

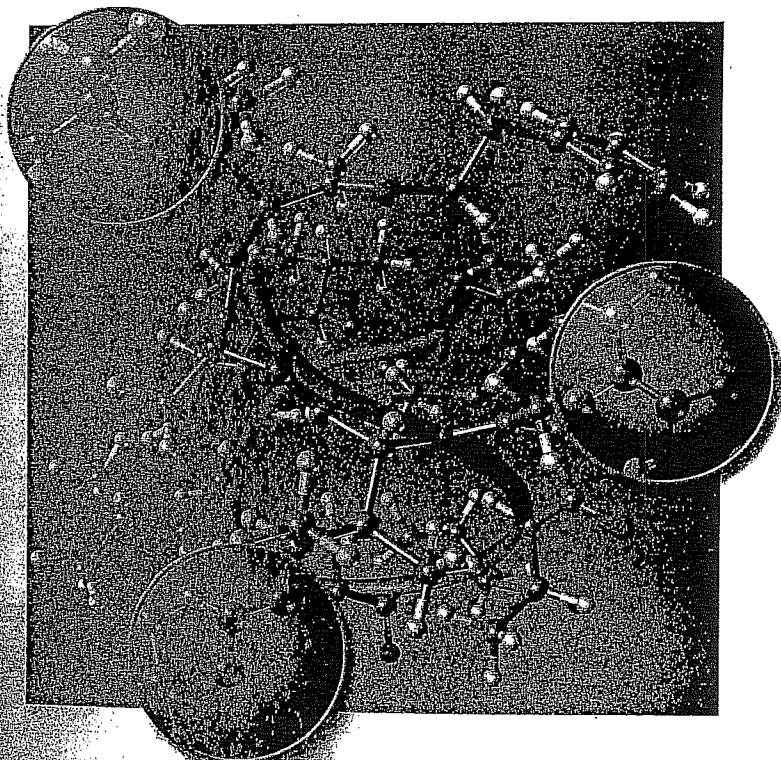
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Amino Acids, Peptides and Proteins in Organic Chemistry

Volume 1

Origins and Synthesis of Amino Acids



573

14

Synthesis of γ -Aminobutyric Acid Analogs

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14.1

Introduction

Given the likely varied roles of γ -aminobutyric acid (GABA; 4-aminobutanoic acid) (1) as a ubiquitous signaling molecule in most living organisms, new GABA analogs are continuously being sought in order to probe metabolic roles and to develop new biologically active agents. The considerable interest in synthesizing analogs of GABA derives from the vital role of this nonprotein amino acid in brain function. GABA is essential to maintaining a functioning brain by acting as the major inhibitory neurotransmitter by balancing the effects of the major excitatory neurotransmitter L-glutamate [1]. Insufficiency of synaptic inhibition may lead to anxiety, epilepsy, insomnia, or memory problems. Overactive synaptic inhibition may be associated with anesthesia, coma, or sedation. Recent reviews on aspects of the central nervous system (CNS) pharmacology of GABA include the ionotropic GABA receptors (GABA_A and GABA_C) as drug targets [2–4], especially receptor subtypes [5], the G-protein-coupled GABA_B receptors [6], GABA transporters [7], and patents on novel GABA analogs [8].

Several GABA analogs are used clinically (Figure 14.1), including the antiepileptic drug vigabatrin (Sabril) (2), which was designed as an irreversible inhibitor of the enzyme that degrades GABA, resulting in increases in the level of GABA in the brain [9]. GABA analogs substituted in the 3-position have been of particular interest [10]. The selective GABA_B agonist, baclofen (Lioresal) (3) has been used for many years to treat spinal spasticity. Gabapentin (Neurotenin) (4) and pregabalin (Lyrica) (5) are the newest GABA analogs on the CNS drug market for the treatment of epilepsy and neuropathic pain, with sales of the recently marketed Lyrica reaching US\$1.8 billion in 2007. While they are 3-substituted GABA analogs, they do not appear act directly on any known GABA neurotransmitter system in the brain. They act as selective inhibitors of voltage-gated calcium channels containing the $\alpha_2\delta_1$ subunit [11]. They are not the first therapeutically useful drugs to be designed as GABA analogs that have turned out to act predominately on systems apparently unrelated to GABA – the prototypical antipsychotic drug haloperidol acting

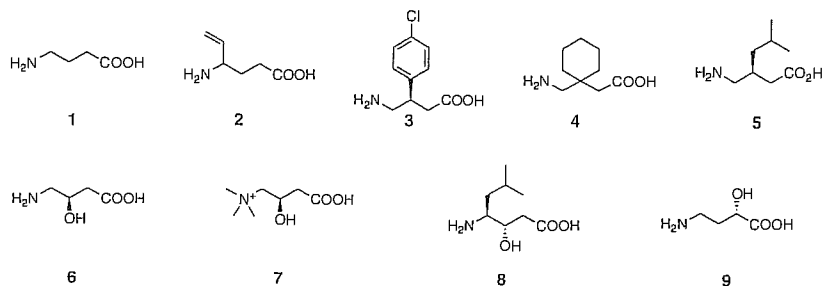


Figure 14.1

at dopamine receptors was designed as a GABA analog able to penetrate the blood–brain barrier [12].

GABA occurs extensively in plants, fungi, bacteria, insects, invertebrates, and vertebrates. It has been described as a conserved and ubiquitous signaling system [13]. Recently, it has been suggested that GABA mediates communication between plants and other organisms [14]. GABA is thought to facilitate communication via diverse mechanisms, including activation of neuronal receptors and induction of enzymes and transporters.

Several biologically active GABA analogs occur naturally (Figure 14.1). These include (*S*)-4-amino-3-hydroxybutanoic acid (GABOB) (6), also found in the cyclic depsipeptide hapalosin, and L-carnitine (7) (used in the treatment of myopathies) found in mammalian tissues [15]. Statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid] (8) is regarded as the key pharmacophore in the rennin inhibitor pepstatin isolated from bacteria [16]. Statine (8) and its analogs are useful as building blocks for peptidomimetics [17]. Homoisoserine (2-hydroxy-4-aminobutyric acid) (9) acts as an inhibitor for GABA uptake, exhibits antitumor activity, is found in many antibiotics, and is also used to construct peptidomimetics [18].

In mammals, GABA is found in many organs outside of the CNS where it serves various functions [19]. GABA is involved in cell proliferation and migration, and may play a role in cancer [20]. Recent evidence implicates GABA receptors in mucus overproduction in asthma acting on airway epithelial cells [21]. GABA regulates insulin secretion from pancreatic β cells in concert with changes in glucose concentration [22] and may be involved with type 1 diabetes inhibiting the development of proinflammatory T cell responses acting via GABA receptors [23]. Functional GABA_A receptors have also been described in T cells [24] and macrophages [25]. Thus, asthma, cancer, diabetes, and the immune system may also be targets for GABA analogs.

The development of synthetic methodologies for the synthesis of substituted alkyl and conformationally restricted GABA analogs has been the focus of much endeavor [17, 26, 27]. The availability of a range of GABA analogs has played a major role in elucidating the physiological roles of GABA receptors. More recently,

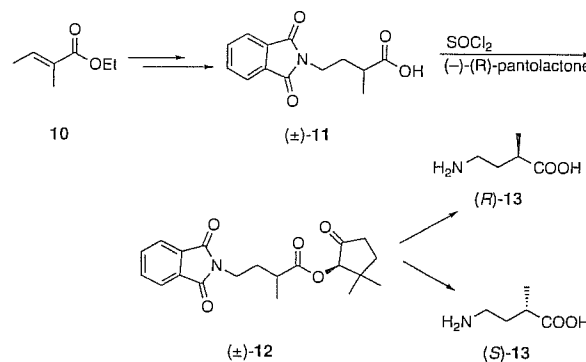
substituted GABA analogs have become of interest for their presence in novel peptides and potential application in constraining peptide sequences in to β - and γ -turns. This chapter focuses on the synthetic procedures for the preparation of linear and alicyclic analogs of GABA.

