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Pyroglutamic acid: a unique chiral synthon

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Contents

1. Introduction

Pyroglutamic acid or 5-oxo-proline has emerged as an important starting material for asymmetric synthesis of many natural products. From the first reported application of pyroglutamic acid in an asymmetric synthesis of Domoic acid **16**[1a] in 1982, the last two decades have witnessed an exponential outgrowth of publications on chemistry and asymmetric/biological uses of pyroglutamic acid.[1b]

Derived from glutamic acid, derivatives of pyroglutamic acids are a cheap source of chirality. The advantage of pyroglutamic acid in asymmetric synthesis lies in a rigid five-membered skeleton with strong stereo-electronic influence of two different carbonyl entities in the molecule which can be differentially functionalized. These features of pyroglutamates have been extensively exploited and the present review makes an attempt to list out all the major advances in this area.

Pyroglutamic acid has two differentially activated carbonyls. The asymmetric use of pyroglutamic acid has exploited their reactivity differences as such or by accentuating these by further derivatizations. The review is aimed to describe these developments and to explore further possibilities on the uses of pyroglutamic acid as a chiral synthon. In the present communication the major uses of pyroglutamic acid as a chiral synthon have been classified on the following lines.

2. Asymmetric use of pyroglutamates with prior modifications

2.1. Reduction of carboxylic groups

The first use of pyroglutamates as chiral synthon in the synthesis of complex molecule was in the synthesis of (−)-Domoic acid by Ofune et al.[1a] The N-protected pyroglutamic acid was reduced to

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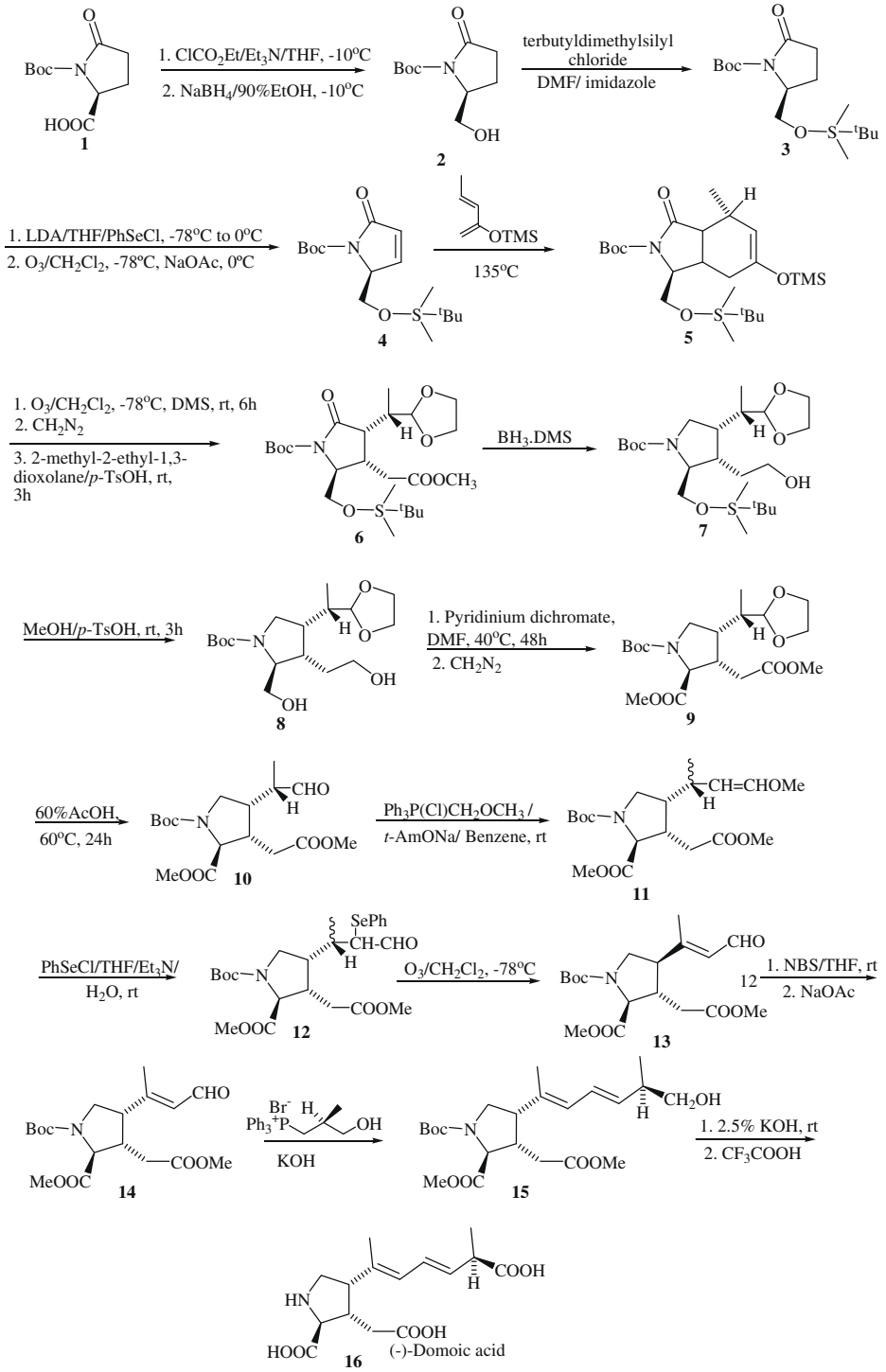
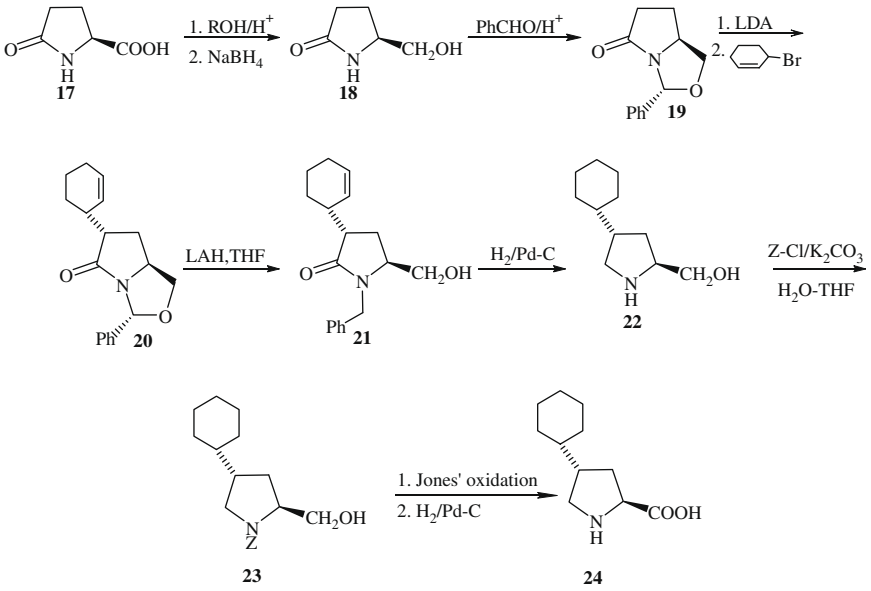
the corresponding alcohol which was protected by TBS. This protected synthon has only one activated carbonyl which was α-alkylated in high enantiomeric excess. The reduction of carbonyl function and its subsequent protection by TBS not only excluded the deprotonation at C-2, that is, loss of chirality, but also influenced the α-approach of electrophile (Scheme 1).

Similar reduction and protection sequence was also used[2] in the synthesis of *trans*-4-cyclohexyl proline **24** (Scheme 2), an intermediate for the synthesis of fosinopril, a potent ACE inhibitor. In this case reaction of pyroglutaminol with benzaldehyde gave a bicyclic system, where phenyl acquires an equatorial position. Alkylation of the lithio enolate proceeded with high facial selectivity to give 4-α-product **24**.

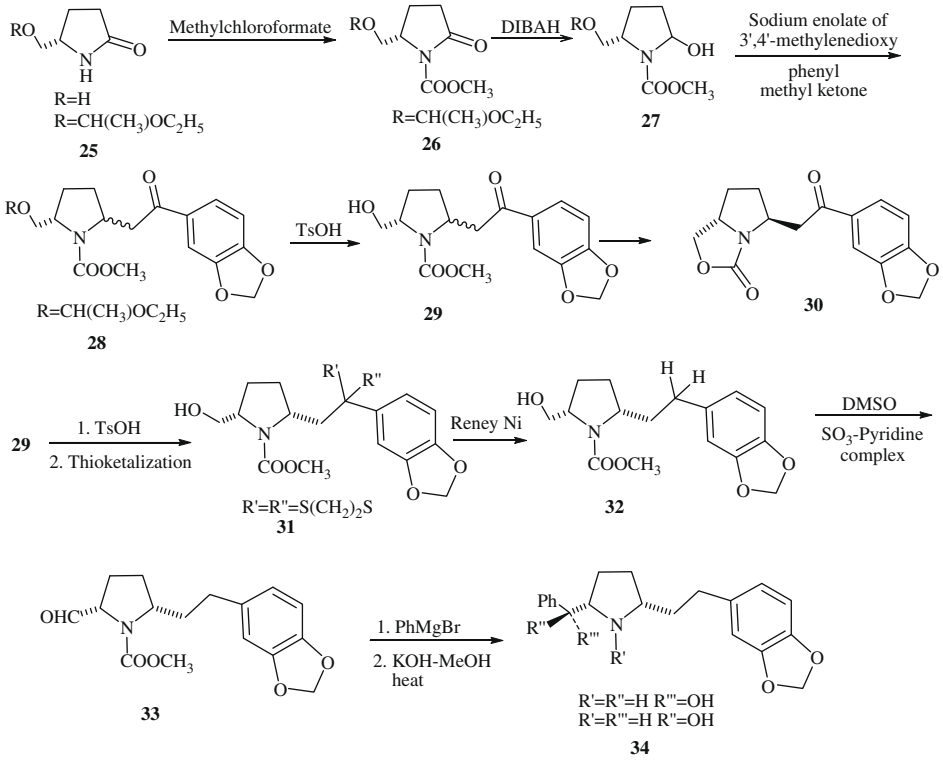
Langlois et al. have carried out asymmetric synthesis of antihypertensive pyrrolidines[3] **34** by using 2-hydroxymethyl pyroglutamate **25** as a chiral synthon (Scheme 3). The protected 2-hydroxymethylpyrrolidine-5-one was reduced to cyclic aminol **27** which was used in C–C-bond forming reaction at C-5. The carbonyl group in **29** was derivatized via thioketalization in the presence of TsOH followed by hydrogenation with Raney Ni to get



Scheme 1.



Scheme 2.



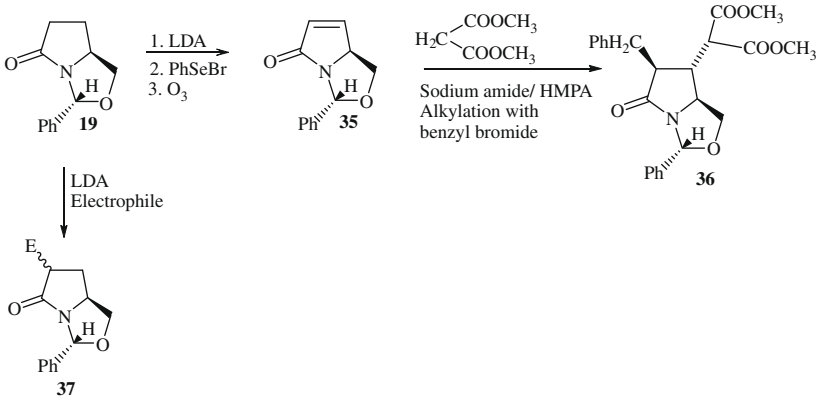
Scheme 3.

compound **32**. The resulting product on oxidation yielded an aldehyde **33** which was converted into the desired antihypertensive agent **34**.

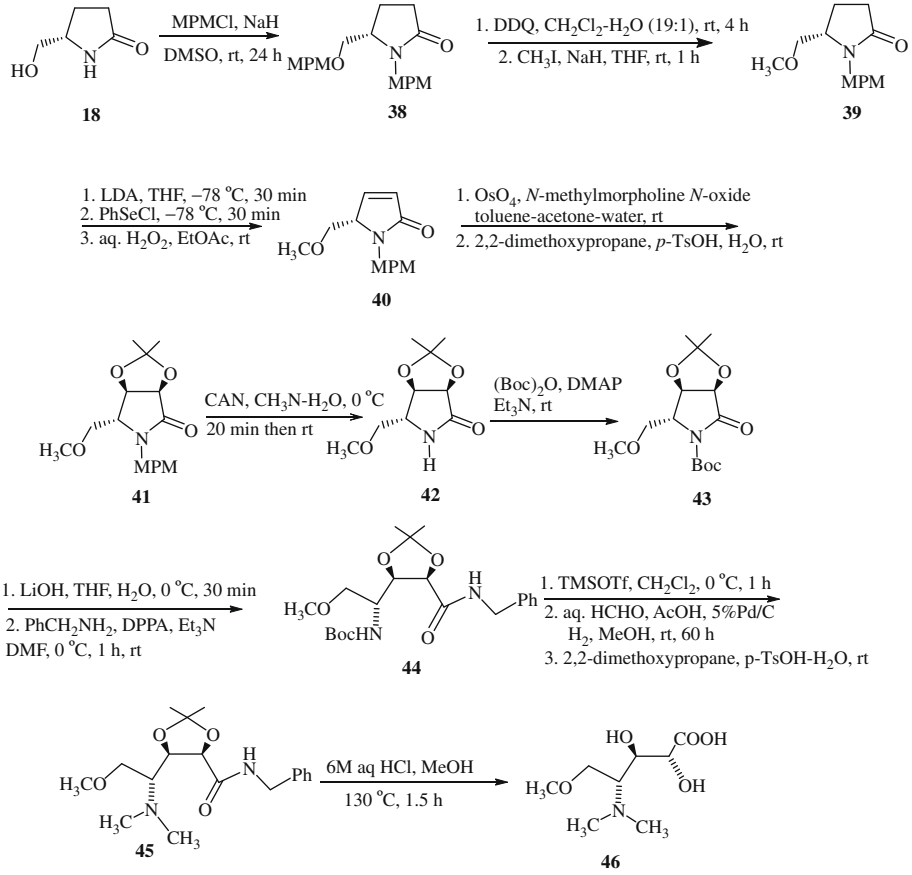
Similarly the pyroglutamate-derived cyclic protected synthon has been used by Baldwin et al.[4] for the generation of a Michael acceptor moiety which was used in one-pot Michael addition–alkylation sequence to yield stereodefined 3,4-disubstituted pyroglutamate derivative **36** (Scheme 4).

Investigations reported by Hamada et al. on the asymmetric use of pyroglutamates with prior reduction of carbonyl group describe the synthesis of the 2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid[5] **46** a fragment of calyculins, starting from (*S*)-5-(hydroxymethyl)-2-pyrrolidinones **18** (Scheme 5).

Making use of pyroglutamic acid as a cheap chiral source, Langlois et al. reported the synthesis of enamidoaldehyde **49** as new common synthons for the preparation of analogs of sibiromycin and other antitumour antibiotics[6] (Scheme 6). Compound **47** was converted into N-acylated derivative **48**, by reaction with NaH and *p*-nitrobenzoyl chloride. Resultant *N*-acyl derivative **48** was converted into aldehyde **49** in three steps as shown in Scheme 6.



Scheme 4.

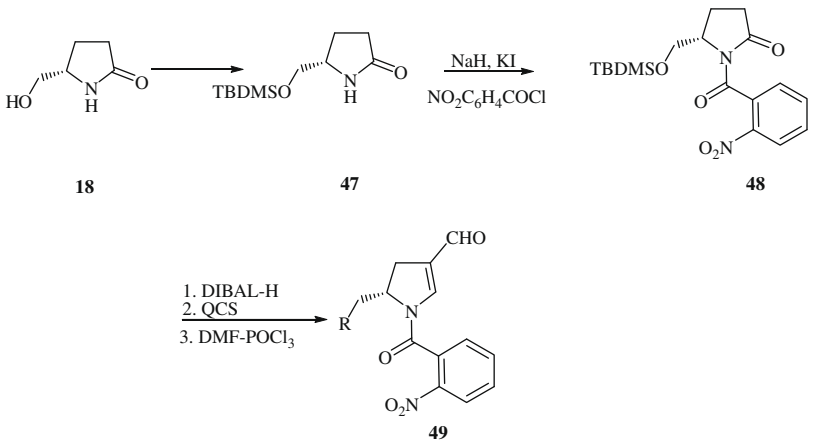


Scheme 5.

A publication by Woo et al. has described the asymmetric synthesis of α-amino acids by reaction at C-3, C-4 and C-5, of pyroglutamate derivatives starting from (*S*)-pyroglutamic acid derivative **50**.[7] They also reported ring opening through 2-lithio-1,3-dithiane at low temperature furnishing compound **52**, whereas reaction of **50** with vinyl magnesium bromide followed by reduction afforded compound **51** (Scheme 7).

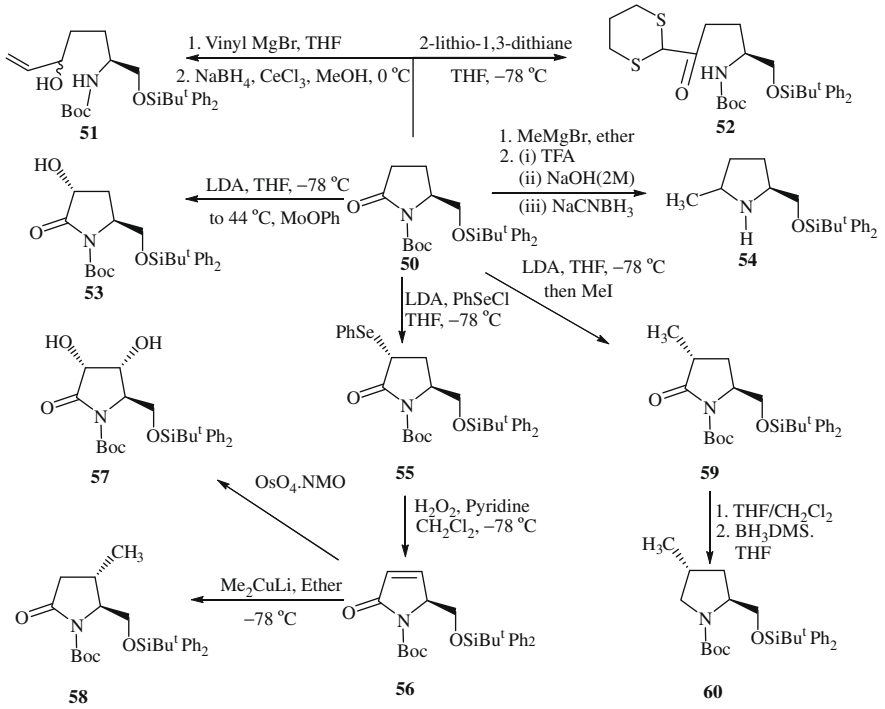
Total synthesis of (+)-monomorine **67**, a natural attractant for Pharaoh ant workers was carried out from chiral cyclic β-enaminoester derived from (*S*) pyroglutamic acid in seven steps by Saliou et al.[8] (Scheme 8). Pyroglutaminol **18** after tosylation was converted to *o*-tosyl derivative **62**. Compound **62** on reaction with di-n-propyl lithium cuprate was converted to compound **63** having *n*-Bu group at position 5. Compound **63** on reaction with dimethylsulfate followed by treatment with Meldrum's acid and on subsequent reaction with sodium methoxide furnished β-enaminoester **64** which on hydrogenation in the presence of H_2/Raney Ni afforded **65** with the desired stereochemistry. Compound **65** after the protection of NH with benzyloxy carbonyl chloride followed by reduction of alcohol group to aldehyde, was subjected to Witting reaction with $CH_3COCH{=}PPh_3$ ylid. The resultant compound on hydrogenation had undergone deprotection, reduction and cyclization to give (+)-monomorine **67**.

Stereoselective methylation of bicyclic lactams derived from D-pyroglutamic acid **68** has been reported by Armstrong et al.[9] The bicyclic compound **70** was converted to 4-methyl pyroglutaminol,



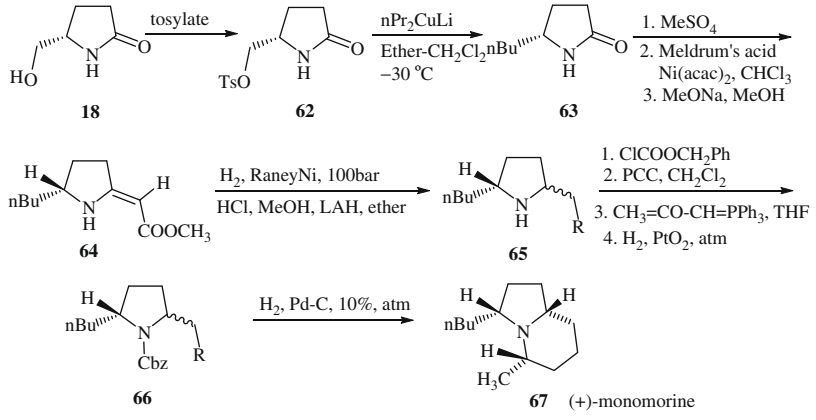
18 47 48 49

Scheme 6.



51 52 53 50 54 57 55 59 58 56 60

Scheme 7.



18 62 63 64 65 66 67 (+)-monomorine

Scheme 8.

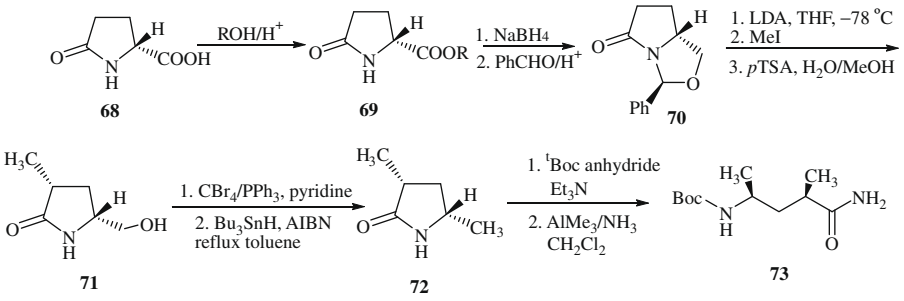
which on reduction afforded 2,4-dimethyl pyrrolidone **72** the chiral antipode, which was converted to N-protected *cis*-2,4-dimethylglutamide **73** in three steps (Scheme 9).

Kohn et al.[10] carried out the synthesis and characterization of chiral 1,2-diamines from pyroglutamic acid where pyroglutamic acid **17** on reaction with anhydrous chloral in the presence of toluene afforded bicyclic derivative **74** which on reaction with primary amine in toluene underwent ring opening of the oxazolidinone ring of bicyclic aminal **74** to furnish pyroglutamoyl amide derivative **75**. Compound **75** on reduction of lactam carbonyl as well as amidic carbonyl group with lithium aluminium hydride furnished the desired 1,2-diamines **76** (Scheme 10).

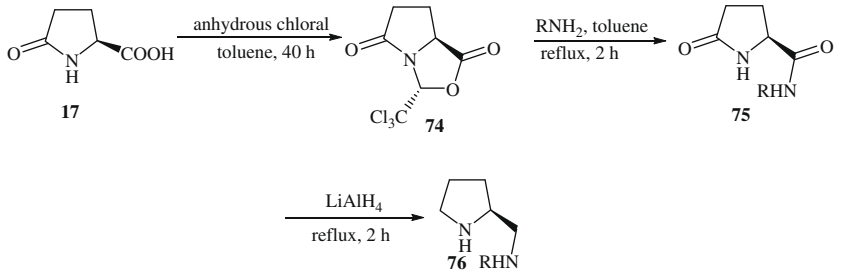
Sengoku et al.[11] carried out asymmetric synthesis of pyrrolizidine alkaloids (+)-hyacinthacine B_1 and (+)-B_2. The representative synthesis of (+)-hyacinthacine B_1 is described here (Scheme 11). Pyroglutamic acid derivative **77** on catalytic sharpless asymmetric dihydroxylation(AD) with AD-mix-α [$(DHQ)_2$ PHAL ligand] afforded compound **78**, which after protection, deprotection coupled with cyclization afforded compound **79**. Deprotection of compound **79** with tetrabutyl ammonium fluoride in THF followed by deprotection of hydroxyl groups with trifluoroacetic acid afforded (+)-hyacinthacine B_1 **80**.

Moeller et al. have modified carboxylic functional group of pyroglutamates with an objective to synthesize spirocyclic L-pyroglutamide building blocks[12] **86** (Scheme 12). Pyroglutamic acid was converted to its menthyl ester followed by deprotection at C-2 using Pt wire, *n*-Bu_4PF_6 and methanol as a solvent to afford C-2 methoxylated menthyl ester **82** which on reaction with allyltrimethylsilane and $TiCl_4$ was converted to C-2 alkylated product **83**. Compound **83** on reaction with methanolic ammonia and NaCN was converted to primary amide **84**. Compound **84** on oxidation with aqueous OsO_4/$NaIO_4$ followed by reaction with triethylsilane and TFA using nitro methane as a solvent underwent hydrodehydroxylation to give **86** as building block.

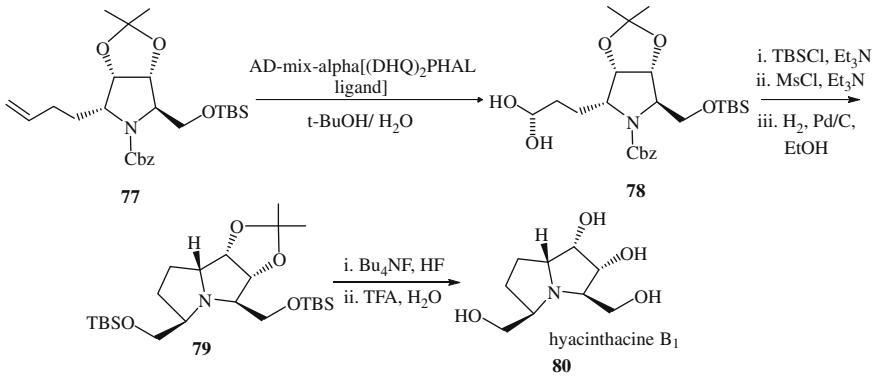
Magni et al. carried out the synthesis of (*R*)-3-[(*S*)-(5-oxo-2-pyrrolidinyl)carbonyl]-thiazolidine-4-carboxylic acid (Pidotimod) **90** as an immunostimulating agent[13a,b] from pyroglutamic acid (Scheme 13). Here pyroglutamic acid was treated with ethyl L-thiazolidine 4-carboxylate in the presence of DCC and CH_2Cl_2 to afford compound **88**, which upon alkaline hydrolysis gave carboxylic acid



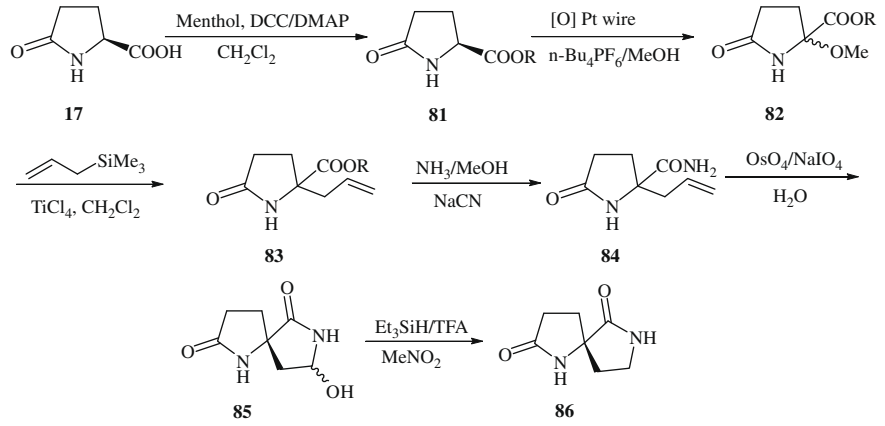
Scheme 9.



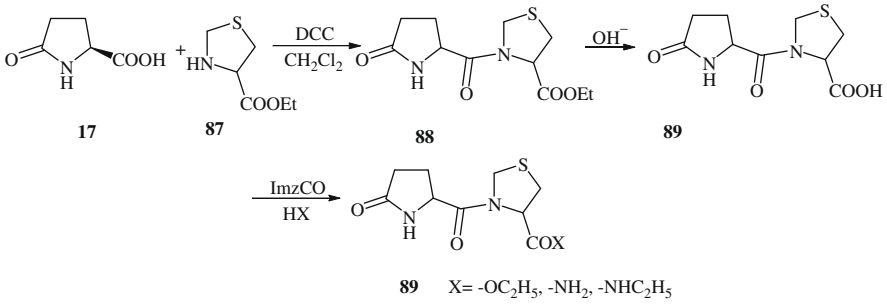
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

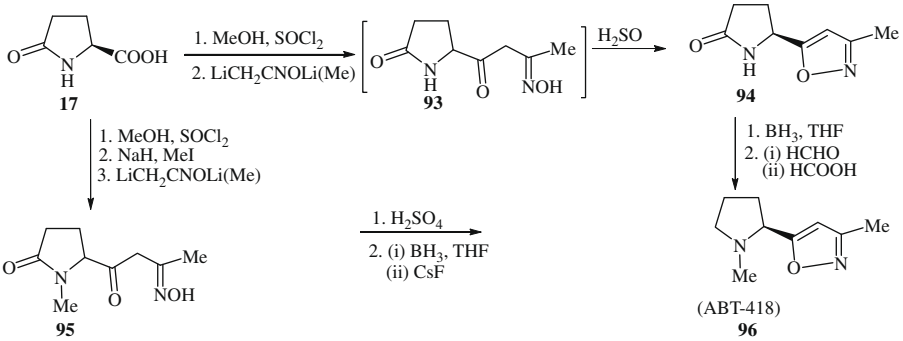
89. The carboxylic acid was converted to its derivatives **90** by reaction with various nucleophiles.

Lin et al. synthesized[14] (*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxasole **96** as a cholinergic channel activator with potent cognitive and anxiolytic activities from pyroglutamic acid **17** (Scheme 14). Pyroglutamic acid was converted to its methyl ester in situ and was subjected to Claisen condensation with acetone oxime dianion, thereby affording compound **93**. The acetone oxime component in compound **93** in the presence of H_2SO_4 as a catalyst underwent cyclization to afford **94**, which on reduction of lactam amide with borane, followed by N-methylation gave the desired ABT-418 derivative **96**.

