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Stereoselective synthesis of γ-amino acids

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Abstract—γ-Amino acids have attracted considerable attention as biologically active compounds in the central nervous system (CNS) of mammals. Over the last few years, significant interest in the stereoselective synthesis and practical application of linear and cyclic chiral γ-amino acids in the synthesis and design of α,β- and β,γ-hybrid peptides with definite secondary structures and design of nanotubes has been reported, thus demonstrating the theoretical interest and the practical importance of γ-amino acids. An overview of synthetic approaches to linear and cyclic chiral γ-amino acids and derivatives is presented. Data on the practical applications of γ-amino acids are also discussed.

Contents

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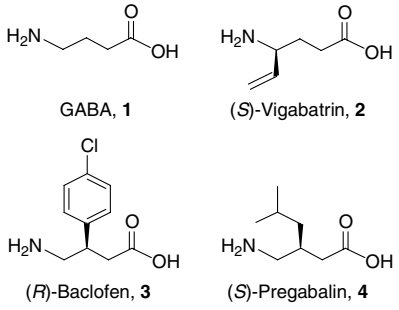
1. Introduction

γ-Aminobutyric acid (GABA) **1** is the major inhibitory neurotransmitter in the central nervous system (CNS) of mammals,[1] and exerts its physiological action through the interaction with three receptor subtypes, termed $GABA_A$, $GABA_B$, and $GABA_C$. Both $GABA_A$ and $GABA_C$ receptors are ligand-gated ion channels permeable to anions and convey the fast synaptic transmission, whereas $GABA_B$ is a G-protein coupled receptor, which modulates the synaptic transmission through intracellular effector systems.[2]

GABA deficiency is also associated with several important neurological disorders such as Huntington's and Parkinson's disease, epilepsy, and other psychiatric disorders, such as anxiety and pain.[3] However, the administration of GABA orally or intravenously is not an efficient therapy due to its low lipophilicity, and its very poor ability to cross the blood–brain barrier (BBB).[4] Consequently, the synthesis of more lipophilic GABA derivatives capable of crossing the blood–brain barrier, which would inhibit the GABA transaminase (GABA-T), the enzyme that degrades GABA,[5] has been the target of a great number of studies. For example, 4-amino-5-hexenoic acid (γ-vinyl GABA, Vigabatrin®) **2**, a synthetic analogue of GABA, is an important anticonvulsant drug marketed in racemic form as Sabril®. However, only the (*S*)-enantiomer is pharmacologically active[6] as selective enzyme-activated inhibitor of GABA-T in the mammalian brain with the net effect of increasing GABA levels.[7] On the other hand, 4-amino-3-(*p*-chlorophenyl)butyric acid (Baclofen or PCPGABA) **3** is also one of the most promising drugs in the treatment of the paroxysmal pain of trigeminal neuralgia[8] as well as spinal spasticity without influencing sedation.[9] Baclofen is commercialized in its racemic form as Lioresal® and Baclon®; however, literature observations suggested that the biological activity of **3** resides in the (*R*)-enantiomer.[10] Another GABAergic agonist recently commercialized is (*S*)-3-aminomethyl-5-methylhexanoic acid (Pregabalin) **4**, a potent anticonvulsivant related to the inhibitory neurotransmitter γ-aminobutyric acid,[11] but in this case the biological activity resides in the (*S*)-enantiomer.[12]



Over recent years, there has been increasing interest in the development of new achiral and chiral γ-amino acid derivatives. Typical representative agonists, partial agonists, and antagonist GABA derivatives with pharmacological and therapeutic activity that show an interaction with modulatory sites associated with GABA receptors are shown in Figure 1.

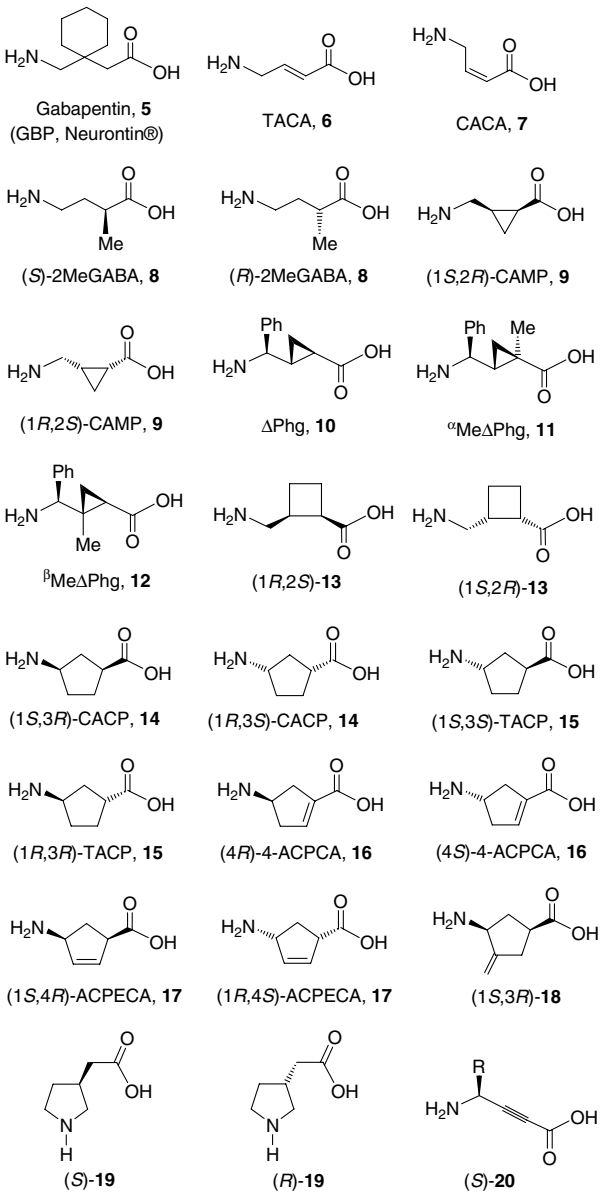
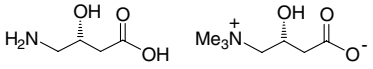


Figure 1. Structures of GABA derivatives that show agonist, partial agonist and antagonist effects at GABA receptors.

On the other hand, over the past few years, γ-amino acids have been a focus of attention due their potential application in the design and synthesis of α,γ- and β,γ-hybrid peptides (oligomers) that fold into definite secondary structures. These peptides being unusual foldamers and novel helical folds are an interesting field for synthetic chemists.[13] Additionally, it has recently been reported that lineal and cyclic γ-amino acids can be a considerable promise for the design of nanotubes, α,γ-peptides segments with novel structural and internal cavity properties, and these compounds called self-assembling peptide nanotubes (SPNs) have attracted attention recently, because of the probable ease with which they may be endowed with struc-

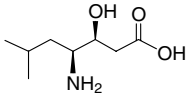
tural and functional properties of interest for applications in biology and materials science.[14]

Another important γ-amino acid is 4-amino-3-hydroxybutyric acid (GABOB) **21**, an unusual amino acid that has been recently identified as a key fragment of the microsclerodermins, a family of marine cyclic peptides possessing antitumor and antifungal activity.[15] It is also a well known drug substance that functions as an agonist of α-aminobutyric acid (GABA) **1** and is a compound of great pharmacological importance due to its biological function as a neuromodulator in the mammalian central nervous system due to its hypotensive and antiepileptic activity.[16] In this context, the (*R*)-GABOB **21** has been found to have a greater biological activity than the (*S*)-enantiomer.[17] GABOB has also been used as a synthetic precursor for some heterocyclic GABA-receptor agonists.[18] Moreover, the related (*R*)-carnitine **22**, readily available by methylation of **21** or by other methods, plays an important role in human energy metabolism via transport of the long chain fatty acids into the mitochondria.[19] In addition, it has been found that (*R*)-carnitine **22** has clinical applications as a hypolipidemic agent in hemodialysis patients as well as in the treatment of myocardial ischemia and seizure, whereas (*S*)-carnitine acts as a competitive inhibitor of carnitine acyltransferase causing depletion of (*R*)-carnitine.

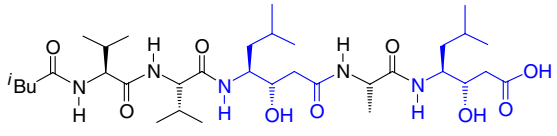


(*R*)-GABOB, **21** (*R*)-Carnitine, **22**

On the other hand, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (statine) **23** is an unusual β-hydroxy-γ-amino acid, and is an essential component of pepstatine **24**,[20] a natural hexapeptide antibiotic, which acts as an inhibitor of aspartic acid protease.[21] Aspartic protease plays a crucial role in the onset or proliferation of many diseases, including AIDS (HIV protease),[22] hypertension (renin),[23] malaria (plasmepsin), and Alzheimer's disease (β-secretase). In this context, it has been found that the β-hydroxy group of the statine is important for tight binding of pepstatine, and its stereochemistry has a large effect on protease inhibition, a *syn* diastereoisomeric relationship between the amine and hydroxy groups being required.[24]



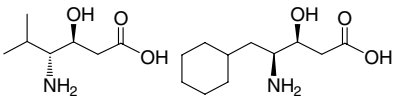
Statine, **23**



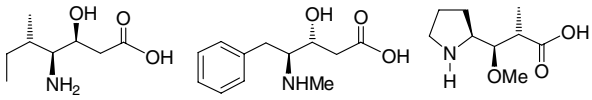
Pepstatine, **24**

Norstatine **25**, cyclohexylstatine **26**, isostatine **27**, (3*R*,4*S*)-3-hydroxy-4-methylamino-5-phenylpentanoic acid **28**, and dolaproine **29** have been also used in the synthesis of potentially therapeutic small peptides, including Tamandarin A **30**,[25] Hapalosin **31**,[26] and Dolastatine 10 **32**.[27]

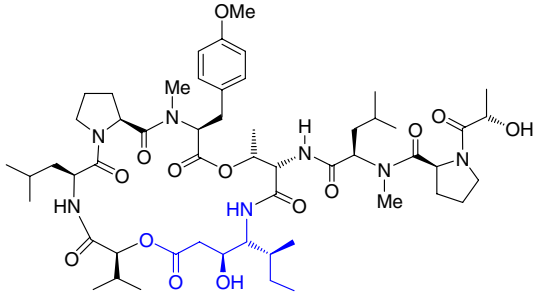
(*R*)-3-Amino-4-(trimethylammonio)butanoate [(*R*)-aminocarnitine] **33**[28] and (3*S*,4*S*)-3,4-diamino-6-methylheptanoic acid (3-aminodeoxystatine or aminostatine) **34**[29] are also very important derivatives. In fact, (*R*)-aminocarnitine **33** and its *N*-acyl derivatives have shown powerful inhibitory activity of fatty acid oxidation, hypoglycemic, antiketogenic[30] and antidiabetic activity.[31] On the other hand, aminostatine **34** has been incorporated in small peptides



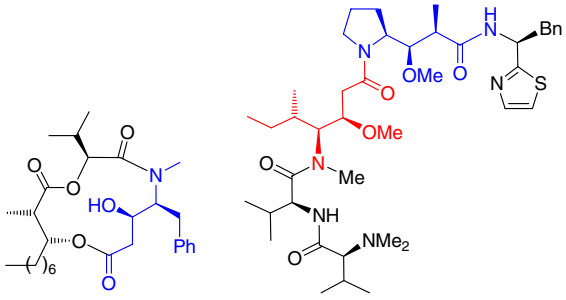
Norstatine, **25** Cyclohexylstatine, **26**



Isostatine, **27** **28** Dolaproline, **29**

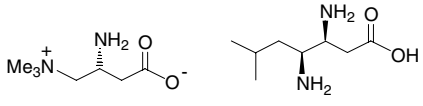


Tamandarin A, **30**



Hapalosin, **31** Dolastatine 10, **32**

and recently their human rennin inhibitory activity has been evaluated.[29e] Nevertheless, in spite of their significance these compounds have not been considered in this review, because we have adopted the criterion that the presence of an additional amino group in the α- or β-position of a γ-amino acid results in compounds better considered as α- or β-amino acid derivatives.



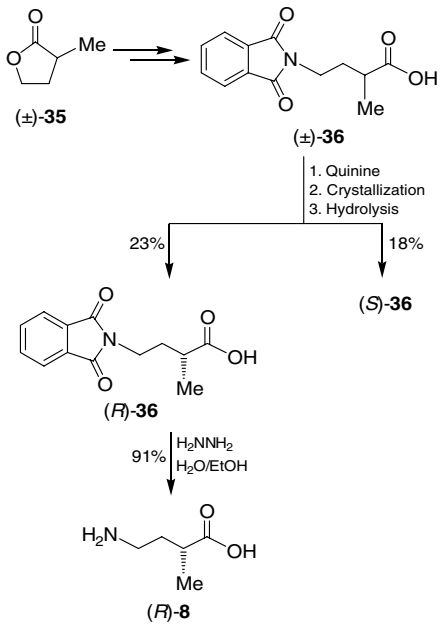
(*R*)-Aminocarnitine, **33** Aminostatine, **34**

The above information shows that the biological activity of γ-amino acids is largely determined by the absolute configuration of the stereogenic carbon atom, and over the recent years, a significant number of methods for the stereoselective synthesis and practical application of chiral γ-amino acids and derivatives have been reported, which clearly show the theoretical interest and practical importance of γ-amino acids. The present review covers the stereoselective synthesis of linear and cyclic γ-amino acids substituted in different positions,[32] and their biological and chemical importance.

2. Stereoselective synthesis of γ-amino acids

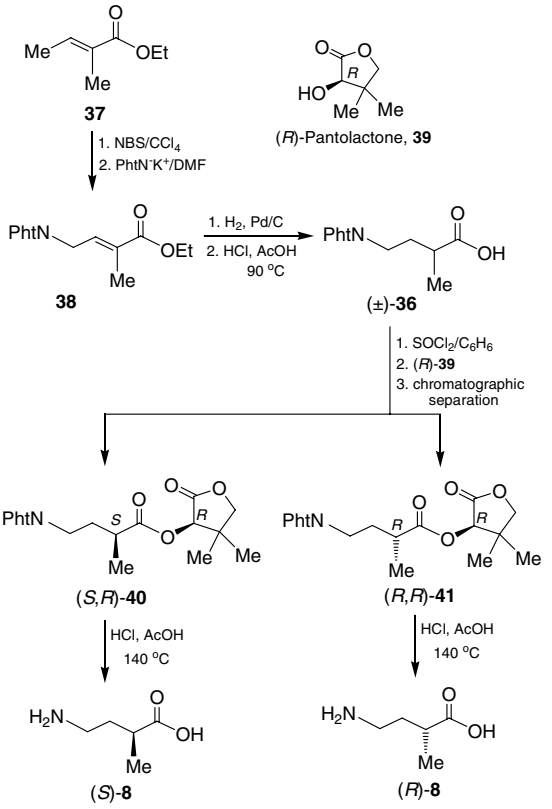
2.1. α-Substituted γ-amino acids

(*R*)-4-Amino-2-methylbutanoic acid [(*R*)-2MeGABA] **8**, an important GABA antagonist,[33] was obtained for the first time more than 40 years ago by resolution procedures. Thus, treatment of (±)-2-methyl-4-phthalimidobutyric acid **36**, readily obtained from 2-methylbutyrolactone **35** with quinine gave a mixture of diastereoisomeric salts, which by crystallization and subsequent hydrolysis afforded enantiomerically pure (*R*)-**36** and (*S*)-**36** in 23% and 18% yield, respectively. Finally, hydrazinolysis of (*R*)-**36** afforded the enantiomerically pure (*R*)-2MeGABA **8** in 91% yield (Scheme 1).[34]



Scheme 1.

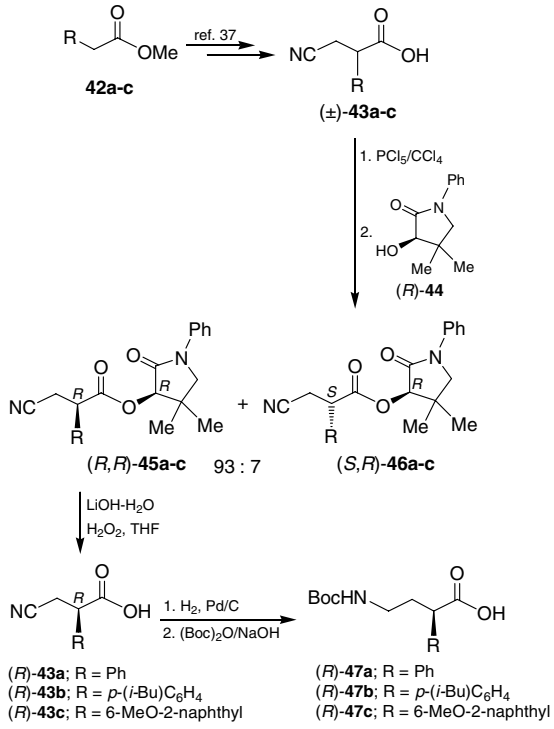
More recently, Duke et al.[35] reported the synthesis of enantiomerically pure (*R*)- and (*S*)-2MeGABA **8** in seven steps using tiglic acid ethyl ester as the starting material. In this context, treatment of tiglic acid ethyl ester **37** with *N*-bromosuccinimide, followed by coupling with potassium phthalimide, afforded ethyl 4-phthalimido-2-methylbut-2-enoate **38**. Catalytic hydrogenation of ester **38**, followed by hydrolysis, gave (±)-2-methyl-4-phthalimidobutanoic acid **36**. Condensation of carboxylic acid **36** with (*R*)-pantolactone **39** produced a mixture of diastereoisomeric pantolactone esters (*S*,*R*)-**40** and (*R*,*R*)-**41**. Hydrolysis of diastereoisomers (*S*,*R*)-**40** and (*R*,*R*)-**41** gave enantiomerically pure (*S*)- and (*R*)-2MeGABA **8**, respectively (Scheme 2).



Scheme 2.

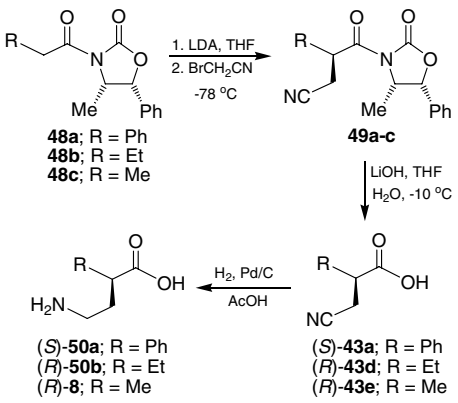
Camps et al.[36] have reported the preparation of (*R*)- and (*S*)-*N*-Boc-α-aryl-γ-amino acids **47a**–**c** involving, as the key step, the deracemization of (±)-3-cyano-2-arylpropionic acids **43a**–**c** readily available from methyl arylacetates **42a**–**c**, using (*R*)- or (*S*)-*N*-phenylpantolactam **44** as the resolution agent. Thus, treatment of (±)-3-cyano-2-arylpropionic acids **43a**–**c** with PCl_5 followed by the condensation with (*R*)-*N*-phenylpantolactam **44**[37] afforded a diastereoisomeric mixture of *N*-phenylpantolactam esters (α*R*,3′*R*)-**45a**–**c** and (α*S*,3′*R*)-**46a**–**c** in a 93:7 diastereoisomeric ratio. Basic hydrolysis of diastereoisomerically pure (α*R*,*R*)-pantolactam esters **45a**–**c** gave the carboxylic acids **43a**–**c**, which by catalytic reduction of the cyano group and subsequent treatment with di(*tert*-butyl)dicarbonate $(Boc)_2O$ produced the (*R*)-*N*-Boc-α-aryl-γ-amino acids **47a**–**c** in >99% ee (Scheme 3). The same reaction sequence was followed for the preparation of γ-amino acids (*S*)-**47a**–**c** using the (*S*)-*N*-phenylpantolactam.

Asymmetric synthesis is a key methodology in modern organic chemistry.[38] A great variety of strategies for the formation of stereoisomerically pure organic compounds have been developed. Stereocenters present in the starting material are used to direct the trajectory of an incoming reagent



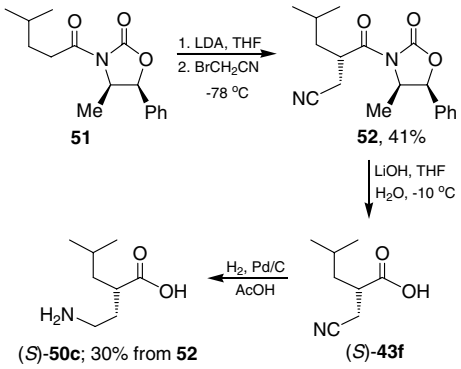
Scheme 3.

(substrate induction) or chiral reagents leading to stereochemical differentiation at the reactive center (reagent induction). In this context, enantiomerically pure acyloxazolidinones, Evan's oxazolidinones, have proven to be versatile intermediates for the synthesis of a wide variety of compounds of biological interest.[39] For example, the reaction of lithium or sodium enolates derived from (4*S*,5*R*)-3-acyl-4-methyl-5-phenyl-1,3-oxazolidin-2-ones **48a**–**c** with bromoacetonitrile at −78 °C afforded the cyanomethylated product **49a**–**c** with moderate chemical yield and diastereoselectivity. Selective hydrolysis of the oxazolidinone chiral auxiliary **49a**–**c** using lithium hydroxide in aqueous THF at −10 °C gave the corresponding cyano derivatives (*S*)-**43a** and (*R*)-**43d**–**e**, which on catalytic hydrogenation afforded the α-substituted γ-amino acids **50a**,**b** and (*R*)-**8** (Scheme 4).[40]



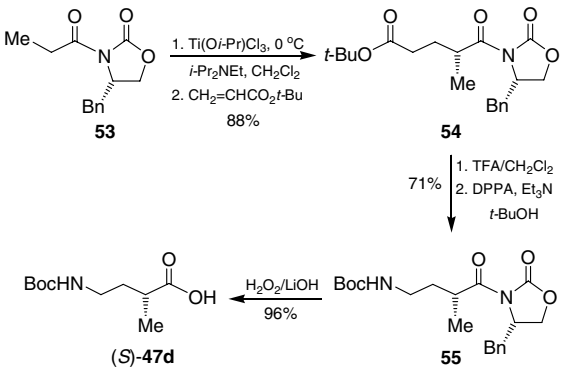
Scheme 4.

In a similar way, Wustrow et al.[41] have reported the stereoselective synthesis of (*S*)-2-(2-aminoethyl)-4-methylpentanoic acid **50c**, an analogue of pregabaline **4**, using the (4*R*,5*S*)-3-acyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one **51** as a starting material (Scheme 5).



Scheme 5.

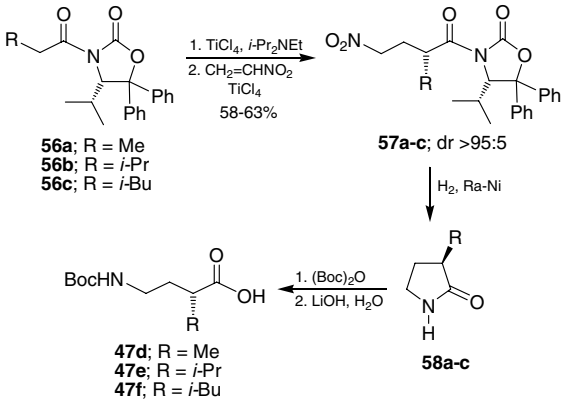
On the other hand, Michael addition of the titanium enolate derived from *N*-propionyloxazolidinone **53** to *tert*-butyl acrylate afforded ester **54** as a single diastereoisomer in 88% yield. Hydrolysis of *tert*-butyl ester in **54** with trifluoroacetic acid (TFA) followed by Curtius rearrangement of the resulting carboxylic acid with diphenylphosphoryl azide (DPPA), Et_3N and *tert*-butyl alcohol gave **55**, which upon hydrolysis with lithium hydroxide and hydrogen peroxide provided the (*S*)-*N*-Boc-2MeGABA **47d** in 96% yield (Scheme 6).[42]



Scheme 6.

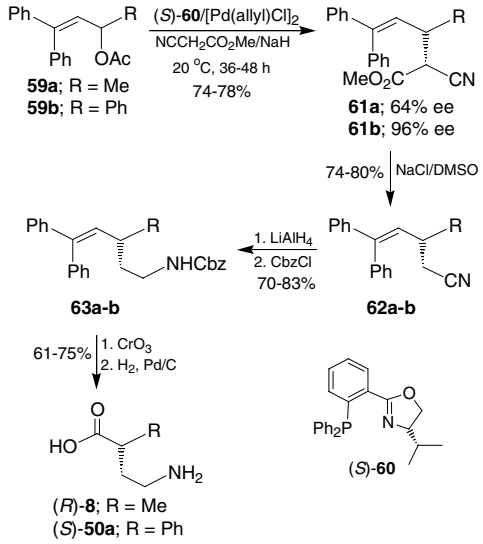
Similarly, Michael addition of the titanium enolate generated from *N*-acyloxazolidinones **56a**–**c** to nitroethene afforded the α-substituted γ-nitro derivatives **57a**–**c** in high diastereoselectivity. Catalytic hydrogenation of **57a**–**c** in the presence of Raney-nickel led directly to the γ-lactams **58a**–**c**. Treatment of the γ-lactams **58a**–**c** with di(*tert*-butyl)-dicarbonate $(Boc)_2O$ followed by basic hydrolysis gave the *N*-Boc-α-substituted γ-amino acids **47d**–**f** (Scheme 7).[43]

Highly enantioselective palladium-catalyzed allylic substitution reactions have been achieved by many research



Scheme 7.

groups.[44] Williams et al.[45] have employed this methodology as the asymmetry-producing key step in the synthesis of enantiomerically enriched (*R*)-2MeGABA **8** and (*S*)-2PhGABA **50a**. Thus, addition of methyl cyanoacetate to allylic acetates **59a**,**b** in the presence of (4*S*)-4,5-dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole **60** and $[Pd(allyl)Cl]_2$ afforded the cyanoester derivatives **61a**,**b** with moderate to good enantioselectivity. Decarboxylation of cyanoesters **61a**,**b** under Krapcho conditions[46] gave the corresponding nitriles **62a**,**b**. Reduction of the cyano group with $LiAlH_4$ followed by protection of the resulting amino group with benzylchloroformate (CbzCl) led to carbamates **63a**,**b**. Oxidative cleavage of the double bond and subsequent deprotection of the Cbz group under catalytic hydrogenation provided enantiomerically pure (*R*)-2MeGABA **8** and (*S*)-2PhGABA **50a** (Scheme 8).

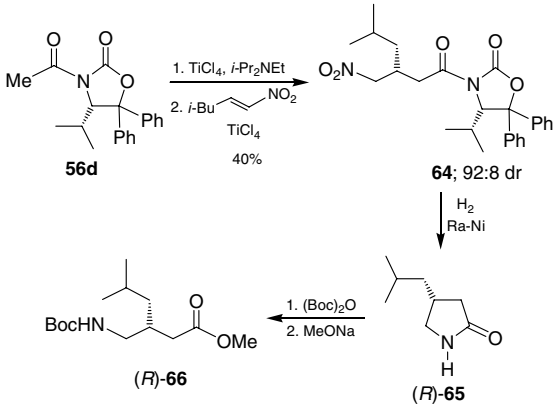


Scheme 8.

2.2. β-Alkylsubstituted γ-amino acids

(*S*)-3-Aminomethyl-5-methylhexanoic acid (Pregabalin) **4** or CI-1008, as it has been named by Parke–Davies, is possibly the most important β-substituted γ-amino acid, since it is more active than gabapentin in preclinical models of epilepsy,[47] although early studies showed that only the (*S*)-enantiomer has the desired pharmacological activity. Therefore, a short and efficient synthesis of enantiomerically pure (*S*)-pregabalin is of great interest. In this context, in 1997 Hoekstra et al.[12] published a mini review, which included several manufacturing processes for the preparation of (*S*)-pregabalin **4**, and we describe herein an update over stereoselective synthesis of (*S*)-pregabalin and derivatives from 1997 to 2006.

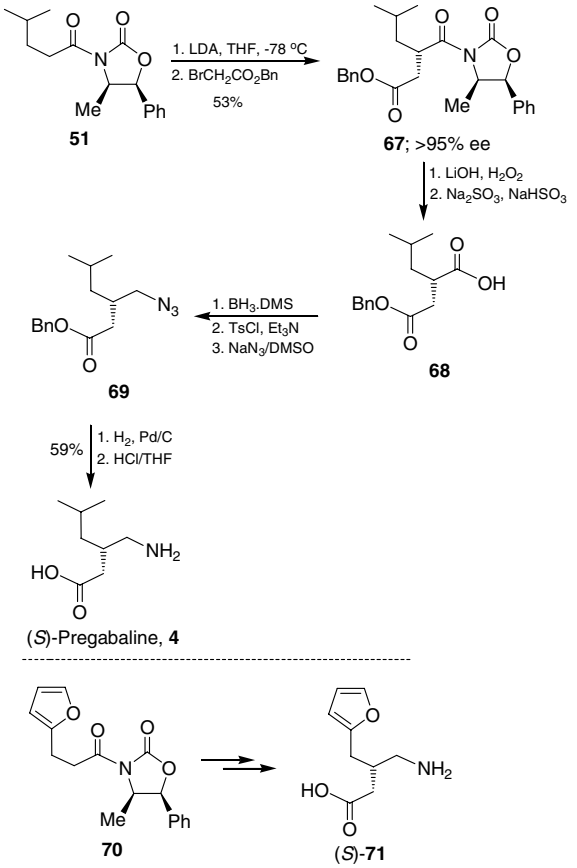
In order to obtain the (*R*)-*N*-Boc-pregabalin methyl ester **66**, Brenner and Seebach[43] carried out the Michael addition of the titanium enolate generated from *N*-acetyloxazolidinone **56d**, to the appropriate nitroalkene, obtaining the β-substituted γ-nitro derivative **64** in high diastereoselectivity and with a moderate chemical yield. Catalytic hydrogenation of **64** led directly to the γ-lactam (*R*)-**65**. Protection of the amino group in **65** with di(*tert*-butyl)dicarbonate and subsequent methanolysis with MeONa provided the (*R*)-*N*-Boc-pregabalin methyl ester **66** (Scheme 9).



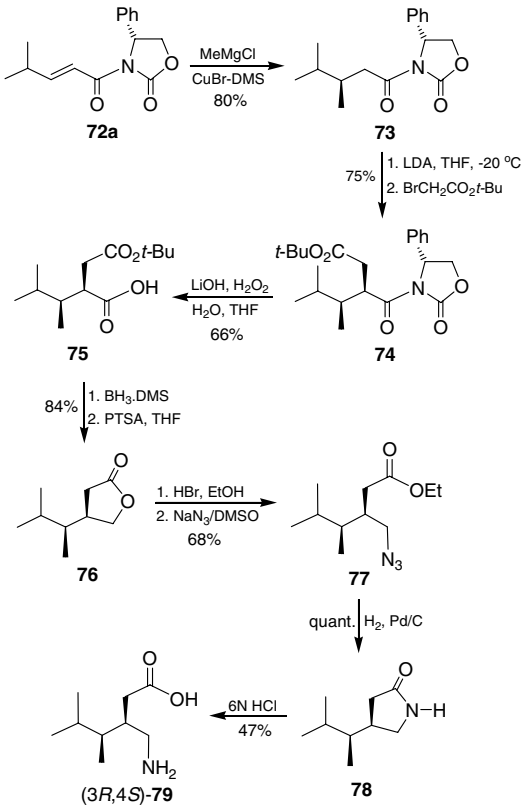
Scheme 9.

On the other hand, Yuen et al.[48] have reported the stereoselective synthesis of enantiomerically pure (*R*)- and (*S*)-pregabaline **4**. In this context, the reaction of the lithium enolate derived from *N*-acyl-(4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone **51** with benzyl bromoacetate afforded the alkylated product **67** in 53% yield and >95% ee. Cleavage of the chiral auxiliary in **67** with LiOH in the presence of H_2O_2 followed by treatment with sodium sulfite and sodium bisulfite gave the corresponding carboxylic acid **68**. Reduction of the carboxylic acid with borane dimethyl sulfide complex, followed by tosylation and subsequent reaction with sodium azide gave the derivative **69** in 64% overall yield. Catalytic hydrogenation of the azide function followed by hydrolysis of the benzyl ester provided (*S*)-pregabaline **4** (Scheme 10). In a similar way, the *N*-acyloxazolidinone **70** was transformed into (*S*)-γ-amino acid β-(2-furylmethyl)-substituted **71**, an analogue of pregabalin **4**. (*R*)-γ-Amino acid **71** can be obtained using the (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinones **51** and **70**, respectively.

On the other hand, Wustrow et al.[41] have reported the stereoselective synthesis of (3*R*,4*S*)-3-aminomethyl-4,5-di-



Scheme 10.

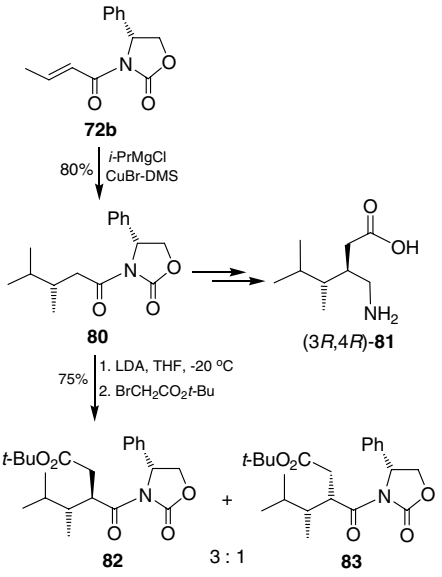


Scheme 11.

methylhexanoic acid **79**, which is a substituted analogue of pregabalin **4**. In this context, Michael addition of MeMgCl in the presence of CuBr to α,β-unsaturated imide **72a**, readily available, furnished **73** as a single diastereoisomer in 80%. The reaction of the lithium enolate derived from **73** with *tert*-butyl bromoacetate gave the alkylated product **74** again as a single diastereoisomer. Cleavage of the oxazolidinone with LiOH in the presence of H_2O_2 gave the corresponding carboxylic acid **75** in 66% yield. Reduction of carboxylic acid with borane dimethyl sulfide complex, followed by treatment with *p*-toluenesulfonic acid, gave directly the γ-lactone **76** in 84% yield. The ring opening of **76** with an anhydrous ethanolic solution of HBr led to the corresponding bromo ester, which by displacement with sodium azide gave derivative **77** in 68% overall yield. Catalytic hydrogenation of the azide function followed by hydrolysis of γ-lactam **78** led to the (3*R*,4*S*)-γ-amino acid **79** (Scheme 11).

In a similar way, (3*R*,4*R*)-3-aminomethyl-4,5-dimethylhexanoic acid **81** could be obtained from *N*-acyloxazolidinone **80**, readily available from α,β-unsaturated imide **72**.[49] However, alkylation of the lithium enolate derived from **80** with *tert*-butyl bromoacetate afforded a 3:1 mixture of inseparable alkylated products **82** and **83** (Scheme 12). The low diastereoselectivity was explained by 1,3-allylic strain effects on the enolate.[50]

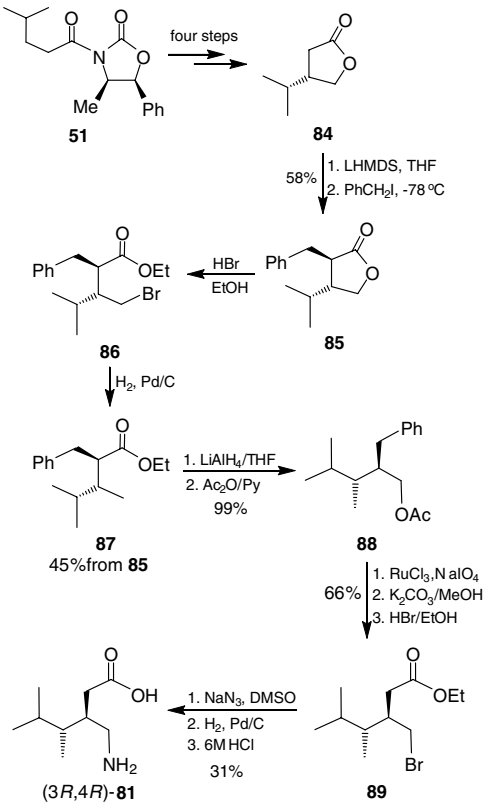
An alternative strategy for obtaining (3*R*,4*R*)-**81** has been reported by using the chiral γ-lactone **84** readily available



Scheme 12.

in four steps from *N*-acyloxazolidinone **51**. Thus, alkylation of the lithium enolate generated from deprotonation of chiral γ-lactone **84** with lithium bis(trimethylsilyl)amide (LHMDS) with benzyl iodide afforded the corresponding benzylated compound **85** in high *trans*-diastereoselectivity and moderate yield, which on lactone ring opening with HBr/anhydrous EtOH gave bromoester **86**. Catalytic

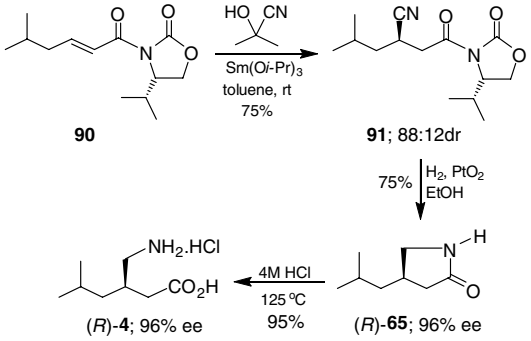
hydrogenation of the bromomethyl group in **86** gave ester **87**. Reduction of ester **87** with $LiAlH_4$, followed by treatment with acetic anhydride, led to the acetylated product **88**. Oxidative cleavage of the phenyl ring and subsequent hydrolysis and treatment with HBr/EtOH gave the *trans*-disposed bromoester **89**. Displacement of the bromide with sodium azide followed by catalytic reduction of the azide function and subsequent hydrolysis afforded the pregabalin analogue (3*R*,4*R*)-**81** (Scheme 13).



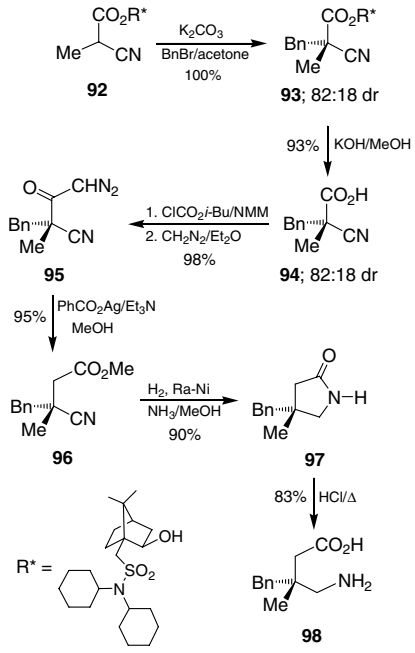
Scheme 13.

Recently Armstrong et al.[51] have reported the synthesis of enantiomerically pure (*R*)-pregabalin **4** via conjugate addition of cyanide to chiral α,β-unsaturated oxazolidinone **90**. In this context, conjugate addition of commercial acetone cyanohydrin to α,β-unsaturated oxazolidinone **90** in the presence of $Sm(Oi\text{-}Pr)_3$ afforded the hydrocyanated product **91** in 75% yield and 88:12 dr. Catalytic hydrogenation of diastereoisomerically pure **91** using platinum oxide gave the corresponding γ-lactam (*R*)-**65** in 75% yield and 96% ee, whose acidic hydrolysis produced the (*R*)-pregabalin **4** as a hydrochloride in 95% yield and 96% ee (Scheme 14).

More recently, the first asymmetric synthesis of β,β-disubstituted γ-amino acid **98** has been reported. In this context, the treatment of 2-cyanopropanoate **92** with benzyl bromide in the presence of K_2CO_3 afforded benzylated product **93** in quantitative yield and 82:18 dr. Hydrolysis of diastereoisomerically pure cyanoacetate derivative **93** gave the corresponding carboxylic acid **94** in 93% yield, which was converted into diazoketone **95** in excellent yield. Wolff rearrangement of **95** in the presence of silver benzoate in methanol produced ester **96**. Catalytic hydrogenation of the cyano group in **96** provided γ-lactam **97**, which by acidic hydrolysis led to β,β-disubstituted γ-amino acid **98** (Scheme 15).[52]



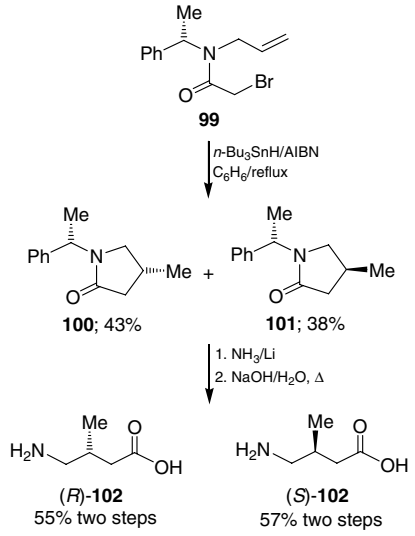
Scheme 14.



Scheme 15.

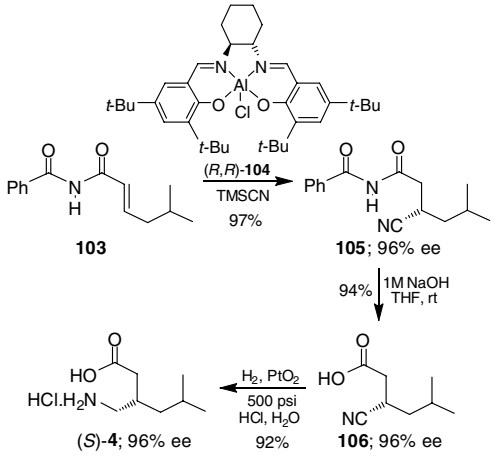
On the other hand, Quintero et al.[53] have reported the synthesis of (*R*)- and (*S*)-3MeGABA **102** via 5-*exo*-*trig* radical cyclization reaction of free radical precursor **99**, readily available in two steps from (*S*)-α-methylbenzylamine. Thus, 5-*exo* radical cyclization of **99** with *n*-Bu_3SnH in the presence of catalytic amounts of 2,2′-azobisisobutyronitrile (AIBN) afforded a mixture of pyrrolidinones **100** and **101** in 43% and 38% yield, respectively. Hydrogenolysis and hydrolysis of **100** and **101** after separation gave (*R*)- and (*S*)-3MeGABA **102**, respectively (Scheme 16).

Catalytic methods for the synthesis of enantiomerically pure compounds are of great importance for the preparation of biologically active substances.[54] For example, Sammins and Jacobsen[55] have described a highly enantioselective synthesis of pregabalin **4**, via catalytic conjugate



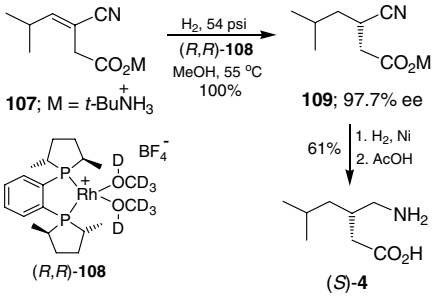
Scheme 16.

addition of cyanide to α,β-unsaturated imide **103**. In this context, the addition of TMSCN to imide **103** in the presence of (salen)Al^{III} catalysts (*R*,*R*)-**104** generated the cyano derivative **105** in excellent yield and enantioselectivity. Basic hydrolysis of imide group in **105** gave carboxylic acid **106**, which by hydrogenation in the presence of HCl afforded the (*S*)-pregabaline **4** as a hydrochloride salt (Scheme 17).



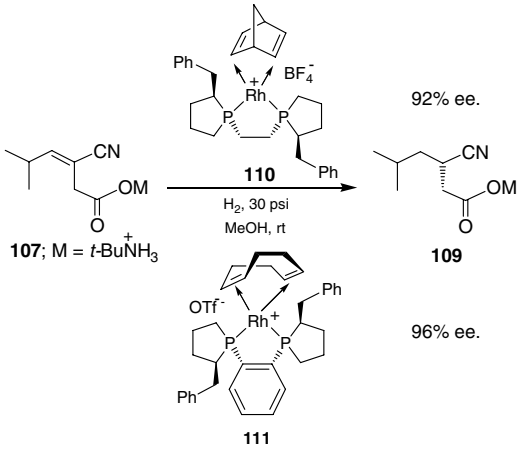
Scheme 17.

On the other hand, Ramsden et al.[56] reported the enantioselective synthesis of (*S*)-pregabalin **4** using the asymmetric hydrogenation of 3-cyano-5-methylhex-3-enoic acid *tert*-butylammonium salt **107** as a key step. Thus, the asymmetric catalytic hydrogenation of prochiral precursor **107**, in the presence of (*R*,*R*)-(Me-DuPHOS)Rh(COD)BF$_4$ **108** as a catalyst, gave the corresponding cyano derivative **109** in quantitative yield and 97.7% ee. Catalytic hydrogenation of the cyano function in **109** followed by treatment with acetic acid provided (*S*)-pregabalin **4** in 61% yield and 99.8% ee (Scheme 18). This process has been scaled up to multi-kilogram quantities without significant difficulties.



Scheme 18.

In a similar way, the asymmetric hydrogenation of **107** using 1,2-bis(1*R*,2*S*)-2-benzylphospholanoethane rhodium (I) tetra-fluoroborate **110**[57] as a catalyst afforded the cyano derivative **109** in 92% ee, whereas when using 1,2-bis-(1*S*,2*R*)-2-benzylphospholanobenzene rhodium (I) triflate **111**[58] as the catalyst, it gave **109** in 96% ee (Scheme 19).

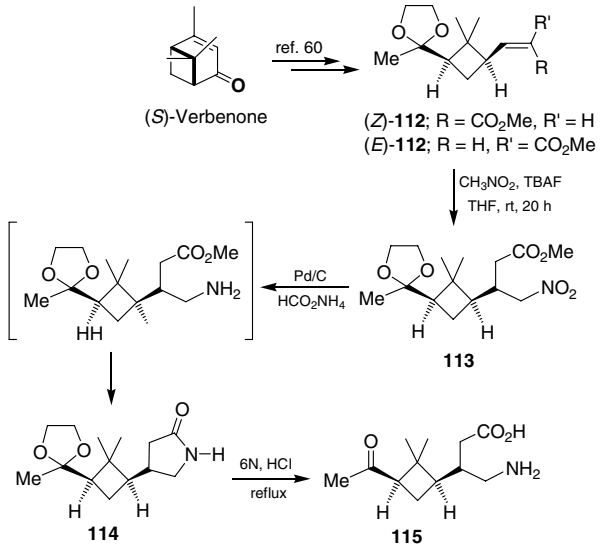


Scheme 19.

Enantiomerically pure β-cyclobutyl γ-amino acid **115** from (*S*)-verbenone was obtained by Ortuño et al.[59] Thus, the addition of nitromethane to (*Z*)- and (*E*)-isomeric conjugated esters **112**, which are readily available from (*S*)-verbenone,[60] in the presence of tetra-*n*-butylammonium fluoride (TBAF), produced the nitroester derivative **113** as only one diastereoisomer. It is noteworthy that the geometry of the double bound did not influence the π-facial diastereoselection of the nucleophilic addition, since the same product was obtained from the corresponding (*Z*)- or (*E*)-isomer. Catalytic hydrogenation of the nitro group in **113** with ammonium formate in the presence of Pd/C led to γ-lactam **114**, which by acidic hydrolysis afforded γ-amino acid **115** (Scheme 20).

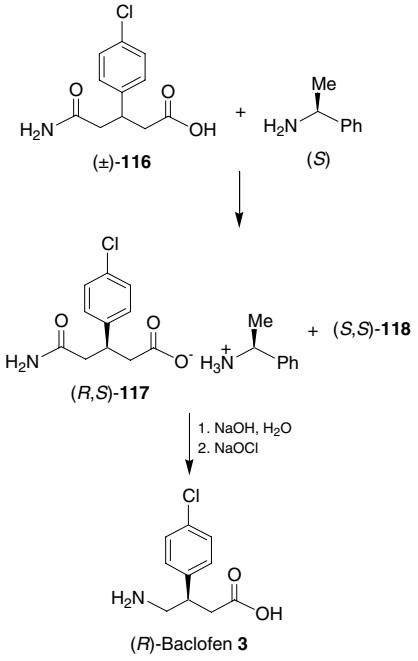
2.3. β-Arylsubstituted γ-amino acids (Baclofen analogues)

Despite the available alternative techniques, optical resolution via diastereoisomeric salt formation remains one of the most widely used methods for preparing pure enantiomers.[61] For example, treatment of (±)-3-(*p*-chlorophenyl)glutaramic acid **116** (GAM) with (*S*)-α-methyl-



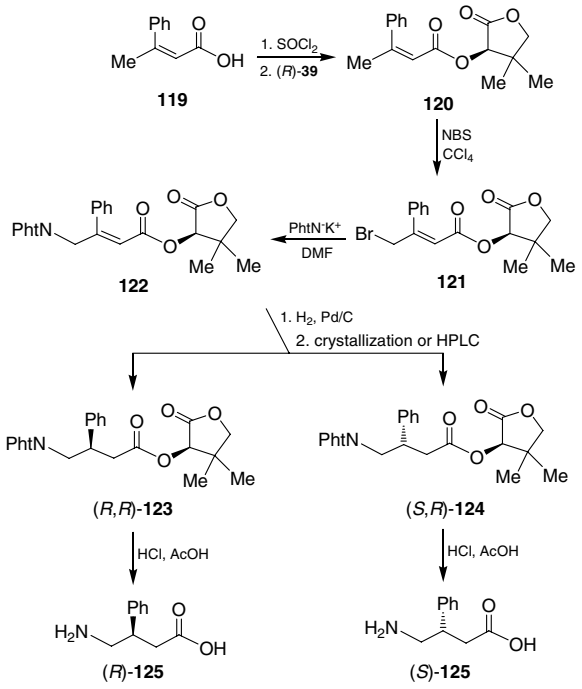
Scheme 20.

benzylamine [(*S*)-α-MBA] gave the diastereoisomeric salts (*R*,*S*)-**117** and (*S*,*S*)-**118**. Hydrolysis of (*R*,*S*)-**117** after separation followed by Hoffmann degradation produced (*R*)-baclofen **3** (Scheme 21).[62]



Scheme 21.

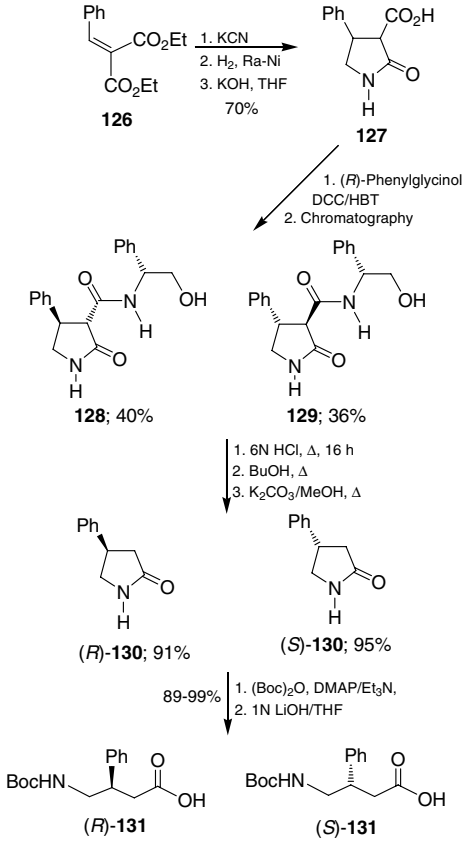
4-Amino-3-phenylbutyric acid **125** (β-PhGABA) is used clinically for different purposes, and can be obtained by resolution using (*R*)-pantolactone **39**. Thus, the reaction of α,β-unsaturated carboxylic acid **119**, readily available from acetophenone with $SOCl_2$ and (*R*)-pantolactone **39** provided ester **120**, which was transformed into monobrominated product **121** using *N*-bromosuccinimide (NBS). The reaction of **121** with potassium phthalimide ($PhtN^-K^+$) gave **122**, which by catalytic hydrogenation gave a mixture of diastereoisomeric esters (*R*,*R*)-**123** and (*S*,*R*)-**124**, which were separated by crystallization or HPLC. Finally, hydrolysis of both protecting groups in (*R*,*R*)-**123** and (*S*,*R*)-**124** with HCl afforded the enantiomerically pure (*R*)- and (*S*)-β-PhGABA **125** (Scheme 22).[63]



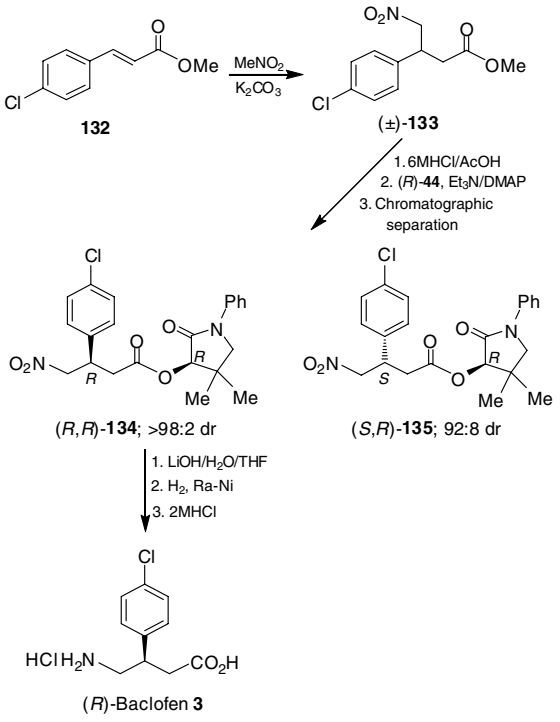
Scheme 22.

On the other hand, (*R*)- and (*S*)-*N*-Boc-4-amino-3-phenylbutyric acids **131** have also been obtained by resolution of 4-phenyl-2-pyrrolidinone derivative **127**.[64] In this context, the treatment of **127**, readily obtained from commercially available diethyl benzylidenemalonate **126** with (*R*)-phenylglycinol gave a mixture of diastereoisomeric amides **128** and **129** in 40% and 36% yield, respectively, after separation by chromatography. One-pot hydrolysis and decarboxylation of **128** and **129** provided enantiomerically pure (*R*)- and (*S*)-**130** in 91% and 95%, respectively. Finally, protection of pyrrolidinones **130** with di(*tert*-butyl)-dicarbonate followed by hydrolysis with lithium hydroxide provided enantiomerically pure (*R*)- and (*S*)-*N*-Boc-γ-amino-3-phenylbutyric acids **131** (Scheme 23).

Recently, enantiomerically pure (*R*)- and (*S*)-baclofen **3** have been obtained by resolution using (*R*)- or (*S*)-*N*-phenylpantolactam **44** as a chiral resolving reagent.[65] In this context, the addition of nitromethane to methyl *p*-chlorocinnamate **132** afforded the nitro derivative (±)-**133**. Saponification of (±)-**133** and subsequent esterification with (*R*)-*N*-phenylpantolactam **44** gave in good yield a 50:50 diastereoisomeric mixture of the corresponding pantolactam esters (*R*,*R*)-**134** and (*S*,*R*)-**135**. Carefully conducted column chromatography allowed the isolation of (*R*,*R*)-**134** with (>98:2 dr) and (*S*,*R*)-**135** with 92:8 dr, respectively. Hydrolysis of (*R*,*R*)-**134** with LiOH followed



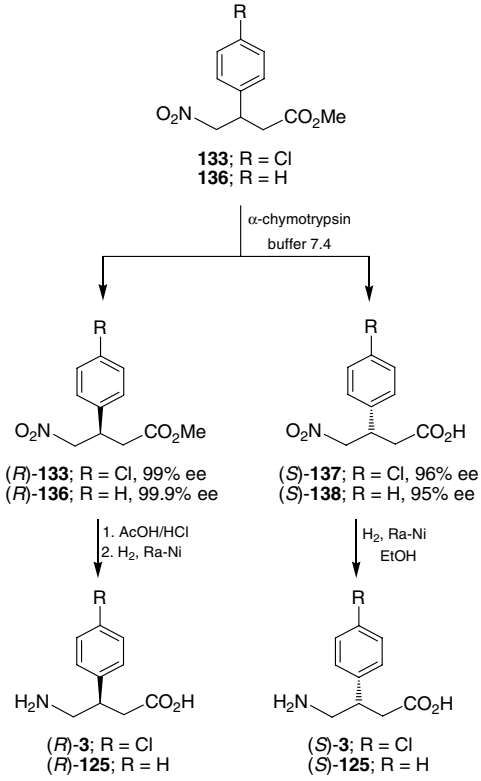
Scheme 23.



Scheme 24.

by reduction of the nitro group and subsequent treatment with hydrochloric acid afforded the enantiomerically pure (*R*)-baclofen **3**, as hydrochloride salt (Scheme 24). The same reaction sequence was used for the preparation of (*S*)-baclofen **3**, using (*S*)-*N*-phenylpantolactam **44**.

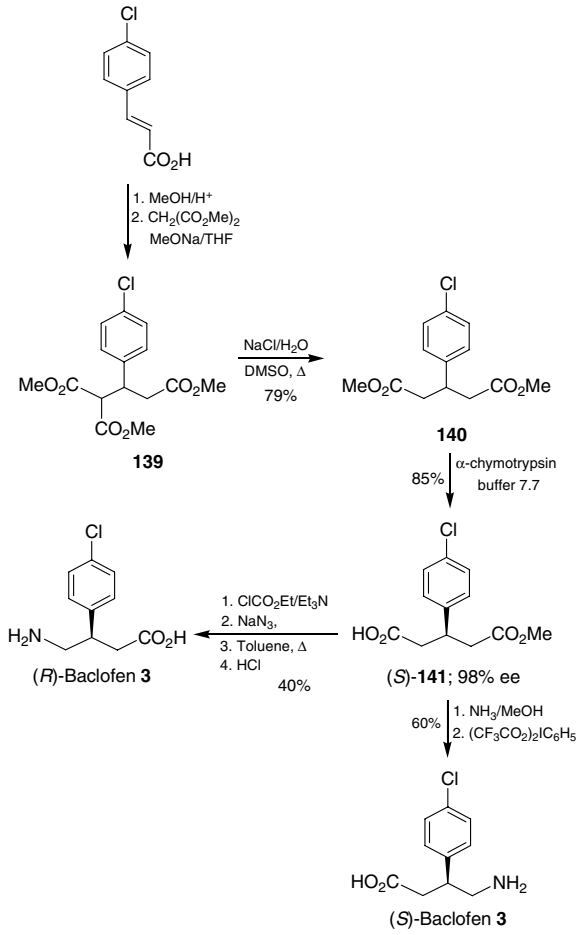
More recently, Felluga et al.[66] have reported the preparation of both enantiomers of baclofen **3** and β-PhGABA **125** via an enzymatic process. Thus, the hydrolysis of racemic nitroester derivative (±)-**133** using α-chymotrypsin in a buffered solution at pH 7.4 afforded (*R*)-methyl ester **133** and (*S*)-carboxylic acid **137** in 99% and 96% ee, respectively. Whereas the hydrolysis of (±)-**136** under the same conditions provided (*R*)-methyl ester **136** and (*S*)-carboxylic acid **138** in 99.9% and 95% ee, respectively. Hydrolysis of methyl esters (*R*)-**133** and (*R*)-**136**, followed by catalytic hydrogenation of the nitro group, led to (*R*)-baclofen **3** and (*R*)-β-PhGABA **125**, respectively. On the other hand, reduction of the nitro group in (*S*)-**137** and (*S*)-**138** afforded (*S*)-baclofen **3** and (*S*)-β-PhGABA **125**, respectively (Scheme 25).



Scheme 25.

Chênevert and Desjardins[67] have also reported the preparation of both enantiomers of baclofen, where the key step was the enzymatic desymmetrization of methyl 3-(*p*-chlorophenyl)glutarate **140**. In this context, esterification of *p*-chlorocinnamic acid with methanol followed by the base-catalyzed Michael addition of dimethyl malonate afforded triester **139**. Decarboxylation of **139** under Krapcho conditions gave the corresponding glutarate **140**. Desymmetrization of glutarate **140** using α-chymotrypsin in aqueous dimethyl sulfoxide (DMSO) produced the chiral derivative (*S*)-**141** in 85% yield and ⩾98% ee. In a similar

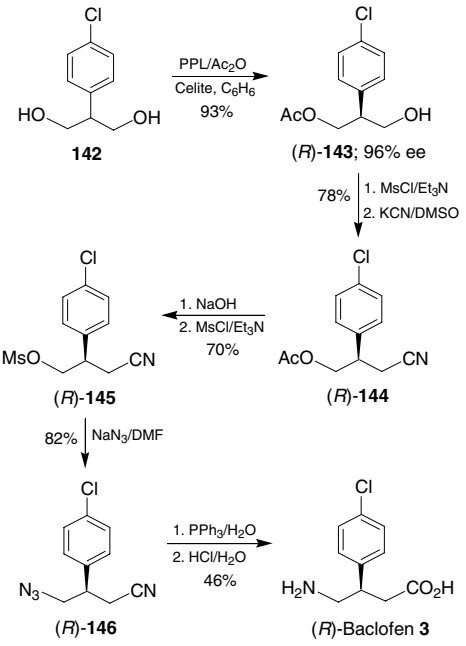
way, desymmetrization of **140** with pig liver esterase (PLE) gave (*R*)-**141** in only 80% ee. Curtius rearrangement of (*S*)-**141** followed by hydrolysis gave (*R*)-baclofen **3** in 40% yield. On the other hand, treatment of (*S*)-**141** with ammonia in methanol followed by a Hoffmann rearrangement using [bis(trifluoroacetoxy)iodo]benzene [$(CF_3CO_2)_2IC_6H_5$] gave (*S*)-baclofen **3** in 60% yield (Scheme 26).



