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Amino Acids Chirons: A Tool for Asymmetric synthesis of Heterocycles

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Amino acids as chiral pool have been extensively used by synthetic organic and medicinal chemists for access to heterocycles (monocycles, bicycles or polycycles either bridged or fused) owing to their easy availability in enantiomerically enriched form and having synthetically transformable diverse functional groups. This review describes diverse asymmetric heterocycles with various membered rings (n=3-9) followed by benzo or heteroannulated ones for the period from 1996 to Dec, 2013. It details on those solution phase synthetic methodologies in which the naturally occurring α-amino acid is incorporated, totally or partially, in the final product.

1.1 Introduction

Search for new and effective biodynamic properties of chemical compounds is a continuous research exercise in the field of new drug developmental research. This is necessary because the clinical experience with a particular drug on the market demands its replacement with another one of better proven performance. The desired biodynamic property, in principle, may be rationalised with a particular skeletal structure of a molecule and towards this perspective, design of new structural frameworks and chemical synthetic routes for their assembly have typically focused on asymmetric synthesis of heterocycles and related diversity[1a]. The interest in this field has greatly increased in recent years because of several factors such as the enantiospecific interaction and response between receptor and drugs, the increasing demand to market chiral drugs as single enantiomers by the pharmaceutical industry, and the strong drive for synthetic efficiency. Towards this objective, chiral pool plays as an important tool to the synthetic organic chemists for the synthesis of bioactive and pharmaceutically important heterocycles[1a]. In this respect, chirally pure α-amino acids (in both forms *S* or *R*) serve as chiral pool in the asymmetric synthesis of structurally complex or simple drug or drug like molecules. The proteinogenic α-amino acids are extensively used today in the pharma industries because of their easy availability in enantiomerically enriched form and significant number of functional groups which are synthetically transformable into others. In addition, for their biological and therapeutical relevancy, they took the central role in diverse areas such as antimicrobials, infectious, cardiovascular and nervous system disorders, genital tract diseases, estrogen related disorders and bone remodelling. The α-amino acids gained significant value not only due to the previously mentioned reasons but the molecules derived from those are very much like natural ligands, biocompatible (chance of cytotoxicity is less probable), water soluble (essential for drug candidate) and of course the increased resistance to proteolysis.

The main focus of this review is the specific use of enantiomerically enriched α-amino acids as building blocks for the synthesis of chiral heterocycles (monocycles, bicycles or polycycles either bridged or fused) for the period from 1996 to Dec, 2013. To the best of our knowledge, two outstanding reviews on this subject have been reported previously by the group of Henry Rapoport and Manfred T. Reetz[1a].

Another short account of the use of amino aldehydes and chiral pool amino acids in synthesis of several heterocyclic compounds has also appeared[1a].

This review details on those solution phase synthetic methodologies in which the naturally occurring α-amino acid is incorporated, totally or partially, in the final product. The use of amino acids as removable chiral auxiliaries for asymmetric induction is not mentioned. The synthesis of other alicyclic or cyclic unnatural amino acids (UAAs) or cyclic α-quaternary-α-amino acid derivatives is also not covered. The solid phase syntheses of amino acids derived heteocycles are also not included. To begin with, chiral heterocycles with various membered rings (n=3-9) followed by benzo or heteroannulated ones are described.

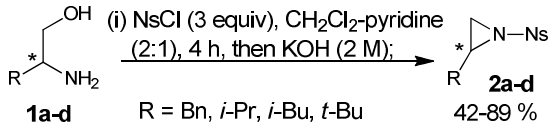
1.2 Chiral Heterocycles

1.2.1 Three Membered Chiral Heterocycles

1.2.1.1 Aziridine

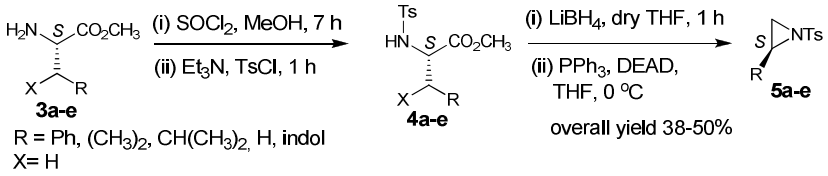
Aziridine is a versatile starting building block for the synthesis of different types of chiral heterocycles. As a three membered heterocycle, it has ring strain and can readily undergo ring opening reaction with different types of nucleophiles.[1] Franzyk and coworkers synthesized aziridine **2a-d** from amino alcohols **1a-d** by a single step involving *in situ* nosylation of alcohols and base mediated nucleophilic displacement of-ONs group (Scheme 1).[2]

Scheme 1

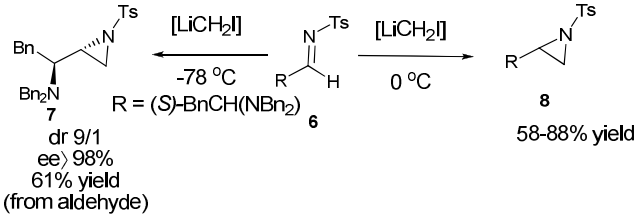


Samanta *et al.* have reported an easy synthesis of amino acids derived chiral aziridines **5a-e** which were prepared in good yields from α-amino acids **3a-e** following four synthetic steps, involving esterification of acids **3a-e**, tosylation on amines and $LiBH_4$ reduction of ester groups of **4a-e** followed by Mitsunobu cyclization (Scheme 2).[3]

Scheme 2



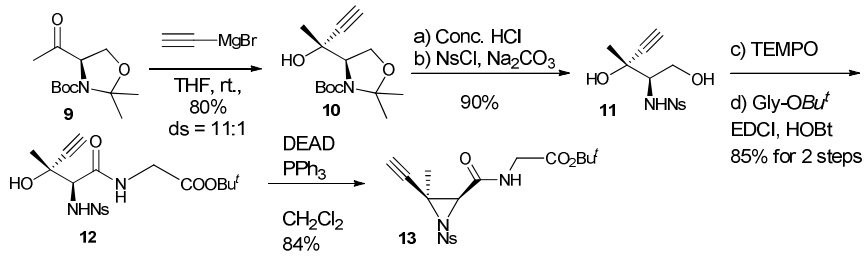
Scheme 3



Concellon *et al.* reported an efficient and general synthesis of aziridines **8** by the reaction of imines **6** derived from *p*-toluene sulfonamides with *in situ* generated

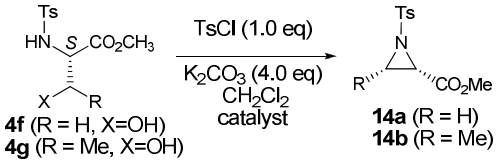
iodomethyllithium. The reaction with the chiral aldimine derived from phenylalaninal allowed access to (2*R*,1′*S*)-2-(1′-aminoalkyl)aziridine **7** with high diastereoselectivity (Scheme 3).[4]

Scheme 4



Li *et al.* reported the synthesis of ethynyl aziridine **13** from methyl ketone **9** by four step sequences from D-serine. Grignard addition of ethynylmagnesium bromide to **9** afforded chiral tertiary alcohol **10** in 80% yields with 11:1 diastereomeric ratio. Deprotection of amino alcohol with concentrated HCl, followed by selective protection of the amino group gave 2-nitrobenzenesulfonamide **11** in one pot. TEMPO-catalyzed oxidation of primary hydroxyl group of diol gave carboxylic acid, which was coupled with glycine *tert*-butyl ester to provide dipeptide **12** (85% over two steps) without affecting the tertiary hydroxyl group. Mitsunobu reaction converted **12** to ethynyl aziridine **13** in 84% yield (Scheme 4).[5]

Scheme 5



S.N.	Starting Material	Product	Isolated Yield (%) Catalyst	
			Aliquot 336	18-crown-16
1	Methyl L-serinate.HCl	**14a**	52	54
2	Methyl L-threoninate.HCl	**14b**	28	38
3	Methyl *N*-tosyl-L-serinate (**4f**)	**14a**	54	73
4	Methyl *N*-tosyl-Lthreoninate (**4g**)	**14b**	49	50

Marzorati *et al*. reported the synthesis of *N*-tosyl aziridine-2-carboxylate methyl esters **14** from methyl *N*-tosyl-L-serinate **4f** or *N*-tosyl-L-threoninate **4g**, tosyl chloride, and K_2CO_3 under phase-transfer catalysis (PTC) conditions (Scheme 5).[6]

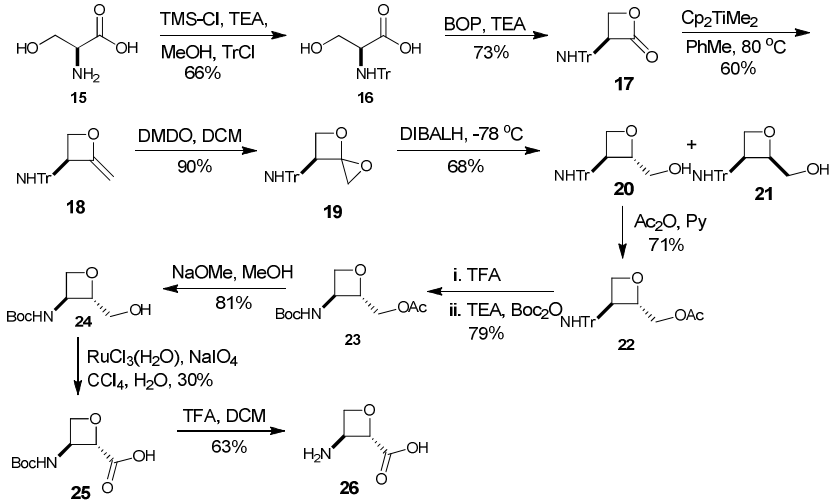
1.2.2 Four Membered Chiral Heterocycle

1.2.2.1 *epi*-Oxetin

Blauvelt *et al*. reported the synthesis of *epi*-oxetin *via* serine-derived 2-methyleneoxetane **18** which was oxidized with DMDO to provide **19** (as 2:1 mixture of

diastereomers). Dioxaspirohexane **19** was reduced with DIBALH to give two diastereomers **20** and **21** (2:1 ratio). **20** was converted to *epi*-oxetin **23** *via* protection/deprotection of hydroxyl methyl and amine group, hydroxyl methyl oxidation and finally, Boc-deprotection (Scheme 6).[7] While this reported procedure[7] gave disubstituted derivatives, trisubstituted ***epi*-Oxetin** is yet to be synthesized from amino acids.

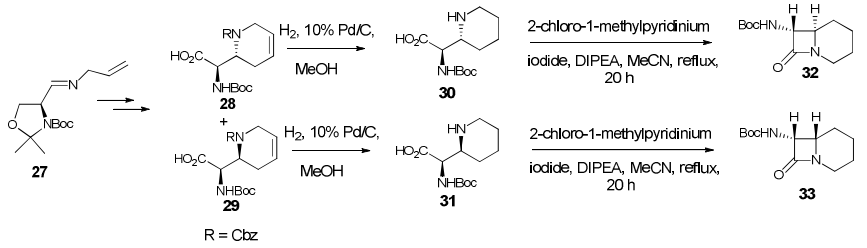
Scheme 6



1.2.2.2 Beta-lactam

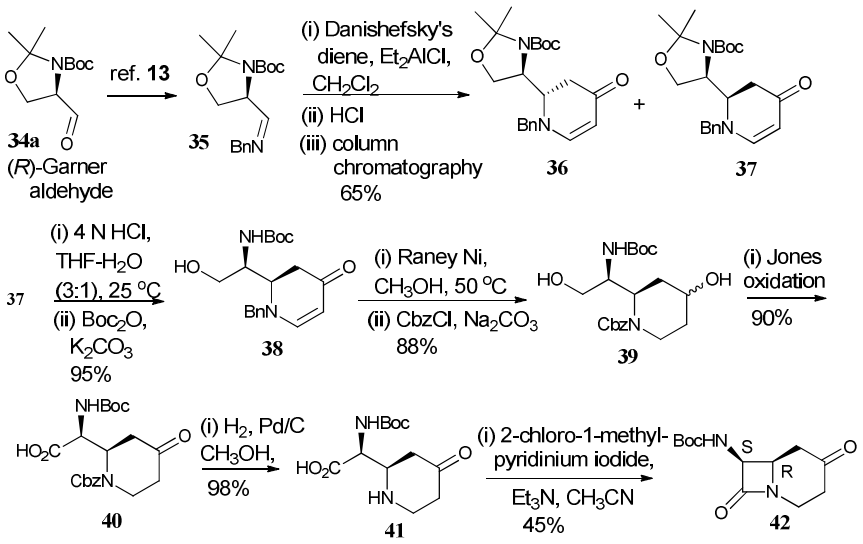
Chattopadhyay *et al.*[8] reported a stereodivergent route to epimeric 2-piperidinylglycines **28** & **29**, as precursors of carbocyclic β-lactam derivatives (**32** & **33)**. The key intermediates **28** & **29** were synthesized from serine derived Garner aldehyde *via* allylic nucleophilic addition and ring closing metathesis. **28** & **29** were converted to β-lactam in two steps: hydrogenation of the double bond and hydrogenolysis of the *N*-Cbz group followed by lactam formation with Mukaiyama's reagent[9] (Scheme 7).

Scheme 7



Carbacephams, ring fused β-lactams, play significant role as the precursors of carbacephems and are important to investigate the biological behavior of β-lactam antibiotics. Synthesis of this novel heterocycle was reported by Avenoza *et al*. in 2002 using a hetero Diels-Alder reaction (HDA) of the benzylimine derived from the enantiomer of Garner's aldehyde (**34a**) with Danishefsky's diene as the key step (Scheme 8).[10]

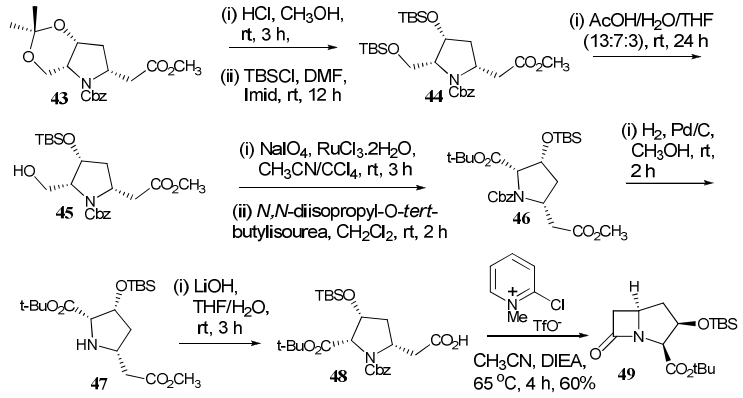
Scheme 8



The cycloadduct **37** was then converted into **39** following a sequence of reactions including acetonide removal; Raney Ni mediated reduction-debenzylation followed by Cbz protection. The furnished alcohol **39** was then subjected to Jones oxidation to afford **40**, which was hydrogenated and cyclized into the final product **42**.

In 2003, Hart *et al.* reported an efficient route to carbapenam core starting from L-serine derived **43**. Compound **43** was first converted into **44** *via* acetonide deprotection followed by TBS protection of the alcohol. Then selective removal of primary TBS group and Pinnick oxidation/esterification sequence provided **46**. Compound **46** upon treatment with Pd/C, H_2 and hydrolysis produced acid **48**, which finally gave carbapenam core **49** after cyclization (Scheme 9).[11]

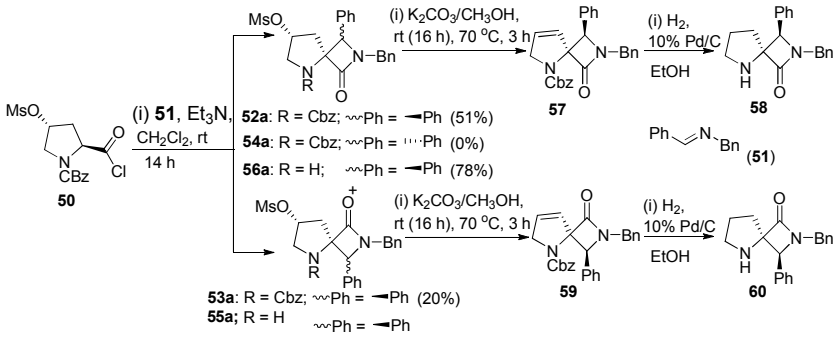
Scheme 9



Conformational constraints developed by introduction of cyclic amino acids, such as proline into peptides or proteins are enhanced by quarternization of the chiral centre and might have significant contribution to the peptidomimetics. In the search of novel β-turn mimetics, Khasanov *et al.* explored a synthetic methodology for the synthesis of optically active proline derived 5,4-spiro β-lactams. To avail the desired spiro β-lactams

58 and **59**, they commenced from L-proline derived **50**. The main feature of the synthetic route was the Staudinger reaction between an *in situ* generated ketene derived from optically active acid chloride **50** and *N*-benzyl-*N*-[(1*E*)-phenylmethylene]amine (**51**) to afford **52a** and **53a**. Finally, the spiro β-lactams **58** and **59** were obtained through elimination followed by hydrogenation (Scheme 10).[12]

Scheme 10

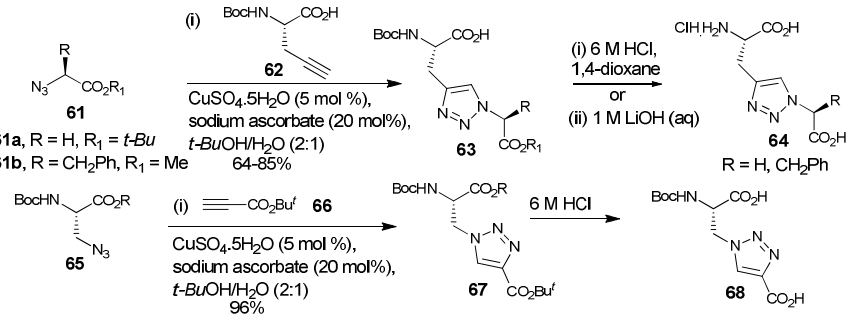


1.2.3 Five Membered Chiral Heterocycles

1.2.3.1. 1,2,3-Triazole

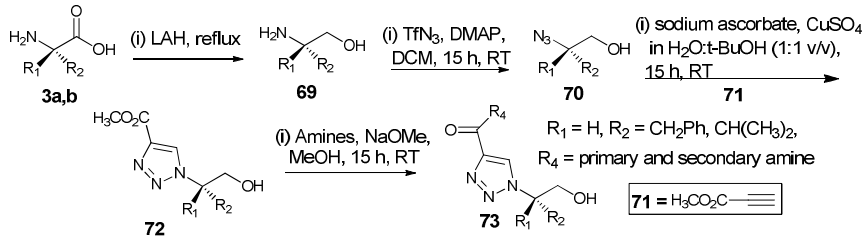
Abell and coworkers reported[13] 1,2,3-triazolyl amino acids (**64** & **68)** as AMPA receptor ligands. The key feature in the synthesis involved copper (II) catalyzed cycloaddition of azides **61** & **65** with alkynes **62** and **66** (Scheme 11).

Scheme 11



Klein *et al.* reported a versatile method for the synthesis of chiral 1,4-disubstituted-1,2,3-triazole derivatives starting from easily accessible naturally occurring D- or L-amino acids. The key reaction involved the conversion of amino acids into azido alcohols **70**, copper catalyzed [3+2] cycloaddition reactions between the azido alcohols **70** and methyl propiolate **71**, and ester aminolysis with primary and secondary amines to afford the target compounds without racemization (Scheme 12)[14].

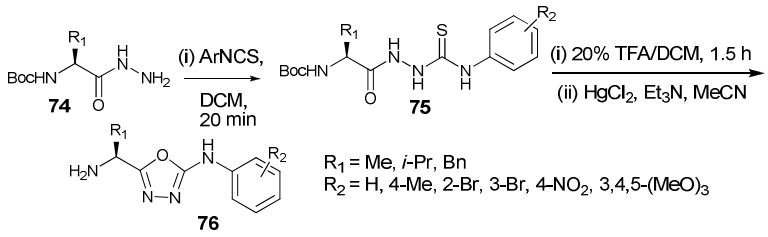
Scheme 12



1.2.3.2 1,3,4-oxadiazoles

Batey and coworkers described a mild method for the synthesis of peptidomimetic 2-aryl amino 5-substituted 1,3,4-oxadiazoles **76** from Boc-protected α-amino acid derived hydrazides **74**. Reaction of the hydrazides **74** with arylisothiocyanates provided the corresponding Boc-thiosemicarbazides **75** which were treated with TFA followed by $HgCl_2$ in the presence of triethylamine in acetonitrile to give the desired oxadiazole products **76** in 78–85% yields (Scheme 13)[15].

