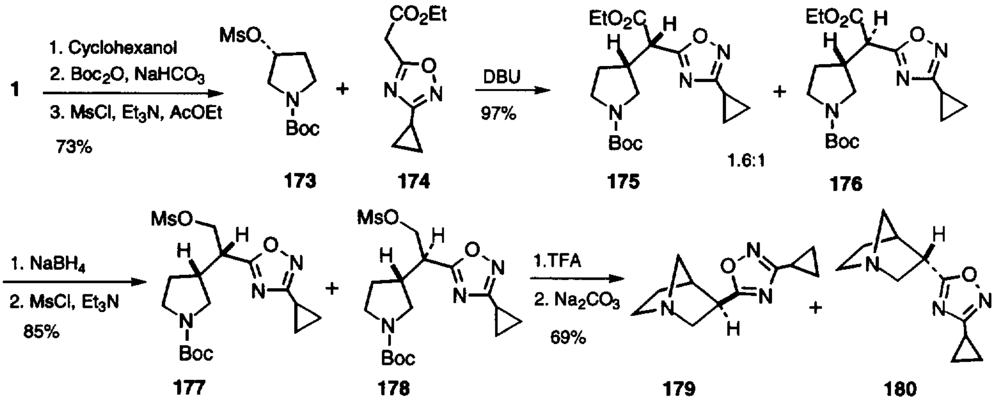
Using known methodology, Remuzon[54] synthesized Seebach's intermediate[55] **162** (Scheme 40) which led to tosylate **163**. This was reduced, tosylated and cyclised to the (1*R*)-1-methyl bridged piperazine **165** after quantitative detosylation with HBr in AcOH.



Scheme 41

Methylated bridged piperazines of type **172** were described by Remuzon[56,57] (Scheme 41). The key step involved the opening of epoxide **167** with dimethylcuprate followed by deprotection and tosylation, allowing the separation of regioisomers **168** and **169**, obtained in a 8:1 ratio. Reduction of the mixture afforded, after separation of diastereomers and tosylation, the pyrrolidines **170** and **171** in a 9:2 ratio. Cyclisation of **171** occurred in good yield with benzylamine to furnish piperazine **172**. Using the same procedure the (1*S*,4*S*,7*S*)-analogue was obtained from **170** in 51% yield. By selective deprotection either with HBr or hydrogenation it was possible to get both (1*R*,4*R*,7*S*) or (1*S*,4*S*,7*S*) isomers of the final quinolones.[57]

Heterocyclic derivatives as 1-azabicyclo[2.2.1]heptanes have potential for the treatment of senile dementia of the Alzheimer's type. Houghton[58] disclosed the enantioselective synthesis of such derivatives (Scheme 42).



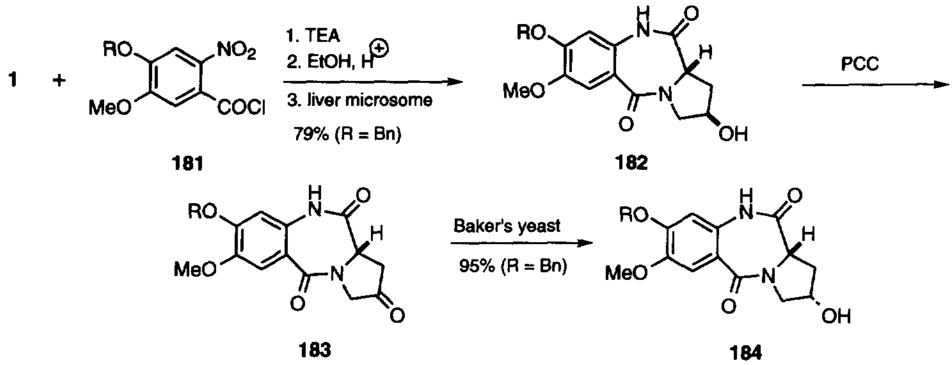
Scheme 42

Reaction of mesylate **173** with an enolate anion of an oxadiazole derivative **174** in DBU gave a mixture of adducts **175** and **176** which after reduction and mesylation afforded a mixture of **177** and **178**. Deprotection of the Boc group and cyclisation gave a 2:1 mixture of **179** and **180**. (3*R*,4*R*)-Azabicyclo[2.2.1]heptane derivative **179** was enriched by epimerization with potassium *t*-butylate (Scheme 42).