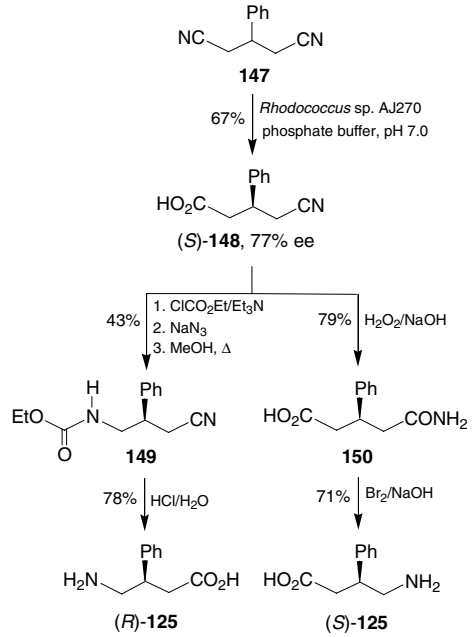
Scheme 26.

In a second approach, enzymatic desymmetrization of 2-(*p*-chlorophenyl)-1,3-propanodiol **142** with porcine pancreatic lipase (PPL) in the presence of acetic anhydride afforded acetyl derivative (*R*)-**143** in >96% ee, which by mesylation and subsequent treatment with potassium cyanide gave cyano derivative **144**. Hydrolysis of the acetyl function in **144**, followed by mesylation, produced the corresponding mesylate **145**. Treatment of **145** with sodium azide produced **146**, which upon reduction of the azido group with triphenylphosphine and subsequent hydrolysis of the cyano functionality led to (*R*)-baclofen **3** in 46% yield (Scheme 27).[67]

On the other hand, enzymatic desymmetrization of 3-phenylglutaronitrile **147** catalyzed by *Rhodococcus* sp. AJ270 cells afforded the corresponding (*S*)-3-phenyl-4-cyanobutanoic acid **148**. Curtius rearrangement of (*S*)-**148** gave **149**, which by acidic hydrolysis produced (*R*)-β-PhGABA **125**. Whereas basic hydrolysis of cyano group in (*S*)-**148** provided the corresponding amide **150**, which by Hoffmann rearrangement led to (*S*)-β-PhGABA **125** (Scheme 28).[68]



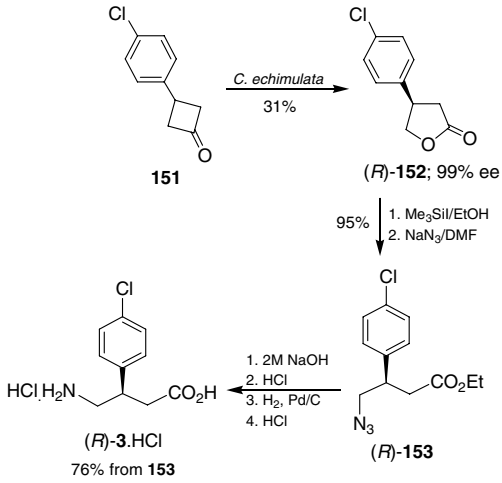
Scheme 27.



Scheme 28.

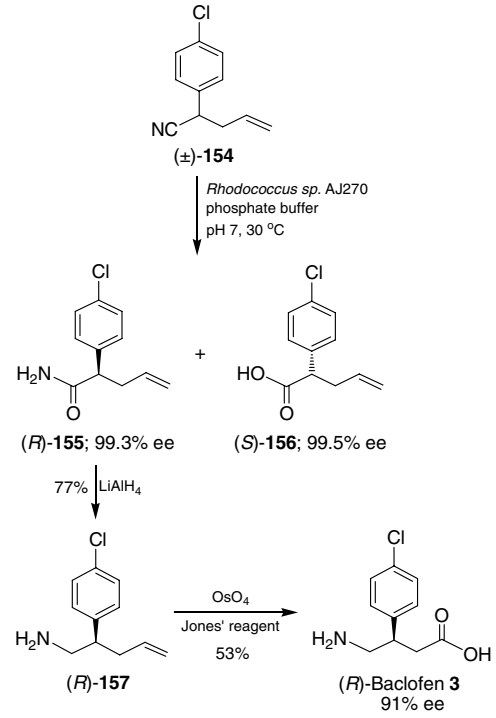
(*R*)-Baclofen hydrochloride **3** was prepared by a seven step enantioselective synthesis involving a microbiological mediated Baeyer–Villiger oxidation as a key step. Thus, enzymatic oxidation of 3-(*p*-chlorophenyl)cyclobutanone **151** obtained from commercially available *p*-chlorostirene with *Cunninghamella echimulata* NRLL 3655 afforded the corresponding (*R*)-*p*-chlorophenyl lactone **152** in excellent enantioselectivity and 31% yield. Regioselective lactone opening with iodotrimethylsilane, followed by treatment

with sodium azide, gave the corresponding azido ester (*R*)-**153** in 95% yield. Hydrolysis of (*R*)-**153** followed by catalytic hydrogenation and subsequent treatment with HCl led to (*R*)-baclofen **3** as a hydrochloride salt (Scheme 29).[69]



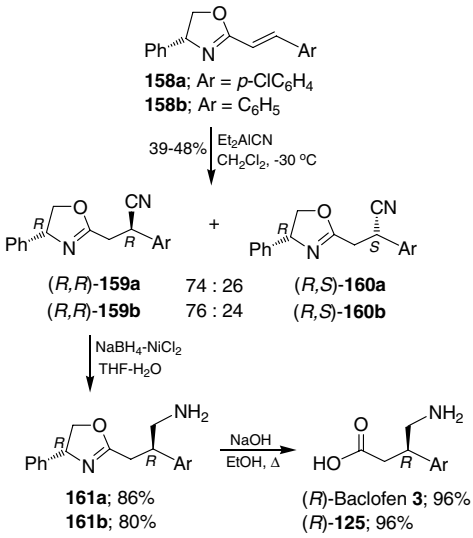
Scheme 29.

On the other hand, enzymatic hydrolysis of (±)-2-(*p*-chlorophenyl)-4-pentenitrile **154** catalyzed by *Rhodococcus* sp. AJ270 cells under very mild conditions afforded the enantiomerically pure (*R*)-2-(*p*-chlorophenyl)-4-pentenamide **155** in 44% yield and 99.3% ee, and (*S*)-2-(*p*-chlorophenyl)-4-pentenoic acid **156** in 50% yield and 99.5% ee. Reduction of the amide function in (*R*)-**155** with $LiAlH_4$ gave the corresponding amine (*R*)-**157**, which by oxidation with the Jones' reagent produced (*R*)-baclofen **3** (Scheme 30).[70]



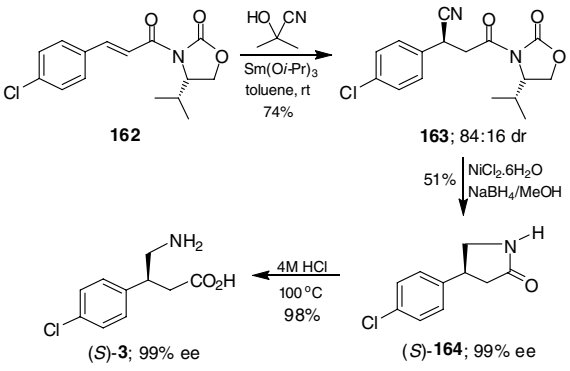
Scheme 30.

Michael addition of Et_2AlCN to oxazolines **158a** and **158b** derived from (*R*)-phenylglycinol gave a diastereoisomeric mixture of cyanooxazolines derivatives (*R*,*R*)-**159a** and **159b** and (*R*,*S*)-**160a** and **160b** in 48% and 39% yield, respectively, in a 3:1 ratio. Reduction of diastereoisomerically pure (*R*,*R*)-**159a** and **159b** with $NaBH_4$ in the presence of $NiCl_2$ afforded the corresponding amines (*R*,*R*)-**161a** and **161b** in good yield. Basic hydrolysis of the oxazoline function in (*R*,*R*)-**161a** and **161b** gave (*R*)-baclofen **3** and (*R*)-β-PhGABA **125** in excellent yield (Scheme 31).[71]



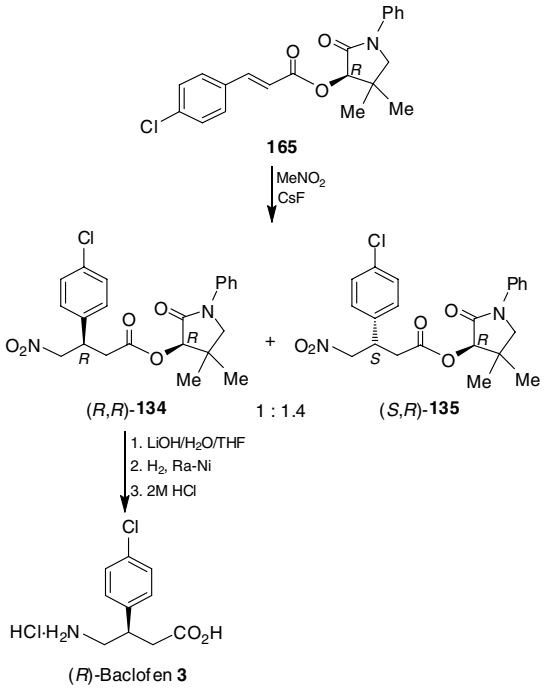
Scheme 31.

More recently, Armstrong et al.[51] have reported the synthesis of enantiomerically pure (*S*)-baclofen **3** via the conjugate addition of cyanide to chiral α,β-unsaturated oxazolidinone **162**. In this context, conjugate addition of commercially available acetone cyanohydrin to α,β-unsaturated oxazolidinone **162** in the presence of $Sm(Oi\text{-}Pr)_3$ afforded the hydrocyanated product **163** in 74% yield and 84:16 dr. Catalytic reduction of diastereoisomerically pure **163** using $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ gave the corresponding γ-lactam **164** in 51% yield and 99% ee, which by acidic hydrolysis produced (*S*)-baclofen **3** in 98% yield and 99% ee (Scheme 32).



Scheme 32.

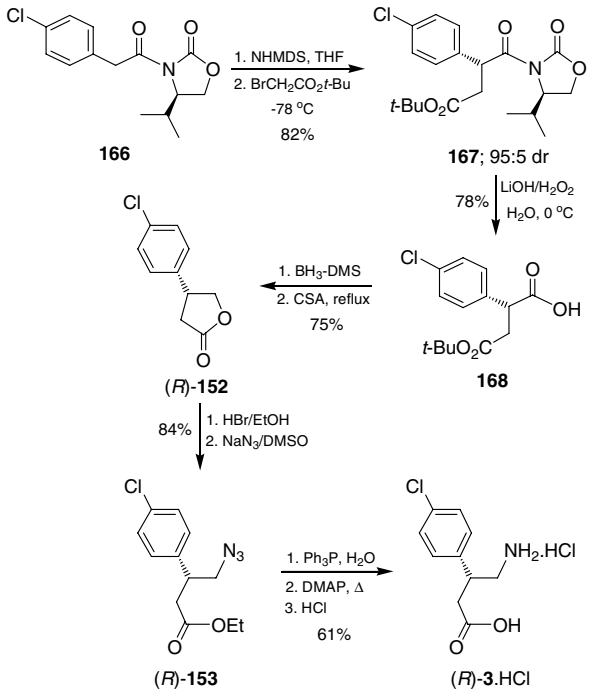
On the other hand, the Michael addition of nitromethane in the presence of CsF to ester (*R*)-**165** obtained by esterification of *p*-chlorocinnamic acid and (*R*)-*N*-phenylpantolactam **44** gave a diastereoisomeric mixture of esters (*R*,*R*)-**134** and (*S*,*R*)-**135** in a ratio 1:1.4. Ester (*R*,*R*)-**134** in 96:4 dr obtained after column chromatographic purification was transformed into (*R*)-baclofen **3** under identical conditions described in Scheme 24 (Scheme 33).[65]



Scheme 33.

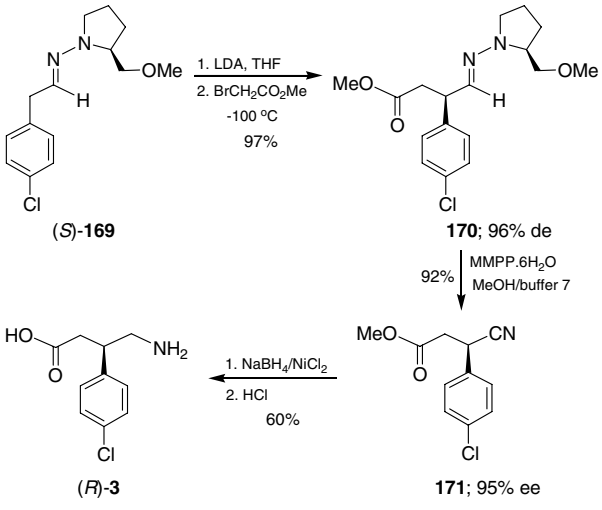
Diastereoselective synthesis of (*R*)-baclofen **3** has been reported via the alkylation of *N*-acyloxazolidinone **166**. Thus, the reaction of sodium enolate of **166** with *tert*-butyl bromoacetate afforded the alkylated product **167** in 82% yield and diastereoselectivity ⩾95:5. Regioselective hydrolysis of the oxazolidinone chiral auxiliary in **167** with H_2O_2/LiOH led to the carboxylic acid derivative **168**. Selective reduction of carboxylic acid in **168** with BH_3–DMS complex, followed by treatment with camphorsulfonic acid (CSA), afforded the corresponding γ-lactone **152** with less than 5% of racemization at the benzylic carbon. The reaction of γ-lactone **152** with HBr/EtOH gave the corresponding bromoester, which by treatment with sodium azide gave azidoester **153**. Reduction of the azide function in **153** under Staudinger[72] procedure, followed by addition of 4-dimethylaminopyridine (DMPA) and subsequent hydrolysis, provided (*R*)-baclofen **3** (Scheme 34).[73]

Recently, Enders and Niemeier[74] reported the asymmetric synthesis of (*R*)- and (*S*)-baclofen **3** employing the SAMP- and RAMP-hydrazone methodology. In this context, the reaction of lithium enolate generated from deprotonation of SAMP-hydrazone **169** with lithium diisopropylamide (LDA) with methyl bromoacetate afforded the alkylated product **170** in 97% yield and ⩾96% de. Oxidative removal



Scheme 34.

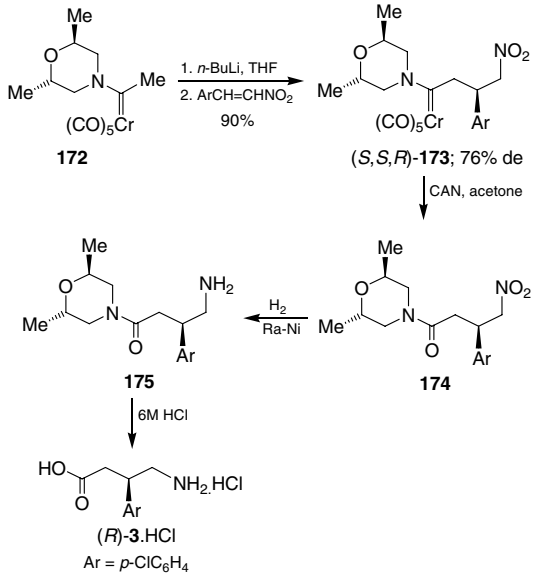
of the auxiliary in **170** with magnesium monoperoxyphthalate (MMPP) led to cyano derivative **171** in 92% yield and 95% ee, which by reduction with $NaBH_4$ in the presence of $NiCl_2$ and subsequent acidic hydrolysis with HCl gave (*R*)-baclofen **3** in 60% yield (Scheme 35). Enantiomerically pure (*S*)-baclofen **3** was obtained using RAMP-hydrazone (*R*)-**162** as the starting material.



Scheme 35.

Metallocarbenes have been used in the stereoselective synthesis of several organic molecules.[75] For example, the Michael addition of the lithium enolate of enantiomerically pure amino carbene complex generated from **172** and *n*-BuLi, to *trans*-*p*-chloronitrostyrene afforded β-substituted

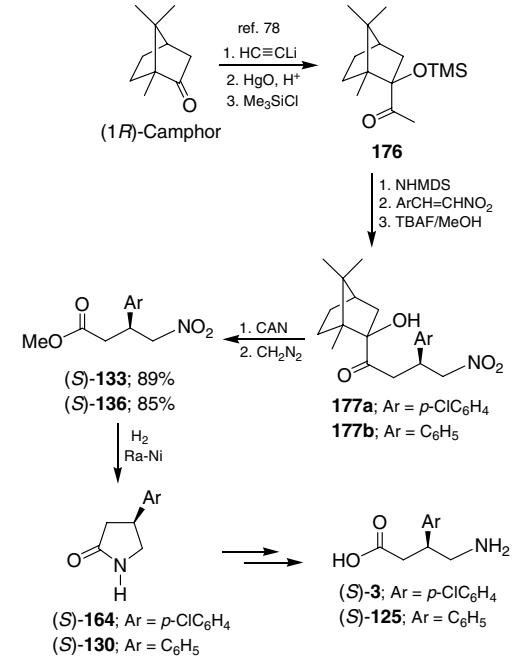
γ-nitro derivative **173** as a mixture of two diastereoisomers in 76% de. The appropriate separation gave diastereoisomerically pure (*S*,*S*,*R*)-**173**, which was transformed into the corresponding nitroamide **174** using cerium ammonium nitrate (CAN) as the oxidizing agent. Catalytic hydrogenation of **174** led to the aminoamide derivative **175**, which by hydrolysis with HCl provided (*R*)-baclofen **3** as hydrochloride salt (Scheme 36).[76]



Scheme 36.

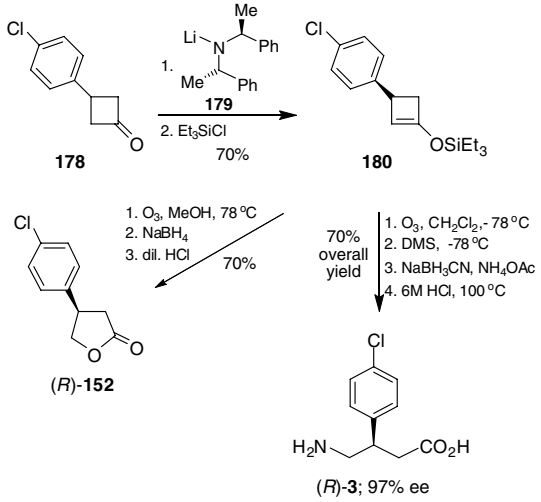
On the other hand, Palomo et al.[77] have reported the synthesis of β-aryl substituted γ-lactams (*S*)-**164** and (*S*)-**130**, which are key precursors of (*S*)-baclofen **3** and (*S*)-β-PhGABA **125**, respectively. In this context, the addition of sodium enolate generated from deprotonation of methyl ketone **176** readily available from (1*R*)-camphor[78] and NHMDS, to nitrostyrene derivatives afforded nitro compounds **177a**,**b**. Treatment of **177a**,**b** with excess of cerium ammonium nitrate (CAN) followed by esterification with diazomethane gave nitromethyl esters (*S*)-**133** and (*S*)-**136**, respectively. Reduction of nitro group in (*S*)-**133** and (*S*)-**136** directly led to γ-lactams (*S*)-**164** and (*S*)-**130**, respectively, which are precursors of (*S*)-baclofen **3** and (*S*)-β-PhGABA **125**, respectively (Scheme 37).

Coelho et al.[79] in 1999 reported an efficient synthesis of (*R*)-baclofen **3** based upon the enantioselective deprotonation of prochiral 3-(*p*-chlorophenyl)cyclobutanone **178**. Thus, the enantioselective deprotonation of ketone **178** with lithium (*S*,*S*)-bisdimethylbenzylamide **179**, followed by the addition of triethylsilyl chloride, gave silylenol ether **180**, although the enantiomeric excess could not be determined at this stage. Ozonolysis of silylenol ether **180** and subsequent reduction of the ozonide with sodium borohydride produced (*R*)-*p*-chlorophenyl lactone **152** in excellent enantioselectivity (⩾97%). On the other hand, treatment of the ozonide derived from **180** with DMS followed by reduction with sodium cyanoborohydride in the presence of ammonium acetate and subsequent acidic



Scheme 37.

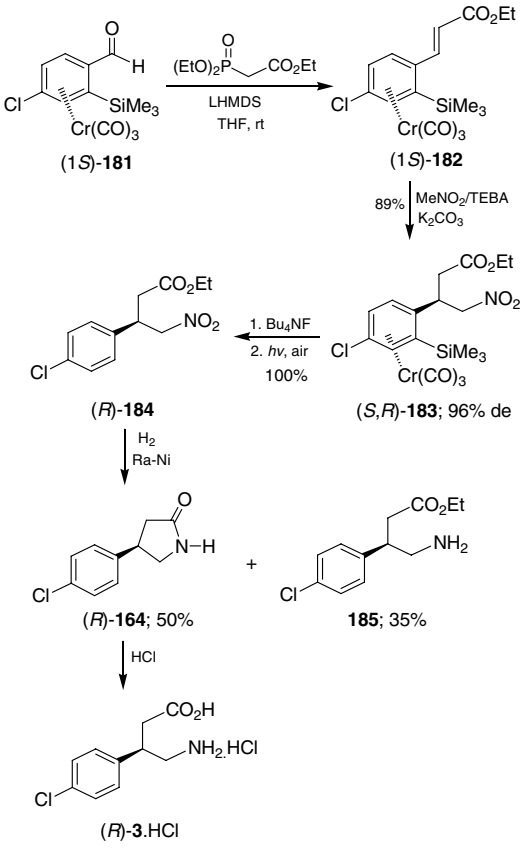
hydrolysis led to (*R*)-baclofen **3** in 70% yield and 97% ee (Scheme 38).



Scheme 38.

Chiral tricarbonyl chromium complexes have emerged as valuable substrates for the stereoselective synthesis of enantiomerically pure organic and organometallic compounds.[80] In this context, the Michael addition of nitromethane under phase transfer catalysts to enantiomerically pure (1*S*)-tricarbonyl(ethyl-*p*-chloro-2-trimethylsilylcinnamate) chromium(0) **182**, obtained from the chiral aldehyde (1*S*)-**181** by means of Horner–Wadsworth–Emmons reaction, afforded the nitroester derivative (*S*,*R*)-**183** in high diastereoselectivity. Treatment of

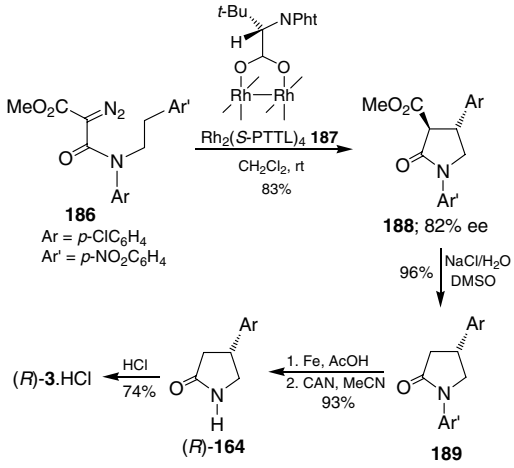
(*S*,*R*)-**183** with tetra-*n*-butylammonium fluoride (TBAF) followed by exposure to air and sunlight led to nitroester (*R*)-**184** in 100% yield. Catalytic hydrogenation of (*R*)-**184** using Raney-nickel as catalyst produced γ-lactam (*R*)-**164** in 50% yield, and ethyl 3-(*p*-chlorophenyl)-4-aminobutanoate (*R*)-**185** in 35% yield, which was converted into (*R*)-**164** by means of refluxing in xylene. Finally, hydrolysis of (*R*)-**164** with hydrochloric acid provided the enantiomerically pure (*R*)-baclofen **3** as a hydrochloride salt (Scheme 39).[81]



Scheme 39.

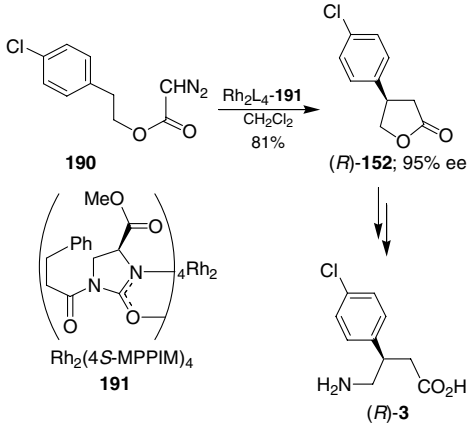
Reaction of the carbenoids derived from α-diazo carbonyl compounds using rhodium(II) catalysts has been in the ascendancy and attracted the attention of many chemists for diverse synthetic applications.[82] For example, the cyclization reaction of *N*-*p*-chlorophenylethyl-*N*-*p*-nitrophenyl-α-methoxycarbonyl-α-diazoacetamide **186** in the presence of chiral Rh_2(*S*-PTTL)$_4$ **187** as catalyst afforded *trans*-3-methoxycarbonyl-4-(*p*-chlorophenyl)-2-pyrrolidinone **188** in 83% yield and 82% ee. Decarboxylation of **188** under Krapcho conditions gave γ-lactam (*R*)-**189**, which by cleavage of *p*-nitrophenyl group under oxidative conditions led to (*R*)-γ-lactam **164**. Hydrolysis of **164** with hydrochloric acid gave (*R*)-baclofen **3** as the hydrochloride salt (Scheme 40).[83] This protocol has also been used for the preparation of several chiral γ-lactams.

Similarly,[84] treatment of 2-(*p*-chlorophenyl)ethyl diazoacetate **190** in the presence of a catalytic amount of chiral



Scheme 40.

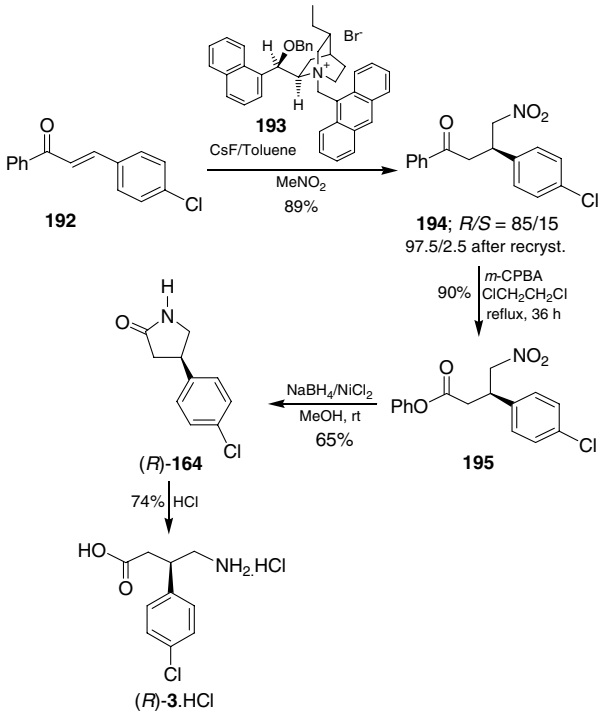
dirhodium(II) carboxamidate Rh_2(4*S*-MPPIM)$_4$ **191** as catalyst afforded (*R*)-γ-lactam **152** in 81% yield and 95% ee (Scheme 41).[85] (*R*)-γ-Lactam **152** was transformed into (*R*)-baclofen **3** under an identical protocol as described in Scheme 34.



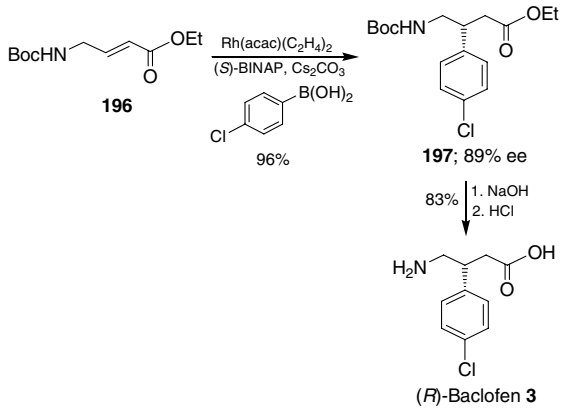
Scheme 41.

Enantioselective Michael addition of nitromethane to *p*-chlorobenzylideneacetophenone **192** in the presence of cinchoninium salt **193** as a chiral catalyst gave the nitro derivative compound **194** with an *R*/*S* selectivity of 85/15 and 89% yield. Recrystallization of this product furnished (*R*)-**194** in 95% ee. Baeyer–Villiger oxidation of (*R*)-**194** afforded γ-nitro ester **195** in 90%, which by reduction with $NaBH_4$ in the presence of $NiCl_2$ gave (*R*)-γ-lactam **164** in 65% yield. Hydrolysis of (*R*)-γ-lactam **164** with HCl led to (*R*)-baclofen **3** as hydrochloride salt (Scheme 42).[86]

On the other hand, the 1,4-addition of *p*-chlorophenylboronic acid to ethyl (2*E*)-4-[(*tert*-butoxycarbonyl)amino]-but-2-enoate **196** in the presence of a catalytic amount of [Rh(acac)(C_2H_4)$_2$], (*S*)-BINAP, and Cs_2CO_3 afforded γ-amino ester **197** in 96% and 89% ee. Hydrolysis of **197** gave (*R*)-baclofen **3** (Scheme 43).[87]



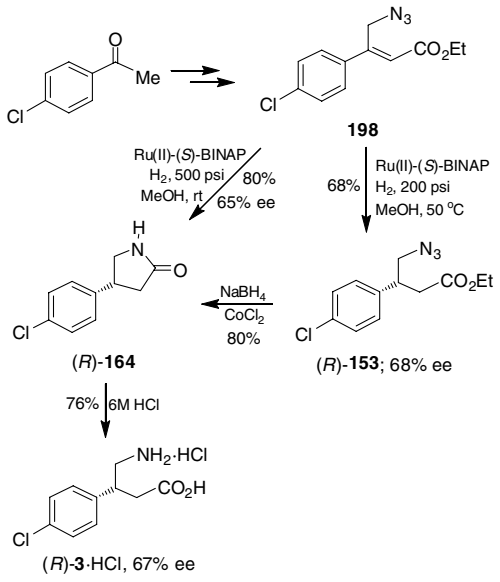
Scheme 42.



Scheme 43.

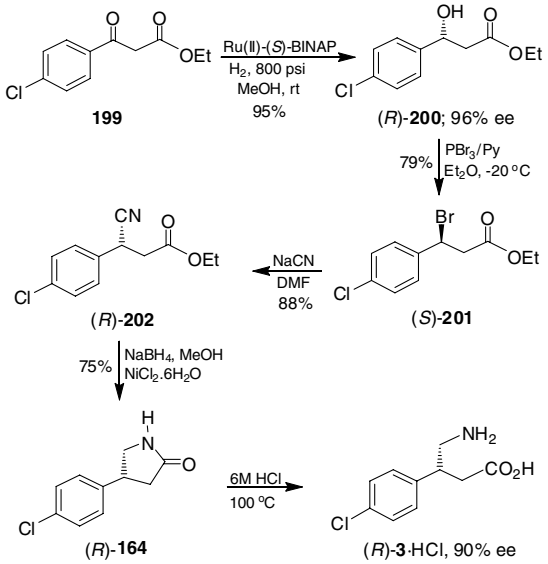
Recently, Sudalai et al.[88] have used the Ru(II)-(*S*)-BINAP as a catalyst in the asymmetric hydrogenation of ethyl 4-azido-3-(*p*-chlorophenyl)-2-butenoate **198** readily obtained from *p*-chloroacetophenone. Thus, the hydrogenation of **198** in the presence of Ru(II)-(*S*)-BINAP in MeOH at 200 psi of H_2 at 50 °C produced the azide derivative **153** in 68% yield and 68% ee. On the other hand, when the hydrogenation of **198** was performed at 500 psi of H_2 at 25 °C, it afforded γ-lactam **164** in 80% yield and 65% ee. Reduction of the azido group in **153** with $NaBH_4$ in the presence of $CoCl_2$ gave γ-lactam (*R*)-**164**, which by hydrolysis with HCl led to (*R*)-baclofen **3** as the hydrochloride salt in 76% yield and 67% ee (Scheme 44).

On the other hand, the asymmetric reduction of the keto function of β-ketoester **199** readily available from *p*-chloro-



Scheme 44.

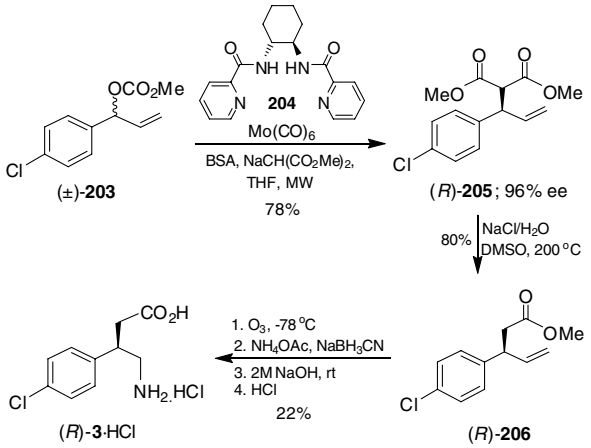
benzaldehyde, using Ru(II)-(*S*)-BINAP complex as catalyst and H_2 at 800 psi at 30 °C gave (*R*)-β-hydroxy ester **200** in 95% yield and 96% ee, which by treatment with PBr_3 produced bromo derivative (*S*)-**201** in 79% yield with complete inversion of the configuration. Nucleophilic displacement of bromide in (*S*)-**201** with NaCN afforded cyano ester (*R*)-**202** in 88% yield. Chemoselective reduction of the cyano group with $NaBH_4$ in the presence of $NiCl_2$ led to (*R*)-γ-lactam **164** in 75% yield and 92% ee. Acidic hydrolysis of (*R*)-**164** provided (*R*)-baclofen **3** as the hydrochloride salt in 26% and 90% ee (Scheme 45).[88]



Scheme 45.

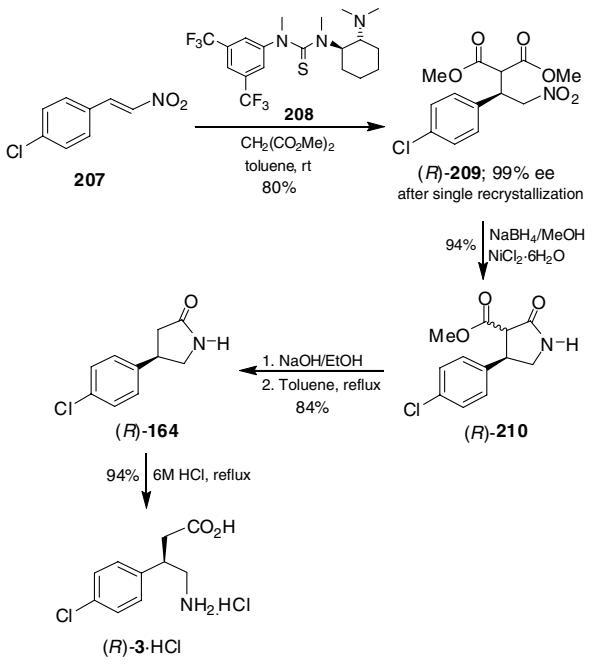
Bispyridylamide **204** derived from (1*R*,2*R*)-1,2-diaminocyclohexane has served as an efficient ligand for molybdenum-catalyzed asymmetric allylic alkylation.[89]

For example, Moberg et al.[90] have employed this methodology as a key step in the enantioselective synthesis of (*R*)-baclofen **3**. Thus, an allylation reaction of sodium dimethyl malonate with the allylic carbonate **203** in the presence of bispyridylamide **204**–$Mo(CO)_6$ complex and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) afforded the alkylated product **205** in 78% yield and 96% ee. Decarboxylation of the geminal diester **205** under Krapcho conditions (NaCl, DMSO/H_2O) afforded the homoallyl ester **206**. Ozonolysis of **206** followed by reduction with $NaBH_3CN$ in the presence of NH_4OAc and subsequent hydrolysis led to (*R*)-baclofen **3** as a hydrochloride salt in 22% overall yield from **206** (Scheme 46).



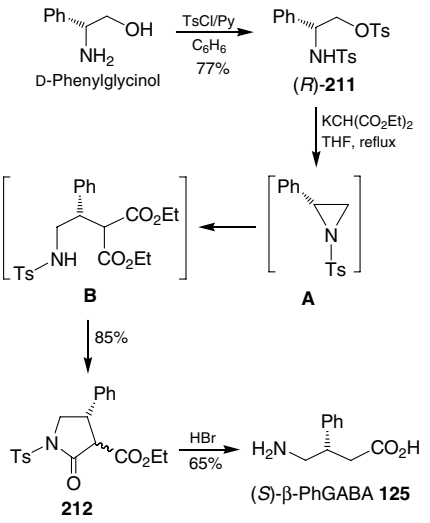
Scheme 46.

On the other hand, the Michael addition of diethyl malonate to *trans*-*p*-chloronitrostyrene **207** in the presence of enantiomerically pure thiourea **208** afforded nitro-diester **209** in 80% and 94% ee, which after single recrystallization led to (*R*)-**209** in 99% ee. Reduction of (*R*)-**209** with $NaBH_4$ in the presence of $NiCl_2$ produced derivative **210**, which after hydrolysis and decarboxylation gave (*R*)-γ-lactam **164** in 84%. Finally, acidic hydrolysis of (*R*)-**164** gave (*R*)-baclofen **3** as hydrochloride salt in 94% yield (Scheme 47).[91]



Scheme 47.

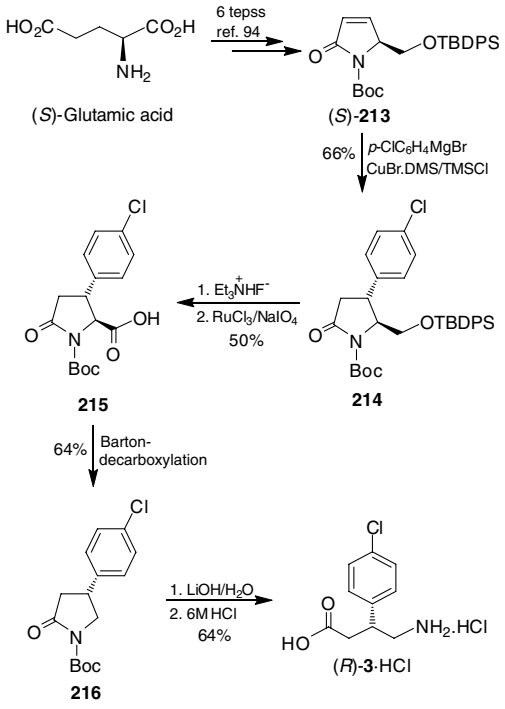
The ready availability and low cost of enantiomerically pure α-amino acids recommend them as a suitable chiral pool for obtaining starting materials for targeted transformations.[92] A two-carbon homologation of α-amino acids has been used as a good strategy for obtaining interesting compounds. For example, treatment of D-phenylglycinol readily available from D-phenylglycine with tosyl chloride in pyridine afforded the corresponding ditosylate derivative **211** in 77% yield, which by reaction with potassium diethyl malonate gave γ-lactam **212** in 85% yield, via intermediates **A** and **B**. Acidic hydrolysis of **212** with hydrobromic acid led to (*S*)-β-PhGABA **125** in 65% yield (Scheme 48).[93]



Scheme 48.

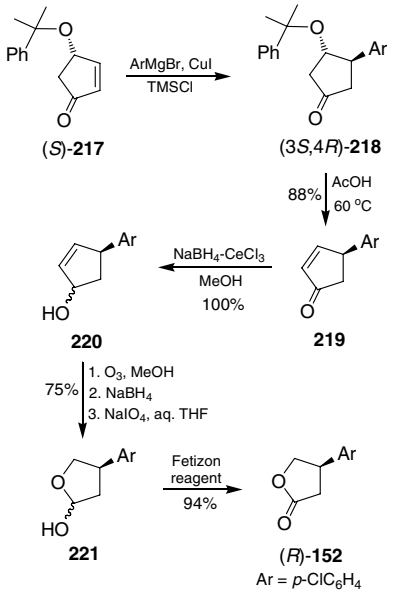
(5*S*)-1-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsiloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one derivative **213** obtained from (*S*)-glutamic acid[94] has been used as a precursor in the synthesis of (*R*)-baclofen **3**. In this context, Michael addition of the Grignard reagent *p*-ClC_6H_4MgBr to (*S*)-**213** in the presence of $CuBr_2$·DMS complex and chlorotrimethylsilane afforded **214** as a single diastereoisomer in 66% yield. Selective cleavage of the TBDPS protective group with triethylammonium fluoride followed by oxidation with $NaIO_4$ in the presence of $RuCl_3$ produced the carboxylic acid derivative **215**, which by Barton decarboxylation provided (*R*)-γ-lactam **216**. Hydrolysis of (*R*)-**216** gave (*R*)-baclofen **3** as a hydrochloride salt in 64% yield (Scheme 49).[95]

Recently, Hayashi and Ogasawara[96] have reported the stereoselective synthesis of (*R*)-4-(*p*-chlorophenyl)-γ-lactone **152**, an important intermediate in the preparation of (*R*)-baclofen **3**. Thus, Michael addition of the Grignard reagent *p*-ClC_6H_4MgBr to enantiomerically pure (*S*)-4-cumiloxy-



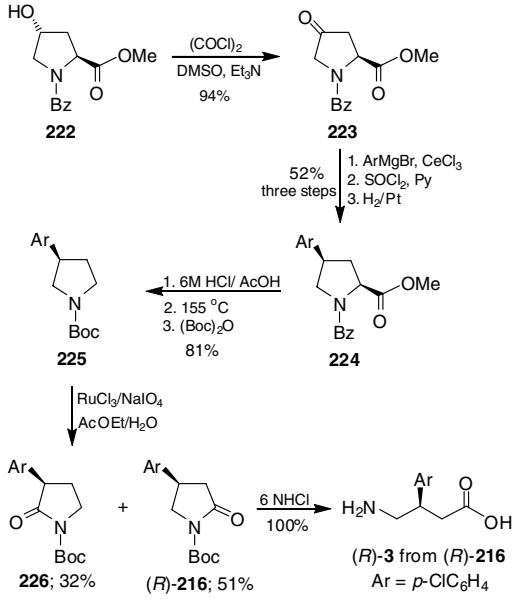
Scheme 49.

cyclopent-2-en-1-one **217** in the presence of CuI and chlorotrimethylsilane afforded *trans*-3,4-disubstituted cyclopentanone (3*S*,4*R*)-**218** as a single diastereoisomer. Treatment of (3*S*,4*R*)-**218** with acetic acid gave 4-arylcyclopent-2-en-1-one **219** in 88% yield, which by reduction with $NaBH_4$ in the presence of $CeCl_3$ led to cyclopentenol **220** as a 3:1 mixture of two diastereoisomers. Ozonolysis of the double bond in **220** followed by reduction with sodium borohydride and subsequent oxidation with sodium periodate ($NaIO_4$) provided hemiacetal **221** as a 17:1 mixture. Finally, treatment of the hemiacetal mixture **221** with Fetizon reagent[97] gave (*R*)-4-(*p*-chlorophenyl)-γ-lactone **152** (Scheme 50).[98]



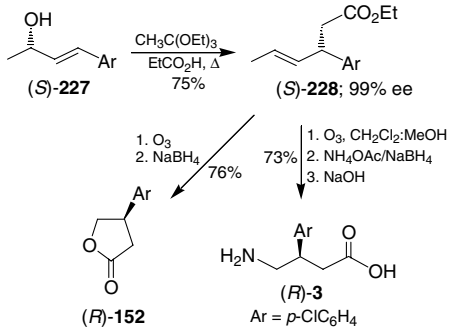
Scheme 50.

On the other hand, in 1995, Yoshifuji and Kaname[99] described the preparation of (*R*)-baclofen **3** from commercially available *trans*-4-hydroxy-L-proline. In this context, the oxidation of N-benzoylated methyl ester **222**[100] obtained from *trans*-4-hydroxy-L-proline, under the Swern protocol,[101] afforded ketoproline derivative **223** in 94% yield. The addition of a Grignard reagent *p*-ClC_6H_4MgBr to **223** in the presence of cerium chloride ($CeCl_3$) at room temperature followed by treatment with thionyl chloride and subsequent catalytic hydrogenation provided the proline derivative **224**. Hydrolysis of the ester group in **224** followed by decarboxylation and subsequent treatment with di(*tert*-butyl)dicarbonate $(Boc)_2O$ provided pyrrolidine derivative **225**. Oxidation of **225** with $RuCl_3$ and $NaIO_4$ gave a mixture of (*R*)-3-(*p*-chlorophenyl)-2-pyrrolidone **226** and (*R*)-4-(*p*-chlorophenyl)-2-pyrrolidone **216** in 32% and 51% yield, respectively. Finally, deprotection and hydrolysis of enantiomerically pure (*R*)-**216** led to (*R*)-baclofen **3** as a hydrochloride salt in quantitative yield (Scheme 51).



Scheme 51.

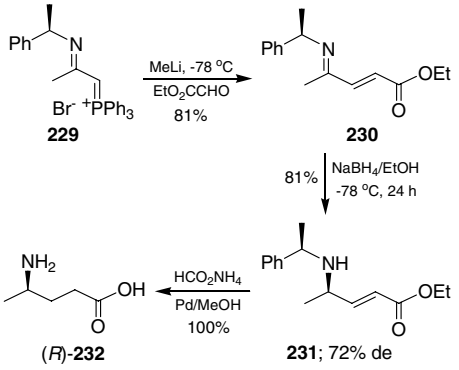
(*R*)-Baclofen **3** has also been obtained from allylic alcohol **227** via an orthoester Claisen rearrangement. Thus, the reaction of allyl alcohol (*S*)-(*E*)-**227** with triethyl orthoester in the presence of propionic acid under Claisen rearrangement conditions[102] afforded the (*S*)-γ, δ-unsaturated ester **228** in 75% yield and 99% ee. Ozonolysis of (*S*)-**228** followed by treatment with sodium borohydride provided enantiomerically pure (*R*)-γ-lactone **152** in 76% yield and 99% ee. On the other hand, ozonolysis of (*S*)-**228** followed by treatment with NH_4OAc and $NaBH_4$ at room temperature, and subsequent basic hydrolysis gave (*R*)-baclofen **3** in 73% yield (Scheme 52).[103]



Scheme 52.

2.4. γ-Substituted γ-amino acids

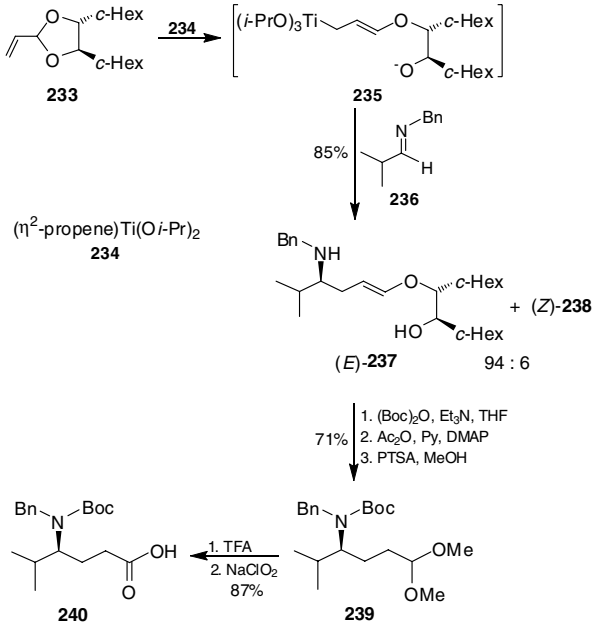
Reduction of 1-azadiene **230** obtained from the reaction of phosphonium salt **229** incorporating (*R*)-α-methylbenzylamine and ethyl glyoxylate with $NaBH_4$ in ethyl alcohol at −78 °C afforded (*E*)-γ-amino-α,β-unsaturated ester **231** in 81% yield and 72% de. Reduction of **230** with $NaBH_3CN$ in CH_3CN led to ester **231** with low diastereoselectivity. Treatment of diastereoisomerically enriched ester **231** with ammonium formate in the presence of Pd/C in MeOH gave (*R*)-γ-amino acid **232** in quantitative yield and high enantioselectivity (Scheme 53). (*S*)-γ-Amino acid **232** was obtained using phosphonium salt **229** incorporating (*S*)-α-methylbenzylamine as the starting material.[104]



Scheme 53.

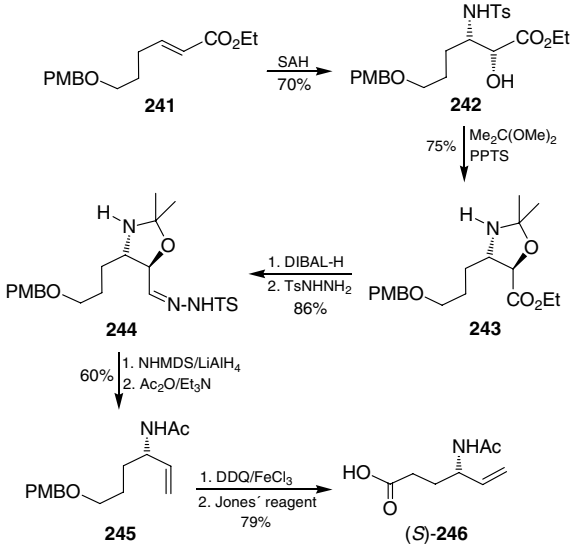
On the other hand, reaction of optically active acrolein 1,2-dicyclohexylethylene acetal **233** with (η^2-propene)Ti(O*i*-Pr)$_2$ **234** gave the chiral allyltitanium compound **235**, which by treatment with prochiral imine **236** afforded the corresponding alkenes (*E*)-**237** and (*Z*)-**238** in 85% yield and a 94:6 ratio, which on purification produced the pure (*E*)-**237**. Treatment of (*E*)-**237** with di(*tert*-butyl)dicarbonate $(Boc)_2O$ followed by acetylation and subsequent acidic methanolysis provided the corresponding γ-amino aldehyde dimethyl acetal **239** in 71% yield. Acidic hydrolysis of acetal **239** followed by oxidation with sodium chlorite provided N,N-diprotected γ-amino acid **240** in 87% yield (Scheme 54).[105]

Sharpless aminohydroxylation (SAH) of (*E*)-α,β-unsaturated ethyl ester **241** afforded the optically enriched amino



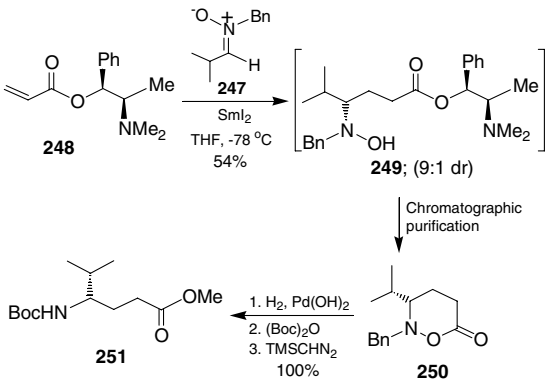
Scheme 54.

alcohol **242** in ⩾85% ee after a single recrystallization, which upon treatment with 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) gave acetonide **243** as the result of the simultaneous cleavage of *N*-Ts bound as well as acetonation with the neighboring hydroxy group. Reduction of the ethyl ester function in **243** with DIBAL-H led to the corresponding aldehyde, which by treatment with *p*-toluene tosylhydrazine produced the β-amino tosylhydrazone **244** in 86% yield. The reaction of chiral hydrazone **244** with NHMDS and $LiAlH_4$ followed by acetylation afforded the acetylated product **245** in 75% yield. Cleavage of the PMB protective group in **245** using DDQ/$FeCl_3$ followed by Jones' oxidation gave the *N*-acyl (*S*)-vigabatrin **246** in 79% yield (Scheme 55).[106]



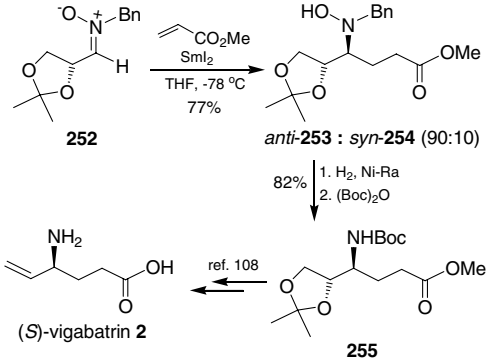
Scheme 55.

SmI_2-Promoted addition of nitrone **247** to chiral α,β-unsaturated ester **248** incorporating (1*R*,2*S*)-*N*-methylephedrine afforded derivative **249** in 54% yield and a 9:1 diastereoisomeric ratio, which on chromatographic purification gave compound **250**. Catalytic hydrogenation of **250** followed by treatment with $(Boc)_2O$ and subsequent esterification led to *N*-Boc-γ-amino acid **251** as the methyl ester in quantitative yield (Scheme 56).[107]



Scheme 56.

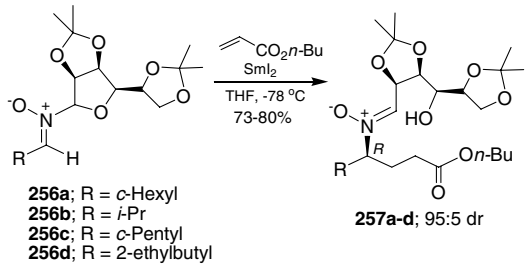
In a similar manner, the addition of chiral nitrone **252** obtained from D-glyceraldehyde acetonide,[108] to methyl acrylate in the presence of SmI_2 gave the 4-substituted γ-*N*-benzylhydroxyamino ester derivatives *anti*-**253**:*syn*-**254** in 77% yield and 90:10 dr. Catalytic hydrogenation of diastereoisomerically pure *anti*-**253** followed by N-protection with di(*tert*-butyl)dicarbonate $(Boc)_2O$ produced **255** in 82% yield, which is a key intermediate[109] in the synthesis of (*S*)-vigabatrin **2** (Scheme 57).[110]



Scheme 57.

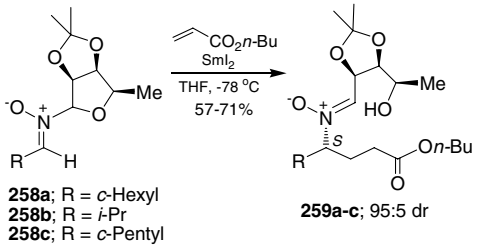
Recently, Skrydstrup et al.[111] reported that the addition of chiral *N*-D-mannose substituted nitrones **256a**–**d** to *n*-butyl acrylate in the presence of SmI_2 to afford the γ-amino acid derivatives **257a**–**d** in moderate yield and 95:5 diastereoisomeric ratio, with predominance of diastereoisomer of (*R*)-configuration at the newly created stereogenic center (Scheme 58).

On the other hand, the reaction of chiral *N*-D-ribose substituted nitrones **258a**–**c** with *n*-butyl acrylate in the presence



Scheme 58.

of SmI_2 afforded the γ-amino acid derivatives **259a**–**c** with an (*S*)-configuration at the newly created stereogenic center, in moderate yield with high diastereoselectivity (Scheme 59).[111] Derivatives **257a**–**d** and **259a**–**c** are useful intermediates for the synthesis of γ-substituted γ-amino acids.

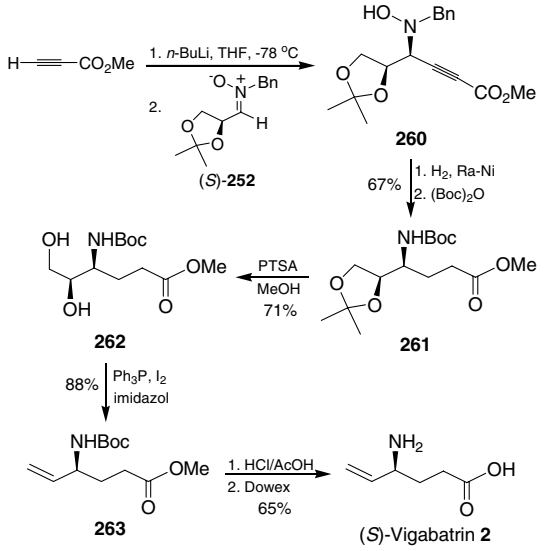


Scheme 59.

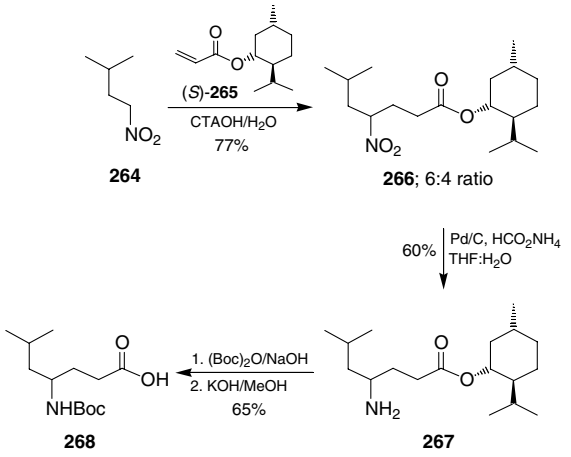
Nucleophilic addition of the lithiated anion generated from propiolate methyl ester and *n*-BuLi, to enantiomerically pure (*S*)-nitrone **252** at −78 °C in THF afforded the *N*-hydroxylamino derivative *syn*-**260** as a single diastereoisomer in 94% yield. Catalytic hydrogenation of *syn*-**260** in the presence of Raney-nickel and $(Boc)_2O$ gave the *N*-Boc-γ-amino methyl ester derivative **261**, in 67% yield. Cleavage of the isopropylidene protective group in **261** with *p*-toluenesulfonic acid (PTSA) gave the corresponding diol **262** in 71% yield, which by reductive elimination of the two hydroxy groups using Ph_3P and I_2 gave the *N*-Boc-vigabatrin methyl ester **263** in 88% yield. Finally, acidic hydrolysis of **263** led to (*S*)-vigabatrin **2** in 65% yield (Scheme 60).[112] Enantiomerically pure (*R*)-vigabatrin **2** was obtained using (*R*)-nitrone **252** as the starting material.

Michael addition of nitroalkane **264** to (*S*)-menthyl acrylate **265** in the presence of a catalytic amount of cetyltrimethylammonium hydroxide (CTAOH) in water as solvent, afforded nitro derivative **266** in 77% yield and 6:4 diastereoisomeric ratio. The absolute configuration at the newly created stereogenic center was not reported. Reduction of the nitro group in **266** with ammonium formate and Pd/C gave the corresponding amino derivative **267**, which by treatment with $(Boc)_2O$ followed by basic hydrolysis gave *N*-Boc-γ-amino acid **268** in 65% yield (Scheme 61).[113]

On the other hand, Pd-catalyzed allylic amination of chiral allylic carbonate (*E*)-**269** with *p*-toluenesulfonamide in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$-dppe catalyst afforded the



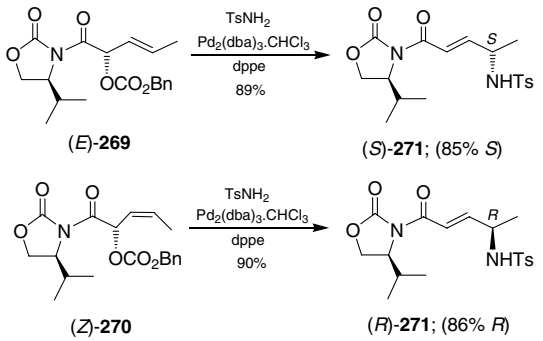
Scheme 60.



Scheme 61.

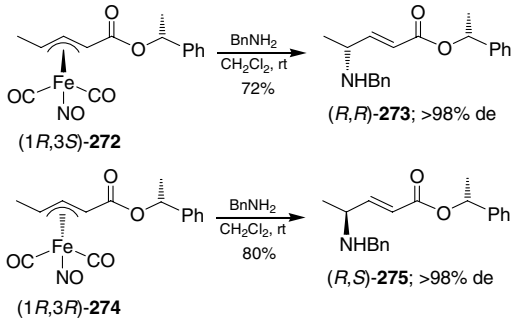
γ-amino-substituted compound **271** of (*S*)-configuration at the newly created stereogenic center, in 89% yield and high level of stereocontrol. Conversely, the allylic amination of (*Z*)-**270** under identical conditions gave the γ-amino-substituted compound **271** with an (*R*)-configuration at the newly created stereogenic center (Scheme 62).[114] Diastereoisomerically pure α,β-unsaturated derivatives (*R*)- and (*S*)-**271** are useful intermediates in the synthesis of γ-substituted γ-amino acids.

Nakanishi et al.[115] have described that the nucleophilic reaction of planar chiral allyl η^3-allyldicarbonylnitrosyliron complex (1*R*,3*S*)-**272** bearing an (*R*)-α-methylbenzyloxy group, with benzylamine proceeded regio- and stereoselectively to give the γ-amino α,β-unsaturated ester (*R*,*R*)-**273** in good yield as a single (*E*)-isomer. The nucleophilic reaction of (1*R*,3*R*)-**274** under identical conditions afforded the γ-amino α,β-unsaturated ester (*R*,*S*)-**275** also as a single (*E*)-isomer (Scheme 63). Diastereoisomerically



Scheme 62.

pure (*R*,*R*)-**273** and (*R*,*S*)-**275** are useful intermediates in the synthesis of γ-substituted γ-amino acids.