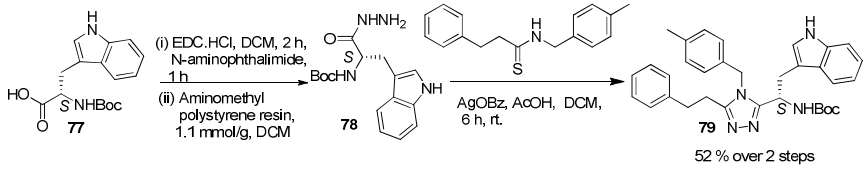
Scheme 13



1.2.3.3 1,2,4-triazoles

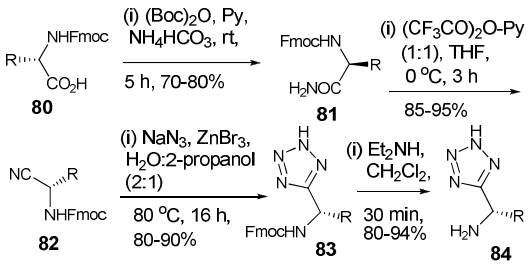
Fehrentz and coworkers reported the synthesis of amino acid side chain substituted, 1,2,4-triazoles with complete retention of stereochemistry. Hydrazide **78** was reacted with achiral thioamide in the presence of silver benzoate affording triazoles **79**. Similarly, other epimeric triazole was synthesized without racemization (Scheme 14).[16]

Scheme 14

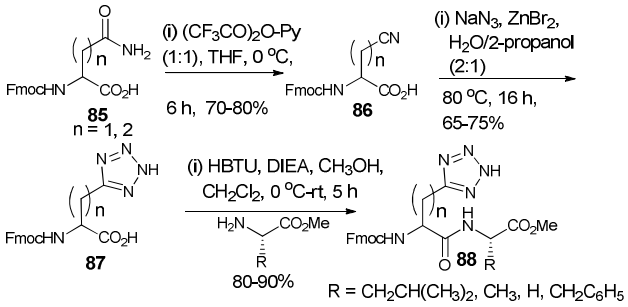


Tetrazoles are widely used as drugs in pharmaceuticals,[17] *cis*-peptide bond mimics,[18] and bioisosteres[19] for carboxylic acids. Again they are important precursors in medicinal chemistry due to their increased resistance toward metabolic degradation pathways and play an important role as catalysts[20] in asymmetric synthesis. In 2007, Sureshbabu *et al.* reported an efficient route to different amino acids incorporated tetrazole derivatives. The four steps synthetic protocol involved Fmoc protected different α-amino acids **80** as starting materials and the key step was the [3+2] cycloaddition of amino acid derived cyanide **82** and azide in presence of lewis acid like $ZnBr_3$ to provide **84** and **88** (Scheme 15 &16).[21]

Scheme 15



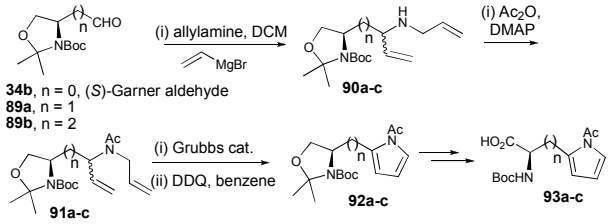
Scheme 16



1.2.3.4 α, β and γ-pyrrole

Chattopadhyay and coworkers described a general route to α, β and γ-pyrrole-branched α-amino acid derivatives **93a-c**, which featured nucleophilic vinylic addition to the imine followed by one-pot ring-closing metathesis of **91a-c** and aromatization reaction as key steps (Scheme 17).[22]

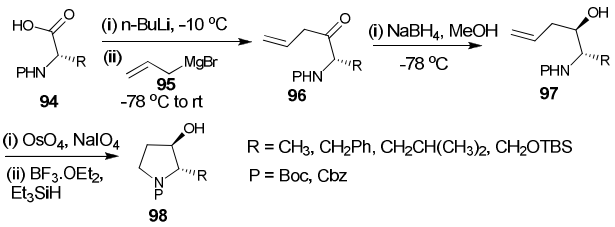
Scheme 17



1.2.3.5 3-Hydroxy-pyrrolidines

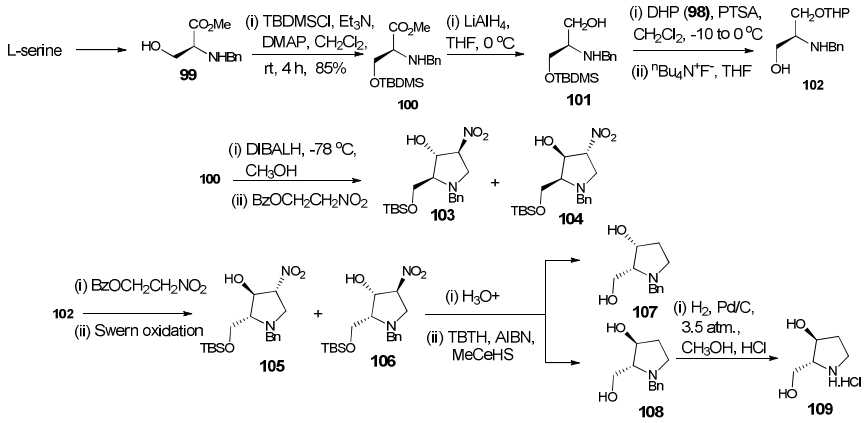
Evano and coworkers reported a practical synthesis of enantiopure substituted 3-hydroxy-pyrrolidines **98** in four steps, starting from commercially available amino acids **94**. This methodology was also useful for an efficient preparation of 3-hydroxy-piperidines as well as azepanes and straight forward asymmetric synthesis of (-)-bulgecinine. The key features of this methodology involved Rapoport's modification of the Tegner reaction,[23] ketone reduction of **96** followed by oxidative cleavage of **97** and reduction (Scheme 18).[24]

Scheme 18



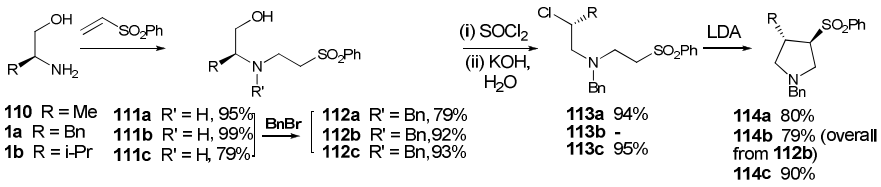
Recently, naturally occurring and synthetic polyhydroxylated pyrrolidines and piperidines have drawn a considerable attention owing to their role as important intermediates for the synthesis of more complex bioactive molecules or to their own biological activities.[25] L-serine was found to be one of the most convenient starting materials for the synthesis of those chirally pure substituted pyrrolidines. Barco and coworkers reported a synthetic methodology starting from L-serine which was first converted into **100** and **102**. These two compounds were finally transformed into required pyrrolidine derivatives **103**, **104**, **105** and **106** through one-pot tandem Michael-Henry protocol (Scheme 19).[26]

Scheme 19



In 2003, Back *et al*. developed a synthetic pathway for the asymmetric synthesis of substituted pyrrolidines **114a-c**, utilizing **110, 1a** and **1b** derived from L-alanine, L-phenylalanine, and L-valine respectively. In their methodology, amino alcohols (**110**, **1a** and **1b**) underwent conjugate addition with sulfone to produce **112a-c**, which on treatment with thionyl chloride, followed by basic work up, underwent a facile rearrangement leading to the stereospecific formation of the corresponding chlorides **113a-c**. Finally, LDA mediated cyclization furnished the required pyrrolidines **114a-c** (Scheme 20).[27] Close analysis of reported procedures for 3-Hydroxy-pyrrolidines suggests that tetrasubstituted pyrrolidines derived from amino acids are yet to be reported.

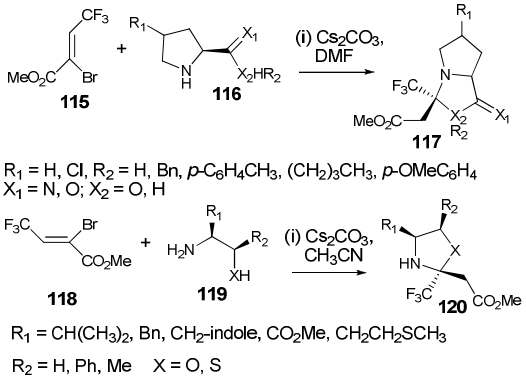
Scheme 20



1.2.3.6. Trifluoromethylated Imidazolidine, Oxazolidine and Thiazolidines

Zhang *et al.* reported[28] optically pure trifluoromethylated imidazolidine, oxazolidine and thiazolidine derivatives (**117**, **120**) through double Michael addition of chiral amino amides, acids, or alcohols (**116**, **119**) to an easily available trifluoromethyl building block methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate (**115**, **118**). These reactions occurred highly diastereoselective (up to 99:1) in good yields (65–96%) under mild conditions (Scheme 21).

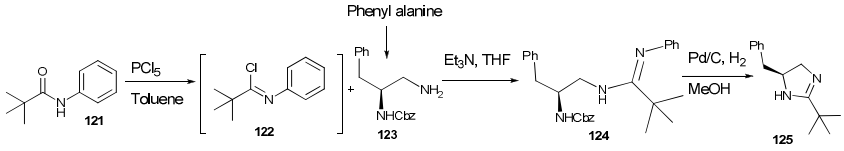
Scheme 21



1.2.3.7 Imidazoline and bicyclic amidine

Zhu et al. reported the synthesis of chiral imidazolines **125** from readily available 1,2-diamines **123** derived from phenyl alanine. The synthetic strategy relies on an intramolecular cyclization which involves a carboxylic amide derived imidoyl chloride **124** as a key intermediate and aniline serving as a leaving group (scheme 22).[29]

Scheme 22

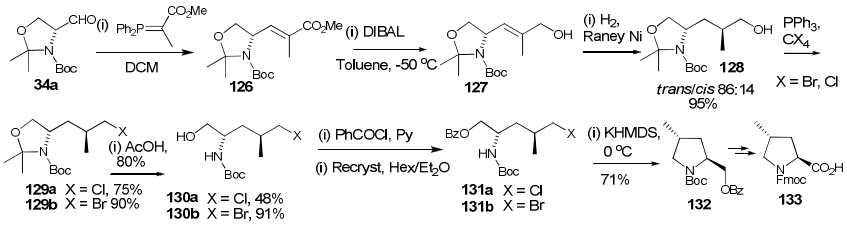


1.2.3.8 Fmoc-Protected *trans*-4-Methylproline

Koskinen and coworkers reported the synthesis of Fmoc-protected *trans*-4-methylproline **133** starting from D-serine derived Garner's aldehyde **34a** which was used to control the diastereoselective formation of the new stereocentres during hydrogenation of allylic alcohol **127**. The diastereoselectivity (*syn*/*anti* ratio) of the process was 86:14, with Raney nickel. A series of transformations led to ring precursor (**130a**, **130b**) which

after recrystallization afforded the *syn* diastereoisomer (dr 95:5). Protected *trans*-4-methylproline **133** was obtained from **132** in a straight forward fashion (Scheme 23).[30]

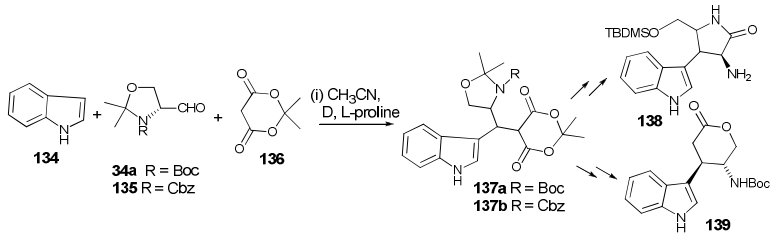
Scheme 23



1.2.3.9 pyrano- and pyrrolidino-fused tryptamines

Sapi and coworkers reported the synthesis of chiral pyrano- **139** and pyrrolidino-fused tryptamines **138** from a common advanced intermediate **137a**/**137b** by a diasteroselective trimolecular condensation between indole (**134**), Garner's aldehyde (**34a**) and Meldrum's acid (**136**), followed by selective functional group transformations (Scheme 24).[31]

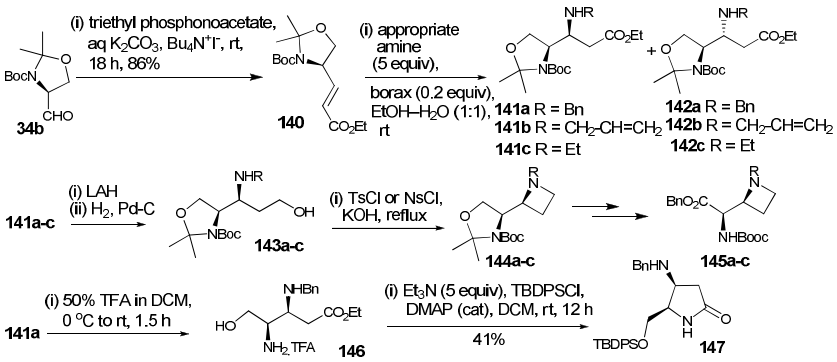
Scheme 24



1.2.3.10 Aminopyrrolidone

Thander *et al.* reported a new route to 2-azetidinylglycine derivatives **145a-c** and an aminopyrrolidone derivative **147** from Garner's aldehyde **34b** which featured diastereoselective conjugate addition of benzyl amine to an α,β-unsaturated ester derivative **140** to afford **141a-c** and **142a-c**. Next, reduction, activation through tosylation/nosylation and cyclization provided azitidine derivatives **144a-c** which were finally converted into **145a-c.** Again, **141a** on treatment with 50% TFA provided **146** which was finally transformed into **147** *via* intramolecular amide coupling (Scheme 25).[32]

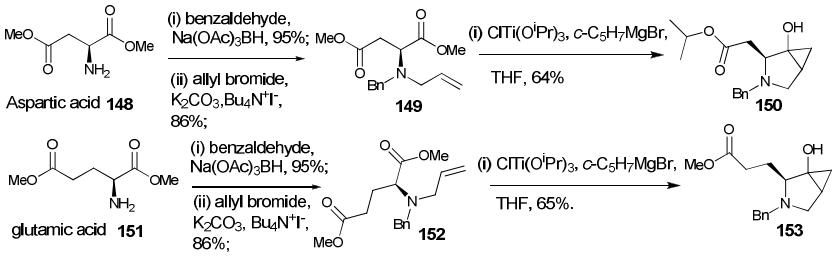
Scheme 25



1.2.3.11 azabicyclo [3.1.0]hexanols

Joullié and coworkers reported the synthesis of azabicyclo [3.1.0]hexanols (pyrrolidine derivatives) **150** and **153** from aspartic (**148**) and glutamic acid (**151**) *via* Ti-mediated Kulinkovich cyclopropanation reaction (Scheme 26).[33]

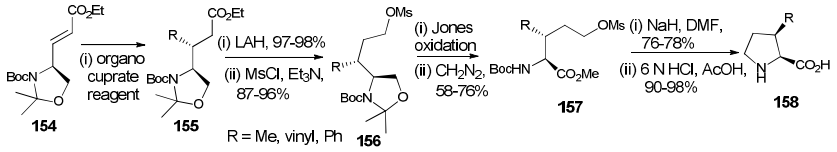
Scheme 26



1.2.3.12 *cis*-3-substituted prolines

Sasaki *et al*. reported an efficient synthetic route to enantiomerically pure *cis*-3-substituted prolines **158**. Organocuprate reagents mediated stereoselective nucleophilic addition to the (*E*)-α, β-unsaturated ester **154**, obtained from the Garner's aldehyde **34a**, and expedient oxidation–cyclization were the key reaction steps (Scheme 27).[34]

Scheme 27

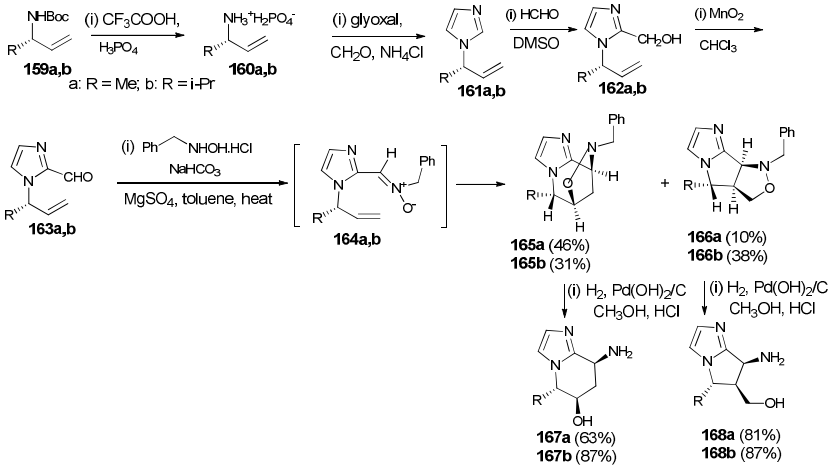


1.2.3.13 imidazo[1,2-a]pyridines and pyrrolo[1,2-a]imidazoles

Beccalli *et al*. reported a synthetic methodology for enantiopure polyfunctionalized imidazo[1,2-a]pyridines **167a/167b** and pyrrolo[1,2-a]imidazoles **168a/168b** as anti-inflammatory and glycosidase inhibitors. L-alanine and L-valine derived N-Boc protected amines **159a,b** were first converted into the desired imidazolecarbaldehydes **163a,b** which were then reacted with the *N*-benzylhydroxylamine to produce nitrone intermediates **164a,b**. These were subsequently transformed into regioisomeric bridged-ring **165a,b** and fused-ring **166a,b** isoxazolidines. The regiochemical outcome of the cycloaddition was very much dependent on the substituent R. Finally, hydrogenolysis in

presence of Pd catalyst in 2 M HCl in methanol furnished the bicyclic compounds **167a,b** and **168a,b** (Scheme 28).[35]

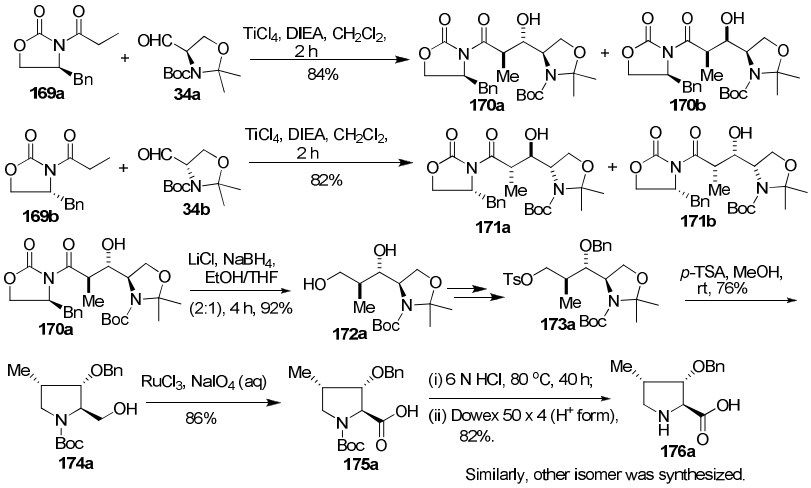
Scheme 28



1.2.3.14 3-hydroxy-4-methylproline

Mohapatra *et al.* described all stereoisomers of 3-hydroxy-4-methylproline **176a**, starting from the aldol products **170a,b** and **171a,b** which were active constituents of some potent antimicrobial therapeutic agents. Ten steps synthetic sequences were achieved with 29% overall yield. Evans' aldol reaction using Crimmins' modified method was pivotal to the success of this strategy (Scheme 29).[36]

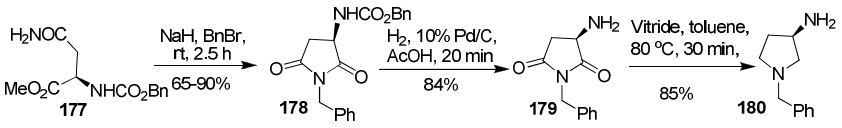
Scheme 29



1.2.3.15 Aminopyrrolidine

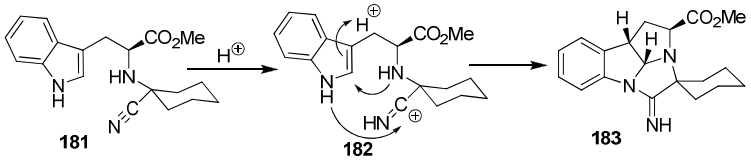
Iding and coworkers reported a chemo-enzymatic route to chiral 3-aminopyrrolidine derivatives **180** from the unnatural D-asparagine derivative **177**. Key steps involving sequential cyclization of **177**, selective deprotection followed by reduction of **178** yielded efficiently benzyl protected (*R*)-3-aminopyrrolidine **180**, a homo-chiral building block, utilized in numerous drug candidates (Scheme 30).[37]

Scheme 30



Herranz and coworkers reported a novel tetracyclic ring system, a hybrid of tetrahydropyrrolo[2,3-*b*]indole and tetrahydroimidazo[1,2-*a*]indole **183** *via* an acid-mediated stereospecific domino tautomerization of a tryptophan-derived α-amino nitrile **181** (Scheme 31).[38]

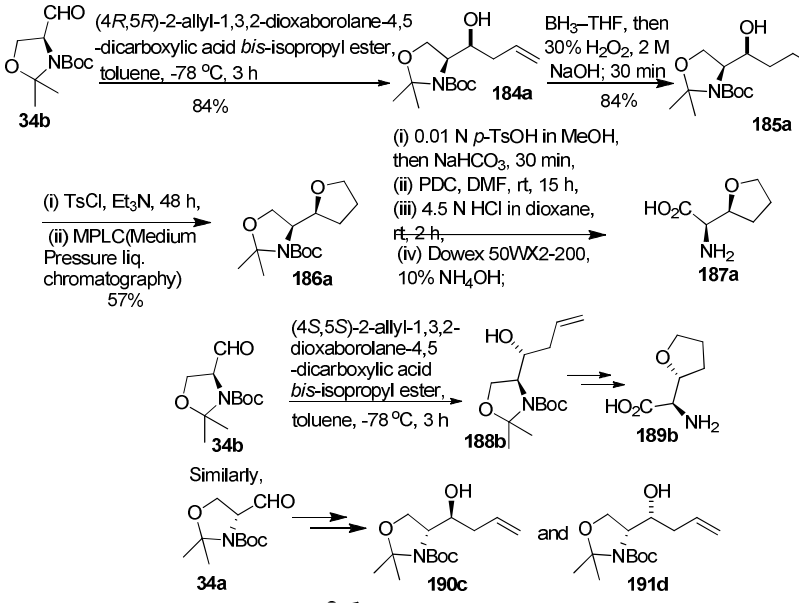
Scheme 31



1.2.3.16 tetrahydrofuran

Pellicciari and coworkers reported the first enantiodivergent synthesis of all four possible 2-(tetrahydrofuran-2-yl)glycine stereoisomers **187a-d** derived from (*S*)- or (*R*)-Garner aldehydes (**34a**/**34b**). The key step involved the highly stereo controlled allylboration on Garner aldehydes **34a,b** to give four chiral homoallyl alcohols **184 a-d** which were converted to title compounds **187a-d** in five steps (Scheme 32).[39]