6. Fused bicyclic derivatives

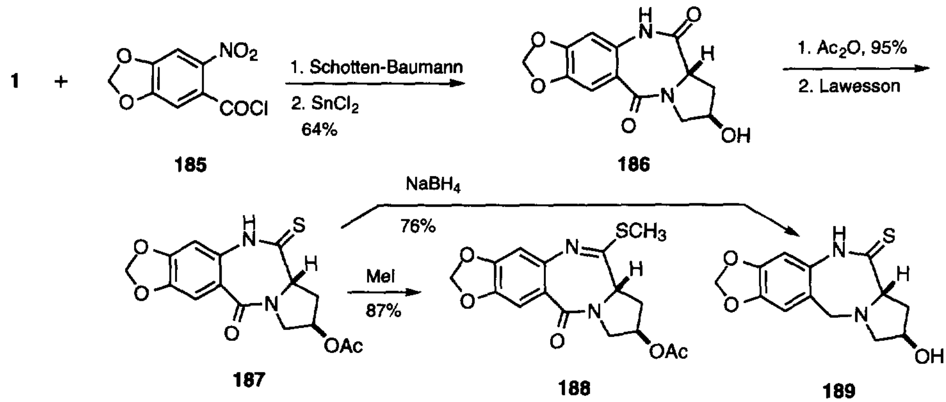
6.1. Benzodiazepine derivatives

Kamal[59] reported the synthesis of benzodiazepines as potential antitumor antibiotics using an enzymatic reductive cyclisation of the ethyl ester adduct of **181** and L-Hyp **1** resulting in the formation of **182** (Scheme 43).



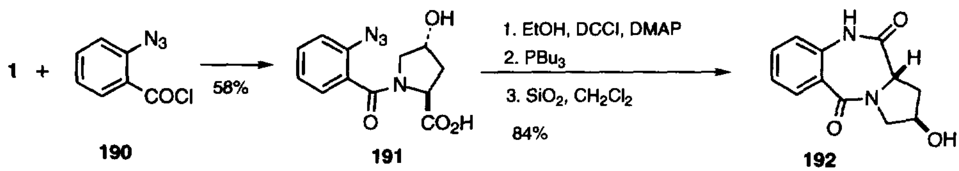
Scheme 43

Oxidation of **182** with pyridinium chlorochromate (PCC) furnished tricyclic derivative **183**. Baker's yeast was found to reduce selectively **183** to give derivative **184** in good yield and 97% ee.



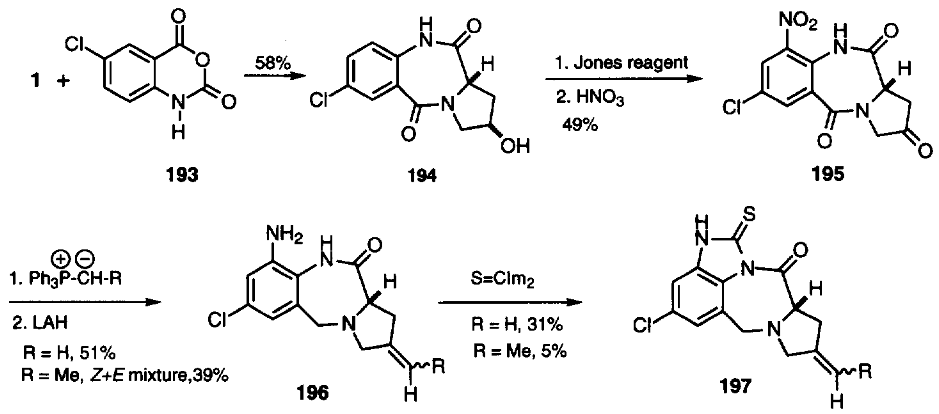
Scheme 44

Using known methodology,[60] Robba[61] prepared some dioxolo analogues of neothramycin and chicamycin such as **187**, **188**, or **189** in order to design new antitumor agents (Scheme 44).