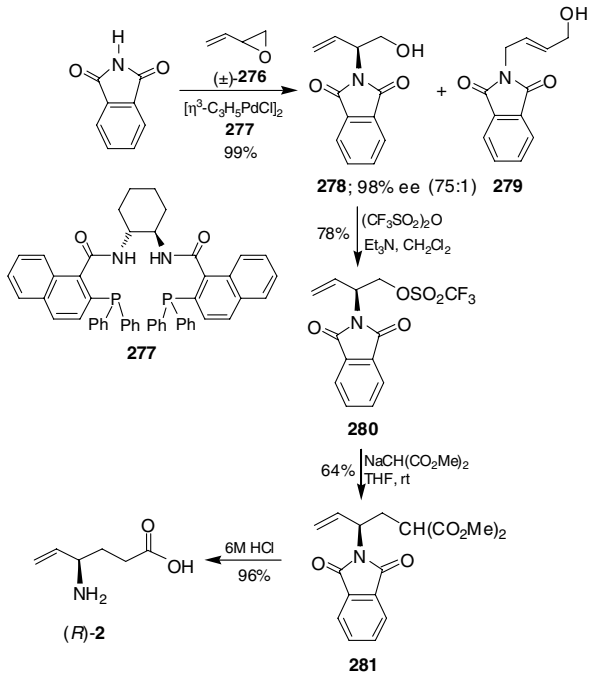


Scheme 63.

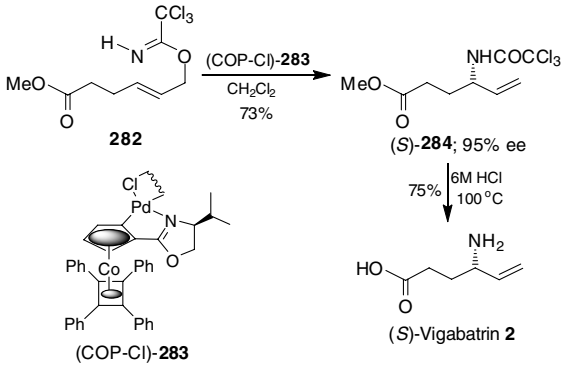
Catalytic reaction of butadiene monoepoxide (±)-**276**, with phthalimide in the presence of a π-allylpalladium chloride dimer $[\eta^3\text{-}C_3H_5PdCl]_2$ and chiral ligand **277**, afforded compounds **278** and **279** in 99% yield and 75:1 ratio. Compound **278** was obtained in excellent regioselectivity and high enantioselectivity (98% ee) by an attack at the more substituted allyl position. The reaction of enantiomerically pure **278** with trifluoromethanesulfonyl anhydride gave the corresponding sulfonate ester **280** in 78% yield, which upon treatment with sodium dimethyl malonate produced the alkylated product **281** in 64% yield. Global deprotection with 6 M hydrochloric acid led to (*R*)-vigabatrin **2** in 96% yield as hydrochloride salt (Scheme 64).[116]

On the other hand, catalytic asymmetric rearrangement of (*E*)-allylic trichloroacetimidate **282** readily obtained from DBU-catalyzed addition of allylic alcohol to trichloroacetonitrile, in the presence of chiral (COP-Cl)-**283** complex, afforded the corresponding (*S*)-allylic trichloroacetamide **284** in 73% yield and 95% ee. Acidic hydrolysis of **284** gave the enantiomerically pure (*S*)-vigabatrin **2** in 75% yield (Scheme 65).[117]

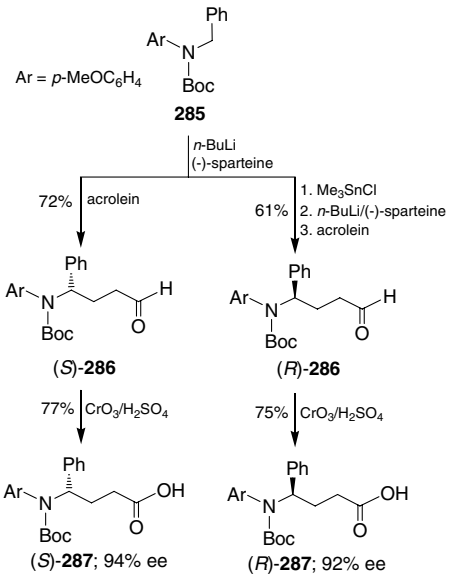
Treatment of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine **285** with *n*-BuLi in the presence of (−)-sparteine followed by the addition of acrolein afforded γ-amino aldehyde derivative (*S*)-**286** in 72% yield. Oxidation of (*S*)-**286** with a CrO_3/H_2SO_4 mixture gave the corresponding N-protected γ-amino acid (*S*)-**287** in 77% yield and 94% ee. When the



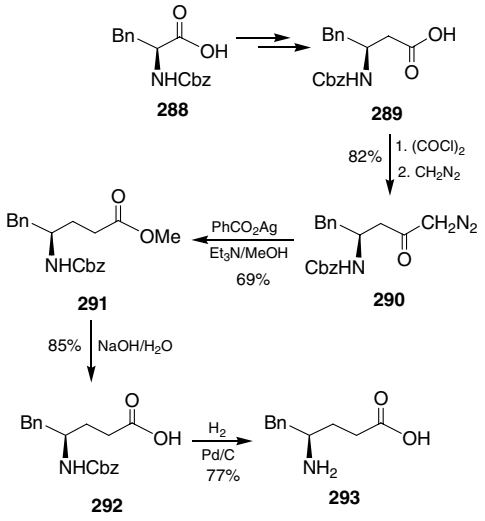
Scheme 64.



Scheme 65.



Scheme 66.



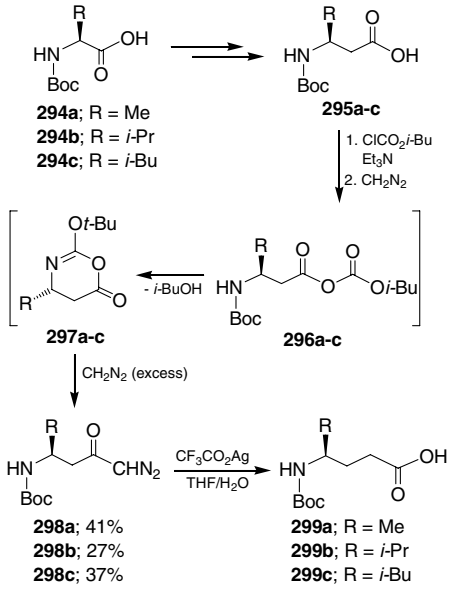
Scheme 67.

lithiation–stannylation–transmetalation protocol was used, (*R*)-γ-amino aldehyde **286** was obtained in 61% yield. Oxidation of (*R*)-**286** produced the N-protected γ-amino acid (*R*)-**287** in 75% yield and 92% ee (Scheme 66).[118]

Enantiomerically pure γ-substituted γ-amino acids can be obtained by a double Arndt–Eistert homologation from the corresponding N-protected α-amino acids.[119] For example, the reaction of (*S*)-*N*-Cbz-β-amino acid **289** obtained from (*S*)-*N*-Cbz-α-amino acid **288** via Arndt–Eistert homologation[120] with oxalyl chloride followed by treatment with diazomethane gave the corresponding β-diazoketone **290** in 82% yield. A Wolff rearrangement of β-diazoketone **290** using silver benzoate and Et_3N in methanol afforded the γ-amino acid methyl ester **291** in 69% yield. Basic hydrolysis of the methyl ester group in **291** gave the corresponding carboxylic acid **292**, which by catalytic hydrogenation led to (*S*)-γ-amino acid **293** in 77% yield (Scheme 67).[121]

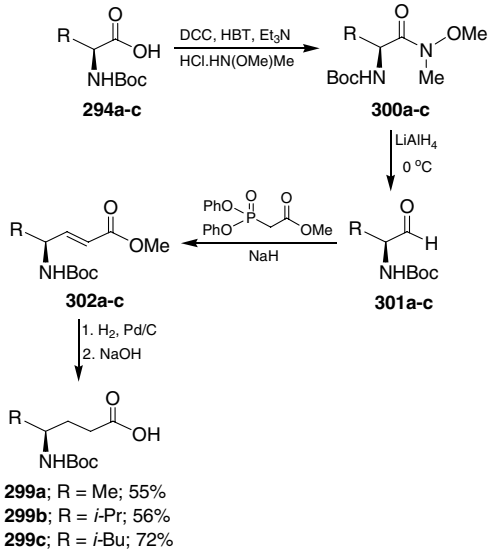
On the other hand, treatment of (*S*)-*N*-Boc-β-amino acids **295a–c** obtained from readily available α-amino acids **294a–c** via Arndt–Eistert homologation,[122] with isobutyl chloroformate in Et_3N gave mixed anhydrides **296a–c**, which produced the heterocyclic imino anhydrides **297a–c**. Treatment of anhydrides **297a–c** with an excess of diazomethane led to diazoketones **298a–c**, which by Wolff rearrangement using silver trifluoroacetate in a mixture of THF–H_2O afforded the *N*-Boc-γ-amino acids **299a–c** (Scheme 68).[123]

Better results were obtained when the *N*-Boc-protected α-amino acids **294a–c** were converted into the Weinreb amides **300a–c**, which on reduction with $LiAlH_4$ gave the *N*-Boc-α-amino aldehydes **301a–c**. Olefination of aldehydes **301a–c** via Horner–Wadsworth–Emmons reaction afforded the α,β-unsaturated *N*-Boc-γ-amino acid methyl esters



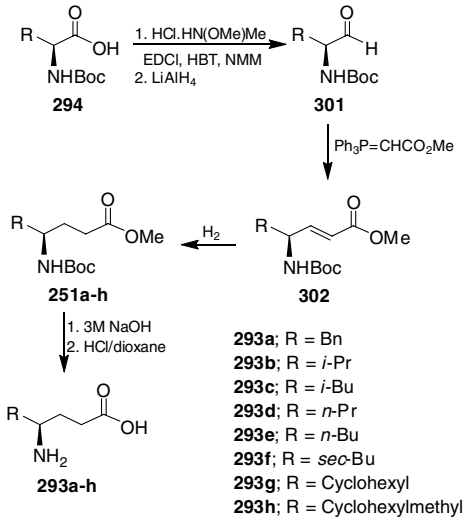
Scheme 68.

302a–**c** as *E*/*Z* mixture (3:1 to 7:1). Catalytic hydrogenation of **302a**–**c**, followed by saponification, gave the *N*-Boc-γ-amino acids **299a**–**c** (Scheme 69).[123]



Scheme 69.

Independently, Prasad et al.[124] described the synthesis of γ-amino acids **293a**–**h** according to Scheme 70. The reaction of *N*-Boc-protected α-amino acids **294** with HN(OMe)Me hydrochloride in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCl), 1-hydroxybenzotriazole (HOBT) and *N*-methylmorpholine (NMM) afforded the corresponding Wenreib amides, which by treatment with $LiAlH_4$ gave *N*-Boc-α-amino aldehydes **301**. Horner–Wadsworth–Emmons reaction of **301** provided the α,β-unsaturated amino esters **302**,[125] which by catalytic hydrogenation were converted into amino esters **251a**–**h**. Saponification and acid treatment of **251a**–**h** led to γ-substituted γ-amino acids **293a**–**h** (Scheme 70).

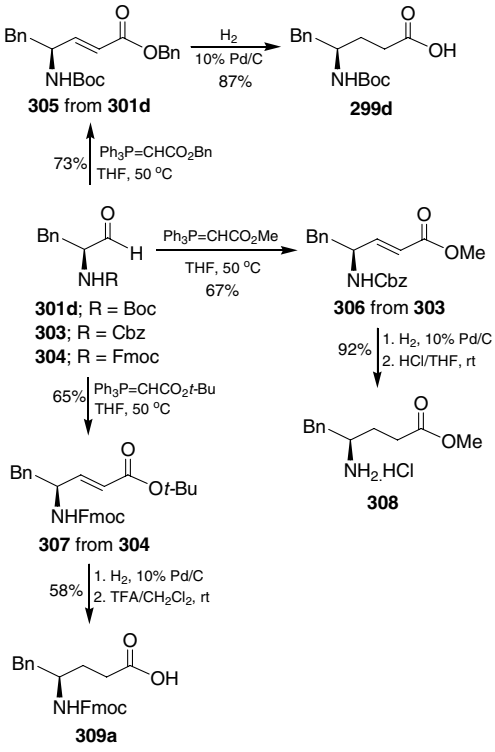


Scheme 70.

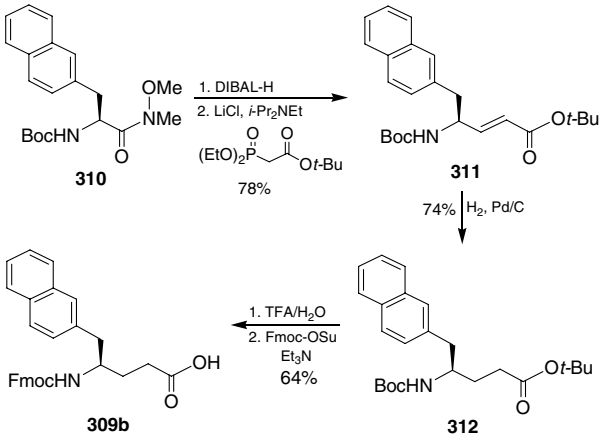
On the other hand, the reaction of α-amino aldehydes **301d**, **303**, and **304** readily available from α-amino acids, with the appropriate ylides gave the α,β-unsaturated amino esters **305**, **306**, and **307** in 73%, 67%, and 65% yield, respectively. Catalytic hydrogenation of the double bond with simultaneous removal of the benzyl group in **305**[126] led to *N*-Boc-γ-amino acid **299d** in 87% yield, while the simultaneous catalytic hydrogenation of the double bond and cleavage of the Cbz group in **306** afforded γ-amino acid methyl ester **308** as a hydrochloride salt in 92% yield. Finally, catalytic hydrogenation of **307** followed by treatment with trifluoroacetic acid produced *N*-Fmoc-γ-amino acid **309a** in 58% yield (Scheme 71).[127]

More recently, Tamamura et al.[128] reported the synthesis of *N*-Fmoc-γ-amino acid **309b** under a similar protocol. Thus, the reduction of amide **310** obtained from L-β-(2-naphthyl)alanine, with DIBAL-H, followed by Horner–Wadsworth–Emmons reaction afforded the *N*-Boc-γ-amino acid *tert*-butyl ester **311** in 78% yield, which by catalytic hydrogenation gave compound **312** in 74% yield. Acidic hydrolysis of the *tert*-butyl ester with simultaneous cleavage of the Boc group in **312** with trifluoroacetic acid provided the corresponding γ-amino acid, which on treatment with Fmoc-OSu produced the *N*-Fmoc-γ-amino acid **309b** in 64% yield (Scheme 72).

Chiral α,β-unsaturated γ-amino acids can be incorporated in several peptides, which have shown to be effective GlyT-2 reuptake inhibitors,[129] and also act as effective inhibitors for the HTLV-1 protease.[130] In this context, the Horner–Wadsworth–Emmons reaction of *N*-Boc-α-amino aldehyde **301d** with (carbomethoxymethylene)triphenylphosphorane in dichloromethane afforded olefin **302a** exclusively as the (*E*)-isomer in 80% yield. On the other hand, **301d** under Still–Gennari olefination reaction[131] gave (*Z*)-α,β-unsaturated ester **313**. Saponification of the methyl esters in **302a** and **313** followed by cleavage of Boc protective group



Scheme 71.

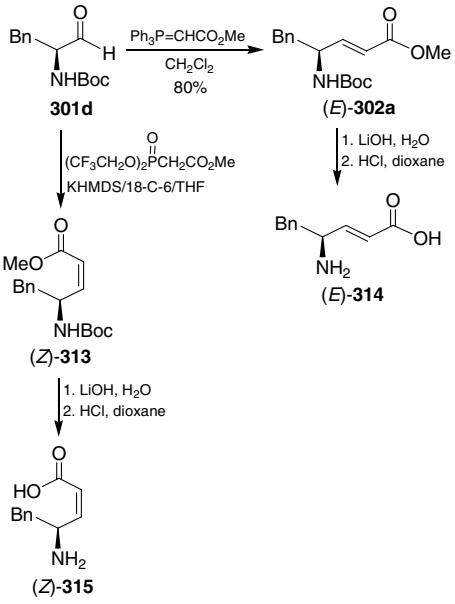


Scheme 72.

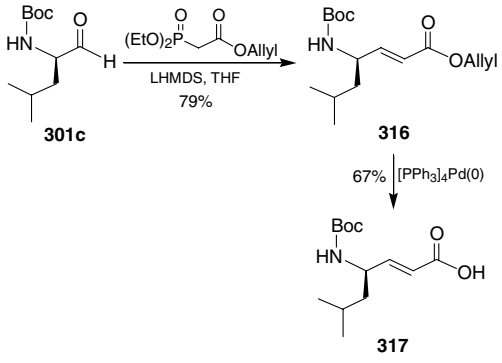
with HCl in dioxane led to unsaturated γ-amino acids (*E*)-**314** and (*Z*)-**315**, respectively (Scheme 73).[129]

On the other hand, reaction of the lithium enolate derived from allyl diethylphosphonoacetate with *N*-Boc-amino aldehyde **301c** afforded the (*E*)-α,β-unsaturated ester **316** in 79% yield. Treatment of allyl ester **316** with $[PPh_3]_4Pd(0)$ led to (*E*)-α,β-unsaturated *N*-Boc-γ-amino acid **317** in 67% yield (Scheme 74).[130]

Treatment of *N*-Boc-phenylalanine **294d** with 1,1′-carbonyldiimidazole (CDI) followed by the addition of lithium enolate derived from ethyl acetate afforded *N*-Boc-γ-amino-β-keto ethyl ester **318**, which by reduction with KBH_4



Scheme 73.

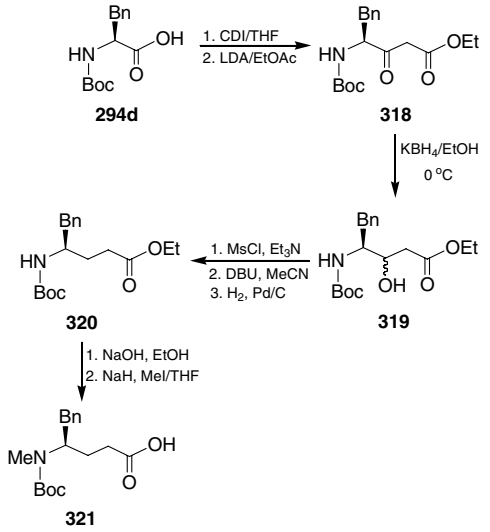


Scheme 74.

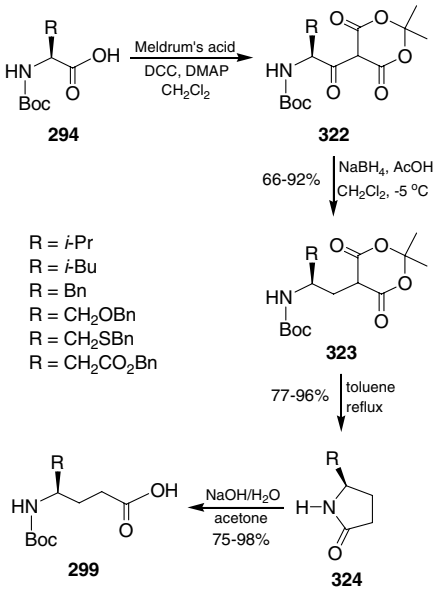
gave the corresponding diastereoisomeric mixture of *N*-Boc-γ-amino-β-hydroxy ethyl esters **319**. Mesylation of **319** followed by elimination and subsequent catalytic hydrogenation produced the *N*-Boc-γ-amino ethyl ester **320**. Finally, saponification of ethyl ester **320** followed by N-methylation led to *N*-Boc-*N*-methyl-γ-amino acid **321** (Scheme 75).[132]

Smrcina et al.[133] reported the synthesis of *N*-Boc-γ-amino acids **299** from the corresponding *N*-Boc-α-amino acids **294** using Meldrum's acid. In this context, the reaction of *N*-Boc-α-amino acids **294** with Meldrum's acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) afforded the β-keto derivatives **322**, which by reduction with $NaBH_4$ in acetic acid produced **323** in 66–92% yield. Heating of **323** in toluene gave γ-lactams **324** in 77–96% yield. Basic hydrolysis of **324** provided the *N*-Boc-γ-amino acids **299** in 75–98% yield (Scheme 76).

Selective protection of L-glutamic acid using concentrated sulfuric acid in EtOH, and subsequent reaction with methyl



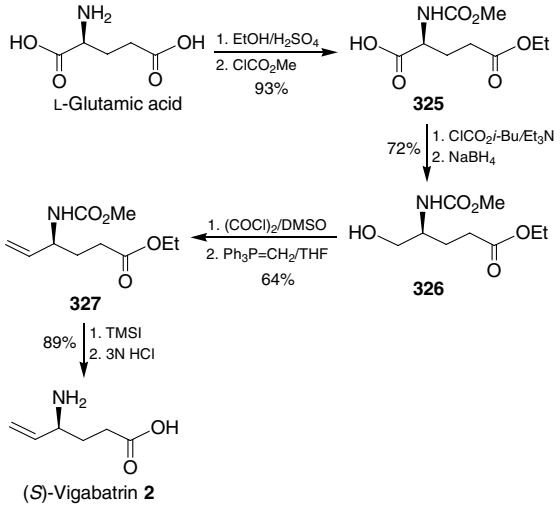
Scheme 75.



Scheme 76.

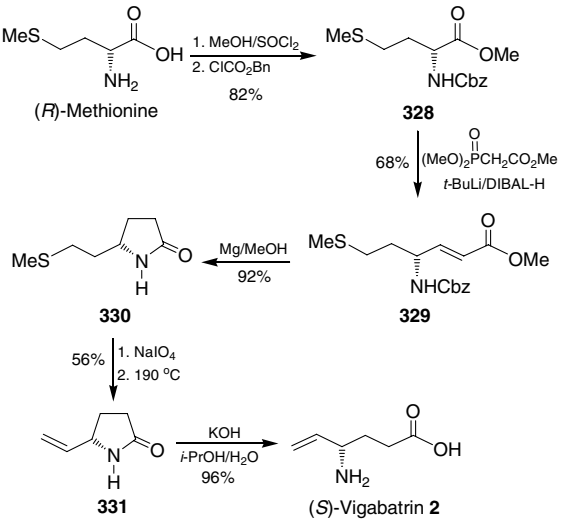
chloroformate afforded the glutamate ethyl ester derivative **325** in 93% yield. Treatment of **325** with $ClCO_2i$-Bu followed by reduction with $NaBH_4$ led to alcohol **326** in 72% yield. Swern oxidation of **326** followed by olefination under Wittig reaction conditions using $Ph_3P{=}CH_2$ produced vinyl compound **327** in 64% yield. Cleavage of *N*-methoxycarbonyl protective group in **327** with TMSI and subsequent hydrolysis of the ester group afforded the enantiomerically pure (*S*)-vigabatrin **2** in 89% yield (Scheme 77).[134]

Wei and Knaus[135] reported the synthesis of (*S*)-vigabatrin **2** using (*R*)-methionine as the starting material via a one-pot reduction–homologation. In this context, esterification of (*R*)-methionine with thionyl chloride in methanol followed by treatment with benzyl chloroformate gave (*R*)-



Scheme 77.

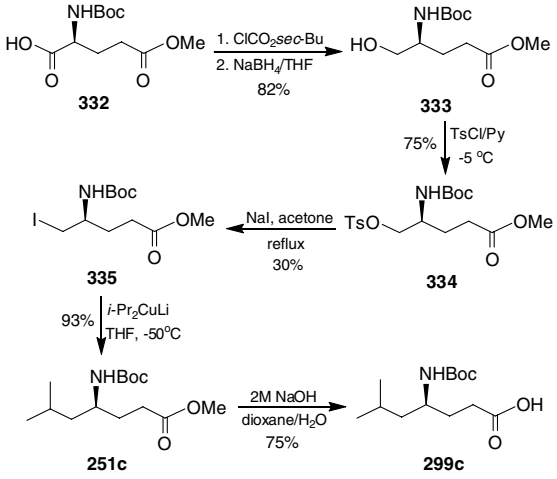
N-Cbz-α-amino carboxylic methyl ester **328** in 82% yield. Using a one-pot reduction–homologation procedure, methyl ester **328** was transformed into (*R*)-*N*-benzyloxycarbonyl γ-amino α,β-unsaturated carboxylate **329** in 68% yield. Hydrogenation of the double bond in **329** using magnesium–methanol afforded γ-lactam **330** in 92% yield. Oxidation of the sulfide function in **330** into the corresponding sulfoxide followed by a thermal elimination reaction gave the (*S*)-5-vinyl-γ-lactam **331** in 56% yield. Finally, basic hydrolysis of γ-lactam **331** led to (*S*)-vigabatrin **2** in 96% yield (Scheme 78).



Scheme 78.

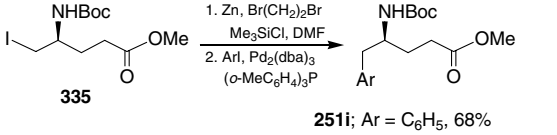
Roumestant et al.[136] have reported an efficient synthesis of enantiomerically pure *N*-Boc-γ-amino acid **299c** using glutamic acid as the starting material. In this context, the reaction of *N*-Boc-glutamic acid monomethyl ester **332** obtained from commercially available methyl glutamate hydrochloride, with $ClCO_2sec$-Bu followed by reduction with $NaBH_4$ afforded alcohol derivative **333** in 82% yield. The reaction of hydroxy derivative **333** with tosyl chloride

in the presence of pyridine gave tosylate derivative **334** in 75%, which by treatment with sodium iodide in acetone produced the iodo derivative **335** in 30% yield. The reaction of **335** with lithium diisopropylcuprate led to the corresponding γ-amino ester **251c** in 93% yield. Finally, basic hydrolysis of **251c** afforded (*R*)-*N*-Boc-γ-amino acid **299c** in 75% yield (Scheme 79). (*S*)-*N*-Boc-γ-amino acid **299c** was obtained when (*R*)-glutamic acid was used as the starting material.



Scheme 79.

On the other hand, treatment of iodo compound **335** with zinc dust activated by the Knochel procedure,[137] and subsequent palladium(0)-catalyzed cross-coupling with several aromatic iodides gave the corresponding *N*-Boc-γ-amino acids **251i–o** (Scheme 80).[138]

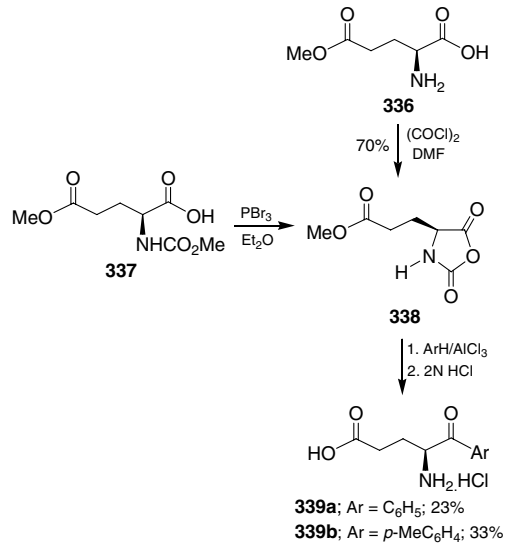


251i; Ar = C_6H_5, 68%
251j; Ar = *p*-MeC_6H_4, 68%
251k; Ar = *o*-$MeOC_6H_4$, 69%
251l; Ar = *p*-$MeOC_6H_4$, 68%
251m; Ar = *o*-$NH_2C_6H_4$, 56%
251n; Ar = *o*-ClC_6H_4, 34%
251o; Ar = *p*-$NO_2C_6H_4$, 80%

Scheme 80.

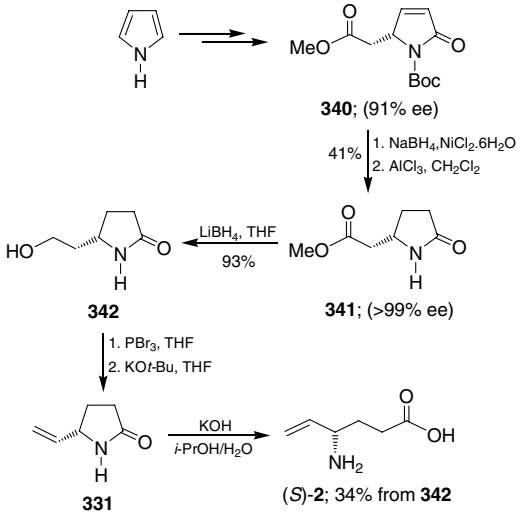
The reaction of *N*-carboxy-α-amino acid anhydride **338** obtained from glutamic acid derivatives **336** and **337** and phosgene or PBr_3, respectively, with benzene or toluene in the presence of $AlCl_3$ followed by acidic hydrolysis gave γ-amino acids **339a** and **339b** in 23% and 33% yield, respectively (Scheme 81).[139]

5-Substituted-3-pyrrolin-2-ones have been introduced as chiral building blocks. For example, the (*R*)-3,4-didehydro-pyrohomoglutamate **340** obtained from pyrrol has been used as the starting material in the synthesis of (*S*)-vigabatrin **2**. In this context, conjugate reduction of **340** with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ followed by



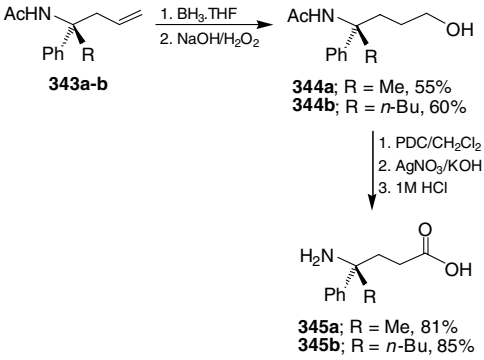
Scheme 81.

N-Boc deprotection using $AlCl_3$ afforded methyl ester derivative **341** in 41% yield and 99% ee after crystallization. Reduction of the methyl ester group in **341** with $LiBH_4$ gave the corresponding alcohol **342** in 93% yield. Treatment of **342** with PBr_3 and subsequent dehydrobromination with KO*t*-Bu produced vinylpyrrolidinone **331**, which by basic hydrolysis led to (*S*)-vigabatrin **2** (Scheme 82).[140]



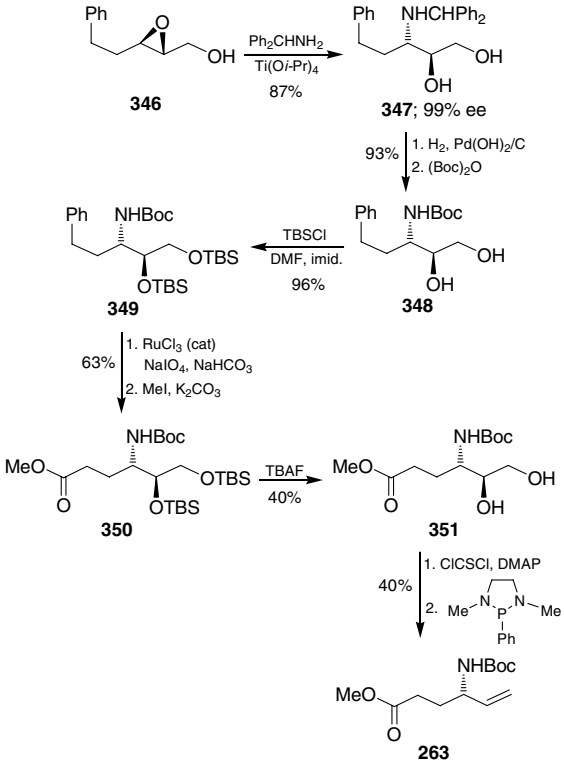
Scheme 82.

On the other hand, hydroboration of enantiomerically pure **343a** and **343b** obtained from *N*-alkylidene-*p*-toluenesulfinamides, with $BH_3{\cdot}THF$ and $NaOH/H_2O_2$ afforded the alcohol derivatives **344a** and **344b** in moderate yield. Oxidation of **344a** and **344b** with pyridinium dichromate (PDC) in CH_2Cl_2 followed by treatment with $AgNO_3$–KOH and subsequent acidic hydrolysis with 1 M HCl gave γ-amino acids **345a** and **345b** in 81% and 85% yield, respectively (Scheme 83).[141]



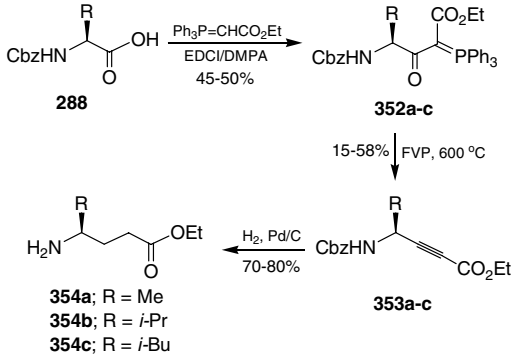
Scheme 83.

(2*R*,3*R*)-5-Phenyl-2,3-epoxypentanol **346** easily available by catalytic Sharpless epoxidation is an important starting material for the stereoselective synthesis of *N*-Boc-vigabatrin methyl ester **263**. In this context, treatment of epoxy alcohol **346** with benzhydrylamine in the presence of titanium tetraisopropoxide took place in high regioselectivity (94.5:5.5) affording aminodiol **347** in 87% yield and 99% ee after a single crystallization. Catalytic hydrogenolysis of the benzhydryl protective group, with simultaneous protection by $(Boc)_2O$, led to *N*-Boc-aminodiol **348** in 93% yield. Treatment of **348** with *tert*-butyldimethylsilyl chloride under standard conditions produced bis-silyl ether **349** in 96% yield. Oxidation of the phenyl ring in **349** gave the corresponding carboxylic acid, which by esterification provided methyl ester **350** in 63% yield. Cleavage of silyl ethers in **350** with TBAF afforded diol **351** in 40% yield. Finally, the reaction of **351** under the Corey–Hopkins deoxygenation protocol[142] led to *N*-Boc-vigabatrin methyl ester **263** (Scheme 84).[109]



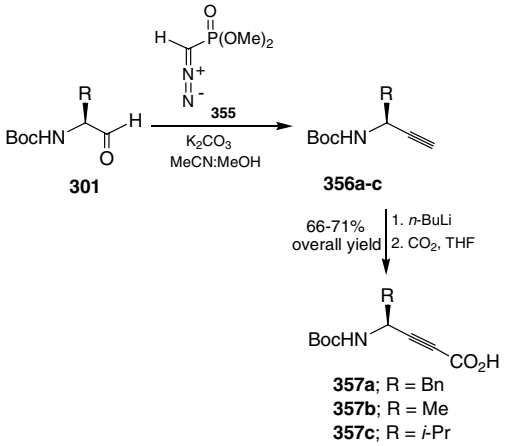
Scheme 84.

The relationship between α-amino acids and extended analogues by the insertion of a C≡C unit, a concept generalized by Chauvin[143] and termed 'carbomers', makes the latter of interest for the formation of modified peptides. In this context, treatment of *N*-Cbz-α-amino acids **288** with $Ph_3P{=}CHCO_2Et$ in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and DMAP afforded ylides **352a–c**, which by flash vacuum pyrolysis (FVP) at 600 °C and 10^{-2} Torr produced acetylenic amino esters **353a–c**. Catalytic hydrogenation of **353a–c** gave γ-amino esters **354a–c** (Scheme 85).[144]



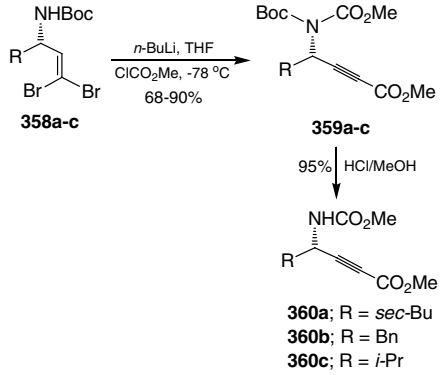
Scheme 85.

Seyferth–Gilbert homologation[145] of *N*-Boc-α-amino aldehydes **301** using dimethyl (diazomethyl)phosphonate **355** generated in situ from dimethyl 1-diazo-2-oxopropylphosphonate (also called Bestmann's reagent)[146] afforded chiral alkynes **356a–c**. Carboxylation of alkynes **356a–c** using *n*-BuLi and carbon dioxide directly gave γ-amino acids **357a–c** in 66–71% overall yield (Scheme 86).[147]



Scheme 86.

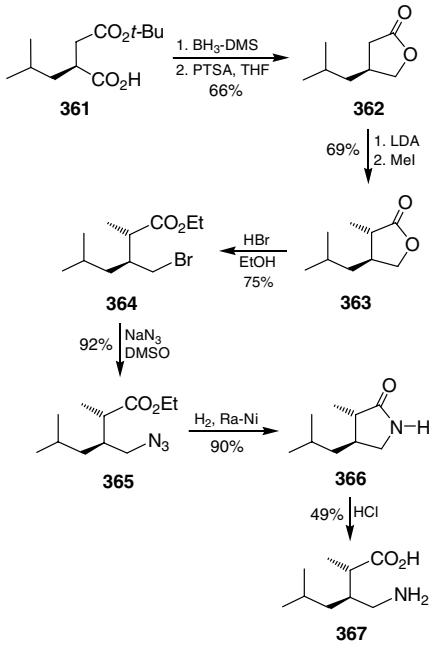
On the other hand, treatment of vinylbromides **358a–c** with *n*-BuLi and an excess of $ClCO_2Me$ afforded the acetylenic ester derivatives **359a–c** in good yield. Cleavage of the Boc protective group in **359a–c** with HCl in methanol gave the N-protected-γ-amino acetylenic esters **360a–c** in excellent yield (Scheme 87).[148]



Scheme 87.

2.5. α,β-Disubstituted γ-amino acids

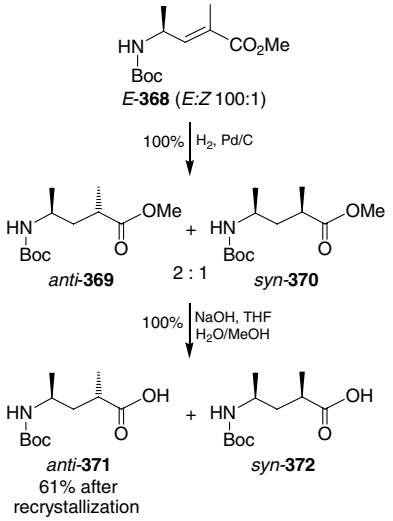
Reduction of the carboxylic acid function in enantiomerically pure **361** with BH_3·DMS complex followed by a cyclization reaction afforded γ-lactone **362** in 66% yield. The addition of a lithium enolate generated by treatment of **362** with LDA, to iodomethane produced the *trans*:*cis* isomers **363** in 69% yield and a 4.5:1 ratio. The reaction of diastereoisomerically pure *trans*-**363** with an anhydrous ethanolic solution of HBr afforded the alkyl bromide derivative **364** in 75% yield, which by treatment with sodium azide gave azidoester derivative **365** in 92% yield. Catalytic reduction of the azide group in **365** provided γ-lactam **366** in 90% yield, which on acidic hydrolysis led to α,β-disubstituted γ-amino acid **367**, an analogue of (*S*)-pregabalin **4** (Scheme 88).[41]



Scheme 88.

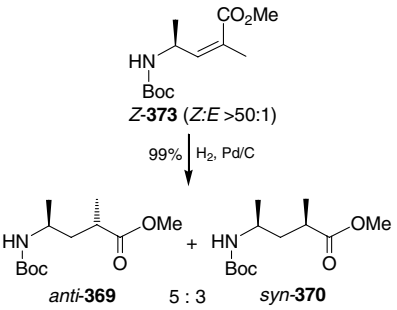
2.6. α,γ-Disubstituted γ-amino acids

Catalytic hydrogenation of (*E*)-γ-amino-α,β-unsaturated methyl ester **368** readily obtained from the corresponding α-amino aldehyde via a Horner–Wadsworth–Emmons reaction produced in quantitative yield a 2:1 mixture of compounds *anti*-**369** and *syn*-**370**. Basic hydrolysis provided the α,γ-disubstituted *N*-Boc-γ-amino acids *anti*-**371** and *syn*-**372** (Scheme 89).[149]



Scheme 89.

Similar results were obtained in the catalytic hydrogenation of *Z*-enoate **373**, and compounds *anti*-**369** and *syn*-**370** were obtained in a 5:3 diastereoisomeric ratio (Scheme 90).[149]



Scheme 90.

The predominance of the *anti*-isomer in the hydrogenation of *E*-enoate **368** was explained on the basis of possible 1,3-allylic strain:[150] *E*-enoate **368** adopts a conformation where the *si*-face is hindered by the Boc group (Fig. 2a). On the other hand, the *Z*-enoate **373** adopts a γ-turn type conformation (Fig. 2b), stabilized by the dipolar interaction between the NH and the ester group.

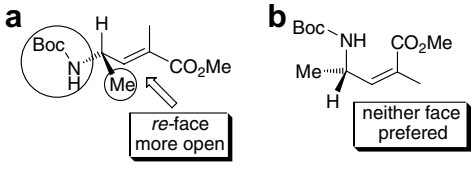
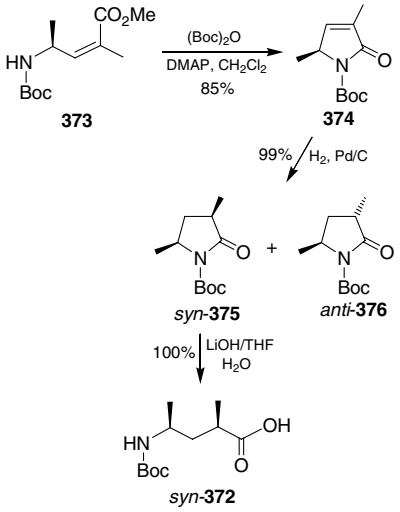


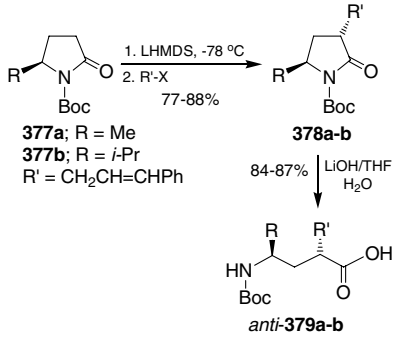
Figure 2.

In order to obtain the *syn*-compound as the principal product, cyclic compound **374** was prepared. In this context, treatment of *Z*-enoate **373** with $(Boc)_2O$, DMAP in CH_3CN under Ragnarsson–Grehn conditions[151] afforded the corresponding cyclic compound **374** in 85% yield. Catalytic hydrogenation of **374** gave a 10:1 mixture of γ-lactams *syn*-**375** and *anti*-**376** in quantitative yield. Finally, basic hydrolysis of diastereoisomerically pure *syn*-**375** gave α,γ-disubstituted *N*-Boc-γ-amino acid *syn*-**372** (Scheme 91).[149]



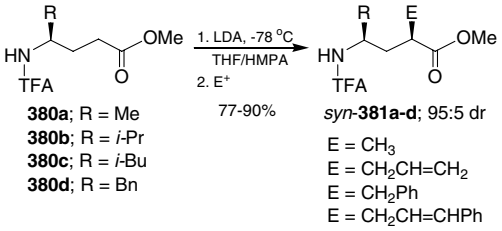
Scheme 91.

Reaction of the lithium enolate derived from pyrrolidinones **377a** and **377b** with cinnamyl bromide afforded the disubstituted γ-lactams **378a** and **378b** in good yield and with high diastereoselectivities (*anti*:*syn* 18:1 and 40:1, respectively). Basic hydrolysis of **378a** and **378b** afforded the α,γ-disubstituted *N*-Boc-γ-amino acids *anti*-**379a** and **379b** in good yield (Scheme 92).[152]



Scheme 92.

On the other hand, alkylation of enolates of N-substituted γ-amino acids methyl esters **380a–d** obtained from readily available α-amino acids by a homologation protocol afforded the α,γ-disubstituted *N*-TFA-substituted γ-amino acid methyl esters *syn*-**381a–d** in good yield and with excellent levels of 1,3-asymmetric induction (Scheme 93).[153]



Scheme 93.

The high levels of 1,3-asymmetric induction have been explained through Zimmerman–Traxler type transition states and by the presence of highly coordinated dianionic species involving two charged sites, as shown in Figure 3.

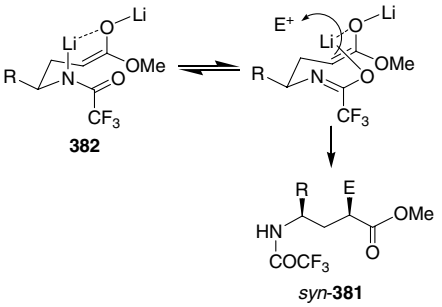
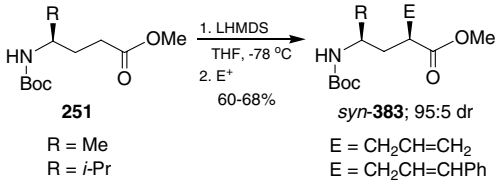


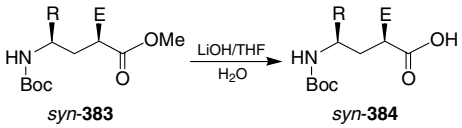
Figure 3.

Identical results were obtained in the alkylation of *N*-Boc-γ-amino acid methyl esters **251** using LHMDS as a base, where the *syn*-alkylated products **383** were obtained with high diastereoselectivity (Scheme 94).[154,155]



Scheme 94.

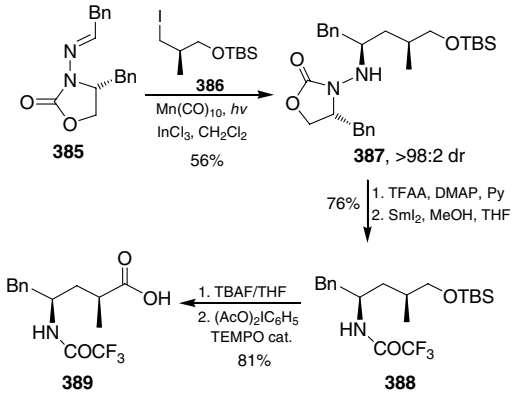
Basic hydrolysis of *N*-Boc-derivatives **383** with lithium hydroxide gave α,γ-disubstituted *N*-Boc-γ-amino acids *syn*-**384** (Scheme 95).[154]



Scheme 95.

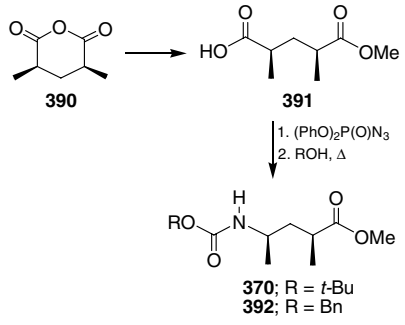
On the other hand, Mn-mediated addition of iodide **386** to hydrazone **385** afforded the corresponding **387** in 56% yield

and >98:2 dr. The reaction of **387** with trifluoroacetic anhydride (TFAA) and DMAP in pyridine, followed by treatment with SmI_2, gave the TFA-protected derivative **388** in good overall yield. Finally, cleavage of the TBS protecting group in **388** with TBAF in THF, and subsequent oxidation of the resulting primary alcohol with $(AcO)_2IC_6H_5$ in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) afforded α,γ-disubstituted *N*-TFA-γ-amino acid **389** in 81% yield (Scheme 96).[155]



Scheme 96.

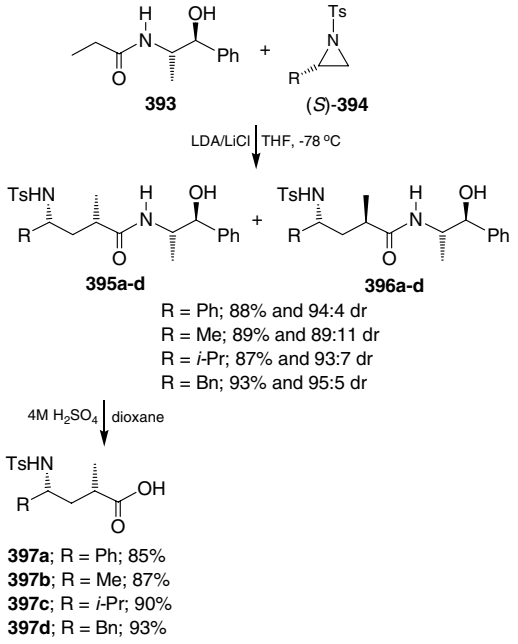
Curtius degradation of monoester **391** readily obtained from *meso*-2,4-dimethylglutaric anhydride **390**, with $(PhO)_2P(O)N_3$ in the presence of the appropriate alcohol gave the α,γ-disubstituted N-protected γ-amino acid derivatives (2*S*,4*R*)-**370** and (2*S*,4*R*)-**392** (Scheme 97).[156]



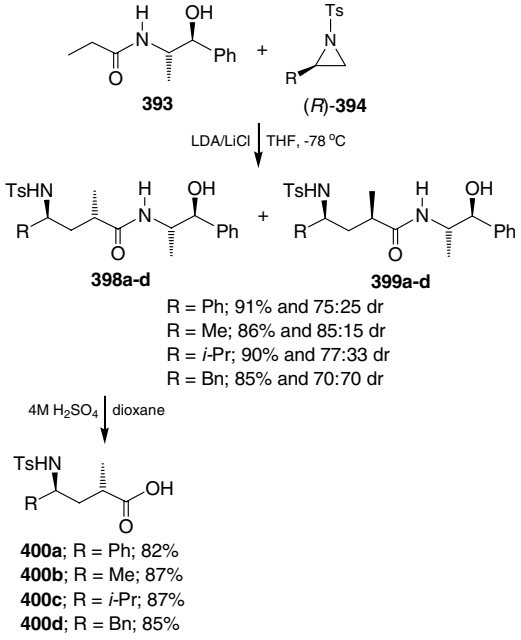
Scheme 97.

Reaction of lithium enolate generated from propionamide **393** with the (*S*)-*N*-tosylaziridine **394a–d** in the presence of LiCl at −78 °C afforded the corresponding γ-aminoamides **395a–d** and **396a–d** in good yield and diastereoselectivity. Acidic hydrolysis of diastereoisomerically pure **395a–d** gave the α,γ-disubstituted *N*-tosyl-γ-amino acids **397a–d** in good chemical yield (Scheme 98).[157]

On the other hand, reaction of lithium enolate derived from propionamide **393** with (*R*)-*N*-tosylaziridine **394a–d** in the presence of LiCl at −78 °C afforded the corresponding γ-aminoamides **398a–d** and **399a–d** in good yield but low diastereoselectivity. Hydrolysis of diastereoisomerically pure **398a–d** gave α,γ-disubstituted *N*-tosyl-γ-amino acids **400a–d** in good chemical yield (Scheme 99).[157]



Scheme 98.



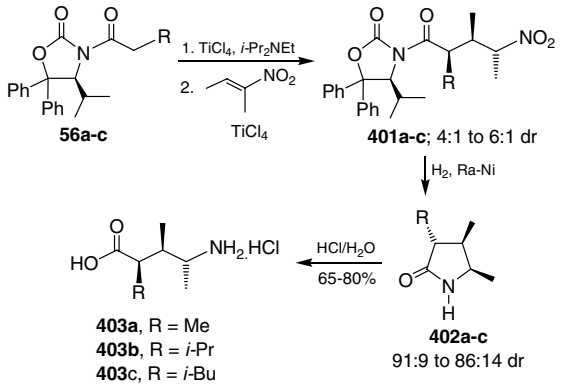
Scheme 99.

In all cases, it was observed that the ring-opening reaction was regioselective, in the sense that only the products arising from attack of the enolate at the less substituted carbon atom of the aziridine ring were obtained. Therefore, it can be concluded that the lithium enolate derived from propionamide **393** and (*S*)-*N*-tosylaziridines **394a–d** afforded a matched combination, leading to γ-aminoamides **395a–d** as principal products. On the contrary, the same enolate

and (*R*)-*N*-tosylaziridines **394a**–**d** gave a mismatched combination leading the γ-aminoamides **398a**–**d** and **399a**–**d** with poor diastereoselectivity.[158]

2.7. α,β,γ-Trisubstituted γ-amino acids

The Michael addition of the titanium enolate generated from *N*-acyloxazolidinones **56a**–**c** to (*E*)-2-nitro-2-butene afforded the nitro derivatives **401a**–**c** in moderate diastereoselectivity (4:1 to 6:1 dr). Catalytic hydrogenation of diastereoisomerically pure nitro compounds **401a**–**c** in the presence of Raney-nickel led to the γ-lactams **402a**–**c** in 91:9 to 86:14 dr. Acidic hydrolysis of γ-lactams **402a**–**c** in refluxing 6 M HCl gave the α,β,γ-trisubstituted γ-amino acids **403a**–**c** in good yield and >98:2 dr (Scheme 100).[159]



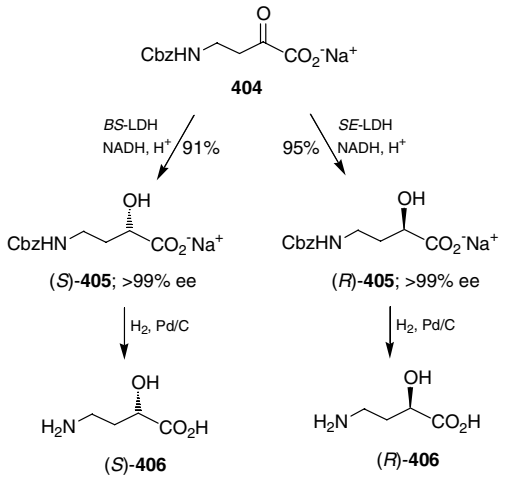
Scheme 100.

3. Stereoselective synthesis of hydroxy-γ-amino acids

3.1. α-Hydroxy-γ-amino acids

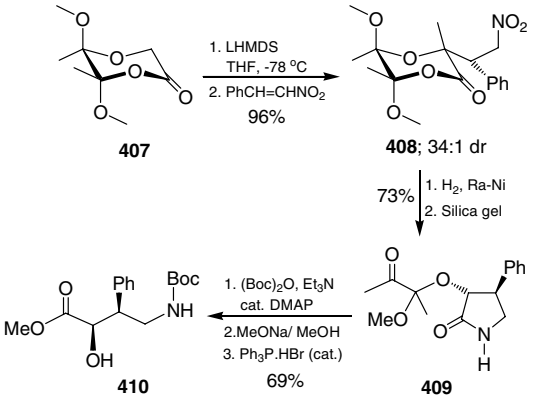
Homoisoserine **406** (2-hydroxy-4-aminobutyric acid), an α-hydroxy-γ-amino acid, is one of the most potent known inhibitors of the neurotransmitter 4-aminobutanoic acid and exhibits anticancer activity.[160] Additionally, **406** is a component of numerous antibiotics, such as arbekacin,[161] amikacin,[162] and butirosin.[163] Therefore, numerous synthetic methodologies have been developed. For example, Willis et al.[164] have reported the enantioselective synthesis of (*S*)- and (*R*)-2-hydroxy-4-aminobutyric acid **406** via lactate dehydrogenase catalyzed reduction of sodium salt of 4-benzyloxycarbonylamino-2-oxobutanoate **404**. In this context, treatment of **404** with commercially available *Bacillus stearothermophilus* (*BS*-LDH) and formate dehydrogenase (FDH) afforded (*S*)-2-hydroxy acid **405** in 91% yield and >99% ee. The reduction of **404** with *Staphylococcus epidermidis* (*SE*-LDH) gave (*R*)-2-hydroxy acid **405** in 95% yield and >99% ee. Catalytic hydrogenolysis of (*S*)- and (*R*)-**405** provided enantiomerically pure (*S*)- and (*R*)-homoisoserine **406**, respectively (Scheme 101).[165]

Michael addition of the lithium enolate generated from glycolate **407** to *trans*-nitrostyrene gave the corresponding nitro derivative **408** in 96% yield and 34:1 diastereoisomeric



Scheme 101.

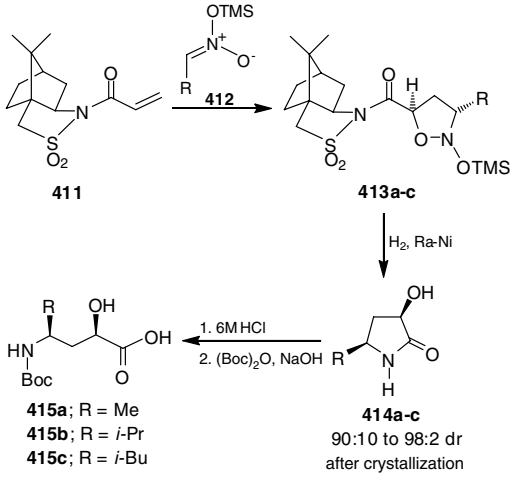
ratio. Reduction of the nitro group in **408** using Raney-nickel led to γ-lactam **409** in 73% yield. Protection of the amino group in γ-lactam **409** with $(Boc)_2O$ followed by reaction with sodium methoxide in methanol and subsequent treatment with catalytic amount of triphenylphosphine hydrobromide in methanol afforded α-hydroxy-γ-amino acid methyl ester **410** in 69% overall yield (Scheme 102).[166]



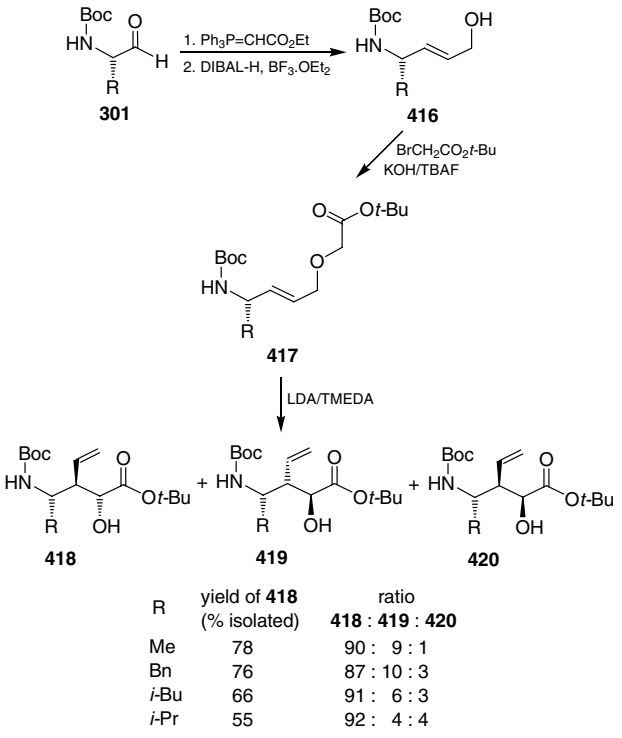
Scheme 102.

On the other hand, 1,3-dipolar cycloaddition reaction of acryloylcamphorsultam **411** with trimethylsilyl nitronates **412** led to the corresponding isoxazolidines **413a**–**c** together with small amounts of the other stereoisomers, which by catalytic hydrogenation using Raney-nickel afforded the γ-lactams **414a**–**c** in 90:10 to 98:2 dr after crystallization. Finally, acidic hydrolysis followed by treatment with di-(*tert*-butyl)dicarbonate $(Boc)_2O$ gave the protected α-hydroxy-γ-amino acids **415a**–**c** (Scheme 103).[167]

Stereoselective rearrangement of enantiomerically pure 4-amino-allyloxy-acetates **417** obtained in three steps from *N*-Boc-α-amino aldehydes **301**, using lithium diisopropylamide (LDA) in the presence of *N*,*N*,*N*′*N*′-tetramethylethylenediamide (TMEDA), afforded α-hydroxy-γ-amino acid **418** as the major product (Scheme 104).[168]



Scheme 103.



R	yield of **418** (% isolated)	ratio **418** : **419** : **420**
Me	78	90 : 9 : 1
Bn	76	87 : 10 : 3
i-Bu	66	91 : 6 : 3
i-Pr	55	92 : 4 : 4

Scheme 104.

In the formation of α-hydroxy-γ-amino acids **418**, an *endo*-transition state **421** can be invoked, in which 1,3-allylic strain[150] is minimized and the heteroatom at the stereogenic center (deprotonated N) is placed in an antiperiplanar manner with respect to the attacking enolate. Transition state **422** is also an *endo*-type, but entails increased 1,3-allylic strain, which led to the minor diastereoisomer **419**. Diastereoisomer **420** was formed via the *exo*-transition state **423** in which the R group and the enolate species undergo unfavorable steric interactions (Fig. 4).