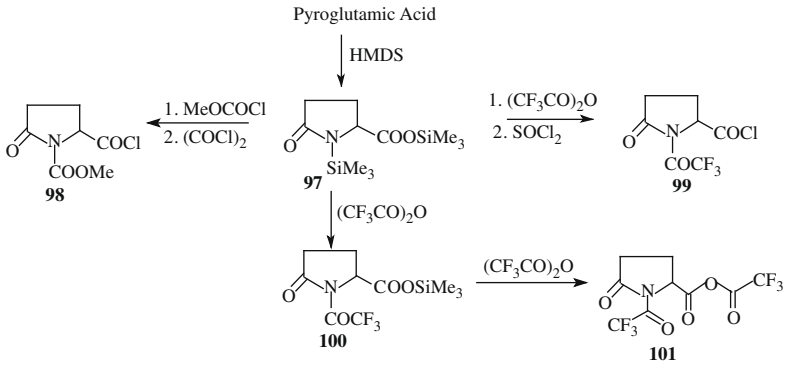
Benoit Rigo et al. investigated[15] various N- and C-protection and deprotection sequences in native pyroglutamate with an aim to develop different reaction methodologies for the synthesis of bioactive molecules (Scheme 15).

Reaction of pyroglutamic acid chloride with isopropylidine malonate (Meldrum's acid) is reported to give C-acylated Meldrum's derivative whose methanolysis gave β-keto ester **103** (Scheme 16), however the reaction of acyl chloride with sodium salt of Meldrum's acid (isopropylidene malonate) in pyridine could not be repeated by Rigo et al.[15,16]

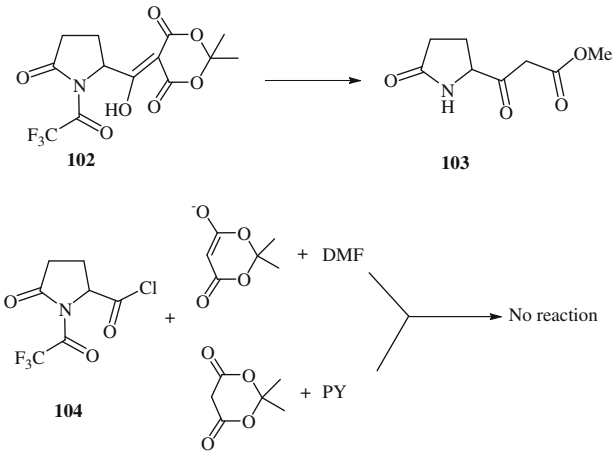
Nagasaka et al.[17] established a new approach to get two enantiomers of 5,5-disubstituted 2-pyrrolidinones **108** with specified configuration starting from pyroglutamic acid through its bicyclic lactam (2*R*,5*S*)-2-aryl-1-aza 3-oxabicyclo[3.3.0]oct-5-en-7-one **105** (Scheme 17). Bicyclic lactam **105** was deprotonated at C-5 by NaH and the resultant anion on Michael addition with methyl acrylate gave two diastereomeric Michael adducts **106** and **107**, which were separated and pure compound **107** on acidic hydrolysis afforded the desired 5,5-disubstituted 2-pyrrolidinone **108**.



Scheme 14.



Scheme 15.



Scheme 16.

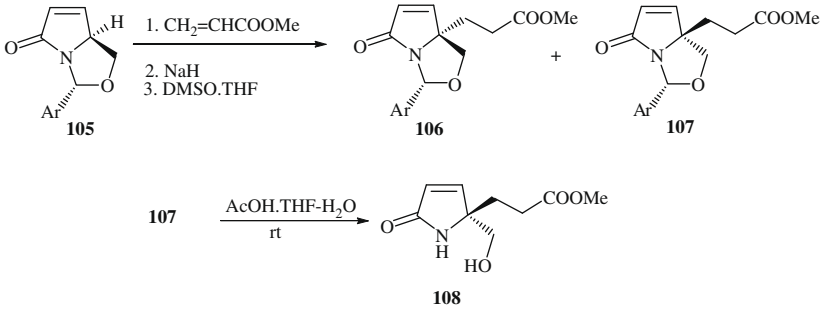
In our studies on the asymmetric use of pyroglutamic acid we synthesized[18] α-benzyl derivative through condensation of pyroglutamic acid with trimethylacetaldehyde to get a bicyclic derivative **109** as a chiral auxiliary which on deprotonation with LiHMDS followed by reaction with electrophiles gave chiral α-substituted pyroglutamate derivative **110** through self-reproduction of chirality (Scheme 18).

Ostendorf et al.[19] established the synthesis of enantiopure hydroxyamidines **116**, utilizing base-catalyzed enantioselective reactions such as Michael reaction (Scheme 19). Methyl pyroglutamate **111** was treated with PhMgBr at low temperature to afford tertiary alcohol, which was converted to silyl ether **112** with TBDMSOTf. Compound **112** on N-derivatization with acrylonitrile afforded compound **113** which on reductive amination of cyano group followed by *N*-Boc protection afforded compound **114**. Compound **114** after a sequence of reactions furnished the desired bicyclic amidine **116**.

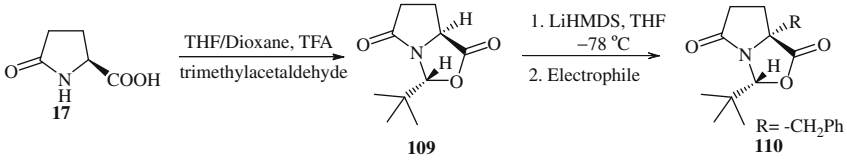
Acevedo et al.[20] synthesized sterically constrained L-glutamine analogues (3*S*,4*R*)-3,4-dimethyl-L-glutamine **123** and (3*S*,4*R*)-3,4-dimethyl-L-pyroglutamic acid from pyroglutamic acid (Scheme 20). Compound **117** already discussed[1a] on methylation with dimethyl lithium cuprate followed by reaction with MeI/Et_2O afforded **118** which after a sequence of reactions was converted to the desired glutamine analogue **123**.

Marchalin et al. developed new methodology for the synthesis of (*S*)-thieno[*f*]indolizinedione **125** from N-alkylated (*S*)-pyroglutamic acid[21] **124** (Scheme 21).

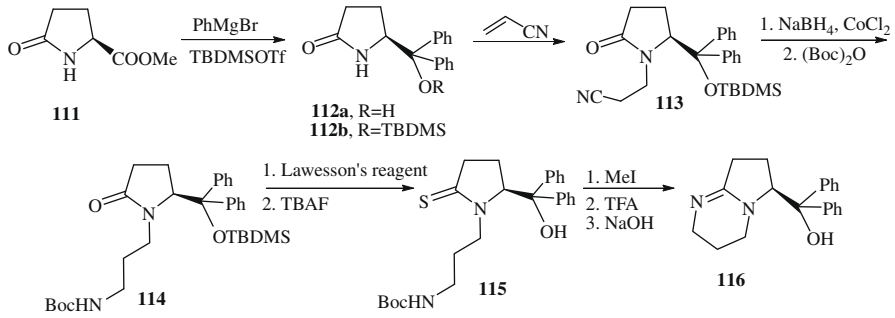
Olson et al.[22a,b] carried out reduction–iodination of methyl *N*-benzyl pyroglutamate **126** to get iodide **127**, which on reaction



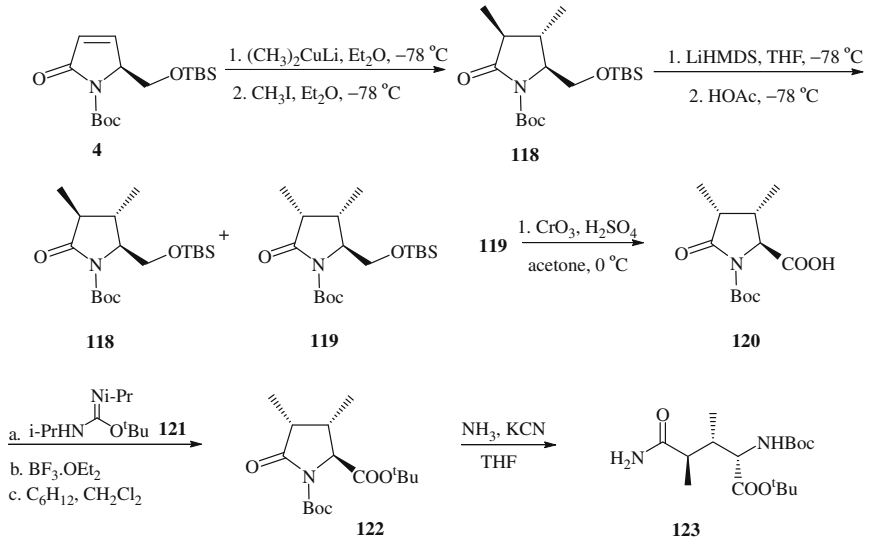
Scheme 17.



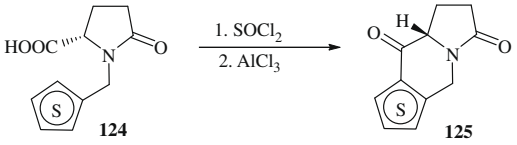
Scheme 18.



Scheme 19.



Scheme 20.



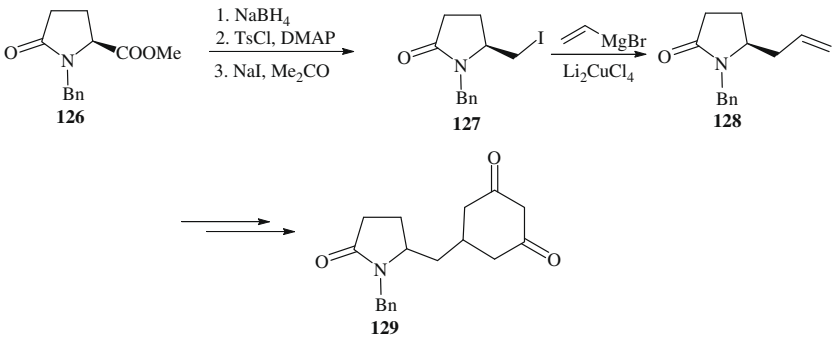
Scheme 21.

with vinyl magnesium bromide and dilithium tetrachloro cuprate gave **128**, a precursor for peptide mimetic of the thyrotropin-releasing hormone (Scheme 22).

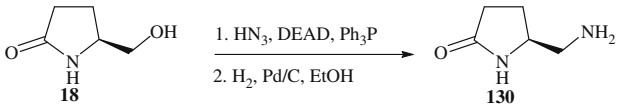
Altman et al. carried out the synthesis of (*S*)-5-(aminoxymethyl)pyrrolidone **130** from (*S*)-5-(hydroxymethyl)pyrrolidone **18** through Mitsunobu reaction with hydrazoic acid followed by the hydrogenation of the resulting azide[23] (Scheme 23).

Wei et al.[24] synthesized (*S*)-5-alkenyl-2-pyrrolinones **132** from *N*-Boc protected methylpyroglutamate **131**. Ester group of compound **131** was reduced to the corresponding aldehyde with diisobutylaluminium hydride at −78 °C. Witting reaction followed by oxidation with pyridinium chlorochromate (PCC) afforded (*S*)-5-alkenyl-2-pyrrolidinones (Scheme 24).

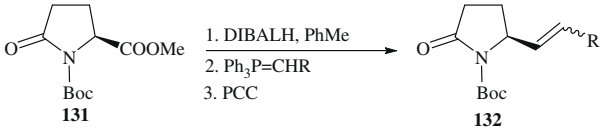
Langlois[25] et al. carried out stereoselective synthesis of (2*S*)-2-hydroxymethylglutamic acid **136** starting from (*S*)-pyroglutaminol



Scheme 22.



Scheme 23.



Scheme 24.

18 through a bicyclic silyloxypyrrole derived from versatile unsaturated lactam (Scheme 25). Compound **133** on reaction with $SnCl_4$ and $NaHCO_3$ was converted to **134** having hydroxyl group at position 5, which on reaction with Me_3SiCN, $SnCl_4$ followed by acidic hydrolysis afforded **136**.

Davies et al. achieved the synthesis and explored the utility of the 3,3-dimethyl-5-substituted-2-pyrrolidinone **140** using pyroglutamic acid as a chiral auxiliary[26] (Scheme 26). Compound **18** on reaction with 2,2,dimethoxypropane in the presence of pTSA, followed by double alkylation at position 7 using LDA and MeI was converted to **138** which on acidic hydrolysis was changed to 4-substituted pyroglutaminol **139**. Treatment of **139** with TBDMSCl in DMF afforded the desired product **140**.

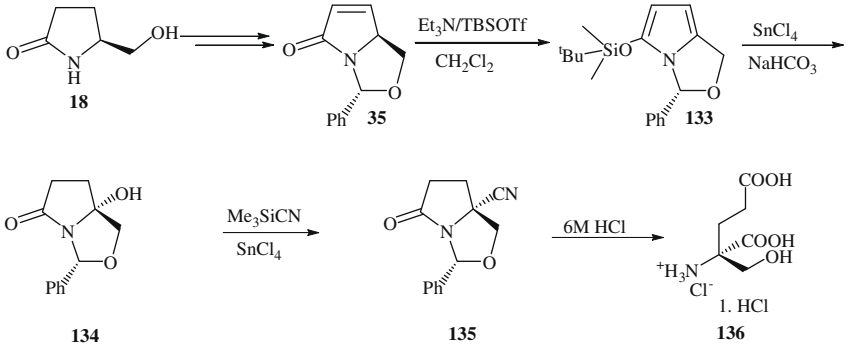
Langlois et al. synthesized racemic and enantiopure (±)-deoxydysibetaine **143** from methyl pyroglutamate[27] **111**. Compound **111** was deprotonated with LiHMDS and alkylated with Eschenmoser's salt to afford **141** which on treatment with CH_3I was converted to quaternary ammonium salt **142**. Compound **142** on passing through alkaline Dowex-550A afforded (±)-deoxydysibetaine (Scheme 27).

Villeneuve et al.[28] carried out the synthesis of pyroglutamic acid fatty esters **145** through lipase-catalyzed esterification with medium chain alcohols (Scheme 28).

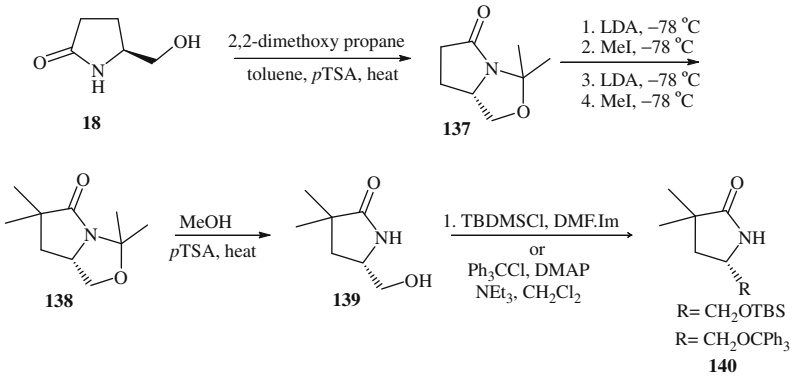
Langlois et al.[29] carried out diastereoselective synthesis of (±)-deoxydysibetaine **152** which was prepared from methyl pyroglutamate through a regioselective Mannich reaction at C-2 (Scheme 29). Compound **146** on reaction with MsCl in pyridine followed by the introduction of azide group at position 2 using NaN_3 was converted to **148**, which on hydrogenation in the presence of H_2/Pd–C afforded **149**. The resultant amine **149** on reaction with CH_3I–iPr_2NEt was converted to **151** and the desired product (±)-deoxydysibetaine **152** was obtained from **151** according to the procedure already described in Scheme 27.

Itoh et al.[30] carried out asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carbolines employing pyroglutamic acid derivative as a chiral auxiliary (Scheme 30).

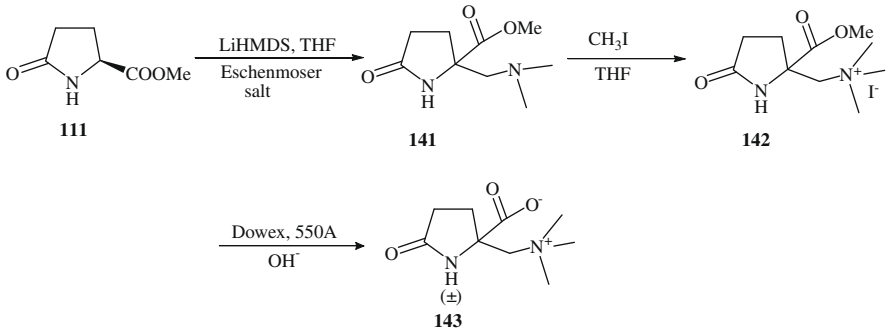
Puschel et al. described the synthesis of pyrrolidinone PNA; novel conformationally restricted PNA analogues, for example, (3*R*,5*R*)(3*S*,5*S*)pyroglutamate-PNA monomers[31] (Scheme 31). Compound **156**, derived from pyroglutamic acid on reaction with MoOPh in the presence of LiHMDS and BuLi followed by the protection of OH group and deprotection of Boc group using Bomchloride and TFA was converted to 3-substituted product **158**, which on reaction with NaH and $BrCH_2COOMe$ afforded N-acylated product **159**. Compound **159** after deprotection gave an alcohol **160** which was converted to **162** by similar steps as described in Scheme 29. Compound **162** on hydrogenation with H_2/Pd–C, followed by protection of amino group using Boc and subsequent reaction with H_2 and $Pd(OH)_2$ afforded **163** with deprotection of Bom. Further



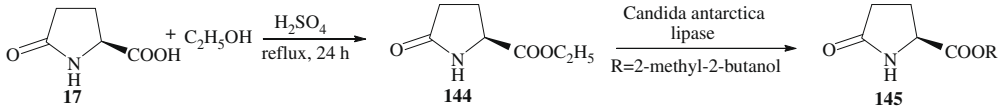
Scheme 25.



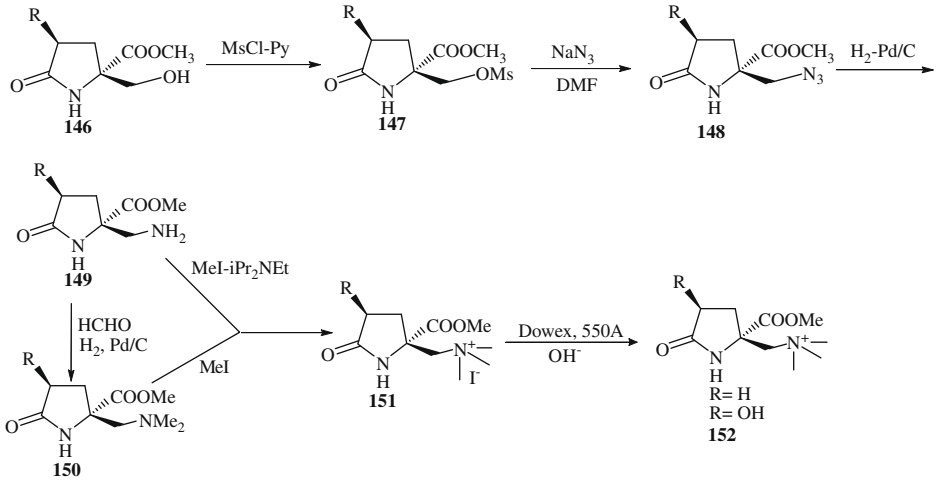
Scheme 26.



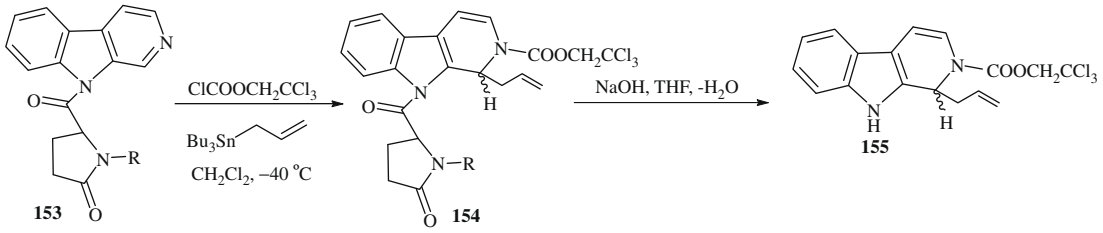
Scheme 27.



Scheme 28.



Scheme 29.

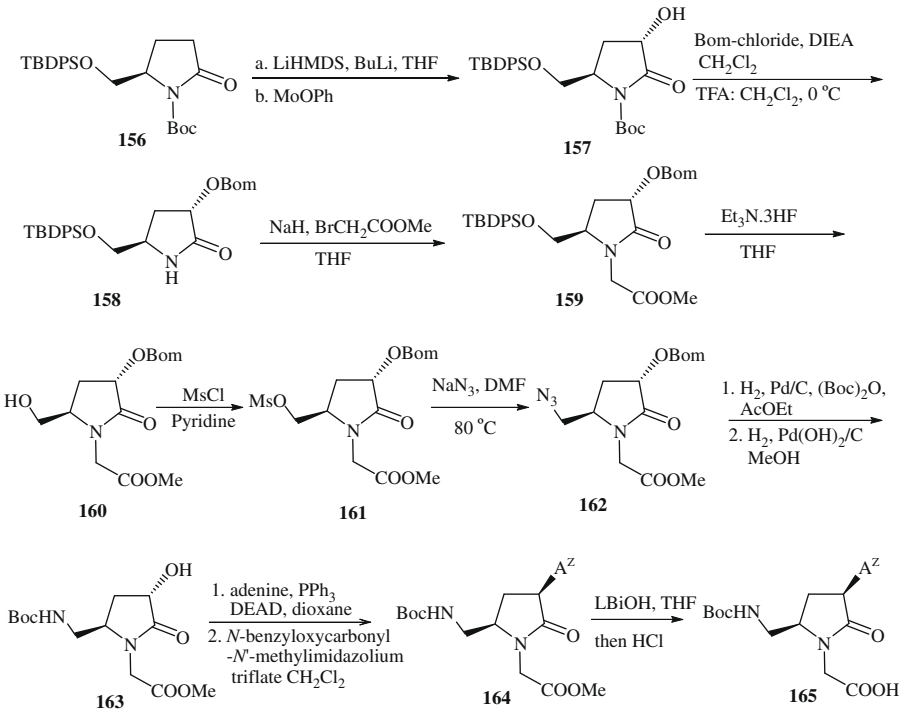


Scheme 30.

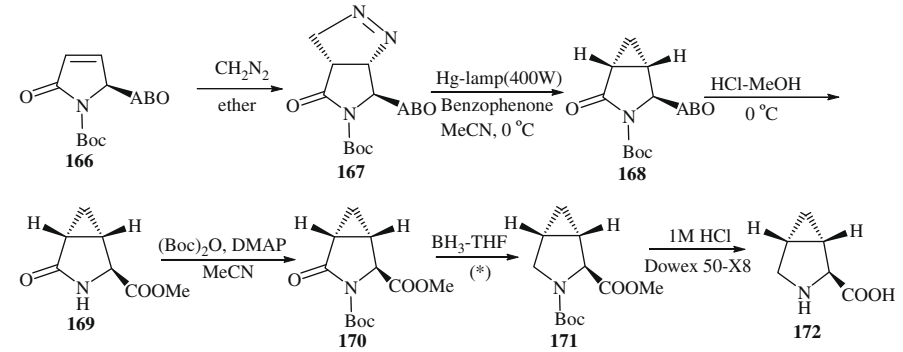
reaction of **163** under Mitsunobu conditions, followed by alkaline hydrolysis afforded **165**.

Oba et al.[32] established novel stereocontrolled approach to conformationally constrained analogues of L-glutamic acid and L-proline via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester. Compound **166** was subjected to 1,3-dipolar cycloaddition with CH_2N_2, followed by photolysis with benzophenone using Hg lamp and compound **168** thus obtained on hydrolysis with MeOH–HCl was converted to methyl ester **169** with deprotection of Boc group. N-Protected compound **170** on reduction with BH_3–THF followed by acidic hydrolysis on Dowex 50-X8 afforded **172** (Scheme 32).

Herdeis et al.[33] carried out the synthesis of unsaturated ortho-pyroglutamic ABO ester **166** from pyroglutamic acid (Scheme 33). Pyroglutamic acid was converted to its alkenyl ester, which on reaction with mCPBA, followed by reaction with zirconocene catalyst and silver perchlorate afforded ABO ester **174**, which was converted to N-protected compound **175**. Compound **175** upon oxidation under usual conditions, followed by oxidative deselenenylation using H_2O_2 afforded **166**.

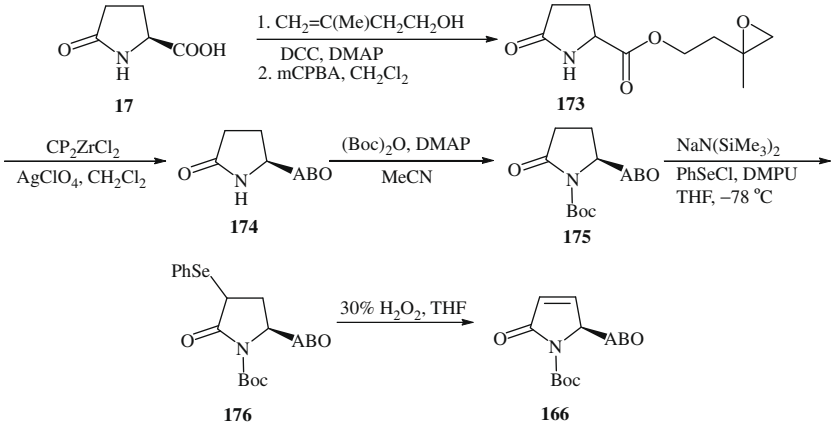


Scheme 31.



*= ABO=5-methyl-2,7,8-trioxabicyclo[3,2,1]oct-lyl

Scheme 32.



Scheme 33.

Stevens et al. reported a short and elegant synthetic pathway for the synthesis of 1,3-dioxo-hexahydropyrido[1,2-*c*][1,3]diazepine carboxylates, a new 1,3-diazepan-2,4-dione **181** containing bicyclic moiety, starting from pyroglutamate[34] (Scheme 34). Compound **177** on reaction with LiHMDS was deprotected at C-2, resultant anion on reaction with electrophile afforded **178**, where lactam carbonyl C–N bond was cleaved using NaH, RNCO to expend the ring and resulting product on reaction with electrophile in the presence of K_2CO_3 yielded **180**. Compound **180** was subjected to cyclization with Grubb's II generation catalyst thereby affording compound **181**.

Bourry et al. reported their studies on pyrrolidinones through reaction of methylene dichloride under Friedal–Crafts conditions, with an objective to synthesize α-hydroxymethyl ketone in the hexahydrobenzo[*f*]indolizine series[35] (Scheme 35) using pyroglutamic acid as a chiral precursor.

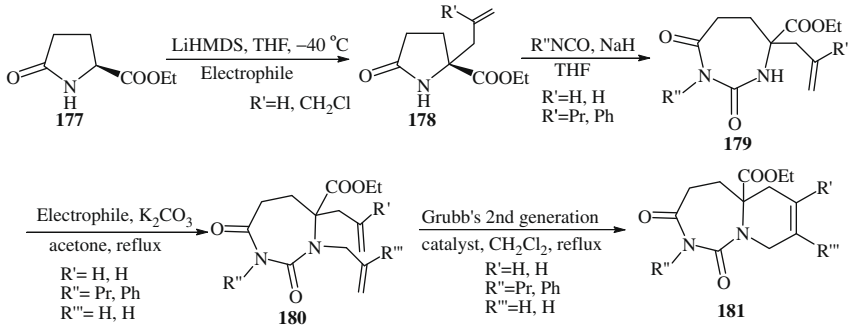
Mavromoustakos et al.[36a,b] reported the synthesis, binding studies and in vivo biological evaluation of antihypertensive analogues **188** using pyroglutamic acid as starting material (Scheme 36). Compound **111** on reaction with NaH, $PhCH_2Br$, followed by reduction using $LiBH_4$ was converted to *N*-benzyl methyl pyroglutaminol **186**, which was converted to its *o*-tosyl derivative **187**. Treatment of **187** with lithium imidazole afforded antihypertensive agent **188**.

Beal et al. described anodic oxidation/olefin metathesis strategy thereby developing a unified approach to the synthesis of bicyclic lactam peptidomimetics using pyroglutamic acid[37] (Scheme 37). Pyroglutamic acid derivative **189** on acidic hydrolysis was converted to intermediate product and subsequent reaction with pyroglutamic acid, followed by amination using NH_3 and MeOH afforded **190**.

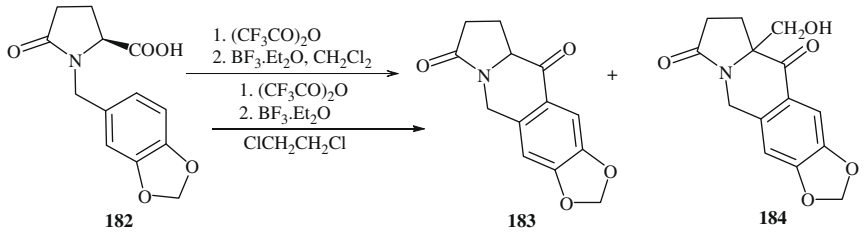
Langlois et al. reported the tandem electrophilic and nucleophilic addition to bicyclic *tert*-butyl-dimethylsilyloxypyrrole derived from (*S*) pyroglutaminol[38] (Scheme 38).

2.2. Activation of lactam carbonyl at C-5 by formation of thiolactam, imino, iminium ethers and as lactam acetals

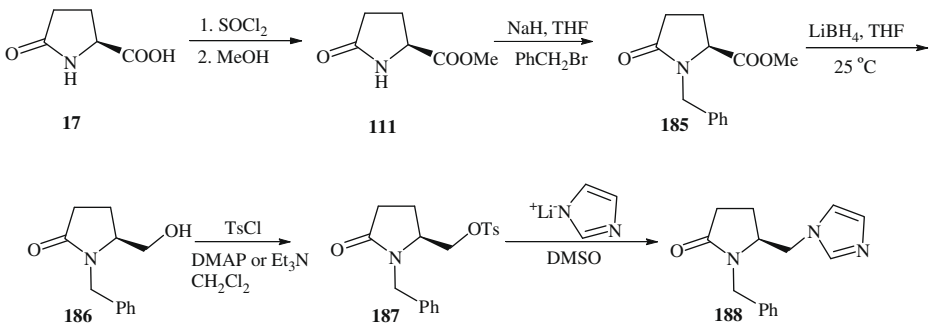
Suitably activated lactams and amides possess great synthetic utility for the construction of many of the nitrogen-containing heterocycles. Activation of the lactam is generally being carried out by conversion to thiolactam, imino, iminium ethers or as lactam ace-



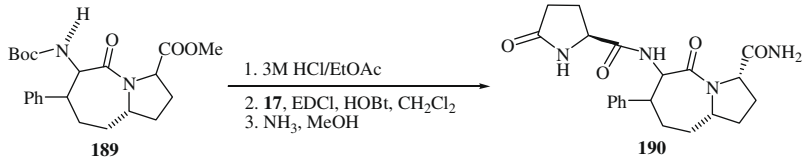
Scheme 34.