Scheme 45

Molina[62] reported an efficient synthesis of prothracarcin **192** by an intramolecular aza-Wittig reaction of 2-azidobenzamide ethyl ester of acid **191** (Scheme 45). Hydrolysis of the resulting iminoether led to **192** in an excellent yield.

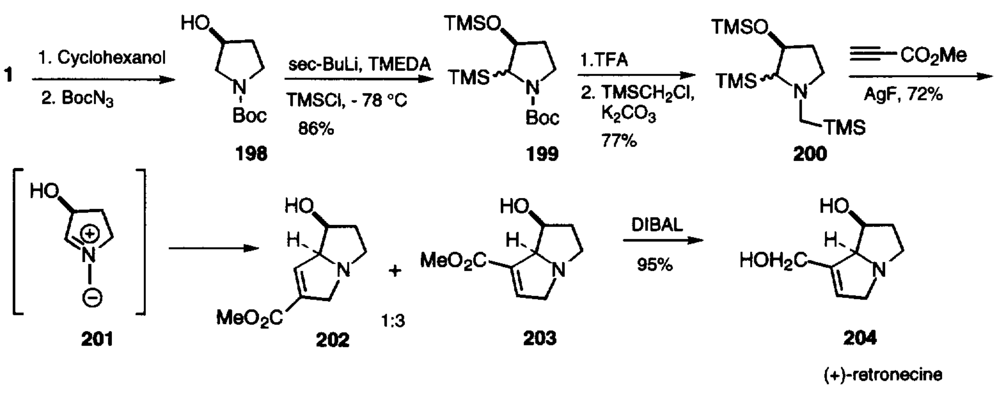


Scheme 46

Breslin[63] has reported the preparation of analogues of TIBO (4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1*H*)-one), a known *in vitro* inhibitor of HIV-1 replication. Condensation of **1** with isatoic anhydride **193** followed by Jones oxidation and nitration afforded **195**. Wittig reaction and reduction with hydride furnished benzodiazepines **196**, which were cyclized to **197** by means of 1,1'-carbonylthioimidazole (Scheme 46).

6.2. Other bicyclic derivatives

A short synthesis of retronecine, a hepatotoxic derivative with some antitumor properties, was described

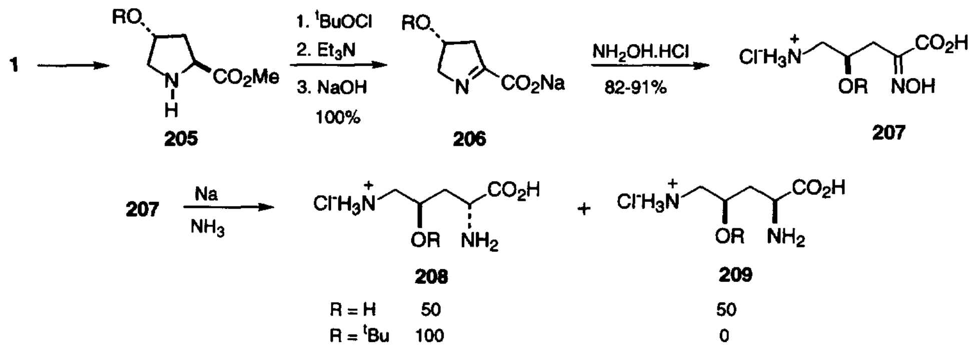


Scheme 47

by Pandey[64] (Scheme 47). Decarboxylated proline **198** was substituted at the 2-position by a silyl group. After trimethylsilylmethyl substitution at the pyrrolidine nitrogen, compound **200** was coupled with methylpropiolate in the presence of AgF to furnish a 3:1 mixture of **202** and **203** through a [3+2] cycloaddition of a non-stabilized azomethine ylide (Scheme 47). Reduction of the methyl ester of **203** led to retronecine **204**.