Treatment of (*S*)-2,4-diaminobutyric acid dihydrochloride **424** obtained from (*S*)-glutamic acid, with sodium nitrite

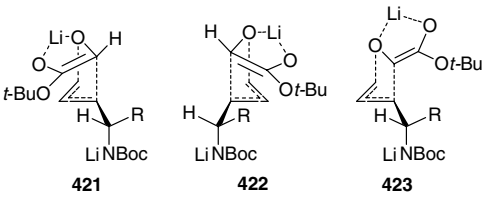
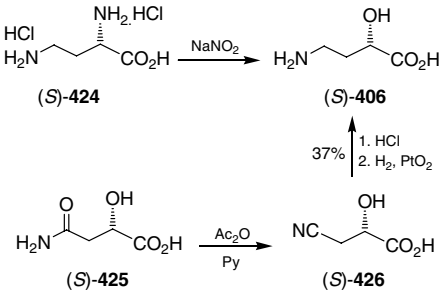


Figure 4.

afforded enantiomerically pure (*S*)-4-amino-2-hydroxybutyric acid **406**.[169] On the other hand, treatment of (*S*)-**425** available from (*S*)-asparagine, with acetic anhydride in pyridine gave the cyano derivative (*S*)-**426**, which on acidic hydrolysis, followed by catalytic hydrogenation using platinum oxide, led to (*S*)-γ-amino-β-hydroxybutyric acid **406** in 37% yield (Scheme 105).[170]



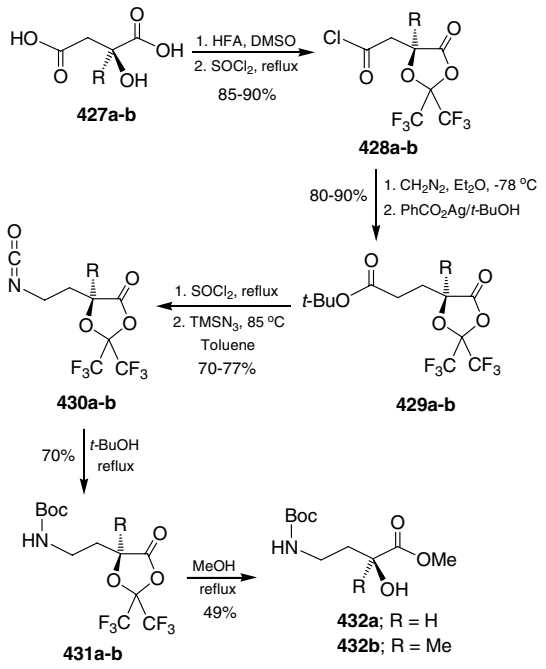
Scheme 105.

Reaction of carboxylic acids **427a** and **427b** with hexafluoroacetone (HFA) in DMSO, followed by treatment with $SOCl_2$, gave the acid chlorides **428a** and **428b**, which were converted into *tert*-butyl ester derivatives **429a** and **429b** via an Arndt–Eistert homologation. The reaction of *tert*-butyl esters **429a** and **429b** with an excess of thionyl chloride at reflux followed by treatment with $TMSN_3$ afforded the isocyanates **430a** and **430b** via Curtius rearrangement. Treatment of **430a** and **430b** with *tert*-butyl alcohol produced the stable γ-*N*-Boc-amino derivatives **431a** and **431b**, which by reaction with methyl alcohol led to enantiomerically pure *N*-Boc-homoisoserine derivatives **432a** and **432b** (Scheme 106).[171]

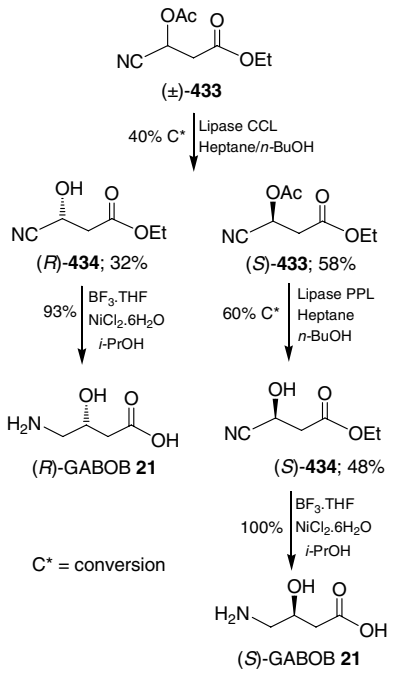
3.2. β-Hydroxy-γ-amino acids (GABOB[172] and Carnitine[173])

Selective enzymatic transesterification of racemic *O*-acetyl cyanohydrin **433** using lipase from yeast *Candida cylindracea* (CCL) afforded optically active (*R*)-cyanohydrin **434** in 32% yield and the enriched (*S*)-*O*-acetyl cyanohydrin **433** in 58% yield. Treatment of enriched (*S*)-*O*-acetyl cyanohydrin **433** with lipase from porcine pancreas (PPL), gave enantiomerically pure (*S*)-cyanohydrin **434** in 48% yield. Reduction of the cyano group in (*R*)- and (*S*)-**434** using a combination of BH_3·THF complex and $NiCl_2·6H_2O$ produced the enantiomerically pure (*R*)- and (*S*)-GABOB **21** in 93 and 100% yield, respectively (Scheme 107).[174]

On the other hand, treatment of 1-carbobenzyloxy-1,2,3,4-tetrahydro-3-hydroxypyridine (±)-**435** obtained from

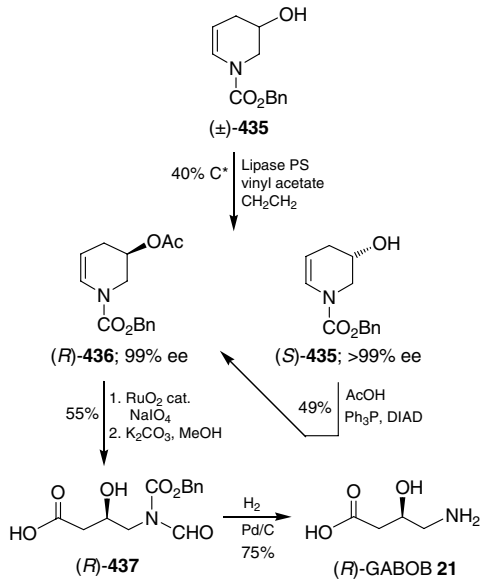


Scheme 106.



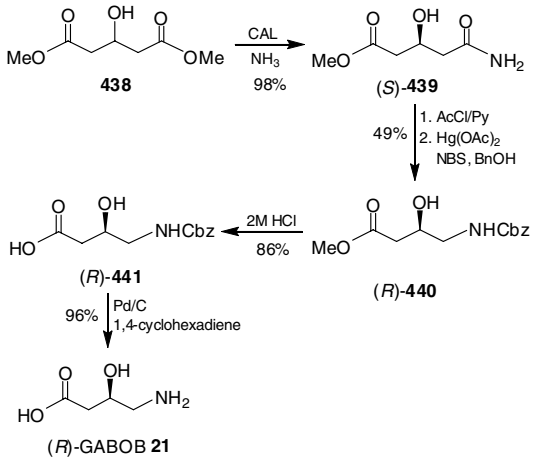
Scheme 107.

3-hydroxypyridine, with lipase PS (*Pseudomonas cepacia*) afforded (*R*)-acetate **436** in 99% ee and the unreacted alcohol (*S*)-**435** in >99% ee. The reaction of (*S*)-**435** with acetic acid and triphenylphosphine in the presence of diisopropyl azodicarboxylate (DIAD) gave (*R*)-acetate **436** in 49% yield. Oxidation of (*R*)-acetate **436** (>99% ee) with $NaIO_4$ and a catalytic amount of RuO_2 followed by treatment with methanol in the presence of potassium carbonate produced β-hydroxy acid **437** in 55% yield, which on catalytic hydrogenation produced the enantiomerically pure (*R*)-GABOB **21** in 75% yield (Scheme 108).[175]



Scheme 108.

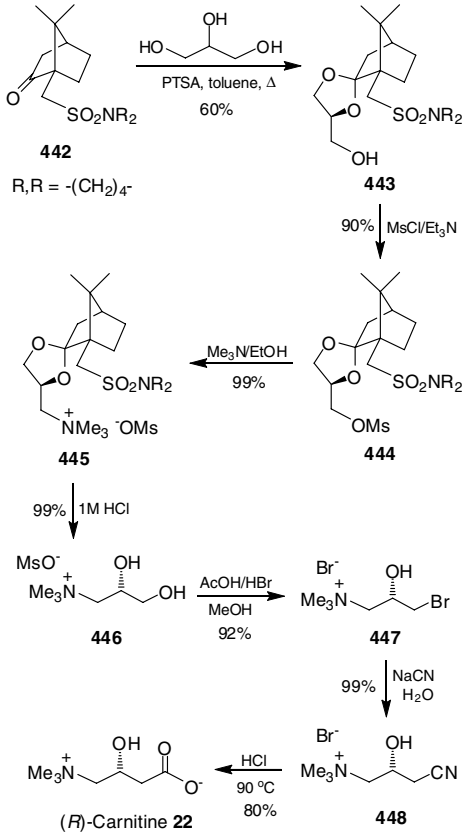
Enzymatic aminolysis reaction of dimethyl 3-hydroxyglutarate **438** using *Candida antarctica* (CAL) afforded the enantiomerically pure (*S*)-monoamide **439** in 98% yield. Acetylation reaction of (*S*)-**439** with acetic anhydride in pyridine followed by treatment with $Hg(OAc)_2$ and NBS in benzyl alcohol gave the benzyl carbamate (*R*)-**440** in 49% yield via a Hoffmann reaction. Acidic hydrolysis of benzyl carbamate (*R*)-**440** led to (*R*)-*N*-Cbz-GABOB **441** in 86% yield. Finally, hydrogenolysis of (*R*)-**441** using Pd/C in 1,4-cyclohexadiene gave enantiomerically pure (*R*)-GABOB **21** in 96% yield (Scheme 109).[176] In a similar way, (*R*)-GABOB **21** was prepared using several microorganisms in the desymmetrization of **438**.[177]



Scheme 109.

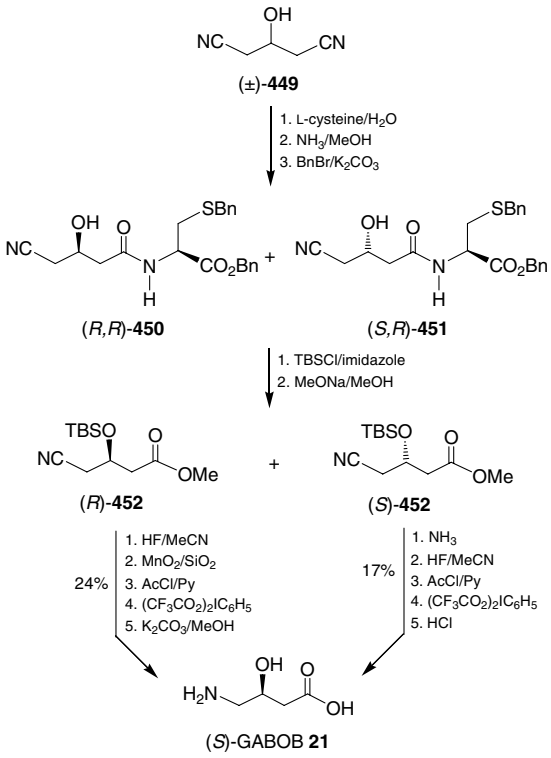
On the other hand, the reaction of sulfonamide derivative **442** with glycerol afforded only the spiro-cetal **443** in 60%

yield. Treatment of acetal **443** with methanesulfonyl chloride and Et_3N gave the corresponding mesylate derivative **444** in 90% yield, which on reaction with Me_3N led to trimethylammonium compound **445** in 99% yield. Cleavage of the chiral auxiliary with HCl provided diol (*S*)-**446** in 99% yield, which upon treatment with HBr in acetic acid gave the bromo derivative (*S*)-**447** in 92% yield. Nucleophilic displacement of the halogen group in (*S*)-**447** with sodium cyanide produced cyano derivative (*R*)-**448** in 99% yield, which by acidic hydrolysis of the cyano group led to (*R*)-carnitine **22** in 80% yield (Scheme 110).[178]



Scheme 110.

A condensation reaction of 3-hydroxyglutaronitrile (±)-**449** with enantiomerically pure L-cysteine, followed by treatment with methanolic ammonia and subsequent addition of benzyl bromide, afforded monoamides (*R*,*R*)-**450** and (*S*,*R*)-**451**. Silylation of the hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl) of diastereoisomerically pure (*R*,*R*)-**450** and (*S*,*R*)-**451** followed by methanolysis gave methyl esters (*R*)- and (*S*)-**452**, respectively. Deprotection of the hydroxy group in (*R*)-**452** with HF, followed by sequential hydrolysis of the nitrile group with a mixture of MnO_2/SiO_2, acetylation, Hoffmann degradation using [bis(trifluoroacetoxy)]iodobenzene $(CF_3CO_2)_2IC_6H_5$ and saponification, led to (*S*)-GABOB **21** in 24% yield. On the other hand, treatment of enantiomerically pure (*S*)-**452** with liquid ammonia, followed by sequential deprotection of the hydroxy group, Hoffmann rearrangement and acidic hydrolysis, gave the enantiomerically pure (*S*)-GABOB **21** in 17% yield (Scheme 111).[179]

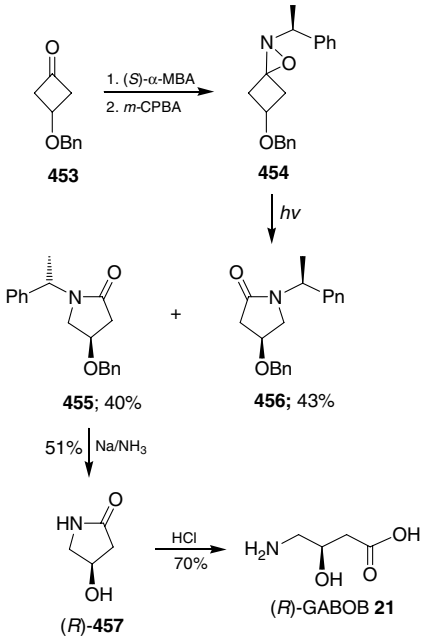


Scheme 111.

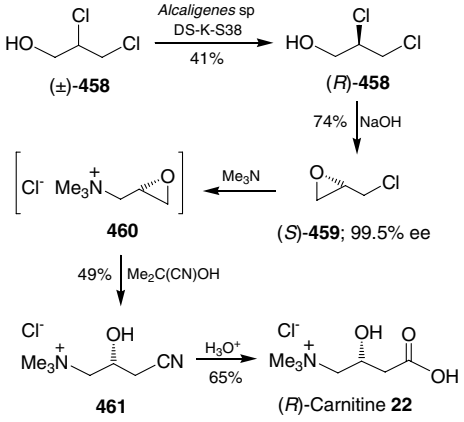
Imine formation of 3-benzyloxycyclobutanone **453** with (*S*)-α-methylbenzylamine [(*S*)-α-MBA] followed by oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded oxaziridines **454** in 70–79% yield and 49:28:17:6 ratio of the four stereoisomers. Photolysis of the mixture of the oxaziridines **454** in acetonitrile gave the readily separable γ-lactams **455** and **456** in 40% and 43% yield, respectively. Cleavage of both protective groups, *N*-α-methylbenzyl and benzyl, in **455** by treatment with sodium in ammonia led to (*R*)-4-hydroxypyrrolidin-2-one **457** in 51% yield, which upon acidic hydrolysis provided (*R*)-GABOB **21** in 70% yield (Scheme 112).[180,181]

On the other hand, treatment of (±)-2,3-dichloro-1-propanol **458** with *Alcaligenes* sp. DS-K-S38 gave enantiomerically pure (*R*)-2,3-dichloro-1-propanol **458** in 41% yield, which by reaction with NaOH afforded (*S*)-epichlorhydrin **459** in 74% yield and 99.5% ee. Addition of Me_3N to (*S*)-**459** followed by treatment with acetone cyanohydrin led to cyano derivative (*R*)-**461** in 49% yield, which on hydrolysis produced enantiomerically pure (*R*)-carnitine **22** in 65% yield as a chloride salt (Scheme 113).[182]

The enzyme-catalyzed hydrolysis of 3,4-epoxybutyrate (±)-**462** using steapsin (700) lipase from *C. cylindracea* afforded (*R*)-3,4-epoxybutyrate **462** in >95% ee, and the carboxylic acid derivative (*S*)-**463**. Treatment of (*R*)-3,4-epoxybutyrate **462** with trimethylamine hydrochloride gave ester derivative **464** accompanied by an extensive amount (ca. 50%) of the corresponding allyl alcohol **465**. The conversion of ester (*R*)-**462** into the corresponding carboxylic acid (*R*)-**463** is difficult to be carried out by conventional chemical methods, but the treatment of (*R*)-**462** with alcalasa 2.0



Scheme 112.

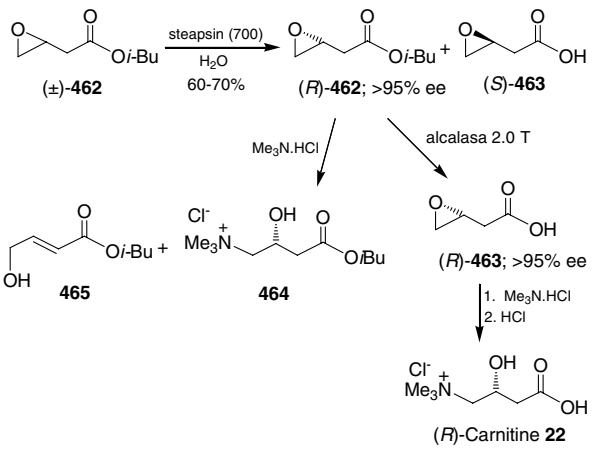


Scheme 113.

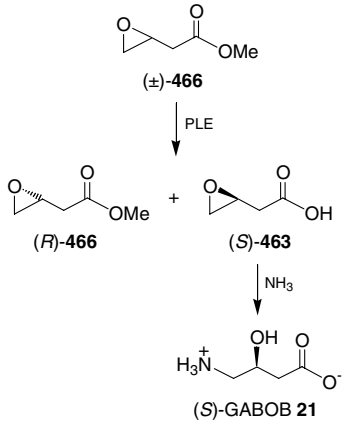
T produced carboxylic acid (*R*)-**463**, which upon reaction with trimethylamine hydrochloride followed by addition of HCl led to the enantiomerically pure (*R*)-carnitine **22** in 79% yield as a chloride salt (Scheme 114).[183]

On the other hand, enzymatic hydrolysis of (±)-**466** using pig liver esterase (PLE) afforded methyl ester derivative (*R*)-**466** and carboxylic acid (*S*)-**463** in 40% and 30% yield, respectively. Treatment of (*S*)-**463** with liquid ammonia led to enantiomerically pure (*S*)-GABOB **21** in 97% ee (Scheme 115).[184]

Selective transesterification of racemic 2,2,2-trichloroethyl-3,4-epoxybutanoate (±)-**467** with poly(ethylene glycols) of low molecular weight in the presence of porcine pancreas lipase (PPL) as a catalyst afforded the corresponding esters (*R*)-**467** and (*S*)-**468**. Hydrolysis of enantiomerically pure (*R*)-**467** using *Pseudomonas* sp. followed by treatment with

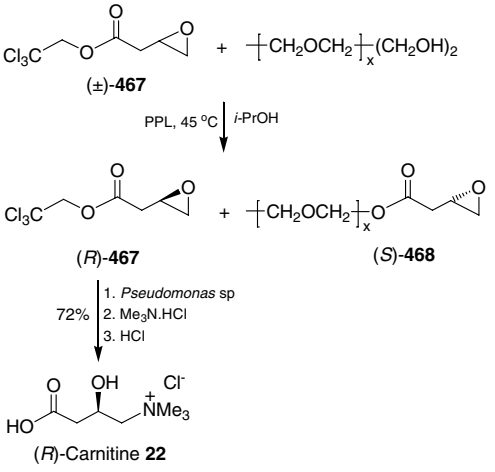


Scheme 114.



Scheme 115.

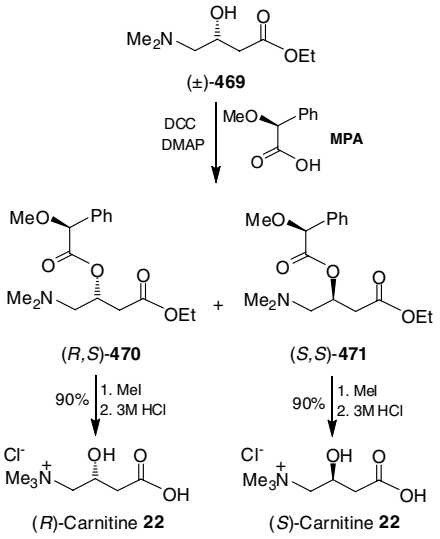
trimethylamine hydrochloride and subsequent addition of HCl gave (*R*)-carnitine **22** as a chloride salt in >96% ee and 72% yield (Scheme 116).[185]



Scheme 116.

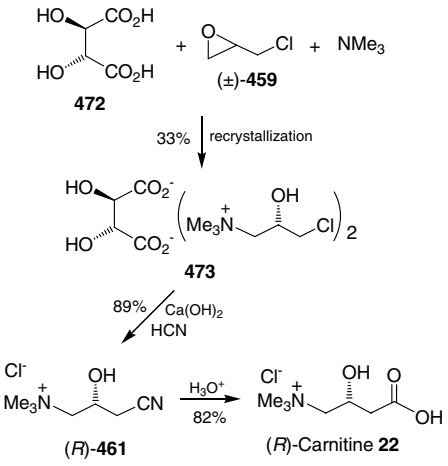
On the other hand, esterification of racemic hydroxy derivative (±)-**469** with (*S*)-α-methoxyphenylacetic acid (MPA)

produced a 1:1 mixture of diastereoisomers (*R*,*S*)-**470** and (*S*,*S*)-**471**. Treatment of diastereoisomerically pure (*R*,*S*)-**470** and (*S*,*S*)-**471** with CH_3I followed by acidic hydrolysis with 3 M HCl provided the enantiomerically pure (*R*)- and (*S*)-carnitine **22**, respectively, in 90% yield (Scheme 117).[186] Similar results were obtained using (*R*)-α-methoxyphenylacetic acid as a resolving agent.



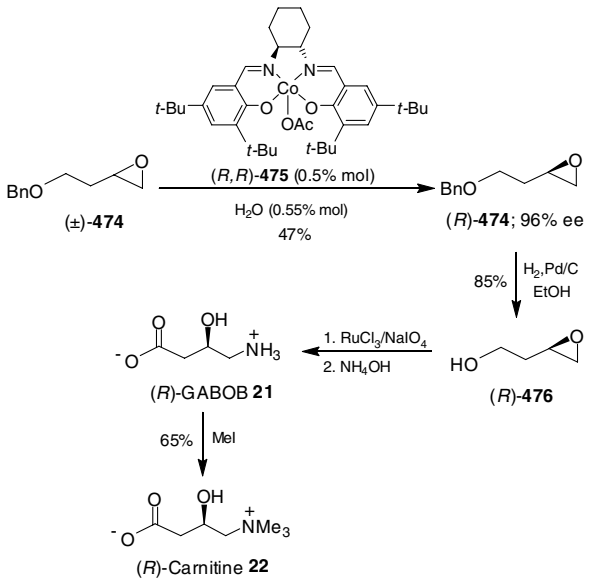
Scheme 117.

The reaction of racemic epichlorohydrin (±)-**459** with trimethylamine in the presence of L-tartaric acid **472** followed by recrystallization gave bis(trimethylammonium) tartrate salt **473** in 33% yield. Treatment of tartrate salt **473** with $Ca(CN)_2$ obtained in situ from the reaction of $Ca(OH)_2$ with HCN afforded the cyano derivative (*R*)-**461** in 89% yield. Acidic hydrolysis of the cyano group in (*R*)-**461** led to (*R*)-carnitine **22** in 82% yield as a chloride salt (Scheme 118).[187]



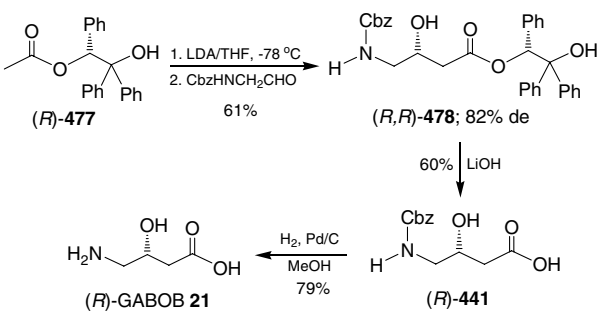
Scheme 118.

More recently, Bose et al.[188] reported a practical approach for the synthesis of (*R*)-GABOB **21** and (*R*)-carnitine **22** using Jacobsen's hydrolytic kinetic resolution technique to resolve epoxide (±)-**474**. Thus, treatment of epoxide (±)-**474** with (*R*,*R*)-salen-Co(III)-OAc **475** complex in water afforded epoxide (*R*)-**474** in 47% yield and 96% ee. Cleavage of the benzyl protective group in (*R*)-**474** by hydrogenolysis gave the corresponding epoxy alcohol (*R*)-**476** in 85%, which by oxidation with $RuCl_3/NaIO_4$ followed by nucleophilic opening of the epoxide ring with a solution of concentrated ammonium hydroxide led to enantiomerically pure (*R*)-GABOB **21**. Finally, methylation of (*R*)-GABOB **21** under basic conditions produced (*R*)-carnitine **22** in 65% yield (Scheme 119).



Scheme 119.

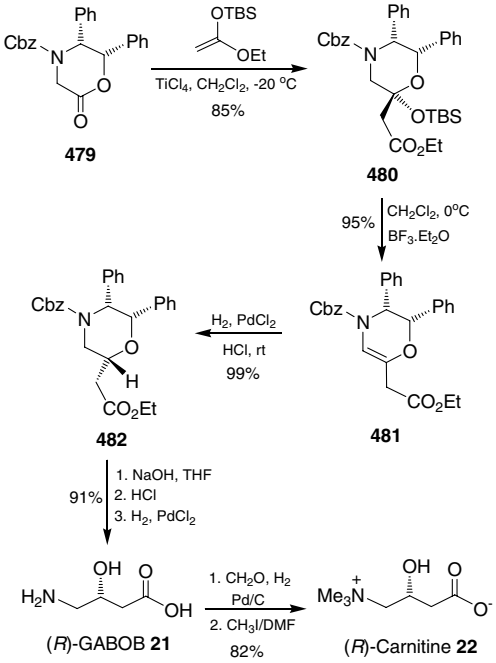
The addition of lithium enolate generated from (*R*)-2-hydroxy-1,2,2-triphenylethyl acetate (HYTRA) **477** to *N*-Cbz-glycinal gave ester (*R*,*R*)-**478** in 61% yield and 82% de. Mild alkaline hydrolysis of (*R*,*R*)-**478** afforded *N*-Cbz-γ-amino acid (*R*)-**441**, which upon hydrogenation led to (*R*)-GABOB **21** in 79% yield and 98% ee, after recrystallization (Scheme 120).[189]



Scheme 120.

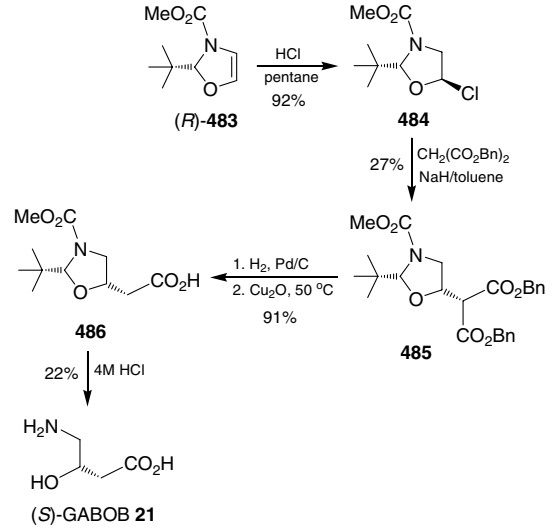
Jain and Williams[190] have described the stereoselective synthesis of (*R*)-GABOB **21** and (*R*)-carnitine **22** from commercially available 1,4-oxazin-2-one **479** via a $TiCl_4$-promoted Mukaiyama-type reaction. In this context, the

reaction of **479** with the *tert*-butyldimethylsilylketene acetal of ethyl acetate in the presence of $TiCl_4$ afforded the *tert*-butyldimethylsilyl (TBS) protected hemiacetal **480** as one single diastereoisomer, which upon treatment with $BF_3{\cdot}Et_2O$ gave the elimination product **481** in 95% yield. Hydrogenation of **481** with H_2 in the presence of $PdCl_2$ led to the *syn*-substituted oxazine **482** in 99% yield. Hydrolysis of **482** followed by hydrogenolysis provided (*R*)-GABOB **21** in 91% yield, which was converted into (*R*)-carnitine **22** in 82% yield (Scheme 121).

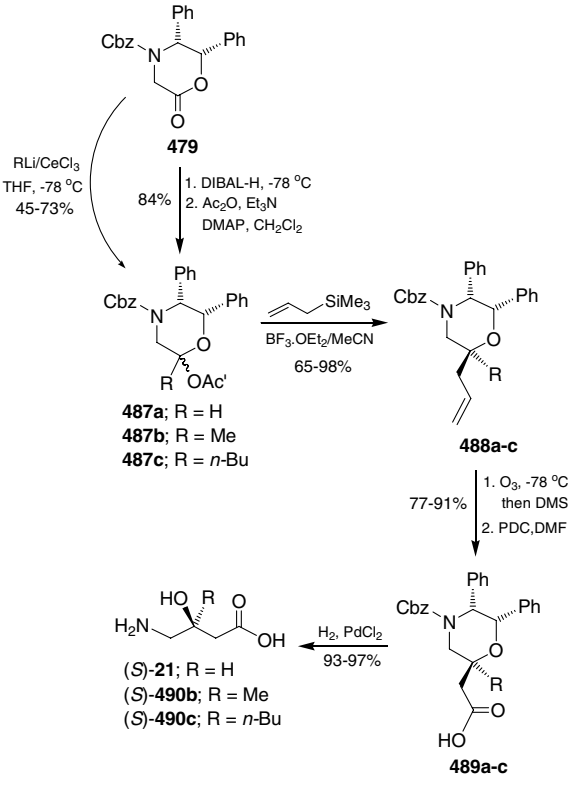


Scheme 121.

Reaction of enantiomerically pure (*R*)-2-*tert*-butyl-1,3-oxazoline **483** readily prepared from L-serine with hydrogen chloride gave the chloro derivative **484** in 92% yield, which by treatment with sodium salt of dibenzylmalonate produced diester **485** in 27% yield. Cleavage of the protective benzyl group in **485** under hydrogenolysis followed by decarboxylation using Cu_2O afforded carboxylic acid **486** in 91% yield. Finally, acidic hydrolysis of **486** provided (*S*)-GABOB **21** in 22% yield (Scheme 122).[191]



Scheme 122.

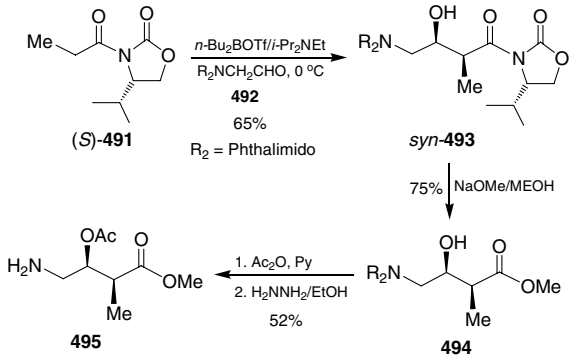


Scheme 123.

On the other hand, treatment of commercially available 1,4-oxazin-2-one **479** with DIBAL-H followed by reaction with acetic anhydride gave the corresponding hemiacetal **487a** in 84% yield, whereas the reaction of **479** with MeLi or *n*-BuLi in the presence of $CeCl_3$ led to hemiacetals **487b**,**c** in 45–73% yield. The reaction of **487a**–**c** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ afforded allyl derivatives **488a**–**c** as a single diastereoisomer. An ozonolysis reaction of **488a**–**c** followed by oxidation with PDC in DMF gave the carboxylic acids **489a**–**c**, which by catalytic hydrogenation in the presence of $PdCl_2$ provided (*R*)-GABOB **21** and their derivatives **490b**,**c** in good yield (Scheme 123).[192]

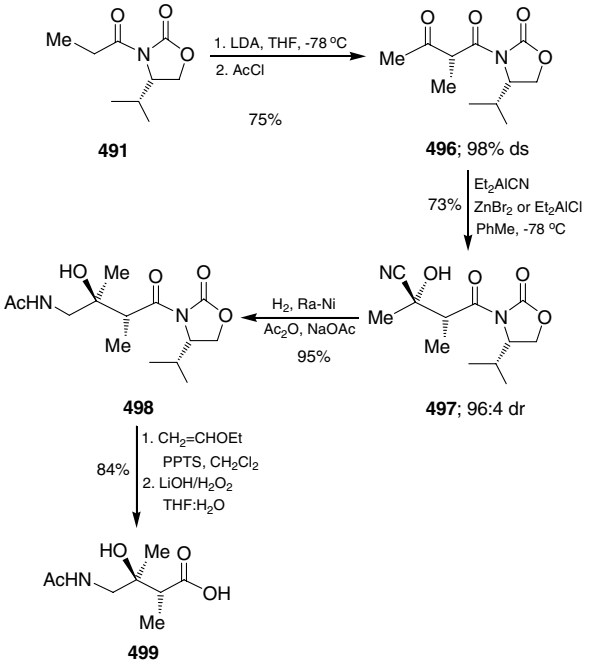
The addition of the boron enolate derived from oxazolidinone (*S*)-**491** to amino aldehyde **492** afforded the *syn* aldol **493** in 65% yield, which by treatment with sodium methoxide gave the γ-amino ester derivative **494** in 75% yield. An acetylation reaction of **494** followed by cleavage of the phthalimido protective group with hydrazine gave **495** in 52% yield (Scheme 124).[193]

On the other hand, the addition of Et_2AlCN to a dicarbonyl derivative **496** readily available from *N*-propio-



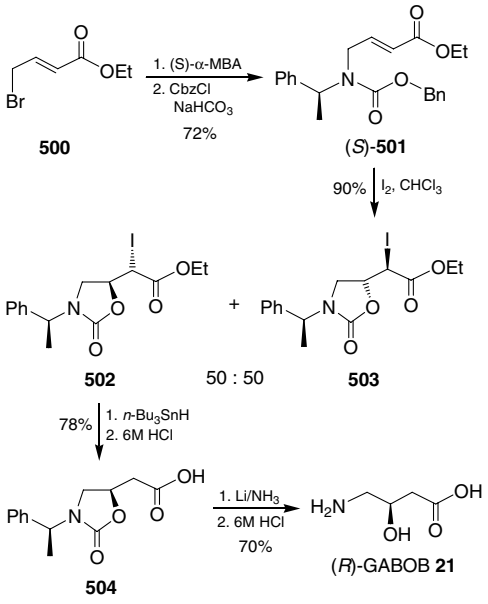
Scheme 124.

nyloxazolidinone (*S*)-**491**, in the presence of $ZnBr_2$ or Et_2AlCl, afforded the corresponding cyanohydrin **497** in 73% yield and 96:4 dr. Catalytic hydrogenation of the cyano group in **497** with Raney-nickel gave amino alcohol derivative **498**, which upon protection of the hydroxy group with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS), followed by cleavage of the chiral auxiliary under basic hydrolysis, provided the *N*-acetyl GABOB derivative **499** in 84% yield (Scheme 125).[194]



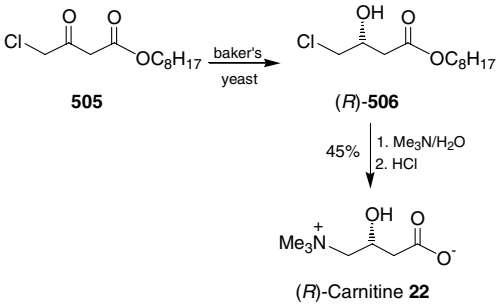
Scheme 125.

Iodocyclization of derivative (*S*)-**501** obtained from (*S*)-α-methylbenzylamine [(*S*)-α-MBA] and (*E*)-4-bromo-2-butenoate **500** gave a readily separable mixture (50:50) of oxazolidin-2-ones **502** and **503**. Cleavage of the C–I bond in diastereoisomerically pure **502** with tri-*n*-butyltin hydride afforded oxazolidinone **504** in 78% yield, which by treatment with lithium in liquid ammonia provided (*R*)-GABOB **21** (Scheme 126).[195] (*S*)-GABOB **21** can be obtained from **503**.



Scheme 126.

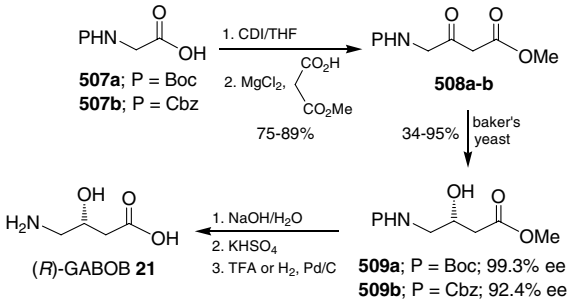
Reduction of 4-chloro-3-oxobutyrate **505** with baker's yeast (*Saccharomyces cerevisiae*) afforded (*R*)-4-chloro-3-hydroxybutyrate **506** in high enantiomeric excess, which upon treatment with excess trimethylamine, followed by acidic hydrolysis, gave (*R*)-carnitine **22** in 45% yield (Scheme 127).[196] (*R*)-GABOB **21** has been obtained in a similar way via reduction of 4-azido-3-oxobutyrate with *S. cerevisiae*.[197]



Scheme 127.

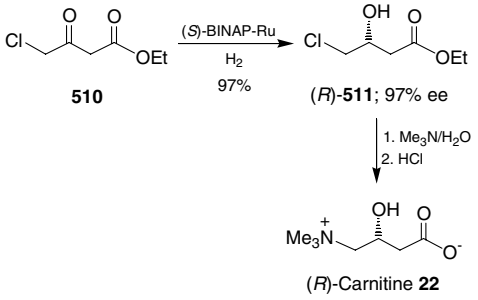
In a similar way, baker's yeast reduction of β-oxo esters **508a** and **508b** readily available from N-protected glycine **507a** and **507b** afforded the corresponding hydroxy esters **509a** and **509b** in good yield and 99.3% ee for **509a** and 92.4% ee for **509b**. Hydrolysis of the methyl ester function in **509a** and **b** followed by cleavage of the protective groups with trifluoroacetic acid or H_2 in the presence of Pd/C produced the enantiomerically pure (*R*)-GABOB **21** (Scheme 128).[198]

On the other hand, homogeneous enantioselective hydrogenation of ethyl 4-chloro-3-oxobutanoate **510** using Ru-$(OCOCH_3)_2$[(*S*)-BINAP] gave ethyl 4-chloro-3-hydroxybutanoate (*R*)-**511** in 97% yield and 97% ee, which could be transformed into (*R*)-carnitine **22** by treatment with



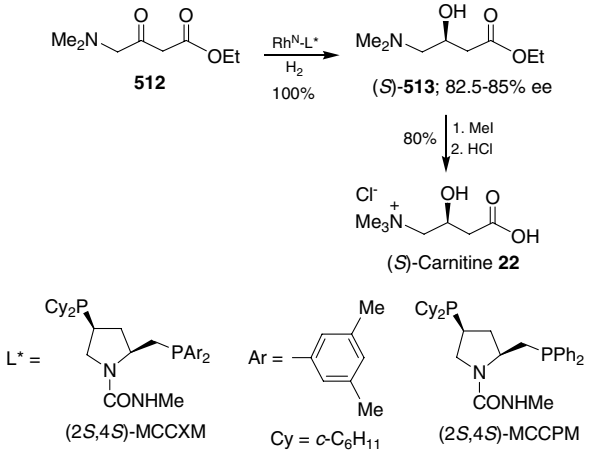
Scheme 128.

trimethylamine followed by hydrolysis (Scheme 129).[199] Ethyl 4-chloro-3-hydroxybutanoate (*S*)-**511** has been prepared via hydrogenation of **510** using $Ru(OCOCH_3)_2$[(*R*)-BINAP] as a catalyst.



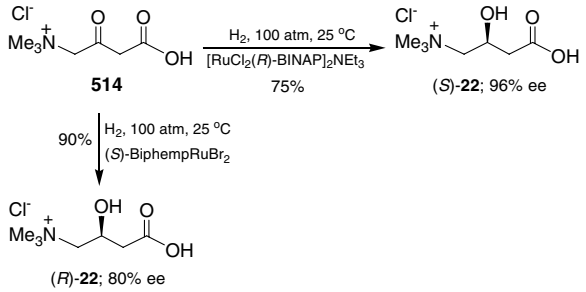
Scheme 129.

Asymmetric hydrogenation of ethyl 4-(dimethylamino)-3-oxobutanoate **512** catalyzed by ligands [4-(dicyclohexylphosphino)-2-(di-3,5-xylylphosphinomethyl)-*N*-methyl-1-pyrrolidinecarboxamide] [referred to as (2*S*,4*S*)-MCCXM] and [4-(dicyclohexylphosphino)-2-(diphenylphosphinomethyl)-*N*-methyl-1-pyrrolidinecarboxamide] [referred to as (2*S*,4*S*)-MCCPM] Rh^N complex gave ethyl 4-(dimethylamino)-3-hydroxybutanoate (*S*)-**513** in quantitative yield and moderate enantiomeric excess. Treatment of (*S*)-**513** with methyl iodide and acidic hydrolysis led to (*S*)-carnitine **22** as a chloride salt in 80% yield (Scheme 130).[200]



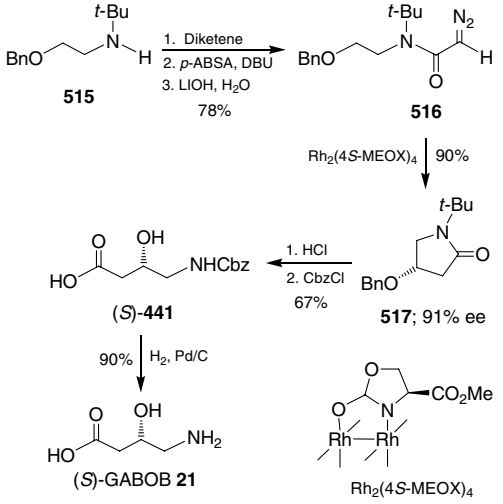
Scheme 130.

Enantioselective hydrogenation of 4-(trimethylammonium)-3-oxobutanoic acid **514** catalyzed by [$RuCl_2$(*R*)-BINAP]$_2NEt_3$ at room temperature and 100 atm afforded (*S*)-carnitine **22** as a chloride salt in 75% yield and 96% ee, whereas hydrogenation of **514** using (*S*)-BiphempRuBr_2 as a catalyst gave (*R*)-carnitine **22** as a chloride salt in 90% yield and 80% ee (Scheme 131). This procedure has also been used for the preparation of 4-chloro-3-hydroxybutanoate (*R*)-**511** in 100% yield and 89% ee.[201]



Scheme 131.

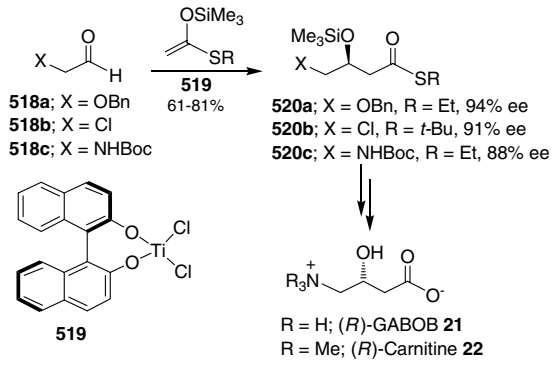
On the other hand, treatment of *N*-(2-benzyloxyethyl)-*N*-(*tert*-butyl)diazocetamide **516** readily obtained from **515** with Rh_2(4*S*-MEOX)$_4$ complex in THF at 20 °C afforded γ-lactam (*S*)-**517** in 90% yield and 78% ee (91% ee after purification). Hydrolysis of γ-lactam (*S*)-**517** with hydrochloric acid followed by treatment with benzyl chloroformate (CbzCl) gave (*S*)-*N*-Cbz-GABOB **441** in 67% yield. In this process, both *N*-*tert*-butyl and *O*-benzyl groups were removed together with the ring opening. Cleavage of Cbz protective group led to (*S*)-GABOB **21** in 90% yield (Scheme 132).[202]



Scheme 132.

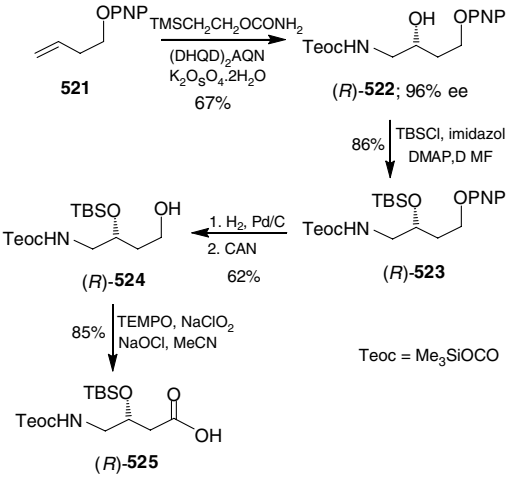
Asymmetric catalytic aldol-type reaction of aldehydes **518a–c** with the trimethylsilylketene acetal of ethyl or

tert-butyl thioacetate in the presence of chiral binaphthol-derived titanium dichloride **519** (BINOL–$TiCl_2$) afforded the aldol products (*R*)-**520a–c** in 61–81% yield and 88–94% ee, which are useful intermediates in the synthesis of (*R*)-GABOB **21** and (*R*)-carnitine **22** (Scheme 133).[203]



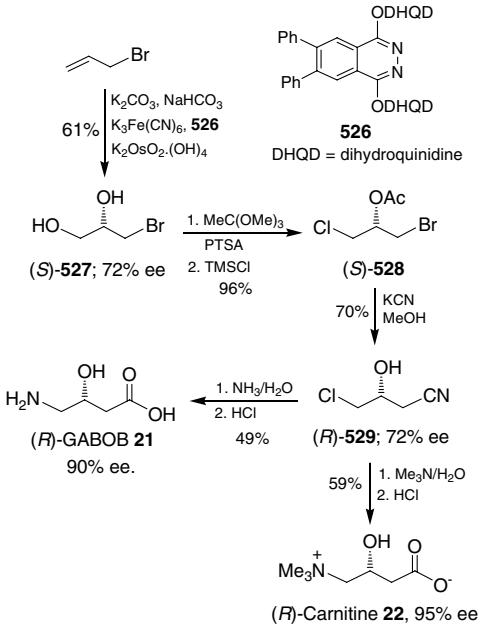
Scheme 133.

Asymmetric aminohydroxylation of ether **521** using dihydroquinidine ligand $(DHQD)_2AQN$ afforded γ-amino alcohol derivative (*R*)-**522** in 67% yield and 81% ee (96% ee after recrystallization), which upon treatment with TBSCl produced the corresponding triprotected compound (*R*)-**523** in 86% yield. Elimination of the *p*-nitrophenyl (PNP) protective group in (*R*)-**523** involving the reduction of the nitro group followed by acetylation and subsequent oxidative cleavage with cerium ammonium nitrate (CAN) provided alcohol (*R*)-**524** in 62% yield. Finally, oxidation of (*R*)-**524** with 2,2,6,6-tetramethyl-1-piperinyloxy (TEMPO) produced the diprotected (*R*)-GABOB derivative (*R*)-**525** in 85% yield (Scheme 134).[204]



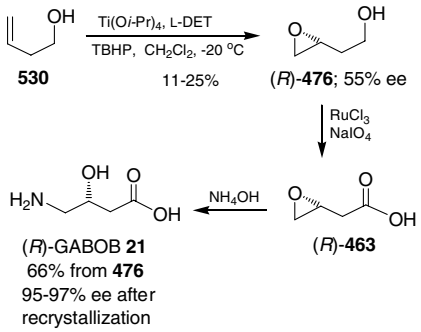
Scheme 134.

On the other hand, asymmetric dihydroxylation of allyl bromide in the presence of bis(dihydroquinidine) phthalazine **526** afforded bromo-diol (*S*)-**527** in 61% yield and 72% ee. The reaction of (*S*)-**527** with trimethyl orthoacetate and *p*-toluenesulfonic acid (PTSA), followed by the addition of trimethylsilyl chloride, gave the corresponding dihalide (*S*)-**528** in 96% yield, which by selective displacement of bromide with KCN produced cyano derivative (*R*)-**529** in 70% yield. Treatment of (*R*)-**529** with saturated aqueous ammonia and subsequent acidic hydrolysis gave (*R*)-GABOB **21** in 49% yield and 90% ee. However, the reaction of (*R*)-**529** with an excess of aqueous trimethylamine followed by hydrolysis with concentrated HCl led to (*R*)-carnitine **22** in 59% yield and 95% ee (Scheme 135).[205]



Scheme 135.

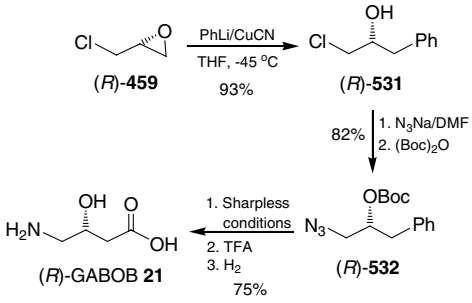
Asymmetric epoxidation of homoallyl alcohol **530** using $Ti(O\textit{i}\text{-}Pr)_4$, L-diethyl tartrate (L-DET), and *tert*-butyl hydroperoxide (TBHP) afforded epoxy alcohol (*R*)-**476** in 55% ee, which by oxidation using $RuCl_3/NaIO_4$ gave the epoxy acid (*R*)-**463**. Treatment of epoxy acid (*R*)-**463** with concentrated NH_4OH produced (*R*)-GABOB **21** in 66% yield from (*R*)-**476** and 49% ee, which by recrystallization provided (*R*)-GABOB **21** in 95–97% ee (Scheme 136).[206]



Scheme 136.

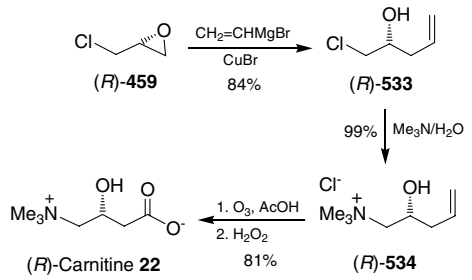
Treatment of commercially available (*R*)-epichlorohydrin **459** with phenyllithium in the presence of CuCN gave chlorhydrin (*R*)-**531** in 93% yield. The reaction of (*R*)-**531**

with sodium azide followed by protection of hydroxy group with di(*tert*-butyl)carbonate $(Boc)_2O$ afforded the compound (*R*)-**532** in 82% yield. Oxidation of (*R*)-**532** under Sharpless conditions,[206] followed by cleavage of the Boc protective group with trifluoroacetic acid (TFA) and subsequent reduction led to (*R*)-GABOB **21** in 75% yield (Scheme 137).[207]



Scheme 137.

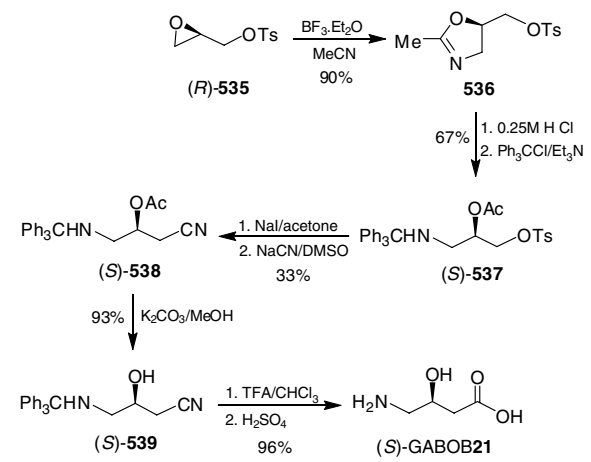
In a similar manner, the addition of vinyl magnesium bromide to (*R*)-epichlorohydrin **459** in the presence of CuBr afforded chlorhydrin (*R*)-**533** in 84% yield. Treatment of (*R*)-**533** with aqueous trimethylamine produced chlorohydrate (*R*)-**534** in 99% yield, which upon oxidative ozonolysis gave enantiomerically pure (*R*)-carnitine **22** in 81% yield (Scheme 138).[208]



Scheme 138.

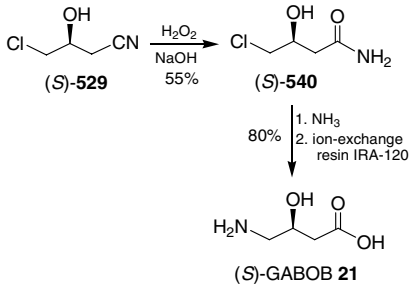
The reaction of commercially available (*R*)-glycidyl tosylate **535** with acetonitrile in the presence of boron trifluoride diethyl etherate gave the corresponding oxazoline **536**, which upon acidic hydrolysis followed by tritylation of the amino group afforded the tosylate derivative (*S*)-**537** in 67% yield. The reaction of (*S*)-**537** with sodium iodide and subsequent nucleophilic displacement with sodium cyanide led to cyano derivative (*S*)-**538** in 33% yield, which upon treatment with potassium carbonate produced cyano-alcohol (*S*)-**539** in 93% yield. Finally, acidic hydrolysis followed by cleavage of trityl protective group gave enantiomerically pure (*S*)-GABOB **21** in 96% yield (Scheme 139).[209]

An efficient synthesis of (*R*)-GABOB **21** from commercially available (*S*)-4-chloro-3-hydroxybutyronitrile (*S*)-**529** has been reported by Kawamoto et al.[210] In this context, the hydrolysis of the nitrile group in (*S*)-**529** with H_2O_2 and NaOH afforded amide (*S*)-**540**, which upon treatment with



Scheme 139.

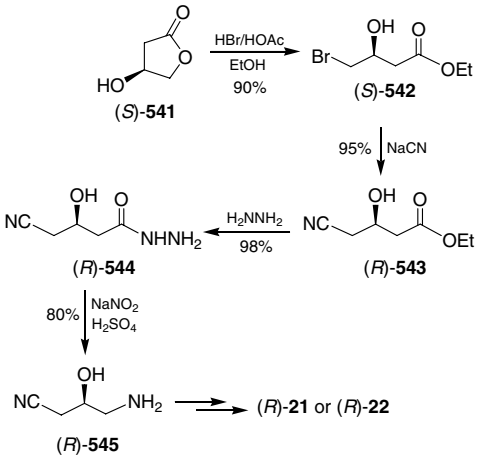
aqueous ammonia and subsequent hydrolysis with ion exchange resin IRA-120 (acid form) gave enantiomerically pure (*S*)-GABOB **21** in 80% yield (Scheme 140).



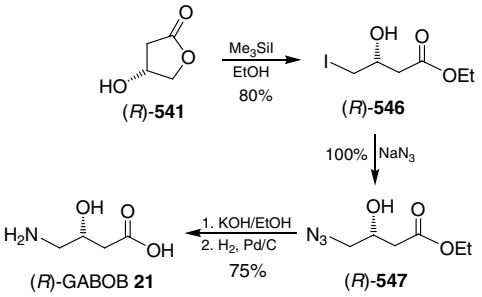
Scheme 140.

On the other hand, Wang and Hollingsworth[211] reported the synthesis of (*R*)-4-amino-3-hydroxybutyronitrile **545**, a key intermediate in the synthesis of (*R*)-GABOB **21** and (*R*)-carnitine **22**, using (*S*)-3-hydroxy-γ-butyrolactone **541** as the starting material, which is readily obtained from carbohydrates including lactose, maltose, and maltodextrins.[212] Thus, the reaction of γ-butyrolactone (*S*)-**541** with HBr and acetic acid in ethanol gave the bromoester derivative (*S*)-**542** in 90% yield, which by nucleophilic displacement with sodium cyanide afforded cyano compound (*R*)-**543**. Treatment of (*R*)-**543** with hydrazine led to derivative (*R*)-**544** in excellent yield. Finally, the reaction of (*R*)-**544** with sodium nitrite and sulfuric acid gave (*R*)-4-amino-3-hydroxynitrile **545** in 80% yield (Scheme 141). Compound (*R*)-**545** could then be transformed into (*R*)-GABOB **21** and (*R*)-carnitine **22** using the protocol described above.

On the other hand, treatment of (*R*)-3-hydroxy-γ-butyrolactone **541** with trimethylsilyliodide (Me_3SiI) in ethanol afforded iodohydrin (*R*)-**546** in 80% yield. Nucleophilic displacement of iodide in (*R*)-**546** with sodium azide gave the corresponding azidoester (*R*)-**547** in quantitative yield, which upon hydrolysis and subsequent catalytic hydrogenation gave enantiomerically pure (*R*)-GABOB **21** in 75% yield (Scheme 142).[213]



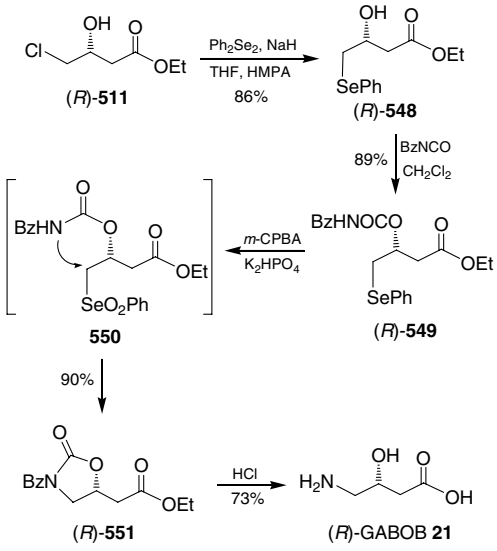
Scheme 141.



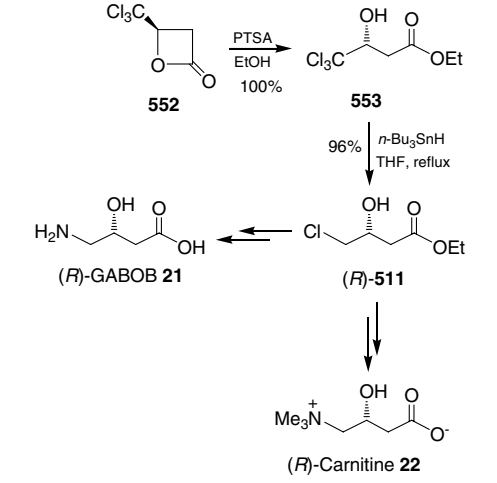
Scheme 142.

Recently Tiecco et al.[214] reported a simple and stereoselective synthesis of (*R*)- and (*S*)-GABOB **21**, through organoselenium intermediates, starting from commercially available ethyl (*R*)- or (*S*)-4-chloro-3-hydroxybutyrate **511**. In this context, the reaction of (*R*)-**511** with diphenyl diselenide in the presence of NaH afforded the corresponding β-hydroxyalkyl phenyl selenide (*R*)-**548** in 86% yield, which upon treatment with benzoyl isocyanate gave *N*-benzoylcarbamate derivative (*R*)-**549** in 89% yield. Oxidation of (*R*)-**549** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of K_2HPO_4 produced the corresponding selenone intermediate **550**, which led to the 1,3-oxazolidin-2-one (*R*)-**551** as a result of an intramolecular displacement of the selenoyl group by the nitrogen atom in the carbamate. Finally, acidic hydrolysis of (*R*)-**551** provided the enantiomerically pure (*R*)-GABOB **21** in 73% yield (Scheme 143). (*S*)-GABOB **21** was obtained in an identical way using (*S*)-**511** as the starting material.

On the other hand, ethanolysis of (*R*)-4-(trichloromethyl)-oxetan-2-one **552** in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) afforded trichlorobutyrate (*R*)-**553** in quantitative yield. Selective bis-dechlorination of (*R*)-**553** with *n*-Bu_3SnH gave (*R*)-4-chloro-3-hydroxybutyrate (*R*)-**511** in 96% yield, which can be transformed into (*R*)-GABOB **21** and (*R*)-carnitine **22** (Scheme 144).[215] Additionally, Pellegata et al.[216] have reported the preparation of (*R*)-**511** using β-pinene as the starting material, which was also transformed into (*R*)-GABOB **21** and (*R*)-carnitine **22**.



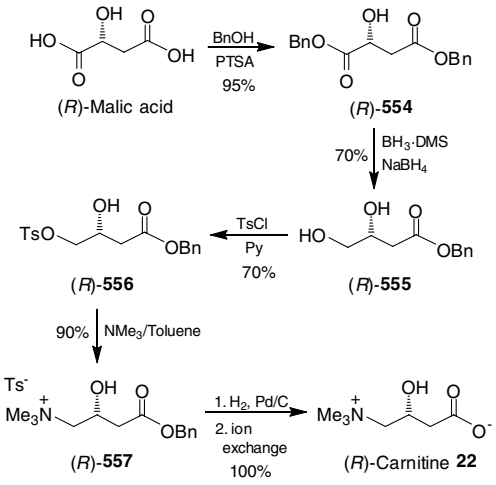
Scheme 143.



Scheme 144.