14.2

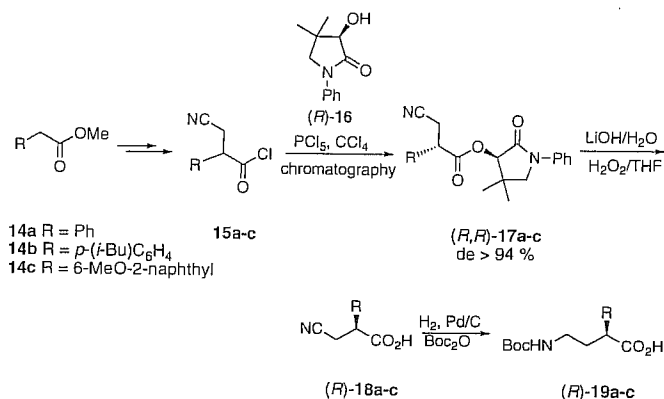
α -Substituted γ -Amino Acids

(*R*)- and (*S*)- α -Methyl-GABAs (13) were originally prepared by reaction of 2-methylbutyrolactone with potassium phthalimide and resolution by fractional crystallization of the phthalimido derivatives as quinine salts. Hydrolysis and cleavage of the phthalimido group afforded the enantiomerically pure amino acids in low overall yields [28]. Duke *et al.* described the synthesis of (13) starting from tiglic acid (10), which was esterified, allylically brominated, and coupled with phthalimide to introduce the nitrogen atom. Hydrogenation and ester hydrolysis afforded (\pm)-(11) which was resolved by derivatization as the (*R*)-pantolactone ester (12) and chromatographic separation and acid hydrolysis afforded enantiomerically pure (*R*)-(13) and (*S*)-(13) in good overall yield (Scheme 14.1) [29].

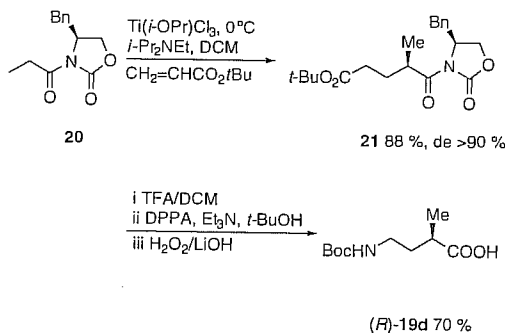
Esterification of racemic α -aryl- β -cyanopropionic acid chlorides (15a–c) (Scheme 14.2), from methyl 2-arylacrylates (14a–c), with (*R*)-*N*-phenylpantolactam (*R*)-(16) as the chiral auxiliary results in the predominant formation of (α ,*R*,3'*R*)-(17a–c) in nearly quantitative yields with diastereomeric ratios of up to 93 : 7 achieved through a dynamic kinetic resolution process. The use of (*S*)-(16) similarly affords (α ,*S*,3'*S*)-(17a–c). Chromatographic purification of the diastereoenriched cyano esters, followed by hydrolysis of the resulting diastereopure cyano esters under nonracemizing conditions, gave enantiopure α -aryl- β -cyanopropionic acids (18a–c), which were readily converted in high yields into enantiopure *N*-Boc- α -aryl-GABAs (*R*)-(19a–c) or (*S*)-(19a–c) [30].



Scheme 14.1



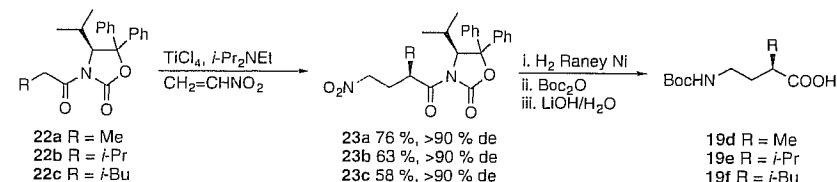
Scheme 14.2



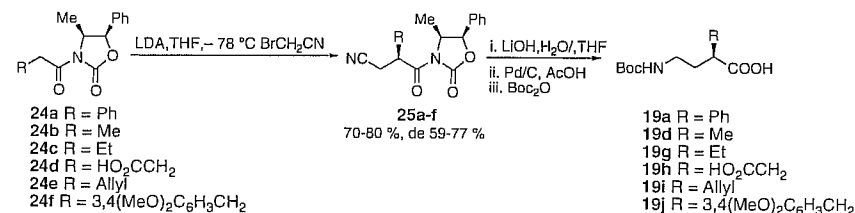
Scheme 14.3

Evans *et al.* have reported a diastereoselective Michael reaction of *tert*-butyl acrylate with the titanium enolate derived from *N*-propionyloxazolidinone (20) (Scheme 14.3) that affords enantiomerically pure ester (21). Hydrolysis of the ester, subsequent Curtius rearrangement, and removal of the chiral auxiliary afforded the desired amino acid (*R*)-19d [31].

Similarly, Seebach *et al.* have used the titanium enolates of valine-derived auxiliaries (22a–c) (Scheme 14.4) to give a range of 4-nitro derivatives (23a–c) in high diastereoselectivities (80 to >95%) and good yields (50–75% of purified samples of diastereoselectivity > 98%). Reduction of the nitro group, recovery of the insoluble auxiliary and ring opening of the *N*-Boc-lactams affords the (*R*)-*N*-Boc-amino acids (19d–f) [32].



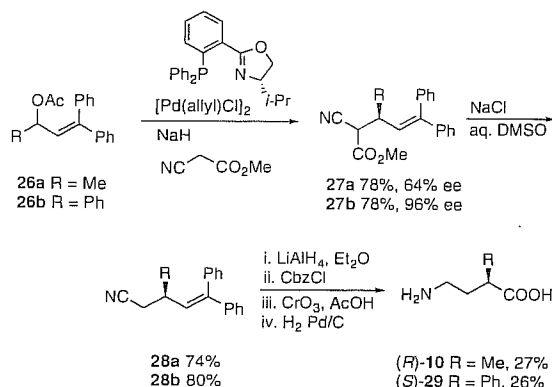
Scheme 14.4



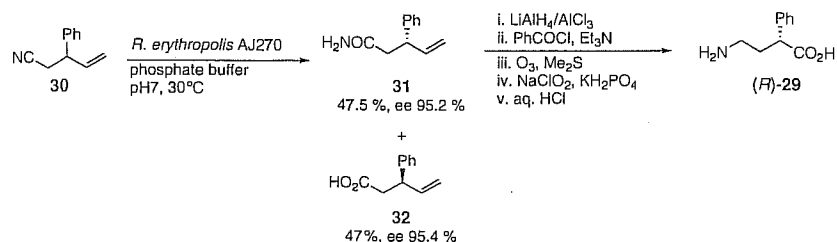
Scheme 14.5

Cyanomethylation of sodium or lithium enolates from 3-acyloxazolidinones (24a–f) (Scheme 14.5) with bromoacetonitrile affords the nitriles (25a–f) providing a general approach to the enantioselective synthesis of 2-substituted GABA derivatives (19a, d and g–j). Relative poor diastereomeric excesses (60–77%) compared to similar methodology are attributed to the relatively small size of bromoacetonitrile, combined with its high reactivity as an electrophile [33].

Enantioselective palladium-catalyzed allylic substitution of readily available allylic acetates (26) (Scheme 14.6) using methyl cyanoacetate provides substitution



Scheme 14.6



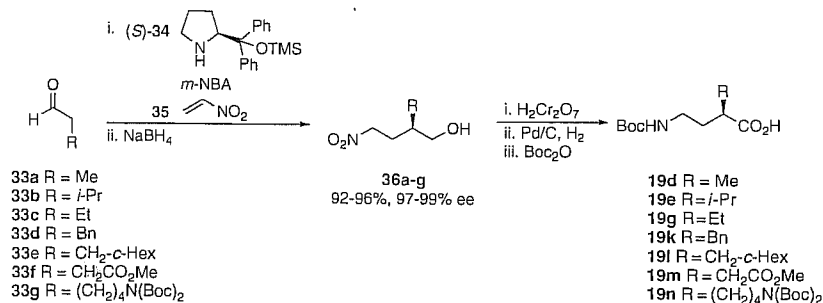
Scheme 14.7

products (**27**) that can be rapidly converted in to α -substituted γ -amino acids. Krapcho decarboxylation, reduction of the nitrile (**28**) to the amine which was protected as a carbamate, allows oxidative cleavage of the alkene affording (*R*)-(**10**) or (*S*)-(**29**) in good yields and moderate to high enantiomeric excess [34].

(\pm)- α -Substituted GABA analogs have been prepared by a range of synthetic methodologies, including the palladium-catalyzed rearrangement of α -cyanocyclopropanone hydrates, which occurs with internal proton transfer, providing access to selectively deuterated α -amino acids [35] and zirconium-mediated intramolecular ester transfer reaction of *N*-alkenyl-*N*-tosyl carbamates derivatives [36].

Enantioselective biotransformation of racemic 3-arylpent-4-enitrile (**30**) (Scheme 14.7) with *Rhodococcus erythropolis* AJ270 provides a straightforward and scalable route to highly enantiopure (*S*)-3-phenylpent-4-enoic acid amide (**31**) and (*R*)-3-phenylpent-4-enoic acid (**32**). The amide (**31**) can be converted to (*R*)-(**29**) via reduction of the carboxamido group and oxidation of the vinyl group [37].