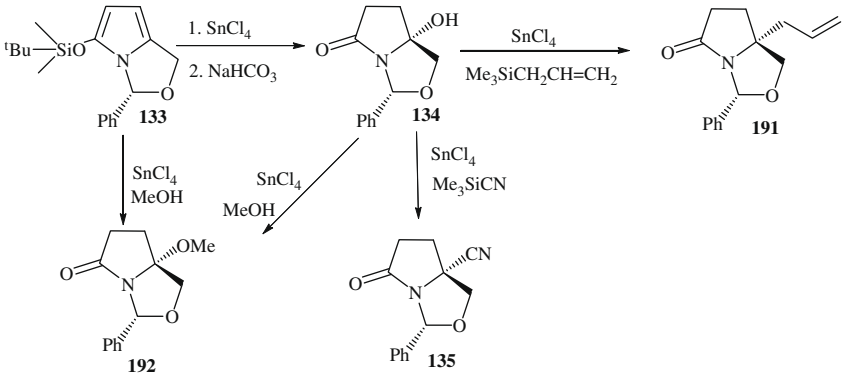
Scheme 35.



Scheme 36.



Scheme 37.



Scheme 38.

tals. Among the activated lactams, lactam acetals are particularly useful as these react with both nucleophiles and electrophiles at C_1 and C_2, respectively, and with bifunctional reagents to form annulated products. Because of these reasons many workers have made use of pyroglutamates via the activation of the lactam carbonyl at C-5 of pyroglutamate.

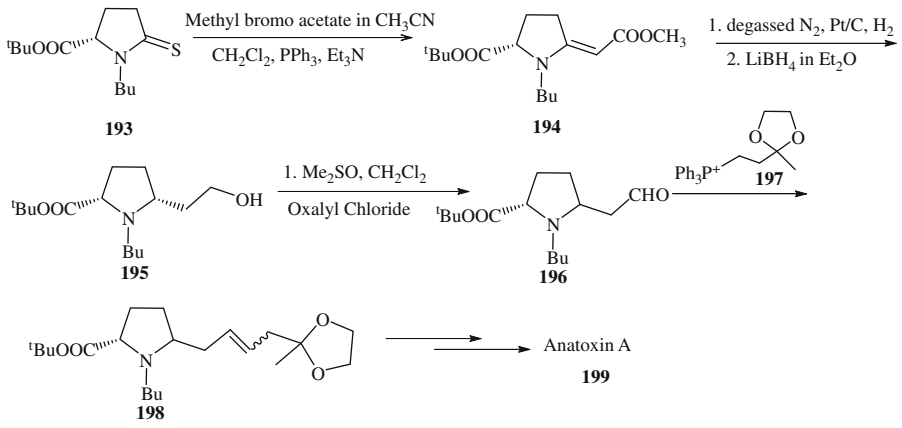
L-Pyroglutamic acid has been used as chiral starting material for the synthesis of anatoxin-a, a potent nerve depolarizing agent, via intermediacy of thiolactam.[12] C–C bond formation at C-5 was effected by a sulfide contraction reaction[39] (Scheme 39).

Bachi et al. have described[40] the synthesis of carbapenam-3-carboxylates **207**(**a**) and **207**(**b**) starting from ethyl (*S*)-pyroglutamate which was converted to the corresponding 5-thioxo derivative for C–C bond formation at C-5 (Scheme 40). Compound **200** on reaction with ethyl-2-bromo-3-oxobutyrate, followed by hydrogenolysis with CH_3COOH and TFA (20%) was converted to diastereomeric compounds **202**, **203a** and **203b**, in which **203a** on reaction with KOH and $(Boc)_2O$ afforded N-protected acid **204**. Compound **204** was converted to its PNB ester **205** which after *N*-Boc deprotection followed by cyclization was converted to **207a** and **207b** using substituted carbodiimide.

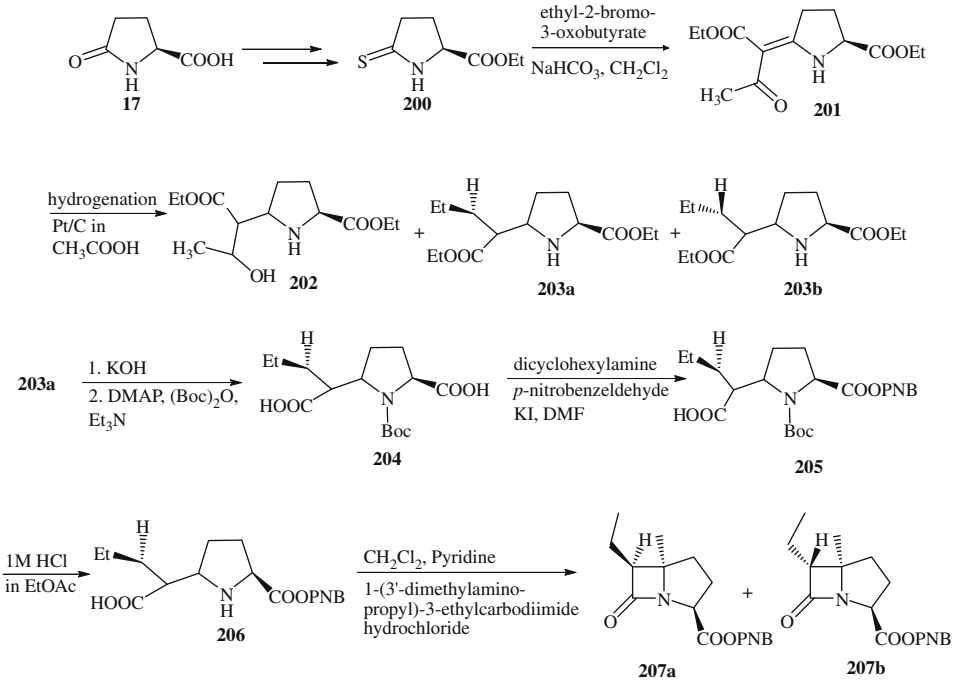
Fang et al. have carried out[41] the annulation of diazomethylvinyl ketone with a variety of thiolactams prepared from (*S*)-pyroglutamic acid. Thiolactam derivative of pyroglutamic acid **209** was converted to **210** by Michael addition which was cyclized to get **211** in the presence of $[Rh(OAc)_2]_2$, W-2 and Ra-Ni. Resultant material on oxidation with OsO_4 and H_2S in methanol, followed by protection of OH group with TBSCl was converted to **212**. Lithium enolate-derived reaction of **212** with *t*-butyl propionate afforded **213** which upon selective reduction of the double bond of side chain followed by deprotection afforded **214**. Thus this synthetic strategy provided a novel route for dihydropyridones like ISO A58365A **214**, the γ-pyridone analog of the potent ACE inhibitor A58365A (Scheme 41).

Rosset et al. have described[42] the enantioselective synthesis of (5*R*)-2-(5-hexenyl)-5-nonyl-3,4-dihydro-2*H*-pyrrole and (2*R*,5*R*), 2-(5-hexenyl)-5-nonyl pyrrolidine, Monomorium minutum ant venum alkaloids, from (*S*)-pyroglutamic acid through lactam ether (Scheme 42).

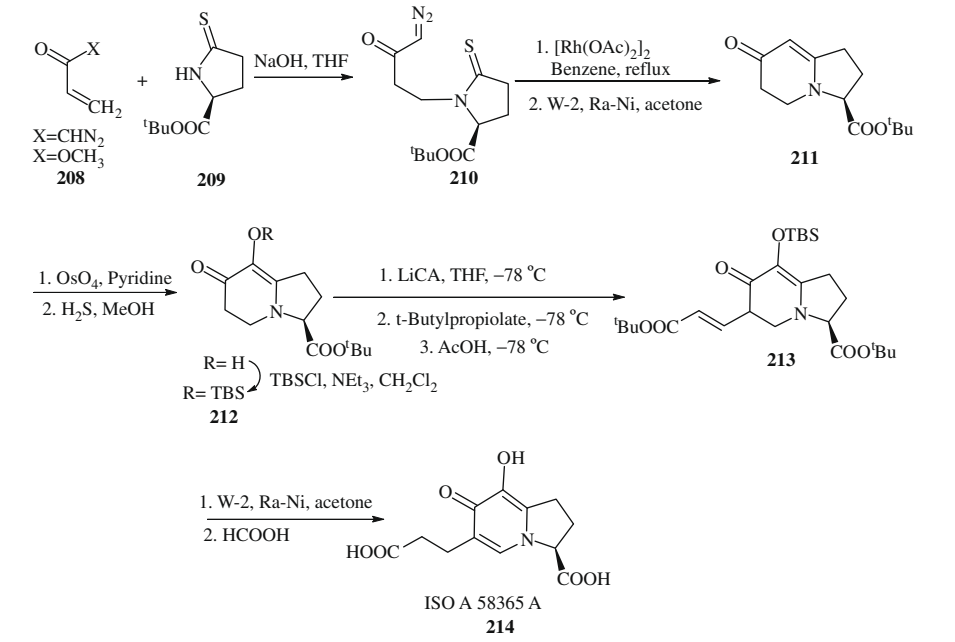
Both D- and L-pyroglutamic acids have been used[43a,b] with prior activation at C-5 for the synthesis of semicorrin metal complexes as enantioselective catalysts (Scheme 43). These semicorrins[43b]



Scheme 39.



Scheme 40.

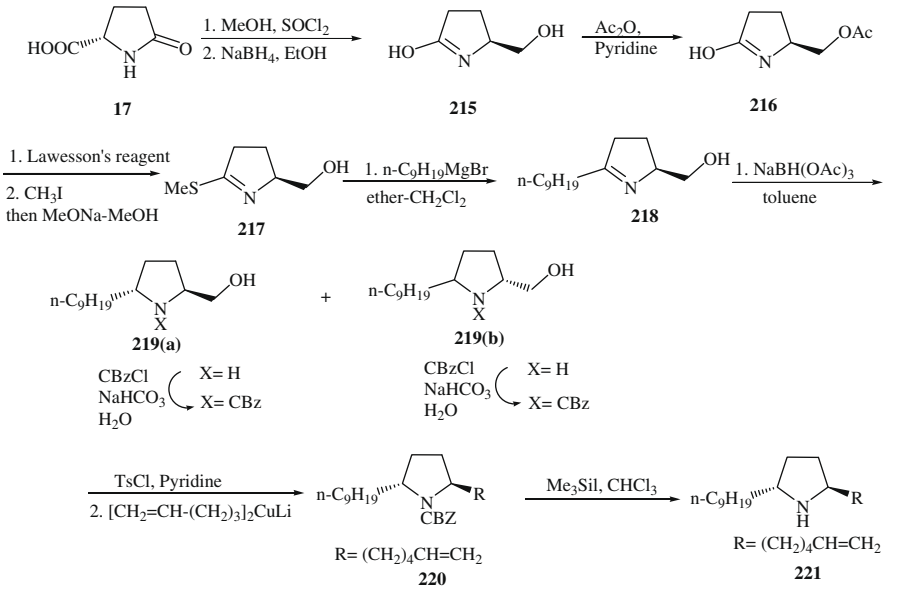


Scheme 41.

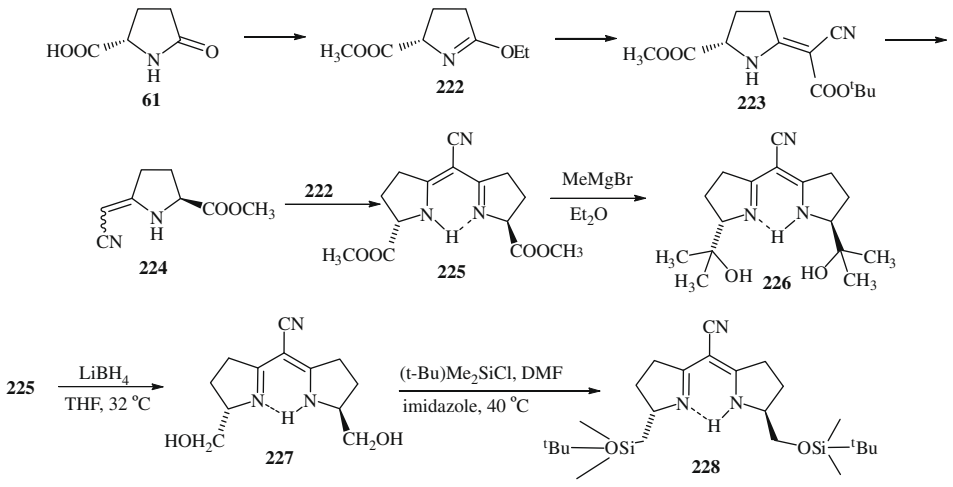
225–228 possess several features that make them attractive ligands for enantioselective control of metal-catalyzed reactions.

Singh et al. described[44] a simple and efficient synthesis of 8-methyl-3,8-diazabicyclo[3.2.1]octane (azatropane) and 3-substituted azatropanes using pyroglutamic acid as starting material and exploiting amide activation methodology (Scheme 44). Pyroglutamic acid was converted to *N*-methyl pyroglutamate which on reaction with Lawesson's reagent was converted to the corresponding thio lactam. Treatment of thio lactam with methyl iodide in benzene, followed by reaction with nitro methane in the presence of triethylamine yielded nitroenamine **230**. Nitroenamine **230** after catalytic hydrogenation over Pd–C in the presence of ammonium formate in absolute methanol afforded compound **231**. Compound **231** on reduction of lactam carbonyl with $LiAlH_4$ followed by N-alkylation under usual conditions furnished the desired compound **233**.

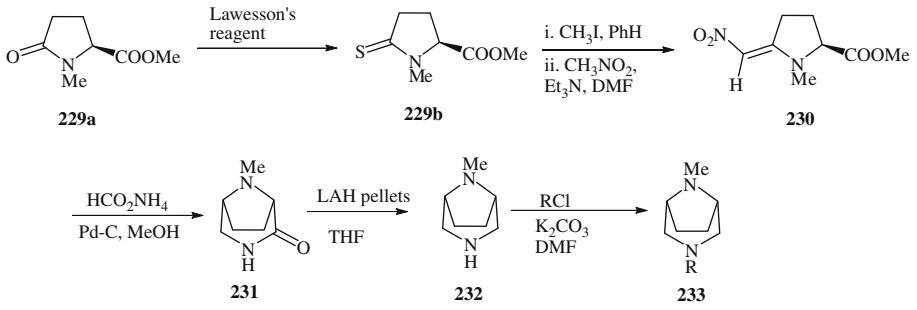
Liyanage et al. established[45] the synthetic route for carbapyochelins via diastereoselective azidation of 5-(ethoxycarbonyl) methyl proline derivative (Scheme 45). Pyroglutamic acid derivative **234** on reduction of azide group, followed by EDC-mediated coupling of crude amine with *O*-benzyl salicylic acid afforded compound **235**, which was subjected to the reduction



Scheme 42.



Scheme 43.

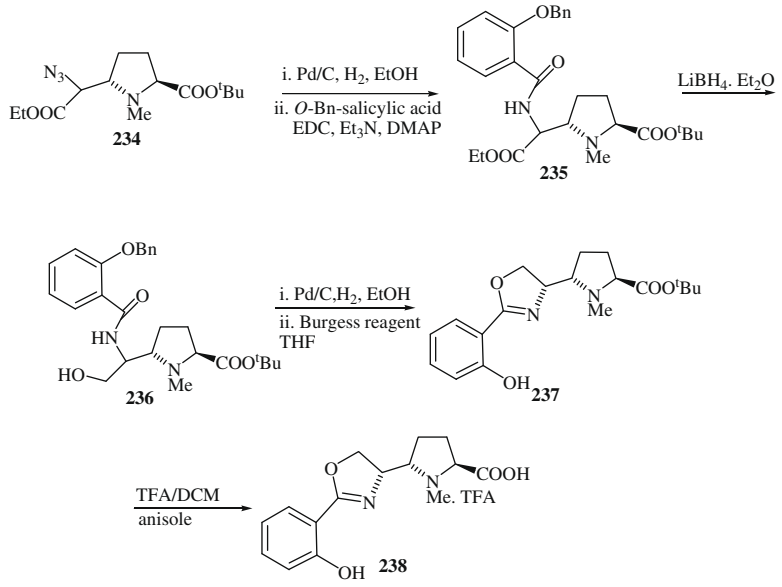


Scheme 44.

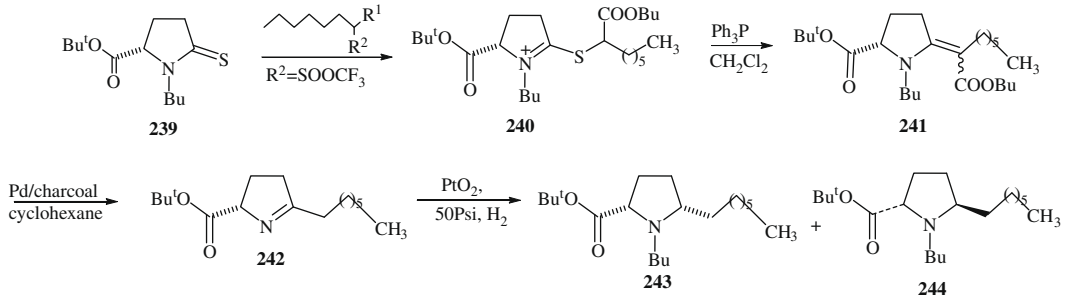
of ethyl ester group in the presence of lithium borohydride to give **236**. Compound **236** on further hydrogenolysis followed by cyclization with Burgess reagent afforded **237**. Compound **237** on deprotection of *t*-butyl group afforded the desired carbapyochelins **238**.

In a view to develop methodologies for the chirospecific synthesis of 5-butyl-2-heptyl pyrrolidines, Shiosaki et al. reported a procedure[46] for the asymmetric synthesis of 5-substituted prolines from pyroglutamates, in which the key steps adopted were the thiolactam formation from lactam of pyroglutamates followed by induction of side chain at C-5 through sulfide contraction and reduction sequences (Scheme 46).

Corey et al.[47] have utilized C-5 centre of the pyroglutamate by reduction for the synthesis of poly functional, structurally defined



Scheme 45.

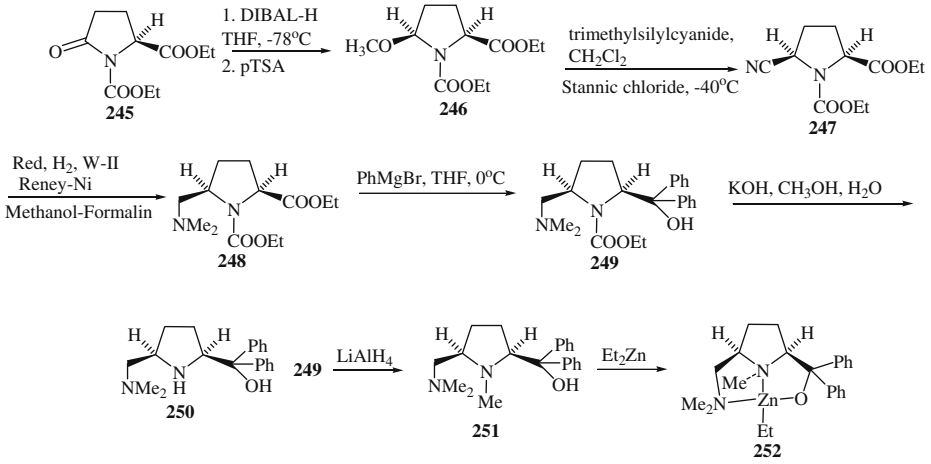


Scheme 46.

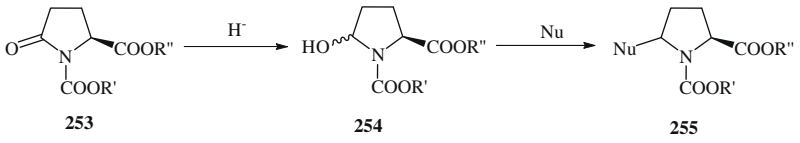
catalyst **252**, which finds use in the enantioselective addition of dialkylzinc reagents to aldehydes (Scheme 47).

Wistard et al. have reported the synthesis of 5-substituted pyrrolidines from N-acylated pyroglutamic acid[48a,b] (Scheme 48).

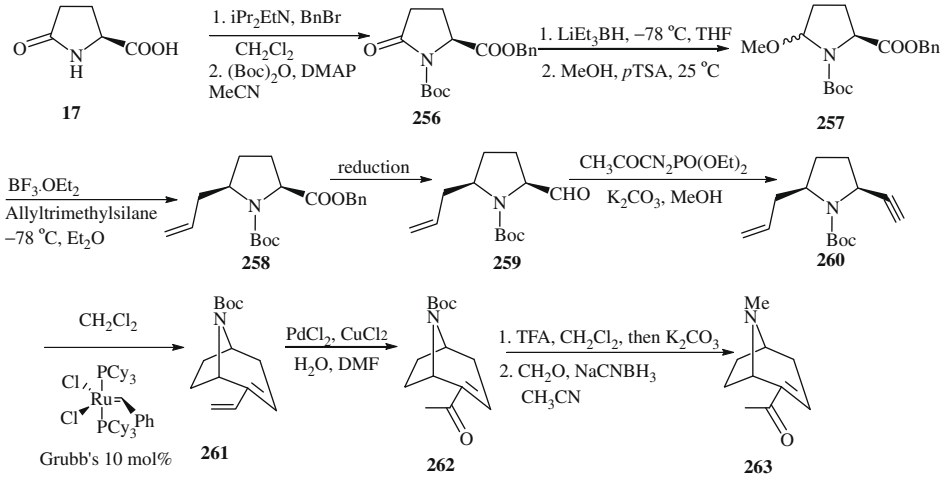
Agarwal et al. established a concise asymmetric approach to the bridged bicyclic tropane alkaloid (+)-Ferreiginine using enyne ring-closing metathesis[49] (Scheme 49). Pyroglutamic acid was converted to its benzyl ester, followed by reduction using $LiEt_3BH$ and MeOH/pTSA to afford C-5 methoxylated ester **257**, which was subsequently subjected to C-5 allylation to afford **258** with stereoselectivity. Compound **258** on reduction followed by acetylenic carbon insertion under modified Witting conditions and subsequent hydrolysis of the resultant product afforded **260**. Treatment of **260** with Grubb's catalyst yielded **261** which after a sequence of reactions afforded the desired product (+)-ferreiginine **263**.



Scheme 47.

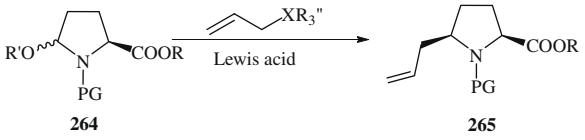


Scheme 48.



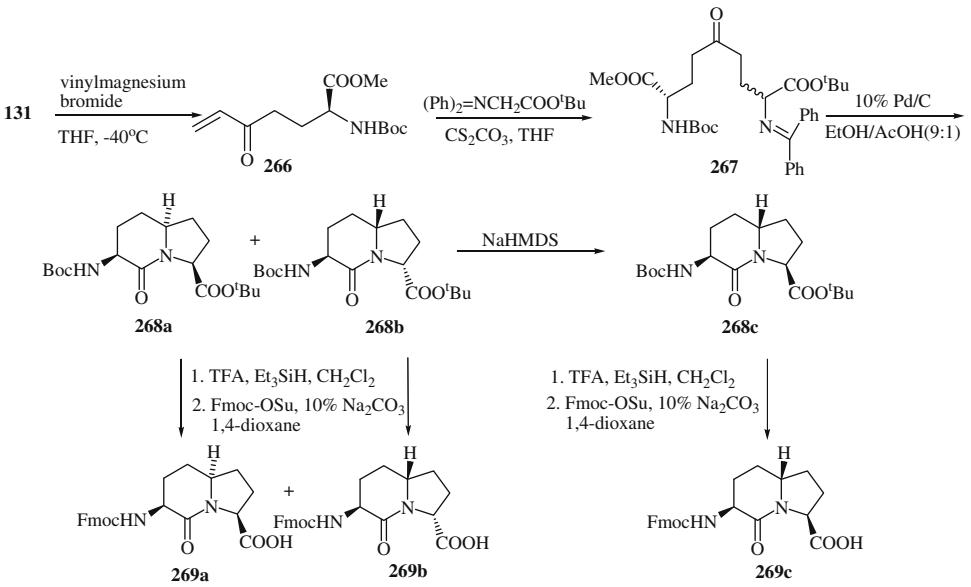
Scheme 49.

Another approach for the preparation of pyrrolidine allylation products involving diastereoselective enzymatic ester hydrolysis (Scheme 50) has also been reported.[50] An important application of this reaction is in the addition of trimethylsilane to various N-acyliminium ions bearing ester side chains. As a result the precursor **264** could be converted to its allylated derivative **265**.



Scheme 50.

Mandal et al. described an efficient synthesis of the constrained peptidomimetic 2-oxo-3-(*N*-9-fluorenyloxy carbonylamino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acid from pyroglutamic acid[51] (Scheme 51). *N*-Boc methyl pyroglutamate **131** on reaction with vinyl magnesium bromide afforded Micheal acceptor **266**, which on reaction with Schiff's base in the presence of Cs_2CO_3 followed by hydrogenation using Pd/C in EtOH/AcOH (9:1) coupled with cyclization, was converted to diastereomeric compounds **268a** and **268b**. Compound **268b** was epimerized to **268C** in the



Scheme 51.

presence of NaHMDS. Treatment of each diastereoisomer of **268** under usual conditions afforded the desired stereospecific isomers of **269**.

Hanessian et al.[52] synthesized *N*-acyloxyiminium ions generated from 4-substituted L-pyroglutamic esters with 4-(3-butenyl),4-(3-butynyl),4-(3-cinnamylmethyl) and 4-allenic ethers which subsequently underwent rapid Lewis acid-mediated carboxycyclization to afford stereodefined azacyclic compounds (Scheme 52).

Conchon et al. described[53] asymmetric synthesis of 3,5-disubstituted indolizidines by intramolecular addition of an allylsilane on an *N*-acyliminium ion derived from pyroglutamic acid. Compound **273** on reaction with benzylchloroformate in the presence of *n*-BuLi, followed by reduction was converted to **274**, which on reaction with α-hydroxy β-trimethylsilyl-γ-allyl derivative in the presence of $SnCl_4$ was converted to **276** and subsequent reaction with PDC led to cyclization, thereby affording **278**. Compound **278** after hydrogenation afforded isomers **279** and **280** (Scheme 53).

Peng et al. reported the designing and synthesis of a 1,5-diazabicyclo[6,3,0]dodecane amino acid derivatives as novel dipeptide reverse-turn mimetics[54] (Scheme 54). Pyroglutamic acid derivative **281** on reaction with TBSCl, followed by hydrogenation using Pd/C catalyst was converted to **282**, which after N-acylation coupled with the deprotection of OH group afforded **283**. Oxidation of side chain OH group of **283** followed by N-deprotection coupled with cyclization gave the desired compound **285**.

Angiolini et al. carried out[55] synthesis of azabicyclo alkane amino acid scaffolds as reverse-turn inducer dipeptide mimics (Scheme 55). Compound **286** upon oxidation, followed by reaction with (±)-(*Z*)-α-phosphonoglycine trimethyl ester and subsequent protection of NH group afforded **287**. Compound **287** on alkaline hydrolysis afforded **288**, which on hydrogenolysis followed by cyclization was converted to the desired molecules **289** and **290** as diastereomers.

Ghammarti et al. described the synthesis of 1,5,6-10b-tetrahydro-2*H*-pyrrolo[1,2-*c*]quinazoline-3-ones from pyroglutamic acid[56] (Scheme 56).

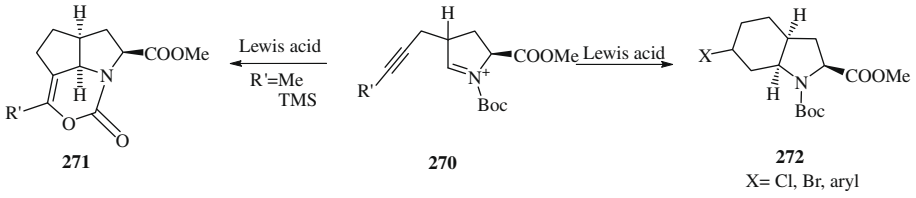
Danishefsky et al.[57] described total synthesis of salinosporamide A, (Scheme 57) using pyroglutamic acid as a chiral starting material.

Manzoni et al. reported the synthesis of spiroazabicycloalkane amino acid scaffolds as reverse-turn inducer dipeptide mimics[58] starting from pyroglutamate (Scheme 58). Compound **303** on swern oxidation afforded aldehydic ester **304**, which on witting reaction as described in Scheme 55 gave **305**. Compound **305** after protection, deprotection and cyclization sequences afforded diastereomers **307a** and **307b**.

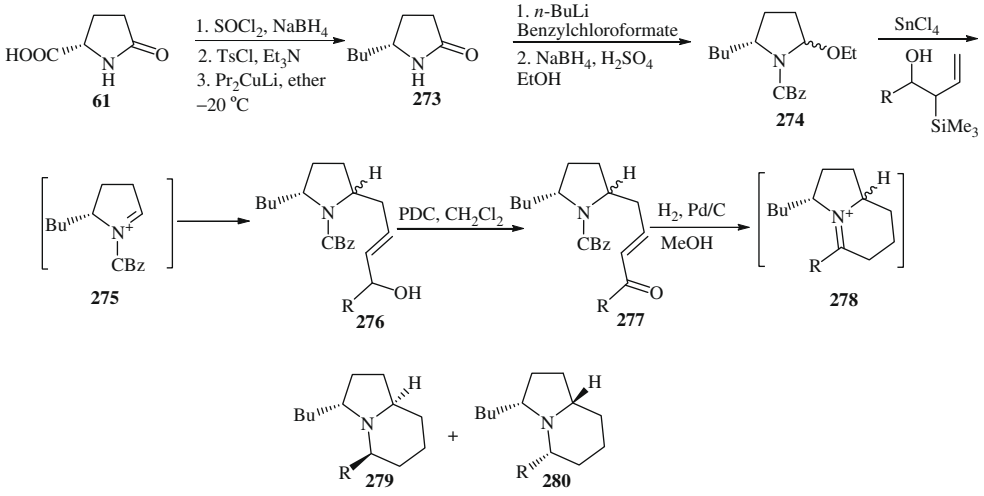
Mulzer et al. synthesized rigid dipeptide mimetics. They have carried out stereocontrolled synthesis of all eight stereoisomers of 2-oxo-3-(*N*-Cbz-amino)-1-azabicyclo[4,3,0]nonane-9-carboxylic acid esters[59] (Scheme 59). Compound **308** upon oxidation followed by witting reaction as described in Scheme 55 was converted to **310** and alkene component was subsequently reduced to get **311**. Compound **311** after *t*-butyl ester hydrolysis, cyclization and conversion of carboxylic to its methyl ester afforded **312**.