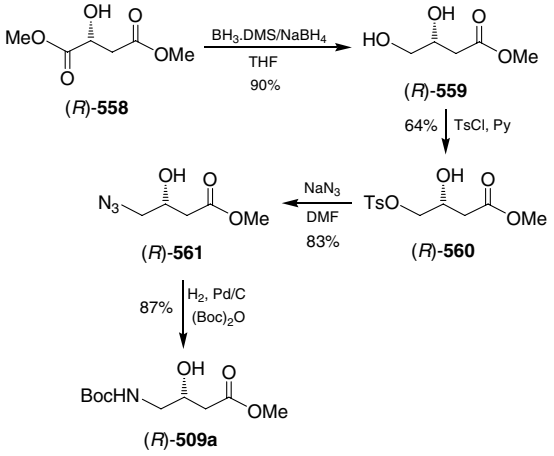
Commercially available (*R*)- and (*S*)-malic acid have been used as a starting material in the synthesis of both enantiomers of GABOB and carnitine. For example, treatment of (*R*)-malic acid with benzyl alcohol in the presence of PTSA afforded diester (*R*)-**554** in 95% yield, which upon chemoselective reduction with BH_3·DMS complex and $NaBH_4$ gave the corresponding diol (*R*)-**555** in 70% yield. The reaction of diol (*R*)-**555** with *p*-toluenesulfonyl chloride (TsCl) produced the ditosylate (*R*)-**556** in 90% yield, which by nucleophilic displacement with trimethylamine provided the amino derivative (*R*)-**557** in 90% yield. Finally, cleavage of benzyl group in (*R*)-**557** by hydrogenolysis led to (*R*)-carnitine **22** in quantitative yield (Scheme 145). (*S*)-Carnitine **22** was obtained in an identical manner using (*S*)-malic acid as starting material.[217]

Chemoselective reduction of (*R*)-malic acid dimethyl ester **558** with BH_3·DMS complex in the presence of $NaBH_4$ gave diol (*R*)-**559** in 90% yield, which by treatment with



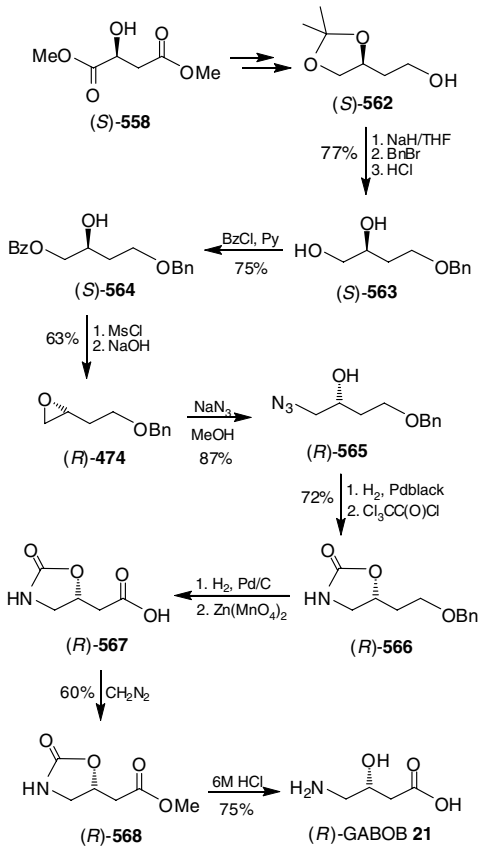
Scheme 145.

p-toluenesulfonyl chloride produced the monotosylate derivative (*R*)-**560** in 64% yield. Nucleophilic displacement of the tosyl group in (*R*)-**560** with sodium azide afforded the corresponding azide (*R*)-**561** in 83% yield, which by catalytic hydrogenation in the presence of $(Boc)_2O$ gave the diprotected (*R*)-GABOB **509a** in 87% yield (Scheme 146).[218,219]



Scheme 146.

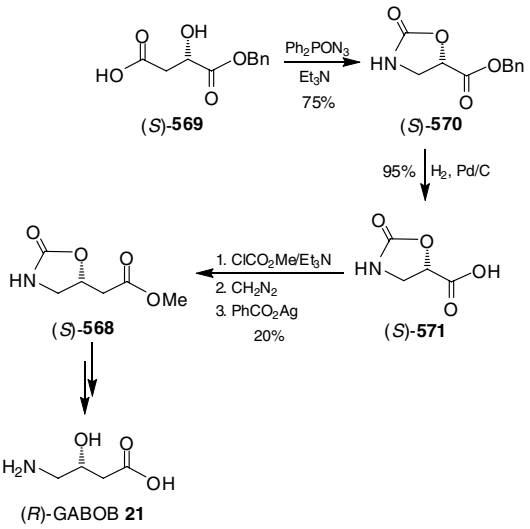
The reaction of acetal (*S*)-**562** obtained from (*S*)-malic acid dimethyl ester **558**, with NaH and benzyl bromide followed by hydrolysis, gave diol (*S*)-**563** in 77% yield, which upon treatment with benzoyl chloride afforded compound (*S*)-**564** in 75% yield. Conversion of (*S*)-**564** into the mesylated compound followed by ring closure furnished epoxy derivative (*R*)-**474**. Ring opening in (*R*)-**474** with sodium azide produced the corresponding alcohol-azide derivative (*R*)-**565** in 87% yield, which on catalytic hydrogenation and subsequent addition of trichloromethyl chloroformate led to oxazolidin-2-one (*R*)-**566** in 72% yield. Cleavage of the benzyl protective group in (*R*)-**566** followed by oxidation with zinc permanganate gave carboxylic acid (*R*)-**567**, which on treatment with diazomethane afforded methyl ester (*R*)-**568**. Finally, acidic hydrolysis of (*R*)-**568** provided the enantiomerically pure (*R*)-GABOB **21** in 75% yield (Scheme 147).[220]



Scheme 147.

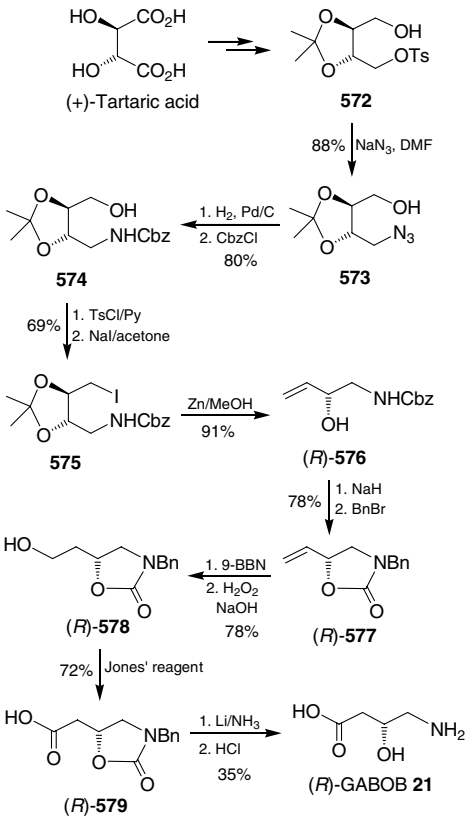
The same authors have reported the synthesis of (*R*)-GABOB **21** using (*S*)-malic acid monobenzyl ester **569** as a starting material.[221] In this context, treatment of (*S*)-**569** with diphenylphosphoryl azide gave oxazolidinone (*S*)-**570** in 75% yield, which on cleavage of the benzyl protective group under hydrogenolysis afforded carboxylic acid (*S*)-**571** in 95% yield. Treatment of (*S*)-**571** using Arndt–Eistert conditions led to methyl ester (*S*)-**568** in 20% yield, which was transformed into enantiomerically pure (*R*)-GABOB **21** (Scheme 148).

On the other hand, treatment of monotosylate **572** obtained from (+)-tartaric acid with sodium azide afforded alcohol-azide **573** in 88% yield, which on catalytic hydrogenation and subsequent reaction with benzyloxycarbonyl chloride gave the corresponding *N*-Cbz-amino derivative **574**. Treatment of **574** with *p*-toluenesulfonyl chloride (TsCl) followed by reaction with sodium iodide produced compound **575** in 69% yield, which by treatment with activated zinc provided olefin (*R*)-**576** in 91% yield. The reaction of (*R*)-**576** with sodium hydride followed by the addition of benzyl bromide gave oxazolidin-2-one (*R*)-**577** in 78% yield. Hydroboration–oxidation of the double bond in (*R*)-**577** provided alcohol (*R*)-**578**, which on Jones oxidation led to carboxylic acid (*R*)-**579**. Finally, cleavage of the benzyl protective group using lithium in liquid ammonia



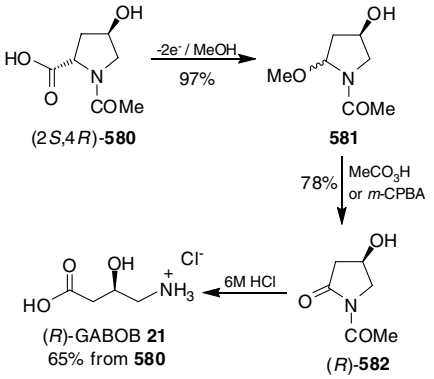
Scheme 148.

followed by acidic hydrolysis afforded the enantiomerically pure (*R*)-GABOB **21** in 35% yield (Scheme 149).[222]



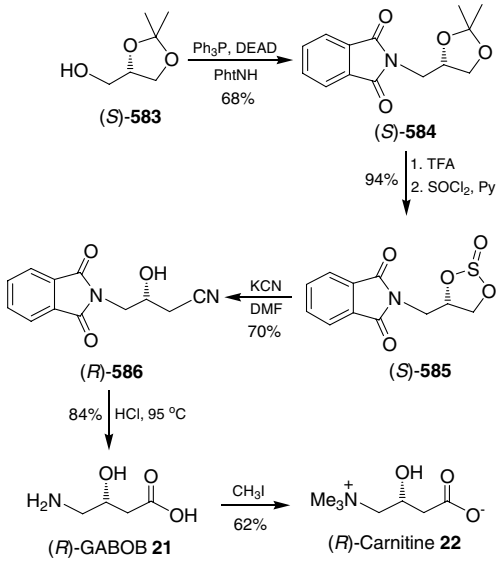
Scheme 149.

Renaud and Seebach[223] have reported the synthesis of (*R*)-GABOB **21** on preparative scale using (2*S*,4*R*)-*N*-acetyl-4-hydroxyproline **580** as the starting material. In this context, electrochemical oxidation of (2*S*,4*R*)-**580** in methanol gave the 2-methoxypyrrolidine derivative **581** in 97% yield, which upon treatment with peracetic acid or *m*-chloroperoxybenzoic acid (*m*-CPBA) furnished γ-lactam (*R*)-**582**. Finally, acidic hydrolysis of (*R*)-**582** led to enantiomerically pure (*R*)-GABOB **21** in 65% overall yield from **580** (Scheme 150).



Scheme 150.

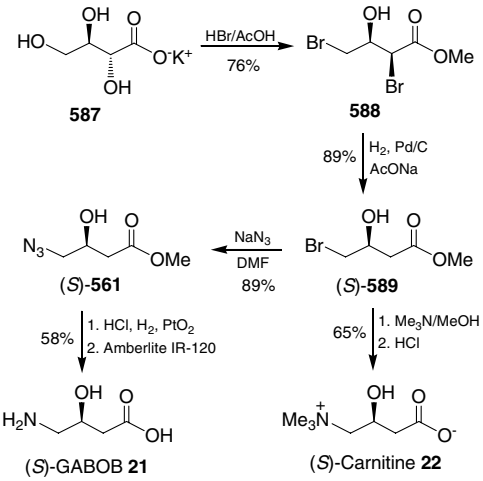
Treatment of (*S*)-glycerol acetonide **583**, readily available from D-manitol, with phthalimide under Mitsunobu conditions using Ph_3P and diethylazodicarboxylate (DEAD) afforded the phthalimide derivative (*S*)-**584** in 68% yield. Hydrolysis of (*S*)-**584** with trifluoroacetic acid, followed by treatment with thionyl chloride in pyridine, gave cyclic sulfite (*S*)-**585** in 94% yield. The reaction of (*S*)-**585** with potassium cyanide produced the cyano derivative (*R*)-**586** in 70% yield, which by acidic hydrolysis led to enantiomerically pure (*R*)-GABOB **21** in 84% yield as a hydrochloride salt. Treatment of (*R*)-**21** with an excess of iodomethane provided (*R*)-carnitine **22** in 62% yield (Scheme 151).[224] Jung and Shaw have reported the preparation of (*R*)-GABOB **21** using (*R*)-glycerol acetonide **583** as the starting material.[225]



Scheme 151.

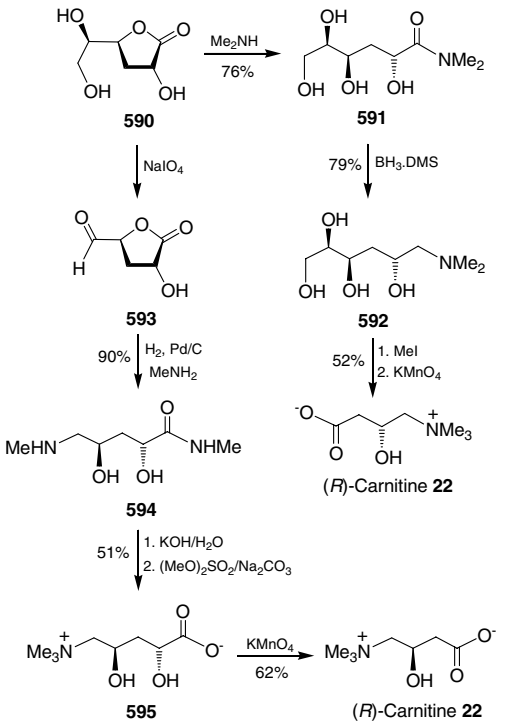
On the other hand, treatment of potassium D-erythronate **587**, readily prepared from D-arabinose, with HBr in acetic

acid followed by the addition of methanol afforded dibromo methyl ester **588** in 76% yield. Selective hydrogenolysis of **588** gave 4-bromo methyl ester (*S*)-**589** in 89% yield, which by nucleophilic displacement with sodium azide provided the corresponding azide derivative (*S*)-**561** in 89% yield. Catalytic reduction of the azide group in (*S*)-**561** followed by hydrolysis of methyl ester led to enantiomerically pure (*S*)-GABOB **21**. Additionally, treatment of (*S*)-**589** with trimethylamine followed by hydrolysis produced (*S*)-carnitine **22** in 65% yield (Scheme 152).[226] (*R*)-GABOB **21** and (*R*)-carnitine **22** were obtained in a similar way via 4-bromo methyl ester (*R*)-**589** obtained from either L-arabinose or L-ascorbic acid.



Scheme 152.

Bols et al.[227] have reported the synthesis of (*R*)-carnitine **22** using 3-deoxy-D-*xylo*-hexono-1,4-lactone **590** as the starting material. In this context, treatment of **590** with aqueous dimethyamine afforded the corresponding amide **591** in 76% yield, which by reduction with the BH_3·DMS complex gave dimethylamine **592** in 79% yield. The reaction of **592** with MeI in methanol followed by oxidation with $KMnO_4$ in acidic media produced enantiomerically pure (*R*)-carnitine **22** in 52% yield, after crystallization. In an alternative approach, oxidation of **590** using $NaIO_4$ afforded the aldehyde-lactone derivative **593** in quantitative yield, which by hydrogenation in the presence of methylamine gave the amide-amine derivative **594** in 90% yield. Hydrolysis of the amide functionality in **594** followed by treatment with $(MeO)_2SO_2/Na_2CO_3$ led to ammonium salt **595** in 51% yield, which was converted into (*R*)-carnitine **22** by oxidation with $KMnO_4$ (Scheme 153).



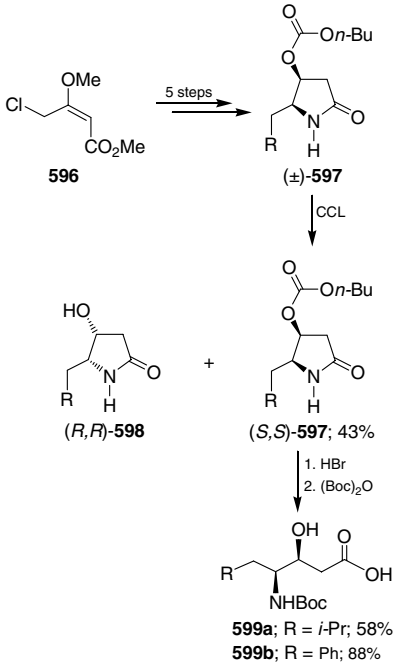
Scheme 153.

3.3. β-Hydroxy-γ-amino acids (statine and analogues)[228]

(3*S*,4*S*)-4-Amino-3-hydroxy-6-methylheptanoic acid **23** (statine) and its analogues, cyclohexylstatine **26**, (3*S*,4*S*,5*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (isostatine **27**), (3*R*,4*S*)-3-hydroxy-4-methylamino-5-phenylpentanoic acid **28**, and (2*R*,3*R*,2′*S*)-3-(2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid (dolaproine **29**), are essential components of several natural and synthetic compounds.[20–27] These key structural units are found in molecules showing several types of pharmacological activities including protease inhibitors, antineoplastic agents, antibacterials, and anticancer drugs. The significance of these molecules is also evident given the number of research publications dedicated to their synthesis. In this context, in 1992 Shibuya et al.[229] published a review, which includes the synthesis of γ-amino-β-hydroxy acids from α-amino acids. Now we described herein an update over the stereoselective synthesis of statines and its analogues from 1992 to 2006.

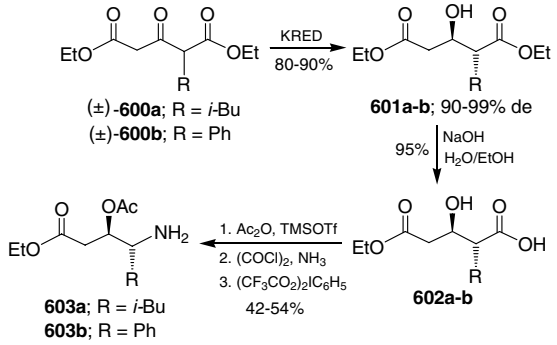
Kinetic resolution of racemic γ-lactams (±)-**597** obtained in five steps from methyl (*E*)-4-chloro-3-methoxybut-2-enoate **596**, using *Candida cylindracea* Lipase (CCL), afforded compound (*S*,*S*)-**597** in 43% and >99% ee, and alcohol (*R*,*R*)-**598**. Hydrolysis of (*S*,*S*)-**597** with concentrated HBr followed by treatment with di(*tert*-butyl)carbonate $(Boc)_2O$ gave *N*-Boc-β-hydroxy-γ-amino acids **599a** and **599b** in good yield (Scheme 154).[230]

Recently Kambourakis and Rozzel[231] reported a chemoenzymatic method for the synthesis of ethyl ester derivatives **603a** and **603b**, which are key intermediates in the synthesis of statine **23** and phenylstatine derivatives. In this context, reduction of racemic 2-substituted diethyl ketoglutarates **600a** and **600b** readily available by alkylation of diethyl 1,3-acetonedicarboxylate with the appropriate alkyl halide, using the commercially available ketoreductases (KRED-10,000), afforded only one of the diastereoisomeric alcohols **601a** and **601b** in high yield. Regioselective basic hydrolysis of **601a** and **601b** gave the corresponding mono-acids **602a** and **602b** in 95% yield, which by acetylation of the hydroxy group followed by treatment with oxalyl chloride and ammonia, and subsequent rearrangement under Hoffmann



Scheme 154.

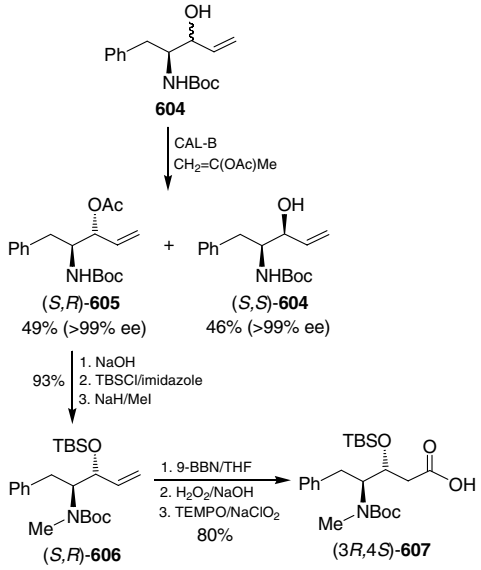
conditions using $[(CF_3CO_2)_2IC_6H_5]$ led to γ-amino esters **603a** and **603b** (Scheme 155).



Scheme 155.

On the other hand, resolution of 4-amino-1-alken-3-ol **604** using *Candida antarctica* (CAL-B) gave the acetylated derivative (*S*,*R*)-**605** in 49% yield and 99% ee, and (*S*,*S*)-**604** in 46% yield and 99% ee. Basic hydrolysis of the acetyl function in (*S*,*R*)-**605** followed by *O*-silyl protection and subsequent N-methylation gave compound (*S*,*R*)-**606** in 93% yield. Hydroboration of (*S*,*R*)-**606** followed by oxidation led to diprotected (*S*,*R*)-β-hydroxy-γ-amino acid **607**, which has been utilized as a chiral building block in the synthesis of hapalosin[26] (Scheme 156).[232]

The effectiveness of non-racemic sulfoxides as a chiral auxiliary in asymmetric synthesis (its high optical stability and its accessibility in both enantiomers)[233] has established the chiral sulfinyl group as one of the most efficient and versatile chiral controllers in C–C bond formation.[234] In this context, the addition of a lithium salt of (*R*)-*p*-tolyl-γ-butenyl sulfoxide **608** to imine **609** afforded, with overwhelming preference, two diastereoisomeric *N*-PMP-β-amino sulfoxides **610** and **611** out of the four theoretically possible, in 2.75:1.0 ratio. Treatment of the mixture of diastereoisomeric sulfoxides **610** and **611** with ceric ammonium nitrate (CAN) followed by flash chromatography and subsequent reaction with benzyl chloroformate gave *N*-Cbz-amino sulfoxide **612** in good yield. A Pummerer reaction[235] of **612** afforded derivative **613**, which by treatment with an excess of $NaBH_4$ provided β-amino alcohol **614** in 94% yield and with an overall stereoselectivity >98/2. Finally, oxidative cleavage of the double bond using $KMnO_4$ led to *N*-Cbz protected *syn*-γ-trifluoromethyl γ-amino-β-hydroxybutyric acid **615** (γ-Tfm-GABOB) (Scheme 157).[236]

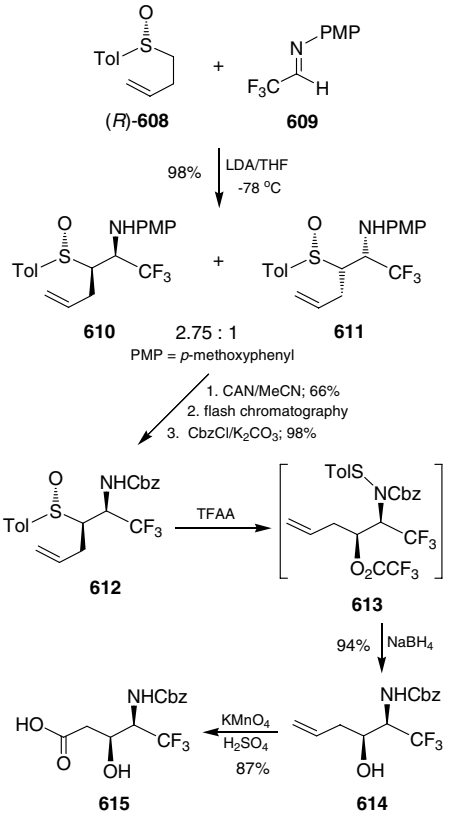


Scheme 156.

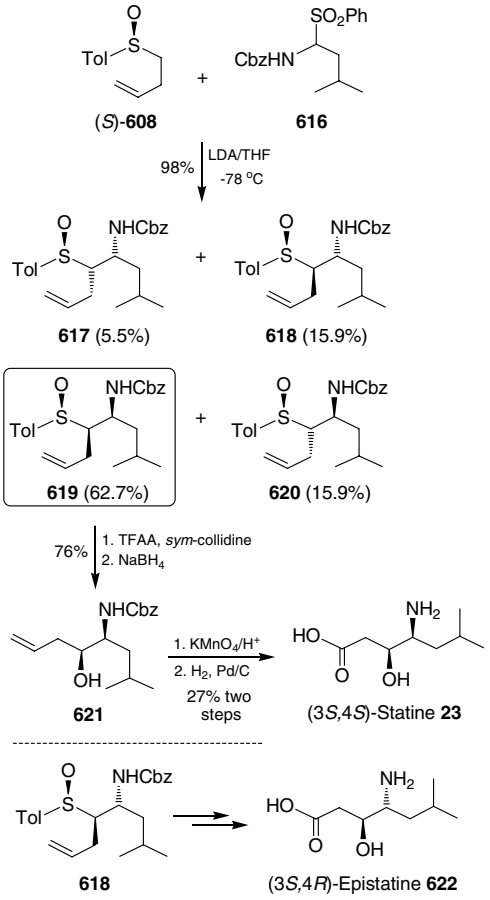
The preferential formation of diastereoisomer **610** can be explained by the fact that the lithiated butenyl sulfoxide derived from **608** reacted mainly in the *anti*-geometry, having *p*-tolyl and allyl groups *trans* with respect to the plane defined by the O–S–C–Li bonds, through a Zimmerman–Traxler[237] (aldol-type) transition state (Fig. 5).

However, the addition of the lithium salt of (*S*)-*p*-tolyl-γ-butenyl sulfoxide **608** to α-amidoalkyl sulfone **616** readily obtained from isobutyraldehyde gave a mixture of the four diastereoisomeric sulfoxides **617**–**620** in excellent overall yield, with compound **619** as the major diastereoisomer. A Pummerer reaction of diastereoisomerically pure **619** with trifluoroacetic anhydride (TFAA) and *sym*-collidine followed by treatment with $NaBH_4$ afforded the corresponding amino alcohol **621**, which by oxidation and subsequent catalytic hydrogenation led to diastereoisomerically pure (3*S*,4*S*)-statine **23** (Scheme 158).[238] (3*S*,4*R*)-Epistatine **622** was also obtained from **618**.

Yuste et al.[239] described the synthesis of *N*-Boc-statine **629a** and *N*-Boc-epistatine **630a** from β-ketosulfoxide **623**. Thus, the reduction of β-ketosulfoxide **623**, readily obtained from L-leucine, with DIBAL-H in the presence



Scheme 157.



Scheme 158.

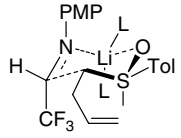


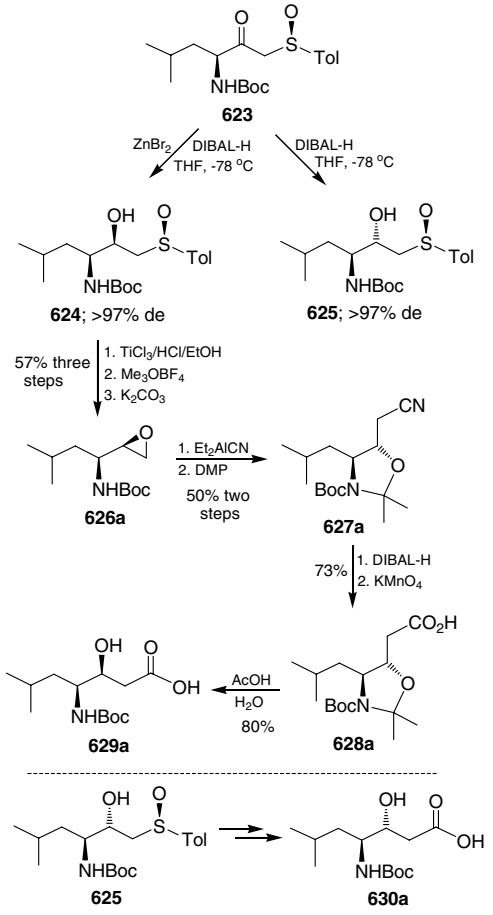
Figure 5.

of $ZnBr_2$ afforded the corresponding (2*R*,3*S*,R_S)-β-hydroxysulfoxide **624** in 75% yield and >97% de.[240] On the other hand, the reduction of **623** with only DIBAL-H gave (2*S*,3*S*,R_S)-β-hydroxysulfoxide **625** in 71% yield and >97% de.[240] The reduction of the sulfinyl group in **624** accomplished by reaction with $TiCl_3$ in ethanol, followed by treatment with trimethyloxonium tetrafluoroborate and subsequent addition of K_2CO_3, provided epoxide **626a** in 57% overall yield. Regioselective oxirane opening in **626a** with Et_2AlCN led to an hydroxynitrile derivative, which by reaction with 2,2-dimethoxypropane (DMP) produced *N*-Boc-oxazolidine **627a** in 50% yield. Reduction of the nitrile group in **627a** into an aldehyde using DIBAL-H, followed by the oxidation with $KMnO_4$, afforded the carboxylic acid **628a** in 73% yield. Finally, acidic hydrolysis with acetic acid gave *N*-Boc-statine **629a** in 80% yield. *N*-Boc-epistatine **630a** was obtained in a similar way using β-hydroxysulfoxide **625** as the starting material (Scheme 159).

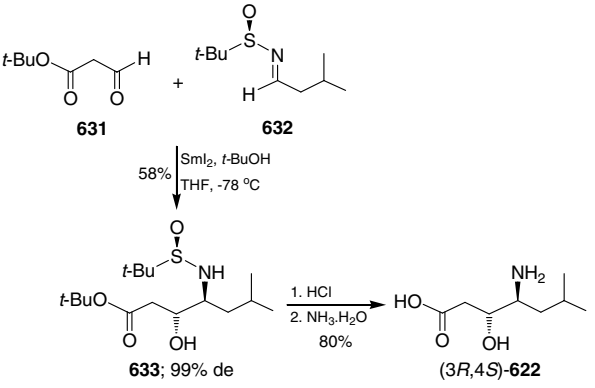
On the other hand, reductive cross-coupling of aldehyde **631** with chiral *N*-*tert*-butanesulfinyl imine **632** in the presence of SmI_2 afforded β-amino alcohol derivative **633** in 58% yield and 99% de, which upon acidic hydrolysis followed by treatment with aqueous ammonia gave the (3*R*,4*S*)-epistatine **622** in 80% yield (Scheme 160).[241]

Williams et al.[242] have reported the asymmetric synthesis of statine **23** and cyclohexylstatine **26** from commercially available glycine templates (2*R*,3*S*)-diphenyloxazinone **634**. Thus, alkylation of lithium enolate derived from **634** afforded the alkylated products **635a** and **635b** in high diastereoselectivity, which by treatment with DIBAL-H followed by an acetylation reaction gave hemiacetals **636a** and **636b**. Condensation of **636a** and **636b** with *tert*-butyldimethylsilylketene acetal of ethyl acetate in the presence of $ZnBr_2$ gave the coupling products **637a** and **637b** and **638a** and **638b** in 4:1 ratio. Hydrolysis of diastereoisomers **637a** and **637b**, and subsequent reduction with lithium in liquid ammonia provided statine **23** and cyclohexylstatine **26** in 69% and 82% yield, respectively (Scheme 161).

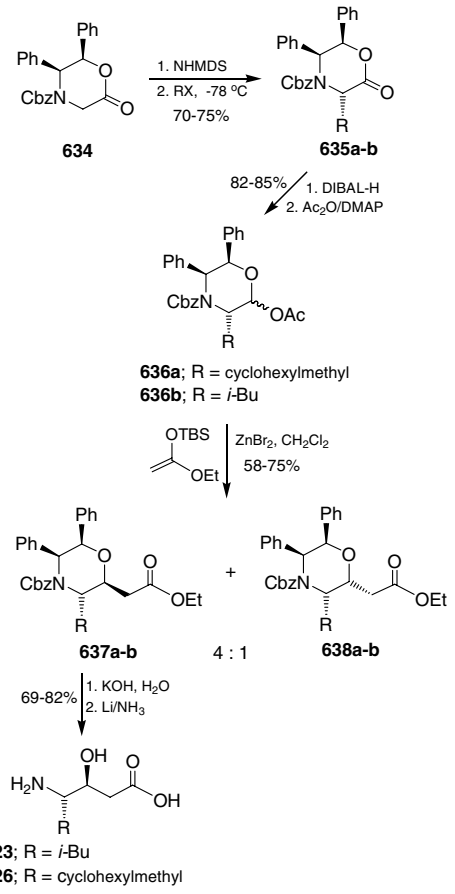
On the other hand, the addition of allyltrimethylsilane to *ent*-**636b** in the presence of $TiCl_4$ afforded allyl derivative **639** as the only diastereoisomer in 90% yield. Oxidation of **639** with ozone followed by treatment with PDC in DMF gave the corresponding carboxylic acid **640**, which upon reduction with lithium in liquid ammonia provided (3*S*,4*R*)-epistatine **622** in 80% yield (Scheme 162).[243]



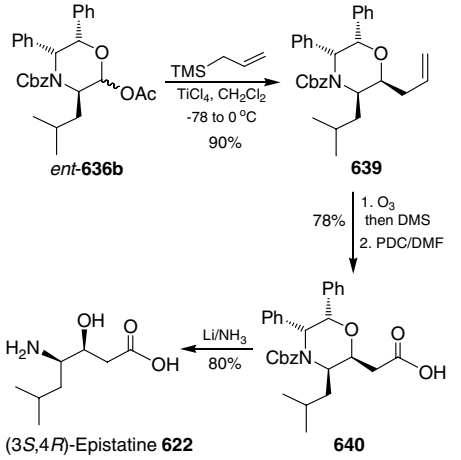
Scheme 159.



Scheme 160.



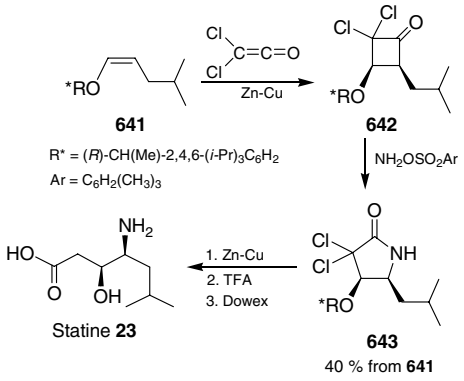
Scheme 161.



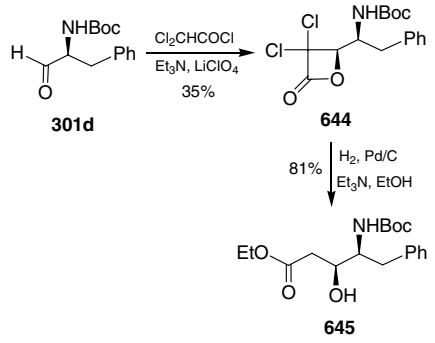
Scheme 162.

α,α-Dichlorocyclobutanones have been used in the diastereoselective synthesis of statine analogues. For example, diastereofacial selective [2+2] cycloaddition of chiral *O*-alkyl enol ether **641** and dichloroketene afforded α,α-dichlorocyclobutanone **642**, which under Beckmann ring expansion with Tamura's reagent [*O*-(mesitylenesulfonyl)-hydroxylamine][244] gave α,α-dichloro-γ-lactam **643**. Treatment of **643** with Zn–Cu followed by the ring opening of γ-lactam with trifluoroacetic acid produced statine **23** in 60% yield (Scheme 163).[245]

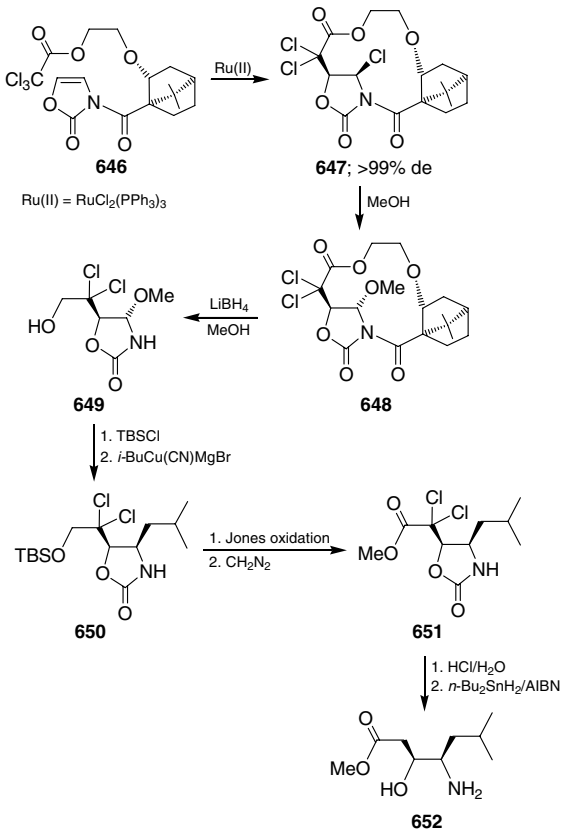
In a similar manner, [2+2] cycloaddition of chiral *N*-Boc-α-amino aldehyde **301d** and dichloroketene, generated from dichloroacetyl chloride and triethylamine, gave β-lactone **644** in 35% yield, which under catalytic hydrogenation in the presence of triethylamine and ethanol afforded the corresponding phenylstatine derivative **645** in 81% yield (Scheme 164).[246]



Scheme 163.



Scheme 164.



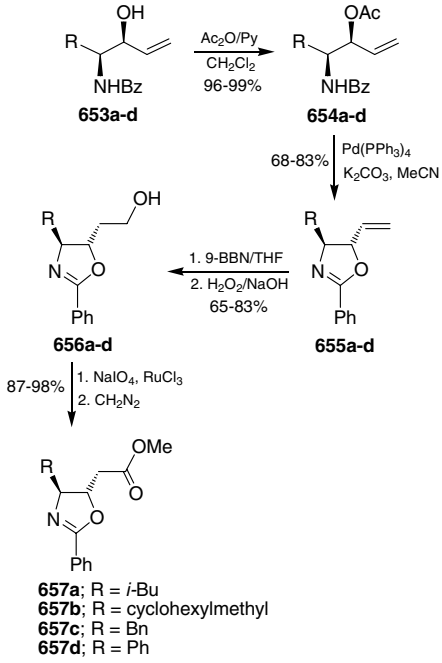
Scheme 165.

On the other hand, intramolecular ruthenium(II) $[RuCl_2(PPh_3)_3]$-catalyzed cyclization of 3-acyl-2-oxazolone **646** gave the 12-membered lactone **647** with perfect regio- and diastereoselectivity, which by treatment with methanol afforded the 4-methoxy-2-oxazolidinone derivative **648** in quantitative yield. Reductive cleavage of the lactone function in **648** with $LiBH_4$ in methanol produced the corresponding alcohol **649**, which by protection with *tert*-butyldimethylsilane (TBSCl) and subsequent substitution of methoxy group by the cyano group using *i*-Bu-Cu(CN)MgBr in the presence of $BF_3{\cdot}Et_2O$ provided the corresponding 4-isobutyl derivative **650** with complete retention of configuration.[247] Jones' oxidation of **650** followed by esterification with diazomethane led to methyl ester **651**. Finally, cleavage of oxazolidinone **651** by hydrolysis and subsequent reductive dechlorination using *n*-Bu_2SnH_2 produced the protected statine **652** (Scheme 165).[248]

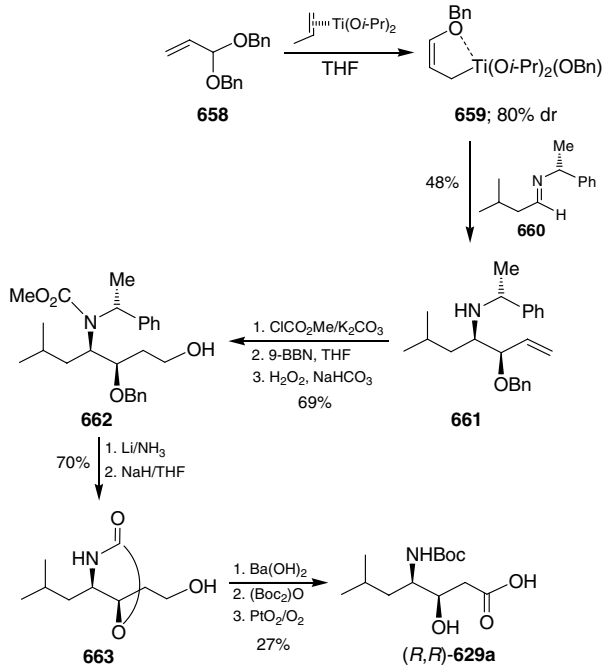
4-Amino-1-alken-3-ols are important starting materials in the stereoselective synthesis of γ-amino-β-hydroxy acids. For example, the enantiomerically pure 4-amino-1-alken-3-ols **653a–d** have been used as key intermediates in the synthesis of statine and analogues conveniently protected as oxazolines **657a–d**. In this context, intramolecular palladium(0)-catalyzed reaction of acetyl derivatives **654a–d** readily obtained from 4-amino-1-alken-3-ols **653a–d** gave *trans*-oxazolines **655a–d** in good yield and high diastereoselectivity. Hydroboration reaction of **655a–d** with (9-BBN) followed by oxidative workup provided alcohols **656a–d**, which on direct oxidation with $NaIO_4/RuCl_3$ and subsequent treatment with diazomethane afforded γ-amino-β-hydroxy acids **657a–d** conveniently protected as oxazolines in good yield (Scheme 166).[249]

The high diastereoselectivity of the cyclization of **654a–d** may arise due to the differences of steric interactions between the bulky R group, and the hydrogen of the π-allylpalladium complex in the transition states **A** and **B**. Consequently, the cyclization proceeds through the more favored transition state **A** as shown in Figure 6.

On the other hand, the reaction of (γ-alkoxyallyl)titanium **659**, generated by the reaction of acrolein dibenzyl acetal **658** and the divalent titanium reagent (η^2-propene)$Ti(OiPr)_2$, with chiral imine **660**, prepared from aldehydes and enantiomerically pure (*R*)-α-methylbenzylamine, afforded in a regiospecific manner the enantiomerically pure *syn*-1-vinyl-2-amino alcohol derivative **661** in 48% yield and 80% de. Although four diastereoisomeric products are possible for the reaction of **659** with **660**, the 1-vinyl-2-amino alcohol derivative **661** having and anti-Cram-*syn* structure was produced as the principal product. Protection of amino group in diastereoisomerically pure **661** as its methyl carbamate using $ClCO_2Me$ and K_2CO_3 followed by oxidative hydroboration reaction with (9-BBN) gave the corresponding alcohol **662** in 69% yield. Debenzylation of **662** under Birch reduction conditions and subsequent cyclization using NaH in THF led to oxa-



Scheme 166.



Scheme 167.

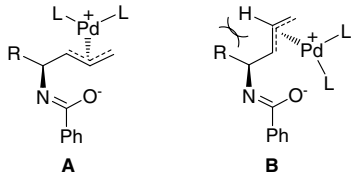
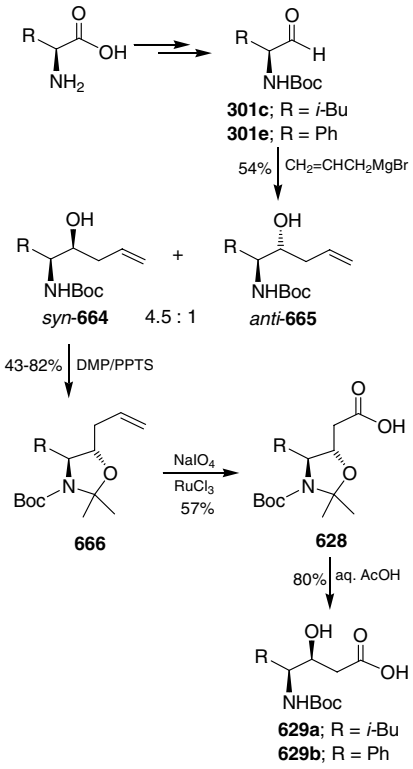


Figure 6.

zolidinone derivative **663** in 70% yield. Sequential hydrolysis of **663** using $Ba(OH)_2$ in ethanol, *N*-Boc protection of the amino group and selective oxidation of alcohol using PtO_2/O_2 under conditions described by Sakaitani and Ohfune[250] led to *N*-Boc statine **629a** (Scheme 167).[251]

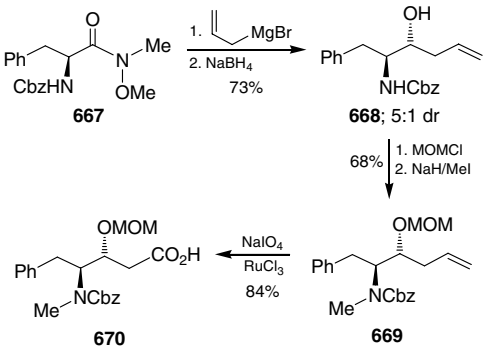
The addition of allylmagnesium bromide to aldehydes **301c** and **301e** readily obtained from L-leucine and L-phenylglycine, respectively, afforded allylic alcohols *syn*-**664** and *anti*-**665** in 54% yield and with moderate diastereoselection (*syn*/*anti* = 4.5/1).[252] Treatment of diastereoisomerically pure *syn*-**664** with 2,2-dimethoxypropane (DMP) in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) gave oxazolidine derivative **666** in 43–82% yield. Oxidation of **666** under modified Sharpless conditions using sodium periodate and catalytic ruthenium chloride produced the corresponding carboxylic acid **628** in 57%, which upon hydrolysis led to *N*-Boc statine **629a** and *N*-Boc phenylstatine **629b** in good yield (Scheme 168).[253]



Scheme 168.

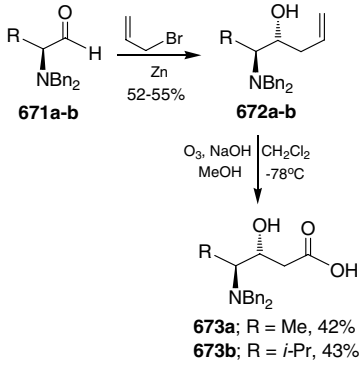
On the other hand, the addition of allylmagnesium bromide to Weinreb amide **667** readily obtained from L-phenylalanine afforded the corresponding ketone, which on reduction with $NaBH_4$ gave allylic amino alcohol **668** as a mixture (5:1) in 73% yield. Protection of the hydroxy group in the diastereoisomerically pure **668** with methoxymethyl chloride (MOMCl) followed by N-methylation with sodium hydride and methyl iodide produced the corresponding protected amino alcohol derivative **669** in

68% yield. Oxidation of the double bond under modified Sharpless conditions using sodium periodate and catalytic ruthenium chloride led to protected γ-amino-β-hydroxy acid **670** in 84% yield (Scheme 169).[254]



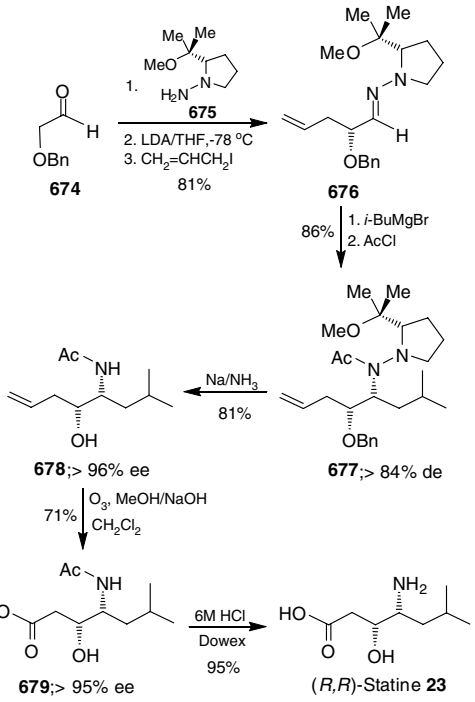
Scheme 169.

The addition of allylzinc bromide to *N*,*N*-dibenzylamino aldehydes **671a** and **671b** readily obtained from L-alanine and L-valine, respectively, according to the Reetz procedure,[255] gave the corresponding homoallylic alcohols **672a** and **672b** in very high *anti*-diastereoselectivity (*anti*/*syn* >97/3). The high diastereoselectivity can be explained by allylation from the less hindered *re* face of the carbonyl group following a non-chelated Felkin–Anh model.[256] Cleavage of the double bond in diastereoisomerically pure homoallylic alcohols **672a** and **672b** with ozone in CH_2Cl_2–MeOH in the presence of sodium hydroxide afforded the protected γ-amino-β-hydroxy acids **673a** and **673b** in moderate yield (Scheme 170).[257]



Scheme 170.

On the other hand, the reaction of readily accessible benzyl protected α-hydroxyacetaldehyde **674** with (*S*)-1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine (SADP) **675**, followed by treatment with LDA and subsequent addition of allyl iodide, gave alkylated hydrazone **676** in 81% yield and >98% de. The addition of *i*-BuMgBr to hydrazone **676** and subsequent trapping of the metalated hydrazide with acetyl chloride produced N-acetyl protected hydrazine **677** in 86% yield and >84% de. Cleavage of the *N*–*N* bond and simultaneous removal of the benzyl protecting group with sodium/ammonia led to alcohol derivative **678** with >96% ee, which by oxidative cleavage of the double bond with ozone in alkaline methanol-dichloromethane provided methyl ester **679** in 71% yield. Hydrolysis of **679** with HCl afforded (*R*,*R*)-statine **23** in 95% yield (Scheme 171).[258]

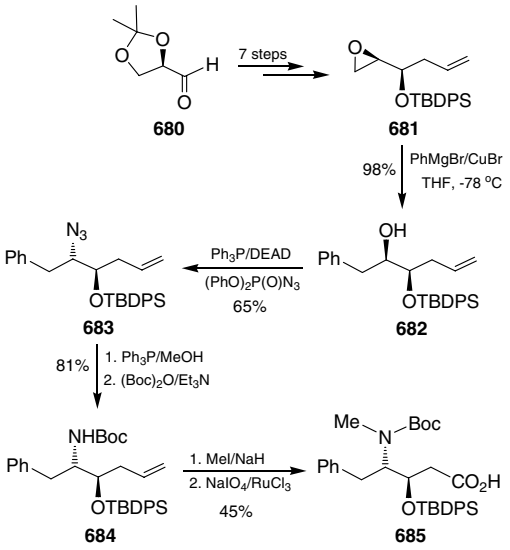


Scheme 171.

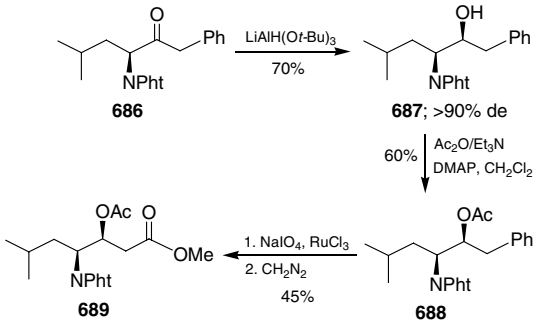
Cu(I)-catalyzed ring opening of diastereoisomerically pure epoxide **681** obtained in seven steps from (*S*)-glyceraldehyde acetonide **680** with PhMgBr afforded alcohol **682** in 98% yield, which by treatment with diphenylphosphoryl azide under Mitsunobu reaction conditions gave the corresponding azide **683** in 65% yield. Reduction of the azide function in **683** with Ph_3P followed by treatment with $(Boc)_2O$ led to the *N*-Boc derivative **684** in 81% yield, which by N-methylation and subsequent oxidation of double bond under modified Sharpless conditions using $NaIO_4$ and catalytic $RuCl_3$ produced protected γ-amino-β-hydroxy acid **685** in 45% yield, which is a key segment of hapalosin (Scheme 172).[259]

The reduction of *N*-phthaloyl α-amino ketone **686** obtained in three steps from L-leucine with $LiAlH(Ot\text{-}Bu)_3$ afforded *syn*-amino alcohol **687** in 70% yield and >90% de which by treatment with acetic anhydride in the presence of Et_3N and catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane gave the acetylated product **688** in 60% yield. Oxidation under modified Sharpless conditions using $NaIO_4$ and catalytic amount of $RuCl_3$ followed by esterification with diazomethane gave the diprotected statine **689** in 45% yield (Scheme 173).[260]

On the other hand, the reaction of epoxyketone **690** obtained from ethyl glycidate,[261] with triacetoxyborohydride in the presence of methylamine gave aminoepoxide **691** in 70% yield as the single diastereoisomer, which by treatment with

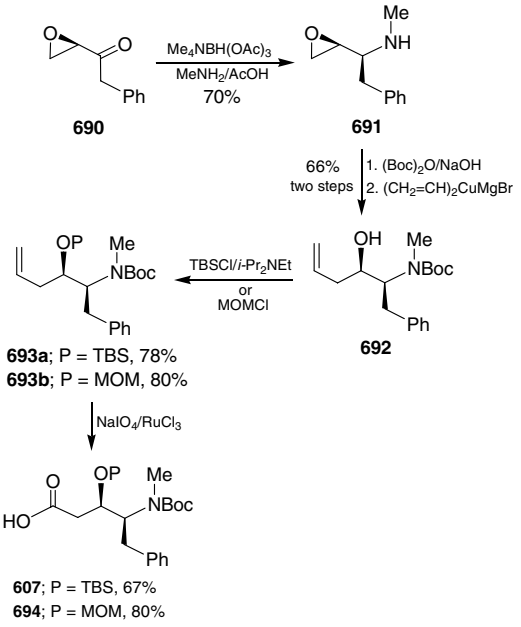


Scheme 172.

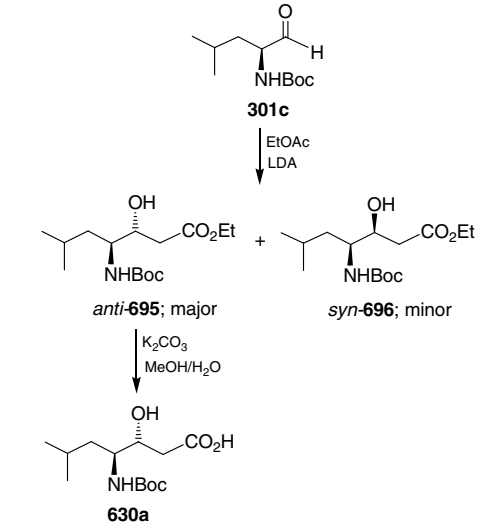


Scheme 173.

(Boc)$_2$O followed by addition of divinylmagnesiumcuprate afforded allylic amino alcohol derivative **692** in 66% yield. Protection of the hydroxy group in **692** with *tert*-butyldimethylsilyl chloride (TBSCl) or methoxymethyl chloride (MOMCl) produced **693a** and **693b** in 78% and 80% yield, respectively. Cleavage of the double bond in **693a**–**b** with $NaIO_4$ and a catalytic amount of $RuCl_3$ led to protected γ-amino-β-hydroxy acids **607** and **694** in good yield (Scheme 174).[262]



Scheme 174.

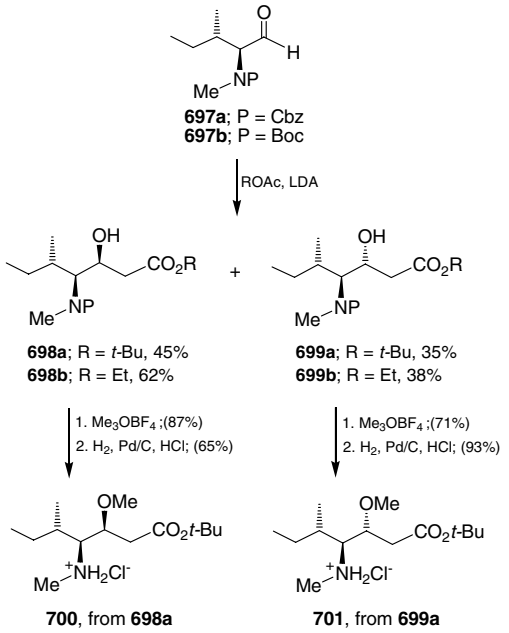


Scheme 175.

Stereoselective aldol additions are amongst the most useful synthetic transformations in organic synthesis. The development of highly diastereo- and enantioselective variants has been amply documented in numerous recent reviews.[263] A highly stereoselective synthesis of γ-amino-β-hydroxy acids can be achieved by using an aldol reaction of chiral protected α-amino aldehydes with non-chiral ester enolates. For example, the aldol reaction of *N*-Boc-L-leucinal **301c** with the lithium enolate of ethyl acetate afforded a mixture of aldol products *anti*-**695** and *syn*-**696**. Hydrolysis of the major product *anti*-**695** gave *N*-Boc epistatine **630a** (Scheme 175).[264]

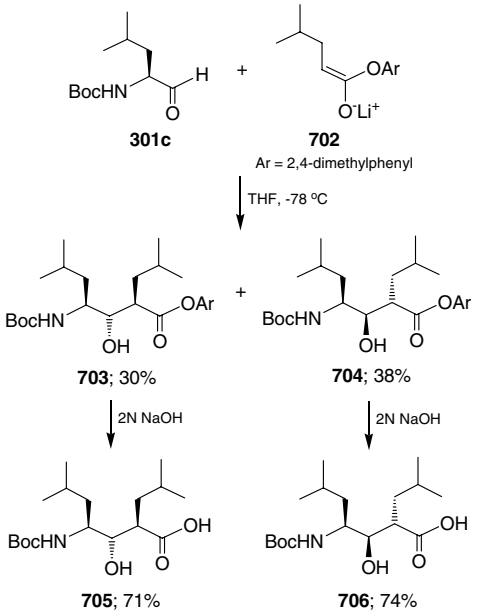
Aldol condensation of α-amino aldehyde **697a** derived from L-isoleucine, with the lithium enolate derived from *tert*-butyl acetate afforded a mixture of aldol products *syn*-**698a** and *anti*-**699a** in 45% and 35% yield, respectively. Identical results were obtained when aldehyde **697b** was treated with the lithium enolate derived from ethyl acetate. Treatment of the aldol products **698a** and **699a**, after separation, with trimethyloxonium tetrafluoroborate and subsequent catalytic hydrogenolysis and hydrolysis gave the γ-amino-β-hydroxy acid *tert*-butyl esters derivatives **700** and **701** in good yield, which were useful key components in the synthesis of Dolastatin **32**[265] (Scheme 176).[266]

In a similar way, the addition of lithium *E*-enolate **702** to *N*-Boc-leucinal **301c** gave the pair of 2,3-*anti* aldol products **703** and **704** via the Zimmerman–Traxler transition state.[237] Saponification of the diastereoisomerically pure



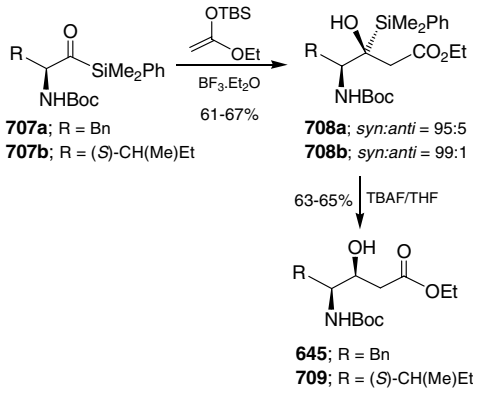
Scheme 176.

703 and **704** produced the protected γ-amino-β-hydroxy acids **705** and **706** in 71% and 74% yield, respectively (Scheme 177).[267]



Scheme 177.

Ricci et al.[268] have reported the stereoselective two-carbon elongation of carbon skeleton of aminoacylsilanes **707a** and **707b** by introducing an acetate moiety. In this context, the aldol reaction of **707a** and **707b** with *O*-ethyl-*O*-*tert*-butyldimethylsilyl ketene acetal in the presence of $BF_3{\cdot}Et_2O$ gave products **708a** and **708b** in good yield and high diastereoselectivity in favor of the *syn* product, which by treatment with tetra-*n*-butylammonium fluoride (TBAF) led to the protected γ-amino-β-hydroxy acids **645** and **709** in 63% and 65%, respectively (Scheme 178).



Scheme 178.

The highly preferred *syn* selectivity has been accounted by a preferential attack on the less hindered *si* face on the starting acylsilanes, in which the $BF_3{\cdot}Et_2O$ predominantly coordinates to the carbonyl group (Fig. 7).

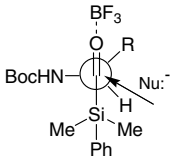
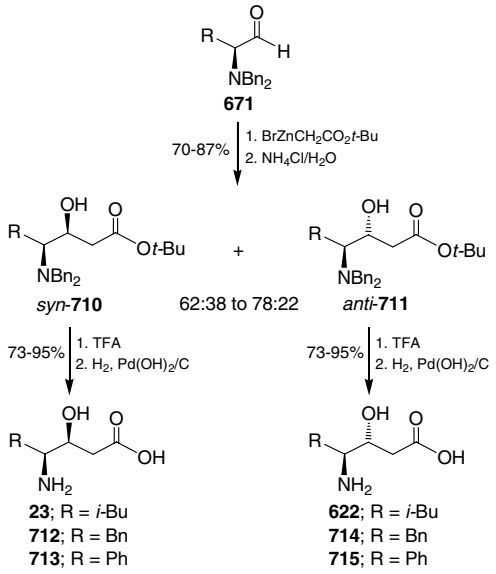


Figure 7.