Two groups have reported organocatalyzed asymmetric conjugate addition reactions of aldehydes (**33**) to nitroethylene (**35**). The reactions, catalyzed by either proline containing peptides [38], or (*S*)-diphenylprolinol silyl ether (**34**) (Scheme 14.8) [39], afford (**36**) in high yield (95%) and enantioselectivity (>95% e.e.), after reduction with NaBH₄. The use of *m*-nitrobenzoic acid with (*S*)-(**34**) results in greater catalyst efficiency. Jones oxidation of the aldehyde, reduction of the nitro group, and protection of the resulting amine affords the protected amino acids (**19d**, **e**, **g** and



Scheme 14.8

k–**n**) in high overall yield [39]. The use of the peptide catalyst produces compounds with the opposite stereochemistry to those produced by (*S*)-(**34**) [38].

The addition of bromoacetonitrile to the dianions of carboxylic acids has been reported as a two-step process to afford α -substituted amino acids. Although high yielding, the use of chiral bases resulted in only minimal chiral induction [40].

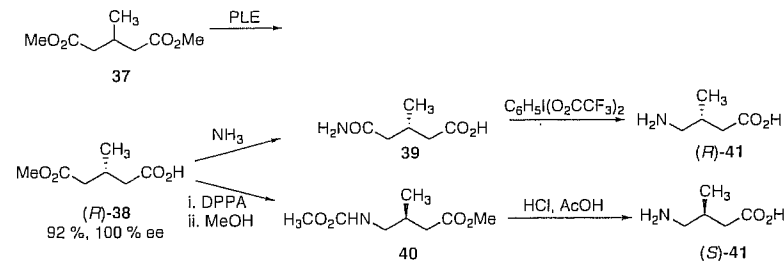
14.3

 β -Substituted γ -Amino Acids

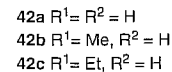
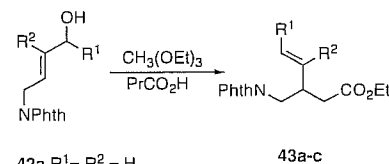
Many of the methods employed for the synthesis of α -substituted γ -amino acids are also applicable to the synthesis of β -substituted γ -amino acids, including reaction of titanium enolates of valine-derived auxiliaries [32] and the rearrangement of α -cyanocyclopropanone hydrates [35].

(*R*)- and (*S*)-4-Amino-3-methylbutanoic acids (**41**) (Scheme 14.9) were synthesized in a stereodivergent route via an initial enantioselective hydrolysis of dimethyl 3-methylglutarate (**37**) to give methyl (*R*)-3-methylglutarate (**38**) with pig liver esterase (PLE). Conversion of the ester group to an amide (**39**) by ammonolysis and subsequent Hoffmann rearrangement gives (*R*)-4-amino-3-methylbutanoic acid (*R*)-(**41**). Conversion of the carboxylic acid to the carbamate (**40**) via a modified Curtius rearrangement affords (*S*)-4-amino-3-methylbutanoic acid (*S*)-(**41**) [41].

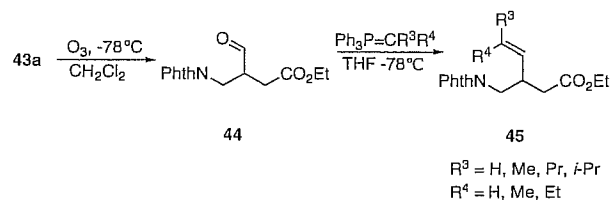
A general route to a range of 3-vinyl-substituted GABA derivatives (**43** and **45**) from substituted 4-phthalimido-2-buten-1-ols (**42**) has been described (Schemes 14.10



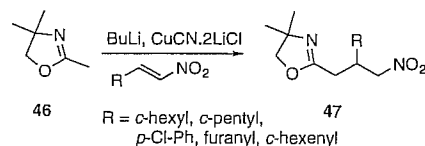
Scheme 14.9



Scheme 14.10



Scheme 14.11

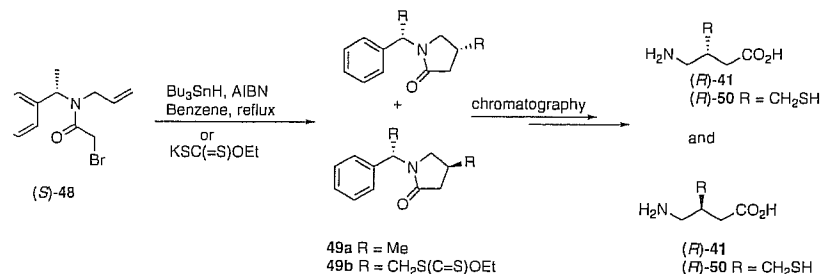


Scheme 14.12

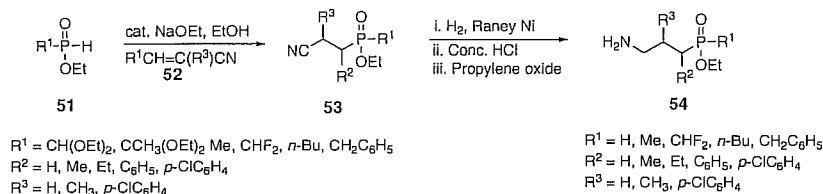
and 14.11). Acid-catalyzed Claisen rearrangement in ethyl orthoacetate formed the (*E*)-3-substituted phthalimido esters (43), which can be easily deprotected to yield the amino acids (Scheme 14.10). Alternatively, the synthesis of ω -disubstituted or *cis*-monosubstituted derivatives (45) can be obtained by a Wittig reaction on the aldehyde (44) obtained by ozonolysis of ethyl 4-phthalimidomethylpent-4-enoate (43a) (Scheme 14.11) [42].

The addition of cyanocuprates of oxazolines (46) to conjugated nitroalkenes has been reported as an efficient method for the synthesis of a variety of β -substituted γ -nitrooxazolines (47) (Scheme 14.12), which are precursors of a variety of β -substituted γ -amino acids [43].

Enantiomerically pure 3-methyl- (41) and 3-mercaptomethyl- γ -amino acids (50) have been prepared by a novel route for the synthesis of optically pure β -substituted GABA derivatives (Scheme 14.13). (*S*)-Phenylethylamine was used as a chiral auxiliary of the radical precursor (*S*)-48 for a 5-*exo*-trig radical cyclization as the strategy for the construction of the 4-substituted pyrrolidinones (49). Chromatographic separation of



Scheme 14.13



Scheme 14.14

the diastereoisomers, removal of the chiral auxiliary followed by an aqueous hydrolysis provided the corresponding optically pure β -substituted GABA derivatives (41 and 50) [44].

Pregabalin (5) has also been prepared via a stereoselective Bu_3SnH -mediated radical cyclization. In the presence of the Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$ a diastereoisomeric ratio of 88:12 was achieved [45].

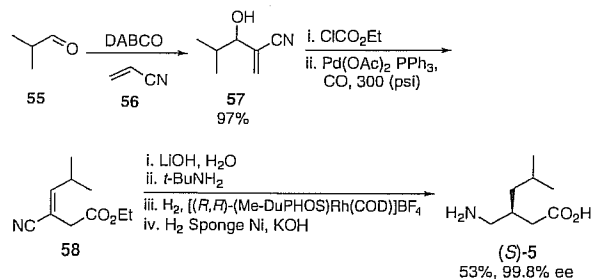
A wide range of α -, β -, and α,β -substituted phosphinic and alkylphosphinic GABA analogs have been reported [46, 47]. Conjugate addition of the phosphinate (51) to acrylonitrile (52) gave the cyano esters (53) (Scheme 14.14), which upon hydrogenation (or reductive amination) yielded amino ester. After acidic hydrolysis, phosphinic or alkyl phosphinic acids (54) were obtained [46, 47].

14.3.1 Pregabalin

The multistep discovery synthesis of pregabalin (5) utilized an asymmetric Evans alkylation with alkyl bromoacetate of the chiral auxiliary prepared from (+)-norephedrine. Cleavage of the chiral auxiliary to give the acid, reduction to the alcohol, conversion to the amine via the tosylate, and deprotection afforded pregabalin in high enantiomeric purity, but relatively low overall yield. This synthesis was not suitable for the large-scale preparation of the anticonvulsant and the significant efforts to develop a low-cost manufacturing process have been fully reviewed [48]; however, pregabalin (5) has remained an interesting synthetic target.