Hussaini et al.[60] reported a concise approach for the synthesis of *cis*-2,5-disubstituted pyrrolidines starting from pyroglutamic acid (Scheme 60). 5-Thioxo ethyl prolinate **200** was converted to 5-alkylidine derivative **313** on reaction with diethyl bromomalonate in the presence of sodium bicarbonate. Compound **313** after N-benzolylation afforded N-protected derivative **314**. Compound **314** on hydrogenation in the presence of H_2 (Pd–C), EtOH and CH_2Cl_2 gave *N*-benzoyl 2,5 disubstituted pyrrolidine **315**.

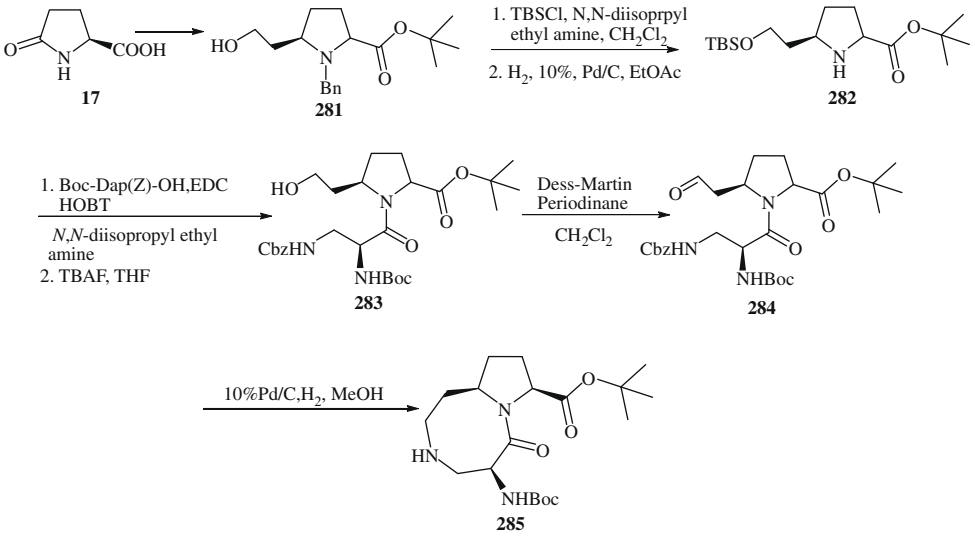
In another publication the same researchers have described a new methodology for the diastereoselective synthesis of 2,5-disubstituted pyrrolidine by the reduction of enamines derived from



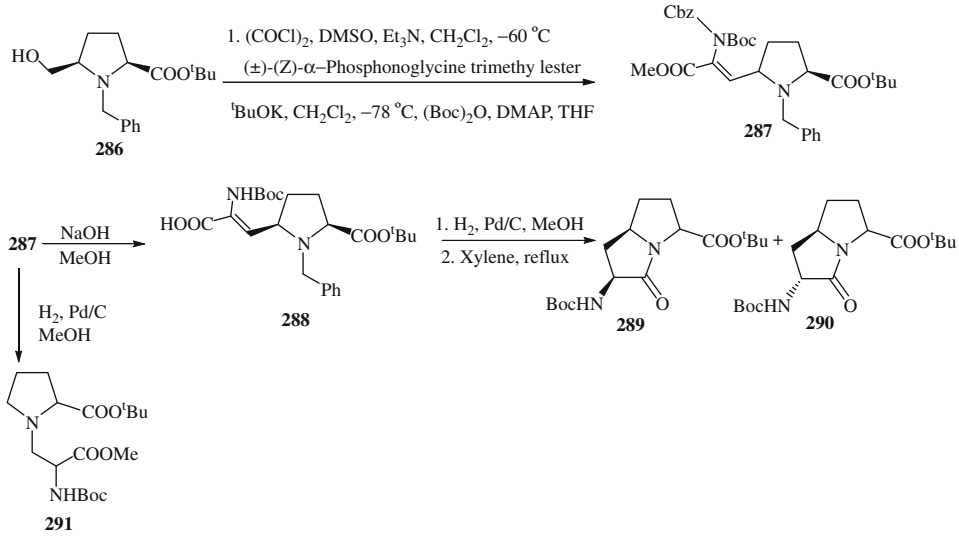
Scheme 52.



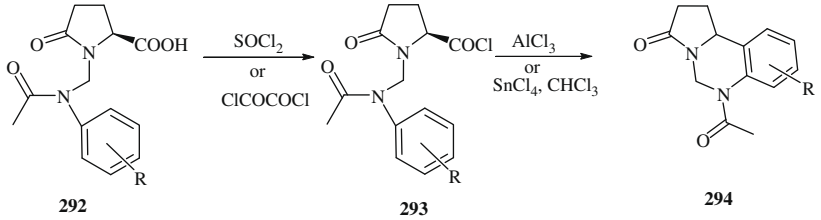
Scheme 53.



Scheme 54.



Scheme 55.

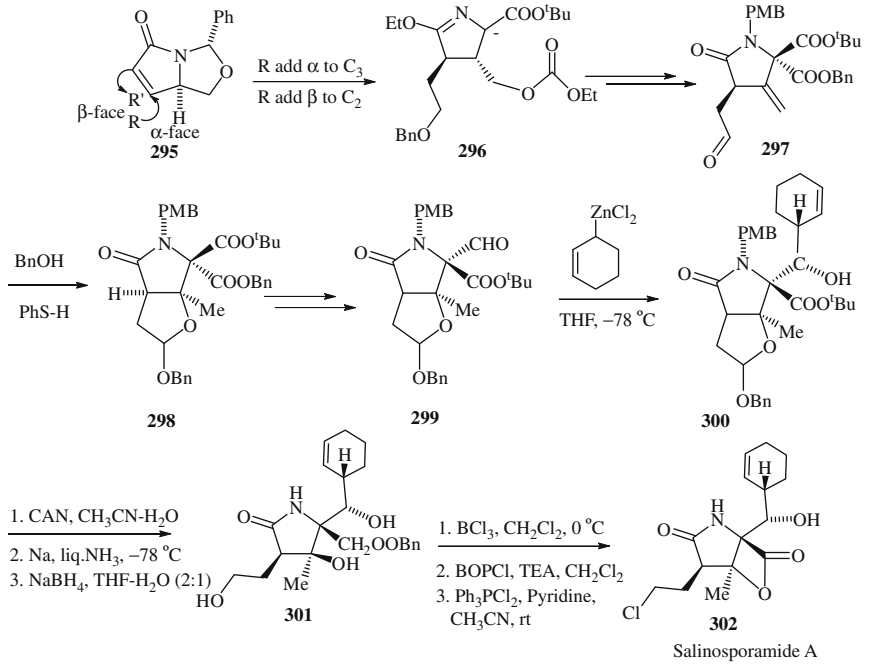


Scheme 56.

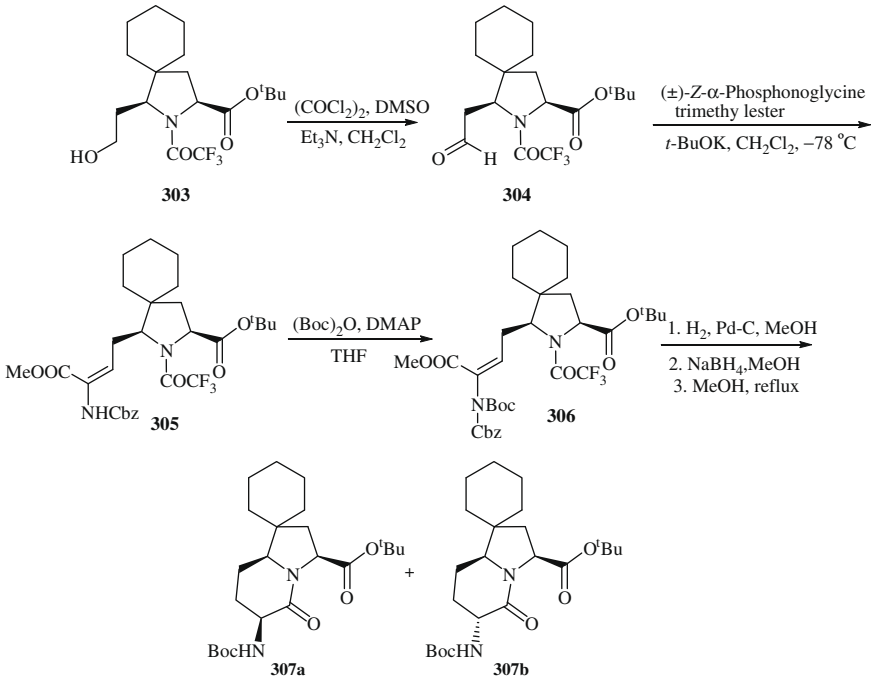
pyroglutamic acid[61] (Scheme 61). Compound **316** was converted to its *N*-Boc derivative which upon reduction in the presence of $NaBH_4$ gave the desired product **318**.

Moloney et al. described[62,144] a direct and versatile synthetic route for the reliable synthesis of *trans*-2,5-disubstituted pyrrolidines from pyroglutamic acid. *N*-Boc ethyl pyroglutamate **319** was reduced to 5-substituted product **320**, which on reaction with $PhSO_2H$ gave **321** (Scheme 62).

Chan et al.[63a–c] described the conjugated addition of activated nitrogen nucleophiles, to α,β-unsaturated bicyclic lactams with an objective to synthesize enantiopure β-aminopyrrolidinones (Scheme 63) and α,β-diaminopyrrolidinones[64] (Scheme 64), respectively, from (*S*)-pyroglutamic acid. Lithium enolate-derived Michael addition of **324** with di.*tert*-butyl azodicarboxylate afforded diamino lactam **325**. This compound was transformed to the corresponding lactam **326** by deprotection with TFA which on



Scheme 57.



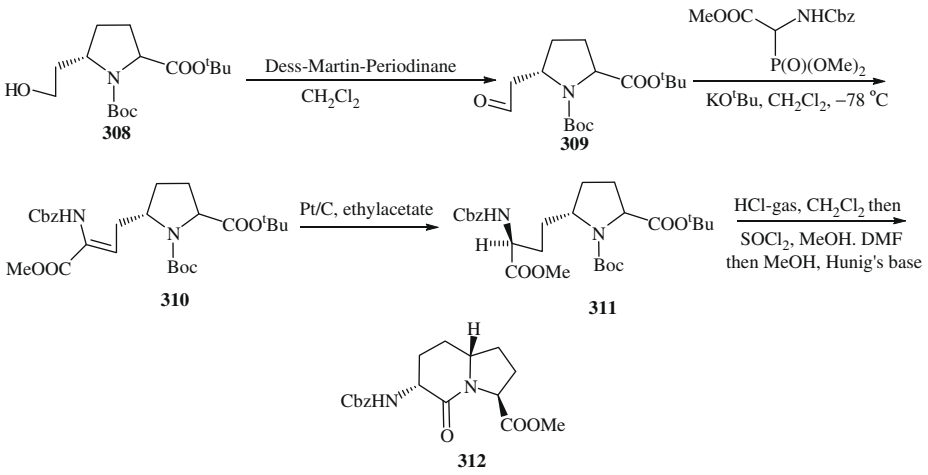
Scheme 58.

hydrogenolysis using Pd/C in glacial acetic acid afforded 3,4 diamino pyroglutaminols **327a** and **327b**.

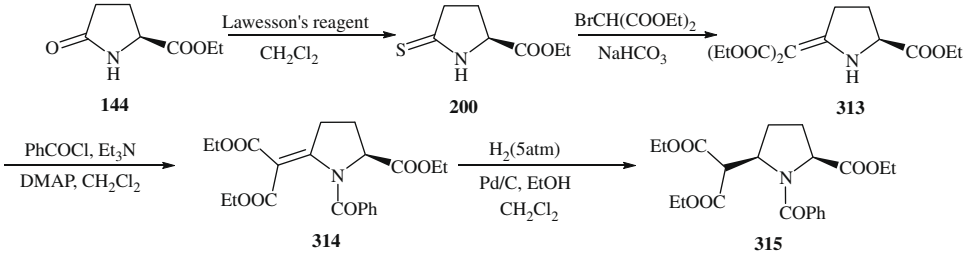
Hara et al.[65] described remarkable endo selectivity on hydroxylation of bicyclic lactam enolates **328** with MoOPD and MoOPH to afford hydroxylated products **329a** and **329b** (Scheme 65) derived from pyroglutamic acid.

In another approach Bailey et al. described the diastereoselectivity during alkylation of bicyclic lactams[66] (Scheme 66). Compound **330** on reaction with acetophenone dimethyl acetal using pTSA (catalytic amount) was converted to the corresponding product **331a**, which after Li enolate-derived benzylation reaction at C-7 was converted to **331b**.

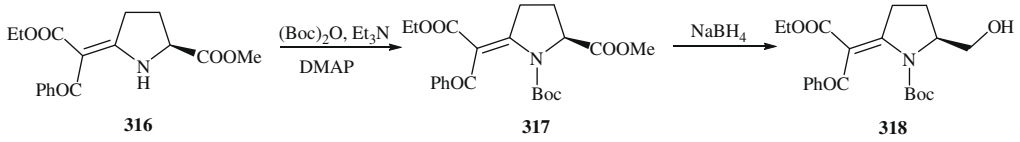
Colombo et al. reported[67] synthesis of new bicyclic lactam peptidomimetics through ring-closing metathesis reactions (Scheme 67). *N*-Boc-5-allyl-L-proline methyl ester **332** was converted to **333** by acidic hydrolysis with deprotection of Boc group, compound **333** on reaction with 2 benzyl 2 benzyloxycarbonylamine but-3-enoic acid and PyBrop^R in the presence of DIEA and DMAP



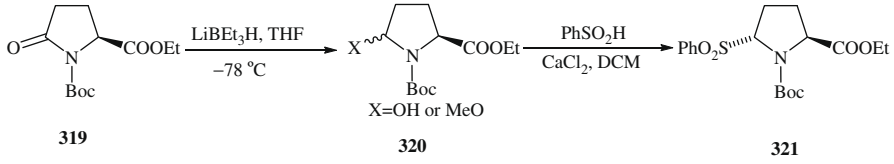
Scheme 59.



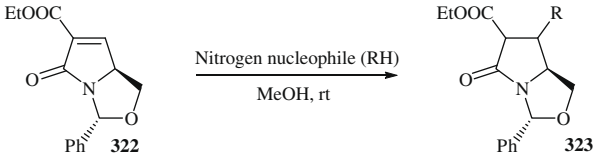
Scheme 60.



Scheme 61.



Scheme 62.

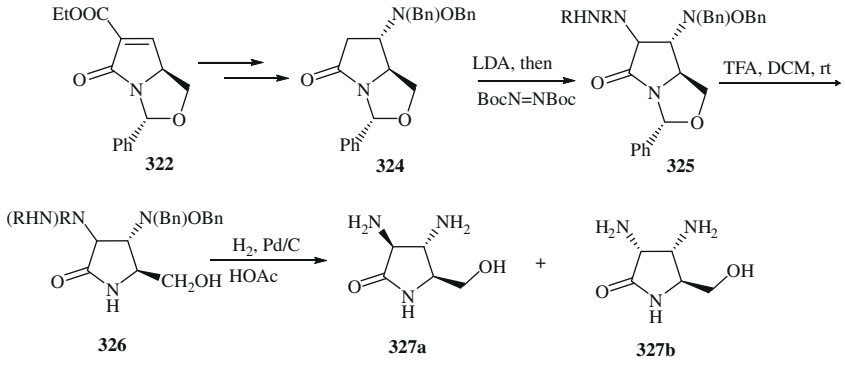


Scheme 63.

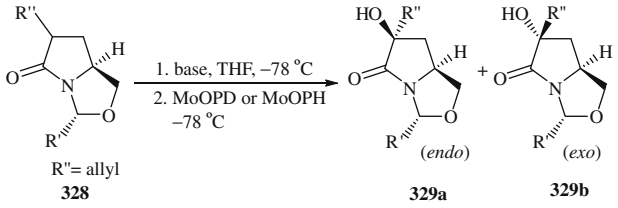
afforded dipeptide **334**. Compound **334** on cyclization in the presence of Grubb's reagent, followed by catalytic hydrogenation gave the desired peptidomimetic **336**.

Hanessian et al.[68] reported design and synthesis of diversified azacyclic inhibitors of endothelin converting enzyme. A series of azacyclic phosphonic acids were synthesized from L-pyroglutamic acid (Scheme 68) *N*-Boc methyl pyroglutamate **131** on reaction with allyl bromide in the presence of LiHMDS was converted to 4-substituted diastereomeric products **337a** and **337b**, where compound **337a** was converted to its dimethylphosphonates **338a** and **338b**. Further reaction of allyl intermediate **338a** with BH_3·THF and NaOH, followed by tosylation and induction of the naphthalamide moiety gave **339**. Compound **339** after a sequence of reaction was converted to **340**.

Brana et al.[69] developed a route for the synthesis of spiro-bis-γ-lactam utilizing a chemoselective Michael reaction as a key step for



Scheme 64.

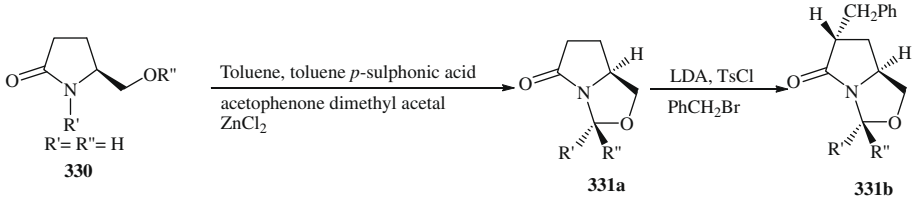


Scheme 65.

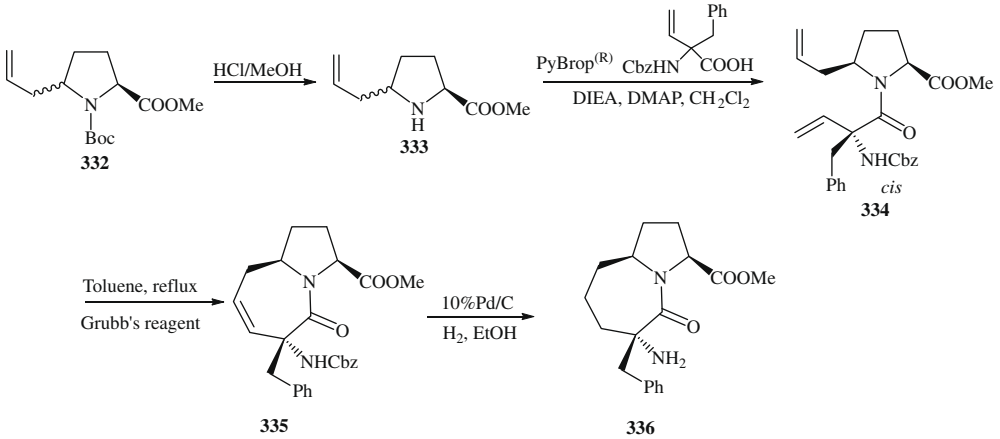
the synthesis (Scheme 69). Methyl *N*-(-*p*-methoxybenzyl) pyroglutamate on deprotonation with LiHMDS followed by reaction with electrophiles gave 2-substituted product **342**, which on hydrogenation with Raney Ni afforded spirobis cyclic lactam **343**.

Harris et al.[70] developed a route for the synthesis of seven macrocyclic analogues of the neuroprotective tripeptide glycyl-L-prolyl-L-glutanic acid (GPE) using pyroglutamic acid (Scheme 70) as a chiral precursor. N-Protected pyroglutamate **311** on selective reduction of lactam carbonyl group with $LiEt_3BH$ followed by $BF_3{\cdot}Et_2O$ mediated allylation with allyltributylstannane was converted to **344** which after deprotection of Boc, followed by N-acylation gave **347**. Compound **347** after cyclization under normal conditions afforded **348** which on hydrolysis of ethyl ester afforded acid **349**. Subsequent reaction of **349** with **350** in the presence of BOP-Cl gave olefin **351**. Treatment of olefin over PtO_2 followed by immediate deprotection of Boc and esters group afforded **352**.

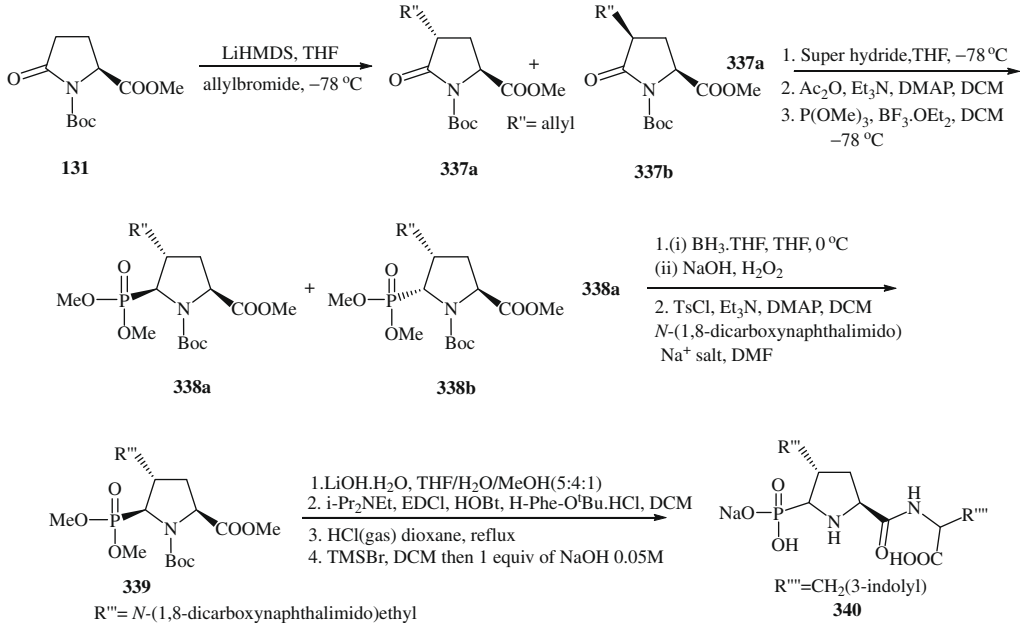
Langlois et al. described[71] the synthesis of new polyhydroxylated indolizidines from bicyclic silyloxy pyrrole (Scheme 71). Compound **134** upon oxidation was converted to regioselective isomers **353** and **354**, where bicyclic derivative **353** after deprotection followed by protection with TBDMSCl, and subsequent sodium enolate-derived reaction with allyl bromide gave N-allylated products **356** and **357** which on treatment with Grubb's catalyst underwent cyclization to give **358**. Compound **358** on oxidation with OsO_4 gave diols **359** and **360**.



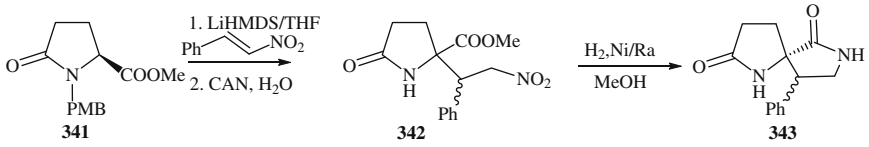
Scheme 66.



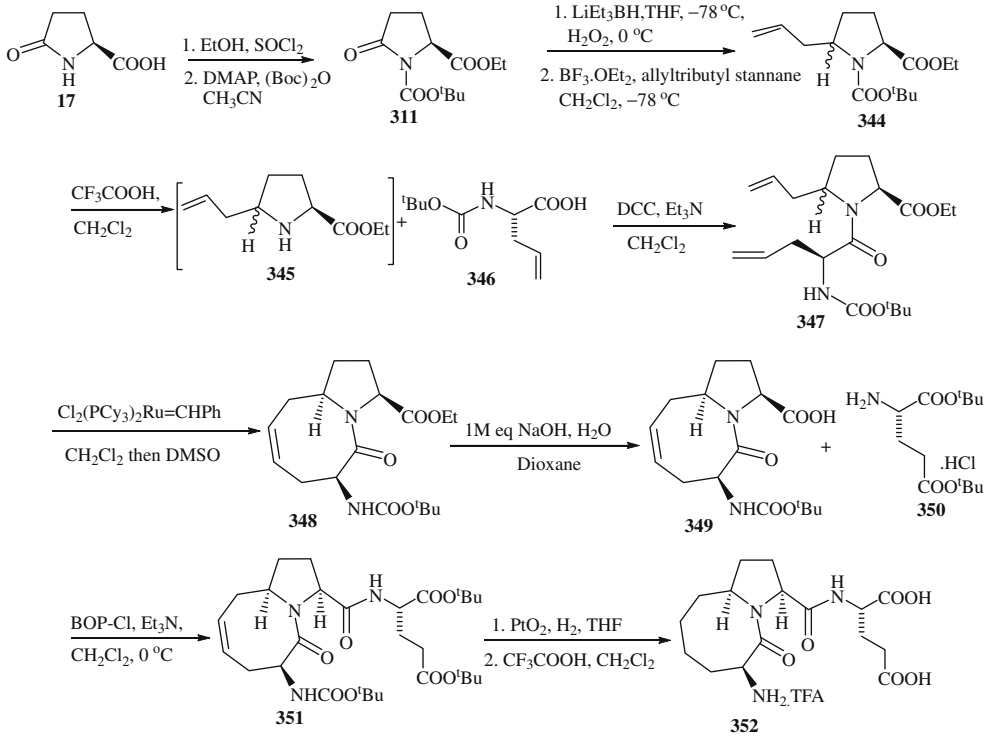
Scheme 67.



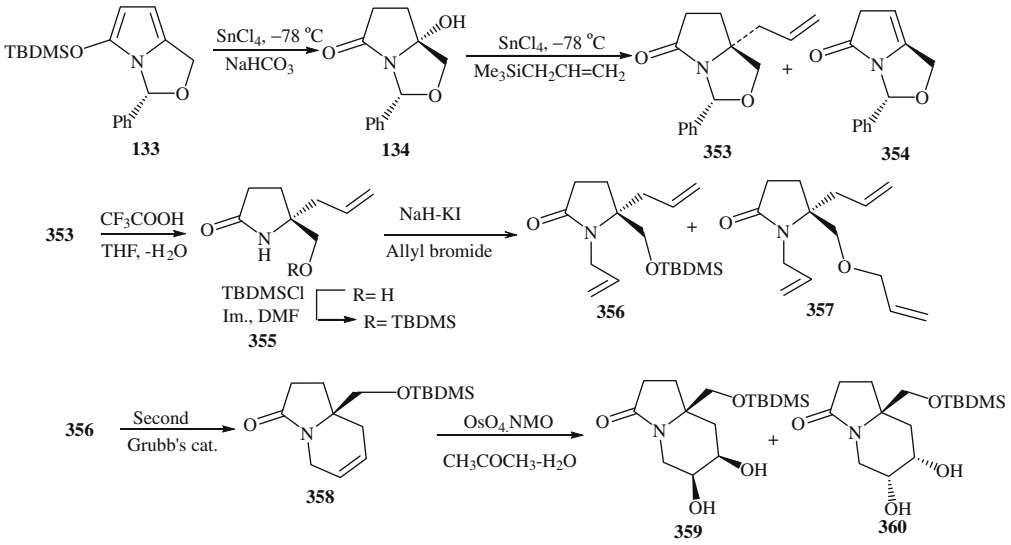
Scheme 68.



Scheme 69.



Scheme 70.



Scheme 71.

Deyine et al. reported stereoselective synthetic route for the synthesis of enantiopure 3,4,5-trisubstituted piperidines, using (*S*)-pyroglutaminol as a chiral precursor[72] (Scheme 72).

Davies et al. reported[73] the synthesis of an external β-turn, based on the GLDV motif of cell adhesion proteins. Pyroglutamates **364** was converted to thio ester **366** then to 5-substituted product **367** which upon hydrogenation followed by treatment with MeOH–TFA gave **368** as starting material for cyclization to get **370** (Scheme 73).

Gedu et al. established the synthesis of new isoquinolines **372** starting with pyroglutamic acid via substituted ketones[74] (Scheme 74).

Olivo et al. achieved[75] the synthesis of (−)-stemoamide **377** in 11 steps from 5 acetoxy-*N*-crotyl-pyrrolidinone. A chiral *N*-acyl thiazolidinethione synthesized as an intermediate was employed for stereoselective addition to a cyclic *N*-acyl iminium ion (Scheme 75).

Manzoni et al. reported[76] stereoselective alkylation approaches for the synthesis of eight enantiopure, sterically constrained C^{α}-tetrasubstituted azabicyclo alkane amino acids (Scheme 76). Pyroglutamate derivative when reacted with benzyl bromide in the presence of base gave alkylated derivatives **379** and **380** as diastereoisomers.

Bracci et al. described stereoselective synthesis of functionalized 2-oxo-1-azabicyclo alkane through a ring-closing metathesis reaction thereby able to construct a seven-membered lactam **388**, starting with pyroglutamate derivatives[77] (Scheme 77). Compound **381** on reduction, followed by reaction with MeOH and PPTS was converted to **383** with methoxy group at C-5 *O*-silyl derivative **383** was converted to *O*-acetyl derivative **384** so as to avoid O-deprotection. Compound **384** was transformed to 5-propenyl proline **385** on reaction with propenyl bromide in the presence of Li, CuBr·Me_2S and $BF_3{\cdot}Et_2O$. Compound **385** after *N*-Boc deprotection followed by N-acylation was converted to **387**. Compound **387** was subjected to cyclization in the presence of Grubb's catalyst and followed by reduction in the presence of nickel boride thereby affording cyclized products **388**.