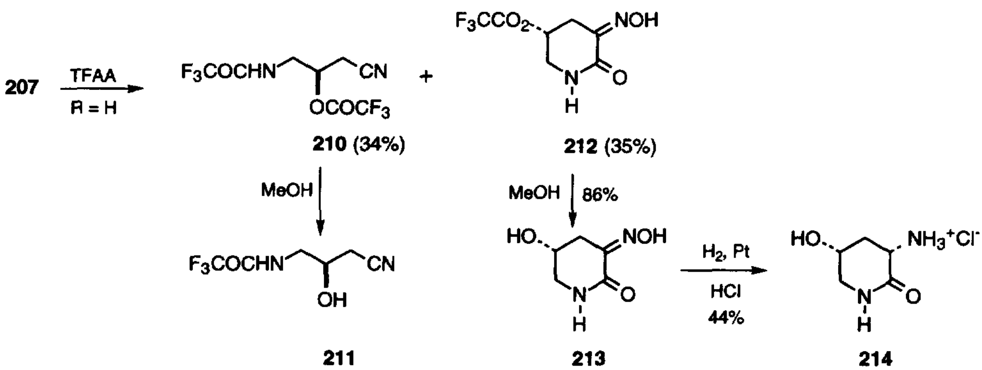
7. Higher homologues of pyrrolidine rings

Haüsler[65] reported the preparation of 4-hydroxyornithines **208** and **209** from **1** and also piperidone **214**.



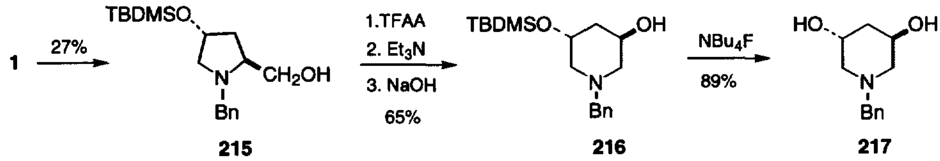
Scheme 48

The cyclic azomethine **206** easily underwent ring-opening with hydroxylamine (Scheme 48). Birch reduction of the oximino derivative (R = *t*-Bu) gave stereoselectively the protected ornithine **208**, while with no protection (R = H), a 50:50 ratio of **208** and **209** was obtained.



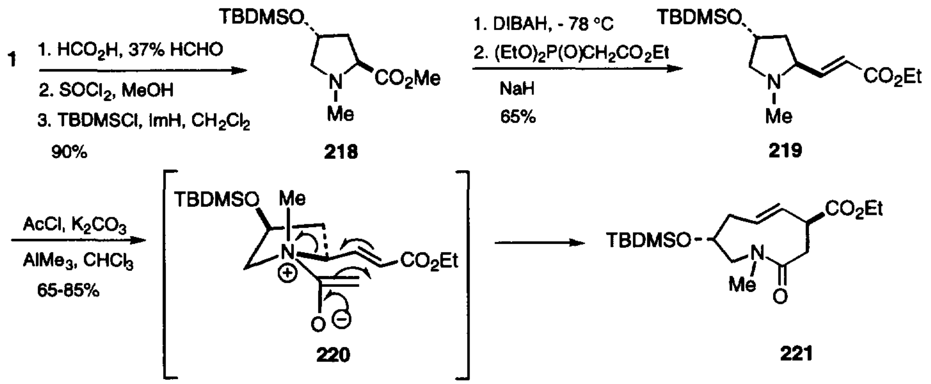
Scheme 49

Trifluoroacetic anhydride transformed oxime **207** into a mixture of nitrile **210** and piperidone **212**,[65] which was further hydrolyzed to **213** and hydrogenated to give 3-amino-5-hydroxypiperidone **214** (Scheme 49).