A Baylis–Hillman reaction between isobutyrylaldehyde (55) and acrylonitrile (56) yields 3-hydroxy-4-methyl-2-methylenepentanenitrile (57) (Scheme 14.15) [49]. Conversion to the *N*-ethyl carbonate and palladium-catalyzed carbonylation in ethanol afforded the ester (58), which was hydrolyzed. Hydrogenation of the ethyl ester proceeded with poor enantioselectivity, however hydrogenation of the *tert*-butyl ammonium salt and hydrogenation in the presence of a chiral rhodium catalyst resulted in high enantioselectivity. Hydrogenation of the nitrile with a heterogeneous nickel catalyst afforded (*S*)-5 [50].

Conjugate addition of cyanide, generated *in situ* from trimethylsilyl cyanide to unsaturated imides using commercially available (*salen*)Al(III) catalysts has been reported to provide a facile synthesis of β -substituted γ -amino acids. Hydrolysis of the resulting imide and nitrile reduction affords the amino acids such as pregabalin



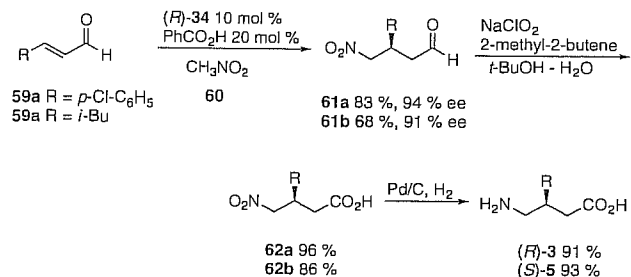
Scheme 14.15

(5) [51]. Alternatively, (*R*)-pregabalin (*R*)-(5) and baclofen (3) have been prepared via conjugate addition of cyanide catalyzed by Sm(III) isopropoxide to an appropriately substituted Evan's chiral auxiliary [52].

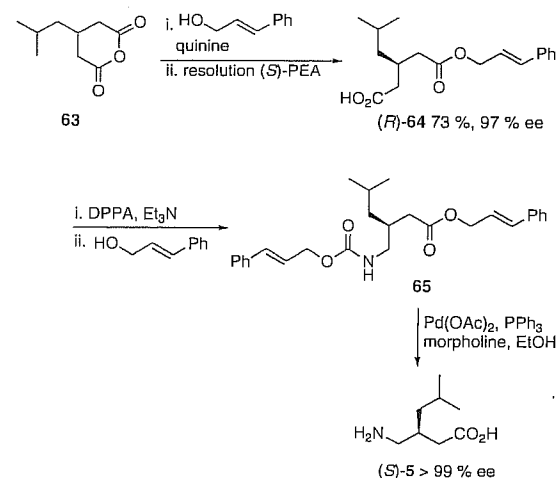
A catalytic enantioselective Michael reaction of nitroalkanes with α,β -unsaturated aldehydes using (*R*)-(34), as an asymmetric organocatalyst has been used to synthesize both baclofen (3) and pregabalin (5) (Scheme 14.16). Conjugate addition of nitromethane (60) to 5-(*p*-chlorophenyl)-enal (59a) or 5-isobutyl-hex-2-enal (59b) afforded enantiomerically pure 3-substituted nitrobutanals (61), which were converted to (3) or (5), respectively, in two steps via the nitro acid (62) [53].

3-Isobutylglutaric anhydride (63) (Scheme 14.17) prepared from cyanoacetamide and isovaleraldehyde undergoes desymmetrization via a quinine-mediated ring opening with cinnamyl alcohol. The crude monoacid (64) prepared in 72% e.e. underwent purification by crystallization with (*S*)-phenylethylamine, affording the acid (64) in 73% yield and 97% e.e. A Curtius rearrangement and subsequent deprotection provided pregabalin (*S*)-(5) in 45% overall yield [54].

A general, convenient and scalable synthetic method for enantiomerically pure β -substituted γ -butyrolactones, of either configuration, has been reported. The desired chiral bicyclic lactone (67) (Scheme 14.18) is prepared in one pot from chiral

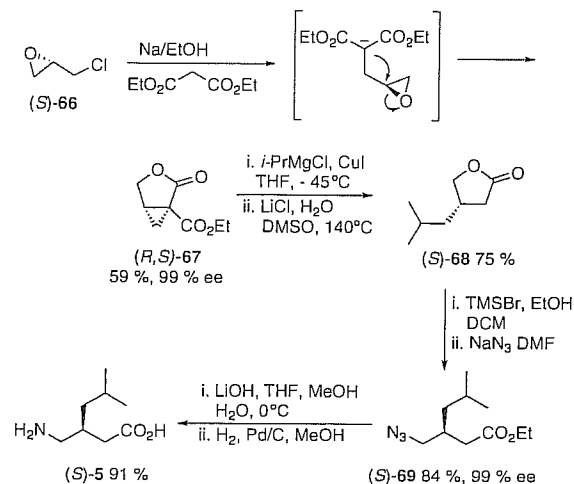


Scheme 14.16



Scheme 14.17

epichlorohydrin (66) by intramolecular double displacement of the alkyl malonate anion followed by lactonization [55]. Ring opening of the cyclopropane ring with isopropyl Grignard reagent and decarboxylation provides access to the isopropyl substituted lactone (68), which can be converted to pregabalin (2) via the azide (69) in



Scheme 14.18

four steps. The use of other Grignard reagents affords access to a range of β -substituted γ -amino acids [56].

(\pm)-*N*-Boc-pregabalin has been synthesized in low overall yields via a hetero-Diels–Alder addition of 3-nitrosoacrylate to ethyl vinyl ether [57]. D-Mannitol has also been used as the primary source of chirality in a high-yielding (28% overall yield), multistep synthesis of (*S*)-pregabalin (**5**) [58]. A series of racemic heteroaromatic analogs of pregabalin have been synthesized via reaction of the anion of heteroaryl β -esters with *tert*-butyl bromoacetate [59].

14.3.2

Gabapentin

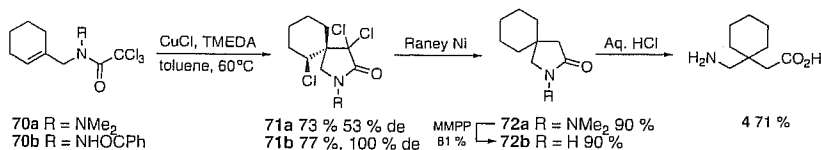
The original syntheses of gabapentin (**4**) starting from cyclohexanone, based on formation of the Guareshi salt and its conversion to a spiro anhydride, or a Knoevenagel condensation with ethyl cyanoacetate, have been reviewed [10]. Since the discovery of the anticonvulsant activity of gabapentin, a variety of analogs have been prepared, including alkyl substituted cyclohexanes [60–62], carboxylate bioisosteres including tetrazole and phosphonic acid [63], and conformationally restricted spiro and fused bicyclic compounds [64].

Cu(I)-mediated radical cyclization of halo-amides (**70**) has been utilized to afford functionalized pyrrolidinones via a 5-*exo*-trig radical cyclization pathway (Scheme 14.19). The chloro-substituted cyclohexyl pyrrolidinones (**71**) can be dechlorinated to the pyrrolidinone (**72**) and converted to gabapentin (**4**). The chlorine atoms potentially allow for the selective introduction of a variety of substituents at the 2- and 4-positions of gabapentin, providing a useful route to synthesizing substituted analogs [65]. The use of the benzoylamino group as the radical cyclization auxiliary facilitates concomitant dehalogenation and deprotection of the chlorinated *N*-substituted pyrrolidin-2-one (**72b**) using Raney nickel [66].

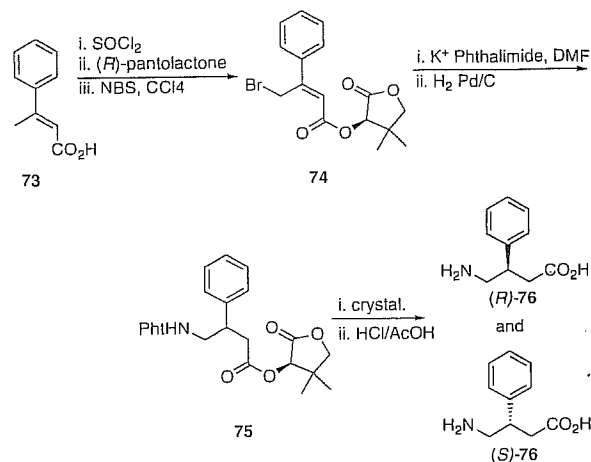
14.3.3

Baclofen and Analogs

Enantiomerically pure β -phenyl-GABA (**76**) was originally prepared via separation of (*R*)-(-)-pantolactone esters. Ethyl (*E*)-3-phenylbut-2-enoic acid (**73**) (Scheme 14.20) was synthesized by a modified Wittig–Horner reaction on acetophenone and



Scheme 14.19

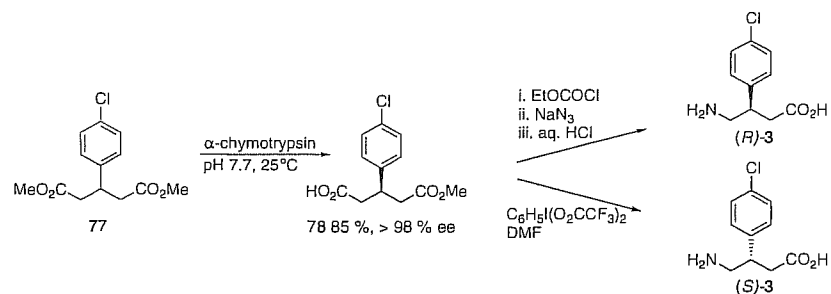


Scheme 14.20

subsequent alkaline hydrolysis of the ester product. Conversion to the (*R*)-(-)-pantolactone ester (**74**), allylic bromination, reaction with potassium phthalimide, and catalytic hydrogenation afforded a mixture of diastereoisomeric esters (**75**) that could be separated by crystallization. Acid hydrolysis of the resolved esters afforded the enantiomerically pure (*R*)- and (*S*)- β -phenyl-GABA (**76**) [67]. This methodology has also been applied to the synthesis of [³H] β -phenyl-GABA [68].