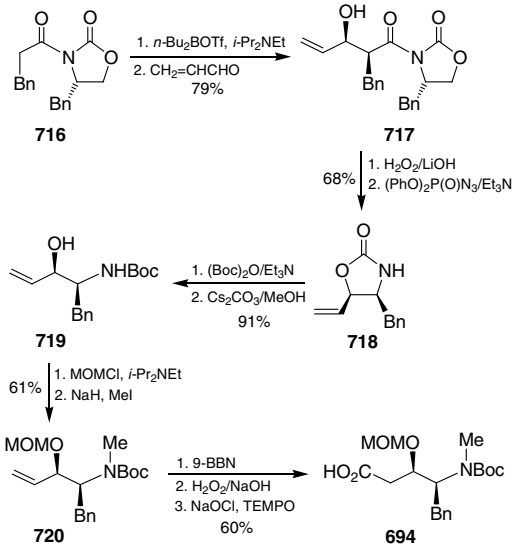
On the other hand, Pedrosa et al.[269] have reported the stereoselective synthesis of γ-amino-β-hydroxy acids via **a** Reformatsky reaction. In this context, the reaction of *N*,*N*-dibenzylamino aldehydes **671** with *tert*-butoxycarbonylmethylzinc bromide led to the γ-dibenzylamino-β-hydroxy esters *syn*-**710** and *anti*-**711** in good chemical yield and moderated diastereoselectivity, with a predominance of the *syn*-diastereoisomers.[270] Hydrolysis of diastereoisomerically pure *syn*-**710** with trifluoroacetic acid (TFA) followed by hydrogenolysis gave statine **23** and the corresponding γ-amino-β-hydroxy acids **712** and **713** in good yield. In a similar way, diastereoisomerically pure *anti*-**711** was transformed into epistatine **622** and its analogues **714** and **715** (Scheme 179).

In the aldol reaction, high stereoselectivities can be achieved using chiral auxiliaries and chiral catalysts. When these methods are used in conjunction with a chiral substrate, these reactions are known as double diastereodifferentiating aldol additions, which have already been studied in detail.[271] The reactions of carbonyl compounds bearing stereogenic centers with chiral auxiliaries are also double diastereodifferentiation strategies, but a careful analysis of the matching–mismatching interaction between the two modes of stereoinduction is required for the installation of new stereogenic centers, which is predictable and controlled. For example, the addition of boron enolate generated from acylated oxazolidinone **716** to acrolein afforded



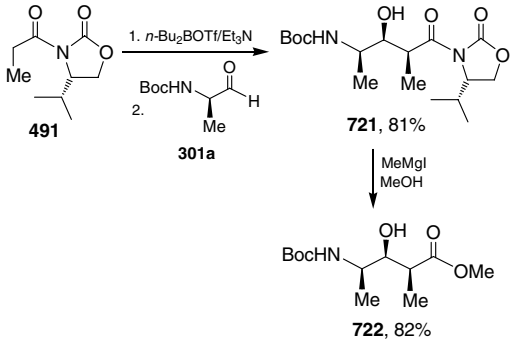
Scheme 179.

the corresponding aldol product **717** in 79% yield, which by hydrolysis followed by Curtius rearrangement using diphenylphosphoryl azide and subsequent intramolecular trapping of isocyanate gave oxazolidinone **718** in 68% yield. *N*-Boc protection followed by hydrolysis with cesium carbonate in methanol provided the N-protected amino alcohol **719** in 91% yield, which by protection of hydroxy group with chloromethylmethyl ether (MOMCl) and subsequent N-methylation gave **720** in 61% yield. Hydroboration of **720** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidation led to the protected γ-amino-β-hydroxy acid **694** in 60% yield (Scheme 180).[272]



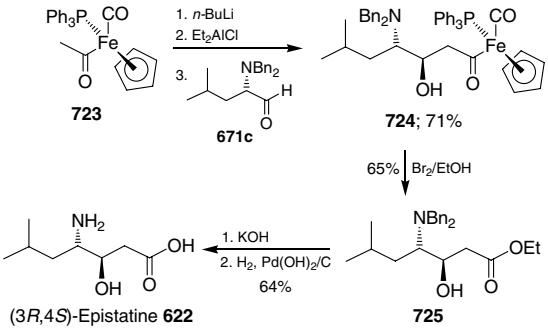
Scheme 180.

Ohno et al.[273] have reported the stereoselective synthesis of γ-amino-β-hydroxy acid methyl ester **722**, an important component of Bleomycin[274] by a double diastereodifferentiating aldol reaction. In this context, the reaction of the corresponding boron enolate of chiral *N*-acyloxazolidinone **491** with (*R*)-2-[(*tert*-butoxycarbonyl)amino]propanal **301a** afforded aldol adduct **721** as only one diastereoisomer, which by treatment with methylmagnesium iodide in methanol gave methyl ester **722** in 82% yield (Scheme 181).



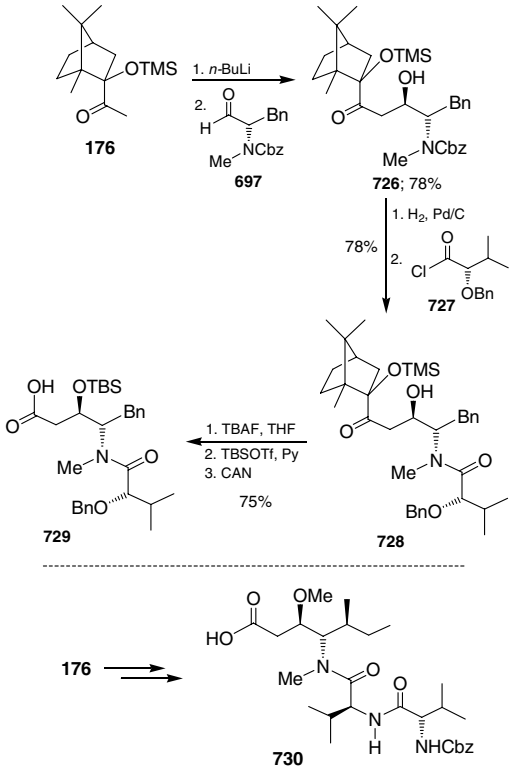
Scheme 181.

On the other hand, the matched pair reaction of diethylaluminum enolate derived from the iron acetyl complex (*S*)-[η^5-C_5H_5]Fe(CO)(PPh_3)COMe **723** with (*S*)-*N*,*N*-dibenzyl leucinal **671c** afforded the alcohol derivative **724** in good diastereoselectivity. Treatment of alcohol **724** with bromine produced ester **725**, which on saponification and subsequent hydrogenolysis provided (3*R*,4*S*)-epistaine **622** (Scheme 182).[275]



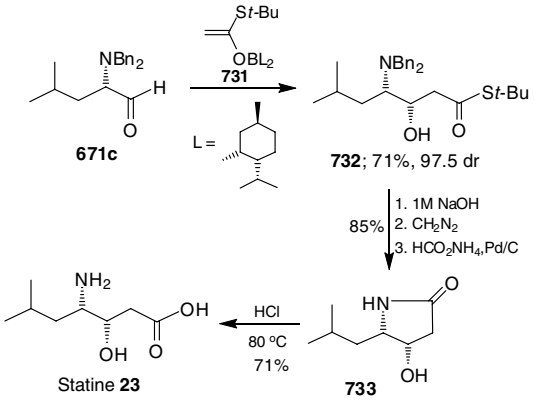
Scheme 182.

Recently Palomo et al.[276] have described that the addition of the lithium enolate derived from **176** with the chiral amino aldehyde **697** gave the corresponding aldol derivative **726** as a single diastereoisomer in 78% yield, which by cleavage of the Cbz protective group followed by reaction with acyl chloride **727** afforded dipeptide **728** in 78% yield. Deprotection of the tertiary hydroxy group in **728** with TBAF, followed by further selective protection of the secondary carbinol as *tert*-butyldimethylsilyl (TBS) ether, and oxidative cleavage using cerium ammonium nitrate (CAN) produced dipeptide **729**, a key component of Halaposin.[26] In a similar way, using the amino aldehyde derived from L-isoleucine gave tripeptide **730**, which is a key component of Dolastatin[27] (Scheme 183).



Scheme 183.

On the other hand, Gennari et al.[277] have reported a highly efficient total synthesis of statine **23** by means of an aldol addition of chiral boron enolates to *N*,*N*-dibenzyl aldehyde **671c**. In this context, the addition of chiral boro enolate of *tert*-butylthioacetate **731** derived from (+)-menthone, to amino aldehyde **671c** gave the corresponding aldol product *syn*-**732** in 71% yield and high diastereoselectivity. Saponification of *syn*-**732**, followed by esterification with diazomethane and subsequent debenzylation using HCO_2NH_4 in the presence of Pd/C afforded γ-lactam **733** in 85% yield. Finally, acidic hydrolysis with concentrated hydrochloric acid led to statine **23** in 71% yield (Scheme 184).



Scheme 184.

The highly preferred *syn*-selectivity in the addition of boron enolate to amino aldehyde **671c** is in accord with the anti-Felkin–Anh aldol addition 'mismatched' (Fig. 8). Amino alcohol *anti*-**734** can be obtained changing the chiral boron ligand configuration.

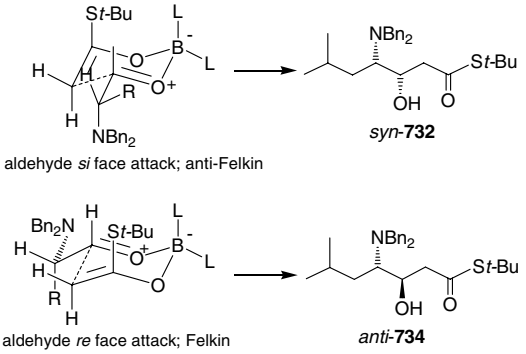
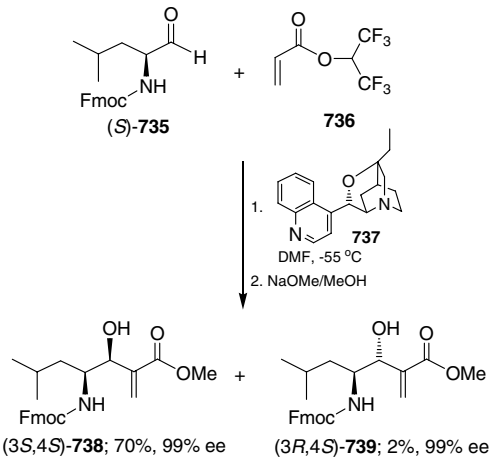


Figure 8.

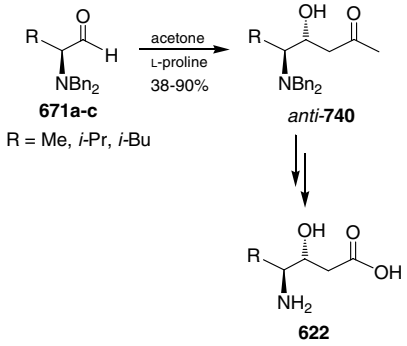
Baylis–Hillman reaction[278] of (*S*)-*N*-Fmoc-leucinal **735** with 1,1,1,3,3,3-hexafluoroisopropyl acrylate **736** in the presence of *cinchone* **737** as a catalyst in DMF at −55 °C, followed by methanolysis, gave the corresponding α-methylene-statine methyl ester (3*S*,4*S*)-**738** in 70% yield and 99% ee and (3*R*,4*S*)-**739** in 2% yield and 99% ee (Scheme 185). Methyl ester (3*R*,4*R*)-**738** has been obtained in a similar way starting from (*R*)-*N*-Fmoc-leucinal **735**.[279]



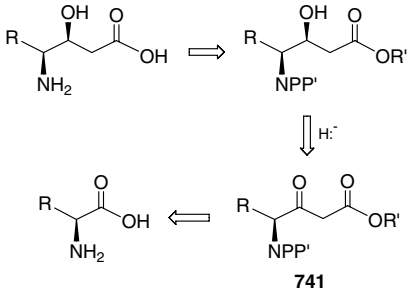
Scheme 185.

On the other hand, the aldol reaction of *N*,*N*-dibenzylamino aldehydes **671** with acetone in the presence of L-proline as a catalyst produced amino alcohols **740** in 38–90% yield and good diastereoselectivity, which can be used in the synthesis of epistatine **622** and analogues (Scheme 186).[280]

One of the simplest conceptual approaches to the stereoselective synthesis of γ-amino-β-hydroxy acids (statine family) is the reduction of γ-amino-β-ketoesters of type **741** or its enantiomers, which are readily available from α-amino acids (Scheme 187). In this context, a number of differ-



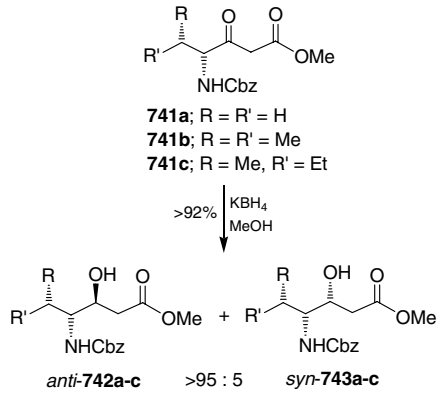
Scheme 186.



Scheme 187.

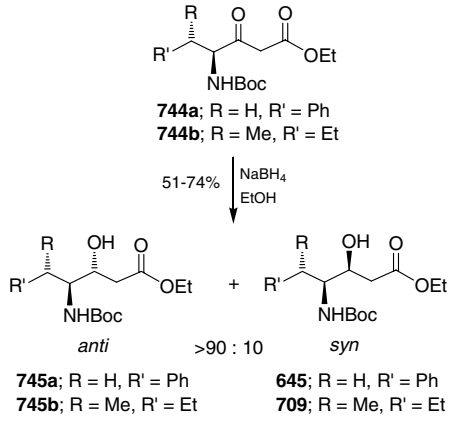
ent protecting groups (P = H and P′ = Boc, Cbz, Fmoc and TFA or P = P′ = Bn) and reducing agents ($NaBH_4$,[281] $LiBH_4$,[282] $Zn(BH_4)_2$, $NaBH_3CN$,[283] KBH_4,[284] and K-Selectride) have been used.

For example, stereoselective reduction of (*R*)-*N*-Cbz-γ-amino-β-keto methyl esters **741a–c** readily obtained from the corresponding D-amino acids with potassium borohydride (KBH_4) in methanol gave a diastereoisomeric mixture of *N*-Cbz-γ-amino-β-hydroxy methyl esters *anti*-**742a–c** and *syn*-**743a–c** in good yield and excellent diastereoselectivity with a predominance of *anti*-**742a–c**, which can be converted into the corresponding γ-amino-β-hydroxy acids (Scheme 188).[285]



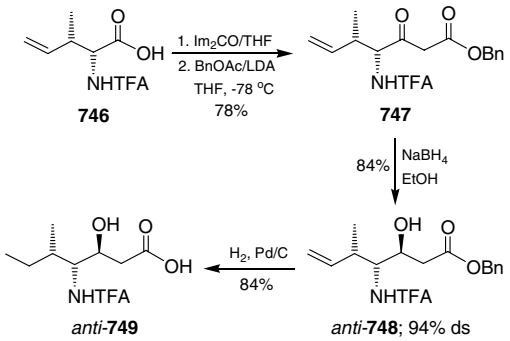
Scheme 188.

In a similar way, the stereoselective reduction of *N*-Boc-γ-amino-β-keto ethyl esters **744a** and **744b** with $NaBH_4$ in ethanol gave the corresponding *N*-Boc-γ-amino-β-hydroxy ethyl esters *anti*-**745a** and **745b** and *syn*-**645** (R = H; R′ = Ph) and *syn*-**709** (R = Me; R′ = Et) in moderate yield and good diastereoselectivity with a predominance of *anti*-**745a**,**b**, which can be converted into the corresponding γ-amino-β-hydroxy acids (Scheme 189).[187,286]



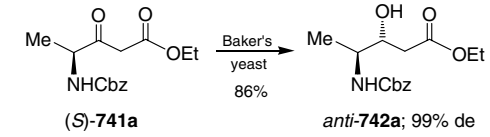
Scheme 189.

Reduction of β-ketoester **747** readily obtained from TFA protected amino acid **746** with $NaBH_4$ in ethanol afforded the amino alcohol *anti*-**748** in 84% yield and 94% ds, which on cleavage of the benzyl protective group gave *N*-TFA-γ-amino-β-hydroxy acid **749** in 84% yield (Scheme 190).[287]



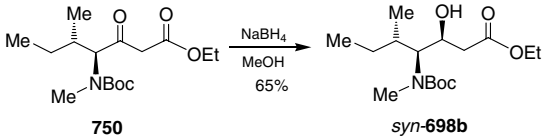
Scheme 190.

A predominance of the *anti*-diastereoisomer has also been observed in the reduction of *N*-Cbz-amino-β-keto ethyl ester **741a** derived from L-alanine with baker's yeast, where the *N*-Cbz-γ-amino-β-hydroxy ethyl ester *anti*-**742a** was obtained in 86% yield and excellent diastereoisomeric purity (99% de) (Scheme 191).[198]



Scheme 191.

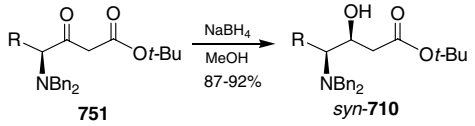
However, the reduction of (*S*)-*N*-Boc-*N*-methylamino-β-keto ethyl ester **750** with $NaBH_4$ in methanol gave the N-protected-γ-amino-β-hydroxy ethyl ester *syn*-**698b** as only one isolable product in 65% yield (Scheme 192).[265]



750 *syn*-**698b**

Scheme 192.

Identically, the reduction of (*S*)-*N*,*N*-dibenzylamino-β-keto *tert*-butyl esters **751a**–**g** with $NaBH_4$ in methanol gave the γ-*N*,*N*-dibenzylamino-β-hydroxy *tert*-butyl esters *syn*-**710a**–**g** in 87–92% yield and excellent diastereoselectivity (88–98%) (Scheme 193).[288]

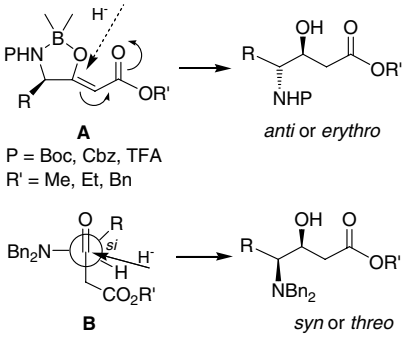


751 *syn*-**710**

710a; R = *i*-Bu, 88% de
710b; R = Bn, 92% de
710c; R = $BnCH_2$, 93% de
710d; R = cyclohexylmethyl, 93% de
710e; R = cyclohexyl, 98% de
710f; R = *i*-Pr, 96% de
710g; R = *sec*-Bu, 97% de

Scheme 193.

The preferential formation of γ-amino-β-hydroxy esters, *anti* or *erythro*, in the reduction of (*R*)-*N*-Cbz-γ-amino-β-keto methyl esters **741**, (*S*)-*N*-Boc-γ-amino-β-keto ethyl esters **744** and (*S*)-*N*-TFA-γ-amino-β-keto benzyl ester **747**, can be explained by cyclic transition state **A** (Fig. 9), formed by the chelation of the boron atom between the protected amino group and the enolized oxygen, in such way that the hydride could then attack either intramolecularly or intermolecularly at the β-position on the least hindered face determined by the R group appendage.[289] The formation of γ-amino-β-hydroxy esters *syn* or *threo* in the reduction of *N*-Boc-*N*-methylamino-β-keto ethyl ester **750** and *N*,*N*-dibenzyl-γ-amino-β-keto *tert*-butyl esters **751** was attributed an open Felkin–Anh transition state **B** (Fig. 9).[290]



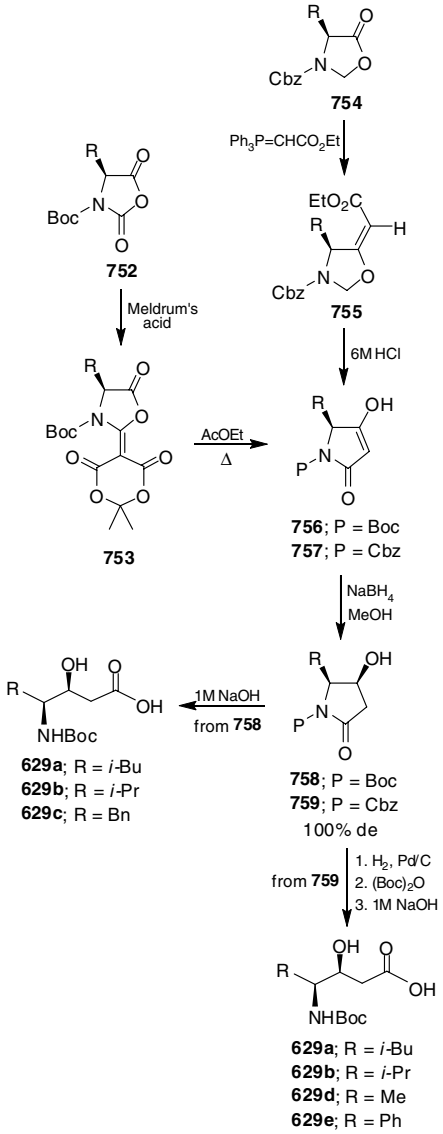
A *anti* or *erythro*

P = Boc, Cbz, TFA
R' = Me, Et, Bn

B *syn* or *threo*

Figure 9.

Diastereoselective reduction of tetramic acids **756** and **757** is another methodology used in the stereoselective synthesis of statine derivatives. In this context, *N*-Boc tetramic acid **756** was readily obtained by the reaction of *N*-Boc-*N*-carboxyanhydride **752** with Meldrum's acid, and subsequent decarboxylation of **753**. Protected *N*-Cbz tetramic acid **757** was obtained by a Wittig reaction of oxazolidinone **754** followed by acidic hydrolysis of **755**. Reduction of **756** and **757** with $NaBH_4$ gave alcohols **758** and **759** as only one isolable diastereoisomer. Hydrolysis of derivatives **758** led to *N*-Boc-γ-amino-β-hydroxy acids **629** in good yield. On the other hand, hydrogenolysis of **759** followed by N-protection with $(Boc)_2O$ and subsequent hydrolysis also afforded the diastereoisomerically pure *N*-Boc-γ-amino-β-hydroxy acids **629** (Scheme 194).[291]

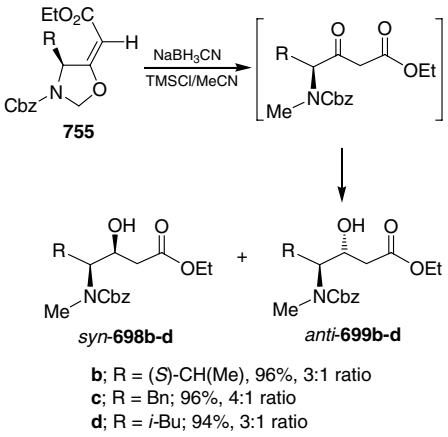


629a; R = *i*-Bu
629b; R = *i*-Pr
629c; R = Bn

629a; R = *i*-Bu
629b; R = *i*-Pr
629d; R = Me
629e; R = Ph

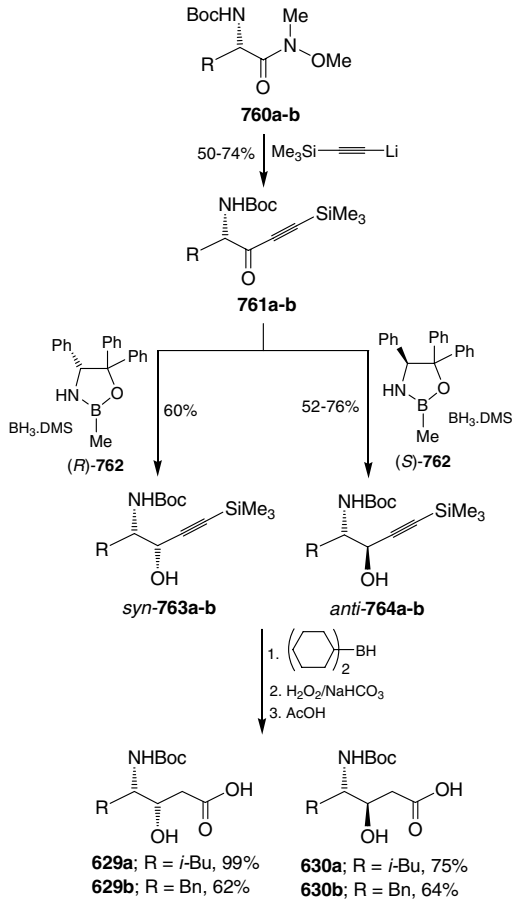
Scheme 194.

On the other hand, the reduction of **755** with $NaBH_3CN$ in the presence of TMSCl in acetonitrile gave *N*-Cbz-*N*-methyl-γ-amino-β-hydroxy ethyl esters *syn*-**698** and *anti*-**699** in a ratio of 3:1 to 4:1 and excellent yield, via the keto-ester derivative (Scheme 195).[292]



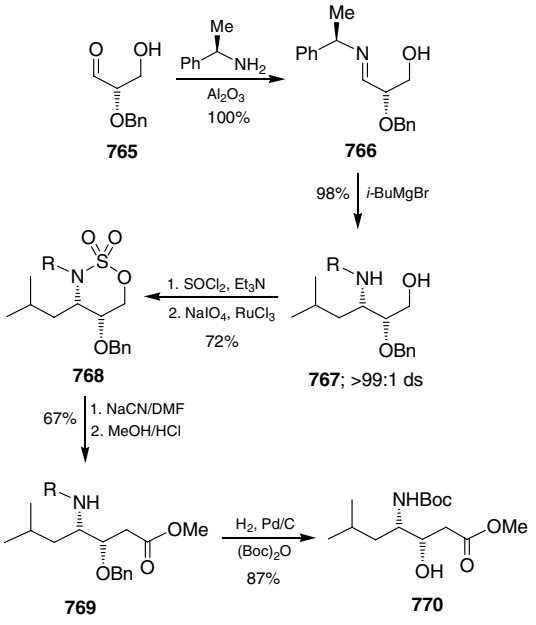
Scheme 195.

In recent years, chiral oxazaborolidines pioneered by Itsuno[293] and developed by Corey[294] have proven to be useful catalysts and reagents in asymmetric transformations.[295] In this context, the reduction of chiral 4-substituted 1-trimethylsilyl-1-alkyn-3-ones **761a** and **761b** readily obtained from the addition of lithium trimethylsilylacetylide to Weinreb amides **760a** and **760b** with BH_3·DMS complex in the presence of (*R*)-oxazaborolidine **762** afforded the corresponding alcohols *syn*-**763** in 60% yield and high diastereoselectivity. On the other hand, the reduction of alkyn-3-ones **761a**,**b** with (*S*)-oxazaborolidine **762** gave alcohols *anti*-**764** in high diastereoselectivity, which is based on a double diastereodifferentiation. Hydroboration of *syn*-**763a** and **763b** with dicyclohexylborane followed by oxidative workup in a basic medium afforded the *N*-Boc-γ-amino-β-hydroxy acids *syn*-**629a** and **629b**. In a similar way, compounds *anti*-**764a** and **764b** were transformed into *N*-Boc-γ-amino-β-hydroxy acids *anti*-**630a** and **630b** (Scheme 196).[296]



Scheme 196.

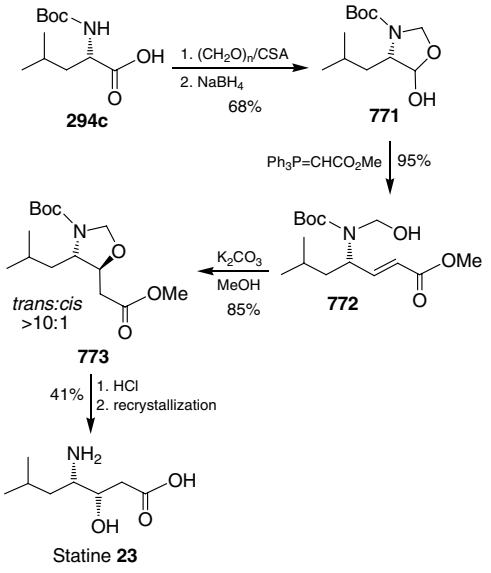
The addition of a Grignard reagent to *N*-(α-methylbenzyl)imine **766** readily obtained from the reaction of 2-*O*-benzylglyceraldehyde **765** and (*S*)-α-methylbenzylamine afforded the corresponding amino alcohol **767** with excellent yield and diastereoselectivity. Treatment of amino alcohol **767** with thionyl chloride and subsequent oxidation of intermediate amidosulfite with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ afforded amidosulfate **768** in 72% yield. The addition of sodium cyanide to **768** followed by methanolysis produced ester **769**, which by cleavage of methylbenzyl protective group and subsequent treatment with $(Boc)_2O$ led to *N*-Boc-γ-amino-β-hydroxy methyl ester **770** (Scheme 197).[297]



Scheme 197.

Kim et al.[298] have described an efficient synthesis of enantiomerically pure statine **23** by stereoselective intramolecular addition of the hydroxy group tethered to the amino group of configurationally stable (*E*)-γ-amino-α,β-unsaturated methyl ester **772**. Thus, treatment of *N*-Boc-L-leucinal derivative **771**, readily obtained in 68% overall yield

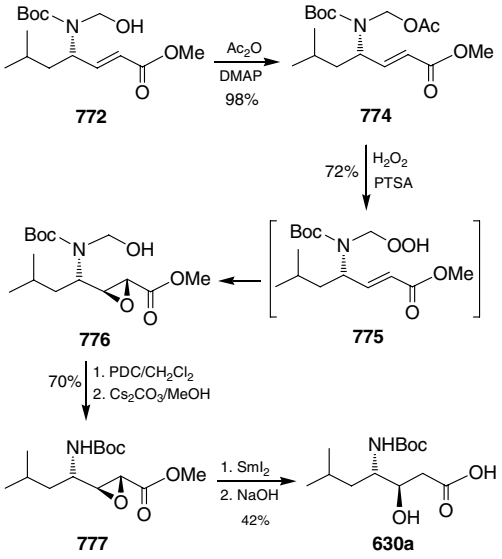
from *N*-Boc-L-leucine **294c** with a stabilized ylide afforded the (*E*)-γ-amino-α,β-unsaturated methyl ester **772** with the *N*-hydroxymethyl group in excellent yield and selectivity. Intramolecular conjugate addition of the hydroxy group in **772** gave oxazolidine **773** in good yield and selectivity *trans*:*cis* (>10:1), which by acidic hydrolysis and recrystallization led to the diastereoisomerically pure statine **23** (Scheme 198).



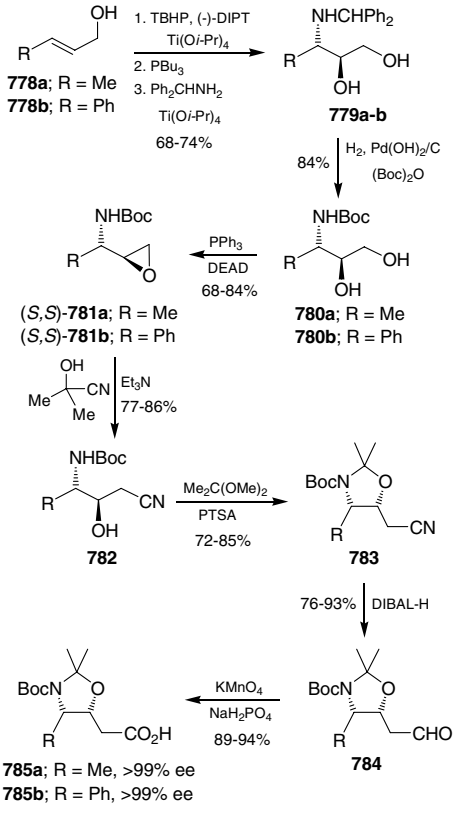
Scheme 198.

On the other hand, acetylation of (*E*)-γ-amino-α,β-unsaturated methyl ester **772** produced the acetylated product **774** in 98% yield, which by intramolecular nucleophilic epoxidation with aqueous H_2O_2 under acidic conditions led to epoxide derivative **776** with high selectivity *anti*:*syn* (>20:1) and 72% yield via the *N*-hydroperoxymethyl derivative **775**. Oxidation of the hydroxymethyl group in **776** with pyridinium dichromate (PDC) followed by reaction with Cs_2CO_3 gave epoxide derivative **777** in 70% yield, which by treatment with SmI_2 and subsequent hydrolysis afforded *N*-Boc-epistatine **630a** in 42% yield (Scheme 199).[299]

Stereoselective synthesis of protected *cis*-γ-amino-β-hydroxy acids **785a** and **b** has been prepared by Moyano et al.[300] using the Sharpless enantioselective epoxidation of allylic alcohols **778a** and **b** in the initial step.[301] Thus, Sharpless enantioselective epoxidation of allylic alcohols **778a** and **778b** under standard methodology afforded the corresponding epoxide, which by regioselective ring opening with benzhydrylamine gave the (2*S*,3*S*)-N-protected-3-amino-1,2-butanodiols **779a** and **779b**,[302] which on hydrogenolysis in the presence of $(Boc)_2O$ led to *N*-Boc-amino diols **780a** and **780b**. Intramolecular Mitsunobu reaction[303] of **780a** and **780b** in the presence of Ph_3P/DEAD afforded epoxides (*S*,*S*)-**781a** and **781b**, which on reaction with acetone cyanohydrin in basic medium gave the corresponding amino cyanohydrines **782a** and **782b**. The reaction of **782a** and **782b** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTSA) furnished *cis*-*N*-Boc-oxazolidines **783a** and **783b**, which by reduction of the cyano group produced aldehydes **784a** and **784b**, which upon oxidation led to the protected *cis*-γ-amino-β-hydroxy acids **785a** and **785b** (Scheme 200).



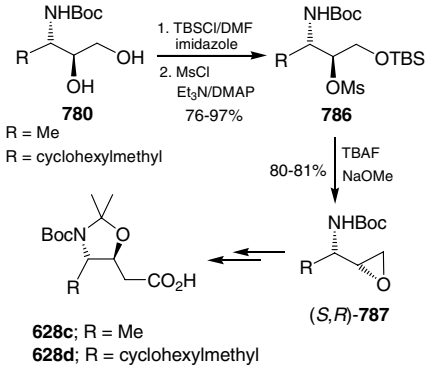
Scheme 199.



Scheme 200.

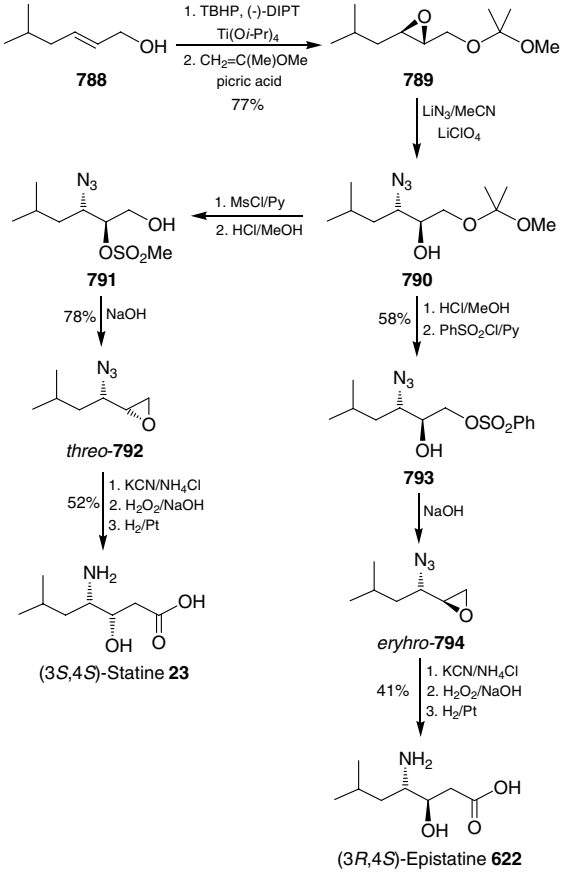
On the other hand, silylation of the primary alcohol in **780a–c** followed by mesylation of the secondary alcohol gave protected derivatives **786**, which upon treatment with

tetra-*n*-bultylammonium fluoride in the presence of sodium methoxide gave the corresponding epoxides (*S*,*R*)-**787** in good yield. Using the same reaction sequence shown in the Scheme 200, epoxides (*S*,*R*)-**787a–c** were converted into *trans*-γ-amino-β-hydroxy acids **628c–d** (Scheme 201).[300]



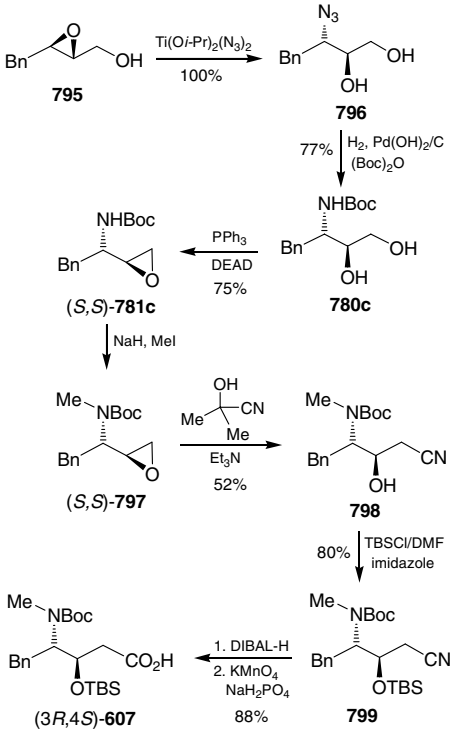
Scheme 201.

On the other hand, enantioselective epoxidation of allylic alcohol **788** according to a Sharpless methodology followed by protection with 2-methoxypropene produced (2*R*,3*R*)-epoxide **789** in 77% yield, which upon reaction with lithium azide in the presence of lithium perchlorate gave azide derivative **790** in good yield and high regioselectivity. Mesylation of **790** followed by hydrolysis of acetal group afforded **791**, which upon treatment with sodium hydroxide led to epoxide *threo*-**792** in 78% yield. On the other hand, hydrolysis of **790** followed by benzenesulfonylation provided benzenesulfonate **793** in 58%, which by base-catalyzed reaction gave the epoxide *erythro*-**794**. Ring opening of *threo*-**792** with potassium cyanide in the presence of ammonium chloride, followed by hydrolysis of cyanide group with sodium hydroperoxide and subsequent reduction of azide group, afforded (3*S*,4*S*)-statine **23** in 52% yield. In a similar way, epoxide *erythro*-**794** was converted into (3*R*,4*S*)-epistatine **622** (Scheme 202).[304]



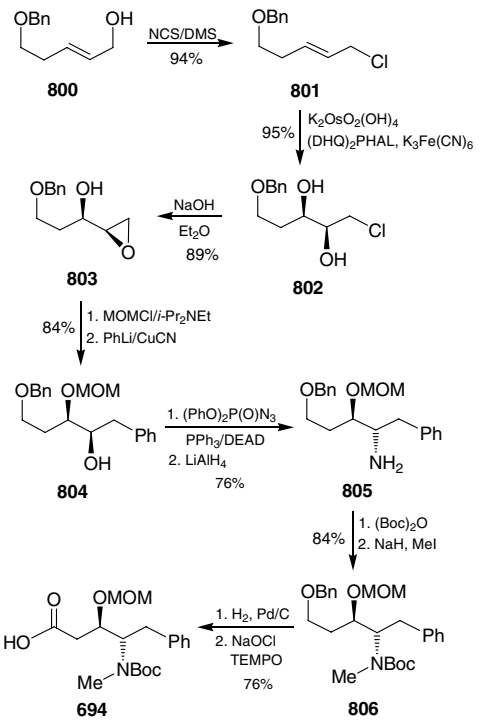
Scheme 202.

In a similar manner, Moyano et al.[305] have reported the stereoselective synthesis of protected *N*-Boc-*N*-methyl-γ-amino-β-hydroxy acid (3*R*,4*S*)-**607**, an essential component of Hapalosin. In this context, treatment of epoxy alcohol **795** readily obtained by catalytic Sharpless epoxidation with titanium diazidodiisopropoxide afforded azido-diol **796** as the only product of the regio- and stereoselective nucleophilic opening at C_3, which on catalytic hydrogenation in the presence of $(Boc)_2O$ gave the corresponding *N*-Boc-amino diol **780c** in 77% yield. Intramolecular Mitsunobu reaction of **780c** led to epoxide (*S*,*S*)-**781c** in 75% yield, which by N-methylation using MeI/NaH gave **797**. Epoxide opening in **797** with acetone cyanohydrin produced cyano derivative **798** in 52% yield, which by protection of hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl), followed by reduction of nitrile group with DIBAL-H and subsequent oxidation produced protected γ-amino-β-hydroxy acid (3*R*,4*S*)-**607** (Scheme 203).



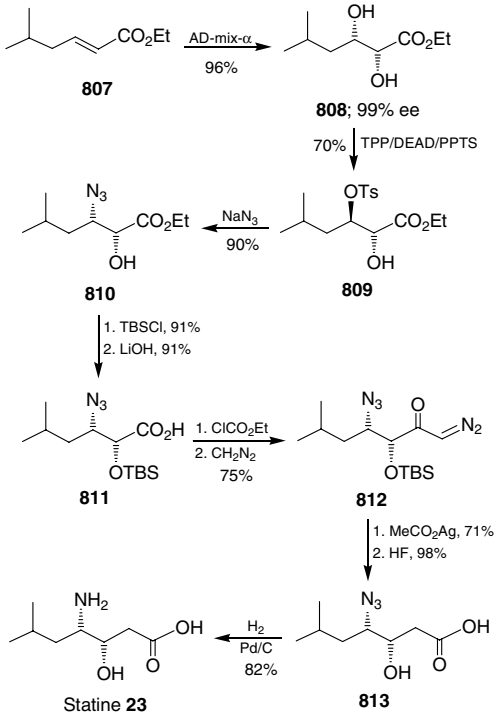
Scheme 203.

Maier et al.[306] have also reported the stereoselective synthesis of **694** using Sharpless enantioselective dihydroxylation as the key step.[307] Thus, chlorination of the allylic alcohol **800** followed by asymmetric dihydroxylation using hydroquinidine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$] as the chiral ligand gave chlorodiol **802** in 95% yield. The reaction of chlorodiol **802** with sodium hydroxide gave the corresponding epoxy alcohol **803** in 89% yield, which by protection of hydroxy group with chloromethylmethyl ether (MOMCl) and subsequent addition of phenyllithium in the presence of copper cyanide led to diprotected triol **804** in 84% yield. Mitsunobu reaction in **804** using diphenylphosphoryl azide in the presence of triphenylphosphine and diethyl azodicarboxylate furnished the azide, which by reduction with $LiAlH_4$ gave amine **805** in 76% yield. Protection of the amino group with $(Boc)_2O$ followed by N-methylation afforded the protected compound **806** in 84% yield. Finally, reductive cleavage of the benzyl protective group in **806** by hydrogenolysis and subsequent oxidation with sodium hypochlorite and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) gave the protected γ-amino-β-hydroxy acid **694** (Scheme 204).



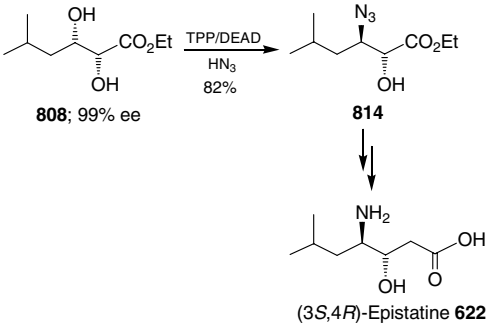
Scheme 204.

Sharpless asymmetric hydroxylation of α,β-unsaturated ethyl ester **807** using (AD-mix-α) afforded (2*R*,3*S*)-*syn*-2,3-dihydroxy ethyl ester **808** in 96% yield and 99% ee. Mitsunobu tosylation of **808** using triphenylphosphine (TPP), diethylazodicarboxylate (DEAD), and pyridinium *p*-toluenesulfonate (PPTS) gave the corresponding *anti*-α-hydroxy-β-tosylate derivative **809** with complete regioselection for the β-hydroxy group. Displacement of the β-tosylate in **809** with sodium azide led to *syn*-α-hydroxy-β-azido ester **810**, which upon protection of α-hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl) and subsequent saponification gave the carboxylic acid **811** in excellent yield. Homologation of **811** via an Arndt–Eistert reaction from **812** followed by cleavage of the TBS protective group with HF afforded carboxylic acid **813**, which by catalytic hydrogenation of azido group gave statine **23** in 82% yield (Scheme 205).[308]



Scheme 205.

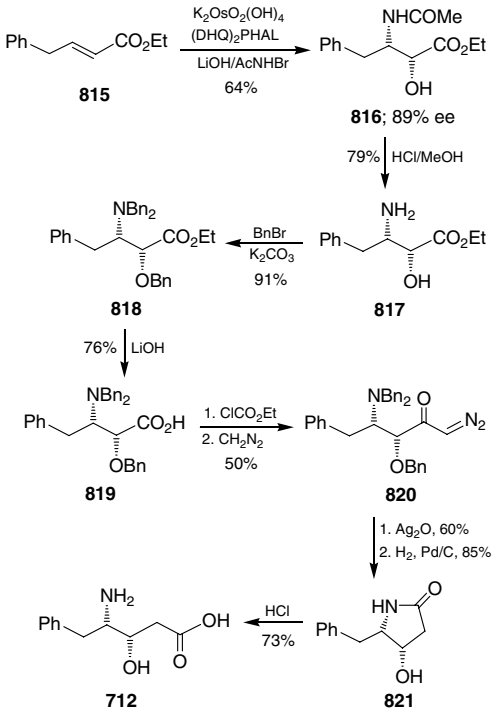
On the other hand, Mitsunobu azidation of **808** using TTP, DEAD, and HN_3 gave *anti*-α-hydroxy-β-azide derivative **814** with complete regioselection for the β-hydroxy group, which was transformed into epistatine (3*S*,4*R*)-**622** under the protocol described above (Scheme 206).[308]



Scheme 206.

Stereoselective synthesis of phenylstatine **712** has been described by Kumar et al.[309] employing a Sharpless asymmetric aminohydroxylation as the key step.[310] Thus, asymmetric aminohydroxylation of α,β-unsaturated ethyl ester **815** using potassium osmate as the oxidant reagent in the presence of $(DHQ)_2PHAL$ as a chiral ligand and

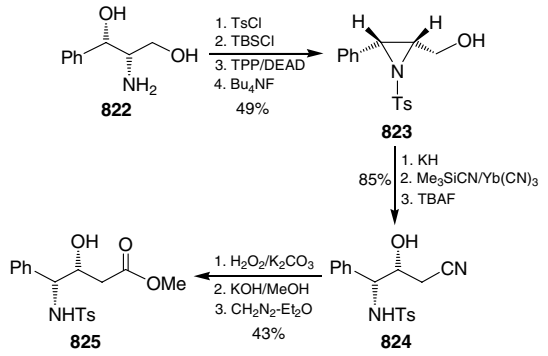
N-bromoacetamide (AcNHBr) as the nitrogen source afforded the corresponding *N*-acetyl derivative **816** in a 10:1 regioisomeric ratio and 64% yield with 89% ee. Cleavage of the *N*-acetyl group in **816** with HCl in methanol gave amino alcohol **817** in 79% yield, which by N- and O-benzylation produced ester **818** in 91% yield. Saponification of **818** led to the corresponding carboxylic acid **819**, which by treatment with ethyl chloroformate followed by reaction with diazomethane furnished the diazo compound **820** in 50% yield. A Wolff rearrangement of **820** followed by cleavage of the benzyl protective group afforded γ-lactam **821**, which by hydrolysis with concentrated HCl provided phenylstatine **712** (Scheme 207).



Scheme 207.

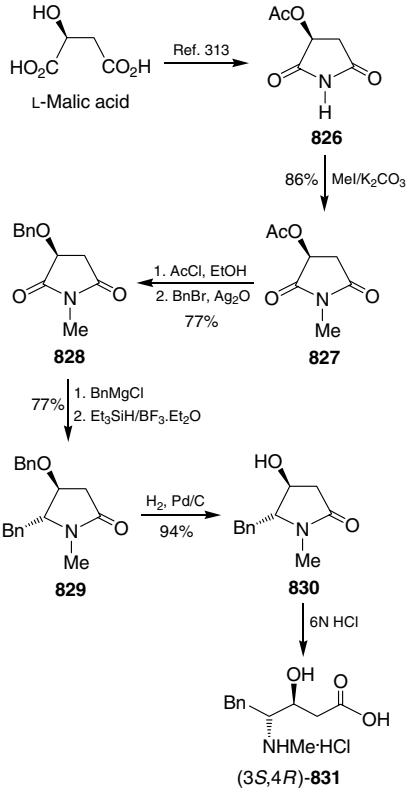
On the other hand, the reaction of commercially available homochiral dihydroxyamine **822** via a four-step sequence involving (1) *N*-tosylation, (2) selective silylation, (3) aziridine-ring formation by triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD), and (4) cleavage of the silyl protecting group afforded aziridine **823** in 49% yield,[311] which upon reaction with KH and Me_3SiCN in the presence of $Yb(CN)_3$ and *n*-Bu_4NF gave cyano derivative **824** in 85% yield. Treatment of nitrile **824** with alkaline hydrogen peroxide followed by basic hydrolysis and subsequent reaction with diazomethane led to diprotected γ-amino-β-hydroxy acid **825** in 43% yield (Scheme 208).[312]

Methylation of (*S*)-3-acetoxy-2,5-pyrrolidinedione **826** readily obtained from L-malic acid,[313] with MeI in the presence of K_2CO_3 afforded **827** in 86% yield, which upon deacylation under acidic conditions using AcCl/EtOH, followed by O-benzylation with benzyl bromide in the presence of Ag_2O, provided *O*-benzyl derivative **828** in 77% yield. The addition of a Grignard reagent followed by a



Scheme 208.

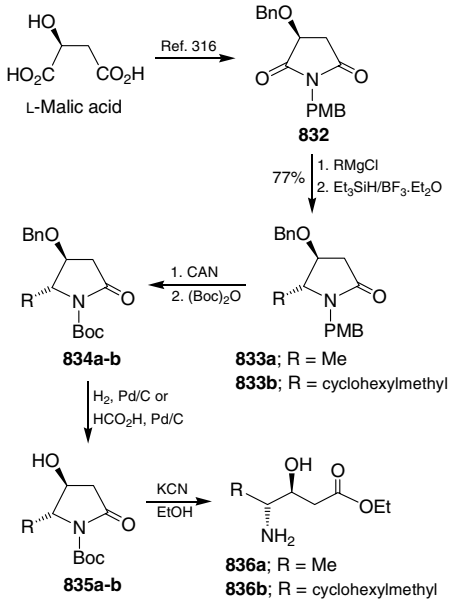
reductive process with Et_3SiH gave γ-lactam **829** in high regio- and *trans*-stereoselectivity, which by O-debenzylation with H_2 in the presence of Pd/C produced β-hydroxy lactam **830** in excellent yield, which by acidic hydrolysis afforded the unnatural γ-amino-β-hydroxy acid (3*S*,4*R*)-**831** (Scheme 209).[314,315]



Scheme 209.

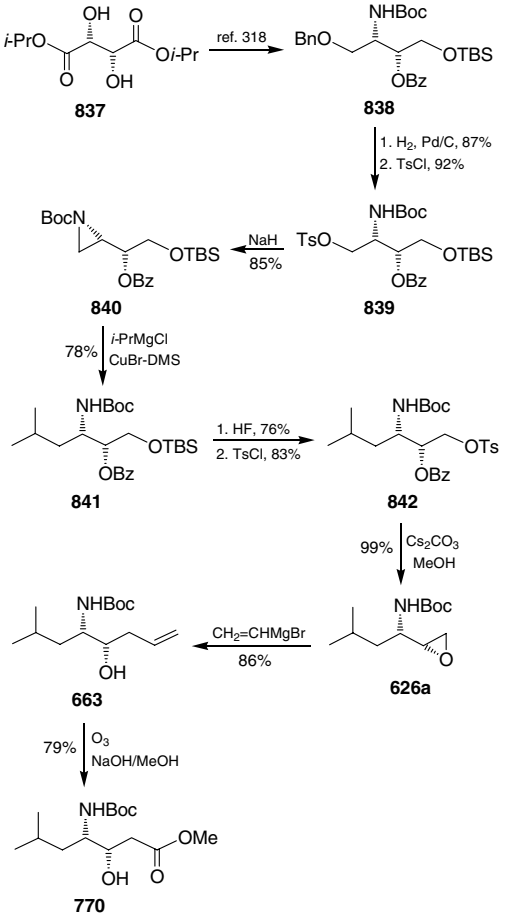
In a similar way, reductive alkylation of malimide **832**[316] gave *anti*-γ-lactams **833a** and **833b** in good yield and as only one diastereoisomer. Oxidative N-deprotection of **833a** and **833b** using ceric ammonium nitrate (CAN), followed by treatment with $(Boc)_2O$ produced *N*-Boc-γ-lactams **834a** and **834b**, which by catalytic hydrogenolysis using H_2 in the presence of Pd/C for **834a** (R = Me), or with HCO_2H in the presence of Pd/C for **834b**

(R = cyclohexylmethyl) gave β-hydroxy-γ-lactams **835a** and **835b** in excellent yield. Finally, ring opening of γ-lactams **835a** and **835b** with potassium cyanide promoted by ethanolysis provided γ-amino-β-hydroxy ethyl esters **836a** and **836b** (Scheme 210).[317]



Scheme 210.

On the other hand, cleavage of the protective benzyl group in **838** obtained from tartrate diisopropyl ester **837**,[318] followed by O-tosylation, gave tosylate derivative **839** in good yield, which by treatment with sodium hydride afforded *N*-Boc-aziridine **840** in 85% yield. Ring opening of aziridine **840** with an isopropyl Grignard reagent in the presence of CuBr as a catalyst led to *N*-Boc derivative **841**. Desilylation of **841** with HF followed by tosylation produced tosylate **842**, which by treatment with Cs_2CO_3 furnished epoxide **626a**. Ring opening of epoxide **626a** using vinyl Grignard reagent in the presence of CuBr gave amino alcohol **663** in 86% yield, which upon ozonolysis in the presence of MeOH/NaOH afforded statine methyl ester **770** in 79% yield (Scheme 211).[319]



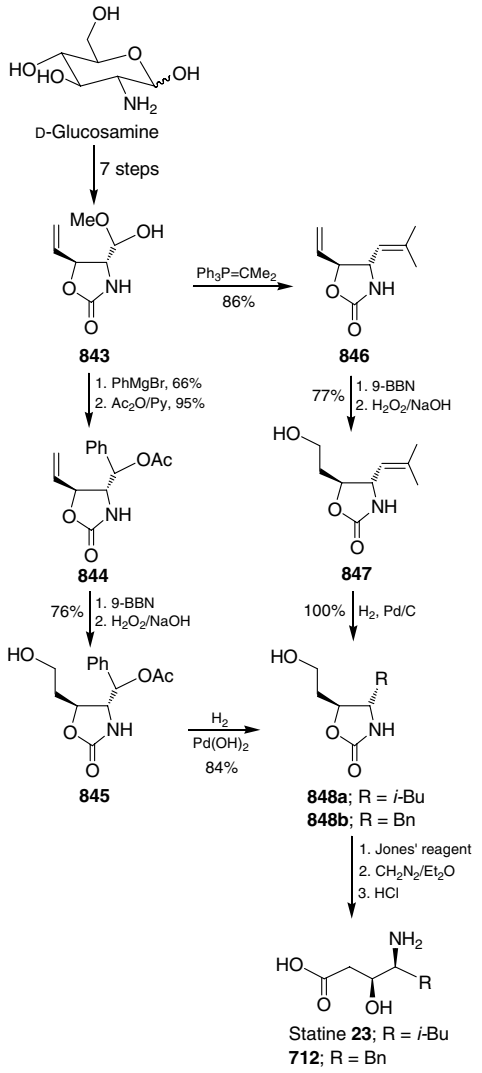
Scheme 211.

Carbohydrates as the starting material have also been used in the stereoselective synthesis of statine and its analogues. For example, Masaki et al.[320] have reported the preparation of **848a** and **848b** from inexpensive and readily available D-glucosamine, which can be transformed into statine **23** and benzylstatine **712**. In this context, the addition of phenylmagnesium bromide to hemiacetal **843** obtained in seven steps from D-glucosamine, followed by acetylation with acetic anhydride produced the acetylated product **844**. Hydroboration–oxidation of **844** afforded alcohol **845** in 76% yield, which on catalytic hydrogenolysis of the acetoxy group regioselectively gave primary alcohol **848b**. On the other hand, Wittig reaction of hemiacetal **843** gave diene derivative **846** in 86% yield, which by hydroboration–oxidation produced alcohol **847** in 77% yield, that by catalytic hydrogenation of the double bond furnished **848a**. Finally, oxidation and hydrolysis[321] of **848a** and **848b** afforded statine **23** and phenylstatine **712** (Scheme 212).

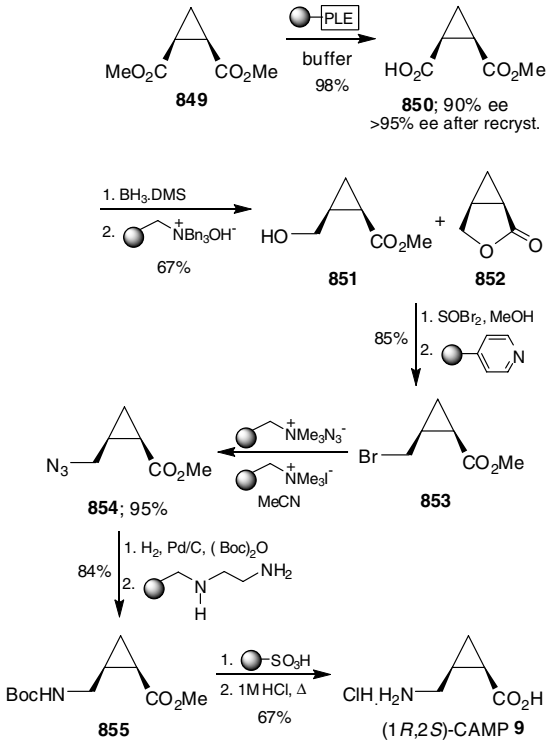
4. Asymmetric synthesis of cyclic γ-amino acids

4.1. Synthesis of $C^{n}_{\alpha,\beta}$ derivatives

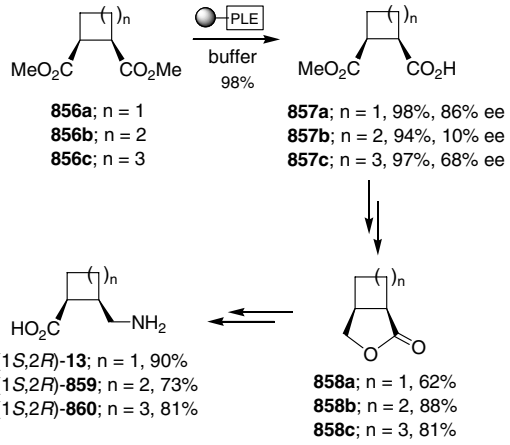
Conformationally restricted cyclic GABA analogues with methylenes incorporated into homocyclic systems containing a three-, four-, five-, and six-membered saturated and unsaturated rings, have been studied extensively. For example, (1*S*,2*R*)-2-(aminomethyl)cyclopropanecarboxylic acid CAMP **9** is a potent and full agonist at human ρ1 and ρ2 GABAc receptors, whereas (1*R*,2*S*)-2-(aminomethyl)cyclopropanecarboxylic acid CAMP **9** is a weak antagonist at human ρ1 and ρ2 GABAc receptors subtypes, and moderately potent antagonist at rat ρ3.[33,322] The significance of these molecules is also evident given that the number of research publications dedicated to their synthesis has been increasing. In this context, Ley et al.[323] reported the synthesis of (1*R*,2*S*)-CAMP **9** from *meso*-diester **849**, via resolution. Thus, desymmetrization of commercially available *meso*-diester **849** with polymer-supported pig liver esterase (PLE) afforded mono-carboxylic acid **850** in 98% yield and >95% ee after recrystallization. Reduction of the carboxylic acid function in **850**



Scheme 212.



Scheme 213.



Scheme 214.

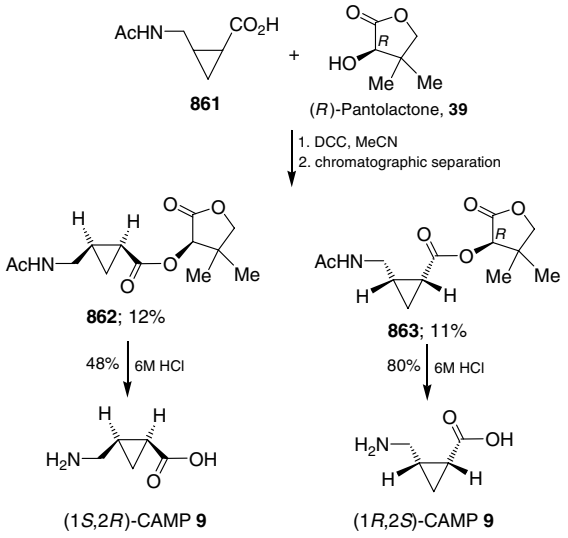
with a BH_3·DMS complex in THF gave a mixture of the corresponding alcohol **851** and γ-lactone **852**, which upon treatment with thionyl bromide and subsequent addition of poly(4-vinylpyridine) produced bromoester **853** in 85% yield. Conversion of bromide **853** into azide **854** followed by catalytic hydrogenation in the presence of $(Boc)_2O$ gave *N*-Boc-γ-amino ester **855** in 84% yield, which upon hydrolysis gave (1*R*,2*S*)-CAMP **9** (Scheme 213).