Scheme 50

Cossy[66] disclosed a simple procedure for obtaining chiral 3-hydroxypiperidine from prolinol derivatives (Scheme 50). Prolinol **215** obtained in three steps from **1**, and reacted with trifluoroacetic anhydride to provide **216**. An intermediate azidirinium ion was postulated. Alkaline hydrolysis of the intermediate trifluoroacetate followed by desilylation of **216** with Bu_4NF allowed isolation of **217** in high enantiomeric purity.

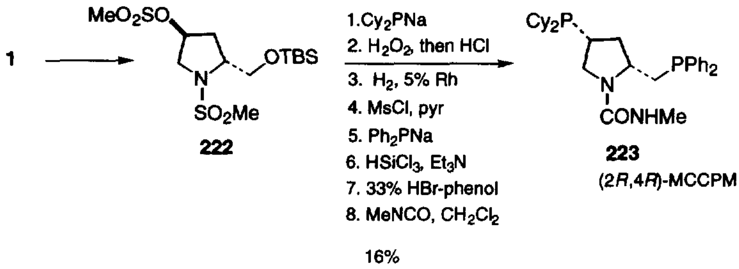


Scheme 51

Nubbemeyer[67] reported the synthesis of an optically active nine-membered ring lactam by a zwitterionic aza-Claisen reaction (Scheme 51). After *N*-methylation, *O*-silylation and methyl ester formation, compound **218** was transformed into an aldehyde which was subjected to a Horner olefination to provide ester **219**. Special two-phase conditions were developed for the Claisen rearrangement of allylamine **219**, giving a [3,3]-sigmatropic rearrangement (rather than a Von Braun degradation) as described with figure **220**. Finally, lactam **221** was isolated in 65% yield.

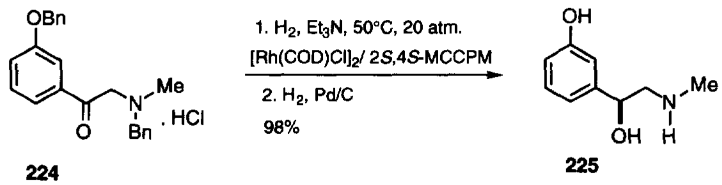
8. Chiral catalysts

New hydrogenation catalysts were developed by Takeda[68,69]. Their preparation is described in Scheme 52. From **1**, prolinol **222** was prepared in 28% yield in 6 steps. Double selective phosphorylation, mesyl deprotection, reduction to the diphosphine, and urea formation with methylisocyanate furnished **223** in 16% yield from **222**.



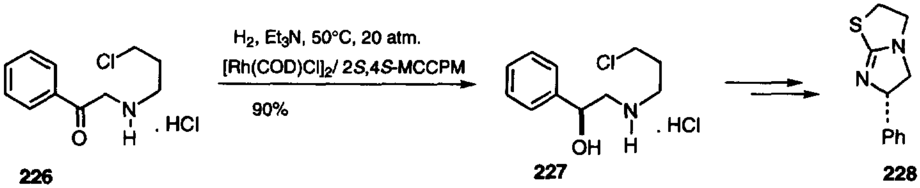
Scheme 52

(*R*)-(-)Phenylephrine **225** was obtained by Takeda[68] by asymmetric hydrogenation of α-aminoacetophenone **224** with the (2*S*,4*S*) enantiomer of *N*-(methylcarbamoyl)-4-(dicyclohexylphosphino)-2[(diphenylphosphino)-methyl]pyrrolidine **223** or MCCPM rhodium catalyst with 85% ee (Scheme 53).