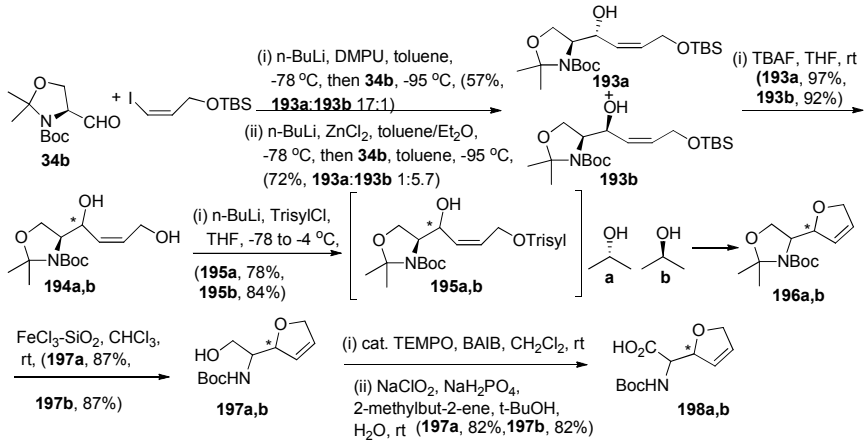
Scheme 32



1.2.3.17 dihydrofuran

In 2011, Passiniemi *et al.* described a methodology for the synthesis of Boc-protected *epi*-norfuranomycin **198a** and **198b** utilizing L-Garner aldehyde **34b**. The key steps of their methodology include the effectiveness of trisyl chloride as an efficient leaving group in the dihydrofuran formation. In addition, TEMPO/BAIB is an effective oxidant for α-amino alcohols **197a,b** avoiding epimerization of the labile α-proton of the product aldehyde and thus delivering the final products **198a,b** after Pinnick oxidation (Scheme 33).[40]

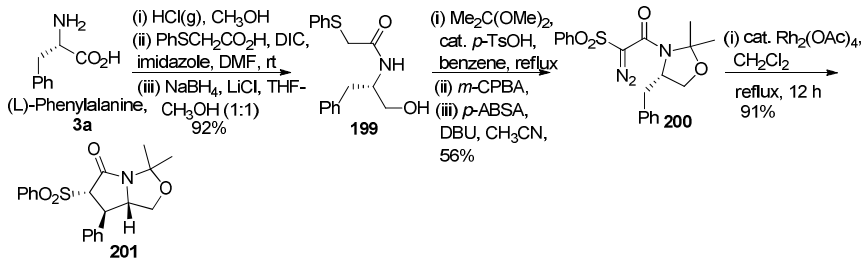
Scheme 33



1.2.3.18 Bicyclic Pyrrolidinones

Pyrrolidinones (γ-lactams) serve as important synthetic intermediate for numerous natural products. L-phenyl alanine **3a** was effectively utilized for the development of a synthetic route to highly functionalized fused γ-lactum **201** by Jung *et al*. in 2002. In their synthetic methodology, L-phenyl alanine **3a** was first converted into **199** *via* esterification, amide coupling followed by reduction of the ester functionality. Diazo compound **200** was achieved from **199** after three steps. Now, the stage was set for the cyclization to afford **201**. The cyclization was done *via* Rh (II)-catalyzed C-H insertion. Again, this methodology was proved to be equally effective for the diazo compounds derived from other L-amino acids (Scheme 34).[41]

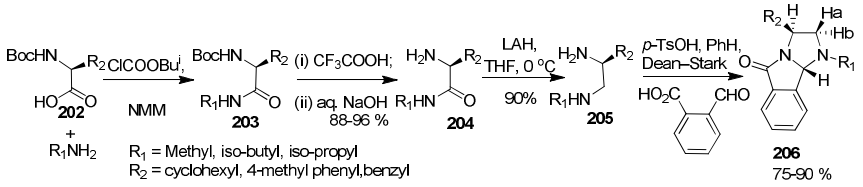
Scheme 34



Katritzky et al. described a stereoselective synthetic route to chiral (3*S*,9b*S*)-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones **206** in 78–93% yields *via* intermolecular condensations of 2-formylbenzoic acids with chiral diamines **205.** Compounds **205** were

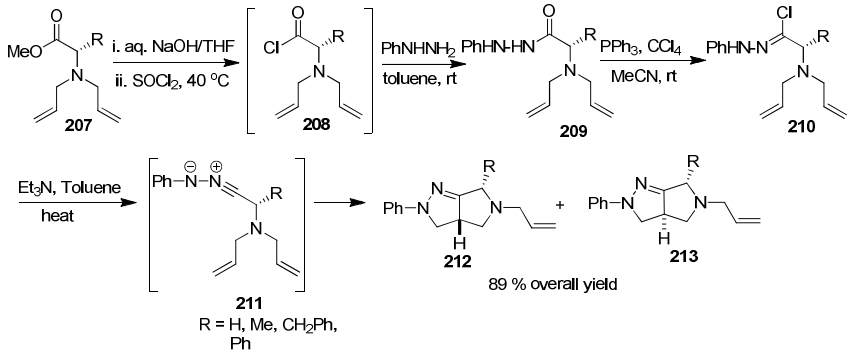
readily prepared in three steps involving amidation, Boc-deprotection and amide bond reduction from optically active *N*-Boc-α-amino acids Scheme 35.[42]

Scheme 35



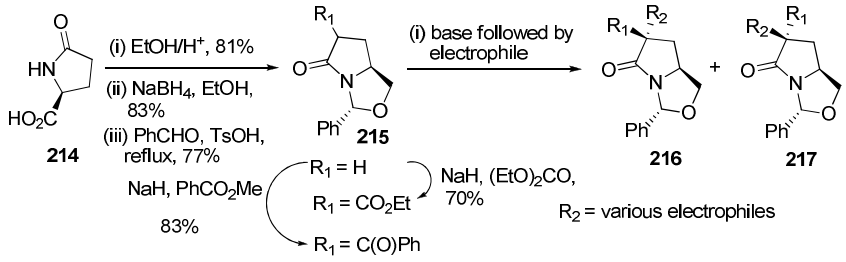
Molteni and coworkers synthesized enantiopure 2,3,3a,4,5,6-hexahydro-pyrrolo[3,4-c]pyrazoles **212** and **213** starting from the methyl esters of glycine, L-alanine, L-phenylalanine and (*S*)-2-phenylglycine respectively. The key step involved a stereoselective intramolecular 1,3-dipolar cycloaddition of homochiral nitrilimines **211** (Scheme 36).[43]

Scheme 36



Densely functionalized pyrrolidines are highly abundant in variety of natural products and pharmaceutically active compounds, either as isolated ring systems or embedded in more complex structures. The use of (*S*)-pyroglutamic acid **214** has been described by Beard *et al.* where bicyclic lactam **215** was achieved through esterification, reduction followed by simultaneous protection of the hydroxyl and amide functionalities as an oxazolidine. Then electrophillic alkylation *via* enolate formation provided different bicyclic pyrrolidinone derivatives **216** and **217** (Scheme 37).[44]

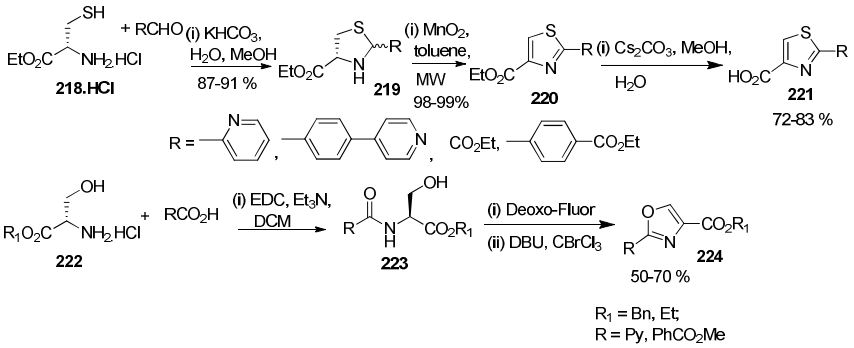
Scheme 37



1.2.3.19 Oxazoles, thiazoles and thiazolidines

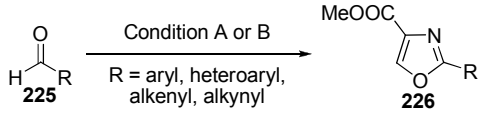
Reginato and coworkers reported the synthesis of new 4-carboxy oxazoles, thiazoles and thiazolidines by condensation of serine (**222**) or cysteine (**218.HCl**) with aldehydes or acids. L-cysteine ethyl ester **218.HCl** was reacted with different pyridyl- and carboxaldehydes to afford the corresponding thiazolidine derivative **219** which was converted to thiazole derivatives **220** by microwave irradiation and MnO_2 mediated oxidation. Similarly, oxazole **224** was prepared by EDC-mediated coupling with serine ethyl or benzyl esters **222** and terephthalic acid monomethyl ester or isonicotinic acid followed by one-pot cyclization and oxidation (Scheme 38).[45]

Scheme 38



Grahm *et al.* reported an expedient method for the direct conversion of aldehydes **225** to 2,4-disubstituted oxazoles **226**. The method relies on the oxidation of an oxazolidine formed from the condensation of serine with an aldehyde and proceeds through 2,5-dihydrooxazole intermediate (Scheme 29).[46]

Scheme 39

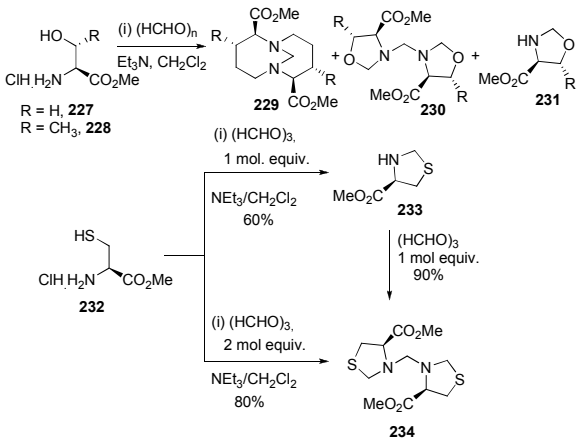


Condition A: (i) Ser-OMe.HCl, Et_3N, $MgSO_4$, THF; (ii) $BrCCl_3$, DBU, CH_2Cl_2
Condition B: Ser-OMe.HCl, K_2CO_3, DMA then $BrCCl_3$, DBU

1.2.3.20 Oxazolidine and thiazolidine

In 2002, Selambarom *et al.* reported one step synthetic protocol for the novel heterocyclic 2:3 adduct *via* condensation of L-cysteine methyl ester (**232**) and L-threonine methyl ester (**228**) or L-serine methyl ester (**227**) with formaldehyde. The outcome of the condensation reaction is either *N*,*N*'- methylene*bis*(thiazolidine) (**234**, L-cys) or –(oxazolidine) (**230**, L-thr) derivatives or to its bicyclo [4.4.1] undecane isomer (**229**, L-ser) as major products (Scheme 40).[47]

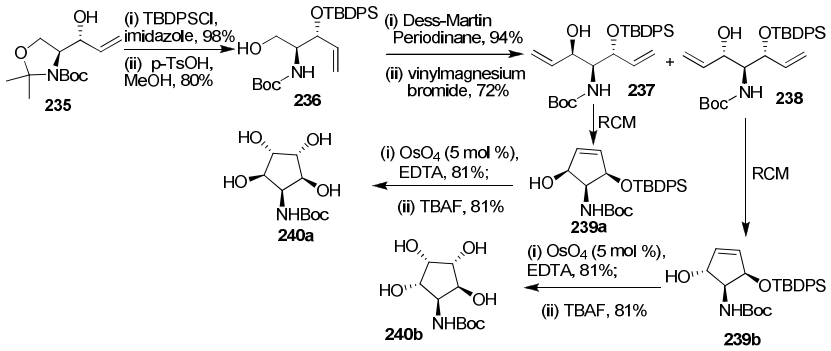
Scheme 40



1.2.3.21 Aminocyclopentitols

Chattopadhyay *et al.* reported stereo-divergent synthetic strategy to biologically important aminocyclopentitol derivatives (**239a,b**) involving diastereoselective vinylation of an α-amino aldehyde, ring-closing metathesis reaction of **237a,b** and diastereoselective dihydroxylation reaction as key steps (Scheme 41).[48]

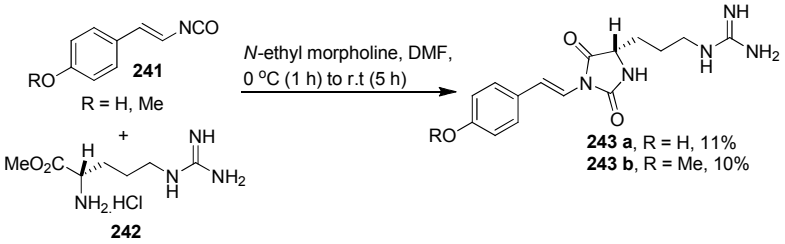
Scheme 41



1.2.3.22 Parazoanthine-A

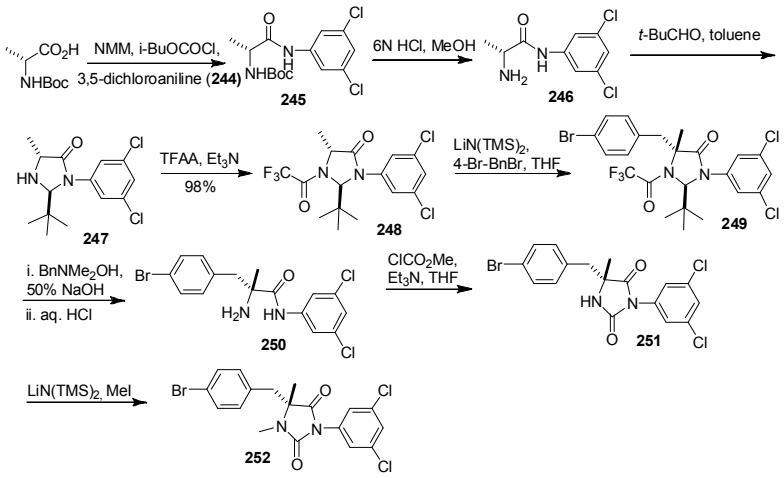
Manzo and coworkers reported concise biomimetic synthesis of parazoanthine A **243a** and its O-methyl derivative **243b** based on the coupling reaction of L-arginine methyl ester dihydrochloride **242** with isocyanate derivatives of *p*-coumaric acid and 4-methoxy-cinnamic acid **241**, respectively. The synthetic path is designed to obtain a wider range of parazoanthine analogs (Scheme 42).[49]

Scheme 42



Yee *et al*. described an efficient enantiospecific synthesis of the cell adhesion inhibitor BIRT-377 **252** derived from Boc-Ala-OH in 38% overall yield after eight steps. The key transformations involved the stereoselective formation of *trans* imidazolidinone **247**, subsequent alkylation, and the efficient hydrolysis of disubstituted imidazolidinone **249,** hydantoin formation **251** and methylation providing the drug BIRT-377 (scheme 43).[50]

Scheme 43



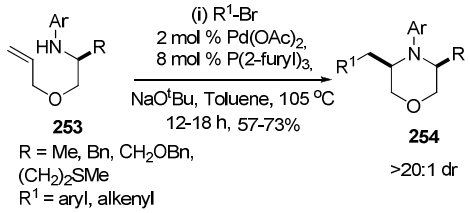
1.2.4 Six Membered Chiral Heterocycles

1.2.4.1 Morpholine

The World Drug Index reaveals that morpholine core containing 100 drugs having biological activites[51](antidepressant[52], antioxidant[53], serotonin agonist, NK-1 and NK-2 receptor antagonist, and antifungal[54]) are available. Synthetic approaches of substituted morpholines employing amino acids are exemplified below.

Leathen *et al.* reported Pd-catalyzed carboamination reaction between amino acids derived substituted ethanolamine derivative **253** and an aryl or alkenyl bromide as an efficient tool to generate enantiopure *cis*-3,5-disubstituted morpholines **254** (Scheme 44).[55]

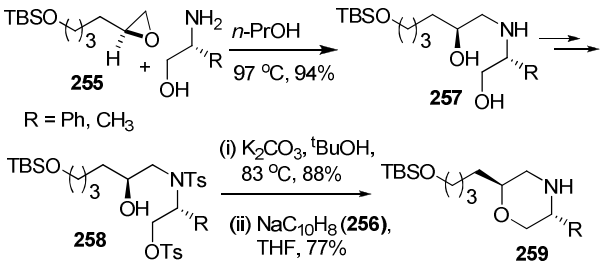
Scheme 44



Myers and co-workers described highly enantio- and diastereoselective syntheses of *trans*-2,5-disubstituted morpholine derivatives **259** by the reaction of enantiopure epoxides **255** with chiral pool amino alcohols. Highly diastereoselective ring opening

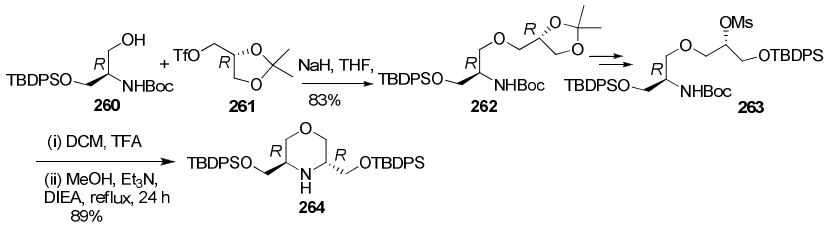
product **257** after ring cyclization gave an access to chiral substituted morpholine **259** as depicted in the scheme 45.[56]

Scheme 45



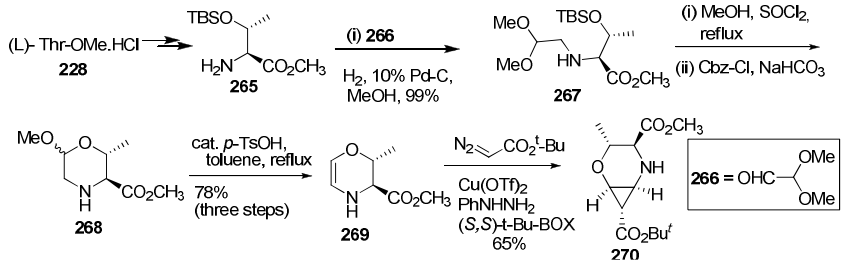
Sasaki and coworkers reported a synthetic methodology towards synthesis of *trans*-3,5-*Bis*(benzyl/*tert*-butyldiphenylsilyloxymethyl)morpholines **264** *via* coupling of a serinol derivative **(260)** with 2,3-*O*-isopropylideneglycerol triflate **(261)** or its equivalent leading to the formation of amine **262**. Finally intramolecular S_N2 ring cyclization of **263** provided desired product **(264)** as illustrated in the scheme 46.[57]

Scheme 46

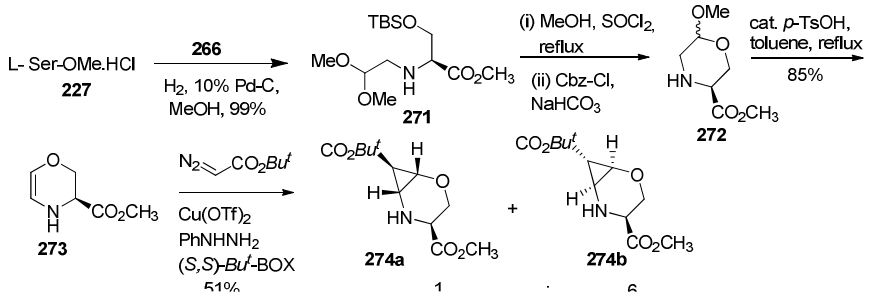


Trabocchi and coworkers reported[58] threonine-**(228)** derived dihydroxazines **(269)** to access new morpholine-based scaffolds and developed the idea of rigidifying a chiral morpholine structure through fusion to a functionalized cyclopropane ring **(270)** as depicted in Scheme 47. Similarly, from serine derivative (**227**), other stereoisomers (**274a,b**) of **270** were achieved (Scheme 48).