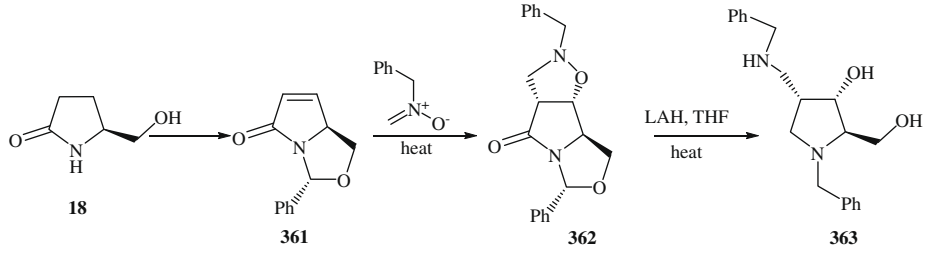
3. Asymmetric use of pyroglutamates without prior modifications

Even though the earlier studies on the asymmetric use of pyroglutamates required prior modifications such as reduction at C-2 or activation at C-5 so as to prevent racemization, however few of the reports are available describing asymmetric use of pyroglutamates without prior modifications.

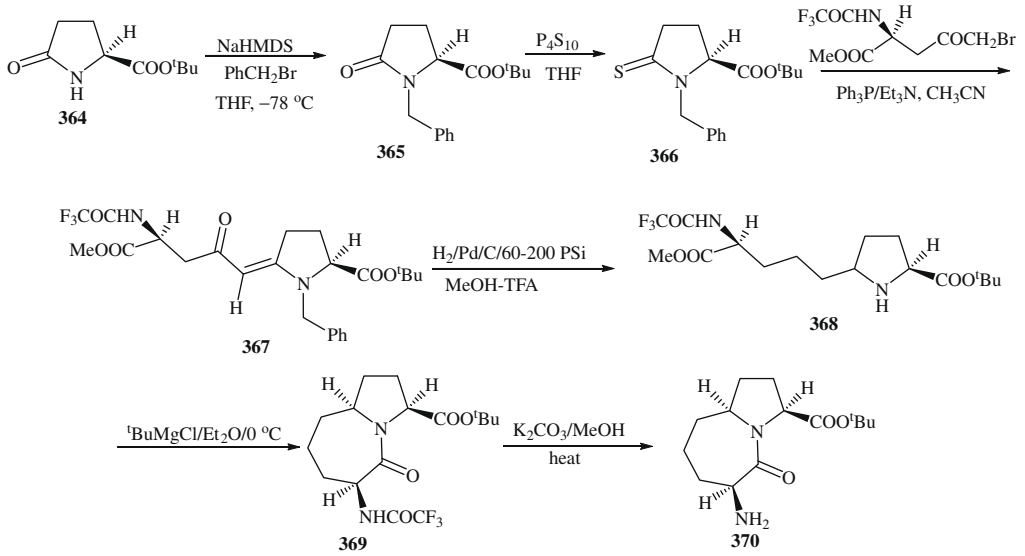
3.1. Direct chain elongation reactions

Katritzky et al.[78] discovered an expedient route for the synthesis of *N*-*Z*-pyroglutamoyl-amino acid derivative by direct coupling of the C-terminus activated N-protected pyroglutamate (Scheme 78).

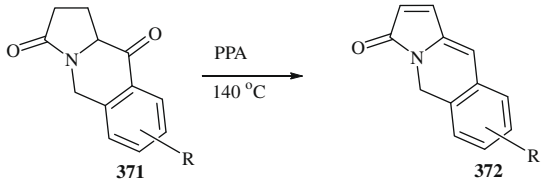
Toyooka et al. discovered enantioselective synthesis of a hydroxyindolizidine alkaloid using pyroglutamic acid as a starting material[79] (Scheme 79). Methyl pyroglutamate was first subjected to N-protection using benzyloxy carbonyl chloride and subsequent reaction with *n*-butyl magnesium bromide in the presence of TMEDA resulted in ring opening coupled with the introduction of *n*-butyl group thereby furnishing **392**. Compound **392** on Martin's



Scheme 72.



Scheme 73.



Scheme 74.

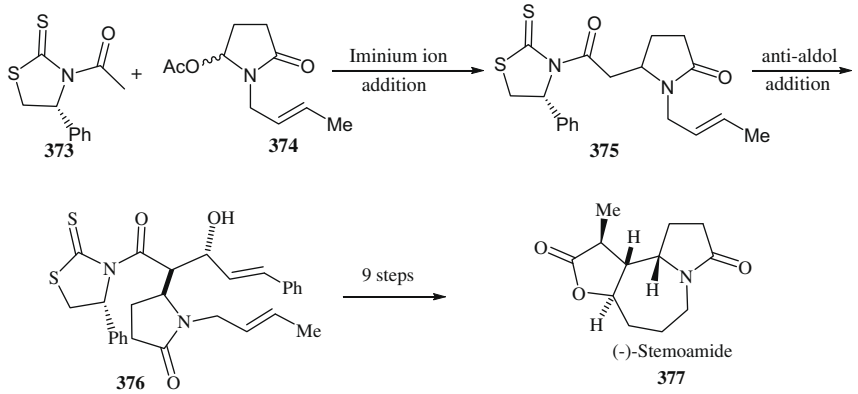
transformation produced 2,5-*cis*-disubstituted pyrrolidine **393**. Treatment of **393** with DIBAL followed by the addition of vinyl Grignard reagent to resultant aldehyde provided alcohol **394** as a mixture of diastereomers. The cross-metathesis reaction of **394** with 1-hexen-3-one in the presence of Grubbs II generation catalyst afforded the homologated product **395**. Exposure of **395** to hydrogenation in the presence of Pearlman's catalyst furnished the two indolizidines **396a** and **396b**, which were separated to get (−)-**396**a as a major diastereomer and **396b** as a minor isomer.

Li et al. reported[80] first enantioselective synthesis of (D)-2-tert-butoxycarbonylamino-5,5-difluoro-5-phenyl-pentanoic acid **400** with an objective to incorporate in growth hormone secretagogues (Scheme 80). *N*-Boc ethyl pyroglutamate **319** on treatment with phenyl magnesium bromide, followed by reaction with 1,2-thioethane in the presence of $BF_3{\cdot}Et_2O$ afforded two compounds **397a** and **397b**. Subsequent N-acylation with acetic anhydride in the presence of triethylamine afforded the desired acetamide **398**. Treatment of acetamide **398** with $NOBF_4$, HF/pyridine, followed by deacetylation yielded amino carboxylic ester **399b** which after protection of primary amine with Boc group followed by ester hydrolysis afforded the desired compound **400**.

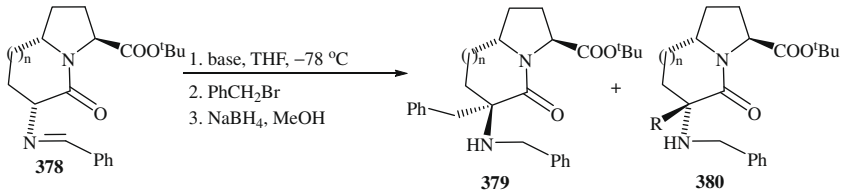
Gu et al. reported[81] a concise synthesis of (2*S*,4*S*)-4-methylglutamic acid **406** (Scheme 81) starting from pyroglutamic acid. Compound **402** on reaction with $LiN(SiMe_3)_2$ in THF and MeI was converted to isomers **403** and **405**, which after alkaline hydrolysis followed by *N*-Boc deprotection afforded **404** and **406**.

Dieterich et al.[82] reported the synthesis of (2*S*,3*S*)-[3-2H1]-4-methylglutamic acid and (2*S*,3*R*)-[2,3-2H2]-4-methyleneglutamic acid. Compound **131** was converted to 4-[*N*,*N*-dimethyl amino]-methylene derivative **407**. Compound **407** on hydrido deamination with DIBAL-H afforded 4-methylene pyroglutamate **408**. Compound **408** on reaction with LiOMe in the presence of MeOH, followed by acidic hydrolysis using HBr furnished substituted glutamic acid **410** (Scheme 82).

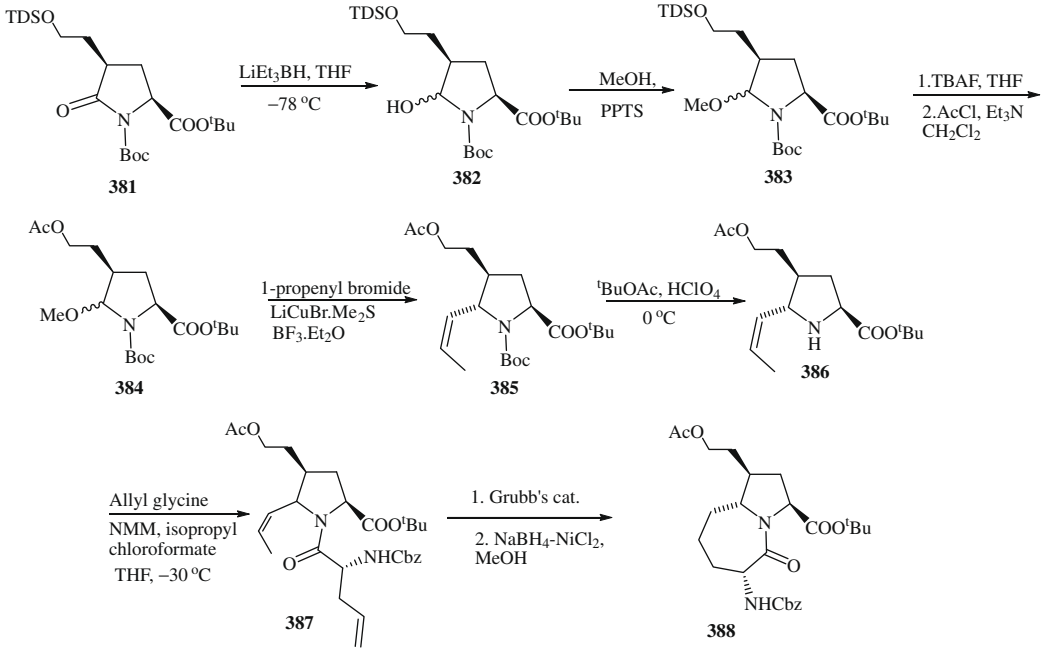
Dinsmore et al.[83] described the use of a modified ring-switching strategy for the synthesis of glutamate antagonist (2*S*)-2-amino-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)propionate **417** and related compounds having two asymmetric centres, from pyroglu-



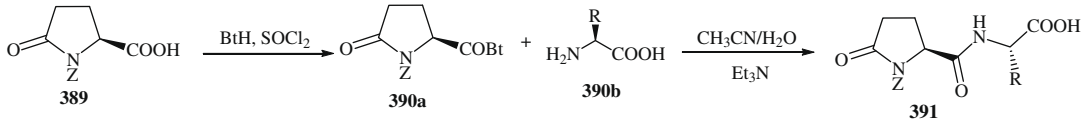
Scheme 75.



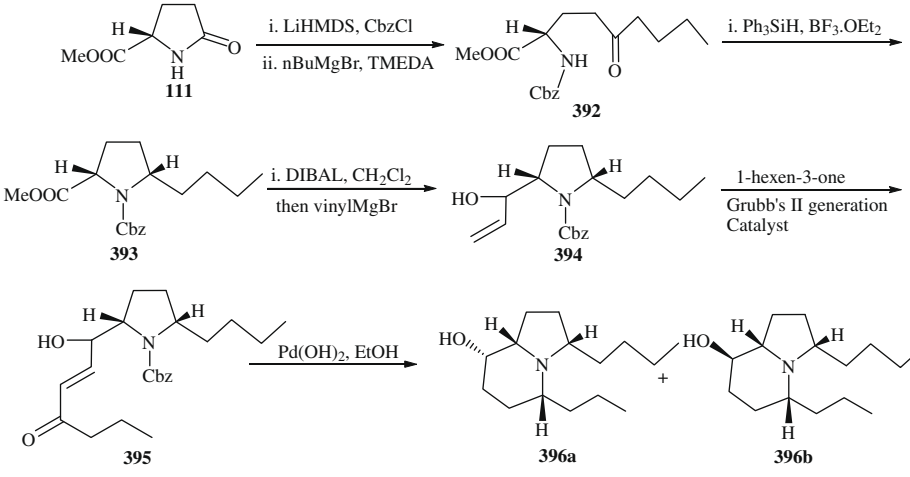
Scheme 76.



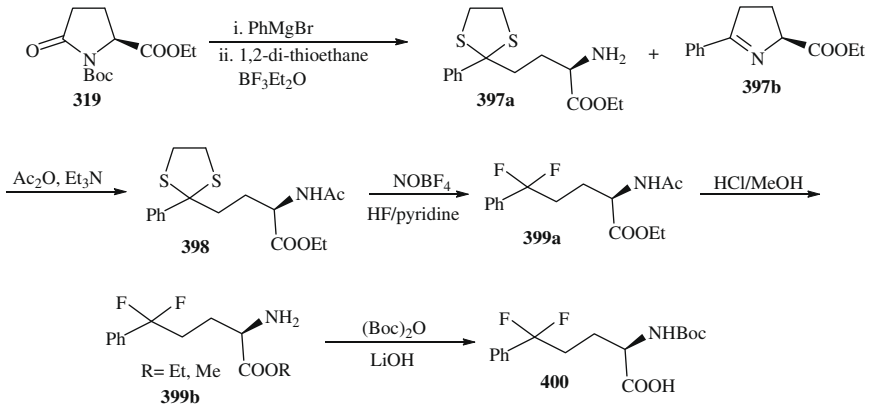
Scheme 77.



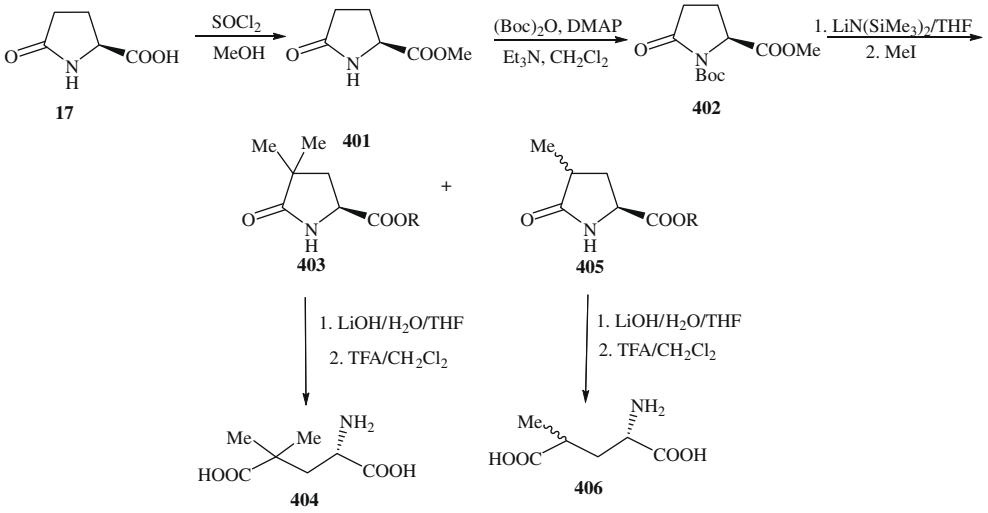
Scheme 78.



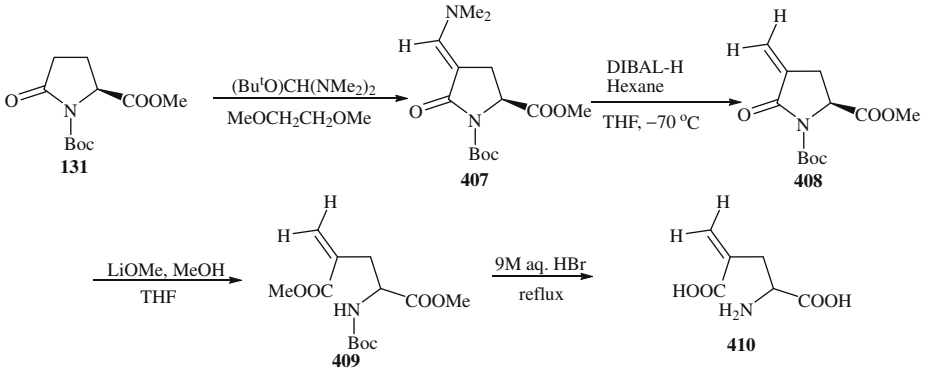
Scheme 79.



Scheme 80.



Scheme 81.

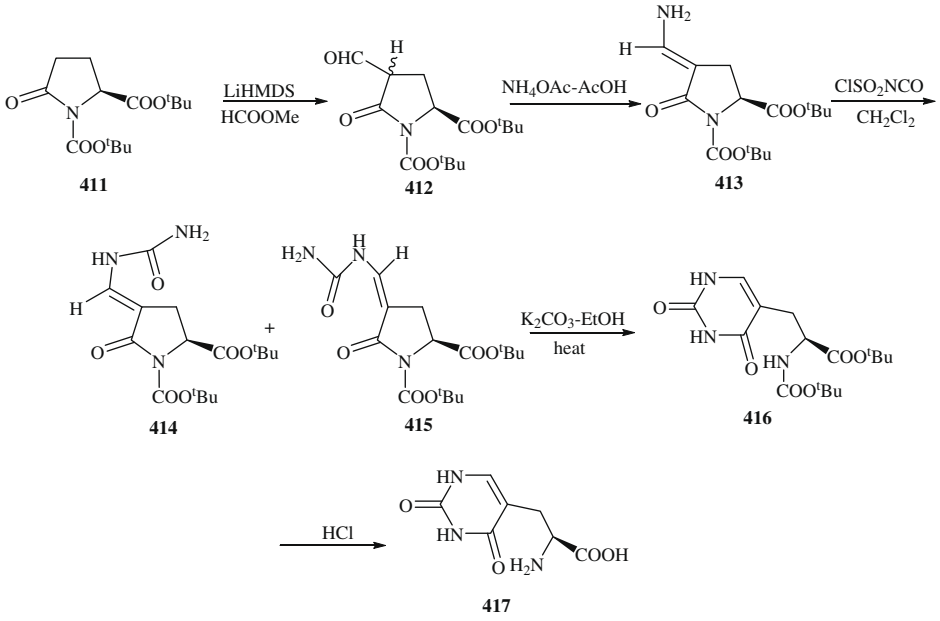


Scheme 82.

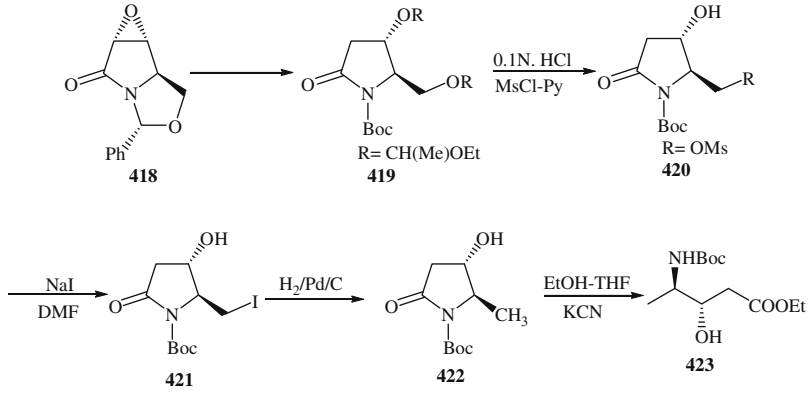
tamic acid (Scheme 83). Aldehydic group was introduced at C-4 of N-protected pyroglutamate **411**. The resultant compound **412** on amination with NH_4OAc–AcOH, followed by reaction with $ClSO_2N$-CO gave diastereomers **414** and **415**, subsequent reaction with K_2CO_3–EtOH, followed by hydrolysis afforded **417**.

Langlois[84a,b] et al. described the diastereospecific formal synthesis of (2*R*,3*S*)-2-amino-tetradeca-5,7-dien-3-ol **423**, a natural product isolated from xestopongia species using epoxidation and epoxide ring-opening sequences in native pyroglutamate moiety (Scheme 84). Compound **418** was converted to **419**, which after O-deprotection at C-4 and O-protection at C-5 gave **420**. Compound **420** on iodonation using NaI in DMF gave **421**, which on hydrogenolysis using H_2–Pd/C was converted to **422**. Compound **422** on reaction with KCN in the presence of EtOH–THF underwent ring opening to give **423**.

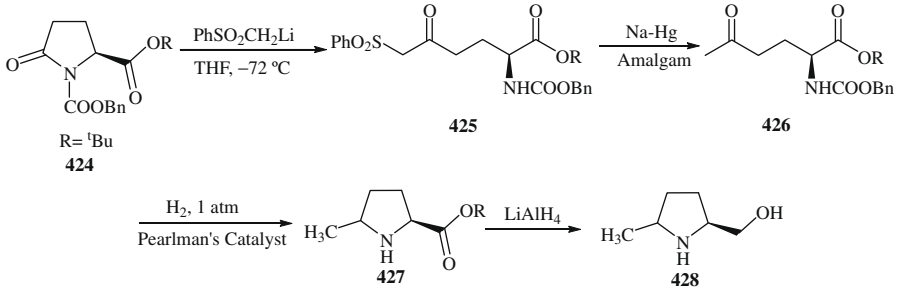
Ring opening of *N*-alkoxycarbonyl γ-lactam **424** with lithium methylphenylsulfone, resulted in the synthesis of enantiopure *cis* 2,5-disubstituted pyrrolidines[85] (Scheme 85). Pyroglutamic acid



Scheme 83.



Scheme 84.



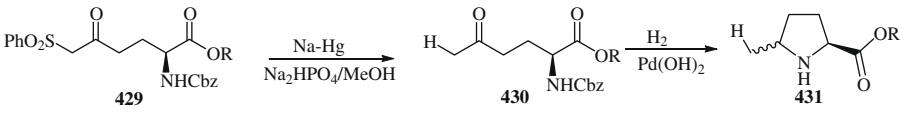
Scheme 85.

derivative **424** on reaction with methylphenylsulfone in nBuLi using THF as a solvent, followed by desulfonylation using Na–Hg and Pearman's catalyst afforded compound **425**, which after hydrogenation followed by reaction with $LiAlH_4$ afforded **428**.

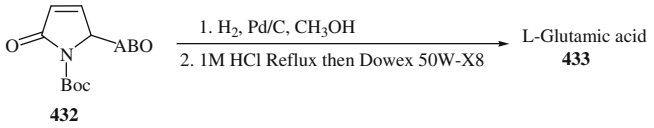
New diastereoselective synthetic route for 2-substituted *cis*-(2*S*,5*S*)-and *trans*-(2*S*,5*R*)-5-alkylprrolidinones as indolizidine and pyrrolizidine scaffolds has been reported by Mota et al.[86] (Scheme 86).

Oba et al.[87] reported the synthesis and reactions of novel 3,4-didehydropyroglutamate derivatives through hydrogenation and ring-opening sequences with H_2 and Pd/C in the presence of CH_3OH. The ABO ester **432** on hydrogenation followed by ring opening afforded L-glutamic acid (Scheme 87).

Another ring-opening strategy via copper (1) mediated cross-coupling of pyroglutamic acid-derived organo zinc reagent with acid chloride was reported by Hjelmgaard et al.[88] (Scheme 88).



Scheme 86.



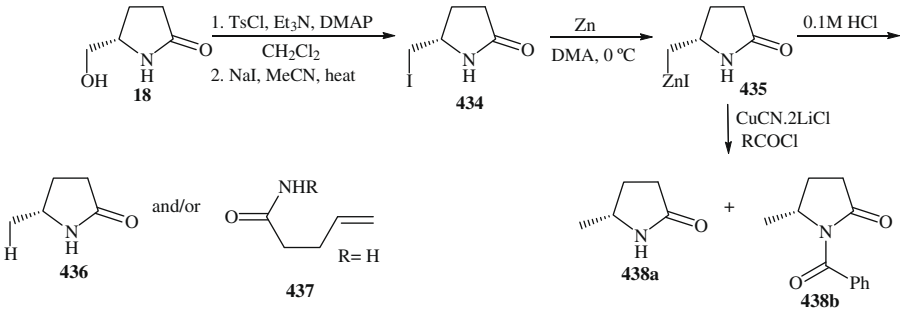
ABO= 2,7,8-trioxabicyclo[3.2.1]octane

Scheme 87.

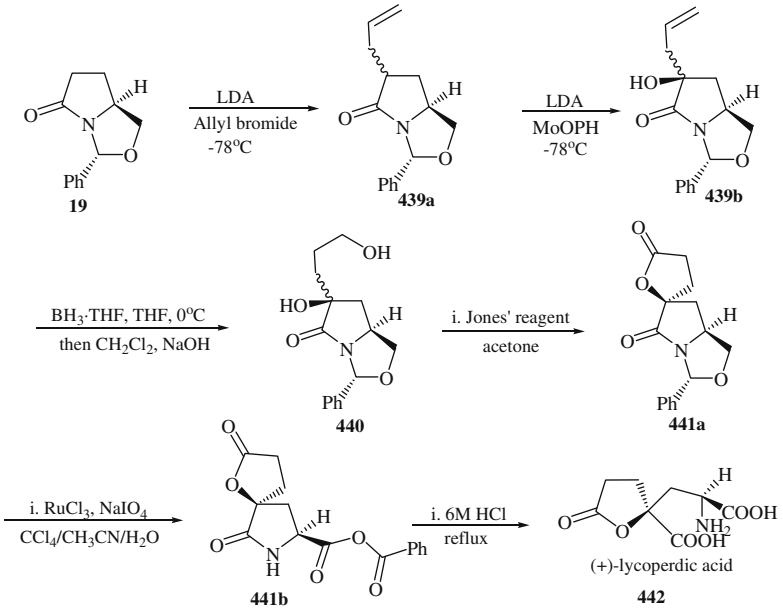
Compound **18** after tosylation, followed by reaction with NaI and MeCN was converted to iodo products **434** and subsequently to organo zinc compound **435**. Compound **435** on reaction with CuCN·2LiCl and RCOCl gave **438a** and **438b** on the one hand and through acidification afforded **436** or **437** on the other hand.

Makino et al. described[89] stereoselective synthesis of (*S*)-(+)-lycoperdic acid through an *endo* selective hydroxylation of the chiral bicyclic lactam enolate with MoOPH (Scheme 89). Lienolate-derived reaction of **19** with allyl bromide afforded 4-allyl derivative **439a**, which on further reaction with LDA and MoOPH gave 4-allyl-4-hydroxy derivative **439b**. Allyl group of **439b** was subjected to hydroboration–oxidation sequences to get diol **440**. Compound **440** after a sequence of reactions was converted to (+)-lycoperdic acid **442**.

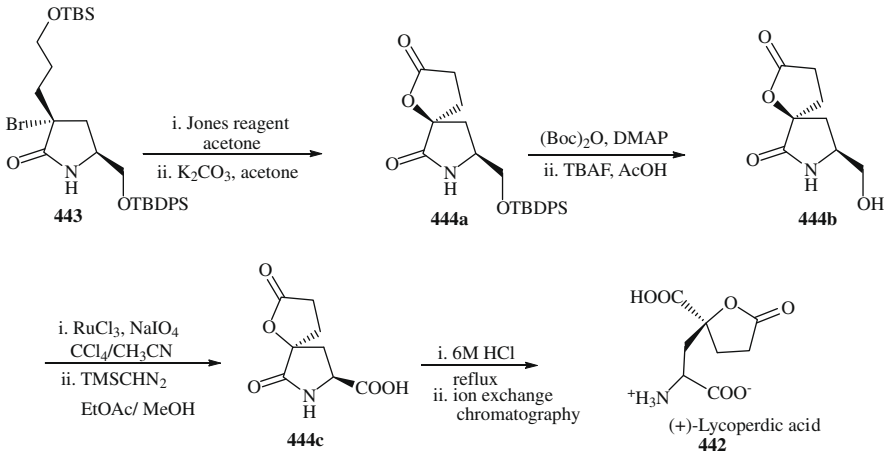
Cohen et al. described the synthesis of (*S*)-(+)-lycoperdic acid[90] **442** starting with pyroglutamic acid derivative **443** (Scheme 90). Bromo lactam compound **443**, when subjected to tandem oxidation–annulation reaction with Jones reagent at 0 °C followed by workup with potassium carbonate delivered spirolactam **444a**. Sequential Boc protection and TBAF desilyation afforded pyroglu-



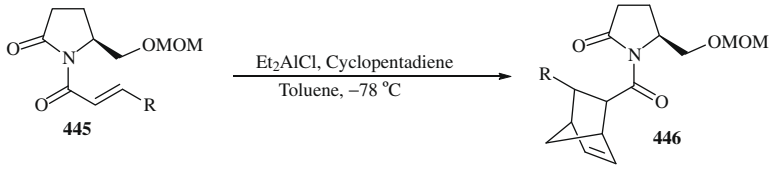
Scheme 88.



Scheme 89.



Scheme 90.



Scheme 91.

taminol **444b**. Oxidation of **444b** with $RuCl_3$ followed by exposure of crude mixture to $TMSCHN_2$ afforded methyl ester **444c** which after acidic hydrolysis followed by purification yielded the desired (*S*)-(+)-lycoperdic acid **442**.

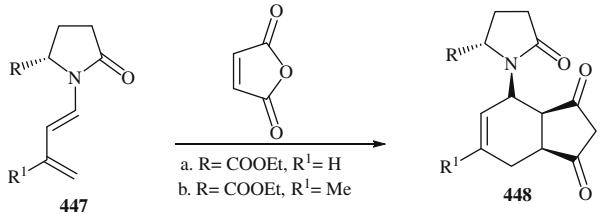
3.2. Use of N-derivatized pyroglutamates for asymmetric synthesis

3.2.1. Diels–Alder reactions

Highly asymmetric Diels–Alder reactions have been carried out using (*S*)-pyroglutamic acid derivatives as chiral dienophiles. Asymmetric Diels–Alder reaction of cyclopentadiene with chiral dienophile **445** derived from (*S*)-pyroglutamic acid derivatives in the presence of a Lewis acid catalyst such as diethylaluminium chloride in toluene afforded cyclo adducts **446** with high stereoselectivity[91] (Scheme 91).

Strong chiral influence of pyroglutamate has also been utilized in diene component of Diels–Alder reaction. Menezes et al. have explored the use of ethyl-*N*-dienyl pyroglutamates as novel asymmetric diene where chiral cyclohexenyl amine derivatives **448** were obtained in good yields[92] (Scheme 92).

Defoin et al.[93] have carried out asymmetric hetero Diels–Alder cycloadditions using chiral *N*-dienyl lactam and acyl nitrosodienophiles (Scheme 93).



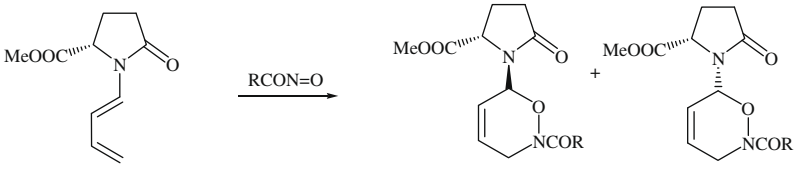
Scheme 92.