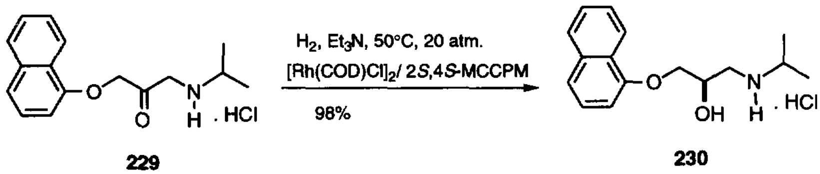
Scheme 53

Using the same catalyst, the same author[69] was able to reduce with high enantioselectivity (90% ee) derivative **226** which was further transformed into (*S*)-(-)-levamisole **228** in a few steps (Scheme 54).



Scheme 54

Finally, enantioselective synthesis[69] of (*S*)-propranolol **230** was achieved from **229** with the MCCPM catalyst in excellent yield and good ee (91%) (Scheme 55).



Scheme 55

9. Conclusion

We have explored a huge variety of chiral molecules, the synthesis of which started with L-Hyp **1**. In a large area of medicine, the drugs arising from L-Hyp **1** or derivatives are present: antibacterials with carbapenems and fluoroquinolones; antibiotics for HIV infections: azaanalogues of nucleosides, puromycin and TIBO analogues; potential antitumor compounds: fluoroglutamic derivatives; immunostimulants: azaanalogues of nucleosides; antitumors: benzodiazepines analogues, retronecine; antifungals: echinocandins; antitussive drugs: baclofen; analgesics: fluoropyrrolidines derivatives; senile dementia: 1-azabicycloheptane derivatives. Also, L-Hyp **1** derivatives act as catalysts for asymmetric hydrogenation.

REFERENCES

1. Aspinall, G.O. *Chemistry of Cell Wall Polysaccharides*. In the Biochemistry of Plants. A Comprehensive Treaty, vol. 3 (J. Preiss, ed.) pp 473-500. New-York. Academic Press, 1980.
2. Eyre, D.R.; *Science*, **1980**, *207*, 1315-1322.
3. Klabunde, H.K. *J. Biol. Chem.* **1931**, *90*, 293-295.
4. Wichmann, C.F.; Liesch, J.M.; Schwartz, R.E. *J. Antibiotics* **1989**, *42*, 168-173.
5. Baker, G.L.; Scott, J.F.; Stille, J.R.; Stille, J.K. *J. Org. Chem.* **1981**, *46*, 2954-2960.
6. Papaioannou, D.; Stavropoulos, G.; Karagiannis, K.; Francis, G.W.; Brekke, T.; Aksnes, D.W. *Acta Chem. Scand.* **1990**, *44*, 243-251.
7. Seki, M.; Matsumoto, K. *Biosci. Biotech. Biochem.* **1995**, *59*, 1161-1162.
8. Hashimoto, M.; Eda, M.; Osanai, Y.; Iwai, T.; Aoki, S. *Chem. Lett.* **1986**, *6*, 893-896.