Resolution of racemic 4-nitro-3-(*p*-chlorophenyl)butanoic acid with (*R*)- or (*S*)-*R*-phenylpantolactam yields the corresponding (3*R*,3'*R*)- or (3*S*,3'*S*)-nitro esters with greater than 96% d.e. after column chromatography. Hydrolysis of the resulting diastereopure nitro esters yields the enantiopure nitro acids, which afford (*R*)- or (*S*)-baclofen after reduction of the nitro group to the amine [69]. (*R*)- and (*S*)-Baclofen have also been prepared in high enantiomeric purity by resolution of the (*S*)-(2)-phenylethylamine salt of 3-(*p*-chlorophenyl)glutaramic acid [70] and β -phenyl-GABA by chromatographic separation of (*R*)-phenylglycinol carboxamides of 4-phenylpyrrolidinone [71].

A variety of chemo-enzymatic methods have been used in the synthesis of baclofen and related analogs. Stereoselective enzymatic hydrolysis of dimethyl 3-(*p*-chlorophenyl)glutarate (**77**) by chymotrypsin afforded the chiral half-ester (**78**) in 85% yield and greater than 98% optical purity (Scheme 14.21). The carboxyl group of the product from the chymotrypsin reaction was converted to an amine with retention of configuration through a Curtius rearrangement and hydrolysis gave (*R*)-baclofen (*R*)-(3). Alternatively, ammonolysis of the ester produced the corresponding amide that was submitted to a Hofmann rearrangement and hydrolysis giving (*S*)-baclofen (*S*)-(3) [72, 73]. Similarly, chymotrypsin-mediated kinetic



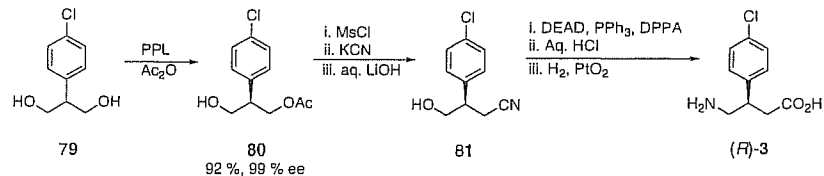
Scheme 14.21

resolutions of racemic of 3-phenyl- and 3-(*p*-chlorophenyl)-4-nitrobutyric acid methyl esters have also been reported to afford both enantiomers of β -phenyl-GABA and baclofen [74].

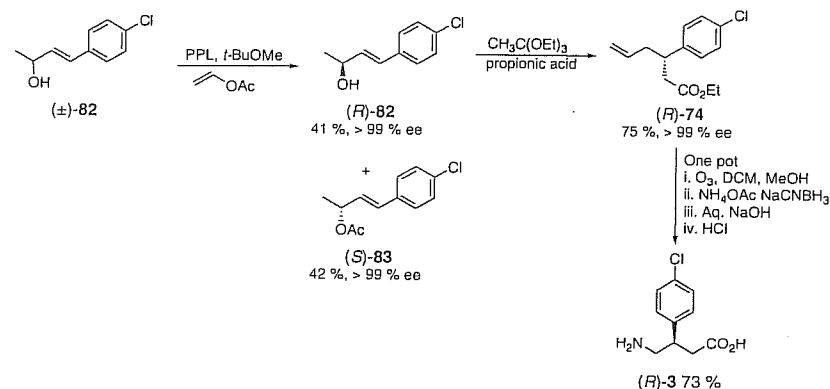
Another approach involves the lipase-mediated asymmetric acetylation of prochiral 2-(aryl)-1,3-propanediols (e.g., 79) (Scheme 14.22). The enantiomerically enriched monoacetate (80) is prepared in good chemical yield and high optical purity [73]. (*R*)-3-Acetoxy-2-(*p*-chlorophenyl)-1-propanol (80) was converted in a six-step sequence via the hydroxy nitrile (81) and an azido nitrile into (*R*)-baclofen (*R*)-3 [75].

The allylic alcohol (\pm)-82 undergoes porcine pancreatic lipase (PPL)-catalyzed kinetic resolution with vinyl acetate affording enantiomerically pure allylic alcohol (*R*)-82 and acetate (*S*)-83 (Scheme 14.23). An orthoester Claisen rearrangement of (*R*)-82 affords (*S*,*E*)- γ,δ -unsaturated esters (*R*)-84 with high stereoselectivity; (*R*)-84 was converted into (*R*)-3 through a one-pot reduction of an ozonolysis mixture followed by alkyl ester hydrolysis [76].

(\pm)-2-(*p*-Chlorophenyl)-4-pentenitrile undergoes enantioselective hydrolyses catalyzed by *Rhodococcus* sp. AJ270 microbial cells to afford excellent yields of enantiomerically pure (*R*)-(-)-2-(4-chlorophenyl)-4-pentenamides and (*S*)-(+)-2-(*p*-chlorophenyl)-4-pentenoic acids. Reduction of the amide to the amine and direct oxidation of the alkene afforded (*R*)-(-)-baclofen [77] in a manner analogous to that described for α -phenyl-GABA (29) (Scheme 14.7).



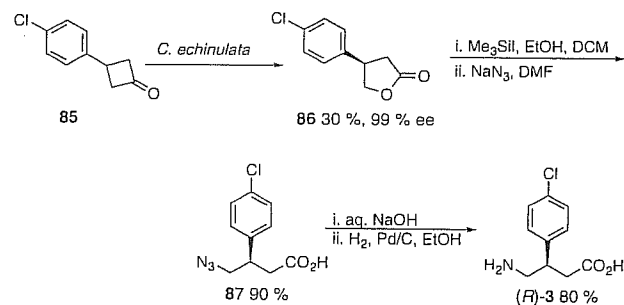
Scheme 14.22



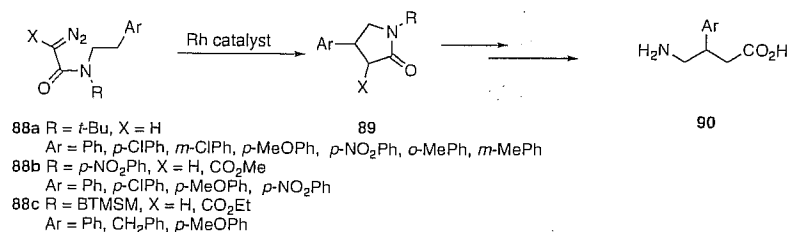
Scheme 14.23

A microbiological Baeyer–Villiger oxidation of the prochiral 3-(*p*-chlorobenzyl)-cyclobutanone (85) mediated by the fungus *Cunninghamella echinulata* yielded the optically pure lactone (86) in very high enantiomeric purity, although modest yield (30%) (Scheme 14.24). The lactone was further transformed to the target molecule (*R*)-baclofen (*R*)-3 via the azide (87) [78].

Rhodium-catalyzed site-selective intramolecular C–H insertion of a variety of α -diazoacetamides has been used to prepare the corresponding γ -lactams (89) that are hydrolyzed to the desired β -aryl GABA analogs (90). These include α -diazoacetamides (88a) prepared from *N*-*tert*-butyl amine with $\text{Rh}_2(\text{cap})_4$ catalyst (Scheme 14.25) [79], α -methoxycarbonyl- α -diazoacetamides (88b) [80], *N*-aryllalkyl, *N*-bis(trimethylsilyl) methyl α -diazoacetamides, and α -carboalkoxy- α -diazoacetamides (88c) [81]. Enantioselectivities of up to 69% were achieved by the use of the di-Rh(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] catalyst $\text{Rh}_2[(\text{S})\text{-PTTL}]_4$ [80, 81].