Scheme 47

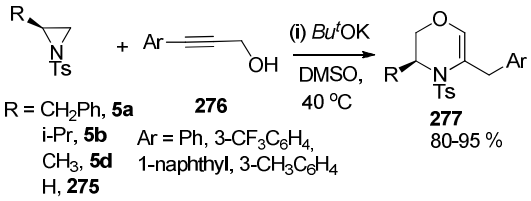


Scheme 48



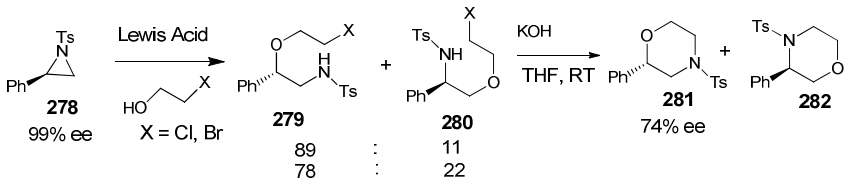
Zhou's group reported a base promoted tandem ring-opening/closing reactions of various amino acids derived *N*-Ts aziridines **(5a,b, 5d, 275)** and aryl propargyl alcohols **(276)** to afford morpholine derivatives **(277)** in moderate to good yields (Scheme 49).[59]

Scheme 49



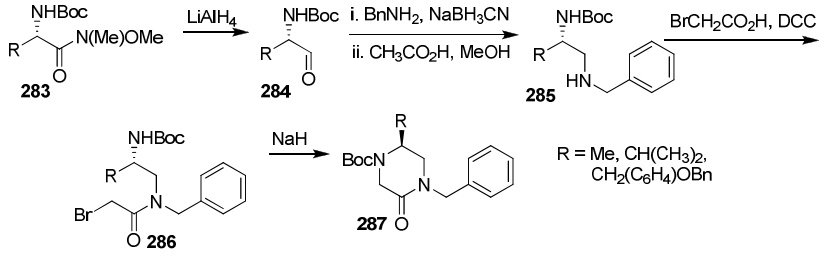
Ghorai *et al*. described enantioselective synthesis of morpholines **(281)** *via* Lewis acid mediated S_N2-type ring opening of activated aziridines **(278)** by suitable halogenated alcohols followed by base-mediated intramolecular ring closure of the resulting haloalkoxy amine **279** (Scheme 50).[60]

Scheme 50



Reginato et al. reported a new versatile and diastereoselective synthesis of polysubstituted 2-oxopiperazines **287** from naturally occurring amino acids. Commercially available Boc-protected L-amino acids were converted into amino aldehydes **284** by reduction of the corresponding Weinreb amides **283**. Reductive amination of aldehyde **284** with benzylamine, bromoacetylation of the diamine **285** and finally base-promoted cyclization gave 5-substituted 2-oxopiperazines (Scheme 51).[61]

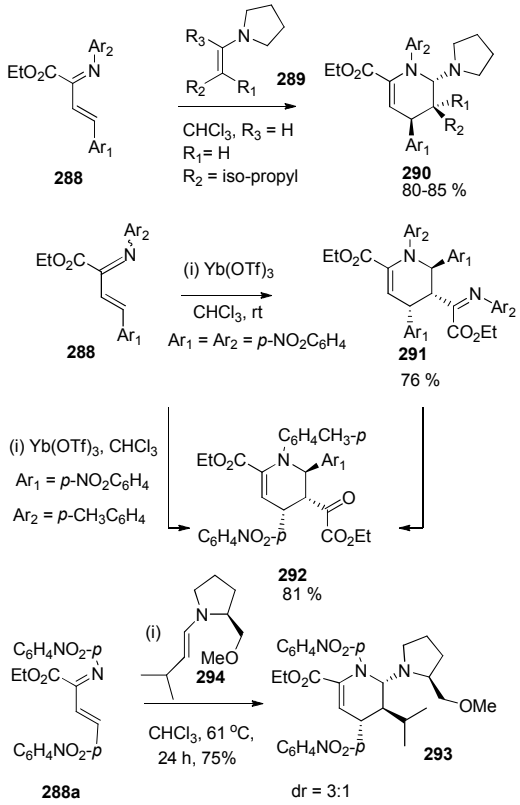
Scheme 51



1.2.4.2 Tetrahydropyridine

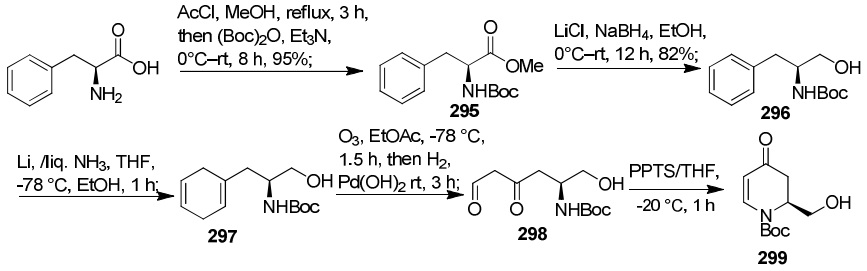
Recently, Vicario *et al*. published one step synthesis of novel chirally pure densely functionalized 1,4,5,6-tetrahydropyridines **290**, **293**. They utilized a diastereoselective inverse electron demand aza-Diels-Alder reaction of *N*-aryl-1-azadienes derived from α-amino acids with enamine dienophiles. When $Yb(OTf)_3$ is used as the activator, then dimerization (**291, 292**) of the azadiene occurs through aza-Diels-Alder reaction, where the alkene double bond of 1-azadiene also adopts the role of dienophile (Scheme 52).[62]

Scheme 52



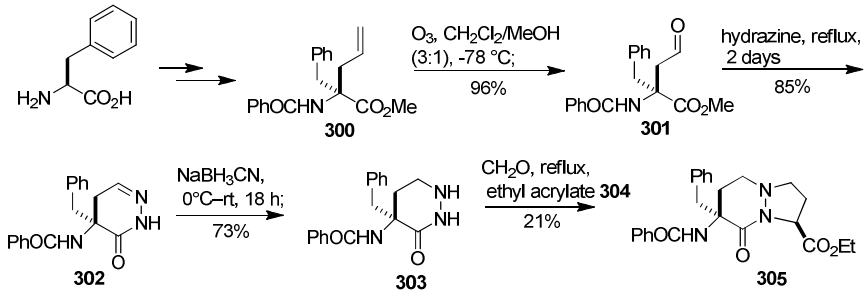
Rao and coworkers developed a versatile and efficient method for the preparation of (2*S*)-2-(hydroxymethyl)-*N*-Boc-2,3-dihydro-4-pyridone **299** from L-(−)-phenylalanine. The key step in the sequence is Birch reduction of phenyl ring, used as a masked keto aldehyde precursor, followed by an intramolecular cyclization of **298** to give 2,3-dihydropyridin-4-ones, Scheme 53.[63]

Scheme 53



Abell and coworkers reported a diastereoseletvive synthesis of tetrahydropyridazinone **305** from (*S*)-phenylalanine. Ozonolysis of the olefin **300** gave aldehyde which upon refluxing with hydrazine gave the cyclic hydrazone **302** in good yield. Reduction of **302** with sodium cyanoborohydride gave the desired tetrahydropyridazinone **303** which was then converted to the bicyclic peptidomimetic **305**, an important class of β-strand mimetic, Scheme 54.[64]

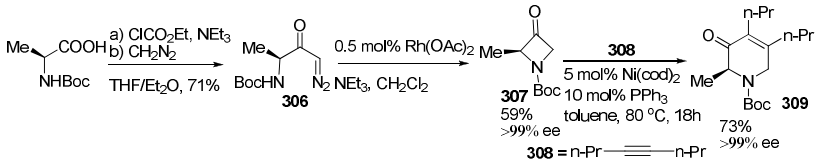
Scheme 54



1.2.4.3 Dehydropiperidinones:

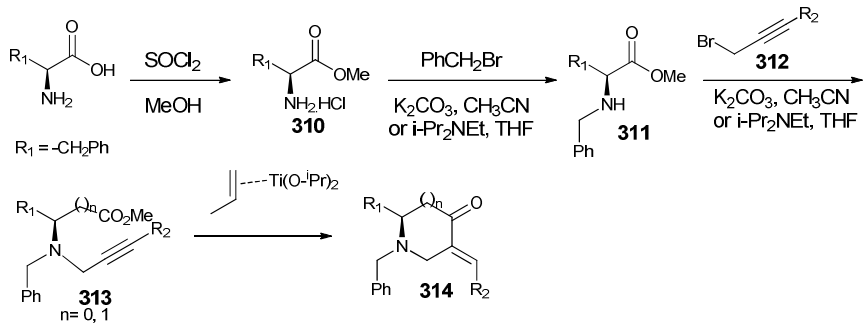
Naoki Ishida *et al*. reported the preparation of chiral dehydropiperidinones in enantiopure form from *R*-amino acids and alkynes *via* azetidin-3-ones. Reaction sequence involved the synthesis of azetidin-3-ones **309**, from *R*-amino acids according to Seebach's method. *N*-Boc-(L)-alanine was treated with ethyl chloroformate/triethylamine, and subsequently with diazomethane, to afford the diazomethyl ketone **306,** which on cyclization with dimeric rhodium (II) acetate, furnished azetidin-3-one **307**. Reaction of azetidinone **307** with 4-octyne **308** in the presence of $Ni(cod)_2$ and PPh_3 in toluene furnished methylpiperidinone **309** in 73% isolated yields (Scheme 55).[65]

Scheme 55



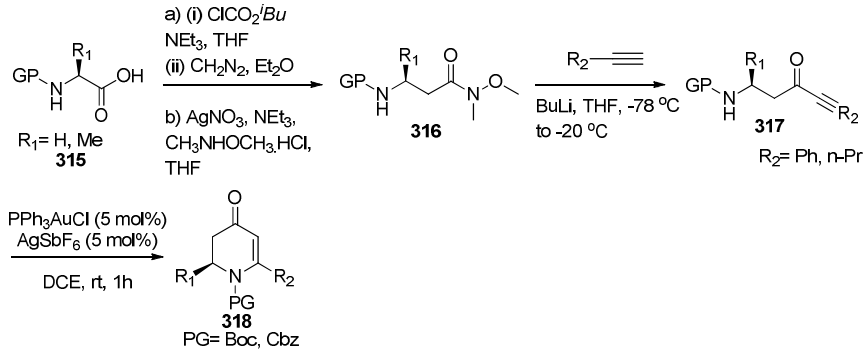
S. Okamoto *et al*. reported the synthesis of piperidine **314** by treatment of *N*-(2- or 3-alkynyl)amino esters **313** with a low-valent titanium reagent diisopropoxy (η^2-propene)-titanium, generated *in situ* by the reaction of Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl followed by an intramolecular nucleophilic acyl substitution (INAS) reaction (scheme 56).[66]

Scheme 56



N. Gouault *et al*. reported gold catalyzed syntheses of pyridinones from amino acids. Amino ynones **317** were produced in two steps with moderate to excellent overall yields (50-97%) from L-amino acids **315**. Reaction of **317** with PPh_3AuCl in the presence of a silver salt in dichloroethane at room temperature afforded **318** in good yield (scheme 57).[67]

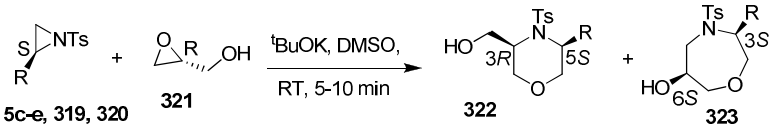
Scheme 57



1.2.4.4 Morpholines and 1,4-oxazepanes

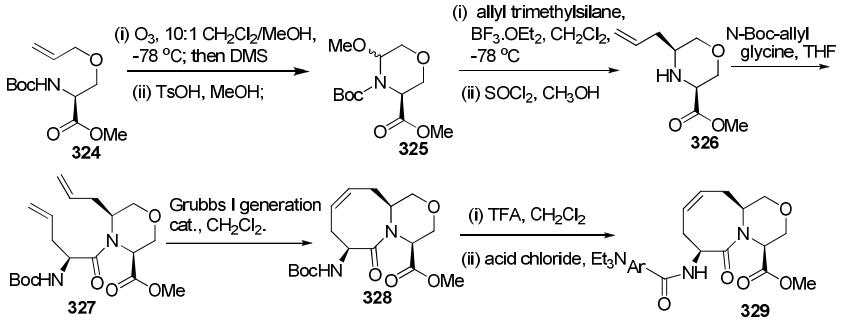
A new one-pot synthetic strategy is described by Samanta *et al.* for the synthesis of enantiomerically pure *cis*-3,5-disubstituted morpholines **322** and 3,6-disubstituted 1,4-oxazepanes **323** *via* tandem aziridine/epoxide ring opening sequences (Scheme 58).[68]

Scheme 58



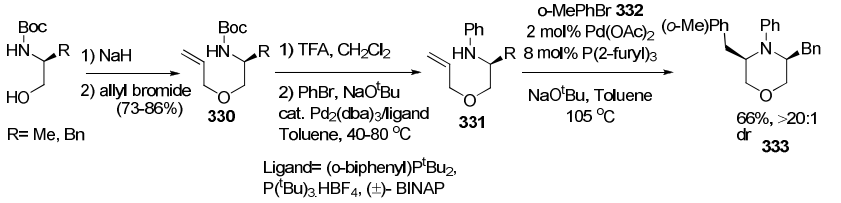
O'Neil and coworkers synthesized morpholine fused 8-membered bicyclic peptidomimetic compounds **(329)** derived from serine derivative **(324)** utilizing ring closing metathesis reaction of (**327)** as one of the key steps, (Scheme 59).[69]

Scheme 59



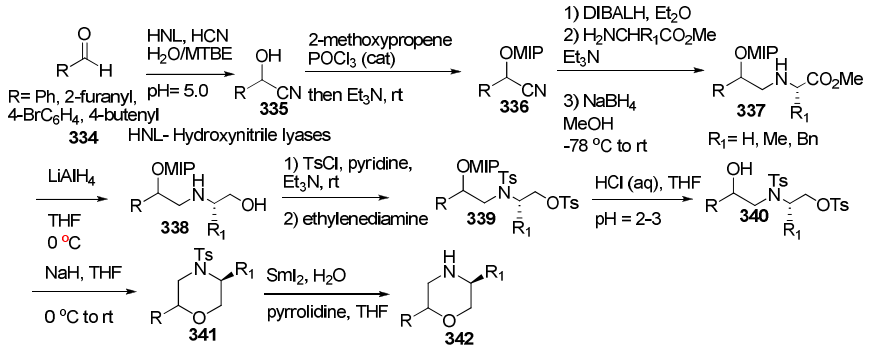
Leathen *et al.* reported four-step synthesis of *cis*-3,5-disubstituted morpholines **333** from enantiomerically pure amino alcohols. The key step in the synthesis is a Pd-catalyzed carboamination reaction between a substituted ethanolamine derivative **331** and an aryl or alkenyl bromide **332**. The morpholine products **333** are generated as single stereoisomer in moderate to good yield (scheme 60).[70]

Scheme 60



Ritzen *et al* reported synthesis of enantiomerically pure *cis*- and *trans*-2,5-disubstituted morpholines **342.** Hydroxynitrile lyase-mediated cyanide addition onto aldehydes **334** provided cyanohydrins **335** with excellent enantioselectivity. Subsequent formation of diastereomerically pure amino esters **337** *via* three-steps, reduction-transimination-reduction sequence followed by reduction and simultaneous protection provided cyclization precursors **341**. Finally, cyclization and SmI_2-mediated reductive detosylation furnished **342** (scheme 61).[71]

Scheme 61



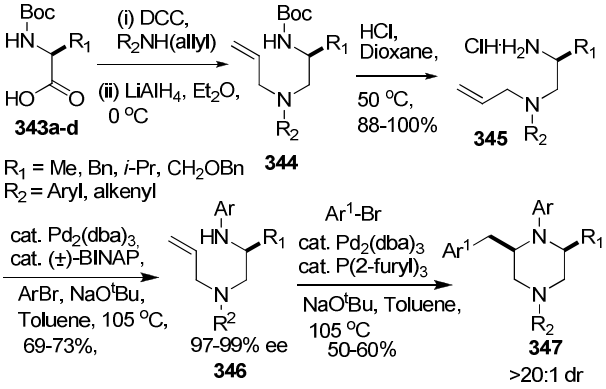
1.2.4.5 Piperazine

Nitrogen-containing heterocycles, such as piperazines, are well known structural units used as pharmaceutical agents. Designed piperazine scaffold, exhibiting wide range of biological activities[72], including 5HT-anxiolytics,[73] dopamine D_3 agents,[74] acting on CNS

receptor,[75] HIV protease inhibitors[58b] such as indinavir, antimicrobial agents such as pefloxacin and related quinolones,[76] antihypertensive agent[77], is considered to be an important privileged structure in drug discovery[58].

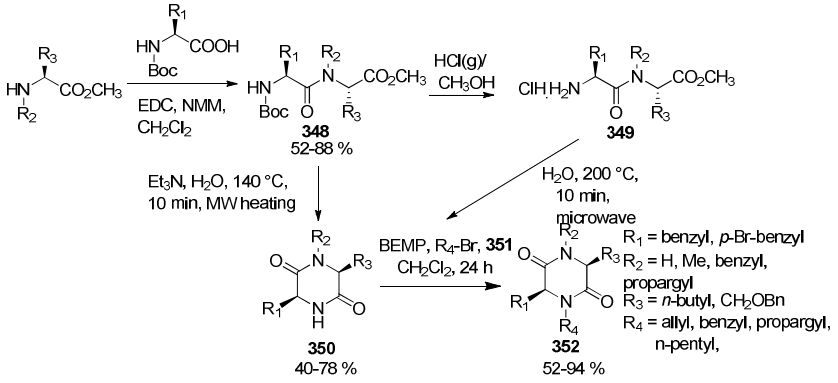
Nakhla *et al*. reported asymmetric synthesis of *cis*-2,6-disubstituted piperazines **(347)** from readily available amino acid precursors **(343a-d)** employing Pd-catalyzed carboamination reaction of N^1-aryl-N^2-allyl-1,2-diamine **(346)** with an aryl bromide (Scheme 62).[78]

Scheme 62



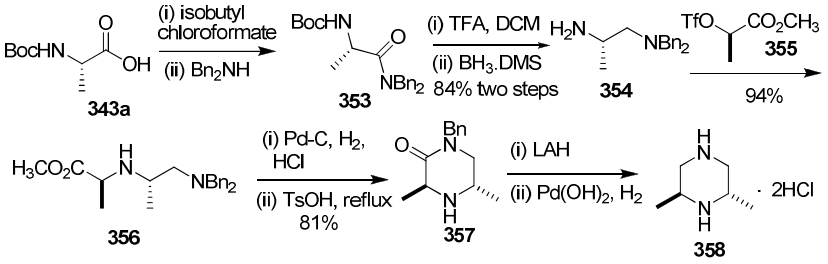
Luthman and coworkers described an efficient method for the synthesis of unsymmetrical 1,3,4,6-tetrasubstituted-2,5-diketopiperazines (DKPs) **(352)** derived from amino acids.[79] Substituted dipeptides (**348),** derived from **c**oupling between amino acids, furnished **349** and **350** respectively under different conditions. **350** after *N*-alkylation provided diketopiperazine **352** (Scheme 63)**.**

Scheme 63



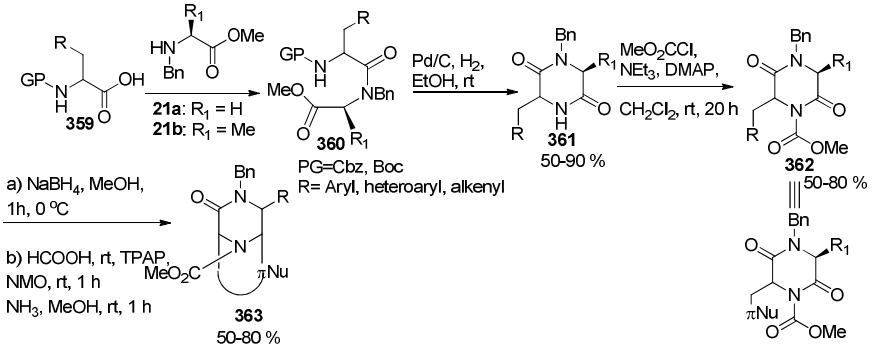
Jacobsen and coworkers synthesized enantiopure (2*S*, 6*S*)-2,6-dimethylpiperazine **(358)** starting from amino acid **(343a),** utilizing diastereoselective triflate alkylation on diamine **(356)**. Ring cyclization of **356** followed by amide bond reduction and debenzylation afforded piperazine **358** (Scheme 64).[80]

Scheme 64



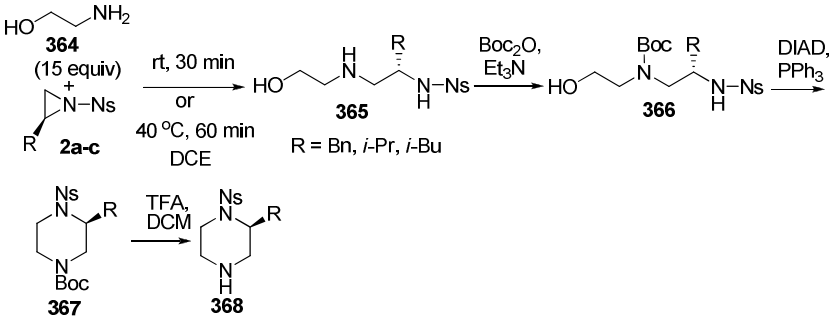
Veerman *et al.* reported synthesis of several 2-substituted and 2,5-disubstituted piperazine-3,6-diones **362** from readily available *R*-amino acids. Activation of a lactam carbonyl **360** *via* introduction of a methoxycarbonyl group onto nitrogen and followed by selective reduction of carbonyl gave **361**. Treatment of the resulting urethane with protic acid generated the corresponding *N*-acyliminium ion, which was trapped by a nucleophilic C2-side chain to provide 2,6-bridged piperazine-3-ones **363** (Scheme 65).[81]