On the other hand, desymmetrisation of *meso*-diesters **856a**–**c** with polymer-supported pig liver esterase (PLE) furnished mono-carboxylic acids **857a**–**c** in good yield, which were transformed into the γ-amino acids (1*S*,2*R*)-**13** ($n = 1$), (1*S*,2*R*)-**859** ($n = 2$), and (1*S*,2*R*)-**860** ($n = 3$) under an identical reaction sequence described above via the lactones **858a**–**c**, respectively (Scheme 214).[323,324]

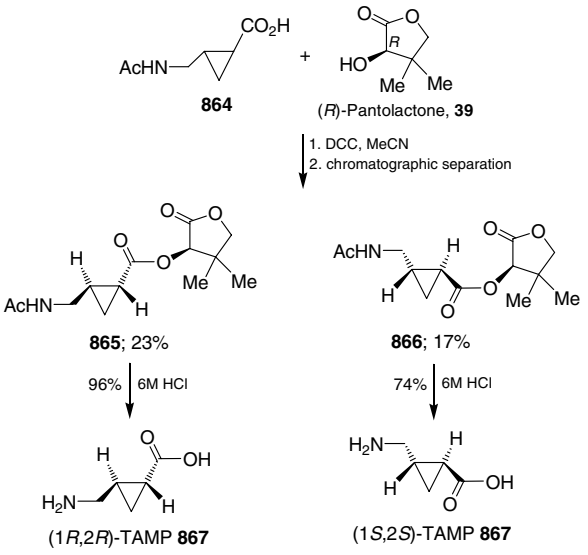
Carbodiimide coupling of *cis*-amino acid derivative **861** with (*R*)-pantolactone **39** gave diastereoisomeric esters **862** and **863** in 12% and 11% yield, respectively, after separation by flash chromatography. Acidic hydrolysis of diastereoisomerically pure **862** and **863** produced the enantiomerically pure (1*S*,2*R*)-CAMP **9** and (1*R*,2*S*)-CAMP **9**, respectively (Scheme 215).[325]

In a similar way, (1*R*,2*R*)- and (1*S*,2*S*)-TAMP **867** were obtained by resolution of racemic *trans*-amino acid derivative **864** with (*R*)-pantolactone **39** (Scheme 216).[325]

Recently, Wipf et al.[326] have described the preparation of cyclopropane γ-amino esters (*S*,*S*,*S*)-**873** and (*R*,*R*,*R*)-**873** by multi-component condensation reaction and resolution. Initially, the addition of Cp_2ZrHCl to TBDPS-protected propargyl alcohol **868**, followed by sequential transmetalation with dimethylzinc, addition to *N*-diphenylphosphinylimine and treatment with bis(iodomethyl)zinc-DME complex,



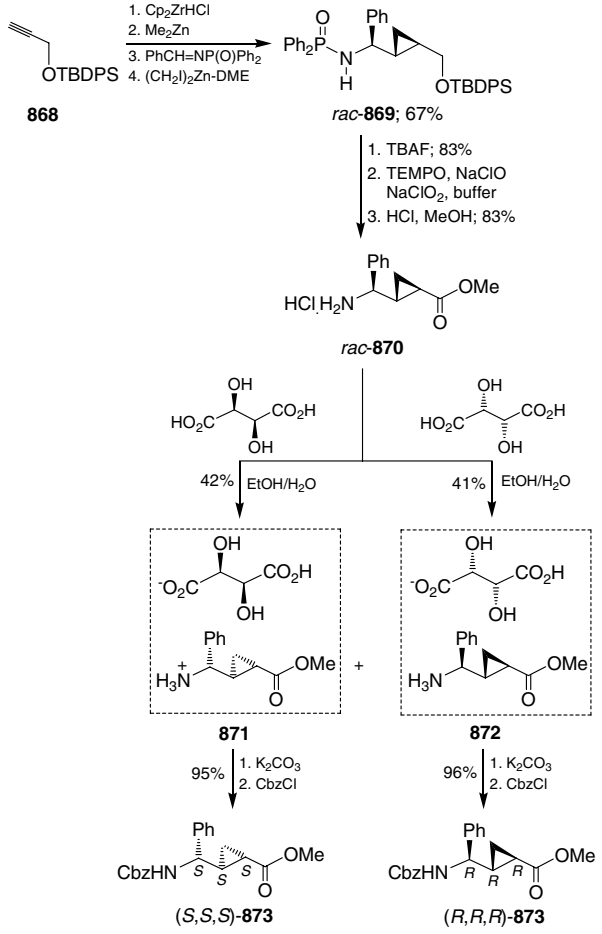
Scheme 215.



Scheme 216.

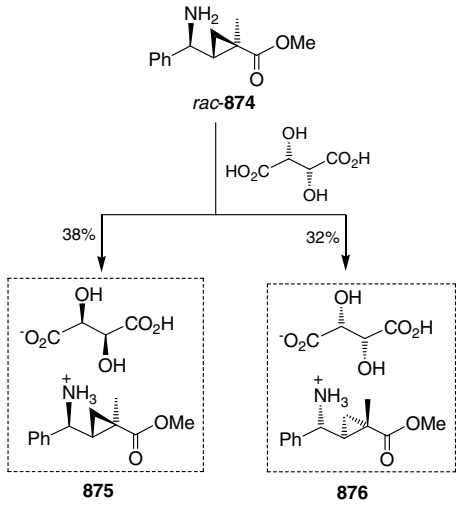
gave the corresponding amide *rac*-**869** in 67% yield and high diastereoisomeric ratio (>19:1). Cleavage of the TBDPS protective group with tetra-*n*-butylammonium fluoride (TBAF) and oxidation of the resulting alcohol afforded the carboxylic acid derivative, which by treatment of HCl in methanol produced the methyl ester hydrochloride salt *rac*-**870**. Resolution of *rac*-**870** with L-tartaric acid gave diastereoisomeric salt **871**. D-Tartaric acid was necessary for the salt formation of **872**. Treatment of diastereoisomeric pure **871** and **872** with aqueous solution of K_2CO_3 followed by N-protection with CbzCl led to *N*-Cbz-γ-amino esters (*S*,*S*,*S*)-**873** and (*R*,*R*,*R*)-**873**, respectively, which are precursors for the preparation of ΔPhg **10** (Scheme 217).

In a similar manner, the γ-amino acid methyl esters salts **875** and **876** were obtained by resolution of *rac*-**874** with



Scheme 217.

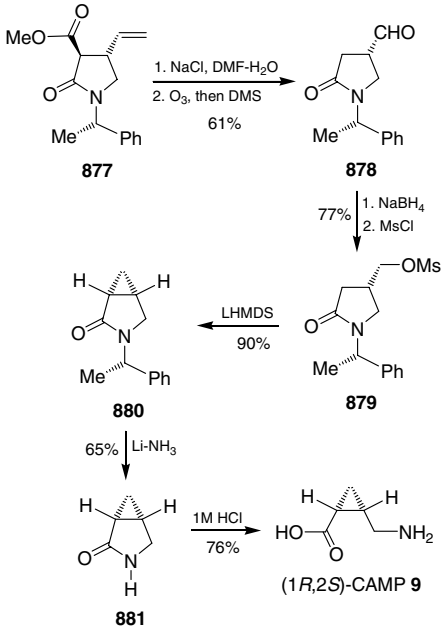
D-tartaric acid. Derivatives **875** and **876** are precursors in the preparation of $^{\alpha}$MeΔPhg **11** (Scheme 218).[327]



Scheme 218.

Orena et al.[328] have described the stereoselective synthesis of diastereoisomerically pure (1*R*,2*S*)-CAMP **9** using pyrrolidin-2-one **877** as the starting material.[329] In this context,

decarboxylation of **877** under Krapcho conditions followed by ozonolysis produced aldehyde **878** in 61% yield, which on reduction with $NaBH_4$ and subsequent mesylation gave mesylate **879** in 77% yield. Treatment of mesylate **879** with LHMDS exclusively afforded bicyclic compound **880** in 90% yield. Reductive cleavage of the methylbenzyl group in **880** with Li–NH_3 gave **881** in 65% yield, which upon hydrolysis led to (1*R*,2*S*)-CAMP **9** in 76% yield (Scheme 219).[330]

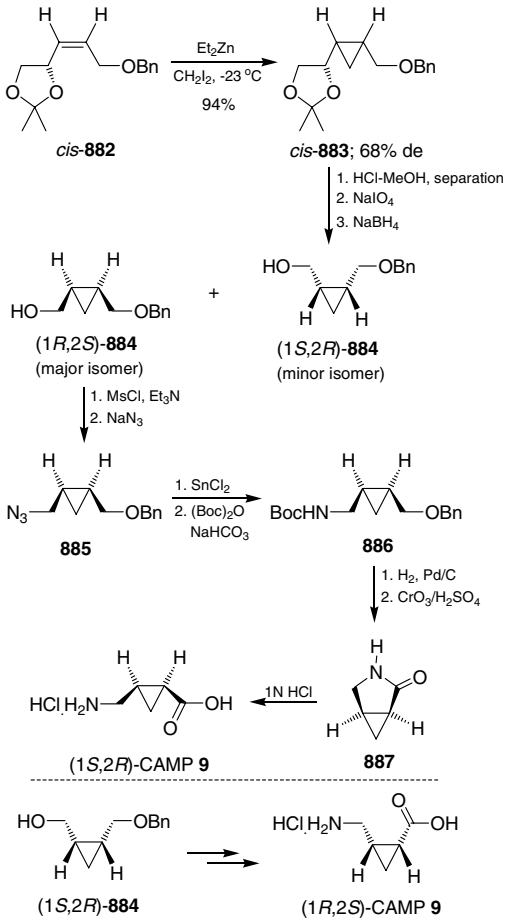


Scheme 219.

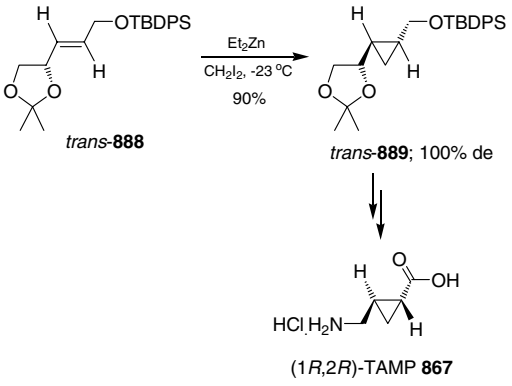
On the other hand, Taguchi et al.[331] have reported the synthesis of enantiomerically pure CAMP and TAMP by Simmons–Smith reaction from allylic alcohol **882**, obtained from 2,3-*O*-isopropylidene-D-glyceraldehyde. Thus, the reaction of *cis*-**882** with Et_2Zn and CH_2I_2 gave cyclopropane *cis*-**883** in 94% yield and 68% de. Acidic hydrolysis of *cis*-**883**, followed by separation, oxidation and reduction, produced the alcohol (1*R*,2*S*)-**884** as a major isomer, which was converted into azide **885** via the mesylate. Reduction of the azide functionality in **885** with tin(II) chloride followed by protection of the amine group with $(Boc)_2O$ led to compound **886**. Cleavage of the benzyl protective group in **886** with H_2 in the presence of Pd/C and subsequent oxidation produced γ-lactam **887**, which by acidic hydrolysis afforded (1*S*,2*R*)-CAMP **9** as hydrochloride salt. In a similar way, (1*S*,2*R*)-**884** was converted into (1*R*,2*S*)-CAMP **9** as hydrochloride salt (Scheme 220).

On the other hand, the reaction of *trans*-**888** with Et_2Zn and CH_2I_2 gave cyclopropane derivative *trans*-**889** in 90% yield and excellent diastereoselectivity (100% de), which was converted into (1*R*,2*R*)-TAMP hydrochloride salt **867** under identical conditions described above (Scheme 221).[331]

Asymmetric cyclopropanation of *trans*-cinnamyl alcohol **778b** in the presence of chiral dioxaborolane chiral ligand

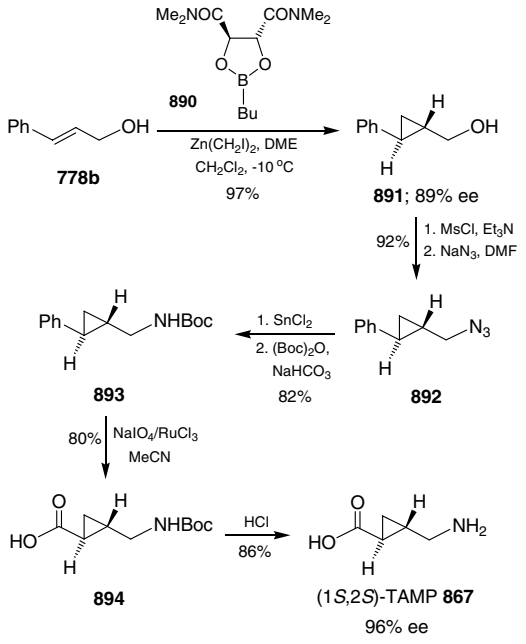


Scheme 220.



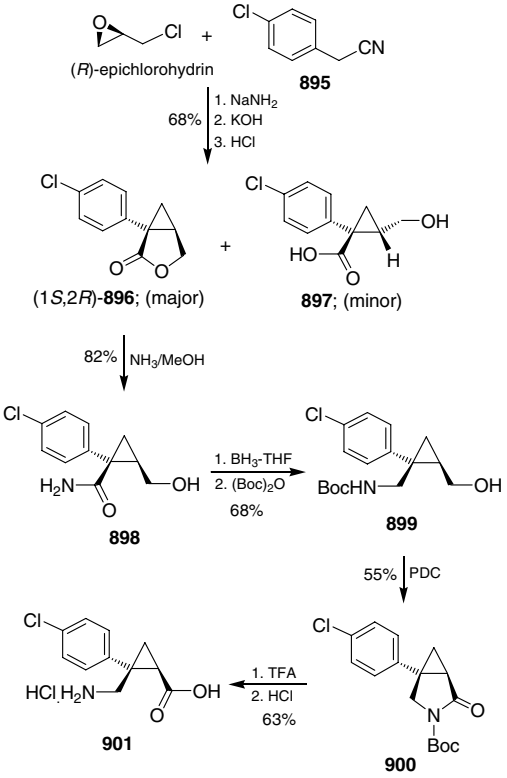
Scheme 221.

890 derived from D-tartaric acid afforded (1*S*,2*S*)-cyclopropyl alcohol **891** in 97% yield and 89% ee. Mesylation of **891** followed by treatment with sodium azide produced the corresponding azide derivative **892** in 92% yield, which upon reduction of the azide group and subsequent Boc protection of the resulting amine led to **893** in 82% yield. Oxidative cleavage of the phenyl ring with $NaIO_4$ in the presence of $RuCl_3$ gave carboxylic acid **894** in 80% yield, which on treatment with HCl provided (1*S*,2*S*)-TAMP **867** in 86% yield and 96% ee (Scheme 222).[332]



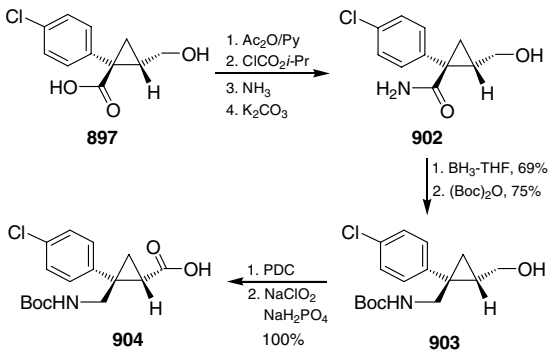
Scheme 222.

Shuto et al.[333] have reported the synthesis of conformationally restricted analogues of baclofen **3**, by the introduction of a cyclopropane ring. In this context, the reaction of (*R*)-epichlorohydrin with the sodium carbanion generated from (*p*-chlorophenyl)acetonitrile **895** and, $NaNH_2$, followed by treatment with KOH and HCl afforded (1*S*,2*R*)-lactone **896** in 68% yield and 93% ee. Ammonolysis of **896** with NH_3/MeOH produced amide **898** in 82% yield, which by reduction with the BH_3·THF complex followed by protection of amino group with $(Boc)_2O$ gave the alcohol derivative **899**. Oxidation of **899** with PDC led directly to γ-lactam **900** in 55% yield, which by treatment under acidic conditions gave conformationally restricted analogue of baclofen **901** in 63% yield (Scheme 223).[334]



Scheme 223.

Under a similar reaction sequence, **897** was converted into *trans*-*N*-Boc-γ-amino acid **904** (Scheme 224).[333]



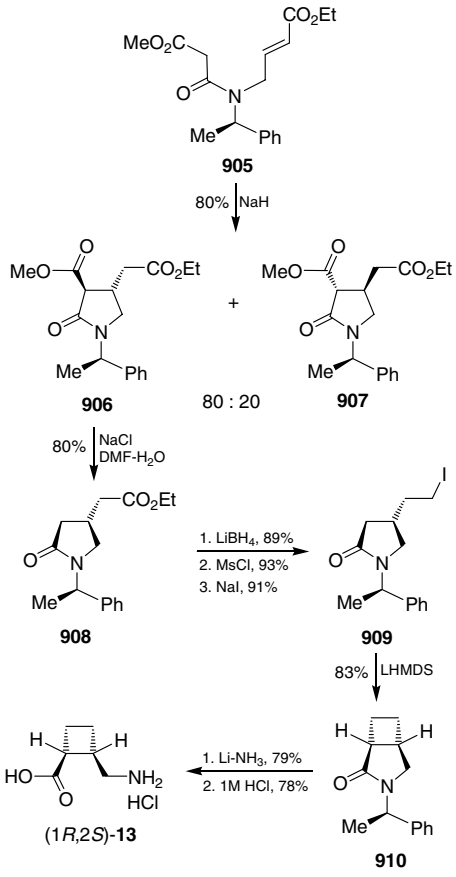
Scheme 224.

On the other hand, treatment of amide **905** with NaH afforded pyrrolidin-2-ones **906** and **907** in 80% yield and 80:20 ratio. Decarboxylation of diastereoisomerically pure **906** using NaCl in the presence of wet DMF gave γ-lactam **908** in 80% yield, which on reduction with $LiBH_4$ followed by mesylation and subsequent treatment with NaI afforded the iodo derivative **909** in good yield. Addition of LHMDS to **909** produced 3-aza-2-oxo[3.2.0]bicycloheptane **910** in 83% yield. Finally, reductive cleavage of methylbenzyl group with Li–NH_3 followed by acidic hydrolysis led to (1*R*,2*S*)-γ-amino acid **13** as a hydrochloride salt in 78% yield (Scheme 225).[335]

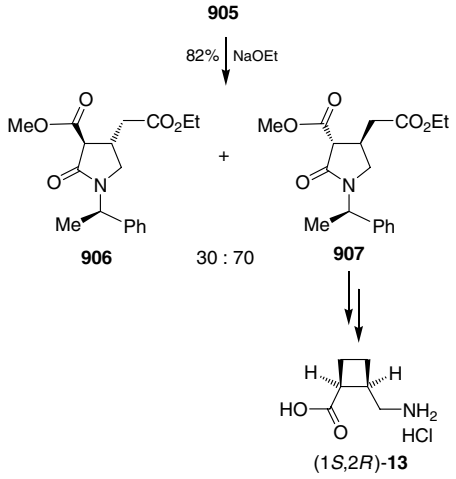
On the other hand, treatment of amide **905** with NaOEt gave γ-lactams **906** and **907** in a 30:70 ratio. Following the same reaction sequence, diastereoisomerically pure **907** was converted into (1*S*,2*R*)-γ-amino acid **13** as hydrochloride salt (Scheme 226).[335]

4.2. Synthesis of $C^{n}_{\alpha,\gamma}$ derivatives

Synthesis of enantiomerically pure *N*-Boc-3-aminocyclobutanecarboxylic acid **915** obtained from (*S*)-verbenone has been reported by Burgess et al.[336] Initially, oxidative cleavage of (*S*)-verbenone, readily available from α-pinene,[337] with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3$ produced keto-acid **911** in 94% yield, which on treatment with benzyl chloride afforded ester **912** in 72% yield. Haloform reaction of methyl ketone in **912** using sodium hypobromite gave the corresponding carboxylic acid **913** in 83% yield. Curtius rearrangement of **913** using diphenylphosphoryl azide in the presence of *tert*-butanol produced *N*-Boc-protected amine **914** in 58% yield, which on hydrogenolysis led to *N*-Boc-γ-amino acid **915** in 79% yield (Scheme 227).



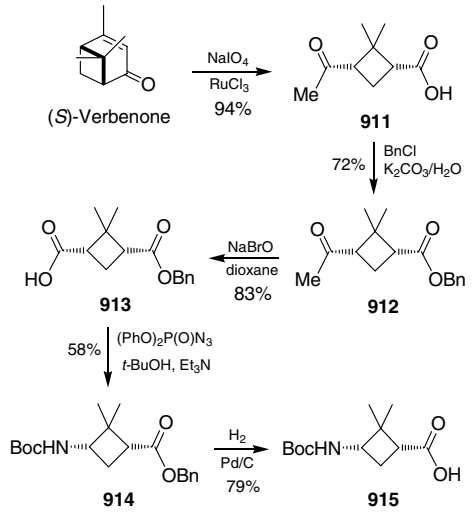
Scheme 225.



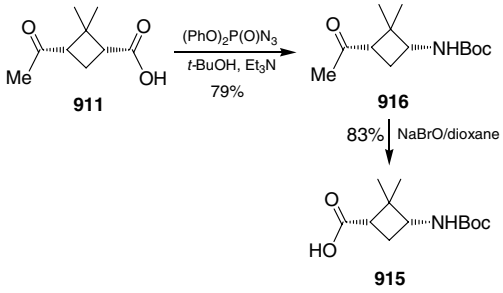
Scheme 226.

In a similar way, Curtius rearrangement of **911** using diphenylphosphoryl azide in the presence of *tert*-butanol produced *N*-Boc-protected amine **916** in 79% yield, which by haloform reaction afforded *ent*-**915** in 83% yield (Scheme 228).[336]

On the other hand, Schmidt rearrangement[338] of ketoester derivative **917** obtained from commercially available (*S*)-verbenone[59] using $NaN_3/MeSO_3H$ produced acetylated

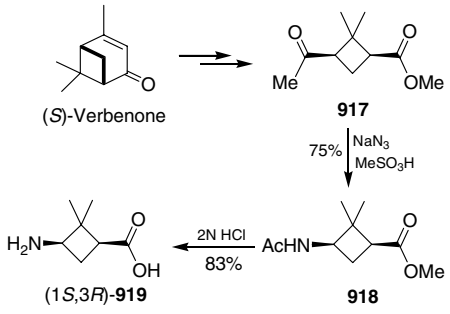


Scheme 227.



Scheme 228.

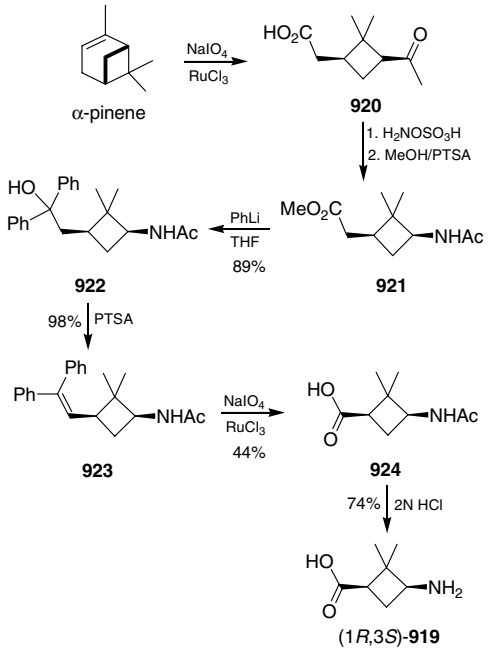
amine derivative **918** in 75% yield, which by acidic hydrolysis led to (1*S*,3*R*)-3-amino-2,2-dimethylcyclobutanecarboxylic acid **919** in 83% yield (Scheme 229).[339]



Scheme 229.

More recently, López et al.[340] have described the stereoselective synthesis of (1*R*,3*S*)-**919** from commercially available α-pinene. In this context, oxidation of α-pinene produced keto-acid derivative **920**,[59] which by treatment with hydroxylamine-*O*-sulfonic acid followed by a Beckmann rearrangement and subsequent esterification gave *N*-acetyl amino derivative **921**.[341] Addition of phenyllithium to ester **921** provided alcohol **922** in 89% yield, which by dehydration afforded the unsaturated product **923** in 98% yield. Oxidative cleavage of the double bond

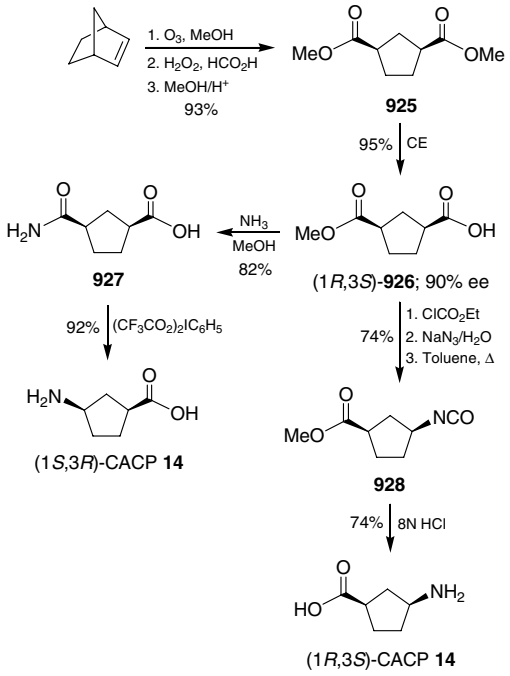
in **923** with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3$ produced carboxylic acid **924** in 44% yield, which upon acidic hydrolysis gave the (1*R*,3*S*)-3-amino-2,2-dimethylcyclobutanecarboxylic acid **919** in 74% yield (Scheme 230).



Scheme 230.

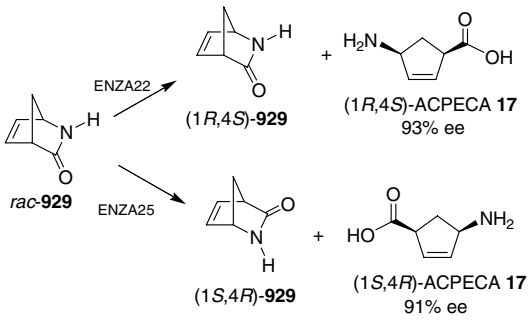
Conformationally restricted *cis*- and *trans*-aminocyclopentanecarboxylic acids (γ-Acp) **14** and **15** analogues of γ-aminobutyric acid GABA **1** have given considerable information about active conformations of GABA at receptors and uptake sites in the nervous system.[342] Additionally, these compounds have been used in the construction of γ-peptides, which have shown the formation of parallel sheet secondary structure, in contrast to helical propensity previously documented for acyclic γ-amino acid residues.[14e] Furthermore, cyclic α,γ-peptides (α,γ-CPs) containing (γ-Acp) units can form stable cylindrical dimers, which can be used for the design of nanotubes with novel structural and internal cavity properties.[14b]

Chênevert et al.[343] have described the preparation of enantiomerically pure (1*S*,3*R*)- and (1*R*,3*S*)-CACP **14** by enzymatic desymmetrization. Thus, ozonolysis of norbornene followed by esterification afforded diester **925** in 93% yield. Cholesterol esterase (CE) or subtilisin Carlsberg (SC) catalyzed hydrolysis of diester **925** producing (1*R*,3*S*)-monoester derivative **926** in 95% yield and 90% ee. Ammonolysis of **926** produced amide **927** in 82% yield,[344] which under Hoffmann rearrangement conditions using bis(trifluoroacetoxy)iodobenzene gave (1*S*,3*R*)-CACP **14** in 92% yield. On the other hand, treatment of **926** with ethyl chloroformate and sodium azide produced through a Curtius rearrangement isocyanate **928** in 74% yield, which on acidic hydrolysis afforded (1*R*,3*S*)-CACP **14** in 74% yield (Scheme 231).



Scheme 231.

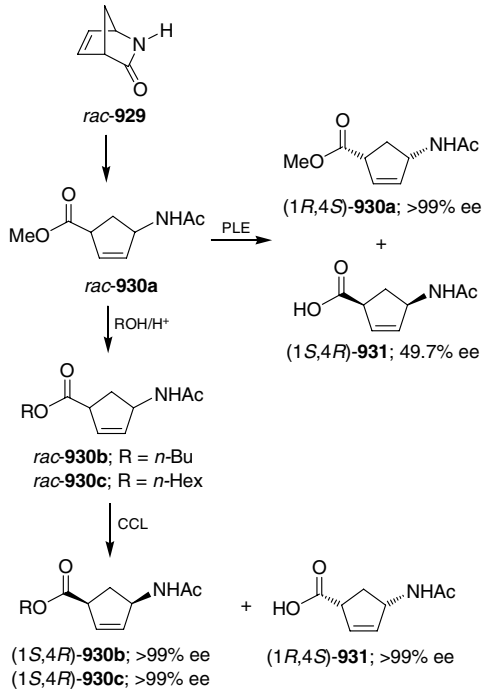
Biocatalytic resolution of 2-azabicyclo[2.2.1]hept-5-en-3-one *rac*-**929** readily obtained from the cycloaddition reaction of cylopentadiene and tosyl[345] or mesyl cyanide, using *Pseudomonas fluorescens* (referred to as ENZA22) produced amide (1*R*,4*S*)-**929**[346] and (1*R*,4*S*)-ACPECA **17** in 93% ee. On the other hand, treatment of *rac*-**929** with *Aureobacterium* species (ENZA25) afforded amide (1*S*,4*R*)-**929** and (1*S*,4*R*)-ACPECA **17** in 91% ee (Scheme 232).[347] (1*R*,4*S*)-ACPECA **17** and (1*S*,4*R*)-ACPECA **17** are considered as analogues of vigabatrin **2**.[348]



Scheme 232.

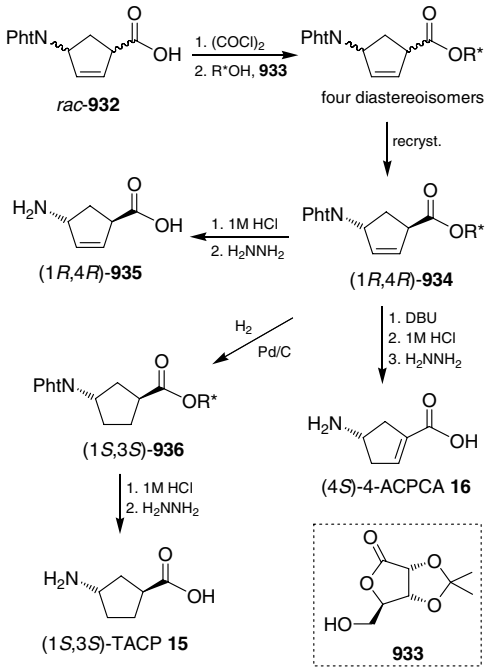
Enzymatic hydrolysis of methyl ester *rac*-**930** obtained from *rac*-**929**, using porcine liver esterase (PLE) gave (1*R*,4*S*)-**930a** in >99% ee and (1*S*,4*R*)-**931** in 49.7% ee. On the other hand, enzymatic hydrolysis of *n*-butyl and *n*-hexyl esters *rac*-**930b**,**c** with lipase *C. cylindracea* (CCL) led to esters (1*S*,4*R*)-**930b**,**c** and carboxylic acids (1*R*,4*S*)-**931** in high enantioselectivity (Scheme 233).[349]

Esterification of *rac*-**932** obtained from *rac*-**929** with 2,3-isopropylidene-D-ribonic acid-1,4-lactone **933** gave a mix-



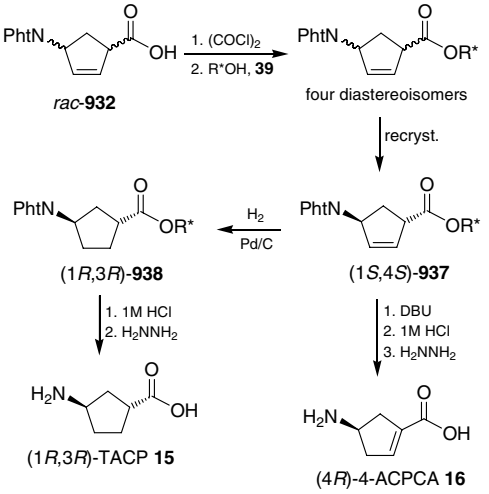
Scheme 233.

ture of four diastereoisomers, from which (1*R*,4*R*)-**934** was obtained by recrystallization. Hydrolysis of (1*R*,4*R*)-**934** produced γ-amino acid (1*R*,4*R*)-**935**. On the other hand, catalytic hydrogenation of **934** gave the corresponding saturated compound (1*S*,3*S*)-**936**, which on hydrolysis afforded (1*S*,3*S*)-TACP **15**. Isomerization of the double bond in (1*R*,4*R*)-**934** in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and subsequent hydrolysis led to (4*S*)-4-ACPCA **16** (Scheme 234).[350]



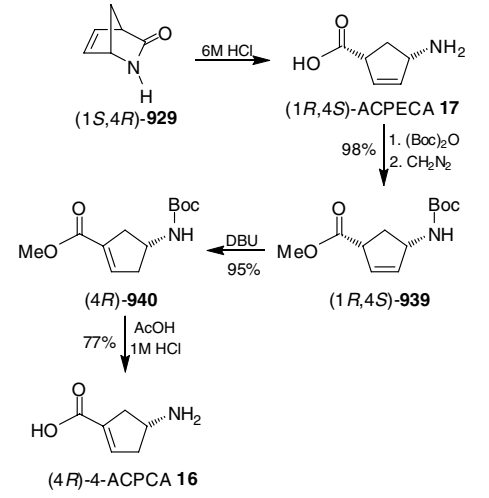
Scheme 234.

In a similar manner, esterification of *rac*-**932** with (*R*)-pantolactone **39** afforded a mixture of four diastereoisomers. Catalytic hydrogenation of diastereoisomerically pure (1*S*,4*S*)-**937** obtained by crystallization gave (1*R*,3*R*)-**938**, which on hydrolysis led to (1*R*,3*R*)-TACP **15**. On the other hand, conjugation of the double bond in (1*S*,4*S*)-**937** and subsequent hydrolysis provided (4*R*)-4-ACPCA **16** (Scheme 235).[350]



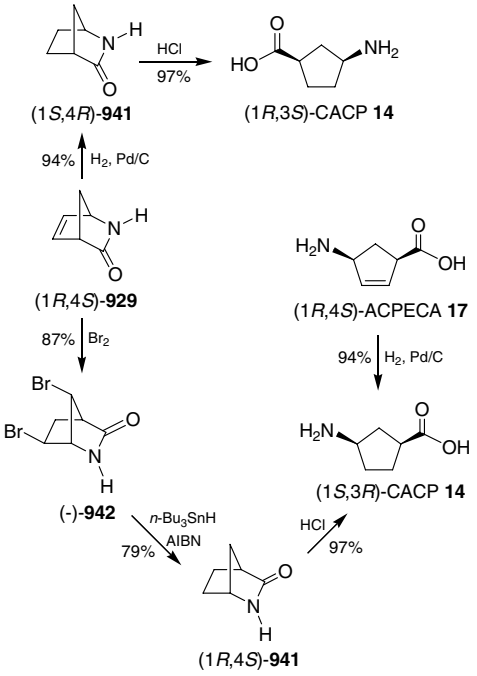
Scheme 235.

Hydrolysis of commercially available enantiopure lactam (1*S*,4*R*)-**929** gave (1*R*,4*S*)-ACPECA **17** in quantitative yield, which after protection of the amino group with $(Boc)_2O$ and esterification produced methyl ester (1*R*,4*S*)-**939** in 98% yield. Isomerization of the double bond in **939** afforded the corresponding derivative (4*R*)-**940** in 95% yield, which by hydrolysis led to (4*R*)-4-ACPCA **16** (Scheme 236).[351,352] (1*S*,4*R*)-ACPECA **17** and (4*S*)-4-ACPCA **16** were obtained using (1*R*,4*S*)-**929** as the starting material.



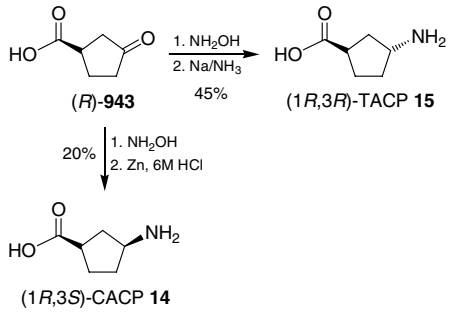
Scheme 236.

Hydrogenation of (1*R*,4*S*)-**929** gave lactam (1*S*,4*R*)-**941** in 94% yield, which on hydrolysis afforded (1*R*,3*S*)-CACP **14** in 97% yield, whereas treatment of (1*R*,4*S*)-**929** with bromine led to adduct (−)-**942** in 87% yield, which through rearrangement of a bromonium ion intermediate underwent a net 'inversion' of the carbocyclic skeleton.[353] Reduction of the dibromo compound **942** with *n*-Bu_3SnH in the presence of 2,2′-azobisisobutironitrile (AIBN) gave lactam (1*R*,4*S*)-**941** in 79% yield, which on hydrolysis produced (1*S*,3*R*)-CACP **14** in 97% yield. Hydrogenation of (1*R*,4*S*)-ACPECA **17** also produced (1*S*,3*R*)-CACP **14** in 94% yield (Scheme 237).[354]



Scheme 237.

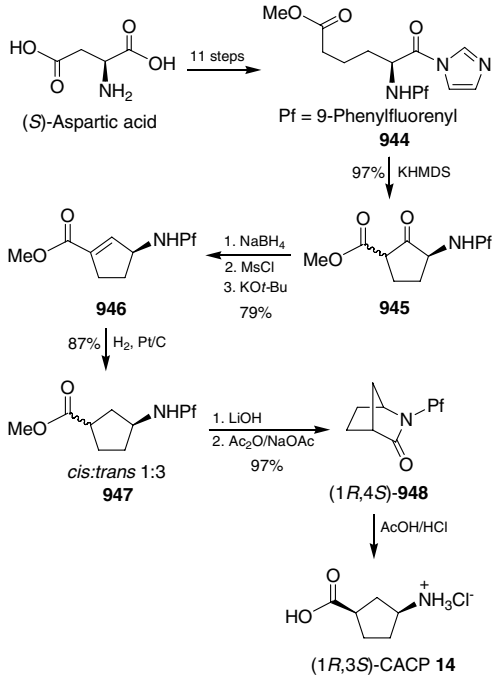
Reduction of the oxime, easily available from (*R*)-keto-acid **943** with sodium amide, afforded a *cis*/*trans* mixture in 55% and 45% yield, respectively, from which the (1*R*,3*R*)-*trans*-3-aminocyclopentanecarboxylic acid, (1*R*,3*R*)-TACP **15**, was obtained by recrystallization. On the other hand, reduction of the same oxime with zinc in 6 M hydrochloric acid led to (1*R*,3*S*)-CACP **14** in 20% yield (Scheme 238).



Scheme 238.

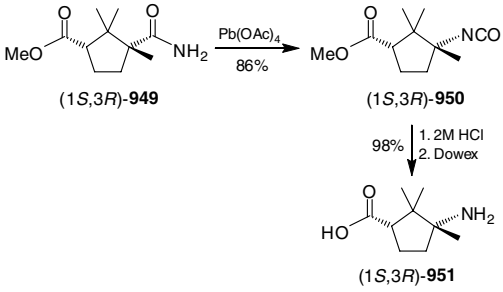
3-Aminocyclopentanecarboxylic acid (1*S*,3*S*)-TACP **15** and (1*S*,3*R*)-CACP **14** were obtained from (*S*)-**943**.[355]

On the other hand, Dieckmann cyclization of **944**, obtained in 11 steps from aspartic acid, in the presence of KHMDS gave ketoester derivative **945** in excellent yield as a 3:2 mixture of diastereoisomers, which under sequential reduction with $NaBH_4$, mesylation, and treatment with KO*t*-Bu produced cyclopentene derivative **946** in 79% overall yield. Catalytic hydrogenation of **946** in the presence of Pt/C afforded **947** as a 1:3 mixture of *cis*/*trans*, which after treatment with LiOH, followed by acetylation with Ac_2O in the presence of NaOAc gave lactam (1*R*,4*S*)-**948** as the only product in 97% yield. Finally, hydrolysis of **948** gave (1*R*,3*S*)-CACP **14** (Scheme 239).[356]



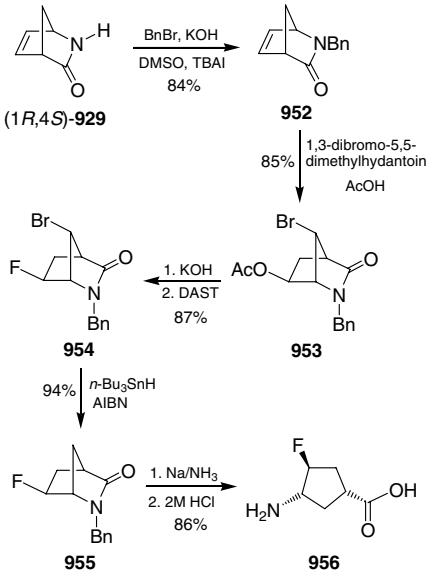
Scheme 239.

Oxidative degradation of **949** readily obtained from (+)-camphoric acid,[357] with lead tetraacetate under anhydrous conditions gave isocyanate (1*S*,3*R*)-**950** in 86% yield, which on hydrolysis produced (1*S*,3*R*)-3-amino-2,2,3-trimethylcyclopentanecarboxylic acid (1*S*,3*R*)-**951** in 98% yield (Scheme 240).[358]



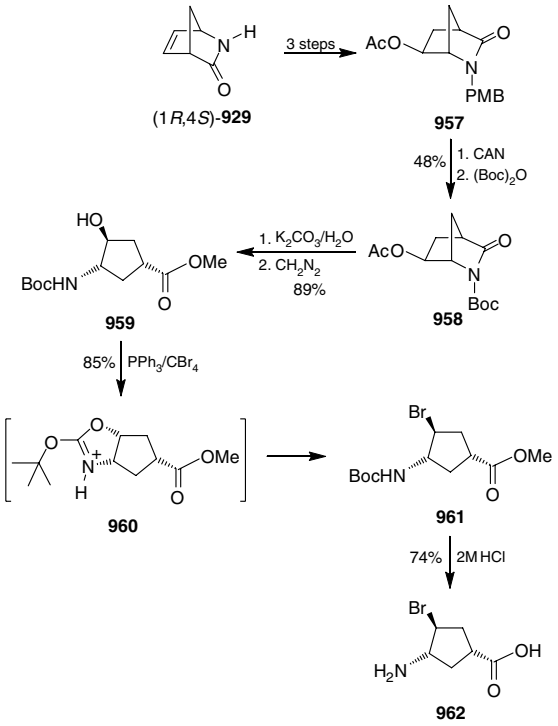
Scheme 240.

Reaction of commercially available lactam (1*R*,4*S*)-**929** with benzylbromide in the presence of potassium hydroxide gave the benzylated lactam **952** in 84% yield, which by treatment with 1,3-dibromo-5,5-dimethylhydantoin in acetic acid afforded the bromo derivative **953** in 85% yield. Basic hydrolysis of **953** followed by the fluorination with (diethylamino)sulfur trifluoride (DAST) produced **954** in 87% yield. Dehydrobromination of **954** with *n*-Bu_3SnH hydride in the presence of AIBN afforded monofluoro lactam **955** in 94% yield, which Birch reduction and subsequent hydrolysis gave γ-amino acid **956** in 86% yield (Scheme 241).[359] A series of halogenated 4-aminocyclopentanecarboxylic acid derivatives were designed as potential, more lipophilic and inactivators of GABA-AT.



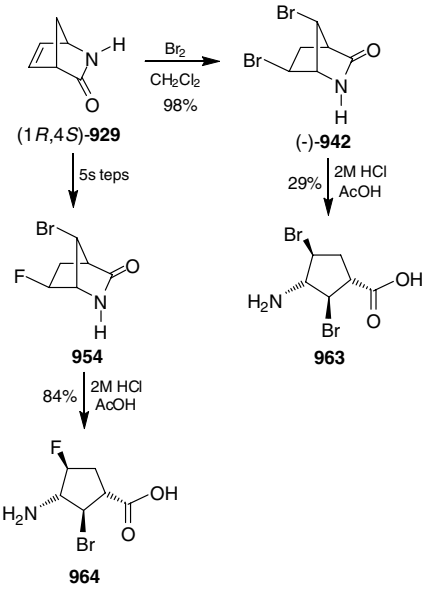
Scheme 241.

On the other hand, cleavage of the *p*-methoxybenzyl protective group in **957** with CAN,[354b] followed by protection with $(Boc)_2O$ gave *N*-Boc protected lactam **958** in 48% yield, which after basic hydrolysis and subsequent treatment with diazomethane afforded methyl ester **959** in 89% yield. A bromination reaction of **959** with carbon tetrabromide and triphenylphosphine afforded bromo derivative **961** with retention of the stereochemistry at C-4 via anchimeric assistance by the carbamate group in intermediate **960**. Finally, acidic hydrolysis of **961** produced γ-amino acid **962** in 74% yield (Scheme 242).[359]



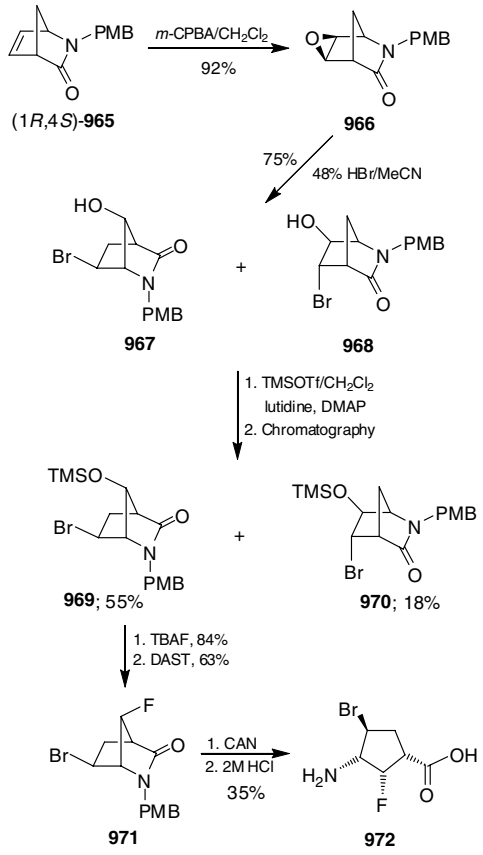
Scheme 242.

On the other hand, bromination of (1*R*,4*S*)-**929** afforded **942** in 98% yield, which by hydrolysis gave γ-amino acid **963** in 29% yield, whereas hydrolysis of enantiomerically pure lactam **954** obtained in five steps from (1*R*,4*S*)-**929** led to γ-amino acid **964** in 84% yield (Scheme 243).[359]

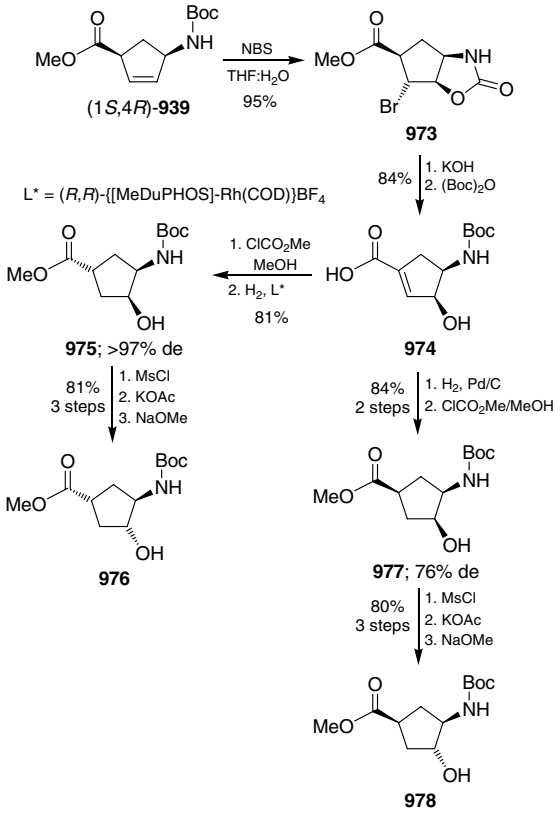


Scheme 243.

Epoxidation of (1*R*,4*S*)-**965** with *m*-CPBA exclusively gave *exo*-epoxide **966** in 92% yield. Ring opening of epoxide **966** with 48% HBr afforded the inseparable halohydrins **967** and **968**, which upon treatment with TMSOTf in the presence of lutidine and DMAP produced the separable compounds **969** and **970** in 55% and 18% yield, respectively. Deprotection of hydroxy group in enantiomerically pure **969** with TBAF, followed by fluorination using DAST produced fluoro derivative **971**, via an S_N2 mechanism. Cleavage of *p*-methoxybenzyl protective group in **971** using CAN and subsequent hydrolysis led to γ-amino acid **972** in 35% yield (Scheme 244).[359]



Scheme 244.



Scheme 245.

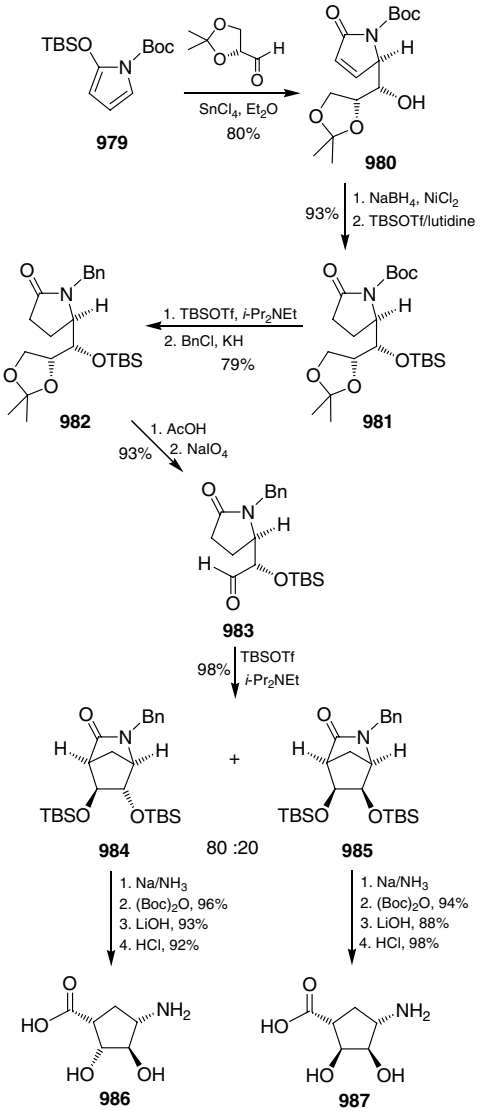
The reaction of enantiomerically pure aminoester (1*S*,4*R*)-**939** with NBS afforded cyclic carbamate **973** in 95% yield, and with the introduction of the oxygen atom with defined stereochemistry. Hydrolysis of **973** followed by *N*-Boc protection furnished carboxylic acid **974** in 84% yield, which by esterification and subsequent homogeneous hydrogenation in the presence of catalytic amounts of (*R*,*R*)-{[MeDuPHOS]-Rh(COD)}BF_4 gave methyl ester **975** in >97% de. On the other hand, catalytic hydrogenation of **974** in the presence of Pd/C followed by esterification led to *cis*-estereoisomer **977** in 84% yield and 76% de. Sequential reactions of mesylation, acetate displacement with inversion of configuration, and hydrolysis with sodium methoxide of **975** and **977** afforded methyl esters **976** and **978**, respectively (Scheme 245).[352]

An aldol-type reaction of pyrrole derivative **979** with 2,3-*O*-isopropylidene-D-glyceraldehyde in the presence of $SnCl_4$ led to *N*-Boc-unsaturated lactam **980** in 80% yield and high diastereoselectivity,[360] which on reduction with $NaBH_4$ in the presence of $NiCl_2$ followed by protection of the free secondary hydroxy group as a TBS-ether gave the fully protected lactam **981** in 93% yield. Selective cleavage of the *N*-Boc protective group using TBSOTf in the presence of *N*,*N*-diisopropylethylamine followed by treatment with benzyl chloride and KH afforded *N*-benzyl derivative **982** in 79% yield. Hydrolysis of the acetonide in **982** and subsequent oxidative fragmentation of the diol moiety with sodium periodate produced aldehyde **983** in 93% yield, which by intramolecular aldol reaction in the presence of TBSOTf and *i*-Pr_2NEt gave **984** and **985** in an 80:20 ratio and 98% yield. Sequential cleavage of the benzyl protective group by a Birch reduction, *N*-Boc protection, and hydrolysis of **984** and **985** provided dihydroxylated cyclopentaneamino acids **986** and **987**, respectively, in good yield (Scheme 246).[361]

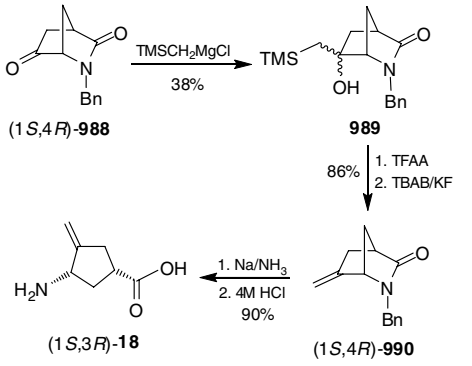
The addition of (trimethylsilyl)methylmagnesium chloride to (1*S*,4*R*)-**988** afforded hydroxy derivative **989** in 38% yield, which by elimination using trifluoroacetic anhydride and tetra-*n*-butylammonium bromide gave the exocyclic unsaturated compound (1*S*,4*R*)-**990** in 86% yield. Cleavage of the *N*-benzyl protective group in **990** under Birch reduction conditions and subsequent hydrolysis led to conformationally rigid vigabatrin (1*S*,3*R*)-**18** in 90% yield (Scheme 247).[362]

On the other hand, Horner–Wadsworth–Emmons reaction of enantiomerically pure (1*S*,4*R*)-**991** with diethyl (difluoromethyl)phosphonate gave the difluoromethylene derivative (1*S*,4*R*)-**992** in 68% yield. Deprotection of the *N*-*p*-methoxyphenyl group in **992** using CAN led to lactam (1*S*,4*R*)-**993** in 68% yield, which by acidic hydrolysis afforded the conformationally restricted γ-amino acid (1*S*,3*S*)-**994**, which is a more potent GABA-AT inactivator than (*S*)-vigabatrin **2** (Scheme 248).[362]

On the other hand, the addition of the lithium anion of fluoromethyl phenylsulfone to amide (1*S*,4*R*)-**991** in the presence of diethyl chlorophosphate gave an inseparable

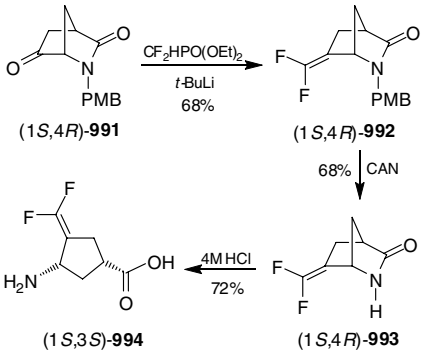


Scheme 246.



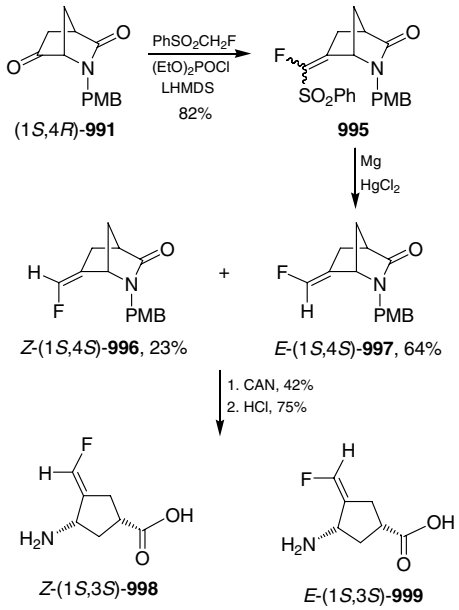
Scheme 247.

mixture of *E*- and *Z*-isomers **995** in 82% yield, which by treatment with magnesium combined with mercury chloride produced the separable *Z*-(1*S*,4*S*)-**996** and *E*-(1*S*,4*S*)-**997** compounds in 23% and 64% yield, respectively. Oxida-



Scheme 248.

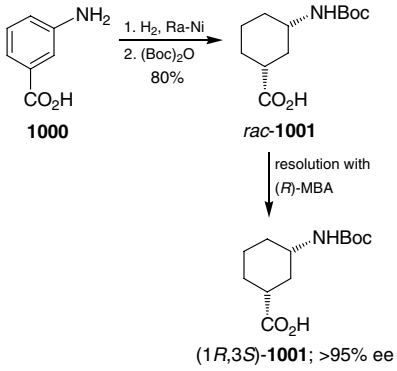
tive deprotection of *N*-PMB group with ceric ammonium nitrate (CAN) and subsequent acidic hydrolysis provided the corresponding conformationally restricted monofluorinated vigabatrin analogues *Z*-(1*S*,3*S*)-**998** and *E*-(1*S*,3*S*)-**999** (Scheme 249).[363]



Scheme 249.

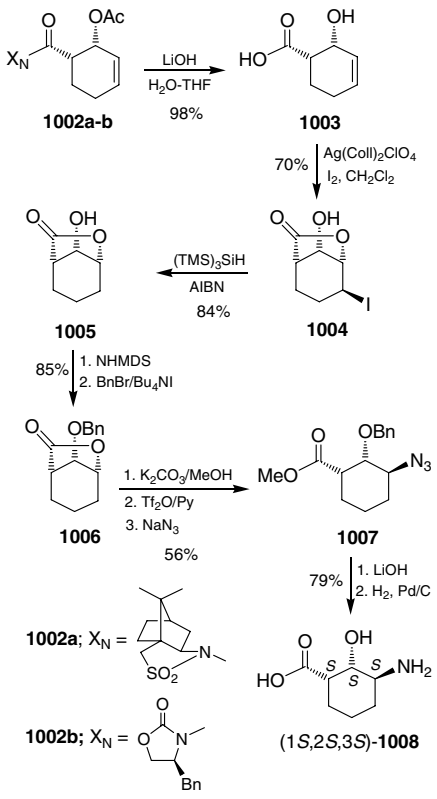
Catalytic hydrogenation of *m*-aminobenzoic acid **1000** in the presence of Raney-nickel followed by treatment with $(Boc)_2O$ gave racemic *cis*-3-aminocyclohexanecarboxylic acid *rac*-**1001** in 80% yield. Resolution with successive recrystallizations from (*R*)-α-methylbenzylamine [(*R*)-MBA] afforded (1*R*,3*S*)-*N*-Boc-3-aminocyclohexanecarboxylic acid **1001** in >95% ee (Scheme 250).[14c] Enantiomerically pure (1*R*,3*S*)-**1001** is a component of cyclic peptides, a new class of peptides nanotubes.[14d]

On the other hand, Joullié et al.[364] have described the stereoselective synthesis of (1*S*,2*S*,3*S*)-3-amino-2-hydroxycyclohexanecarboxylic acid **1008**, a cyclohexyl GABOB analogue. Initially, basic hydrolysis of **1002a** and **1002b**, obtained from a Diels–Alder reaction and from the



Scheme 250.

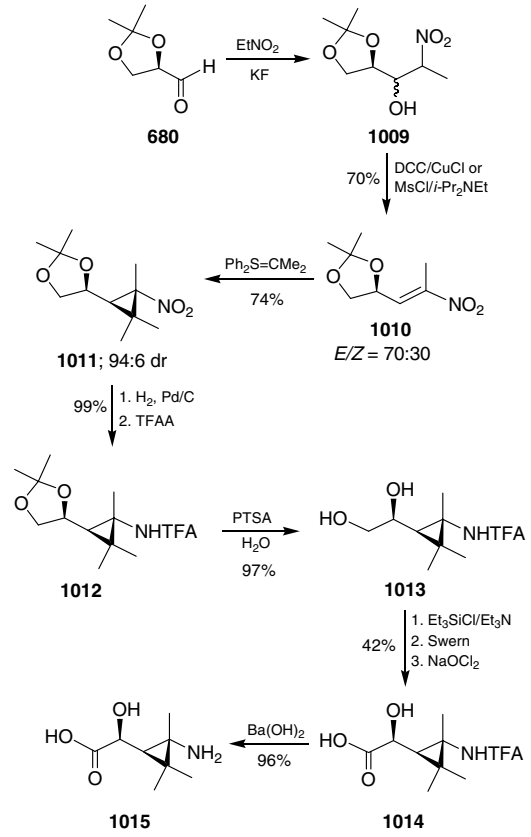
aldol-metathesis approach, respectively, afforded the corresponding carboxylic acid **1003** in 98% yield, which by an iodolactonization reaction with iodonium biscollidine perchlorate gave iodolactone **1004** in 70% yield. Removal of the iodine in **1004** under radical conditions using tris(trimethylsilyl)silane provided alcohol **1005** in 84% yield, which upon protection of the hydroxy group using NHMDS and benzyl bromide in the presence of tetra-*n*-butylammonium iodide produced the benzyl ether derivative **1006** in 85% yield. Transesterification of **1006** with methanol in the presence of dilute potassium carbonate to prevent epimerization, followed by triflate formation and treatment with sodium azide gave the corresponding azide derivative **1007** in 56% yield. Finally, basic hydrolysis of **1007** and subsequent catalytic hydrogenation furnished the γ-amino acid (1*S*,2*S*,3*S*)-**1008** in 79% yield (Scheme 251).[365]



Scheme 251.