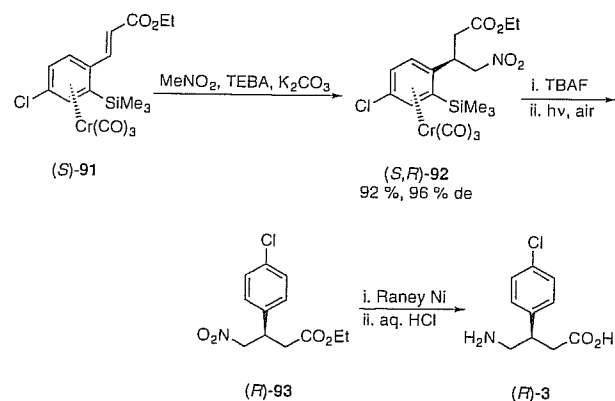
Scheme 14.24



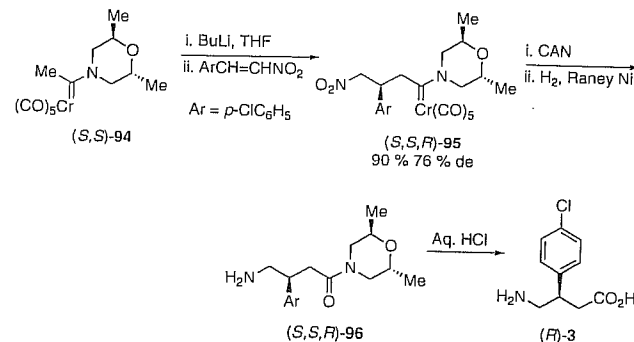
Scheme 14.25

Michael reactions using a variety of substrates as both acceptors and donors have been thoroughly explored as a methodology for the synthesis of β -aryl-GABA derivatives. These include the addition of anions of a chiral carbene to nitroolefins which proceed in low to moderate diastereomeric excess [82], catalytic conjugate addition of cyanide to β -substituted α,β -unsaturated *N*-acylpyrroles using a chiral gadolinium complex [83], addition of the Grignard cuprate (*p*-ClPh)₂CuMgCl to the (*S*)-pyroglutamic acid-derived γ -lactam [84], addition of aryl cuprates to (+)-4-cumyloxycyclopent-2-en-1-one [85], and conjugate addition of cyanide to α,β -unsaturated oxazolines derived from (*R*)-phenyl glycinoles [86].

Under phase-transfer conditions, Michael addition of nitromethane to enantiomerically pure tricarbonyl(ethyl-4-chloro-2-trimethylsilylcinnamate)Cr(0) (*S*)-(91) yielded the tricarbonylchromium nitroester (*S,R*)-(92) intermediate in good yield (88%) and high stereoselectivity (96% d.e.) (Scheme 14.26). Desilylation and decomplexation, afforded the nitrobutanoate (*R*)-(93). Hydrogenation over Raney nickel and subsequent hydrolysis then provided (*R*)-(3) [87].



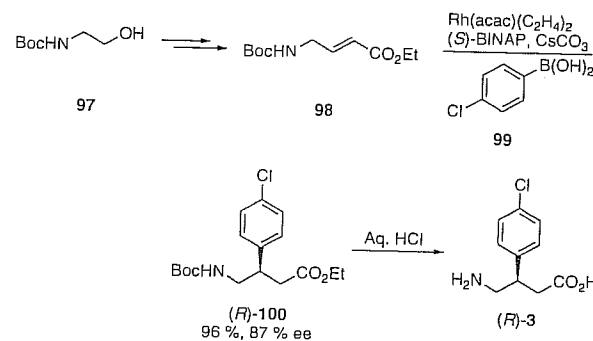
Scheme 14.26



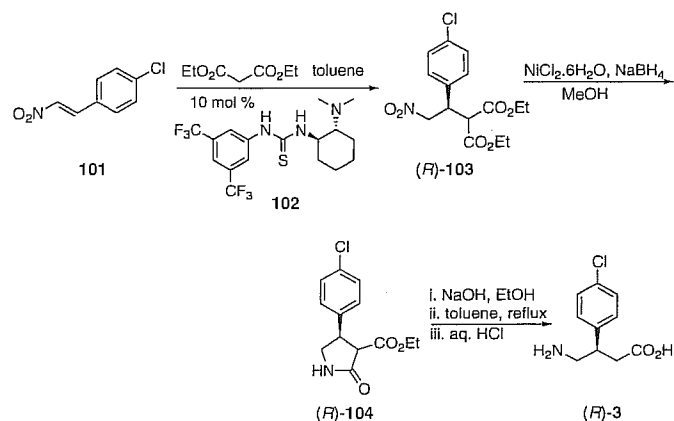
Scheme 14.27

Diastereoselective Michael addition of the conjugate base of the enantiopure chromium complex (*S,S*)-(94) to (*E*)-*p*-chloro-nitrostyrene provided enantiopure (*S,S,R*)-(95) (Scheme 14.27). The carbene complex was oxidized to the corresponding amide and the nitro group was converted to the amine providing (*S,S,R*)-(96). Deprotection of the carboxylic function by acid hydrolysis afforded (*R*)-(3) and the chiral auxiliary as hydrochloride salts which were separated by reverse-phase chromatography [88].

Rhodium-catalyzed asymmetric 1,4-additions of arylboronic acids to 4-amino-2,3-butenic acid derivatives (99) provides a short efficient synthesis of baclofen and related compounds (Scheme 14.28). Substrates were prepared in two steps from 2-aminoethanol derivatives (97). The conjugate addition of the arylboronic acid (98) was carried out in the presence of Rh(acac)(C₂H₄)₂, and (*S*)-2,2'-bis(diphenylphosphino)1,1'-binaphthyl (BINAP), affording the protected amino acid (*R*)-(100) in good yield and enantiopurity. Compound (100) can be converted to (*R*)-3 [89, 90].



Scheme 14.28



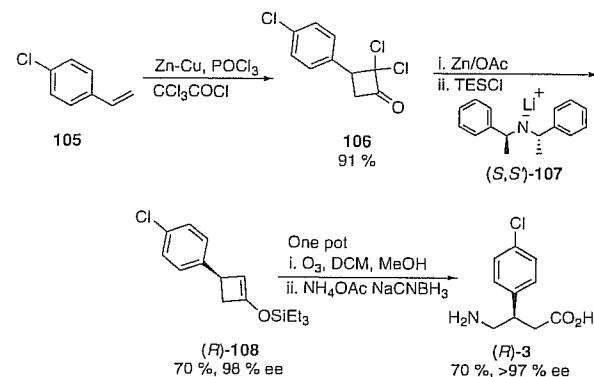
Scheme 14.29

1,4-Addition of diethyl malonate to the nitroolefin (101) in the presence of 10 mol% of the novel thiourea catalyst (102) affords the adduct (103) in 80% yield with 94% e.e. (>99% e.e. after a single recrystallization) (Scheme 14.29). Reduction of the nitro group with nickel borite and *in situ* lactamization gave the lactam (104) in 94% yield. Ester and lactam hydrolysis and decarboxylation afforded (R)-3 [91].

Chiral rhodium complexes have been employed to effect enantioselective reductions of both ketones and alkenes in the synthesis of baclofen. Enantioselective hydrogenation of ethyl 3-(4-chlorophenyl)-3-oxopropanoate using (S)-BINAP-Ru(II) complex (800 psi) affords the corresponding (R)-hydroxy ester in 95% yield and 96% e.e., the hydroxy ester was converted to (R)-3 in four steps, 26% overall yield and 90% e.e. Alternatively, (S)-BINAP-Ru(II) catalyzed hydrogenation (200 psi) of ethyl 4-azido-3-(4-chlorophenyl)but-2-enoate yields the alkyl azide (200 psi), which was hydrolyzed to (R)-3 [92]. Similarly, (Z)-3-(4-chlorophenyl)-4-phthalimidobut-2-enoate ester has been reduced to the protected baclofen derivative using a range of modular chiral BoPhoz-type phosphine-aminophosphine ligands with high yields and enantioselectivities (800 psi) [93]. However, the high pressures required for ruthenium catalyzed reductions limit their utility.

A [2 + 2] cycloaddition of 4-chlorostyrene (105) and dichloroketene yields (±)-2,2-dichloro-3-(p-chlorophenyl)cyclobutanone (106) (Scheme 14.30), which provides an efficient and novel route to (R)-3. Reductive dechlorination and subsequent enantioselective deprotonation with the lithium (S,S')-di(α-methylbenzyl)amide (S,S')-(107) and trapping of the resulting enolate with triethylsilyl chloride provided the silylenol ether (R)-108. A one-pot ozonolysis and reductive amination afforded (R)-3 [94].