9. To our knowledge, the most recent review on proline and analogues was published by Mauger, A.B.; Witkop, B. *Chem. Rev.* **1966**, *66*, 47-86.
10. Takano, S.; Iwabuchi, Y.; Ogasawara, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1527-1528.
11. Mehlführer, M.; Berner, H.; Thirring, K. *J. Chem. Soc., Chem. Commun.* **1994**, 1291.
12. Hudlicky, M.; Merola, J.S. *Tetrahedron Lett.* **1990**, *31*, 7403-7406.
13. Avent, A.G.; Bowler, A.N.; Doyle, P.M.; Marchand, C.M.; Young, D.W. *Tetrahedron Lett.* **1992**, *33*, 1509-1512.
14. Hudlicky, M.; *J. Fluorine Chem.* **1993**, *60*, 193-210.
15. Kaname, M.; Yoshifuji, S. *Tetrahedron Lett.* **1992**, *33*, 8103-8104.
16. Tanaka, K.-i, Sawanishi, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1641-1656.
17. Shinozaki, H. in *Kainic Acid as a Tool in Neurobiology*; McGeer, E.G.; Olney, J.W.; McGeer, P.L., Eds.; Raven Press: New York, 1978, pp 17-35.
18. For a recent review of the synthesis of kainoid amino acids see: Parsons, A.F. *Tetrahedron*, **1996**, *52* 4149-4174.
19. Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625-2628.
20. Thottathil, J.K.; Moniot, J.L. *Tetrahedron Lett.* **1986**, *27*, 151-154.
21. Hashimoto, K.; Shirahama, H. *Heterocycles* **1996**, *42*, 489-492.
22. Baldwin, J.E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163-6166.
23. (a) Horikawa, M.; Shirahama, H. *Synlett* **1996**, 95-96; (b) Thottathil, J.K. US Patent 4,734,508, March 29, 1988; US Patent 4,851,514, July 29, 1989.
24. Baldwin, J.E.; Bamford, S.J.; Fryer, A.M.; Wood, M.E. *Tetrahedron Lett.* **1995**, *36*, 4869-4872.
25. Gill, P.; Lubell, W.D. *J. Org. Chem.* **1995**, *60*, 2658-2659.
26. Sardina, F.J.; Blanco, M.J. *Tetrahedron Lett.* **1994**, *35*, 8493-8496.
27. Lubell, W.D.; Sharma, R. *J. Org. Chem.* **1996**, *61*, 202-209.
28. Baldwin, J.E.; Field, R.A.; Lawrence, C.C.; Lee, V.; Robinson, J. K.; Schofield, J. *Tetrahedron Lett.* **1994**, *35*, 4649-4652.
29. Rüeger, H; Benn, M. H. *Can. J. Chem.* **1982**, *60*, 2918-2920.
30. Goli, D.M.; Cheesman, B.V.; Hassan, M.E.; Lodaya, R.; Slama, J. T. *Carbohydr. Res.* **1994**, *259*, 219-241.
31. Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, 43, 290-295.
32. Barrett, A.G.M.; Pilipauskas, D. *J. Org. Chem.* **1990**, *55*, 5194-5196.
33. Barrett, A.G.M.; Pilipauskas, D. *J. Org. Chem.* **1991**, *56*, 2787-2800.
34. Kronenthal, D.R.; Mueller, R.H.; Kuester, P.L.; Kissick, T.P.; Johnson, E.J. *Tetrahedron Lett.* **1990**, *31*, 1241-1244.
35. Webb, T.R.; Eigenbrot, C. *J. Org. Chem.* **1991**, *56*, 3009-3016.
36. Kemp, D.S.; Curran, T.P.; Davis, W.M.; Boyd, J.G.; Muendel, C. *J. Org. Chem.* **1991**, *56*, 6672-6682.
37. Williams, M.A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3616-3625.
38. Matsumara, H.; Bando, T.; Sunagawa, M. *Heterocycles*, **1995**, *41*, 147-159.