3.2.2. Radical cyclization

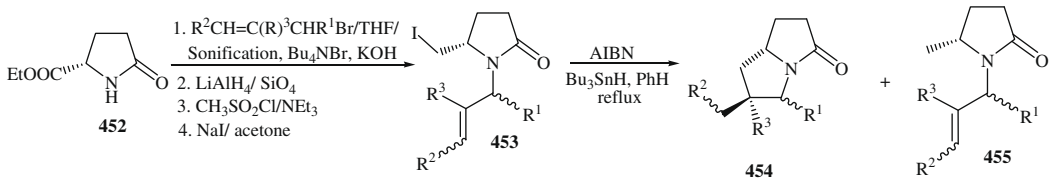
Asymmetric synthesis of pyrrolidinones by radical cyclization of *N*-allylic pyroglutamates which were synthesized from ethyl-(*S*)-pyroglutamate has been carried out[94] (Scheme 94).

3.2.3. N-Acylations/alkylations of native pyroglutamates

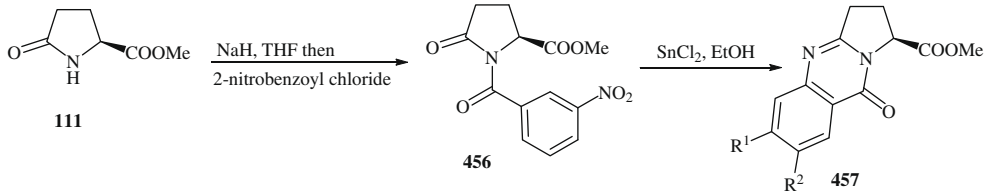
Boisse et al. discovered[95] synthetic strategies for new camptothecin analogs starting with pyroglutamic acid derivative. In one of the approaches methyl pyroglutamate after N-benzoylation with 2-nitrobenzoyl chloride in the presence of NaH, followed by reductive cyclization with $SnCl_2$ in ethanol afforded modified precursor of camptothecins **457** (Scheme 95).



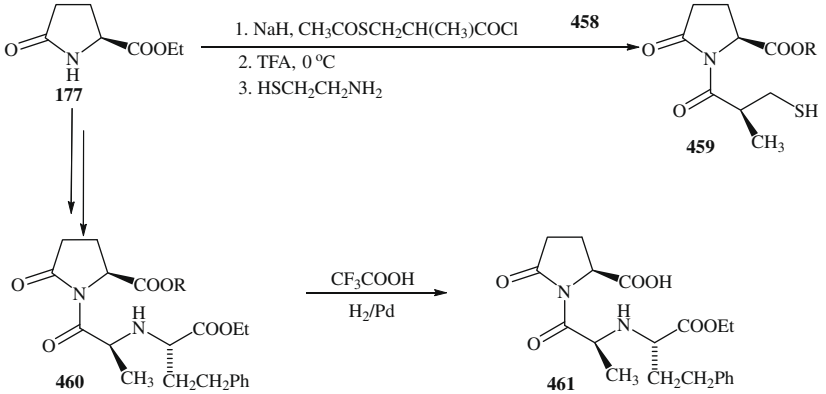
Scheme 93.



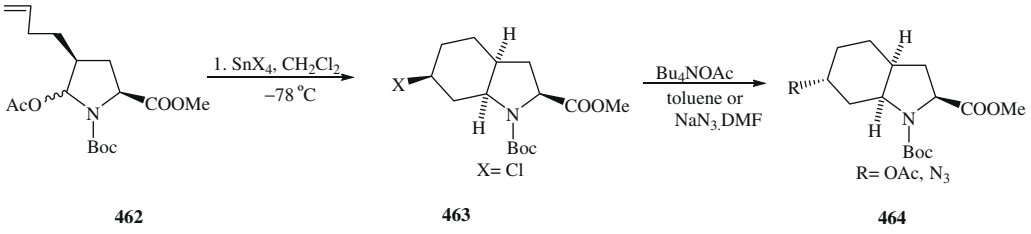
Scheme 94.



Scheme 95.



Scheme 96.



Scheme 97.

In an attempt to develop potent ACE inhibitors such as **459** and **461** derived from pyroglutamates, N-acylations of pyroglutamates have been reported[96a,b] (Scheme 96). These N-acylations have been accomplished by the reaction of pyroglutamate derivative **177** with NaH and acid chloride for the synthesis of modified captopril analog **459**, and with NaH and *p*-nitrophenylester of *Z*-Ala-OH for the synthesis of enalapril analog **461**.

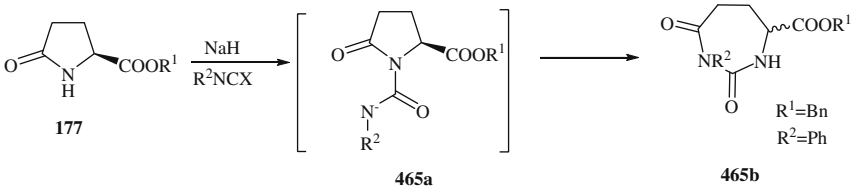
Hanessian et al.[97] reported the synthesis of 6-substituted hydroindole 2-carboxylic acids from pyroglutamic acid derivatives, where compound **462** on reaction with SnX_4 was converted to bicyclic ester **463**, and the resulting product was subsequently converted to **464** using Bu_4NOAc in toluene (Scheme 97).

Straight forward ring expansion of pyroglutamates to Perhydro-1,3-diazepine-2,4-diones was reported by Stevens et al.[98] (Scheme 98).

Bourry et al. described[99] their studies on pyrrolidinones oxidation and rearrangements in the hexahydrobenz[*f*]indolizine-3,10-dione series (Scheme 99). *N*-Benzyl pyroglutamic acid **466** on reaction with thionyl chloride and $ClCH_2CH_2Cl$ afforded compounds **467a**–**467c**, where compound **467a** was converted to pyrrolinone **468** with HCl and O_2 at room temperature.

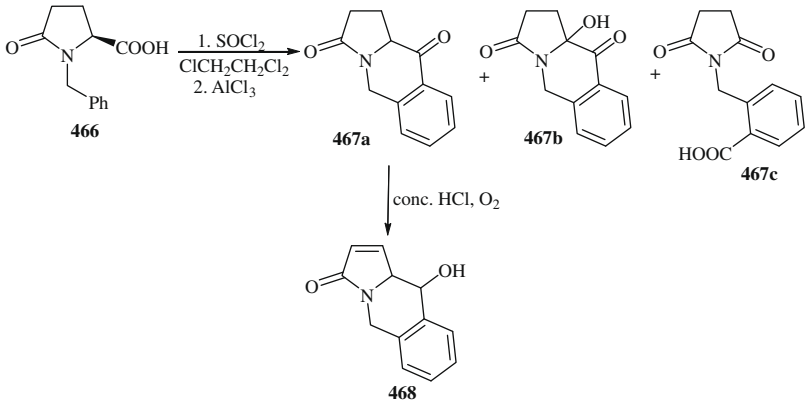
Enders et al. delivered a synthetic strategy for enantiopure triazolium salts from pyroglutamic acid and their evaluation in the benzoin condensation (Scheme 100). Pyroglutamic acid after esterification followed by reaction with phenyl magnesium bromide yielded substituted γ-bytyrolactam **112a**. Reduction of tertiary alcohol group of compound **112a** led to lactam **469**, which was then converted to triazolium salt **470**[100] under usual conditions.

Dudot et al. described the synthesis of chiral pyroglutamate amines through hydrogenation followed by alkaline hydrolytic



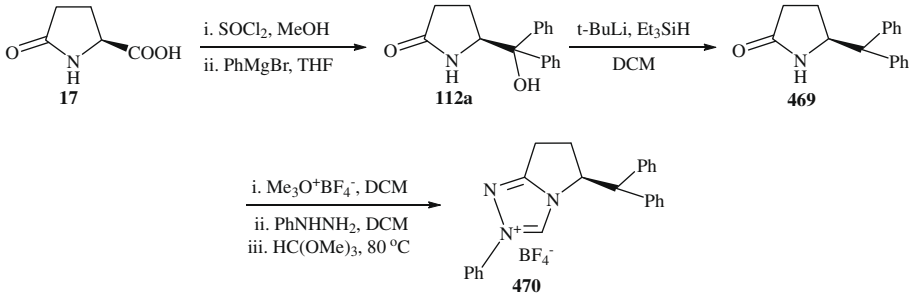
177 465a 465b

Scheme 98.



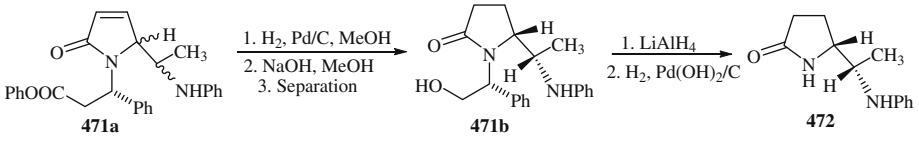
466 467a 467b 467c 468

Scheme 99.



17 112a 469 470

Scheme 100.



471a 471b 472

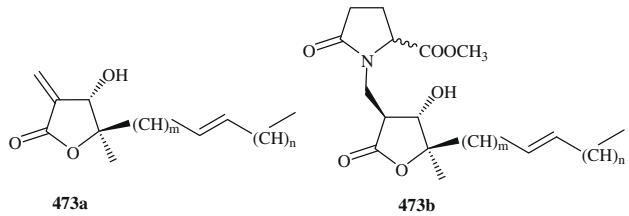
Scheme 101.

cleavage of benzoyl ester[101] (Scheme 101). Compound **471a** was subjected to hydrogenation, followed by alkaline hydrolytic cleavage to get **471b** which on reduction afforded diamine **472**.

Zampella et al.[102] discovered amphiasterins; a new family of cytotoxic metabolites from the marine sponge plakortis quasiamphiaster, which is N-alkylated pyroglutamic acid unit (Scheme 102).

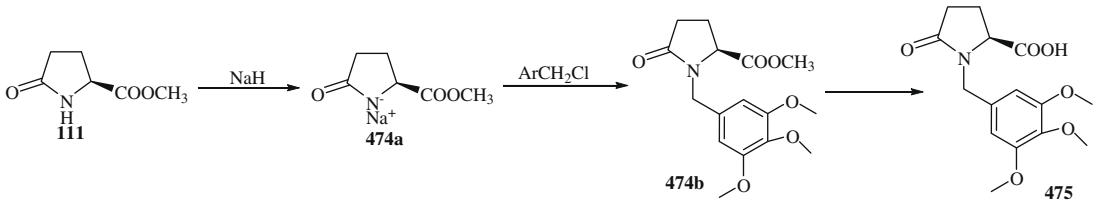
Bourry et al.[103] carried out studies on pyrrolidones. They described an improved synthesis of *N*-arylmethyl pyroglutamic acids (Scheme 103). They have also carried out studies on pyrrolidinones with an objective to improve the anticancer properties of methyl *N*-(3,4,4′,5-tetramethoxybenzhydryl)pyroglutamate (HEI 81)[104] (Scheme 104).

In our recent publication we described the synthesis of *N*-[3′-(acetylthio) alkanoyl] and *N*-[3′-mercaptoalkanoyl]-4-α-(*S*)-(phenyl methyl) pyroglutamic acids and proline as potent ACE inhibitors. Lithium enolate-derived N-acylation of 4-α(*S*)-phenylmethyl pyroglutamate **478** with 3-acetylthioalkanoyl chloride and 3-acet-

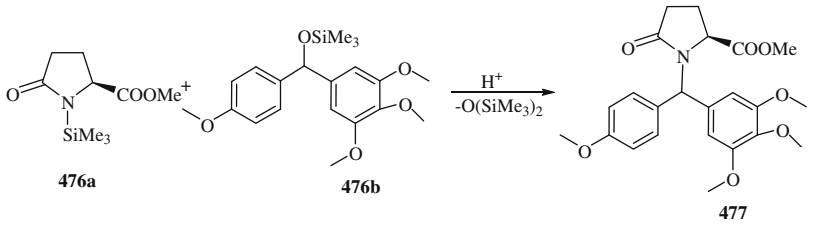


473a 473b

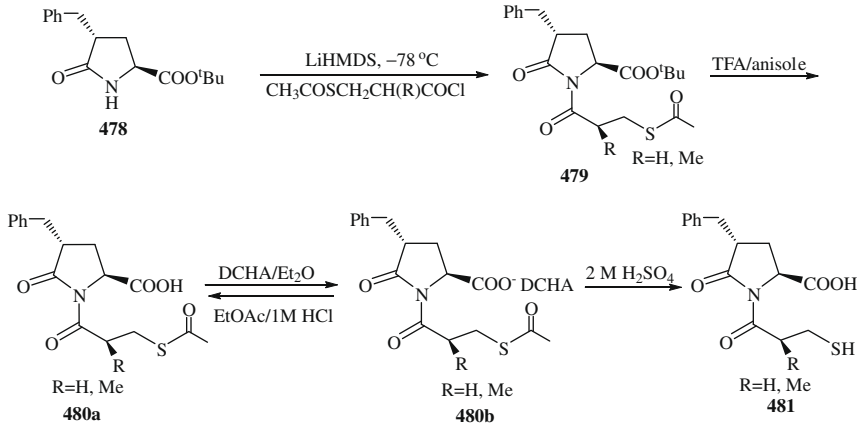
Scheme 102.



Scheme 103.



Scheme 104.



Scheme 105.

ylthio-2(*S*)-methyl alkanoyl chloride afforded compound **479**. Subsequent deprotection and purification yielded the desired ACE inhibitors **481**[105] (Scheme 105).

Hanessian et al.[106] reported the *N*-acyloxyiminium ion aza-Prins route to octahydroindoles leading to total synthesis and structural confirmation of the antithrombolic marine natural product oscillarin (Scheme 106). Pyroglutamic acid derivative **482** after Boc deprotection was subjected to N-acylation using **483** as an acylating agent to get **484**. The resultant material was converted to precursor **486** by coupling with proline derivative **485**, compound **486** on deprotection under acidic condition afforded oscillarin **487**.

They have also described the total synthesis and structural assignment of the marine natural product Dysinosin A: a novel inhibitor of thrombin and Factor vlla[107a] (Scheme 107), utilizing a carbon construct strategy that generates subunits originating from L-glutamic acid, whereas Carroll et al. reported the isolation and structure determination of this new marine natural product Dysinosin A.[107b]

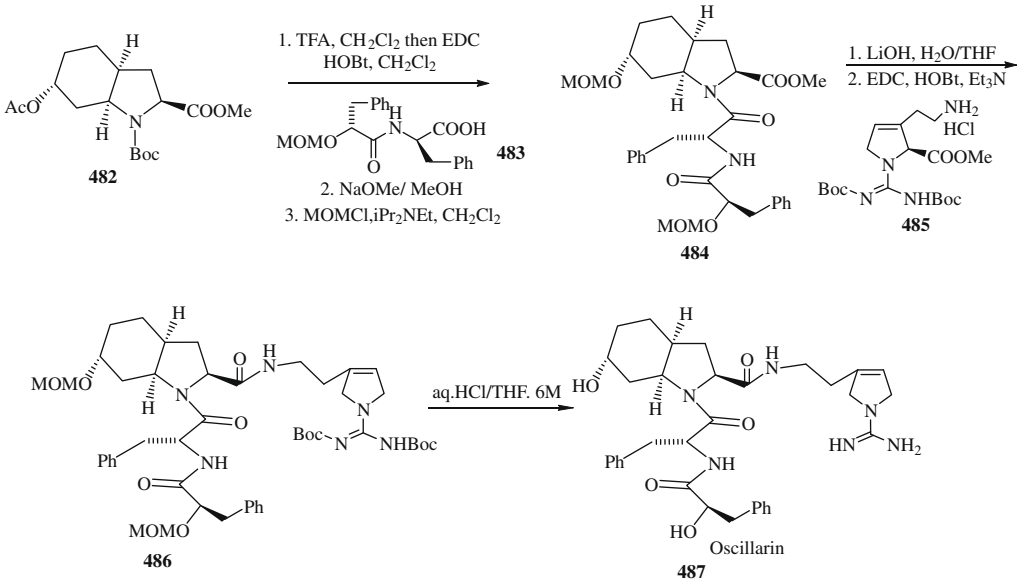
Daiya et al.[108] described diastereoselective heterogeneous catalysis of 2-methyl nicotinic acid **496** using pyroglutamic as chiral auxiliary (Scheme 108). Methyl pyroglutamate **111** on reaction with 2-methyl-nicotinoyl chloride (generated in situ by reaction of 2-methyl nicotinic acid **494** with thionyl chloride) under Schautann Baumann conditions afforded N-acylated pyroglutamate **495** having side chain corresponding to 2-methyl nicotinic acid, which on catalytic hydrogenation afforded *N*-(*Z*-methyl piperidine-3-oyl) methyl pyroglutamate **496** with reduction of *N*-acyl side chain.

Lee et al.[109] carried out asymmetric synthesis of *trans*-1-aminoindolo[2,3-*a*]quinolizidine **502**. *N*-Benzyloxy carbonyl 2(*S*)-methyl pyroglutamate **497** on reaction with arylethylamine in the presence of Me_3Al underwent ring opening. The resultant product on subsequent reduction afforded **499**, which upon dehydration coupled with cyclization gave a tricyclic compound **500**. Compound **500** on hydrogenation using H_2/Pd–C followed by reduction afforded the desired molecule **502** (Scheme 109).

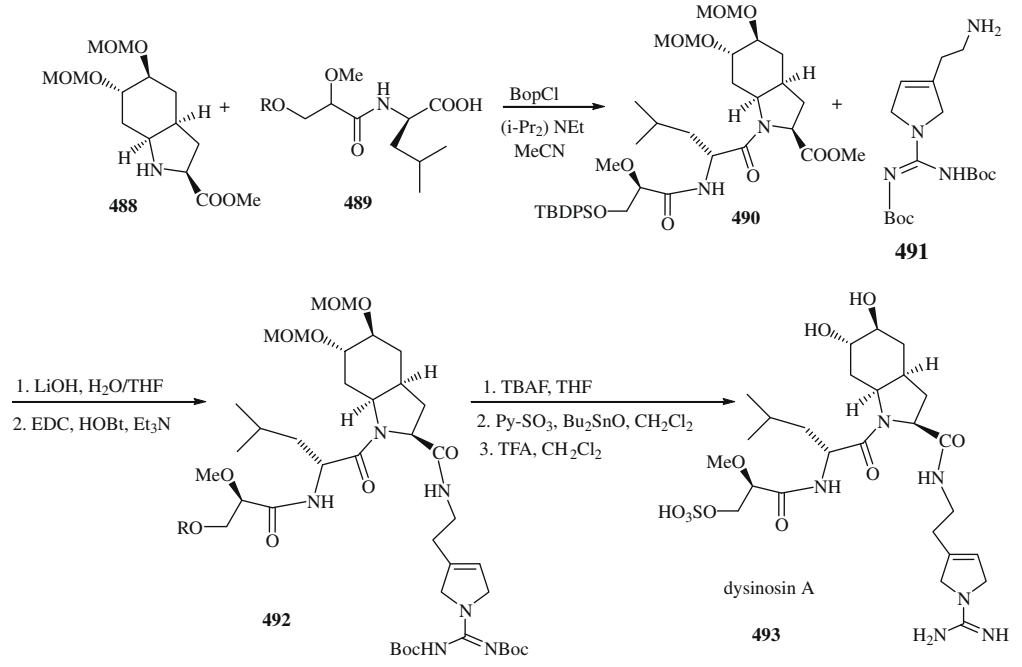
Belvisi et al. reported[110] stereoselective synthesis of conformationally constrained unnatural proline-based amino acids and peptidomimetics, *N*-Boc 4-allyl pyroglutamate derivative **503** was subjected to reduction, allylation sequence on lactam carbonyl thereby furnishing stereoisomers **505** and **506** which on treatment with Grubb's catalyst, followed by hydrogenolysis gave **508** and **510** as stereoisomers (Scheme 110).

Stereoselective alkylation of a bicyclic lactam derived from pyroglutamic acid has been reported by Zhang et al.[111] (Scheme 111).

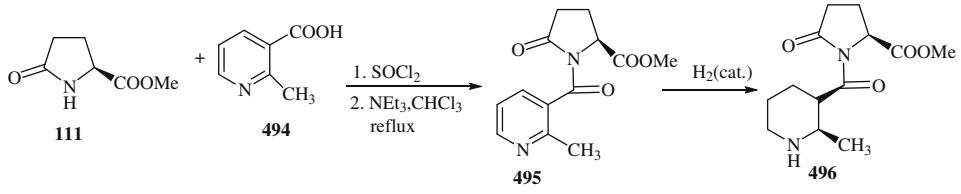
Zhang et al.[112] described a convenient and versatile synthesis of 6,5- and 7,5-fused lactams as peptidomimetics starting with pyroglutamate derivatives (Scheme 112). *N*-Boc-2(*S*)-ethyl pyroglutamate **131** was converted to its corresponding 4-cinnamyl



Scheme 106.

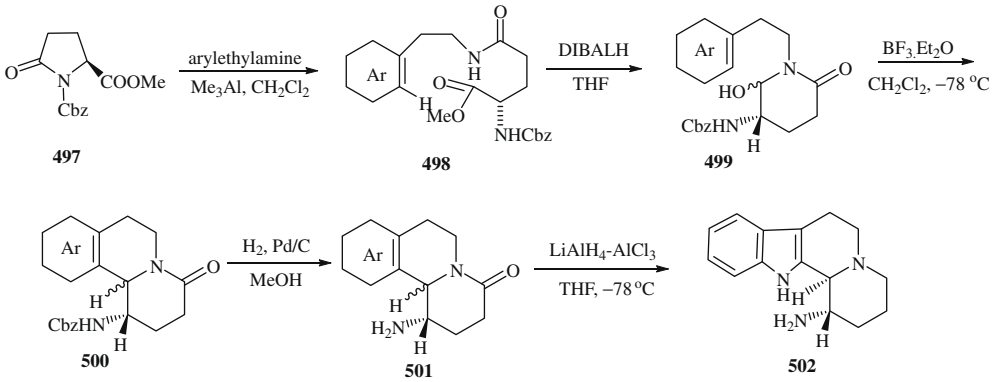


Scheme 107.

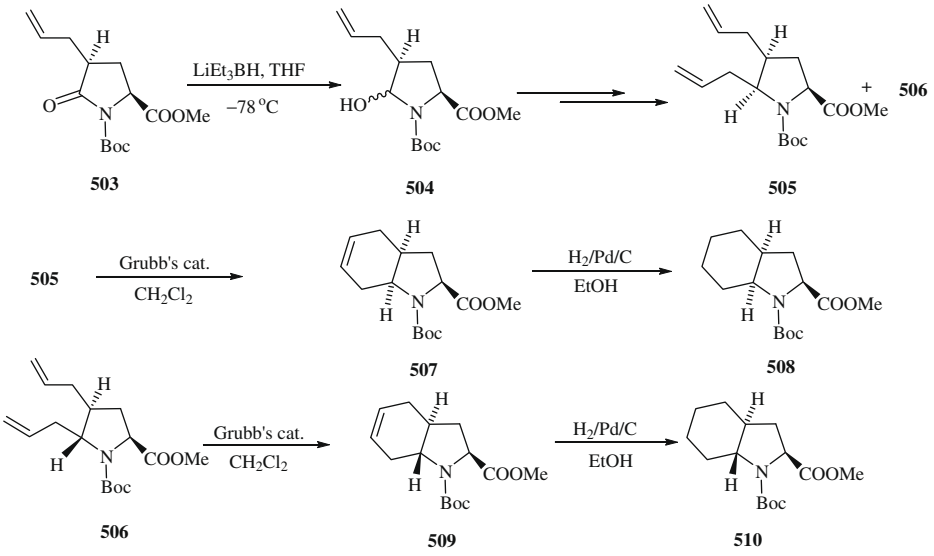


Scheme 108.

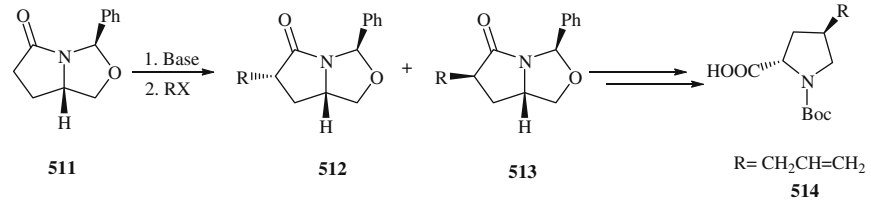
derivative **515**, which after deprotection of Boc group followed by Lienolate-derived N-acylation with Boc (D)-ser-Bzl-Osu afforded compound **517**. Compound **517** on hydrogenolysis using H_2/Pd–C was converted to N-acylated products **518** with deprotection of



Scheme 109.



Scheme 110.



Scheme 111.

o-benzyl group of side chain. Compound **518** on the reduction of lactam carbonyl with $LiBEt_3H$ followed by acid-catalyzed dehydration cyclization sequences gave **520**. Compound **520** upon alkaline hydrolysis afforded the desired peptidomimetics **521**.

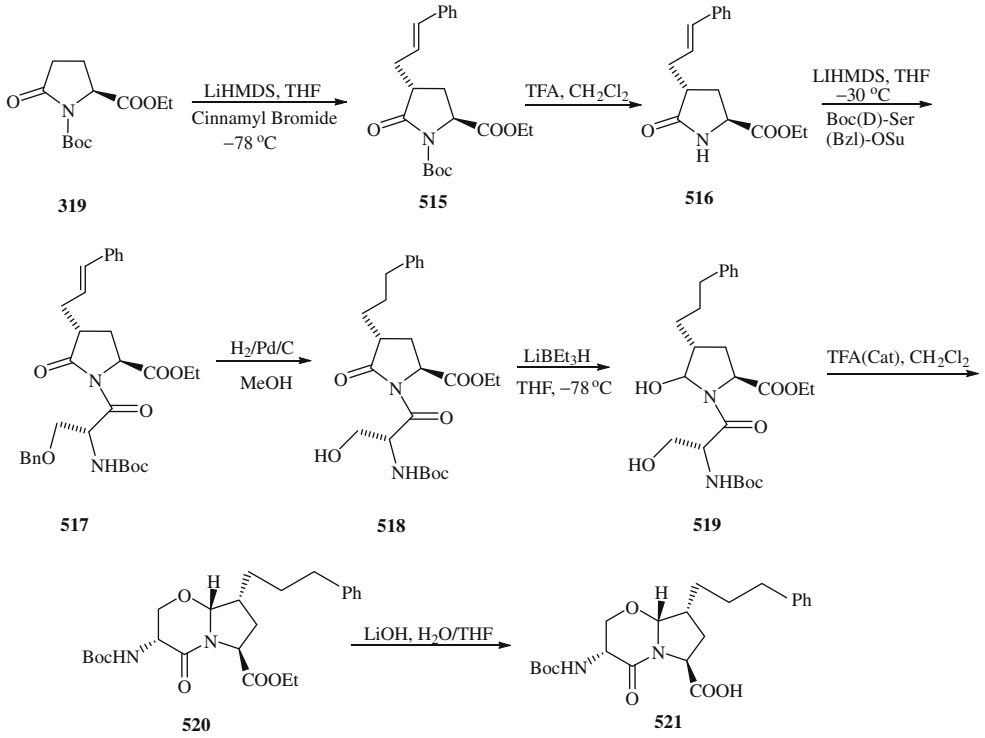
An expedient synthesis of (+)-*trans*-5-allyl hexahydroindolizidin-3-one was carried out by Potts et al.[113] (Scheme 113).

Thanh et al. reported[114] enantioselective synthesis of indolizidine (−)-237A [(3*R*,5*S*,8a*R*)-3-butyl-5-(1-oxopropyl)octahydroindolizine], starting from pyroglutamate derivative. Compound **524** on nucleophilic addition with $(CH_3O)_2PO–CH_2CO–C(OEt_2)Et$ produced **525** which after hydrogenation with H_2 (1 bar), PtO_2 in methanol followed by cyclization gave **527** and the resultant material was reduced with $NaBH_3CN$ to afford a stereoisomer of (−)-Myrmicarine 237A (Scheme 114).

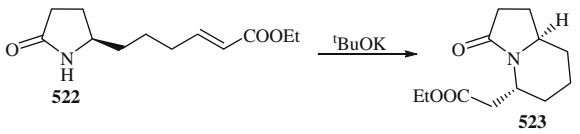
Legrand et al. reported[115] studies on condensation of pyrrolidinones with silyl derivatives. Trimethoxyphenyl naphthylcarbinol trimethyl silyl ether was condensed with the methyl *N*-trimethylsilyl pyroglutamate affording two separable esters (Scheme 115).

3.3. Functionalization at C-2, C-3, C-4, of pyroglutamates

Yamada et al. established[116] an efficient asymmetric synthesis of the functionalized pyroglutamate core unit common to oxazolomycin and neooxazolomycin (Scheme 116). Pyroglutamic acid derivative **533** on protection of carboxylic group as *t*-butyl ester and subsequent N-methylation afforded **534**. Compound **534** on debenzylation at C-3 followed by carboxymethylation of resultant alcoholic functionality delivered a carbonate **535**. The quarterniza-



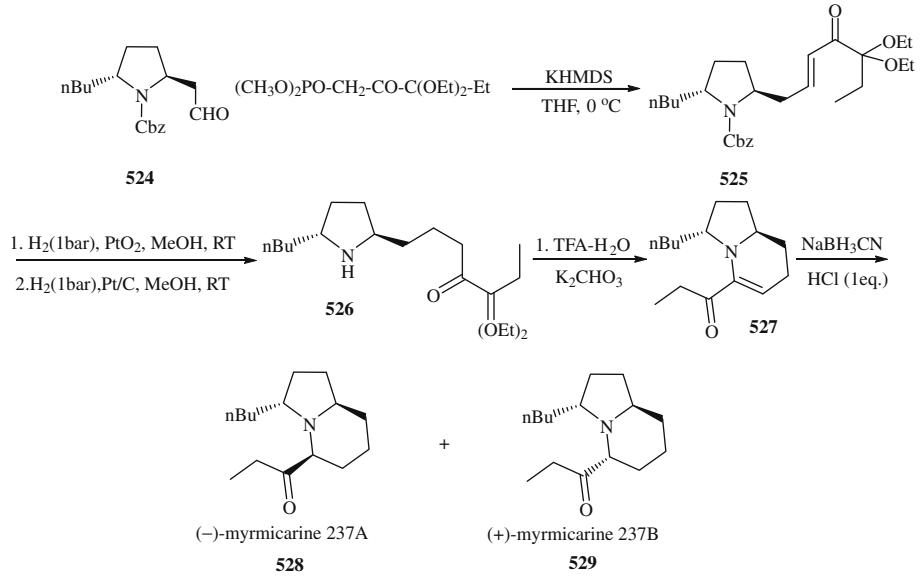
Scheme 112.