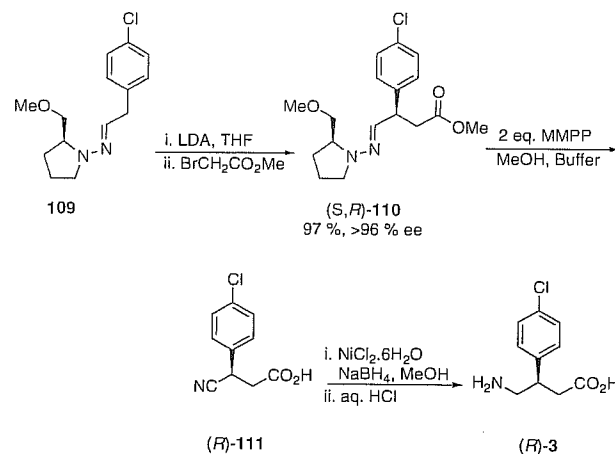
α-Alkylation of (S)-1-amino-2-methoxymethylpyrrolidine (SAMP)-hydrazone with methyl bromoacetate has been used to provide a range of β-substituted GABA analogs



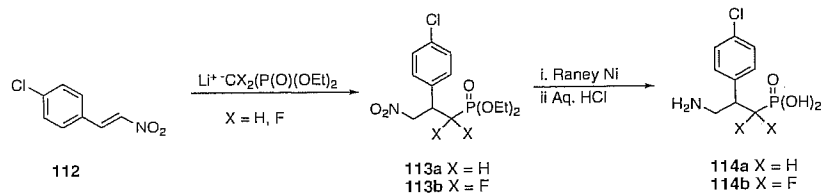
Scheme 14.30

in excellent enantiomeric purity (Scheme 14.31). Alkylation of p-chlorophenyl aldehyde SAMP-hydrazone (109) affords the α-substituted aldehyde hydrazone (S,R)-110 in excellent yield and diastereoselectivity. Oxidative removal of the chiral auxiliary yields the nitrile (R)-111 which was reduced with nickel borite and hydrolyzed to (R)-3 [95].

Baclofen has recently been prepared using Sharpless asymmetric dihydroxylation methodology to introduce the chiral centre. Asymmetric dihydroxylation of (E)-ethyl



Scheme 14.31



Scheme 14.32

p-chlorocinnamate affords the dihydroxy ester which was converted to (*R*)-**(3)** in 14% overall yield and 85% e.e. [96].

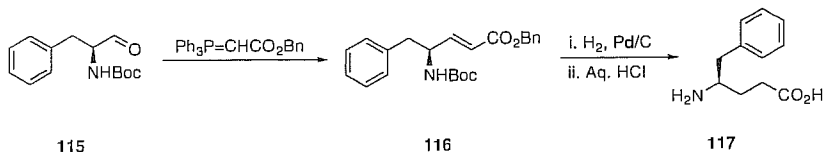
The synthesis of a wide range of baclofen analogs has also been described including the phosphonic analog, phaclofen [97], iodobaclofen [98], heterocyclic analogs [99, 100], hydroxysaclofen [101, 102], homologs [103–106], pyrrolidinone analogs [107], and conformationally restricted derivatives [108, 109]. A highly efficient three-step synthesis of the phosphonic analog of baclofen, (\pm)-phaclofen (**114a**) [110] and its α,α -difluoro analog (**114b**) has been reported (Scheme 14.32) [111]. The key step is a Michael addition of the lithium anion of diethyldifluoromethane-phosphonate to a *p*-chloro- β -nitro styrene (**112**). Reduction of the nitro functionality and ester hydrolysis of (**113**) affords the desired phosphonic amino acids (**114**).

14.4

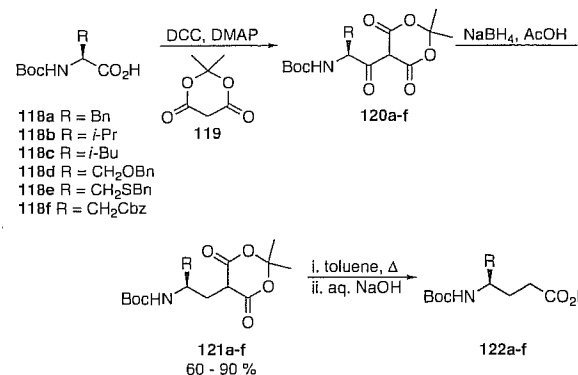
γ -Substituted γ -Amino Acids

γ -Substituted γ -amino acids have been prepared via a two-carbon homologation of α -amino acids using a variety of methodologies. The traditional method being a double Arndt–Eistert homologation in which the multistep sequence can result in low yields [103]. Alternatively, a Wittig reaction with an alkyl (triphenylphosphoranyliden)acetate on α -amino aldehydes such as phenylalaninal (**115**) and subsequent reduction of the resulting alkene (**116**) has been employed (Scheme 14.33). Hydrolysis of the protecting group affords the γ -substituted γ -amino acid (**117**) [112].

A facile procedure for a two-carbon homologation involves coupling of an *N*-Boc- α -amino acid (**118**) with Meldrum's acid (**119**) and complete reduction of the keto



Scheme 14.33

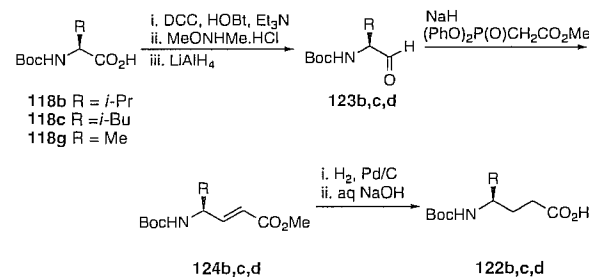


Scheme 14.34

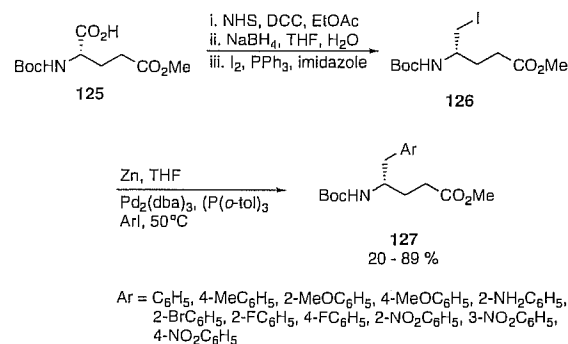
functionality of the α -amino acyl compound (**120**) (Scheme 14.34). The resulting amino alkyl Meldrum's acid (**121**) undergoes thermal decarboxylative ring closure to a 5-substituted pyrrolidinone that yields the corresponding γ -amino acid (**122**) after hydrolysis. The overall yields of the procedure ranges from 40 to 65% [113].

Alternatively, *N*-Boc- α -amino acids (**118**) have been converted to the corresponding Weinreb amides and then reduced to the α -amino aldehydes (**123**) (Scheme 14.35). Olefination yielded the α,β -unsaturated *N*-Boc-protected γ -amino acid methyl esters (**124**) as *trans/cis* mixtures. Hydrogenation with Pd/C and saponification produced the desired Boc-protected γ -amino acids (**122**) in 55–72% yield [114].

The use of glutamic acid derivatives provides access to γ -substituted γ -amino acids of the opposite chirality to those derived from α -amino acids. The iodozinc derivative of (**126**) prepared in three steps from the protected L-glutamic acid (**125**)



Scheme 14.35

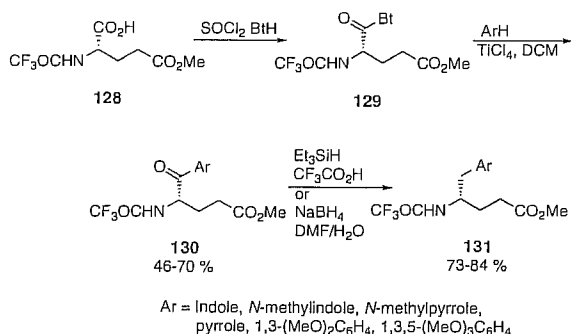


Scheme 14.36

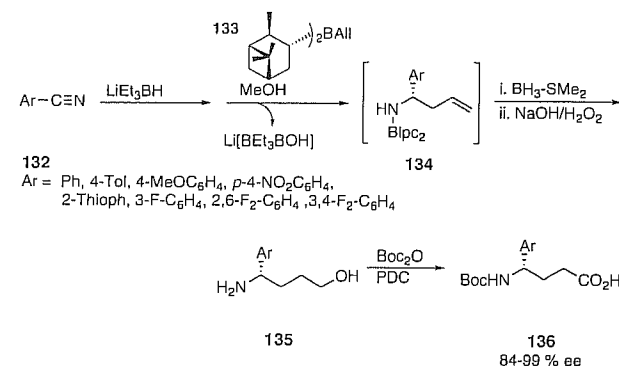
has been reported to undergo coupling with a range of substituted aryl iodides to afford enantiopure γ -aryl substituted GABA (127) derivatives in moderate to good yields (Scheme 14.36) [115, 116].