Scheme 65



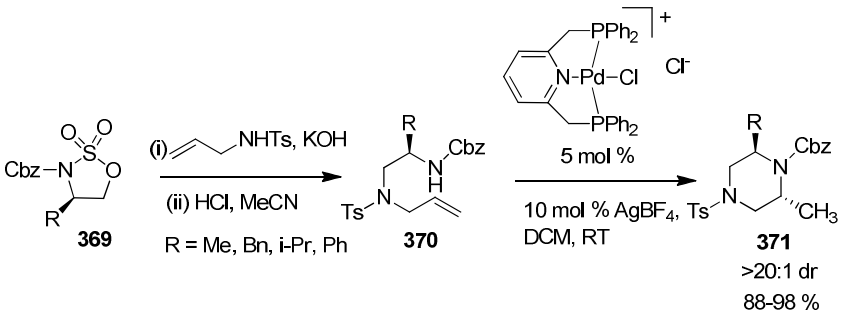
Franzyk and coworkers, reported an expedite protocol for the construction of piperazines **(368)** involving aminolysis of the starting aziridines **(364)** with ω-amino alcohols and subsequent Fukuyama-Mitsunobu cyclization of **366** (Scheme 66).[8]

Scheme 66



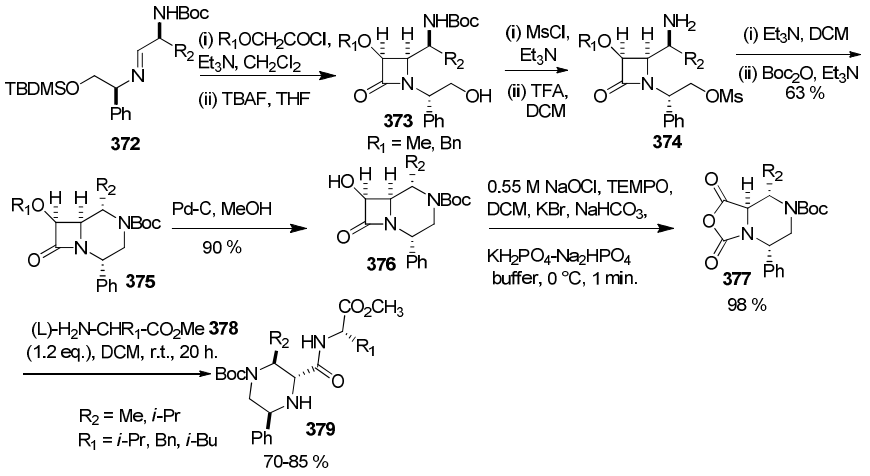
Michael and coworkers developed highly diastereoselective route to the synthesis of 2,6-disubstituted piperazines **(371)** employing Pd-catalyzed hydroamination reaction. The requisite hydroamination substrates **(370)** were prepared in excellent yields by nucleophilic displacement of cyclic sulfamidates **(369)** derived from amino acids, (Scheme 67).[82]

Scheme 67



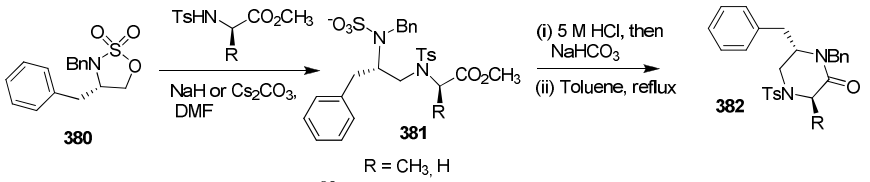
Palomo *et al*. accomplished piperazine-fused 3-hydroxy β-1actams **(376)** *via* [2+2] cycloaddition of alkoxyketenes with imines **(372)** derived from chiral α-amino aldehydes and chiral 1,3-aminoalcohols. The resulting β-1actams **(376)** on exposure to 0.55 M NaOCl and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-l-oxyl (TEMPO) afforded α-amino acid *N*-carboxy anhydrides **(377)** which were formally derived from piperazine-2-carboxylic acids (Scheme 68).[83]

Scheme 68



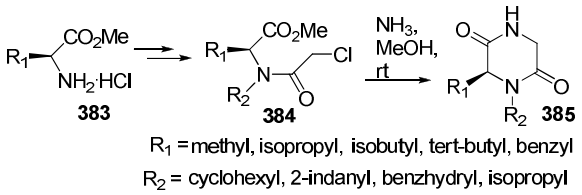
Gallagher and coworkers described that 1,2-cyclic sulfamidates **(380)** underwent regiospecific nucleophilic displacement with α-amino esters, followed by lactamization of **381** (thermal, base-mediated, or cyanide-catalyzed) to give piperazin-2-ones **382** (Scheme 69).[84]

Scheme 69



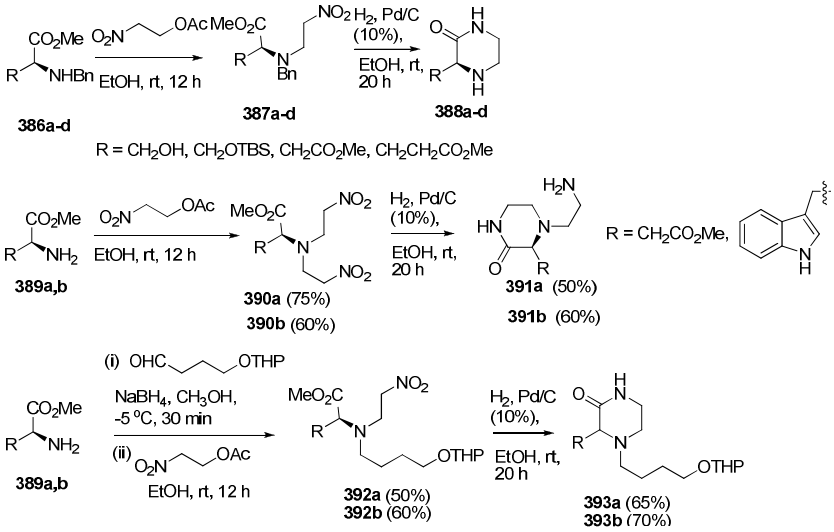
Svete and coworkers reported[85] dialkylpiperazine-2,5-diones (**385**) in three steps from the corresponding (*S*)-α-amino acid esters (**383**) comprising of reductive *N*-alkylation, *N*-acylation and cyclization of **384** (Scheme 70).

Scheme 70



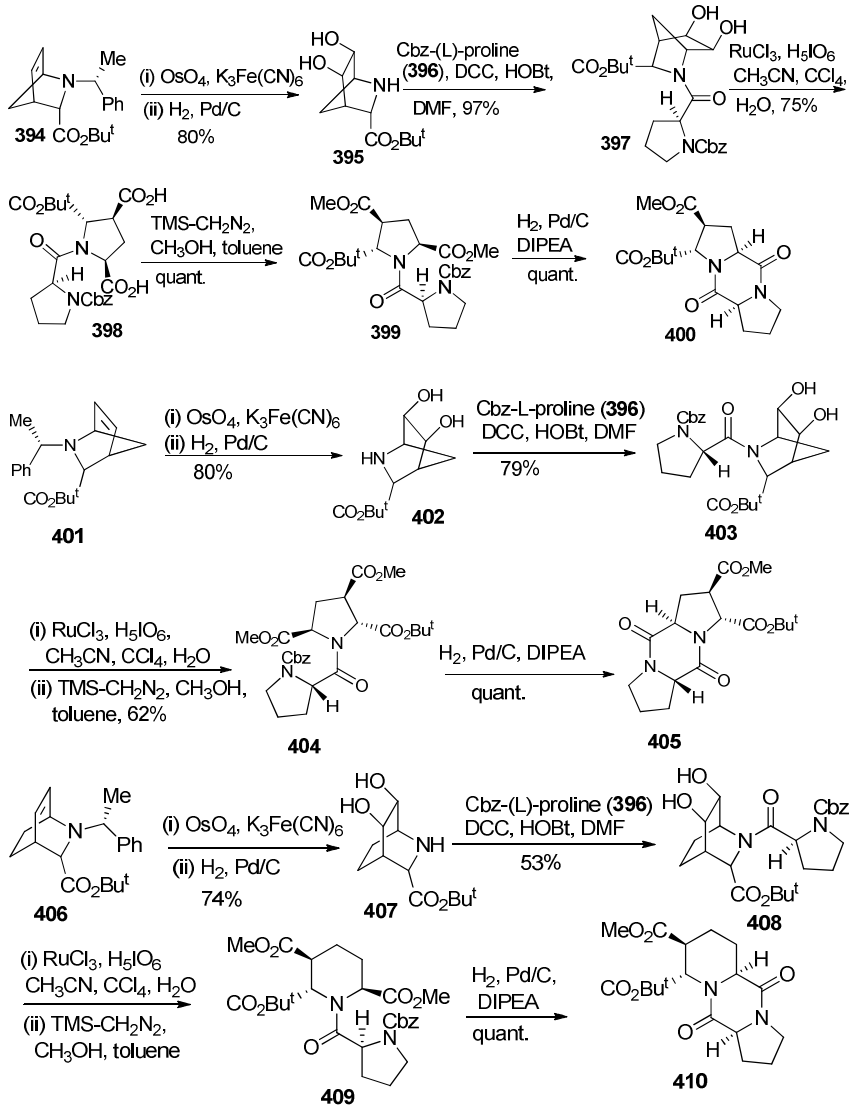
In 2005, Pollini *et al.* developed a simple strategy to synthesize ketopiperazines in enantiomerically pure form starting from **386a-d**, **389a,b** which are easily obtainable from naturally occurring α-amino acids. Reaction between **386a-d/389a-b** and 2-acetoxy-1-nitroethane (2 equiv) proceeded uneventfully to afford the desired Michael adducts **387a-d** and **390a-b**, which were subjected to catalytic hydrogenation allowing the piperazinone derivatives **388a-d** and **391a-b** in good yields. Accordingly, reductive amination of **389a-b** with suitably protected 4-hydroxy-butanal, further reaction of the secondary amines with 2-acetoxy-1-nitroethane and reduction of the intermediate Michael adducts **392a-b** paved the way to compounds **393a-b** in good yields (Scheme 71).[86]

Scheme 71



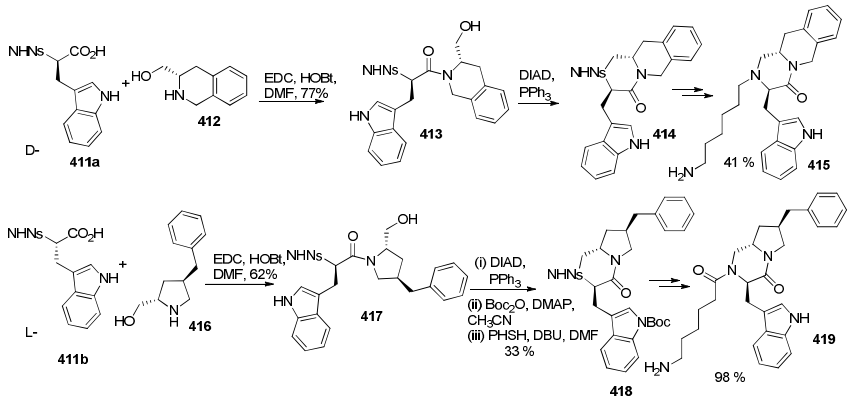
Among small heterocyclic molecules, DKPs (diketopiperazines) have drawn considerable attention from the synthetic communities in recent years for their significant role in developing new therapies and diagnostics. L-proline derivative **396** was effectively used for the synthesis of tricyclic DKPs (**400**, **401** and **410**) by Deppermann *et al.* in 2009 starting from three different bridged bicyclic compounds (**394**, **401** and **406**). The developed synthetic route has been depicted below in Scheme 50. The main features of their methodology rely on high variability with respect to stereochemistry, ring size and substitution pattern of the target compounds (Scheme 72).[87]

Scheme 72



Zapf *et al*. reported the synthesis of the novel scaffolds pyrazino[1,2-*b*]isoquinoline **415** and pyrrolo[1,2-*a*]pyrazine **419** displaying the somatostatin pharmacophores, starting from amino acids **411a,b**. The key steps in this synthesis involved amide coupling reaction followed by Mitsunobu cyclization of the intermediate **413** and **417** (Scheme 73).[88] Analysis of synthetic methodologies of amino acids derived morpholines and piperazines imply tetrasubstituted derivatives of piperazines have been synthesized but similar substituents are yet to be known for morpholines derived from amino acids.

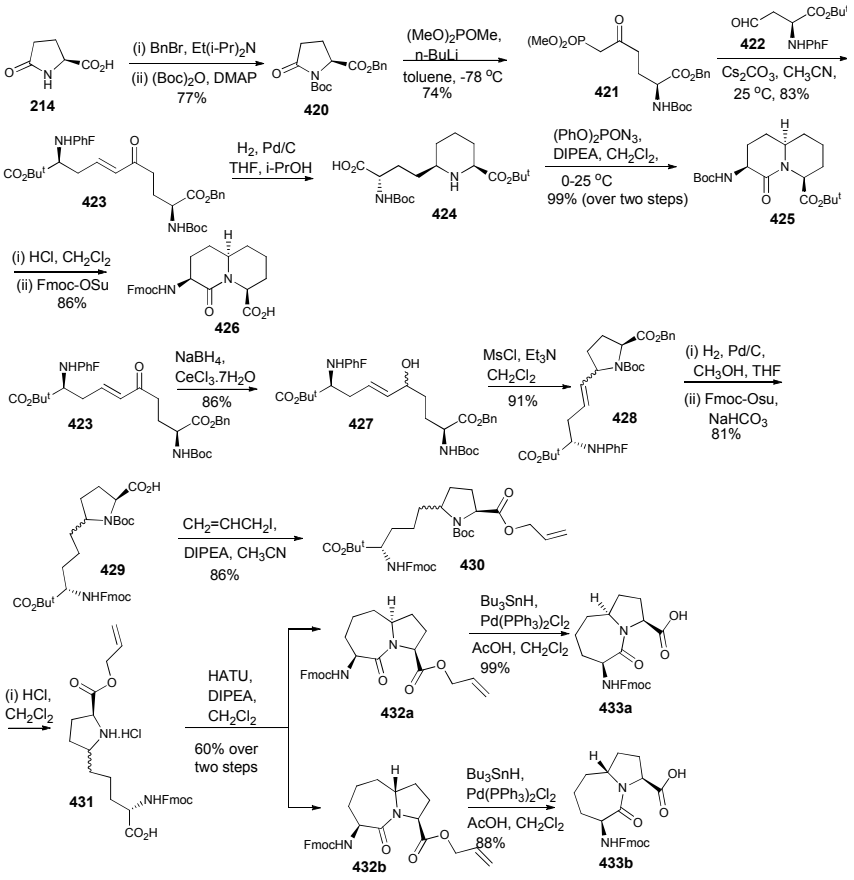
Scheme 73



1.2.4.6 Quinolizidinone and Pyrroloazepinone

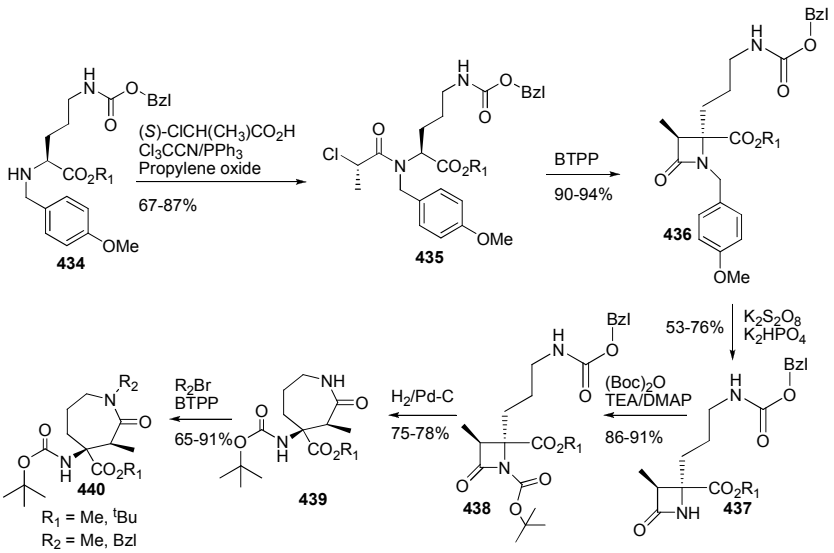
Lubell *et al.* developed short synthetic methodology for the asymmetric synthesis of novel azabicyclo[5.3.0] alkane amino acids namely Quinolizidinone and Pyrroloazepinone Amino Acids **426**, **433a** and **433b** from a common diaminodicarboxylate precursor **423**. They utilized easily available α-amino acid (L-glutamic acid, **214**) as the starting material. To achieve the common synthetic precursor (Diaminodicarboxylate, **423**), L-pyroglutamic acid **214** was first protected, then nucleophillic ring opening furnished the β-keto phosphonate **421** which was subsequently, coupled with aldehyde **422** to afford **423**. This common precursor was finally converted into desired target molecules, Quinolizidin-2-one amino acid **426** and Pyrroloazepin-2-one amino acids **433a,b** following a series of chemical transformations. The main feature of the approach is that, it is highly flexible for the introduction of side-chains onto the heterocycle framework through functionalization of the pyrroglutamate and amino aldehyde precursors, (Scheme 74).[89]

Scheme 74



Villanueva reported the synthesis of 2-oxoazepane **439** by a simple Pd/C catalyzed hydrogenolysis of Orn(*Z*)-derived 2-azetidinones **438**. The rearrangement from four to seven-membered lactam ring is driven by the key intramolecular opening of the 1-Boc-β-lactam, initiated by 7-*exo*-*trig* ring closure from the NH_2 of the Orn side chain (Scheme 75).[90]

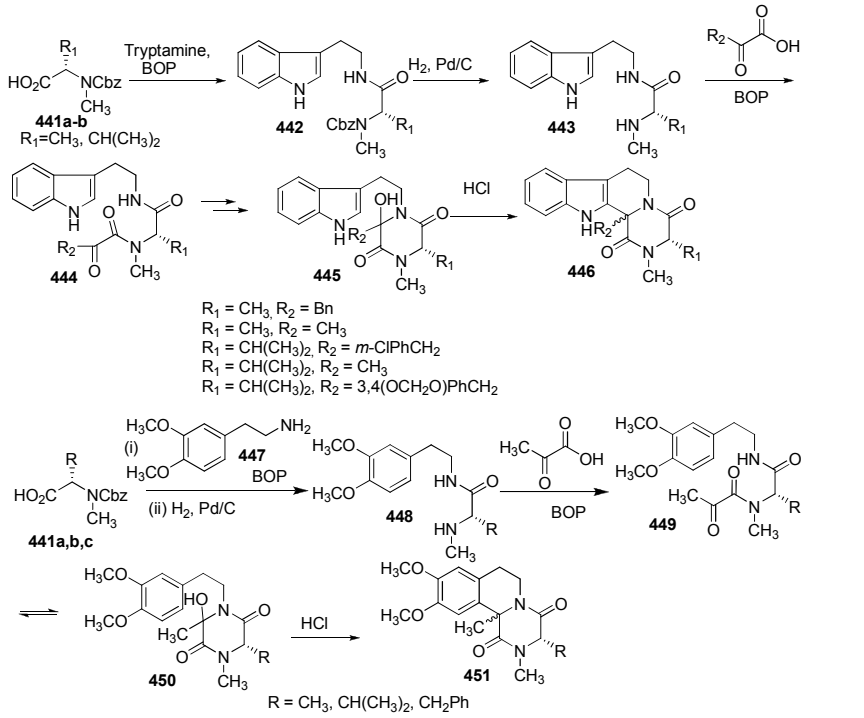
Scheme 75



1.2.4.7 *β*-carboline and isoquinoline

Czarnocki *et al*. reported diastereodivergent synthesis of 2,5-diketopiperazine derivatives of *β*-carboline **446** and isoquinoline **450** from L-amino acids **441a-c**. BOP-mediated coupling of **441a-b** and tryptamine followed by palladium catalyzed deblocking of the nitrogen atom gave amides **443**. Another BOP-mediated coupling of **443** with phenylpyruvic acid and Pictet–Spengler cyclization was used to furnish a tetrahydro-*β*-carboline **446**. To obtain the isoquinoline system **451**, first Bop coupling was carried out between **441a-c** and **447**, and then the same reaction sequence as followed for **443** was performed (Scheme 76). The stereochemistry of the final diketopiperazines, acyclic amino acids gave predominantly the (*R*)-configuration at the newly created stereogenic centre, whereas L-proline afforded the (*S*)-configuration.[91]

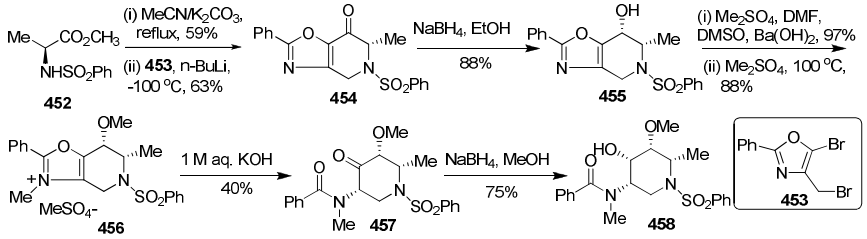
Scheme 76



1.2.4.8 Piperidine

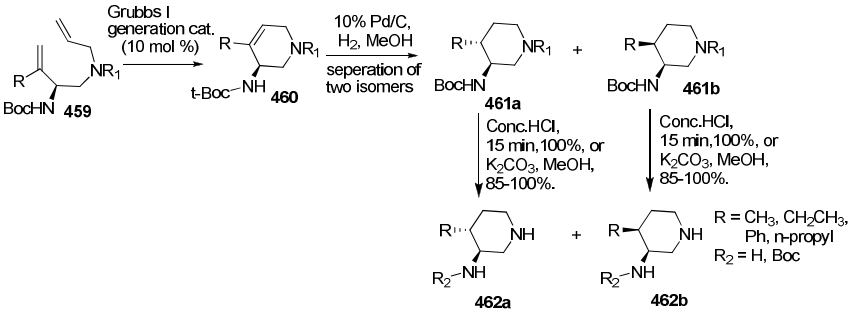
Liebschercis and coworkers reported synthesis of *cis*-3,4-dihydroxy-5-aminopiperidine[92] **458** by a novel route to deoxydiamino sugars. *N*-alkylation of **452** with 5-bromo-4-bromomethyl-2-phenyloxazole **453** and cyclization by bromo-lithium exchange gave oxazolo[4.5-c]pyridone **454** which was reduced to *cis*-hydroxy product **455**. The compound **455** was transformed to the more reactive *N*-methyloxazolium salt **456** which was treated with 1 M aqueous KOH to cleave the oxazole ring creating the third chiral centre again in the *cis* configuration. Finally smooth reduction of the keto group of **457** afforded *cis*- product **458** in enantiomerically pure form (Scheme 77).