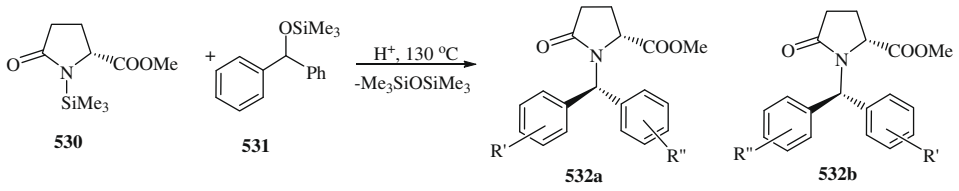
Scheme 113.

tion of C-2 followed by the introduction of exomethylene group at C-3 was carried out by internal nucleophilic trap of the carbonate **535** and lactone opening with the phenylselenide anion. The synthesized core unit **540** could be a useful scaffold for stereoselective functionalization corresponding to the oxazolomycin's polyene segments.

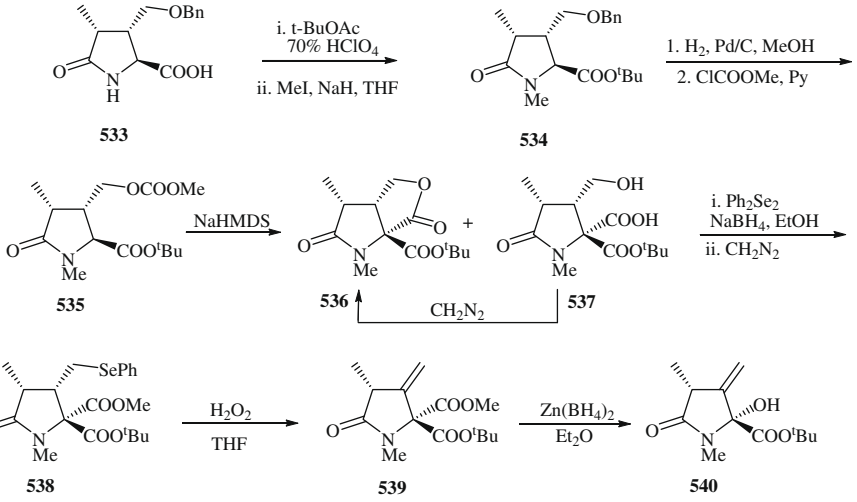
Panday et al. have reported[117] the simple pathway for the synthesis of (−)-bulgecinine (Scheme 117) starting with pyroglutamate derivative. Bicyclic lactam derivative **541** was converted to 6-α-hydroxy substituted product **543** via epoxidation and ring-opening sequences. OH group at C-6 was protected prior to hydrolysis of bicyclic ring to get 4-benzyloxy pyroglutaminol, in which OH group at C-5 was also protected with ethyl vinyl ether in the presence of acid catalyst to get **546** followed by protection of free



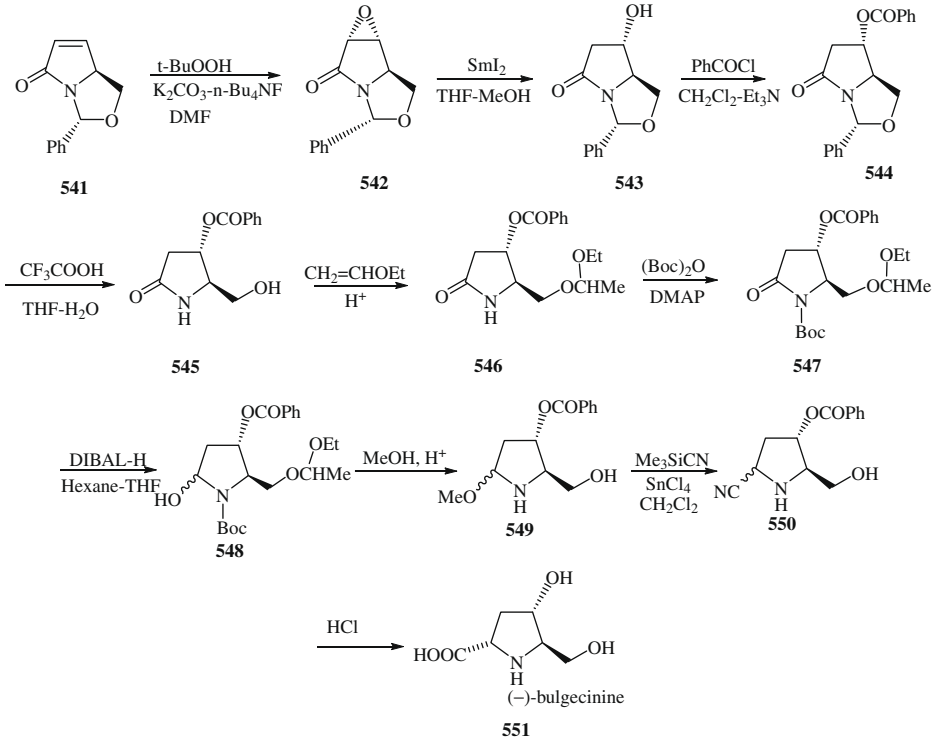
Scheme 114.



Scheme 115.



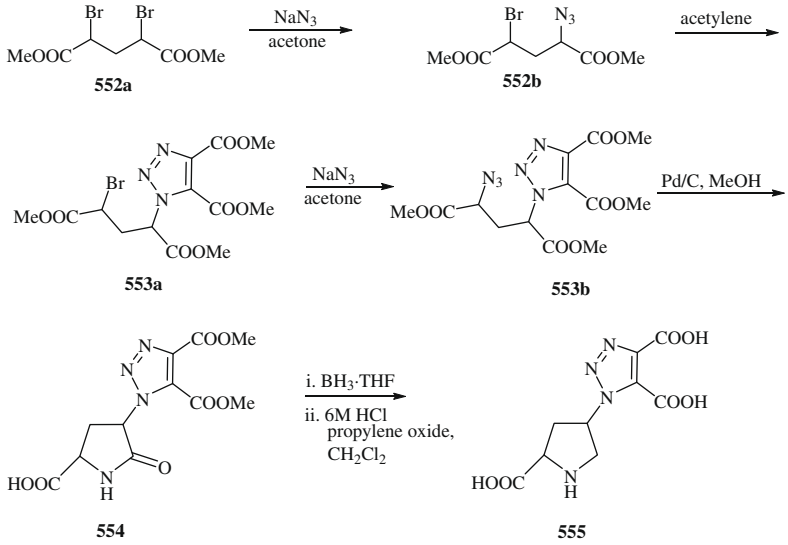
Scheme 116.



Scheme 117.

NH to *N*-Boc. Compound **547** was subjected to reduction of lactam carbonyl with DIBAL-H to get **548**. Treatment of **548** with MeOH/HCl led to the protection of OH group at C-2 as OMe and deprotection at C-5. The resultant product **549** on the introduction of cyano group at C-2 followed by acidic hydrolysis afforded (−)-bulgecinine.

Lenda et al. reported[118] synthetic strategies for new tetrazole and triazole substituted pyroglutamic acid and proline derivatives (Scheme 118). Dimethyl-2,4-dibromoglutarate **552a** was allowed to react with sodium azide, where mono-substituted derivative **552b** was obtained as a major product. 1,3-dipolar addition of azide **552b** with acetylene afforded 1,2,3-triazole derivative **553a**. The



Scheme 118.

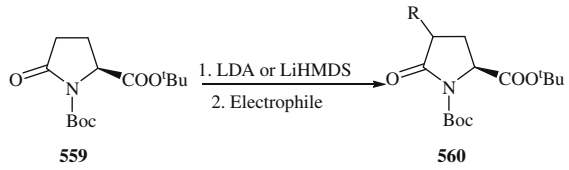
triazole derivative was subsequently reacted with 3 equiv of sodium azide to give **553b**. Compound **553b** on hydrogenation furnished the corresponding substituted pyroglutamic acid **554** via an intramolecular aminolysis. Lactam **554** on selective reduction with BH_3 in THF followed by acid hydrolysis and subsequent neutralization with propylene oxide yielded fully deprotected (±)-4-(4,5-substituted-1*H*-1,2,3-triazol-1-yl) proline derivative **555**.

In an attempt to carry out total synthesis of novel amino acid antibiotic TAN-950, Tsubotani et al. have made asymmetric use[119] of (*S*)-pyroglutamate without prior modification through functionalization at C-4 (Scheme 119).

Later on in their studies on the reactivity of pyroglutamates towards the asymmetric synthesis of 4-substituted pyroglutamates, Baldwin et al. reported[120] that reactions of lithium enolate-derived from 2(*S*)-pyroglutamates with various electrophiles, give exclusively 4-α-substituted products (Scheme 120).

Subsequently in our continuing studies[121] on the behaviour of protected pyroglutamate towards electrophiles we reported detailed studies on chiral alkylation and aldol reaction at C-4 of pyroglutamates through their lithium enolates (Scheme 121) where alkylation at C-4 gave exclusively 4-α-products, whereas aldol reactions afforded 4-α- and 4-β-substituted aldol adducts **566** and **567** in the ratio of 4:1.

We have also explored[122] the direct synthetic pathway for 4-(*S*)-substituted pyroglutamate through 1,3-dipolar addition of

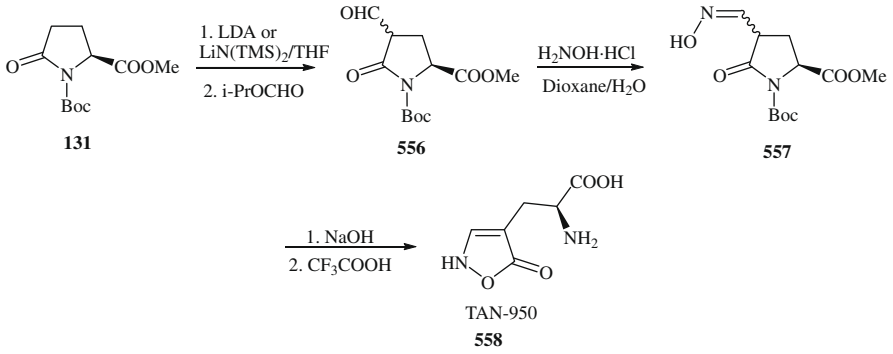


Scheme 120.

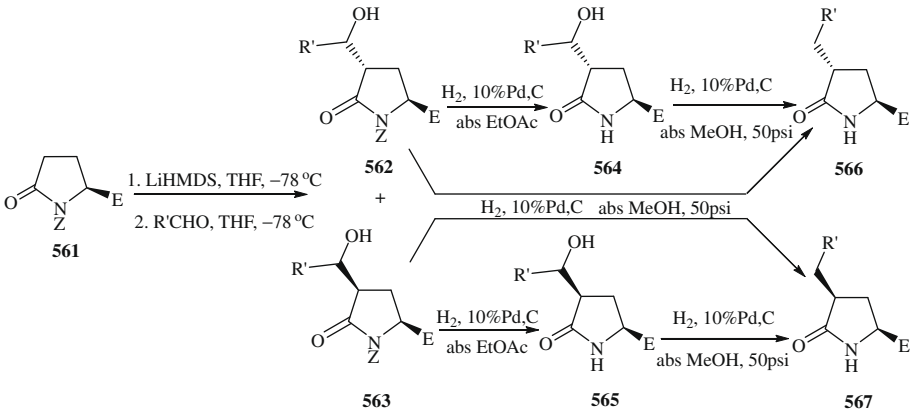
menthylacrylate with amino acid Schiff's bases followed by hydrogenolytic sequences (Scheme 122). These 4-substituted pyroglutamate and prolinates are part of many of the bioactive molecules.

As a part of their work on the synthesis of nonproteinogenic amino acids, Bowler et al. reported[123] reactions of lactam enolates of L-pyroglutamic acid derivatives with various electrophilic imines and found that the reaction proceeds in good yield with complete stereospecificity at C-4 and impressive stereo selectivity at the third asymmetric centre (Scheme 123).

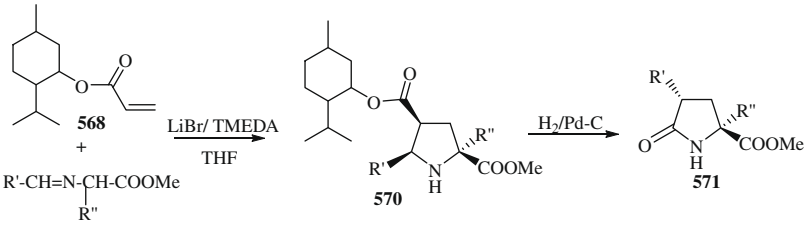
Young et al.[124] reported double stereo differentiation in aldol reaction of pyroglutamic urethane esters **576** (Scheme 124) and the same authors reported the use of acid and aldehyde of pyroglutamate in ring switching reaction leading to lactone **580** as kinetic products[125] (Scheme 125). The 4-substituted pyroglutamate **577** by ozonolysis was converted to aldehyde, in which aldehydic



Scheme 119.

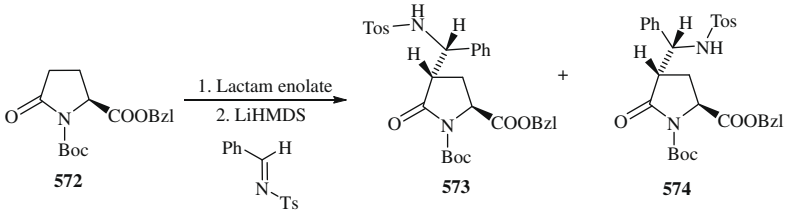


Scheme 121.

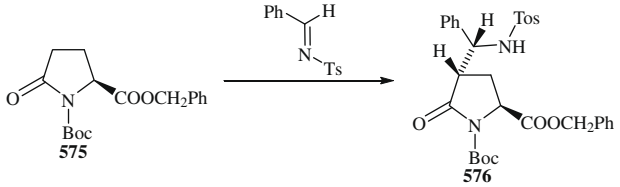


TMEDA= *N*,*N*,*N*′,*N*′-tetra methyl ethylene diamine

Scheme 122.



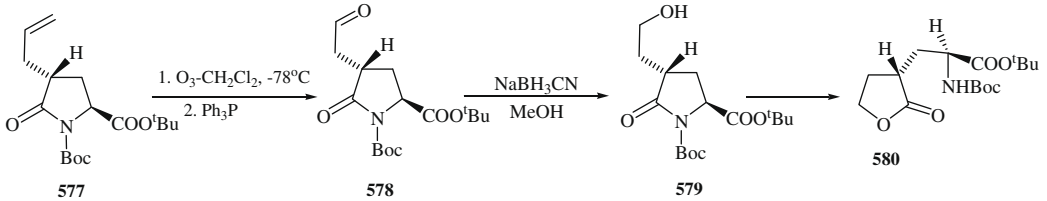
Scheme 123.



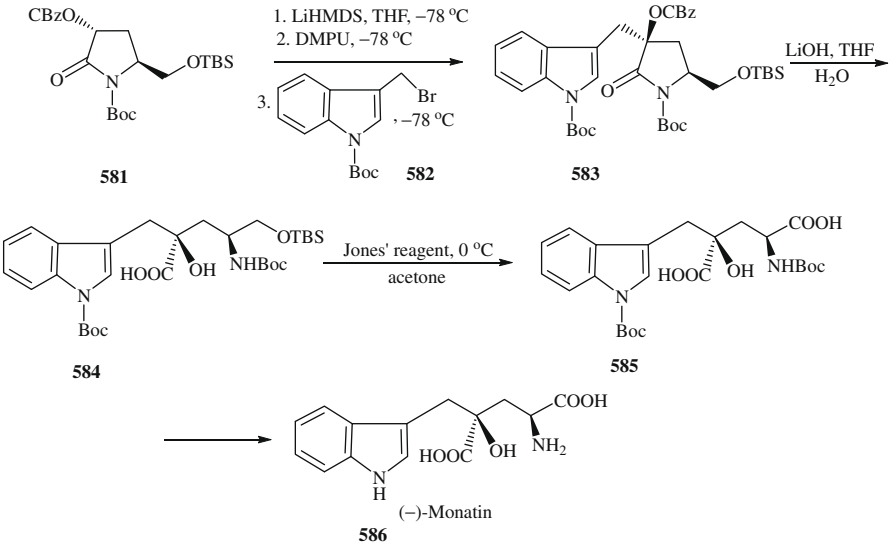
Scheme 124.

group on reduction was converted to alcohol **579** to get ring switched lactone **580**.

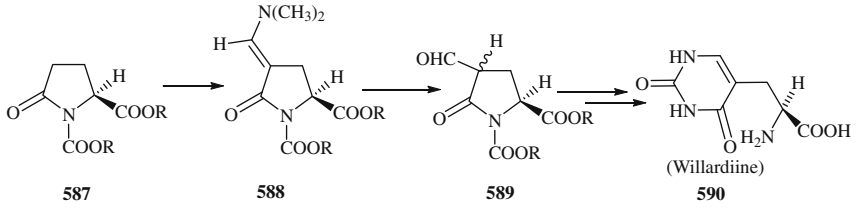
Diastereoselective formation of a quaternary centre in pyroglutamate derivative was reported by Oliveira et al.[126] (Scheme 126). Lithium enolate-derived alkylation of pyroglutamic acid derivative **581** with *N*-Boc-bromomethylindole **582** in the presence of DMPU, furnished intermediate **583**, where lactam part of **583** on alkaline hydrolysis with LiOH gave **584** which after deprotection afforded (−)-monatin **586**.



Scheme 125.



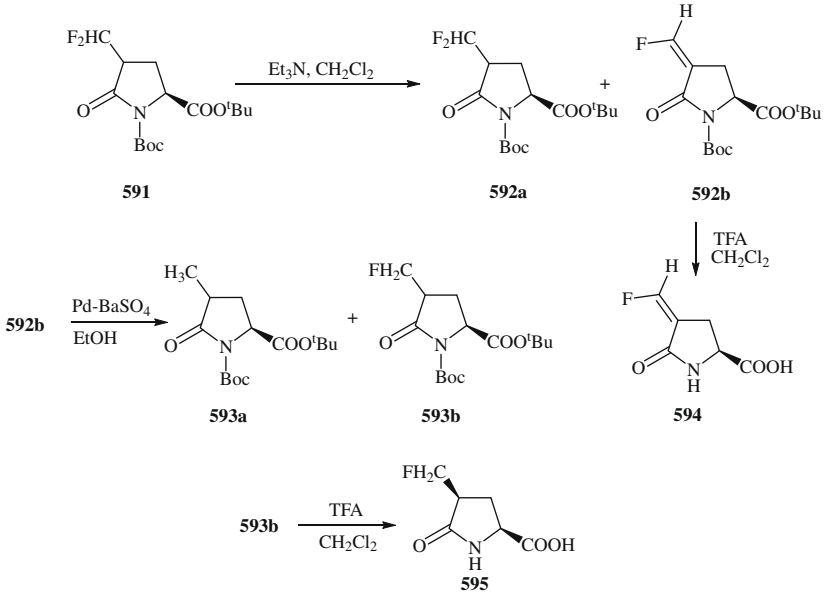
Scheme 126.



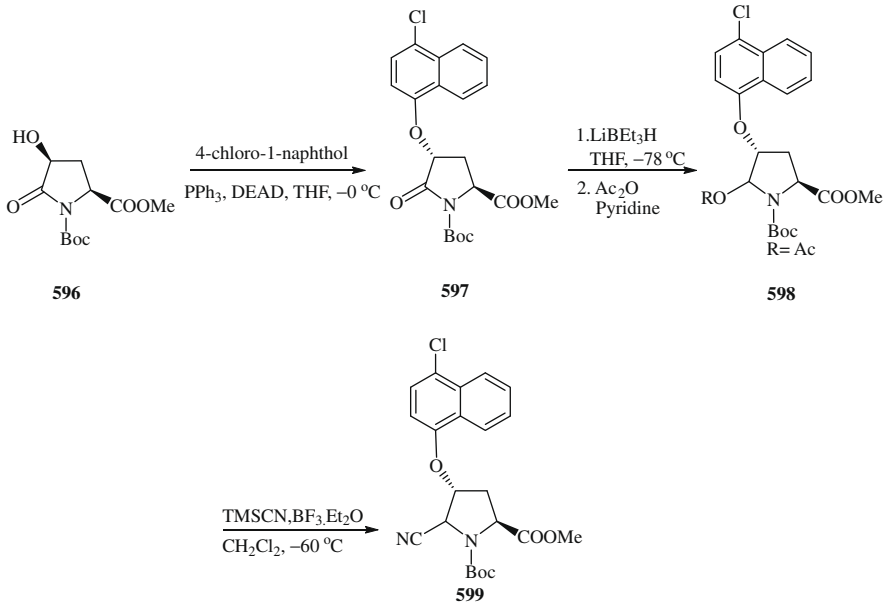
Scheme 127.

Dinsmore et al. reported the extension of ring switching strategy to the glutamate antagonist 2-(pyrimidin-2,4-dione-5-yl-methyl)-(2*S*)-glycine **590**[127] (Scheme 127).

Qiu et al.[128] carried out the synthesis of 4-monofluoromethylenyl **594** and *cis*-monofluoromethyl-L-pyroglutamic acid **595** via a novel dehydrofluorination (Scheme 128). Substrate **591** on reaction with triethylamine in CH_2Cl_2 was converted to compound **592b**, along with compound **592a**, in which compound **592b** after catalytic hydrogenation using Pd–$BaSO_4$ in ethanol afforded **593a**



Scheme 128.



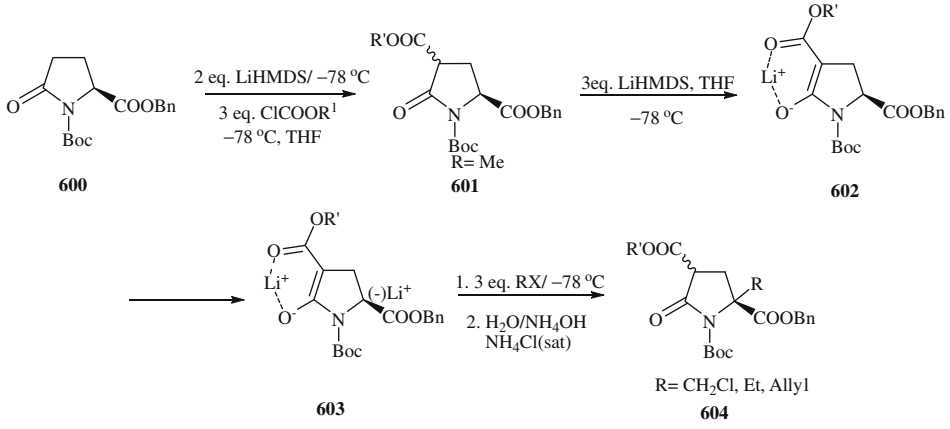
Scheme 129.

and **593b** and subsequently **593b** on hydrolysis using TFA gave the desired compound **595**.

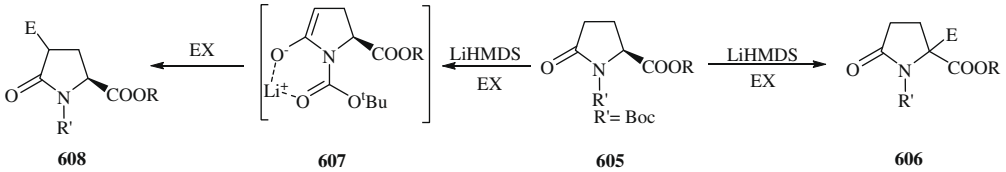
Zhang et al.[129] carried out the synthesis of *N*-Boc-4-O-substituted-5-cynomethyl pyroglutamate **599** (Scheme 129). 4-Hydroxypyroglutamate derivative **596** on Mitsunobu reaction with 4-choro-1-nepthol afforded **597**, which after reduction at C-5 using $LiBEt_3H$, followed by induction of cyano group at C-5 on reaction with TMSCN and $BF_3{\cdot}Et_2O$ gave the desired target molecule **599**.

Stevens et al.[130] reported the regioselectivity in the alkylation of pyroglutamates (Scheme 130). *N*-Boc benzyl pyroglutamate was converted to its 4-carboxylate **601** using Li enolate chemistry, which on further generating lithium enolate at position C-2 and subsequent reaction with electrophiles afforded **604**. In the same way [1,2] Boc migration during pyroglutamate alkylations has also been reported by the same group[131] (Scheme 131).

Kotoh et al.[132] carried out stereoselective synthesis of Nuphor quinolizidine alkaloid (−)-deoxynupharidines **618**–**619** (Scheme



Scheme 130.



Scheme 131.

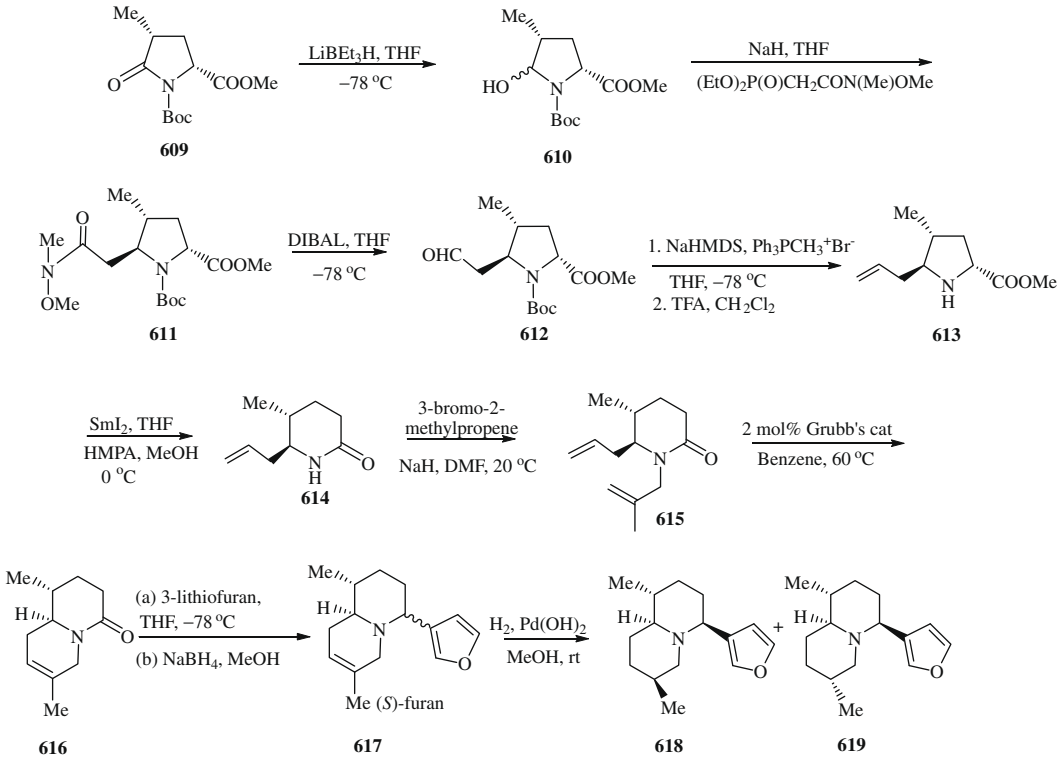
132). Compound **609** on reaction with $LiBEt_3H$, followed by witting reaction gave amide **611**, where amidic part was transformed into aldehydic ester **612** by using DIBAL and subsequently resultant aldehyde **612** on acidic hydrolysis was converted to **613**, which on deamination with SmI_2 in THF–HMPA and methanol gave six-membered ring product **614**. N-Alkylation of **614** with 3-bromo-2-methyl propane in the presence of NaH provided **615**, which on reaction with Grubb's catalyst was converted to **616**. Compound **616** was treated with 3-lithiofuran, subsequently reduced with $NaBH_4$, finally subjected to hydrogenolysis using $Pd(OH)_2$ thereby affording diastereomers **618** and **619**.

Merino et al. described[133] the diastereoselective approach with an objective to synthesize 4-hydroxy derivatives **623** (Scheme 133). 3-Hydroxy-pyrrolidinone **620** after protection of all the functional groups was converted to **622** which on reaction with H_5IO_6 and NaH_2PO_4 gave target molecule **623**.

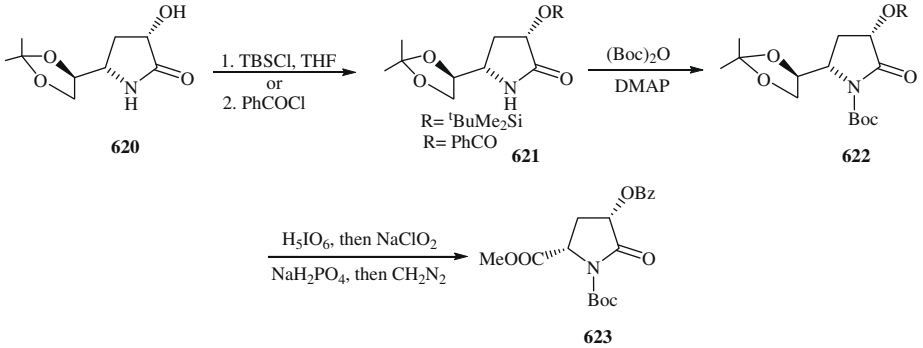
Langlois et al. achieved the total synthesis of salinosporamide-A, a potent proteasome inhibitor, starting from pyroglutamate derivative[134] (Scheme 134). Compound **624** was converted to **625** on reaction with *N*-methylnitrone in toluene through 1,3-dipolar addition and resulting adduct **625** was subjected to hydrogenolysis leading to ring opening, methylation of amino group and subsequently cope elimination to afford salinosporamide-A **628**.

Hill et al. synthesized[135] stereocontrolled spirocyclic bislactams derived from pyroglutamic acid, compound **629** on reaction with NaH and $BrCH_2CN$ afforded **630** which on treatment with $NaBH_4$ and $COCl_2$ underwent reduction coupled with cyclization to give spirobicyclic lactams **631** and **632** (Scheme 135).