4.3. Synthesis of $C^{n}_{\beta,\gamma}$ derivatives

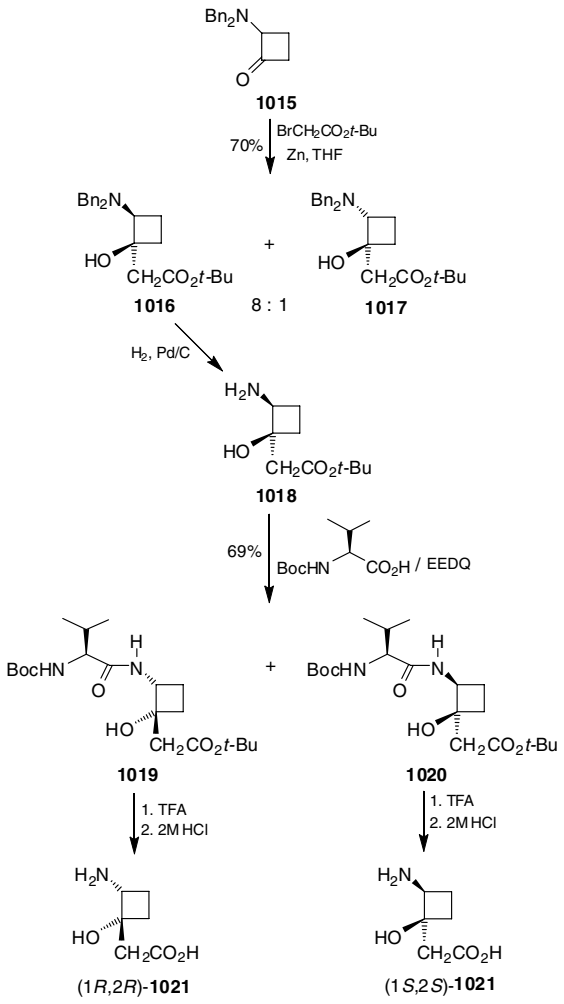
The addition of nitroethane to an acetonide of (*R*)-glyceraldehyde **680** in the presence of KF afforded the nitroaldol derivatives **1009**, which by dehydration produced nitroalkene **1010** in 70% yield and with a selectivity $E/Z = 70{:}30$, respectively. Cyclopropanation of **1010** using a diphenylsulfur ylide gave cyclopropane derivative **1011** in 74% yield and 94:6 dr, which by catalytic hydrogenation and N-protection with TFAA produced *N*-TFA derivative **1012** in excellent yield. Cleavage of the acetonide in **1012** produced the corresponding diol **1013** in quantitative yield, which by protection of the secondary alcohol and subsequent oxidation of the primary alcohol gave carboxylic acid **1014** in 42% yield. Finally, deprotection of the trifluoroacetyl group in **1014** led to γ-amino-β-hydroxy acid **1015** in 96% yield (Scheme 252).[366]



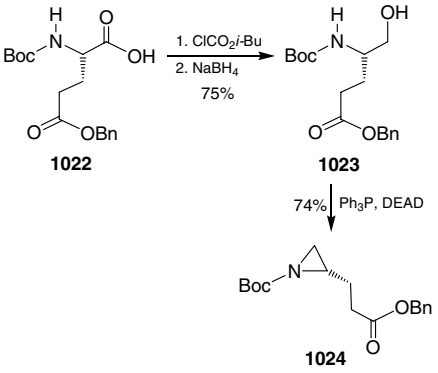
Scheme 252.

On the other hand, Baldwin et al.[367] reported the preparation of (1*R*,2*R*)- and (1*S*,2*S*)-1-hydroxy-2-aminocyclobutane-1-acetic acid **1021** via a short stereoselective synthesis. Initially, the reaction of 2-(dibenzylamino)-cyclobutanone **1015**,[368] under Reformatsky conditions with *tert*-butyl bromoacetate, produced a mixture of racemic *cis*-**1016** and *trans*-dibenzylamino alcohols **1017** in 70% yield and an 8:1 ratio. Cleavage of the *N*-benzyl protective group in **1016** afforded amino alcohol **1018**, which by coupling with *N*-Boc-(*S*)-valine in the presence of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) gave a

mixture of diastereoisomeric dipeptides **1019** and **1020** in 69% yield. Finally, treatment of diastereoisomerically pure **1019** and **1020** under acidic conditions afforded 1-hydroxy-2-aminocyclobutane-1-acetic acids (1*R*,2*R*)- and (1*S*,2*S*)-**1021**, respectively (Scheme 253).

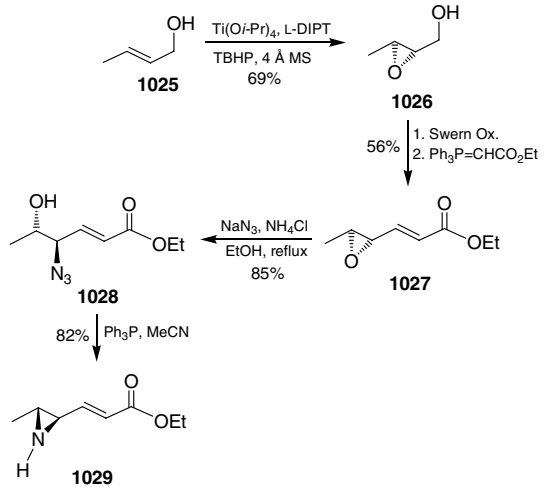


Scheme 253.



Scheme 254.

from Sharpless asymmetric epoxidation of allylic alcohol **1025**, followed by Wittig chain extension with (carboethoxymethylene)triphenylphosphorane afforded the corresponding (*E*)-α,β-unsaturated ethyl ester **1027** in 56% yield, which by treatment with sodium azide gave β-azido alcohol derivative **1028** in 85% yield and 19:1 ratio. Staudinger reaction[370] of azido alcohol **1028** produced the aziridine derivative **1029** in 82% yield (Scheme 255).[371]



Scheme 255.

5. Stereoselective synthesis of azacyclic γ-amino acids

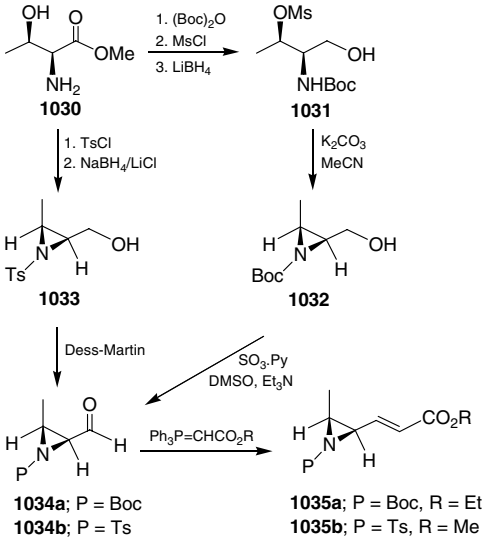
5.1. Synthesis of N, C^{n}_{γ} derivatives

Treatment of the *N*-Boc-α-amino acid derivative **1022** with isobutyl chloroformate gave the corresponding mixed anhydride, which upon reduction with $NaBH_4$ afforded the *N*-Boc-amino alcohol **1023** in 75% yield. The cyclization reaction of **1023** under Mitsunobu conditions produced *N*-Boc-aziridine **1024** in 74% yield, which has been used as a precursor of conformationally restricted γ-amino acids (Scheme 254).[369]

β-Aziridinyl-α,β-enoate **1029** has been used in the preparation of mimetics of dipeptide units, and several methodologies have been described for their synthesis. For example, the Swern oxidation of the epoxy alcohol **1026** obtained

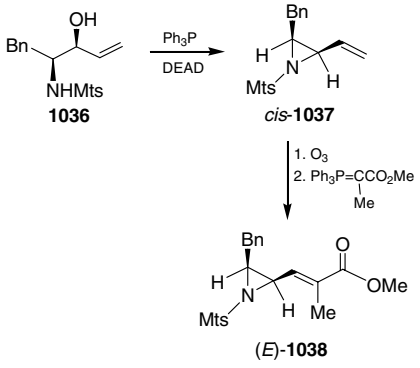
The reaction of L-threonine methyl ester **1030** with $(Boc)_2O$ followed by treatment with mesyl chloride, and subsequent reduction with lithium borohydride gave alcohol **1031** in 73% yield, which on treatment with potassium carbonate afforded aziridine **1032** in 67% yield. Parikh–Doering oxidation[372] of **1032** provided the corresponding aldehyde **1034a**. On the other hand, tosylation of **1030** followed by reduction with $NaBH_4$ in the presence of LiCl gave aziridine **1033** in 32% yield, which by Dess–Martin periodinano oxidation led to aldehyde **1034b**. Finally, Wittig reaction of **1034a** and **1034b** provided the N-protected-*E*-alkenyl-aziridines **1035a** and **1035b** (Scheme 256).[371]

On the other hand, Mitsunobu reaction of amino alcohol *syn*-**1036** obtained from chiral amino aldehydes gave *cis*-aziridine **1037**,[373] which by ozonolysis followed by the



Scheme 256.

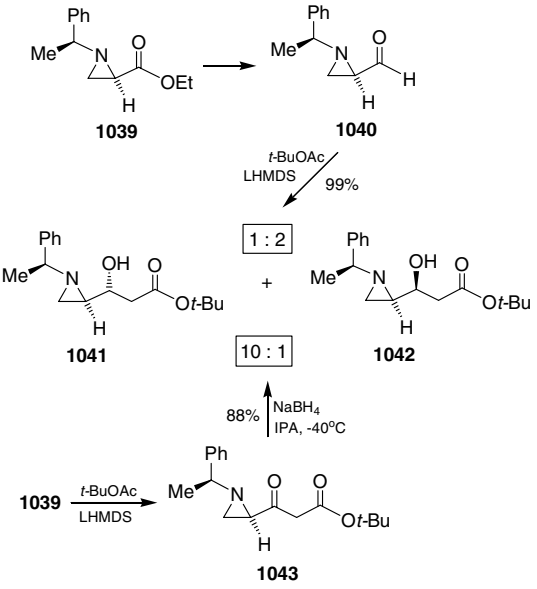
Wittig reaction with (carbomethoxyethylene)triphenylphosphorane produced (*E*)-alkenyl-aziridine **1038** as the principal product (Scheme 257).[374] This methodology has been used in the synthesis of several (*E*)-alkenyl-aziridines.



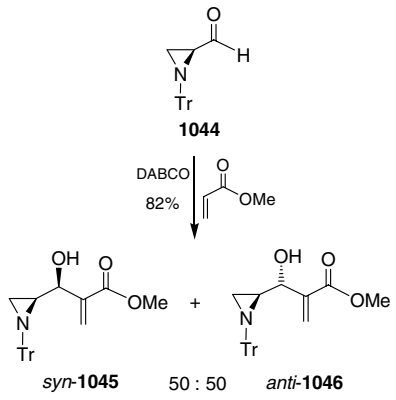
Scheme 257.

The addition of lithium enolate derived from *tert*-butyl acetate to configurationally stable, and enantiomerically pure aziridine 2-carboxaldehyde **1040** readily obtained from ethyl aziridine-2-carboxylate **1039**,[375] afforded a mixture of aldol products **1041** and **1042** in 99% yield but with low diastereoselectivity (1:2 ratio). However, the reduction of β-ketoester **1043**[376] readily obtained from **1039** with $NaBH_4$ in isopropyl alcohol (IPA) at −40 °C provided the aldol products **1041** and **1042** in 88% yield and high diastereoselectivity (10:1) (Scheme 258).[377] Compounds **1041** and **1042** have been used in the synthesis of *threo*-β-hydroxy-L-glutamic acid.

On the other hand, a Baylis–Hillman reaction of *N*-trityl aziridine-2-carboxaldehyde **1044** with methyl or ethyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) produced the corresponding alcohols *syn*-**1045** and *anti*-**1046** in 82% yield as a 50:50 mixture, which can be separated by column chromatography (Scheme 259).[378]



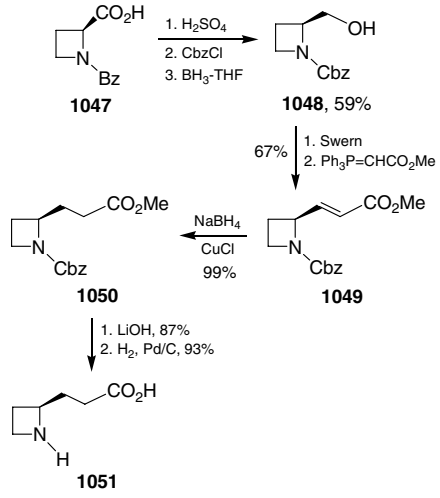
Scheme 258.



Scheme 259.

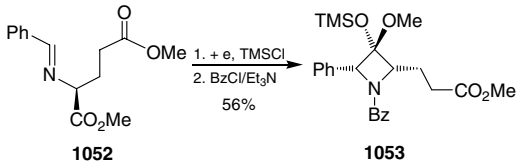
Recently, Barrett et al.[379] reported the synthesis of (*R*)-3-(azetidin-2-yl)propanoic acid **1051** using (*S*)-*N*-benzoyl-azetidinecarboxylic acid **1047** as the starting material. Initially, cleavage of the benzoyl protective group in **1047** followed by treatment with CbzCl, and subsequent reduction with BH_3·THF complex afforded the azetidine-methanol derivative **1048** in 59% overall yield. Swern oxidation and direct olefination under Wittig conditions produced the unsaturated methyl ester **1049** in 67% yield. Reduction of the double bond in **1049** with $NaBH_4$ in the presence of CuCl gave methyl ester **1050** in 99% yield, which by saponification with lithium hydroxide and subsequent hydrogenolysis led to the corresponding γ-amino acid **1051** in good yield (Scheme 260).

More recently, Kise et al.[380] have described that the electroreductive intramolecular coupling of imino ester **1052** prepared from (*S*)-glutamic acid dimethyl ester and benzaldehyde, in the presence of chlorotrimethylsilane, followed by N-protection using benzoyl chloride gave *cis*-2,4-disubstituted azetidine-3-one **1053** as the only product



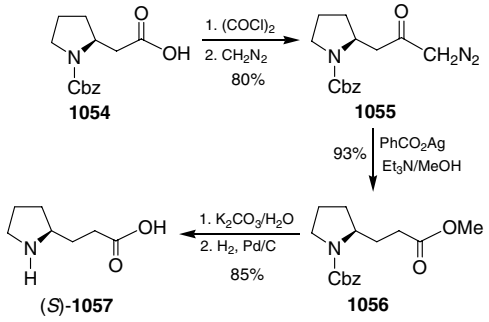
Scheme 260.

in 56% yield (Scheme 261). This result shows that four-membered cyclization is much more favorable than six-membered cyclization in the reductive intramolecular coupling of **1052**, which could be an excellent methodology for the preparation of substituted-3-(azetidin-2-yl)propanoic acids.



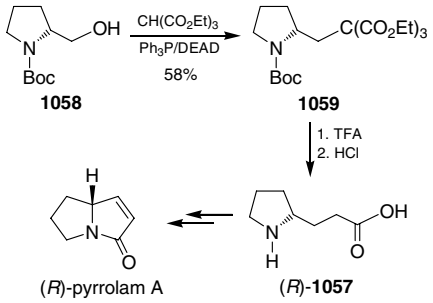
Scheme 261.

(*S*)-3-(Pyrrolidin-2-yl)propionic acid **1057** has been obtained using a double Arndt–Eistert process. Initially, treatment of (*S*)-homoproline **1054** obtained from L-proline via Arndt–Eistert homologation,[381] with oxalyl chloride followed by treatment with diazomethane gave the corresponding β-diazoketone **1055** in 80% yield. A Wolff rearrangement of β-diazoketone **1055** using silver benzoate and Et_3N in methanol afforded γ-amino acid methyl ester **1056** in 93% yield, which by hydrolysis followed by catalytic hydrogenation led to γ-amino acid (*S*)-**1057** in 85% yield (Scheme 262).[121]



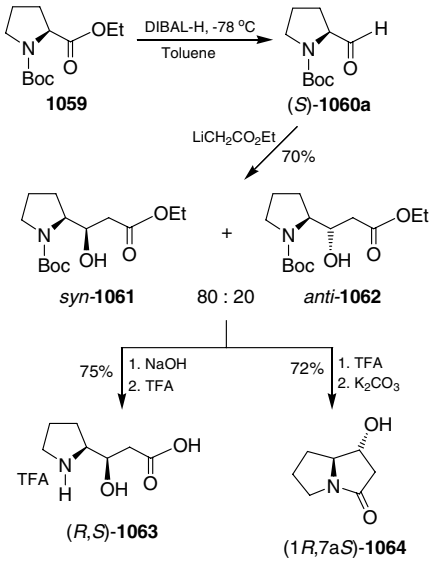
Scheme 262.

On the other hand, treatment of (*R*)-*N*-Boc-prolinol **1058** under a Mitsunobu alkylation protocol using triethyl methanetricarboxylate (TEMT), Ph_3P, and diethyl azodicarboxylate (DEAD) produced the *N*-Boc-triester derivative **1059** in 58% yield. Hydrolysis of **1059** afforded the γ-amino acid (*R*)-**1057**, which was used in the preparation of (*R*)-pyrrolam A (Scheme 263).[382,383]



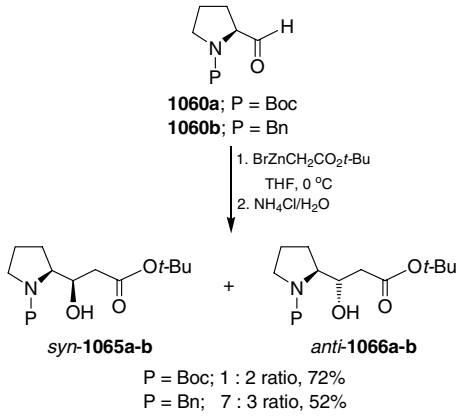
Scheme 263.

Aldol condensation of *N*-Boc-L-prolinal **1060a** readily obtained from *N*-Boc-L-proline ethyl ester **1059** with the lithium enolate derived from ethyl acetate afforded a mixture of aldol products *syn*-**1061** and *anti*-**1062** in a 80:20 ratio and 70% yield. Saponification of the epimeric mixture *syn*-**1061** and *anti*-**1062** with NaOH, followed by cleavage of the *N*-Boc protective group with trifluoroacetic acid (TFA) gave the trifluoroacetate salt of β-(*R*)-hydroxy-2-(*S*)-pyrrolidinepropionic acid (*R*,*S*)-HPPA-OH **1063**, an γ-amino acid analogue of statine **23**. On the other hand, treatment of *syn*-**1061** and *anti*-**1062** with TFA and subsequent treatment with K_2CO_3 afforded the (1*R*,7a*S*)-1-hydroxypyrrolizin-3-one **1064**, an alkaloid nucleus, which represents a convenient chiral synthon for the preparation of certain members of these compounds (Scheme 264).[384]



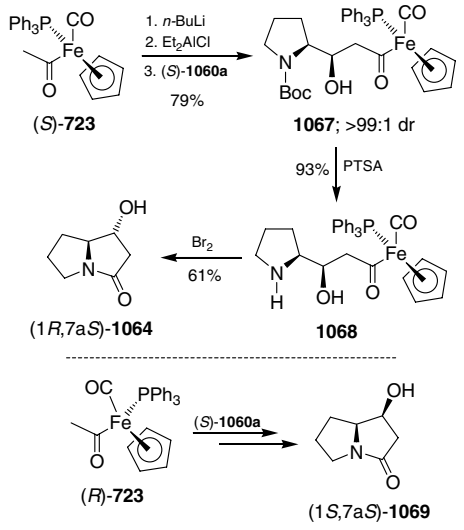
Scheme 264.

A Reformatsky reaction of *tert*-butoxycarbonylmethylzinc bromide with *N*-Boc-L-prolinal **1060a** gave a mixture of aldol products *syn*-**1065a** and *anti*-**1066a** in a 1:2 ratio and 72% yield, whereas the reaction with *N*-benzyl-L-prolinal **1060b** gave a mixture of aldol products *syn*-**1065b** and *anti*-**1066b** in a 7:3 ratio and 52% yield (Scheme 265).[269] Once again, the presence of a benzyl group on the nitrogen produced the *syn*-diastereoisomers as the major product, whereas the *anti*-product was formed predominantly in the *N*-Boc derivatives.



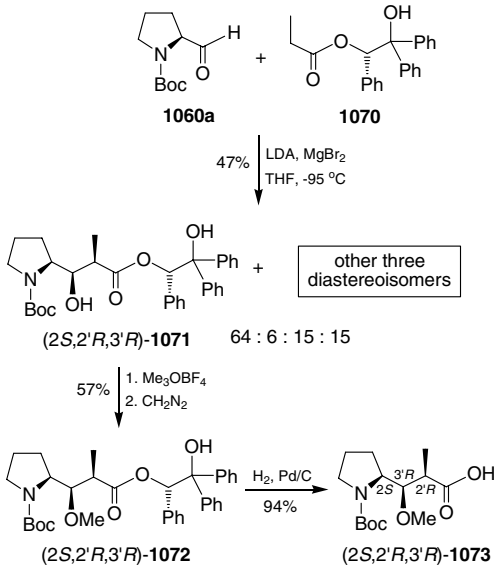
Scheme 265.

On the other hand, the matched pair addition of diethylaluminum enolate derived from de iron acetyl complex (*S*)-**723** to *N*-Boc-L-prolinal **1060a** gave aldol product *syn*-**1067** in >99:1 dr and 79% yield. Cleavage of the *N*-Boc protective group with *p*-toluenesulfonic acid (PTSA) gave the corresponding complex **1068** in excellent yield, which by decomplexation with bromine led to (1*R*,7a*S*)-**1064** in 61%. The diastereoisomer (1*S*,7a*S*)-**1069** was obtained when (*R*)-**723** was used as the starting material (Scheme 266).[384c]



Scheme 266.

Aldol condensation of *N*-Boc-L-prolinal **1060a** with the lithium chiral enolate derived from (2*S*)-(propionyloxy)-1,1,2-triphenylethanol **1070** at −95 °C in the presence of magnesium bromide (to enhance the stereoselectivity) afforded a mixture of aldol products (2*S*,2′*R*,3′*R*)-**1071** and the other three stereoisomers in 64:6:15:15 ratio in 47% yield. Treatment of diastereoisomerically pure (2*S*,2′*R*,3′*R*)-**1071** with diazomethane in the presence of trimethyloxonium tetrafluoroborate gave the (3′*R*)-methyl ether derivative **1072** in 57% yield, which by hydrogenolysis of benzyl ester led to *N*-Boc-(2*S*,2′*R*,3′*R*)-**1073** [*N*-Boc-dolaproline] in 94% yield (Scheme 267). Compound **1073** is a key component of Dolastatin 10 **32**.[385]

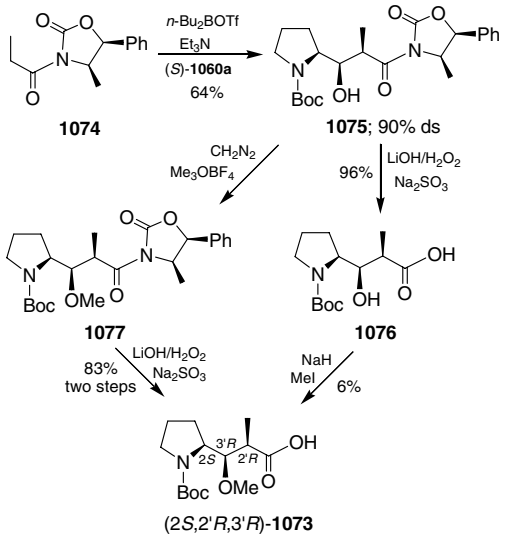


Scheme 267.

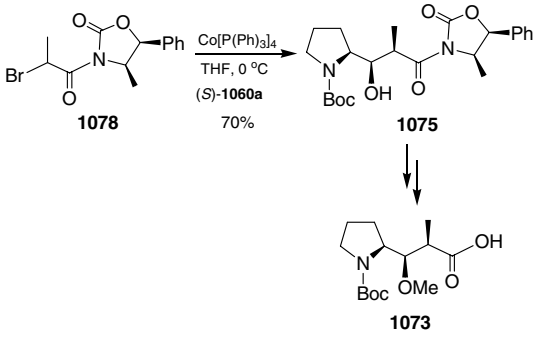
The highly stereoselective aldol condensation of *N*-Boc-L-prolinal **1060a** with the boron chiral enolate derived from oxazolidinone **1074** afforded the corresponding aldol derivative **1075** in 64% yield and 90% stereoselectivity. Cleavage of the chiral auxiliary in **1075** with hydrogen peroxide and lithium hydroxide gave carboxylic acid **1076** in 96% yield, which by O-methylation using sodium hydride and iodomethane led to the *N*-Boc-dolaproline **1073** in 6% yield. On the other hand, O-methylation of **1075** with diazomethane in the presence of trimethyloxonium tetrafluoroborate gave the methyl ether derivative **1077**, which by cleavage of the chiral auxiliary under the same conditions afforded *N*-Boc-dolaproline (2*S*,2′*R*,3′*R*)-**1073** in 83% yield (Scheme 268).[386]

On the other hand, cobalt-triphenylphosphine-promoted Reformatsky reaction between *N*-Boc-L-prolinal **1060a** and (4*R*,5*S*)-3-(2-bromopropionyl)-4-methyl-5-phenyloxazolidin-2-one **1078** gave β-hydroxy amide **1075** in 70% and high stereoselectivity, which was converted in dolaproline (Dap) **1073** under an identical protocol to that described above (Scheme 269).[387]

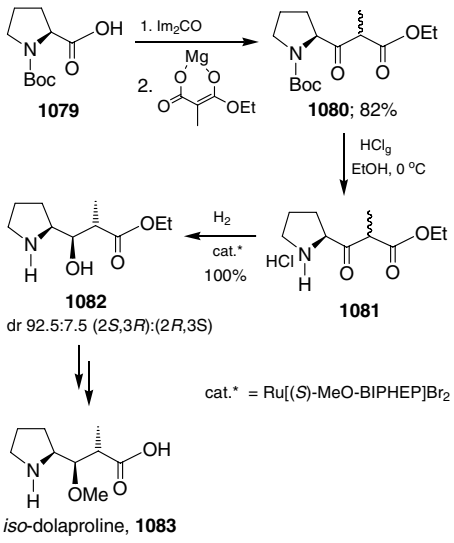
Genet et al.[388] have reported an efficient multigram-scale synthesis of enantiomerically pure *N*-Boc-*iso*-dolaproline



Scheme 268.



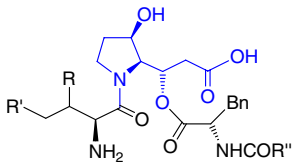
Scheme 269.



Scheme 270.

1083 using a dynamic kinetic resolution (DKR). Thus, reaction of *N*-Boc-(*S*)-proline **1079** with carbonyldiimidazol (Im_2CO) and the magnesium enolate of ethyl hydrogen methylmalonate gave β-ketoester **1080** in 82% yield, which by treatment with hydrogen chloride produced the γ-amino-β-keto ethyl ester hydrochloride **1081**. Catalytic hydrogenation of **1081** using in situ generated Ru[(*S*)-MeO-BIPHEP]Br_2 afforded *anti*-β-hydroxy methyl ester **1082** in quantitative yield and high diastereoselectivity, which was converted into *N*-Boc-*iso*-dolaproline **1083** under an identical protocol described above (Scheme 270).

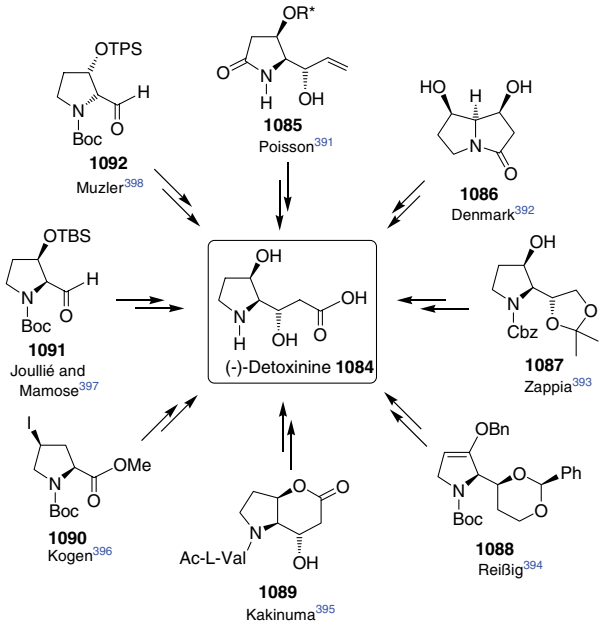
Peptide structures with proline components have received considerable interest over the past few years.[389] For instance, the detoxin complex is a mixture of 12 depsipeptides isolated from *Streptomyces caespitosus* var. *detoxicus* 7072GC_1, which displays a unique detoxifying effect against the nucleoside antibiotic blasticidin S.[390] Coadministration of blasticidin S and the detoxin complex reduces the cytotoxicity of the antibiotic without reducing the curative effect in the treatment of rice blast disease. Moreover, in vivo studies showed that its administration decreased eye irritation caused by the antibiotic, together with a remarkable decrease of conjunctivitis in rats. Ten of the 12 characterized depsipeptides of the detoxin complex possess the unusual amino acid (−)-detoxinine **1084** as the core scaffold.



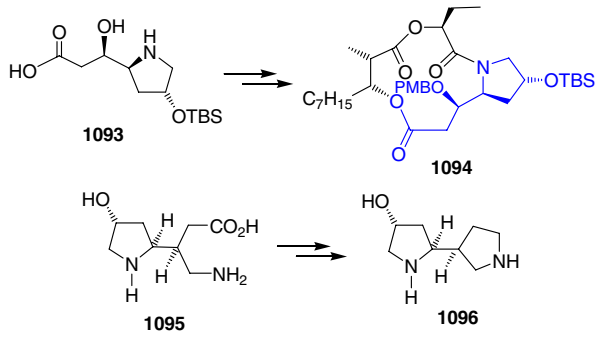
Although (−)-detoxinine **1084** itself did not show any particular biological activity, its incorporation into oligopeptides could promote new and interesting biological applications. Therefore, the efficient synthesis of (−)-detoxinine **1084** has been of great interest. In this context, Poisson et al.[391] have described the synthesis of (−)-detoxinine **1084** from intermediate **1085** obtained via an asymmetric [2+2] cycloaddition of dichloroketene and a chiral enol ether. On the other hand, Denmark et al.[392] have reported the synthesis of **1084** in 10 steps in 13.4% overall yield from commercially available dichlorodiisopropylsilane via an asymmetric tandem inter [4+2] and intra [3+2] cycloaddition and the bicyclic lactam **1086** as a key intermediate. Acetonide **1087**[393] and 1,3-dioxane **1088**[394] have been used as key intermediates in the preparation of **1084**. (−)-Detoxinine **1084** also has been obtained from derivatives **1089**[395] and **1090**.[396] Finally, aldol reaction of **1091**[397] afforded (−)-detoxinine **1084**, whereas **1092**[398] gave (+)-detoxinine **1084** (Scheme 271).

Polyhydroxylated γ-amino acids of type **1093** containing L-proline derivatives have also been used in the synthesis of new analogues of hapolisin **1094**,[398b] and the γ-amino acid **1095**,[399] which has been used in the preparation of **1096**, a component of 1β-methyl carbapenems[400] (Scheme 272).

To the best of our knowledge, the synthesis of enantiomerically pure **1097** has not yet been reported. Another



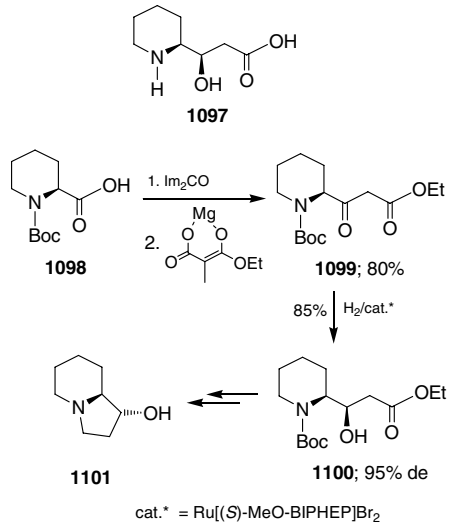
Scheme 271.



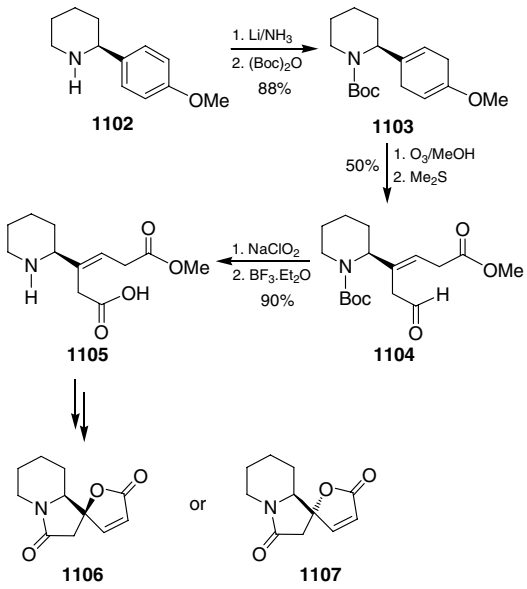
Scheme 272.

derivative is γ-amino-β-hydroxy acid **1100**, which has been used in the preparation of 1-hydroxyindolizidine **1101**. In this context, treatment of (*S*)-*N*-Boc-pipecolic acid **1098** with dicarbonyldiimidazole (Im_2CO) and the magnesium enolate of ethyl hydrogen methyl-malonate gave β-keto-ester **1099** in 80% yield, which upon catalytic hydrogenation using in situ generated Ru[(*S*)-MeO-BIPHEP]Br_2 ligand afforded the (3*R*,2′*S*)-β-hydroxy methyl ester **1100** in 85% yield and high diastereoselectivity, which was converted into (1*R*,8a*S*)-1-hydroxyindolizidine **1101** (Scheme 273).[384c]

Another hydroxy derivative is the γ-amino acid **1105**, which was used in the preparation of tricyclic compounds **1106** and **1107**. Thus, Birch reduction of (*S*)-2-anisylpiperidine **1102** followed by protection of the amino group with $(Boc)_2O$ led to carbamate **1103** in 88% yield, which by ozonolysis provided aldehyde **1104** in 50% yield. Oxidation of **1104** using $NaClO_2$ and subsequent cleavage of the *N*-Boc protective group with $BF_3{\cdot}Et_2O$ gave γ-amino acid **1105** in 90% yield (Scheme 274).[401]



Scheme 273.

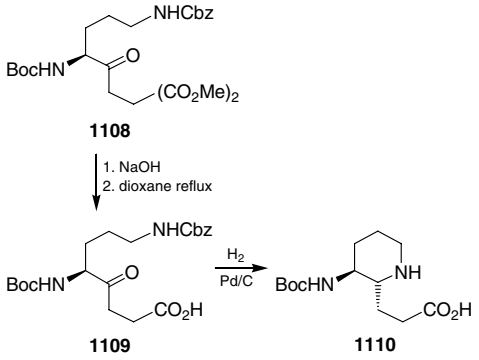


Scheme 274.

On the other hand, saponification and decarboxylation of **1108** obtained from the reaction of dimethyl malonate with the corresponding ornithine halomethyl ketone gave keto-acid **1109**, which by catalytic hydrogenation led to γ-amino acid **1110** (Scheme 275).[402]

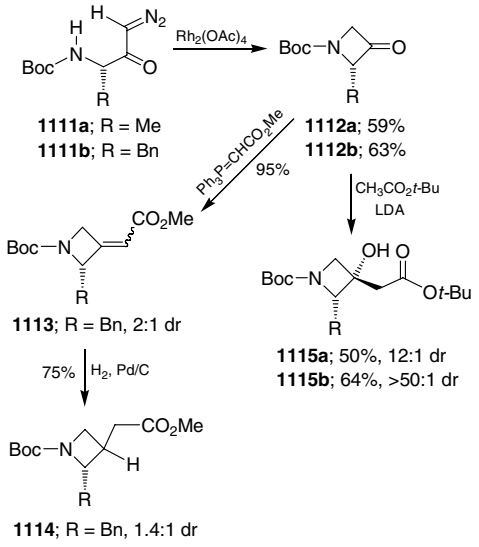
5.2. Synthesis of N, C^{n}_{β} derivatives

Cyclization of diazo derivatives **1111a** and **1111b**, readily available from L-amino acids with $Rh_2(OAc)_4$ gave the azetidin-3-ones **1112a** (R = Me) and **1112b** (R = Bn) in 59% and 63% yield, respectively. Wittig-type olefination of **1112b** with (carbomethoxymethylene)triphenylphosphorane afforded the corresponding unsaturated methyl ester **1113** in 95% yield and 2:1 dr, which on catalytic hydrogenation gave the protected γ-amino acid **1114** in 75% yield and 1.4:1 dr. On the other hand, the addition of the lithium



Scheme 275.

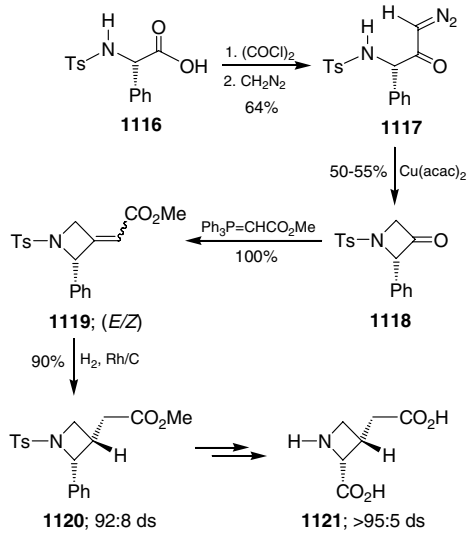
enolate of *tert*-butyl acetate to azetidin-3-ones **1112a** and **1112b** furnished the corresponding γ-amino-β-hydroxy *tert*-butyl esters **1115a** and **1115b** in excellent diastereoselectivity (Scheme 276).[403]



Scheme 276.

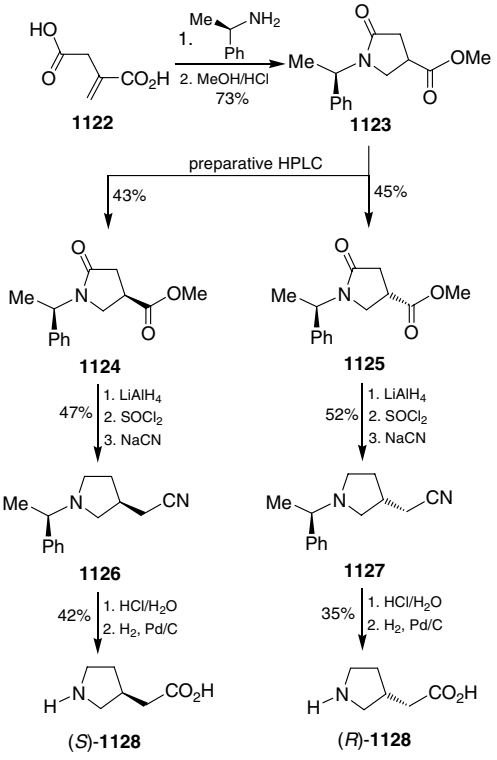
Recently, Burtoloso and Correia[404] reported that the cyclization of diazo derivative **1117** readily available from *N*-tosyl-L-phenylglycine **1116**, using $Cu(acac)_2$ afforded *N*-tosyl azetidin-3-one **1118** in 50–55% yield, whose Wittig olefination using the stabilized ylide (carbomethoxymethylene)triphenylphosphorane gave enoate **1119** as a mixture of *E*/*Z* in quantitative yield. Catalytic hydrogenation of the double bond in **1119** in the presence of Rh/C gave the protected γ-amino acid **1120** in 90% yield and 92:8 ds, which has been used in the synthesis of conformationally constrained glutamic acid **1121** in >95:5 ds[405] (Scheme 277).

2-(Pyrrolidine-3-yl)acetic acid **1128** (homo-β-proline), a cyclic analogue of 4-aminobutyric acid **1** (GABA), is a potent agonist at $GABA_A$ receptors, interacts effectively with GABA-uptake mechanisms, and it is a moderately potent inhibitor of $GABA_B$ receptor binding.[406] (*R*)- and (*S*)-homo-β-proline **1128** have been synthesized via 3-pyrrolidinecarboxylates **1124** and **1125**. Addition–cyclization



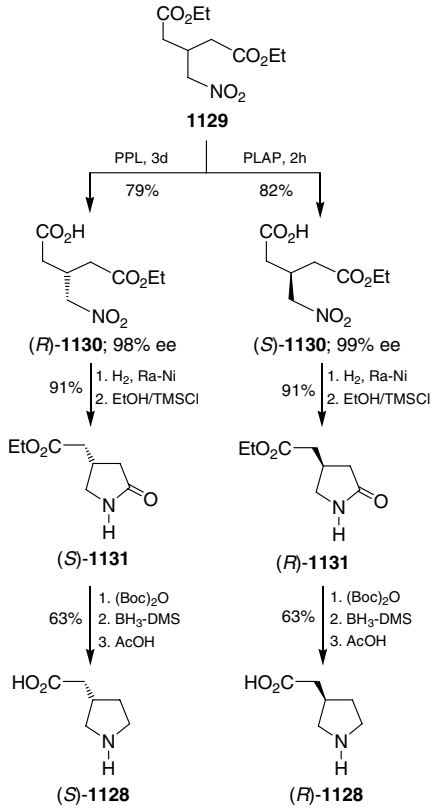
Scheme 277.

reactions of (*R*)-α-methylbenzylamine and itaconic acid **1122** afforded the diastereoisomeric mixture **1123** in 73% yield, which on chromatographic separation gave 3-pyrrolidinecarboxylates (*R*,*R*)-**1124** and (*S*,*R*)-**1125** in 43% and 45% yield, respectively. Reduction of diastereoisomerically pure (*R*,*R*)-**1124** and (*S*,*R*)-**1125** with $LiAlH_4$ followed by treatment with $SOCl_2$ and sodium cyanide afforded cyano derivatives (*R*,*R*)-**1126** and (*S*,*R*)-**1127** in 47% and 52% yield, respectively. Hydrolysis of cyano functionality and cleavage of the methylbenzyl group led to conformationally constrained γ-amino acids (*R*)-**1128** and (*S*)-**1128** in 42% and 35% yield, respectively (Scheme 278).[407]



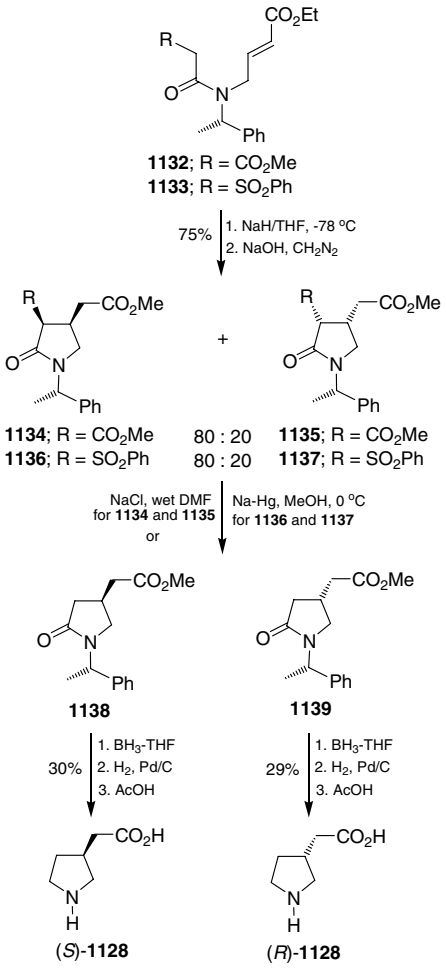
Scheme 278.

Recently Felluga et al.[408] have reported the preparation of (*R*)- and (*S*)-2-(pyrrolidine-3-yl)acetic acid **1128** via a chemoenzymatic disymmetric hydrolysis of 3-nitromethylglutaric acid diethyl ester **1129** obtained from a Michael addition of nitromethane to diethyl glutaconate. Thus, desymmetrization of **1129** using porcine pancreatic lipase (PPL) gave monoester (*R*)-**1130** in 98% ee and 79% yield, whereas treatment of **1129** with crude pig liver esterase (PLAP, pig liver acetone powder) produced monoester (*S*)-**1130** in 99% ee and 82% yield. Reduction of the nitro group in enantiomerically pure (*R*)- and (*S*)-**1130** with H_2 in the presence of Raney-nickel, followed by cyclization, afforded the corresponding γ-lactams (*R*)- and (*S*)-**1131** in 91% yield. *N*-Boc protection of (*R*)- and (*S*)-**1131** followed by removal of the lactam carbonyl function with BH_3·DMS complex and subsequent hydrolysis gave the conformationally constrained γ-amino acids (*R*)- and (*S*)-**1128** in 63% yield (Scheme 279).



Scheme 279.

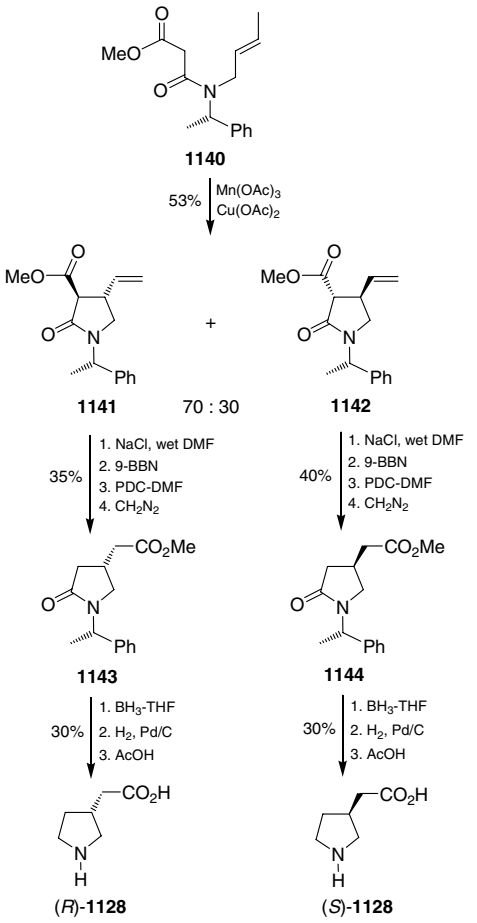
Treatment of **1132** and **1133** with NaH followed by saponification with NaOH and subsequent esterification with diazomethane gave γ-lactams **1134**, **1135** and **1136**, **1137**, respectively, in 75% yield and 80:20 dr. Decarboxylation of **1134** and **1135** with NaCl and wet DMF provided pyrrolidin-2-ones **1138** and **1139**, respectively.[409] Derivatives **1138** and **1139** were also obtained from **1136** and **1137** when these were treated with Na–Hg in methanol. Reduction of the lactam carbonyl function in **1138** and **1139** with a BH_3·THF complex followed by cleavage of methylbenzyl group and subsequent hydrolysis led to conformationally restricted γ-amino acids (*R*)- and (*S*)-**1128** in 30% and 29% yield, respectively (Scheme 280).[410]



Scheme 280.

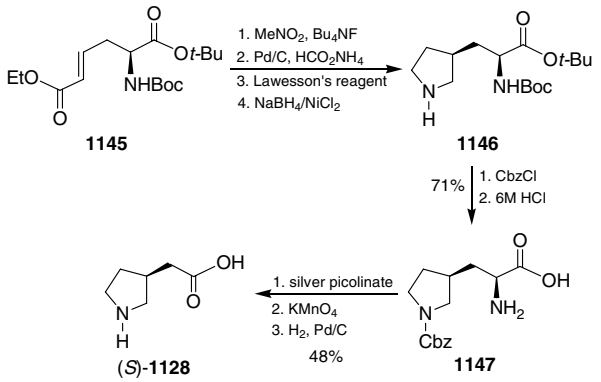
On the other hand, oxidative cyclization of amide **1140** with $Mn(OAc)_3·2H_2O$ and $Cu(OAc)_2·H_2O$ afforded pyrrolidin-2-ones **1141** and **1142** in 53% yield and 70:30 dr, and with a total regioselectivity through a 5-*exo* ring closure. Sequential decarboxylation, hydroboration, oxidation, and esterification of diastereoisomerically pure **1141** and **1142** gave methyl esters **1143** and **1144** in 35% and 40% yield, respectively. Treatment of γ-lactams **1143** and **1144** under identical conditions described above gave (*R*)- and (*S*)-**1128**, respectively (Scheme 281).[411]

The addition of nitromethane to α,β-unsaturated ethyl ester derivative **1145** followed by reduction of the nitro group and subsequent reaction with Lawesson's reagent and reduction with $NaBH_4$ in the presence of $NiCl_2$ afforded the cyclic amino acid **1146**, which by protection of free amino group with CbzCl followed by cleavage of the *N*-Boc protective group gave the *N*-Cbz-protecting amino acid **1147** in 71% yield. Oxidative decarboxylation of **1147** using silver picolinate, and subsequent treatment with $KMnO_4$



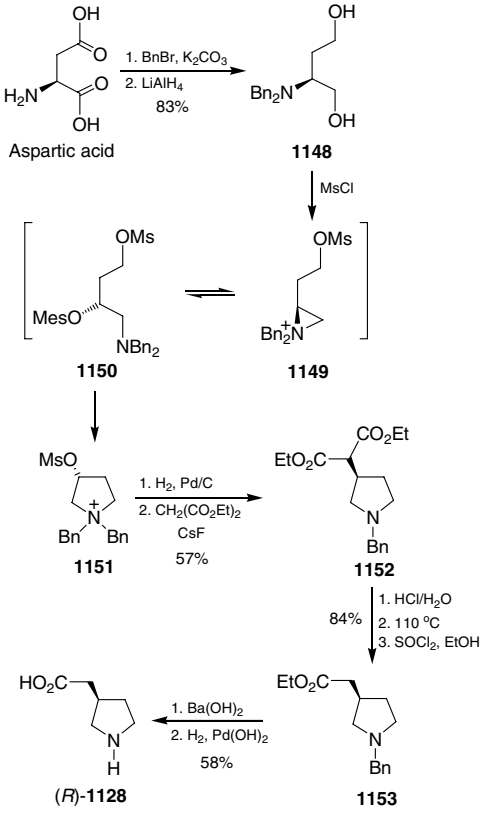
Scheme 281.

and cleavage of the Cbz protective group gave (*S*)-**1128** in 48% yield (Scheme 282).[412]



Scheme 282.

On the other hand, treatment of diol **1148**, readily obtained in 83% yield by perbenzylation and reduction of (*S*)-aspartic acid with an excess of MsCl afforded the dimesylated compound, which by a rearrangement via the aziridinium intermediate **1149** and ring closure of **1150** gave the pyrrolidinium salt **1151**. Selective hydrogenolytic mono-debenzylation of **1151** using Pearlman's catalyst, followed by reaction with diethyl malonate in the presence of CsF, furnished **1152** in 57% yield. Decarboxylation of **1152** and subsequent esterification led to ethyl ester derivative **1153** in 84% yield, which by saponification followed by cleavage of benzyl protective group provided γ-amino acid (*R*)-**1128** in 58% yield (Scheme 283).[413]

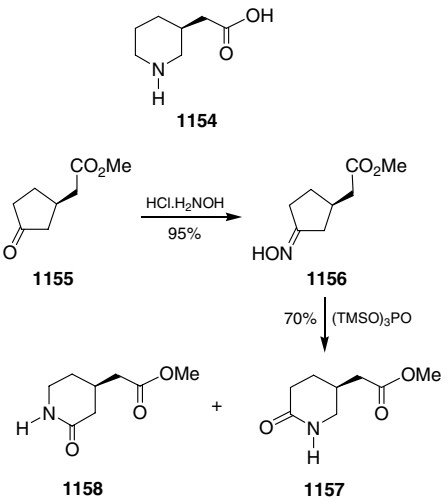


Scheme 283.

5.3. Synthesis of N, C_{α}^{n} derivatives

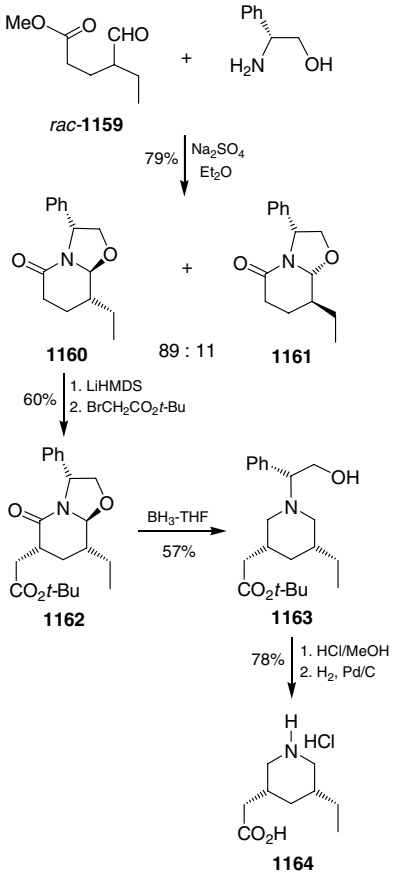
To the best of our knowledge, the synthesis of enantiomerically pure **1154** has not been reported,[414] and another derivative is the γ-amino methyl ester derivative **1157**. In this context, the reaction of enantiomerically pure ketone **1155** with hydroxylamine hydrochloride afforded (*E*)- and (*Z*)-oximes **1156** in 95% yield, which through a Beckmann rearrangement using $(TMSO)_3PO$ gave amides **1157** and **1158** in 70% yield (Scheme 284).[415] Reduction of amide group in **1157** could give the γ-amino acid **1154**.

Recently, Amat et al.[416] have reported the stereoselective synthesis of *cis*-5-ethyl-3-piperidineacetic acid **1164**, which is a key intermediate in the preparation of (20*R*)-dihydrocleavamine.[417] In this context, the cyclocondensation of racemic aldehyde ester **1159** with (*R*)-phenylglycinol under neutral conditions afforded a diastereoisomeric mixture of lactams **1160** and **1161** in 79% yield and 89:11 ratio. The alkylation reaction of diastereoisomerically pure **1160** with *tert*-butyl bromoacetate gave bicyclic compound **1162** in 60% yield and 1:4 *endo*/*exo* ratio. Reductive opening of the oxazolidine ring and reduction of the amide function in **1162** with BH_3·THF complex led to 3,5-dialkylpiperidine *cis*-**1163** in 57% yield, which upon hydrolysis and



Scheme 284.

subsequent catalytic debenzylation provided *cis*-**1164** in 78% yield (Scheme 285).



Scheme 285.

6. Conclusion

In spite of the lack of synthetic procedures to some of the most representative 'pattern compounds', organic chemists have made many efforts to develop competitive alternatives to the preparation of γ-amino acids in such a way that numerous strategies have been reported toward the synthesis of a great variety of compounds, most of them being covered in this review. Taking into account the importance of this family of amino acids, the development of new and competitive procedures to prepare a target compound in enantiomerically pure form on a multigram scale would be welcomed.

7. Abbreviations

ABSA	acetamidobenzene sulfonyl azide
Ac	acetyl
acac	acetylacetonate (ligand)
ACPCA	4-aminocyclopent-1-ene-1-carboxylic acid
ACPECA	4-aminocyclopent-2-ene-1-carboxylic acid
AHPBA	4-amino-3-hydroxy-5-phenylbutanoic acid
AHPPA	4-amino-3-hydroxy-5-phenylpentanoic acid
AIBN	2,2′-azobisisobutyronitrile
AIDS	acquired immune deficiency syndrome
BBB	blood–brain barrier
9-BBN	9-borabicyclo[3.3.1]nonane
BDA	butane-2,3-diacetal
BINALH	lithium 2,2′-dihydroxy-1-1′-binaphthylethoxy-aluminum hydride
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
$(Boc)_2O$	di(*tert*-butyl)dicarbonate
Boc	*tert*-butoxycarbonyl
BS	*Bacillus steraothermophilus*
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bz	benzoyl
CACA	*cis*-4-aminocrotonic acid (*cis*-4-Aminobut-2-enoic acid)
CACP	*cis*-3-aminocyclopentane-1-carboxylic acid
CAL	*Candida antarctica*
CAMP	*cis*-2-aminomethylcyclopropane-1-carboxylic acid
CAN	cerium ammonium nitrate
CbzCl	benzylchloroformate
CCL	*Candida cylindracea*
CDI	1,1′-carbonyldiimidazole
CE	Colesterol esterase
CNS	central nervous system
CSA	camphorsulfonic acid
CTAOH	cetyltrimethylammonium hydroxide
DABCO	1,4-diazabicyclo[2.2.2]octano
Dap	dolaproline
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereoisomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate

DHQD dihydroquinidine
DIAD diisopropyl azodicarboxylate
DIBAL-H diisobuylaluminum hydride
DIPEA disopropylethylamine
DIPT diisopropyl tartrate
DKR dynamic kinetic resolution
DMAP 4-dimethylaminopyridine
DMEP 2,2-dimethoxypropane
DMF *N*,*N*-dimethylformamide
DMP 2,2-dimethoxypropane
DMS dimethyl sulfide
DMSO dimethyl sulfoxide
DPPA diphenylphosphoryl azide
dppe 1,2-bis(diphenylphosphino)ethane (diphos)
dr diastereoisomeric ratio
E entgegen (opposite, *trans*)
ee enantiomeric excess
EDCl 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EEDQ 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
en ethylene diamine
FDH formate deshydrogenase
Fmoc 9-fluorenylmethoxycarbonyl
FVP flash vacuum pyrolysis
GABA γ-aminobutyric acid
GABOB γ-amino-β-hydroxybutyric acid
GAM glutaramic acid
GBP gabapentin
HBT hydroxybenzotriazole
HFA hexafluoroacetone
HIV human immunodeficiency virus
HPLC high performance liquid chromatography
HPPA hydroxypyrrolidinepropionic acid
HTLV human lymphotropic viruses
HYTRA hydroxy-1,2,2-triphenylethyl acetate
IPA isopropyl alcohol
KHMDS potassium bis(trimethylsilyl)amide
LDA lithium diisopropylamide
LHMDS lithium bis(trimethylsilyl)amide
MBA methylbenzylamine
m-CPBA *m*-chloroperoxybenzoic acid
MEM methoxyethoxymethyl
MEOX methyl 2-oxooxazolidine-4(*S*)-carboxylate
MMPP magnesium monoperoxyphthalate
MPA methoxyphenylacetic acid
MOMCl methoxymethyl chloride
MPA methoxyphenylacetic acid
MS molecular sieves
Ms methanesulfonyl
MW microwave
NBA *N*-bromoacetamide
NBS *N*-bromosuccinimide
NHMDS sodium bis(trimethylsilyl)amide
NMM *N*-methylmorpholine
p-ABSA *p*-acetamidobenzene sulfonyl azide
PCPGABA *p*-chlorophenylbutyric acid
PCC pyridinium chlorochromate
PDC pyridinium dichromate
Pf 9-phenylfluorenyl
PhGABA phenyl-γ-aminobutyric acid
PhthN phthalimido
PLE pig liver estereasa
PMB *p*-methoxybenzyl
PMP *p*-methoxyphenyl
PPL porcine pancreatic lipase
PPTS pyridinium *p*-toluenesulfonate
PS *Pseudomonas cepacia*
PTSA *p*-toluenesulfonic acid
Py pyridine
rt room temperature
RAMP (*R*)-1-amino-2-methoxypyrrolidine
SADP (*S*)-1-amino-2-(1-methoxy-1-methylethyl)-pyrrolidine
SAH Sharpless aminohydroxylation
SAMP (*S*)-1-amino-2-methoxypyrrolidine
SC subtilisin Carlsberg
SE *Staphylococcus epidermidis*
SPNs self-assembling peptide nanotubes
TACA *trans*-4-aminocrotonic acid (*trans*-4-amino-but-2-enoic acid)
TACP *trans*-3-aminocyclopentane-1-carboxylic acid
TAMP *trans*-2-aminomethylcyclopropane-1-carboxylic acid
TBAB tetra-*n*-butylammonium bromide
TBAF tetra-*n*-butylammonium fluoride
TBAI tetra-*n*-butylammonium iodide
TBS *tert*-butyldimethylsilyl (also TBDMS)
TBHP *tert*-butyl hydroperoxide
TBDPS *tert*-butyldiphenylsilyl
TEMPO 2,2,6,6-tetramethyl-1-piperidinyloxy
TEMT triethyl methanetricarboxylate
Teoc 2-(trimethylsilyl)ethoxycarbonyl
Tf trifluoromethanesulfonyl
TFA trifluoroacetic acid
TFAA trifluoroacetic anhydride
TMEDA *N*,*N*,*N*′*N*′-tetramethylethylenediamide
TMSCl trimethylsilylchloride
TMSCN trimethylsilylcyanide
TMSI trimethylsilyliodide
TMSOTf trimethylsilyl trifluoromethanesulfonate
TPP triphenylphosphine
Trityl triphenylmethyl
Ts *p*-toluenesulfonyl
Z Zusammen (together, *cis*)

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