Scheme 77



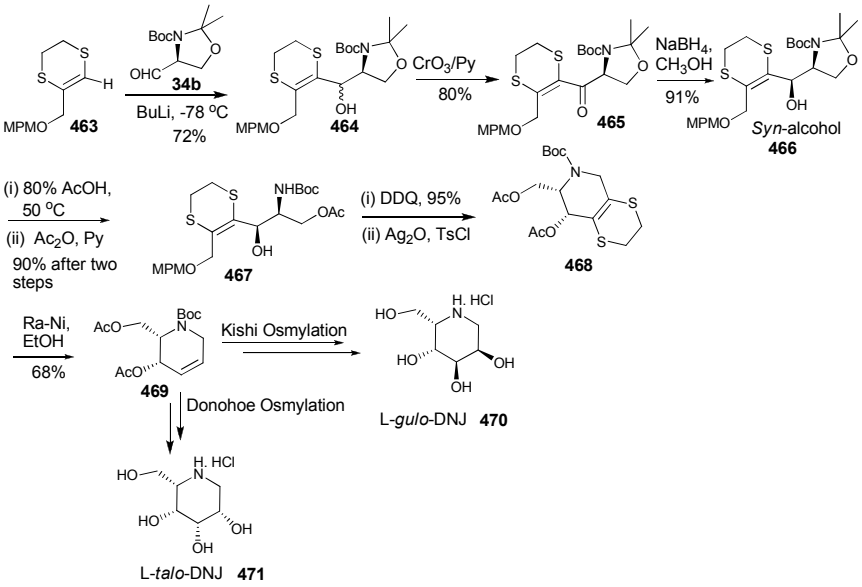
Hu *et al*. reported the first asymmetric route to *trans*-(3*S*)-amino piperidines **462a** bearing various alkyl and aryl substituents at the C-4 position *via* ring-closing metathesis of **459** which was obtained from D-serine. Stereoselective hydrogenation of allylamines **460** provided *trans*-(3*S*)-amino-(4*R*)-alkyl- and -(4*S*)-aryl-piperidines **462a** (Scheme 78).[93]

Scheme 78



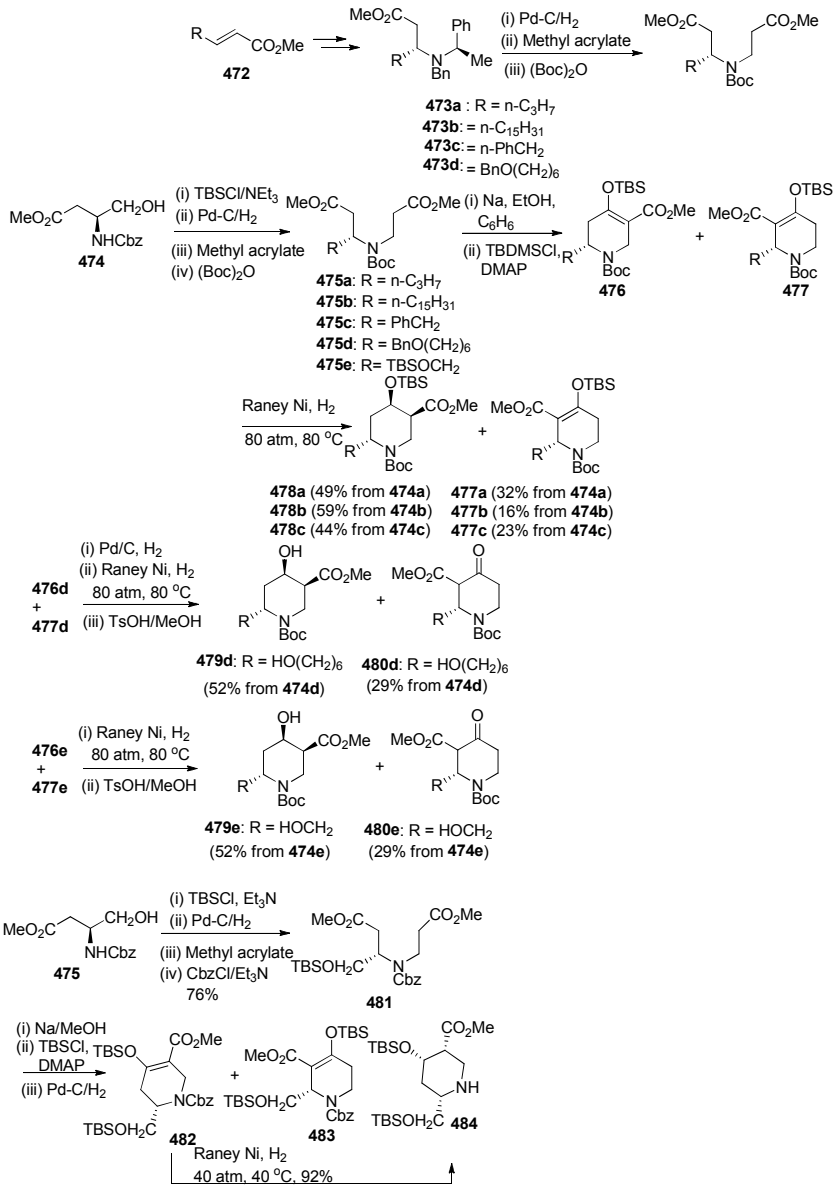
Guaragna *et al*. reported the synthesis of glycosidase inhibitors L-gulo-DNJ **470** and L-talo-DNJ **471**, starting from Garner's aldehyde **34b**. Key feature of this strategy was the construction of the unsaturated piperidine **469**, which on *syn* dihydroxylation under Kishi's and Donohoe's conditions led to the desired iminosugars (Scheme 79).[94]

Scheme 79



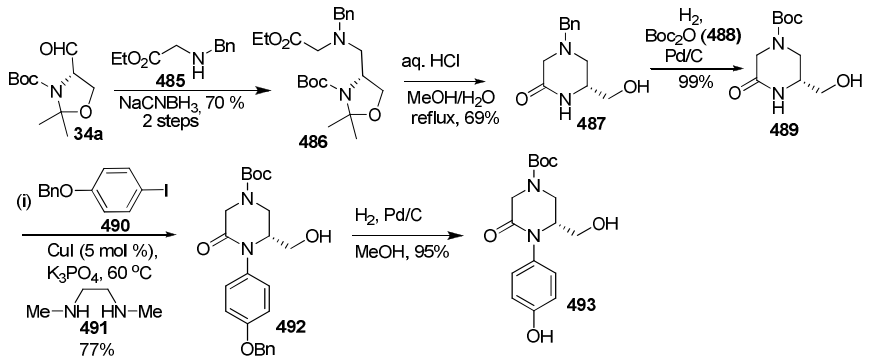
Chirally pure polysubstituted piperidines are the important N-containing heterocycles which are frequently found in biologically active natural products. Many more synthetic methodologies for those kinds of molecules have been documented in the literature. One of such effective methodologies was developed by Ma *et al.* in 2000. The key features of this synthetic effort are the Na/CH_3OH mediated Dieckmann condensation of the diester **475a-e** and **481** and diastereoselective hydrogenation of enol ether intermediates, Scheme 80.[95]

Scheme 80



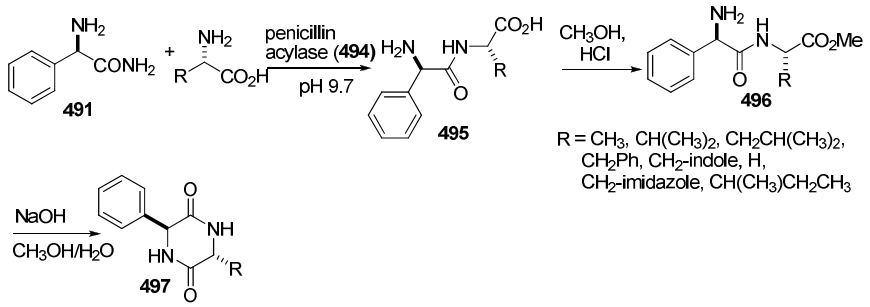
Powell *et al.* described the synthesis of chiral 1-aryl-6-(hydroxymethyl)-2-ketopiperazines **493** derived from Garner aldehyde **34a**. The key features involved reductive amination of Garner aldehyde **34a**, followed by ring cyclization to afford piperazine building block **487** and Buchwald amidation reaction of **489** (Scheme 81).[96]

Scheme 81



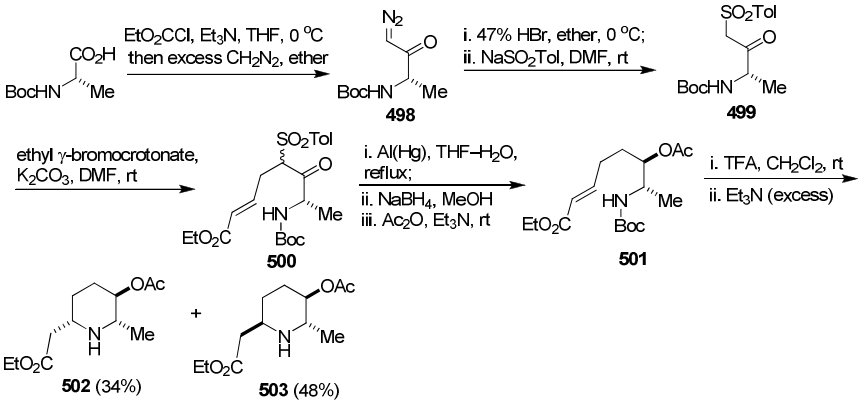
Svedas and coworkers developed a chemo-enzymatic route to stereoisomerically pure diketopiperazines **497**[97] *via* penicilin acylase-catalyzed synthesis of the dipeptides **495** from D-(−)-phenylglycine amide **491** and the corresponding amino acids, followed by their subsequent spontaneous cyclization, (Scheme 82).

Scheme 82



Sengupta et al. described a new synthetic strategy for 2,6-disubstituted-3-hydroxypiperidines *via* intramolecular Michael reaction of an α-amino-β-hydroxy-acrylate **501**. First, Boc-L-alanine **306** was converted to the α-diazoketone **498** which was treated with 47% aqueous HBr to produce α-bromo ketone which was reacted with $NaSO_2Tol$ to give the enantiopure sulfone derivative **499**. Next α-Alkylation of **499** with ethyl γ-bromocrotonate, subsequent desulfonation, keto-group reduction and hydroxy group protection as the acetate gave the key intermediate α-amino-β-acetoxy-acrylate **501** which underwent intramolecular Michael addition in the presence of TFA to remove Boc-group and excess Et_3N to give diastereomeric piperidines **502** and **503**, Scheme 83.[98]

Scheme 83

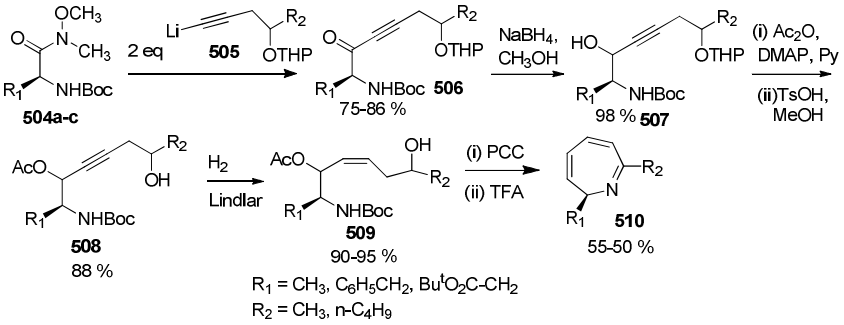


1.2.5 Seven Membered Chiral Heterocycles

1.2.5.1 *2H*-Azepines

Steglich and coworkers[99] described general synthesis of optically active *2H*-azepines **510** starting from α-amino acids **504 a-c**. The linear precursor **507** was acetylated, followed by acid catalyzed cleavage of the tetrahydropyranyl (THP) ether furnished the alkynols **508**. Reduction of triple bond with Lindlar catalyst afforded the (*Z*)-homoallylic alcohols **509**. PCC mediated oxidation of alcohol and then treatment with TFA afforded chiral 2*H*-azepines **510** (Scheme 84).

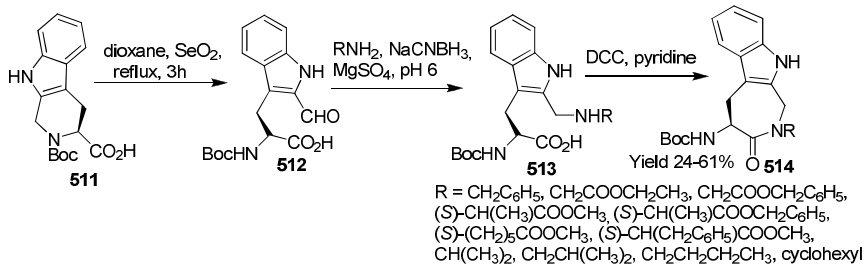
Scheme 84



1.2.5.2. Tetrahydroazepino[3,4-b]indoles

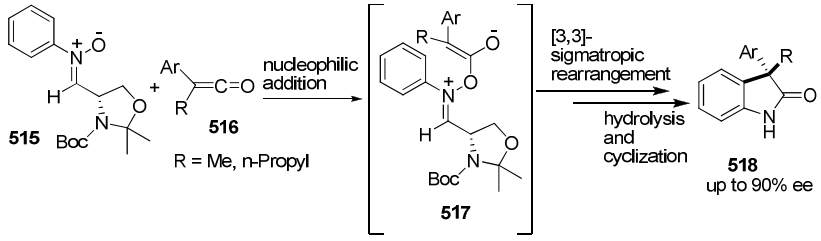
Tourwe and coworkers[100] reported the synthesis of 4-amino-3-oxo-tetrahydroazepino[3,4-*b*]indoles **514**. These were prepared by SeO_2 oxidation of Boc-tetrahydro-β-carboline-3-carboxylic acid **511** which on reductive amination with a variety of amines and amino acid esters using sodium cyanoborohydride, followed by ring closure gave the target compounds **514** (Scheme 85). The constrained Trp derivative has been incorporated into the endomorphin-1 opioid peptide sequence to probe the bioactive conformation.

Scheme 85



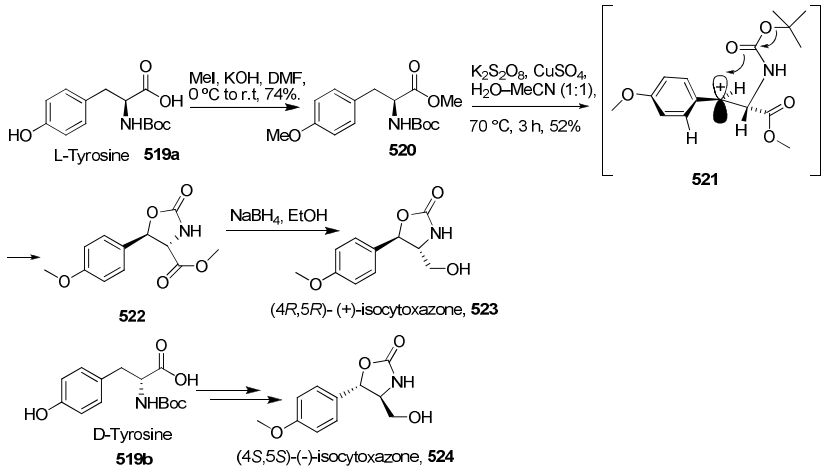
Duguet and coworkers reported the reaction between chiral *N*-phenylnitrone **515** derived from Garner's aldehyde **34b** with alkylarylketenes **516** affording 3-alkyl-3-aryloxindoles **518** in excellent yields with excellent enantioselectivities (up to 90% ee) as depicted in Scheme **86**.[101]

Scheme 86



Buckley *et al*. described three-steps protocol for the highly diastereoselective (>98%) synthesis of both (4*R*,5*R*)- and (4*S*,5*S*)-isocytoxazones **523** and **524** from L- or D-tyrosine (**519a** or **519b**). This synthetic sequence was the highest yielding approach towards enantiomerically pure biologically active oxazolidinones (Scheme 87).[102]

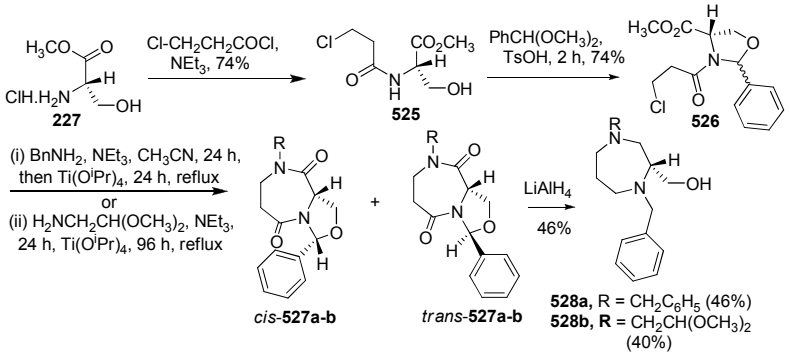
Scheme 87



1.2.5.3 1,4-diazepanes

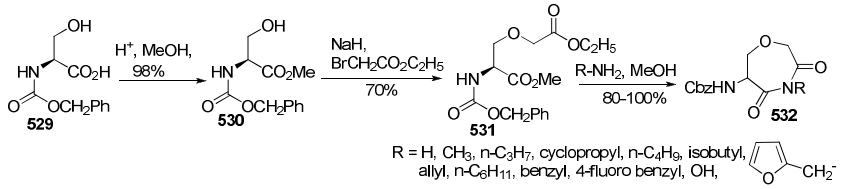
Due to the diverse biological properties,[103] diazepanes have been the major synthetic targets to synthetic and medicinal chemists.[104] Wunsch and coworkers described the synthesis and pharmacological evaluation[105] of chiral non-racemic 1,4-diazepanes **528 a,b** with a hydroxymethyl residue in position 2 starting from the proteinogenic amino acid (*S*)-serine. At first the primary amine of serine was acylated with chloropropionyl chloride and then reaction of the hydroxyamide with benzaldehyde dimethyl acetal afforded an inseparable mixture of diastereomeric oxazolidines (**527**) *cis*-7 and *trans*-7 (30:70) (Scheme 88). Next, Lewis acid $Ti(O^iPr)_4$ promoted conversion of the chloropropionamide **526** into the bicyclic system **527 a-b** took place. In the last step, the bicyclic systems were reduced with $LiAlH_4$ to give directly the hydroxymethyl substituted 1,4-diazepanes **528a** and **528b**, respectively.