39. Mayer, S.C.; Ramanjulu, J.; Vera, M.D.; Pfizenmayer, A.J.; Joullié, M.M. *J. Org. Chem.* **1994**, *59*, 5192-5205.
40. Kurokawa, N.; Ohfune, Y. *Tetrahedron*, **1993**, *49*, 6195-6222.
41. Peterson, M.L.; Vince, R. *J. Med. Chem.* **1991**, *34*, 2787-2797.
42. Pickering, L.; Malhi, B.S.; Coe, P.L.; Walker, R.T. *Tetrahedron*, **1995**, *51*, 2719-2728.
43. Azami, H.; Barrett, D.; Tanaka, A.; Sasaki, H.; Matsuda, K.; Chiba, T.; Matsumoto, Y.; Matsumoto, S.; Ishiguro, K.; Tawara, S.; Sakane, K.; Takasugi, H. *Bioorganic & Med. Chem. Lett.* **1995**, *5*, 2199-2202.
44. Yoshifuji, S.; Kaname, M. *Chem. Pharm. Bull.* **1995**, *43*, 1302-1306.
45. Giardina, G.; Dondio, G.; Grugni, M. *Synlett* **1995**, 55-56.
46. Sanchez, J.P.; Domagala, J. M.; Heifetz, C. L.; Priebe, S. R.; Sesnie, J. A.; Trehan, A. K. *J. Med. Chem.* **1992**, *35*, 1764-1773.
47. Remuzon, P.; Bouzard, D. in *Recent Trends in the Quinolone Field*, Studies in Medicinal Chemistry, vol. 1, Choudhary I. ed., Harwood, Publisher, Amsterdam, 1996, p 173-237.
48. Bouzard, D.; DiCesare, P.; Essiz, M.; Jacquet, J.P.; Kiechel, J.R.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M.; Kessler, R.E.; Fung-Tomc, J.; Desiderio, J. *J. Med. Chem.* **1990**, *33*, 1344-1352.
49. Braish, T.F.; Fox, D.E. *J. Org. Chem.* **1990**, *55*, 1684-1687.
50. Jordis, U.; Sauter, F.; Siddiqi, S.M.; Küenburg, B.; Bhattacharya, K. *Synthesis*, **1990**, 925-930.
51. Portoghese, P.S.; Mikhail, A.A. *J. Org. Chem.* **1966**, *31*, 1059-1062.
52. Remuzon, P.; Bouzard, D.; Dussy, C.; Jacquet, J.P.; Massoudi, M. *Heterocycles*, **1992**, *34*, 241-245.
53. Remuzon, P.; Bouzard, D.; Guiol, C.; Jacquet, J.P. *J. Med. Chem.* **1992**, *35*, 2898-2909.
54. Remuzon, P.; Massoudi, M.; Bouzard, D.; Jacquet, J.P. *Heterocycles*, **1992**, *34*, 679-684.
55. Weber, T.; Seebach, D. *Helv. Chim. Acta*, **1985**, *68*, 155-161.
56. Remuzon, P.; Bouzard, D.; Clemencin, C.; Dussy, C.; Essiz, M.; Jacquet, J.P.; Saint-Germain, J. *J. Heterocyclic Chem.* **1993**, *30*, 517-523.
57. Remuzon, P.; Bouzard, D.; Clemencin, C.; Dussy, C.; Jacquet, J.P.; Fung-Tomc, J.; Kessler, R.E. *Eur. J. Med. Chem.* **1993**, *28*, 455-461.
58. Houghton, P.G.; Humphrey, G.R.; Kennedy, D.J.; Roberts, D.C.; Wright, S.H.B. *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1421-1424.
59. Kamal, A. *J. Org. Chem.* **1991**, *56*, 2237-2240.
60. Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791-5793.
61. Foloppe, M.P.; Caballero, E.; Rault, S.; Robba, M. *Eur. J. Med. Chem.* **1992**, *27*, 291-295.
62. Molina, P.; Diaz, I.; Tarraga, A. *Tetrahedron*, **1995**, *51*, 5617-5630.
63. Breslin, H. J.; Kukla, M.J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G.; Gauthier, D.A.; Chih, Y.H.. Scott, M.K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M.A.C.; Janssen, P.A.J. *J. Med. Chem.* **1995**, *38*, 771-793.
64. Pandey, G.; Lakshmaiah, G. *Synlett* **1994,** 277-278.
65. Haüsler, J. *Liebigs Ann. Chem.* **1992**, 1231-1237.

66. Cossy, J.; Dumas, C.; Michel, P.; Pardo, D.G. *Tetrahedron Lett.* **1995**, *36*, 549-552.
67. Diederich, M.; Nubbemeyer, U. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1026-1028.
68. Takeda, H.; Tachinami,T.; Aburatani, M. *Tetrahedron Lett.* **1989,** *30*, 367-370.
69. Sakuraba, S.; Takahashi, H.; Takeda, H.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 738-747.

(*Received* 21 *July* 1996)