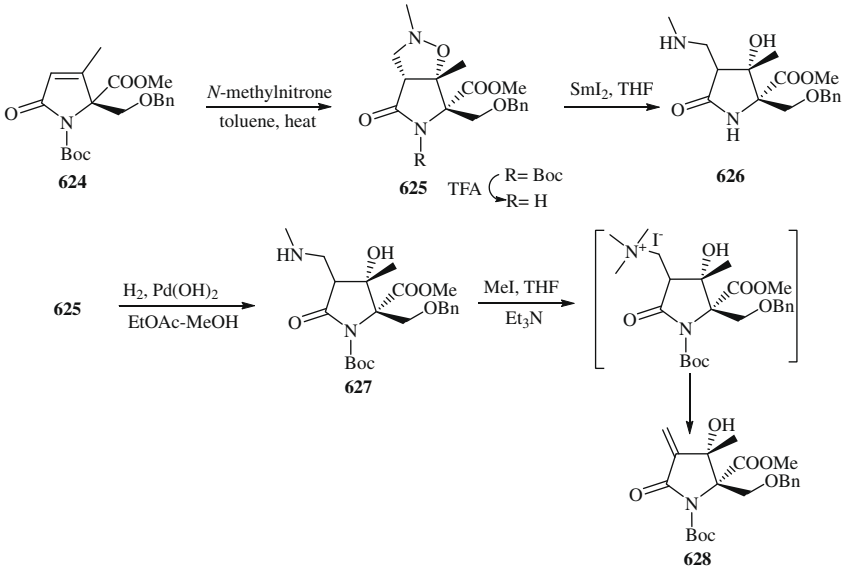
Herdeis et al.[136] carried out a stereoselective synthesis of 3-substituted (*S*)-pyroglutamic acid and glutamic acids through ABO ester derivatives (Scheme 136). Pyroglutamic acid was converted to its ester through condensation, which after protection



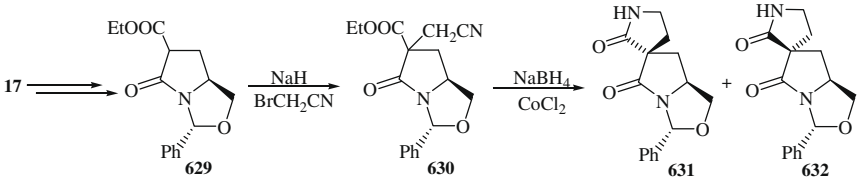
Scheme 132.



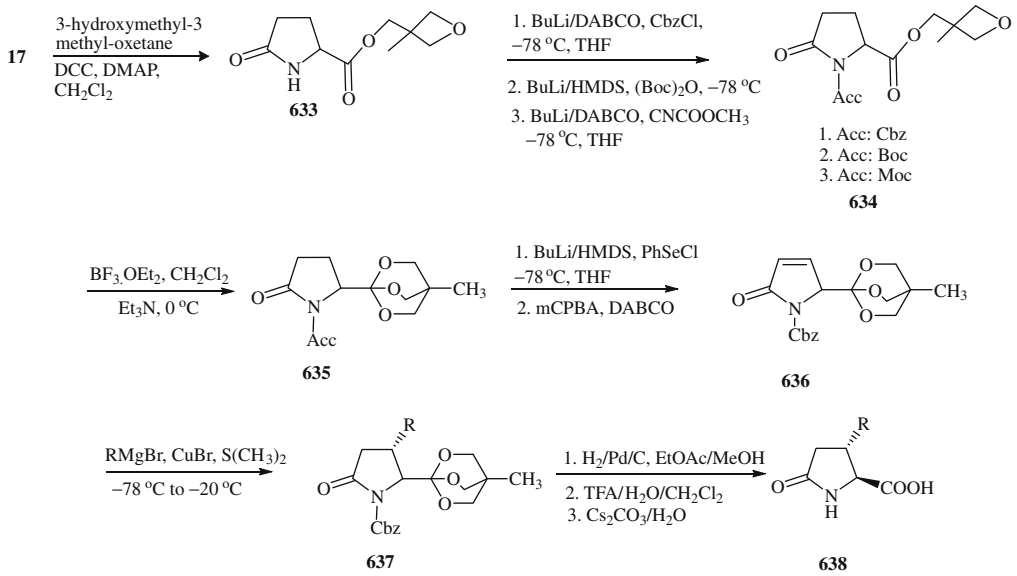
Scheme 133.



Scheme 134.



Scheme 135.

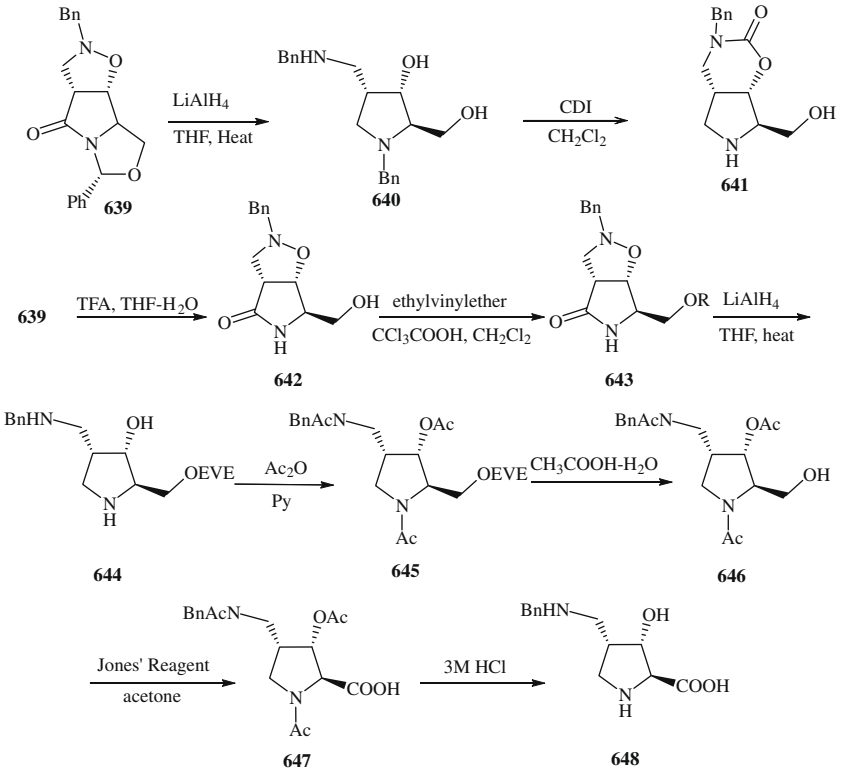


Scheme 136.

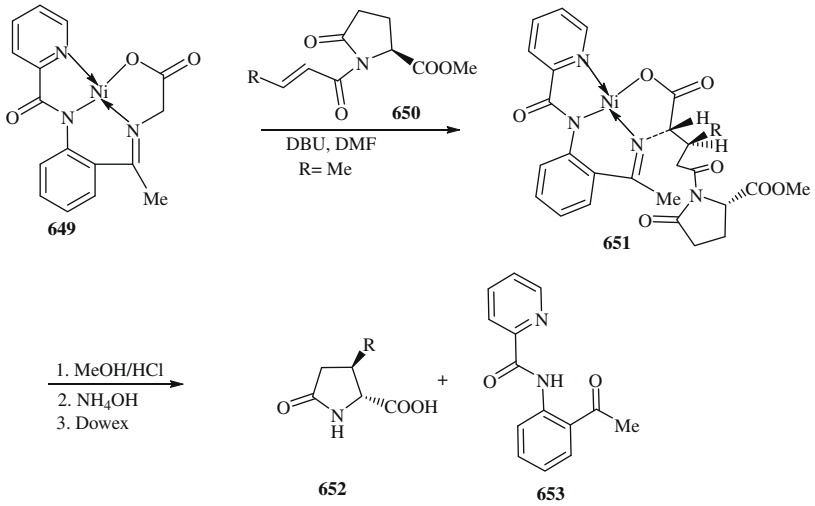
of –NH followed by oxidation was converted to ABO ester **635**. Formation of epoxide at C-3, 4 of **635** following usual chemistry and subsequent ring opening with Grignard reagent afforded **637**. Compound **637** after protection and deprotection sequences afforded the desired 3-substituted pyroglutamate **638**.

Cienfuegos et al. reported stereoselective synthesis of conformationally constrained (2*S*,3*S*)-3-hydroxyornithine[137] (Scheme 137).

Cai et al.[138] described the application of (*S*)-and (*R*)-methyl pyroglutamates as inexpensive, yet highly efficient chiral auxilia-



Scheme 137.



Scheme 138.

ries in the asymmetric Michael addition reactions (Scheme 138). Michael acceptor **650** reacts with Ni(II) complex to give exclusively **651**. Compound **651** on treatment with methanoic HCl and subsequently treatment with NH_4OH and Dowex yielded 3-substituted pyroglutamic acid **652**.

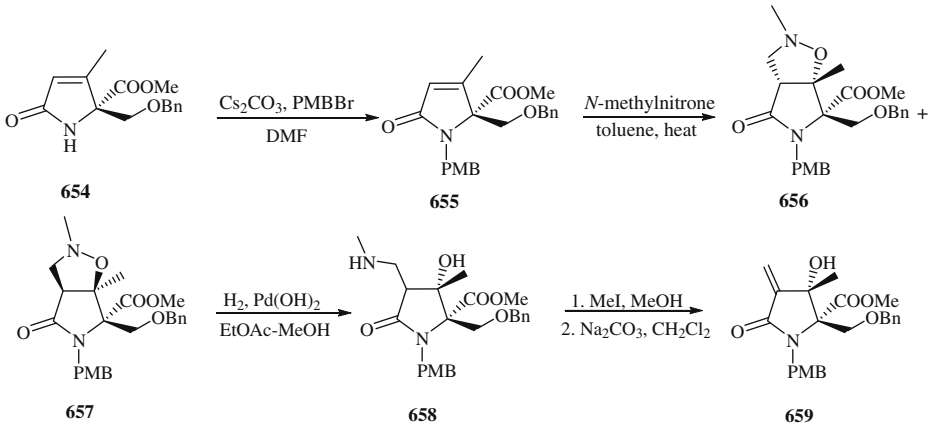
Langlois et al.[139] reported the stereoselective formal synthesis of the proteasome inhibitor salinosporamide A, from (*S*)-methyl 2-hydroxymethylpyroglutamate through chemoselective O-protection (Scheme 139).

Fujita et al. reported reactions of optically active 5-substituted-2-pyrrolidinone derivatives having atropisomeric behaviours. They carried out 3,5-*cis*-selective reactions of their enolates with electrophiles[140] (Scheme 140).

3.4. Conversion of pyroglutamic acid into prolines

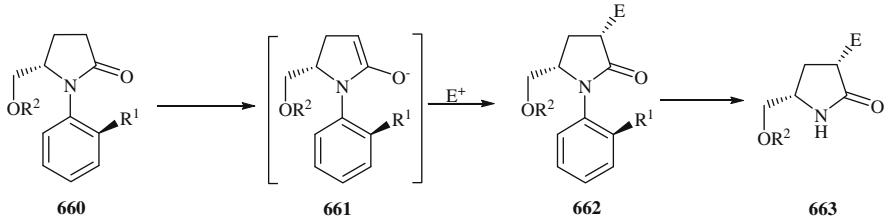
Pyroglutamates can readily be converted into prolines. Rapoport et al. converted 4-phenylpyroglutamate **664** to 4-phenyl prolinate **665** by reducing with BH_3·THF in the presence of a catalytic amount of $NaBH_4$[141] (Scheme 141).

Pyroglutamates could directly be converted into L-proline in 2-step one-pot reaction. The conversion involves the treatment of



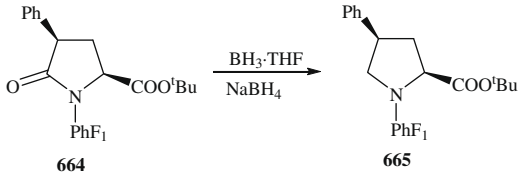
654 655 656 657 658 659

Scheme 139.



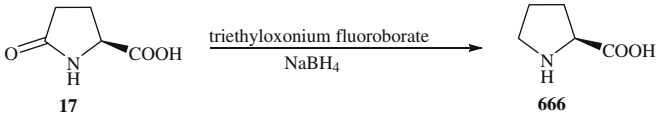
660 661 662 663

Scheme 140.



664 665

Scheme 141.



17 666

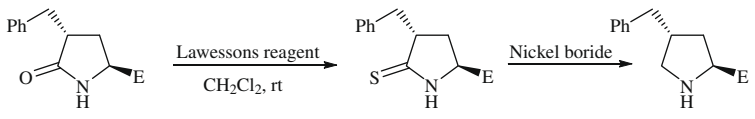
Scheme 142.

pyroglutamic acid with triethyl oxonium fluoro borate and reduction of the resulting crude imino ether with $NaBH_4$[142] (Scheme 142).

We have also reported a simple procedure[121] for the conversion of 4-substituted pyroglutamates to 4-substituted prolinates **669** via the conversion of pyroglutamate to thio lactam followed by reduction to the corresponding prolinate in the presence of nickel boride generated in situ (Scheme 143).

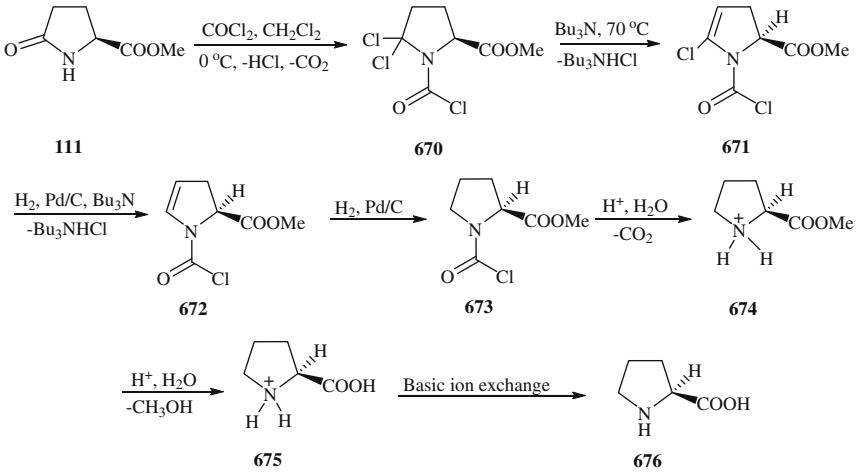
Drauj et al. have converted[143] L-pyroglutamate **111** to 5,5-dichloro-*N*-chloro carbonyl 2(*S*)-methyl pyroglutamate **670** on reaction with $COCl_2$ in dichloromethane at 0 °C with the elimination of HCl and CO_2. Compound **670** on reaction with Bu_3N gave **671** with the elimination of HCl at positions 4 and 5 leading to induction of double bond. Compound **671** on hydrogenation using Pd/C with Bu_3N gave unsaturated product **672**, which on further hydrogenation gave saturated products **673**. Compound **673** after several protection and deprotection sequences afforded L-proline (Scheme 144).

Harris et al.[144] reported the synthesis of cyclic proline containing peptides via ring-closing metathesis (Scheme 145). *N*-Acyl-5-allyl diene **677**, which was obtained from pyroglutamic acid was

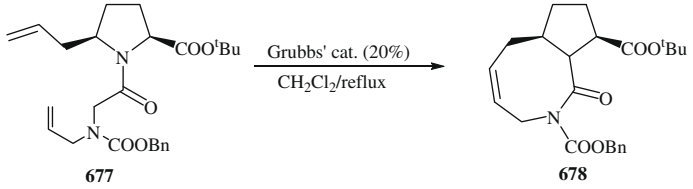


667 668 669

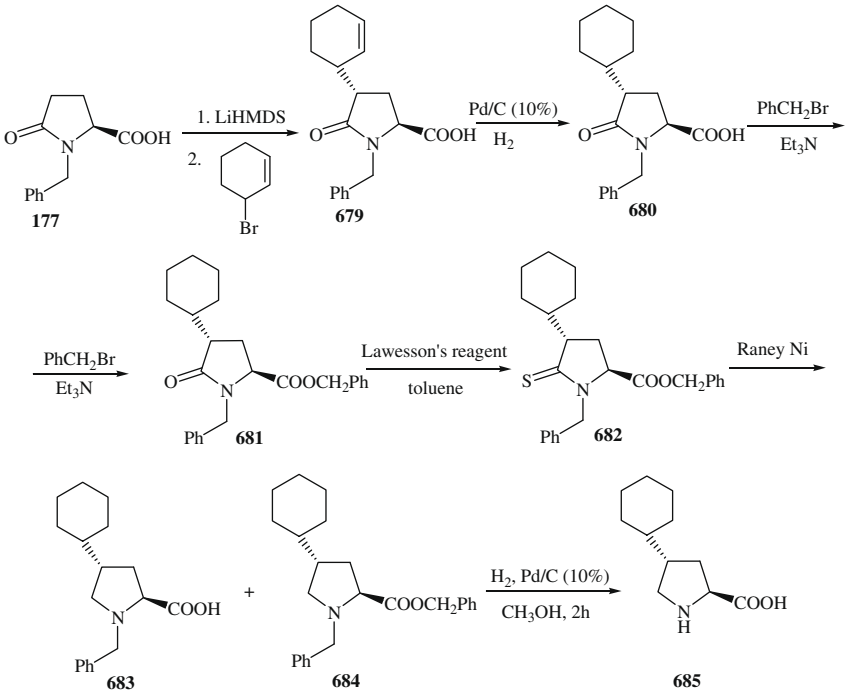
Scheme 143.



Scheme 144.



Scheme 145.



Scheme 146.

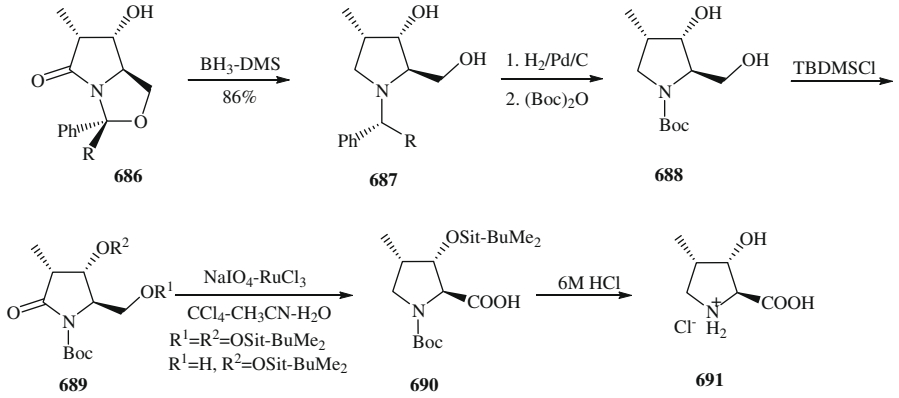
subjected to cyclization in the presence of Grubb's catalyst to afford the expected cyclononenes **678**.

Chen et al. reported a convenient method for the synthesis of *trans*-4-cyclohexyl-L-proline[145] (Scheme 146). *N*-Benzyl pyroglutamic acid was reacted with bromocyclohexene in the presence of LiHMDS, followed by hydrogenolysis with Pd/C to get 4-substituted *N*-benzyl pyroglutamic acid **680** which was condensed with $PhCH_2Br$ to get ester **681**. Treatment of **681** with Lawesson's reagents, followed by reduction with Raney Ni afforded **683** and **684**. Both these products were subjected further to hydrogenolysis using H_2/Pd–C to get 4-cyclohexyl proline **685**.

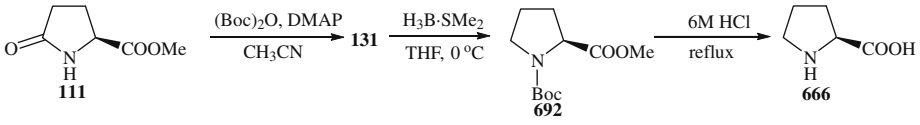
Langlois et al.[146] reported diastereoselective syntheses of (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **691**, a common constituent of several antifungal cyclopeptides (Scheme 147). Compound **686** on reduction using BH_3–DMS was converted to **687**, resultant material on hydrogenolysis, followed by NH protection was converted to **688**. Treatment of **688** with TBDMSCl gave **689** and subsequent reaction with $NaIO_4$–$RuCl_3$ followed by acidic hydrolysis afforded the desired molecule **691**.

Two separate and distinct syntheses of stereospecifically deuterated samples of (2*S*)-proline were reported by Barraclough et al.[147] (Scheme 148). Compound **131** on reduction using $H_3B{\cdot}SMe_2$, followed by acidic hydrolysis afforded proline **666**.

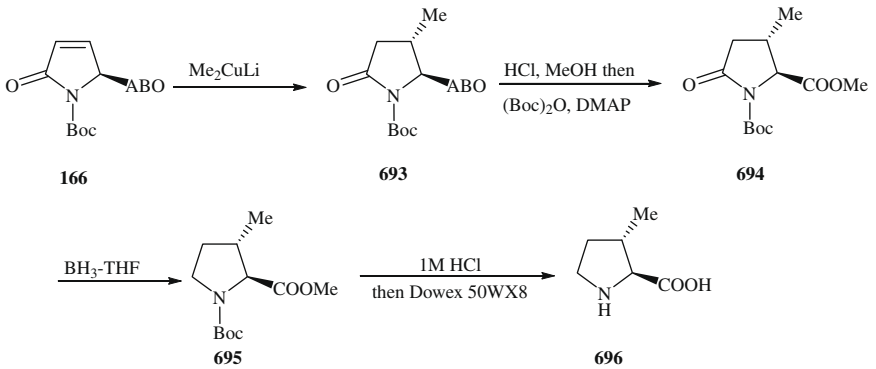
Oba et al.[148] carried out the synthesis of non-proteinogenic amino acids using Michael addition to unsaturated orthopyroglutamate derivative (Scheme 149). Unsaturated pyroglutamate derivative **166** on reaction with Gilman reagent delivered a compound **693** having methyl group at C-3. The ABO ester functionality of **693** was converted to methyl ester through ester exchange reaction with MeOH/HCl. The *N*-Boc group of **693** which was deprotected during acidic conditions was protected again with Boc group to afford **694**. Reduction of lactam carbonyl of **694** with $BH_3{\cdot}THF$ followed by deprotection of methyl ester of **695** in refluxing 1 M. HCl and subsequently ion exchange treatment with DOWEX 50WX8



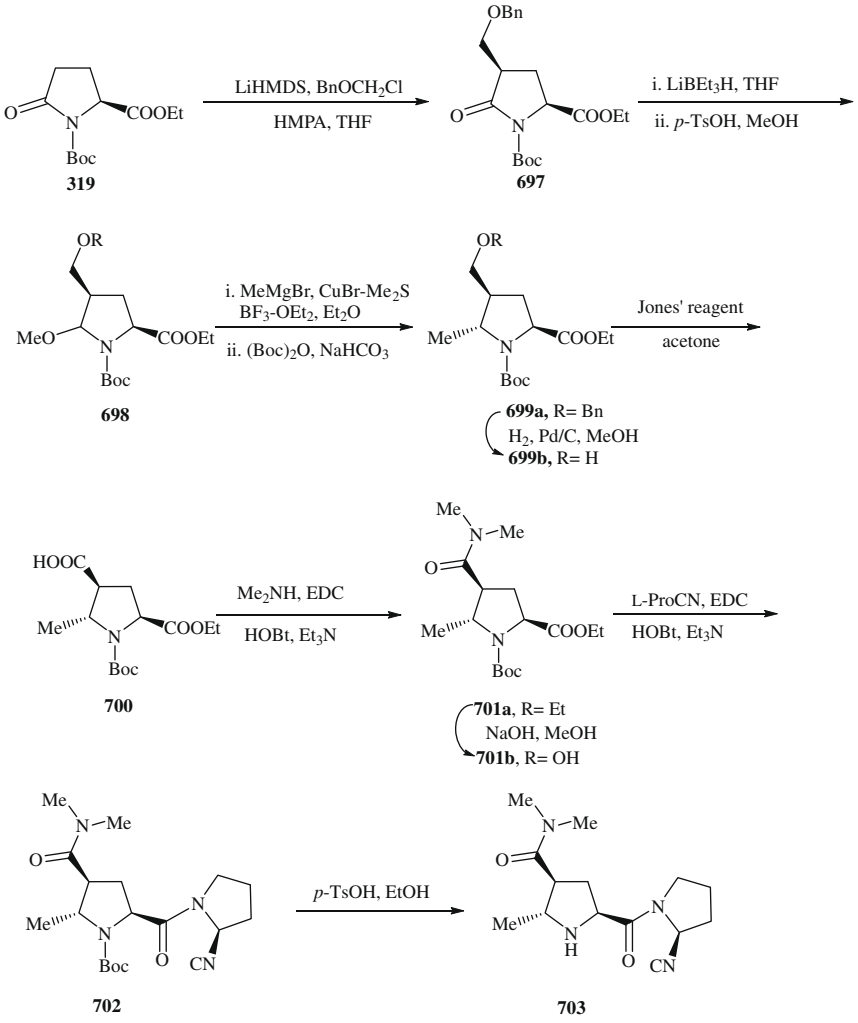
Scheme 147.



Scheme 148.



Scheme 149.



Scheme 150.

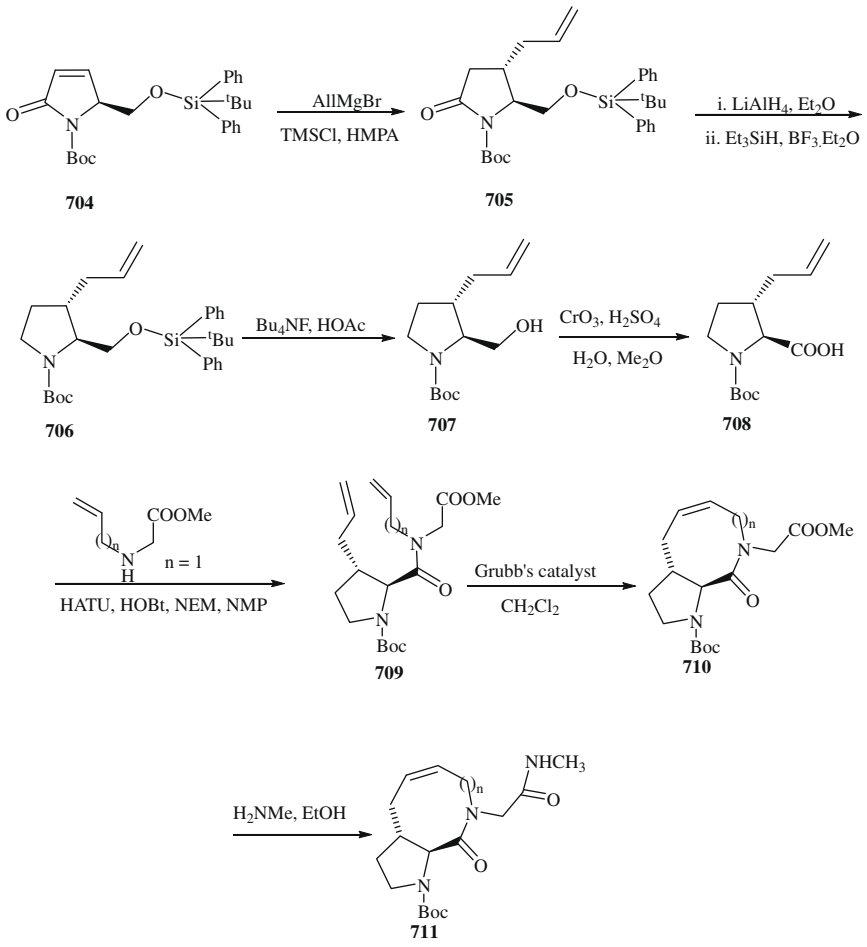
resin furnished (2*S*,3*S*)-3-methylene proline **696** in quantitative yield.

Kondo et al.[149] discovered long acting *N*-(cyanomethyl)-*N*-alkyl-L-prolinamide inhibitors of dipeptidyl peptidase IV (Scheme 150) starting with pyroglutamic acid derivative. Lithium enolate-derived alkylation of N-protected ethyl-L-pyroglutamate **319** with benzyloxymethyl chloride afforded 4-substituted pyroglutamate **697**. Partial reduction of cyclic imide carbonyl of **697**, followed by acetalization gave the methyl acetal **698**. Stereoselective 5 α-methylation of **698** with methyl Grignard reagent and copper(I) bromide-dimethylsulfide complex in the presence of boron trifluoride-etherate, followed by protection of deprotected nitrogen, led to **699a**. Catalytic hydrogenation of **699a** provided the alcohol **699b**. Jone's oxidation of **699b** resulted in carboxylic acid **700**, which on condensation with *N,N*-dimethyl amine produced **701a**. Alkaline hydrolysis of compound **701a** provided carboxylic acid **701b**, which on peptide formation with (2*S*)-2-cyanopyrrolidine afforded **702**. Acidic deprotection of **702** led to the desired compound **703**.

Einsiedel et al. developed a molecular building kit of fused-proline derived peptide mimetics allowing specific adjustment of the dihedral ψ-angle (Scheme 151). Unsaturated pyroglutamic acid derivative **704** on reaction with allyl bromide in the presence of TMSCl and HMPA, followed by reduction of lactam carbonyl delivered **706**, which after deprotection of alcoholic group furnished prolinol derivative **707**. Jones oxidation led to the formation of the C-3 functionalized proline **708**. Amide formation between the asymmetric building block **708** and N-substituted glycine derivatives using coupling mixture HATU/HOAt allowed an efficient synthesis of RCM precursor **709**. Olefin metathesis using Grubb's II generation catalyst afforded seven-membered and eight-membered unsaturated bicyclic lactams **710**. Aminolysis of **710** with methylamine delivered the model peptides **711**.[150]

4. Conclusions

Thus this review gives explicit information about the versatility and importance of pyroglutamate with special attention to asymmetric synthesis of bioactive molecules, natural products as well as chiral intermediates. On the one hand this important moiety has allowed the researchers to synthesize bioactive natural products such as anatoxin A, (−)-bulgecinine and salinosporamide A, whereas on the other hand the use of pyroglutamic acid as a chiral precursor has enabled the researchers to explore the synthetic analysis for designed bioactive molecules such as ACE inhibitors like fosinipril, conformationally constrained peptides as well as peptidomimetics. Various derivatives of pyroglutamic acid have also been used to develop catalyst such as semicorrin metal com-



Scheme 151.

plexes or 2,5-disubstituted pyrrolidines. Therefore it may be concluded that pyroglutamate has undoubtedly emerged as an important chiral synthon and has provided researchers a useful chiral tool to exploit the reactivity differences within the molecule and to use it for the asymmetric synthesis of wide variety of bioactive compounds. The present review is an attempt to describe the useful and important applications on the use of this unique chiral synthon by the researchers all over the world in the recent past, and shall certainly be valuable, to make further progress and to develop new strategies for the asymmetric synthesis based on these literature reports.

Acknowledgements

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