Scheme 88



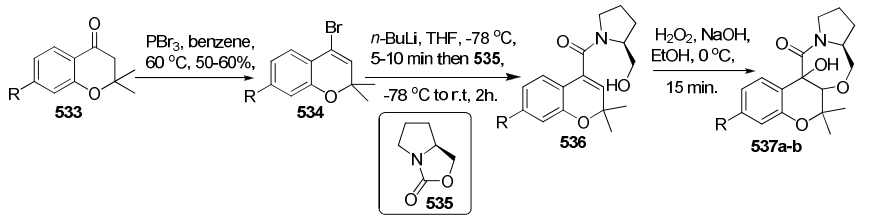
Park and coworkers described the design and synthesis of 6-amino-1,4-oxazepane-3,5-dione derivatives **532** as novel broad spectrum anticonvulsants. The key intermediate **531** was prepared by O-alkylation of compound **530**with ethyl bromoacetate and NaH in acetonitrile in good yields. Final compounds **532** were synthesized by treating the corresponding amine with compound **531 (**Scheme 89).[106]

Scheme 89



A new class of chroman fused *S*-proline derived chiral oxazepinones **537a,b** was synthesized by Panda and co-workers in one pot through epoxide formation and ring opening by primary alcohol **536** to generate quaternary and tertiary stereocenters (Scheme 90).[107]

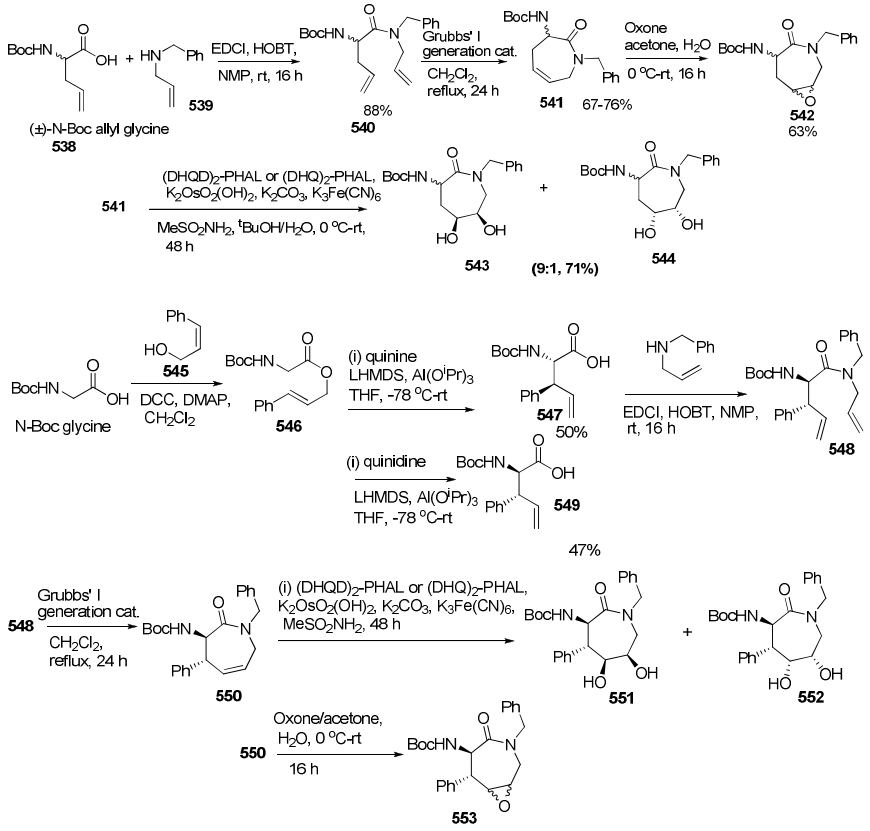
Scheme 90

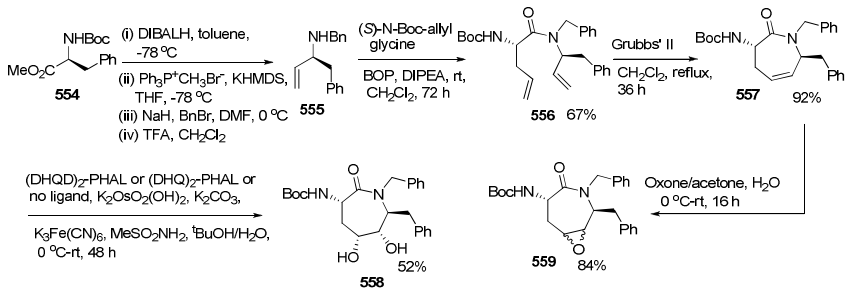


1.2.5.4 Caprolactam

In 2006, Zaman *et al.* reported the synthesis of novel seven membered lactam-based inhibitors of HIV protease for the first time by ring-closing metathesis. The dienes precursors for metathesis have been synthesized from L-glycine derivatives. The cyclic olefins were then transformed into *syn*-diol derivatives (**543**, **544**, **551** and **552**) *via* stereoselective dihydroxylation or epoxides *via* stereoselective epoxidation by *in situ* preparation of dimethyldioxiran form Oxone/acetone. Furthermore, they also utilized L-phenyl alanine to prepare densely functionalized seven membered lactams which serve as new class of HIV protease inhibitors (Scheme 91).[108]

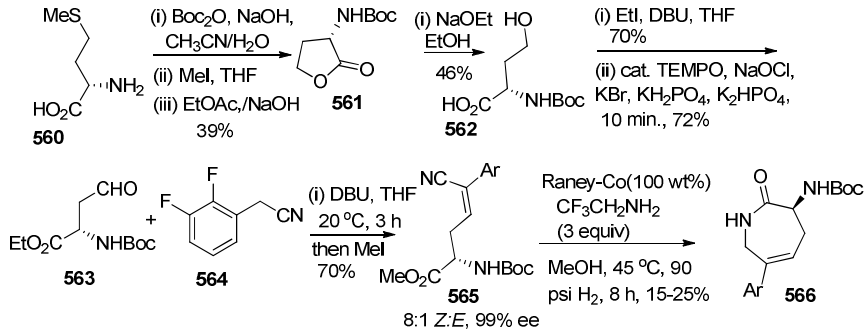
Scheme 91





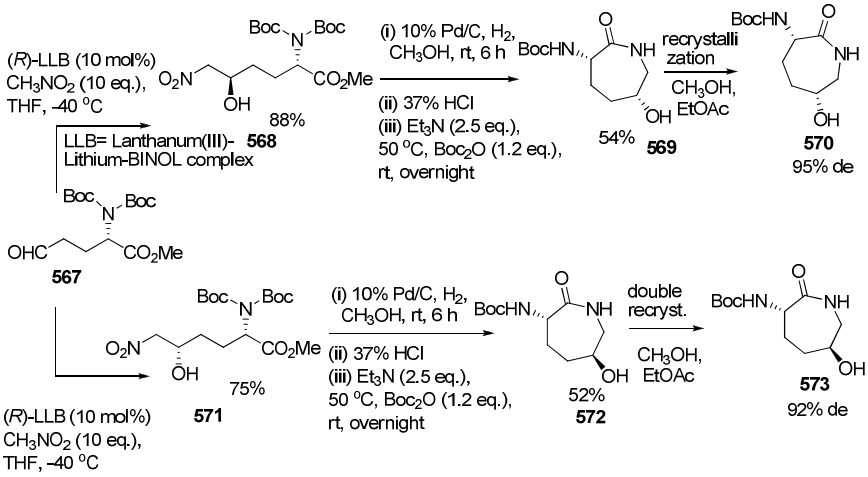
The unsaturated caprolactam **566**, which is an advanced intermediate for the synthesis of a Merck drug candidate, was effectively synthesized by Janey *et al*. in 2008. Their synthesis commenced from readily available L-methionine **560** which was converted into homoserine derivative **562** in four steps. **562** was then transformed into amino acid aldehyde **563** *via* esterification followed by oxidation. This aldehyde was effectively condensed with nitrile **564** by DBU mediated aldol condensation. Chemoselective reduction of nitrile moiety in aldol product **565** followed by concomitant cyclization furnished the desired product **566** (Scheme 92).[109]

Scheme 92



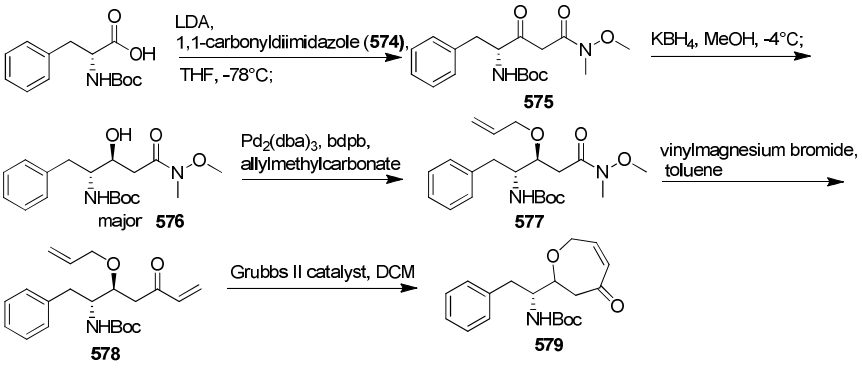
2-Amino-5-hydroxycaprolactam constitutes the core structure of a recently identified anti-tumor agent belonging to the bengamide marine sponge natural products.[110] Whereas the (2*S*,5*S*)-2-amino-5-hydroxycaprolactam is present in natural bengamides,[93] the (2*S*,5*R*)-diastereomer has been used for the synthesis of other analogs.[111] In 2001, Roche *et al.* attempted the asymmetric synthesis of both the isomers starting from L-glutamic acid. L-glutamic acid was first converted into glutamic aldehyde **567** in three steps in 76% overall yield following a literature procedure. This aldehyde **567** was then subjected to nitro-aldol reaction with nitro methane in the presence of chiral catalyst to afford **569** and **572**. The aldol products were then converted into desired lactam moieties **570** and **573** through hydrogenation, protection and reprotection strategy and finally recrystallisation furnished the pure products in good overall yields (Scheme 93).[112]

Scheme 93



Kulesza *et al*. developed five-step synthesis of 1-substituted-3,4-dihydro-7*H*-oxepin-4-one **579** from Boc-D-phenylalanine. First, amino acid was converted to ketoamide **575,** which was subjected to diastereoselective (4:1) reduction of the ketone group to produce alcohol **576** (major). Allylation of the hydroxyl group, introduced a vinylketone system and finally, ring closing metathesis reaction gave heterocyclic eight membered rings containing α,β-unsaturated ketone **579** (Scheme 94).[113]

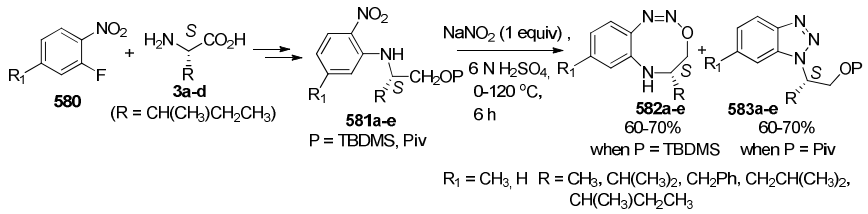
Scheme 94



1.2.6. Benzo/Heteroannulated chiral heterocycles

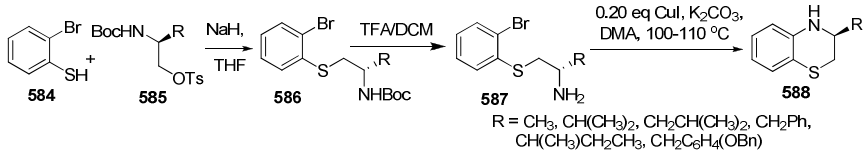
Amino acid derived enantiomerically pure substituted benzo[d][1,2,3,6]oxatriazocine derivatives **582a-e** and 1-alkyl substituted benzotriazoles **583a-e** was synthesized by Bera *et al. via* the diazotization of amino acid-derived **581a-e** (Scheme 95). The first unprecedented diazo-oxygen bond formation in acidic medium led to an entirely new kind of substituted benzo[d][1,2,3,6]oxatriazocine heterocycles.[114]

Scheme 95



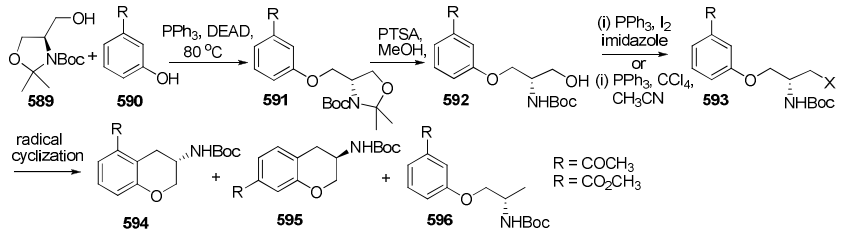
Panda and coworkers reported the synthesis of chiral amino acid derived 3,4-dihydro-2*H*-benzo[b][1,4]thiazine **588** *via* copper-catalyzed intramolecular *N*-aryl amination reaction on substituted 2-(2-bromophenylthio)-ethanamines **587** which were synthesized by the nucleophilic substitution of 2-bromobenzenethiol **584** with Boc-protected amino alcohols **585,** (Scheme 96).[115]

Scheme 96



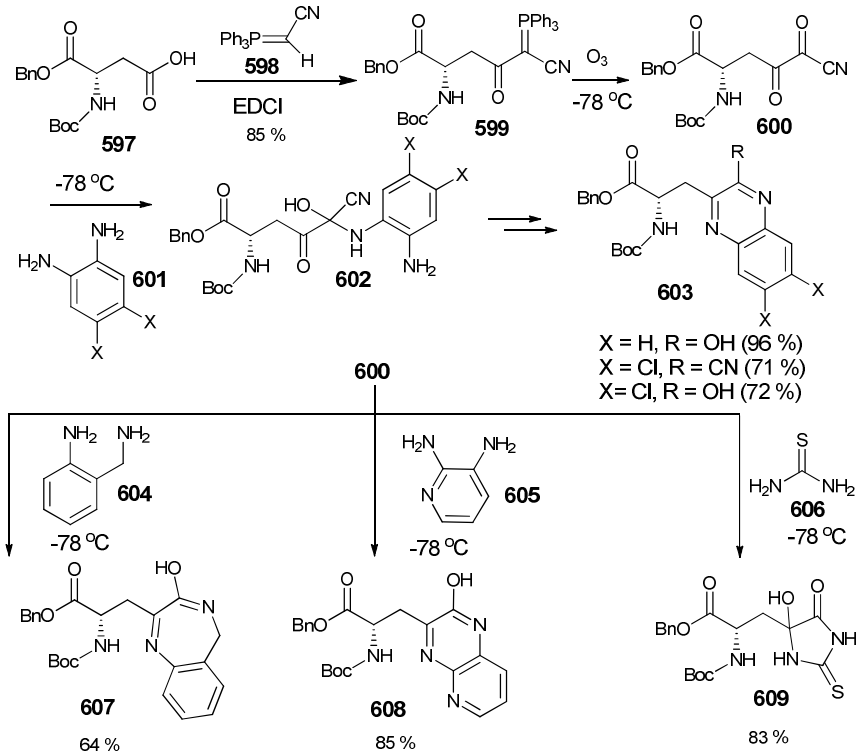
Guillaumet and coworkers reported the enantiomerically pure 5-acetyl-3-amino-3,4-dihydro-2*H*-1-benzopyran **594** and methyl 3-amino-3,4-dihydro-2*H*-1-benzopyran-5-carboxylate **595**, starting from D- or L-serine. The formation of the benzopyran ring **594**/**595** involved a radical cyclization step of **593**. The enantiomeric purities of the final aminochroman derivatives **594**/**595** were determined by capillary electrophoresis using *β*-cyclodextrins as a chiral selector (Scheme 97).[116]

Scheme 97



Wasserman *et al*. described the synthesis of heterocyclic derivatives of amino acids (unnatural amino acids) **603**, **607**-609 derived from aspartic acid derivative **597**. The reactions of mono Boc-protected amino monocarboxylic acids **597** with phosphoranylideneacetonitrile ylido nitriles **598** which were subjected to ozonolysis at low temperature formed labile α,β-diketo nitriles **600**. These derivatives were used *in situ* for reaction with different diamines or related dinucleophiles to yield heterocyclic derivatives as unnatural amino acid **603**, **607**-**609** (Scheme 98).[117]

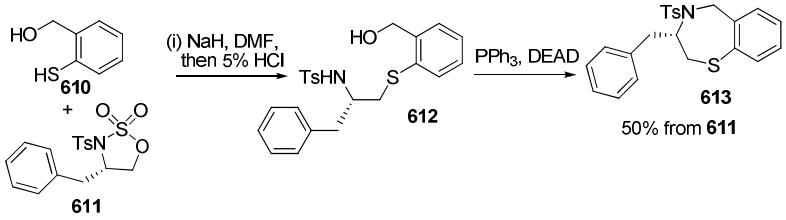
Scheme 98



Benzothiazepines are active constituents of an important class of biologically active compounds such as CGRP receptor antagonist, for treatment of hyperproliferation diseases,[118] IAP (inhibitors of apoptosis proteins) antagonist,[119] interleukin-1 converting enzyme inhibitor,[120] as well as selective bradykinin agonist JMV1116.[121] Synthetic approaches towards amino acids derived benzothiazepine derivatives are exemplified below.

Gallagher *et al*. described nucleophilic cleavage of enantiomerically pure 1,2-cyclic sulfamidates **611** with thiophenol **610** followed by a Mitsunobu Reaction of **612** providing an entry to substituted 1,4-benzothiazepines **613** (Scheme 99).[122]

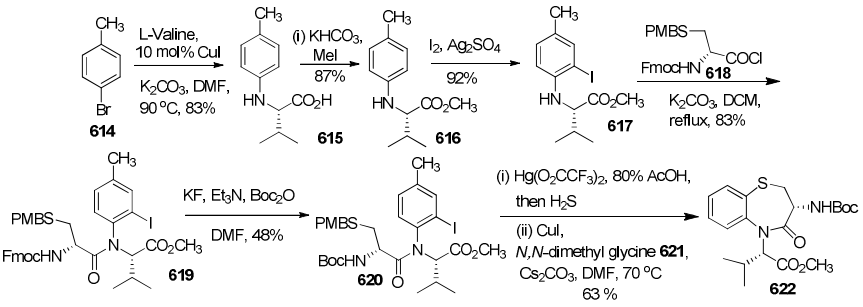
Scheme 99



Ma and coworkers reported a novel route to synthesis of 1,5-benzothiazepine dipeptide mimetics **621** using CuI-catalyzed coupling of 4-methylphenyl bromide **614** with amino acids giving N-aryl amino acids **(615),** which were converted into linear dipeptides **619** *via* iodination and condensation with L-cysteine derived acyl chloride

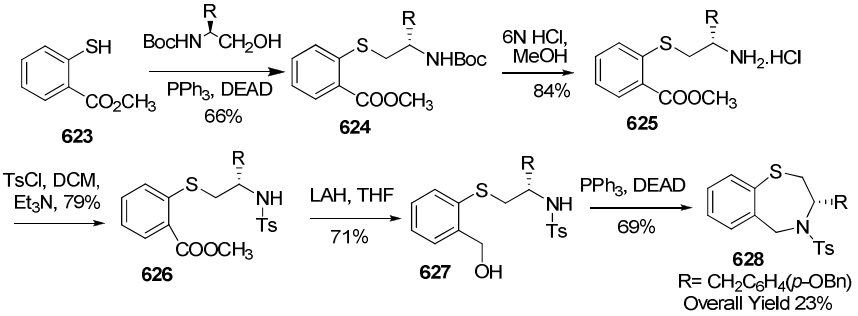
(618). Cyclization was achieved *via* CuI/*N*,*N*-dimethylglycine catalyzed intramolecular coupling of aryl iodides with the liberated thiol to afford 1,5-benzothiazepine dipeptide mimetics **(622)** as illustrated in Scheme 100.[123]

Scheme 100



Mishra and Panda reported the synthesis of 1,4-benzothiazepine derivatives **(628)** employing intermolecular Mitsunobu reaction of methyl thiosalicylate **(623)** with Boc-protected amino alcohol followed by intramolecular Mitsunobu cyclization of intermediate **(627)** as depicted in Scheme 101.[124]

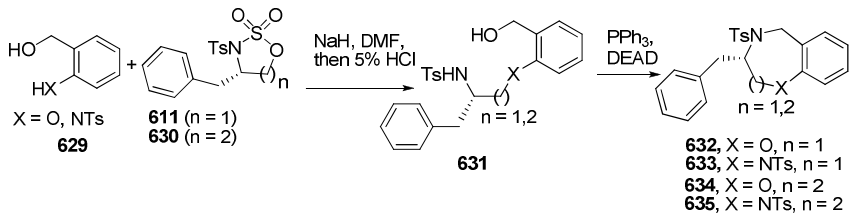
Scheme 101



Benzodiazepines are the class of privileged structures[125] exhibiting pharmacological activities such as antipsychotic, central nervous system along with antibreast cancer.[126] Eight membered benzannulated heterocycle benzodiazocine, such as Teleocidines activate protein kinase C (PKC) isozymes.[127] Benzoxazocine, such as Nefopam hydrochloride[128] is a non-narcotic analgesic drug with antidepressant properties.[129]

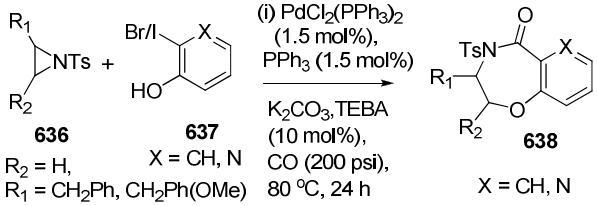
Gallagher and coworkers reported nucleophilic cleavage of enantiomerically pure 1,2-cyclic sulfamidates **(611, 630)** with oxygen and nitrogen nucleophile (**629**), followed by Mitsunobu reaction of **631** which provided an entry to substituted benzoxazepines **(632)** and benzodiazepines **(633)**. Application of this methodology to 1,3-cyclic sulfamidates affords a parallel entry to the analogous substituted 1,5-benzoxazocines **(634)** and 1,5-benzodiazocines **(635)** as depicted in Scheme 102.[104]

Scheme 102



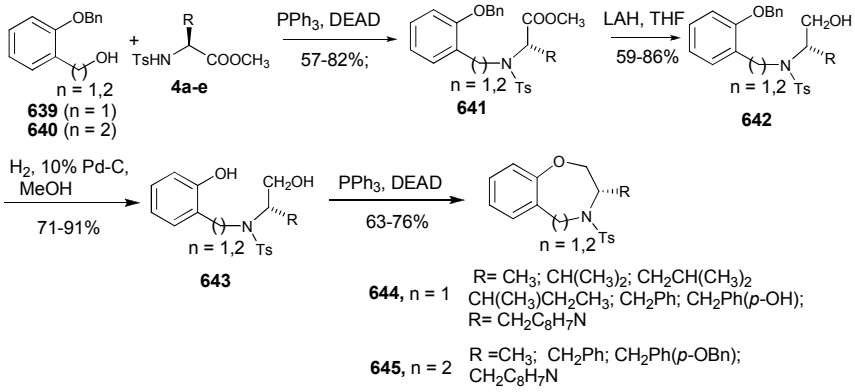
Alper and coworkers reported a domino process for the synthesis of 1,4-benzo- and pyrido-oxazepinones **(638)** by one-pot sequential ring-opening/carboxamidation reactions of various *N*-tosylaziridines **(636)** with a range of 2-halophenols/pyridinol **(637)** under phase-transfer catalysis as illustrated in Scheme 103.[130]

Scheme 103

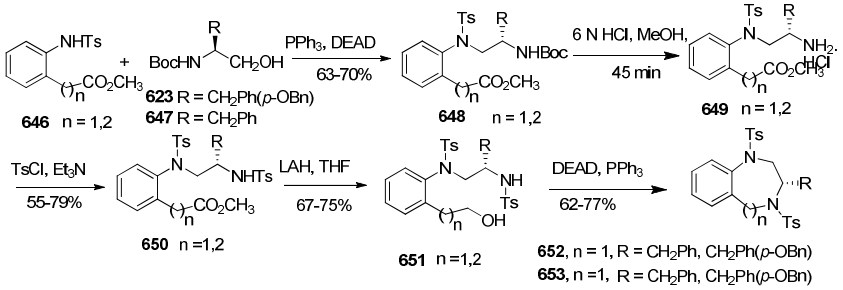


Mishra and Panda reported the diversity oriented synthesis of enantiomerically pure benzannulated oxazepine (**644**), diazocine (**653**), diazepine (**652**) and oxazocine (**645**) scaffolds from naturally occurring *S*-amino acids (**4a-e**) employing inter and intramolecular Mitsunobu reaction (Scheme 104, 105).[106]

Scheme 104

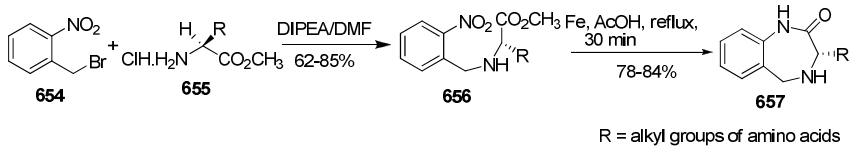


Scheme 105



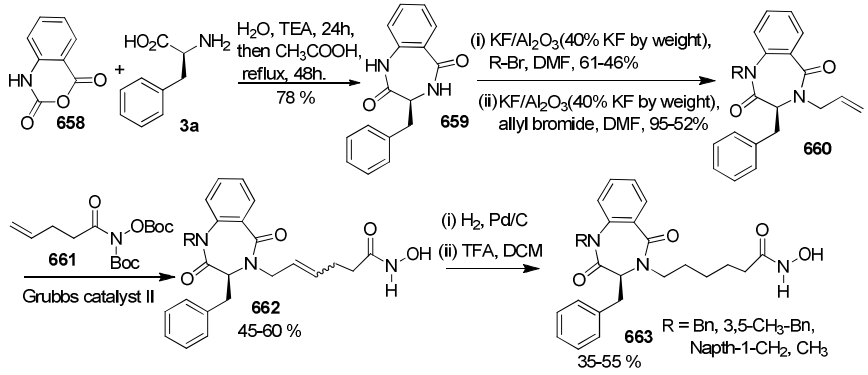
A new two-steps route to chiral 3-substituted [1,4]benzodiazepin-2-ones **657** was described by Mishra *et al.* which involved the coupling of 2-nitrobenzyl bromide **654** with a series of amino acids **655**, followed by diazepine **657** ring formation with Fe/AcOH at 110 °C (Scheme 106).[131]

Scheme 106



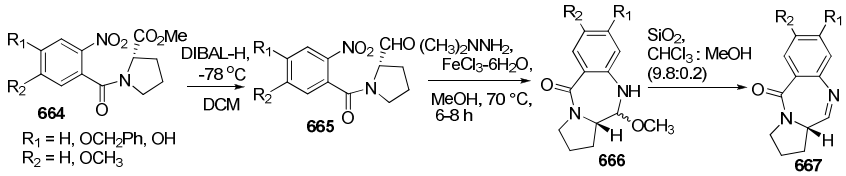
Tranoy-Opalinski and coworkers have reported the design, synthesis and biological evaluation of 1,4-benzodiazepine-2,5-dione **663** as a new histone deacetylase (HDAC) inhibitors. The 1,4-benzodiazepine-2,5-dione **(663)** was prepared according to the Sun procedure[132] *i.e.* condensation of isatoic anhydride **658** with L-phenylalanine **3a** followed by Blass's versatile method for the selective *N*-alkylation of a central 1,4-benzodiazepine-2,5-dione core. Compounds **660**, resulting from N_4-alkylation with allyl bromide were isolated in good yields and then cross-metathesis with alkene **661** in the presence of Grubbs II catalyst led to the formation of **662** as a mixture of diastereoisomers. Hydrogenation of **662** followed by deprotection of the *tert*-butoxycarbonyl (Boc) group with TFA gave the free hydroxamic acid **663** of saturated analogues BZD (Scheme 107).[133]

Scheme 107



Kamal *et al.* described one-pot synthesis of pyrrolo[2,l-c][l,4]benzodiazepine **667**[134] (PBD) ring system *via* reductive cyclization reaction of the nitro aldehyde **665** with $FeC1_3.6H_2O$ and *N*,*N*-dimethyl hydrazine which was converted to their imine forms (**667**) by subjecting to column chromatography (silica gel, chloroform-methanol, 9.8:0.2). They reported the same product by HMDST (hexamethyldisilathiane) mediated[135] reduction of azide followed by ring cyclization. (Scheme 108)

Scheme 108

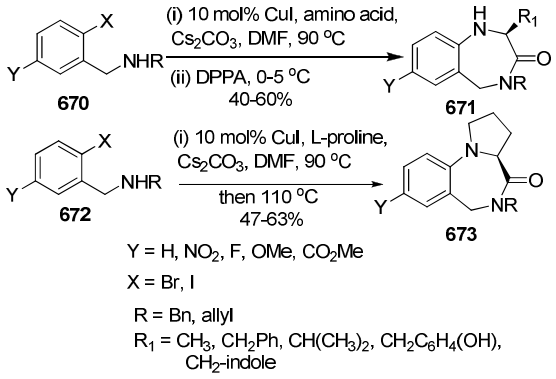


Ma and coworkers[136] reported the synthesis *N*-substituted pyrrolo[2,1-c][1,4]-benzodiazepine-5,11-diones (**669**) *via* copper-catalyzed amination of *N*-heterocycle derived aryl iodides **668** followed by intramolecular condensation affording **669** with good yields. A wide range of heterocycles was assembled by varying primary amines and substituents at aromatic ring of aryl iodides (Scheme 109).

Scheme 109

Same group reported the facile synthesis of 1,4-benzodiazepin-3-ones **671** and **673** from amino acids. Cu-catalyzed coupling of 2-bromobenzylamines **670** and **672** with α-amino acids followed by cyclization provided 1,4-benzodiazepin-3-ones **671** and **673** in moderate yields. Enantiopure products are obtained for L-proline and L-valine whereas for other amino acids, partial racemization occurred (Scheme 110).[137]

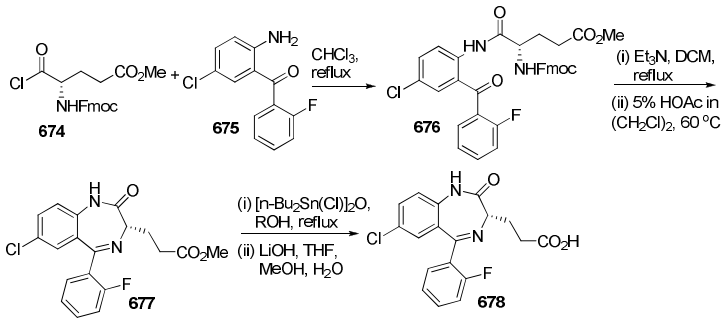
Scheme 110



Feldman and coworkers described the synthesis and evaluation[138] of novel ultra short-acting benzodiazepine (USA BZD) agonists (**678**) derived from glutamic acid. Condensation between the glutamate derived acid chloride **(674)** and 2-

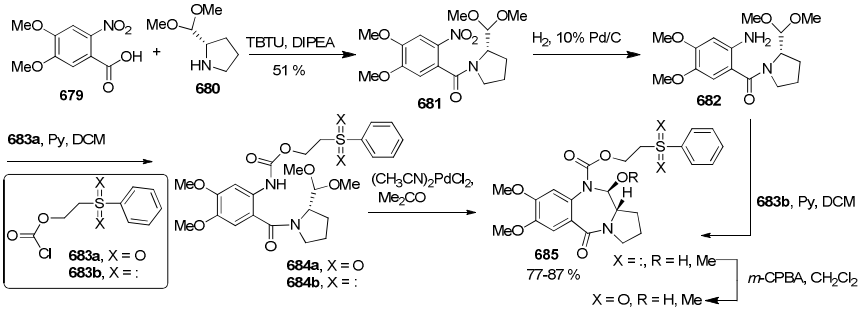
aminobenzophenone **(675)** yielded anilide **676** which was subjected to Fmoc deprotection and cyclodehydration with 5% acetic acid in dichloroethane providing **677** in 55% yield. Transesterification of **677**, followed by saponification provided acid **678** in excellent yield without detectable racemization (Scheme 111).

Scheme 111



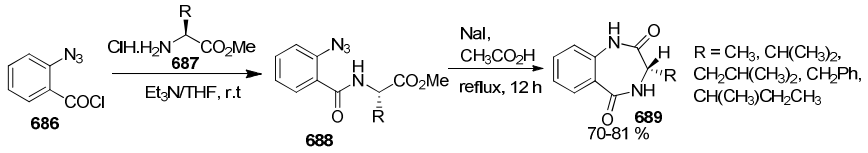
Thurston and coworkers reported synthesis and biological evaluation[139] of an N10-Psec substituted pyrrolo[2,1-c][1,4]benzodiazepine (**685**) as prodrug. 4,5-dimethoxy-2-nitrobenzoic acid (**679)** was coupled with proline derivative **680** under standard procedure and subsequent reduction of the nitro functionality gave aniline **682**. Next, **682** was coupled with **683a-b** followed by cyclization to afford **685 (**Scheme 112).

Scheme 112



Kamal *et al.* reported the synthesis of 1,4-benzodiazepine-2,5-diones **689** *via* one pot NaI/ acetic acid mediated reduction of azides **688** to the corresponding amines and cyclization at room temperature (Scheme 113).[140]

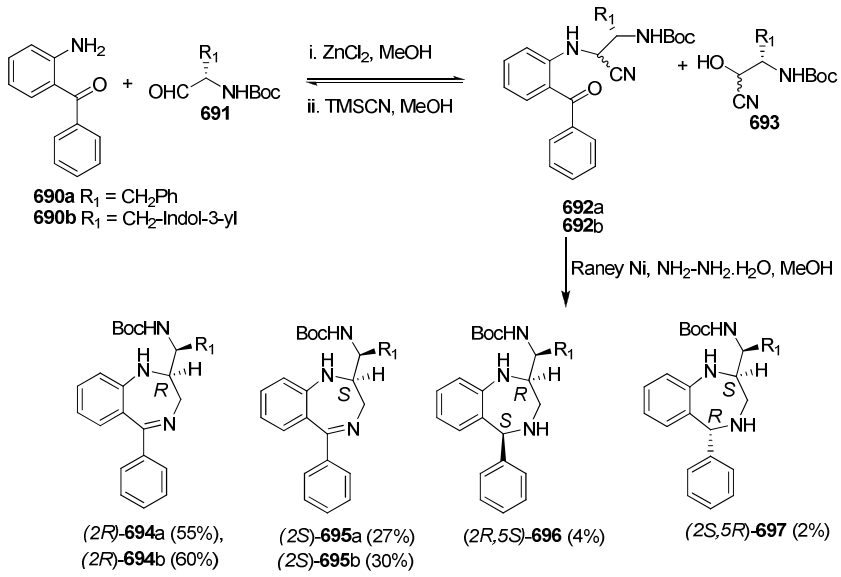
Scheme 113



Herranz's group reported an efficient and stereo controlled synthesis of phenylalanine- and tryptophan-derived 5-phenyl-1,4-benzodiazepines **694-697**. This new methodology involved, by a one-pot cyano reduction and reductive cyclization of the appropriate amino nitrile **692a** and **692b**, which were obtained *via* a modified Strecker reaction of *N*-

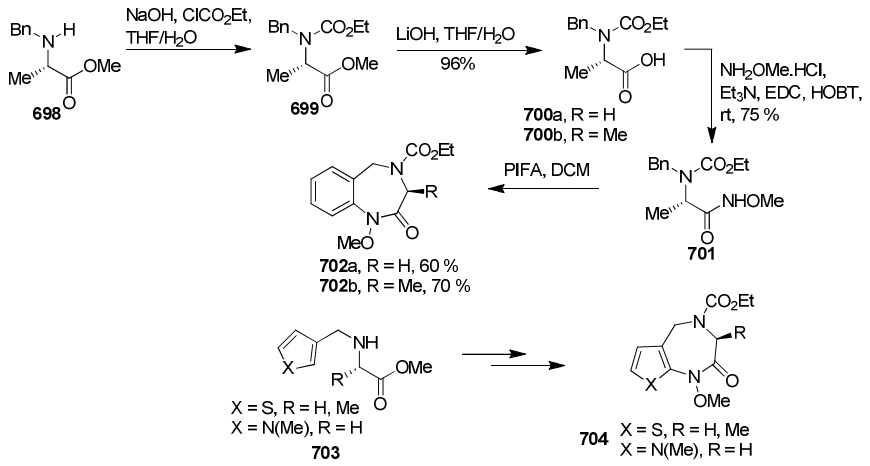
protected *R*-amino aldehydes with 2- aminobenzophenone **690a**, **690b** and trimethylsilyl cyanide.[141] The subsequent reduction of these 2,3-dihydro-1*H*-1,4-benzodiazepines, followed by regioselective alkylation or acylation at position 4, led to 2,4-disubstituted-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (Scheme 114).

Scheme 114



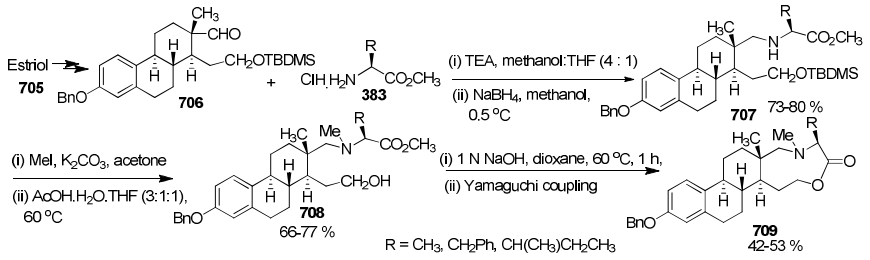
Herrero *et al*. described a novel access to 1,4-benzodiazepin-2-ones starting from glycine and alanine derivatives. The key cyclization step involved phenyliodine(III)*bis*(trifluoroacetate) (PIFA) mediated construction of C(9a)-N(1) bond leading to 1,4-benzodiazepin-2-ones methoxyamide derivatives **702a, 702b** without any racemization, Scheme 118.[142] Same group reported the synthesis of heterocycle-fused 1,4-diazepin-2-ones derivatives **704** using similar kind of strategy (Scheme 115).[143]

Scheme 115



A new type of steroid–amino acid hybrids **709** containing a nine membered D-ring with hetero atoms was reported by Panda and coworkers for the first time from estrone **706** and amino acids **383.** The key intermediate **706** was synthesized from estrone, which was treated with amino acids under reductive amination condition, followed by Yamaguchi coupling reactions affording **709,** Scheme 116.[144]

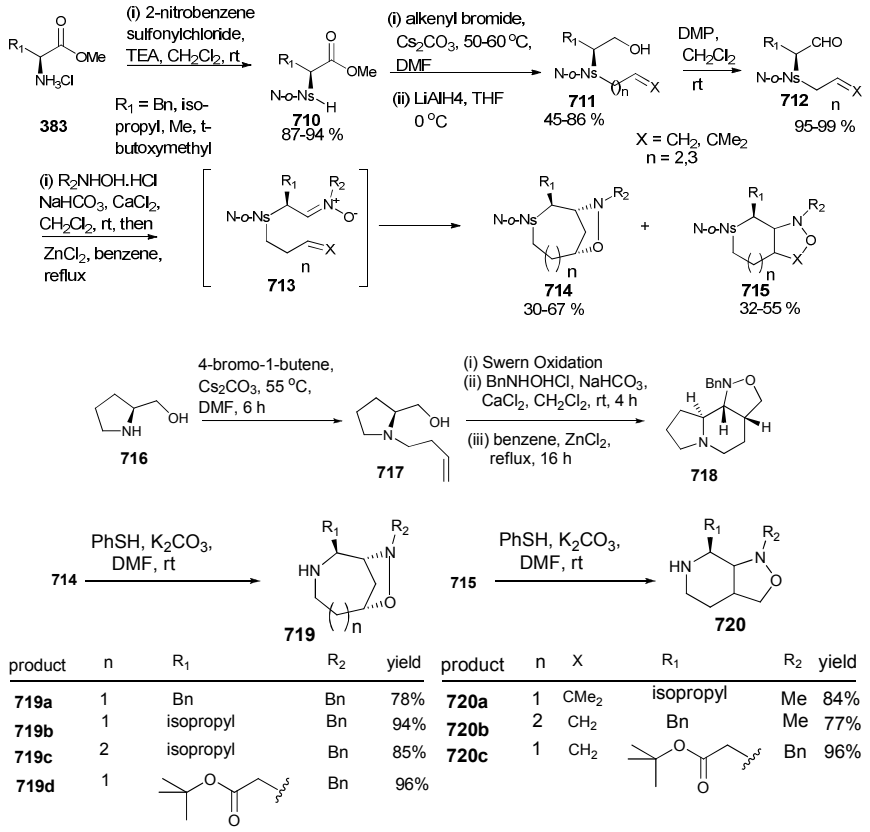
Scheme116



1.2.7 Bridged medium ring system

In 2007, Liu *et al.* developed a synthetic methodology for the synthesis of bridged medium ring systems with diastereoselective control starting from different α-amino acids **383**. The key synthetic features of their methodology rely on the intramolecular nitrone-alkene cycloaddition and protection-deprotection strategy. Nitrones **713** were obtained from different amino acids (**383**) derived aldehydes **712** and *N*-alkylhydroxylamine hydrochlorides in presence of $NaHCO_3$ and $CaCl_2$ at room temperature after overnight stirring. The Lewis acid $ZnCl_2$ was found to be the effective catalyst for the nitrone-alkene cycloaddition reaction (scheme 117).[145]

Scheme 117



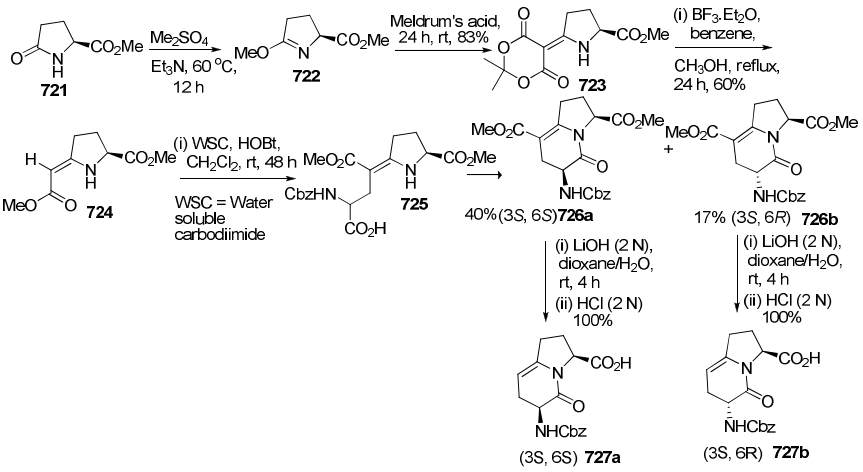
product	n	R_1	R_2	yield
719a	1	Bn	Bn	78%
719b	1	isopropyl	Bn	94%
719c	2	isopropyl	Bn	85%
719d	1		Bn	96%

product	n	X	R_1	R_2	yield
720a	1	CMe_2	isopropyl	Me	84%
720b	2	CH_2	Bn	Me	77%
720c	1	CH_2		Bn	96%

1.2.8 Azabicycloalkane amino acids

6,5-fused azabicycloalkanes **726a,b** as peptidomimetics were attained by Millet *et al*. in 2002. In their synthesis, enantiomerically pure enaminoester **722** was obtained from L-methyl pyroglutamate **721** following a modified literature procedure. The iminoether **722** was achieved from **721** with Me_2SO_4 and Et_3N and following condensation with Meldrum's acid afforded the enaminoester **723**. Meldrum's ring was cleaved following Nagasaka's procedure using $BF_3.Et_2O$ to afford **724**, which was cyclized into bicyclolactam **726a,b** in presence of *N*-benzyloxycarbonyl dehydroalanine and WSC. Finally, azabicycloalkanes **727a,b** were obtained *via* LiOH mediated hydrolysis followed by regioselective decarboxylation of the 8-carboxylic function with 2 N HCl (Scheme 118).[146]

Scheme 118



1.3 Conclusion

The ever increasing growth in the past many years of asymmetric syntheses has been manifested by the biological importance of enantiomerically pure single compound entity factors and further it has been strongly guided by drug regulatory bodies because of its strict rules and regulation about single isomer. It is expected to expand in this manner. A contributing factor to this effect has been, and continues to be, the development of new, novel and efficient methods for accessing single isomer. While more activity has concentrated on chiral auxiliaries, organocatalysts, metal or nonmetal catalysts, the use of readily available, enantiomerically pure chiral synthons has demonstrated its utility as a basis for asymmetric synthesis. In particular, specific enantiomers of *R*- or *S*-amino acids have been used as useful building blocks for accessing diverse heterocycles. This application can only be expected to accelerate as increasingly popular methods are developed for retaining *R- or S*-center configuration intact with generation of another stereogenic center. Chiral Chromatographic methods are being used more and more and may become a requirement to determine of enantiomeric purity.

Not only the new synthetic methods but also new chiral catalysts especially have organocatalysts, special technique to separate chiral drugs been contributing too much to market new drugs to the remedy of numerous health problems. But the source of chirality in the form of starting materials to heterocyclic molecules are of all time importance in this special domain of chiral synthesis and in this respect, the key role of α-amino acids in this respect cannot be denied.

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1.5 References

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