A range of hetero- and benzenoid-aromatics undergo Friedel–Crafts reactions with chiral N -protected (α -aminoacyl)benzotriazoles (129), prepared in three steps from L-glutamic acid derivatives (128) (Scheme 14.37). The resulting α -amino ketones (130) are reduced to yield the corresponding γ -amino acid derivatives (131), in moderate to good overall yields with preservation (>99%) of chirality [117].

A range of N -protected γ -aryl GABA (136) derivatives have been synthesized in good yields without loss of optical activity in a three-step, one-pot process [118]. Sequential reduction of benzonitriles (132) with trialkylborane (133) and methanolysis, allylboration and hydroboration of the intermediate (134) yields the δ -amino alcohols (135) (Scheme 14.38). The aldimine–borane adducts were prepared by room



Scheme 14.37



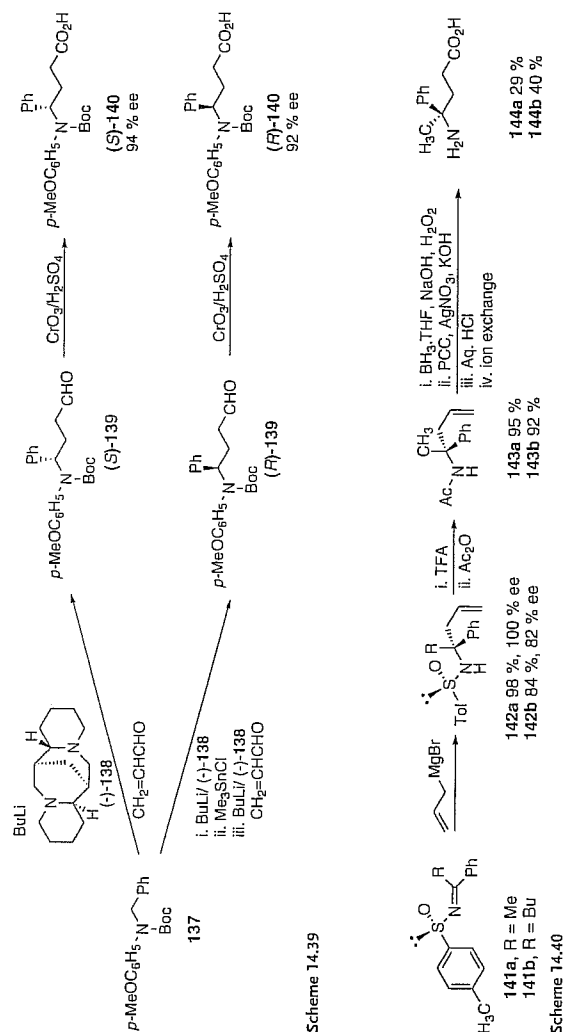
Scheme 14.38

temperature reduction of the nitrile (132) with Super-Hydride. Addition of one equivalent of methanol results in the formation of the aldimine–triethylborane complex (134), which undergoes allylboration and hydroboration. Direct oxidation of the hydroboration product (135) directly to the GABA derivatives with Pyridinium dicarbonate (PDC) resulted in a mixture of products. Therefore, the δ -amino alcohols were protected as the N -Boc derivatives and then oxidized to the corresponding GABA derivatives (136) [118].

The use of $n\text{BuLi}/(-)$ -sparteine $(-)$ -138 as a chiral base in an asymmetric deprotonation and electrophilic substitution sequence has also been used in the synthesis of enantiomerically pure γ -phenyl-GABA (Scheme 14.39). Alkylation of N -Boc- N -(p -methoxyphenyl)benzylamine (137) with acrolein and Jones oxidation of the aldehyde (139) yields (S)- N -protected γ -phenyl-GABA (S)-(140) in 77% overall yield. Alternatively, a lithiation–stannylation–transmetalation protocol yields (R)- N -protected γ -phenyl-GABA (R)-(140) after oxidation in 46% overall yield [119].

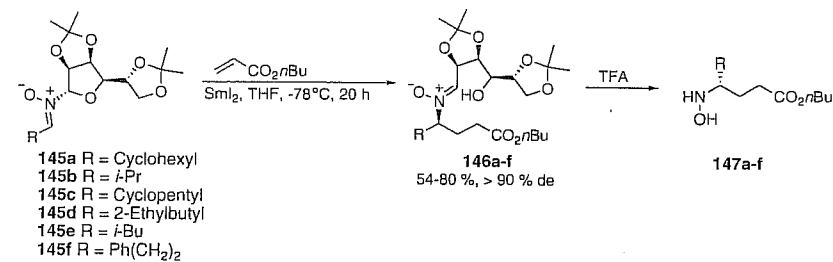
Chiral N -benzylidene- p -toluenesulfonamides (141) prepared by the reaction of benzonitrile with an allyllithium followed by the addition $(-)$ -menthyl (S)- p -tolylsulfinate have been used to induce chirality in the synthesis of γ -amino acids (Scheme 14.40). Reaction with allylmagnesium bromide gave adducts (142) with excellent stereoselectivity. Transformation to the N -acetyl derivative (143), oxidation and deprotection afforded enantiomerically pure aryl, alkyl-disubstituted γ -amino acid derivatives (144) [120].

γ -Substituted γ -amino acids have also been prepared by olefination of β -enamino phosphorus compounds with alkyl glyoxylates and selective reduction of the resulting 1-azadienes with NaBH_4 to yield (E)- γ -amino- α,β -unsaturated esters, which can be further reduced to the corresponding saturated γ -amino esters [121]; 1,4-addition of carbon radicals, generated from a Barton ester derivative of α -amino acids, to form acrylic derivatives [122], and samarium iodide promoted addition of alkyl nitrones to α,β -unsaturated amides and esters [123]. In the presence of N -substituted sugars as



Scheme 14.39

Scheme 14.40



Scheme 14.41

chiral auxiliaries (145) this reaction provides access to variously substituted nitrones (146) with high diastereoselectivity (diastereomeric ratio > 95:5) (Scheme 14.41). Acid hydrolysis affords the *N*-hydroxyl amino acid derivatives (147) [124].

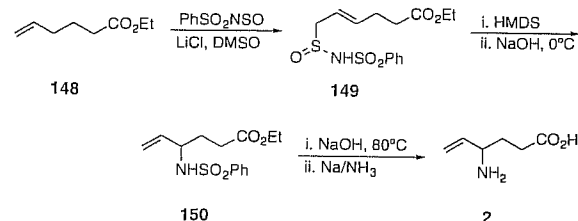
14.4.1

Vigabatrin

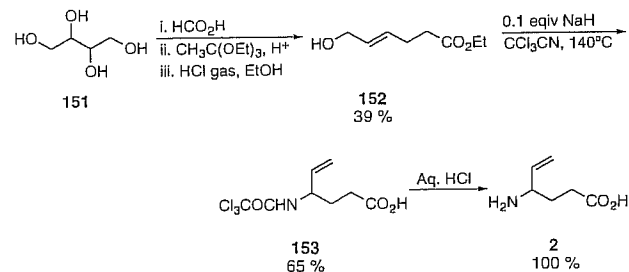
4-Amino-5-hexenoic acid (vigabatrin) (2) was originally synthesized via Birch reduction of racemic 4-amino-5-hexenoic acid or semihydrogenation of methyl 4-amino-5-hexenoate using Lindlar's catalyst and subsequent acid hydrolysis [9]. (\pm)-Vigabatrin has also been prepared by reaction of ethyl hexenoate (148) with *N*-sulfinyl benzenesulfonamide (Scheme 14.42). The adduct (149) undergoes a [2,3] sigmatropic rearrangement on silylation. The resulting allylamine derivative (150) can then be converted to vigabatrin (2) by deprotection in 26.5% overall yield [125].

Ethyl 6-hydroxyhex-4-enoate (152), prepared in three steps from erythritol (151), undergoes an Overman rearrangement on heating in trichloromethyl acetimidate, introducing the amine functionality (Scheme 14.43). Deprotection of (153) afforded (\pm)-vigabatrin (2) in 25% overall yield [126].

[^{14}C]Vigabatrin was synthesized in five steps from the tosylate (154) and [^{14}C] NaCN. After displacement of the tosylate by cyanide, reduction of the resulting nitrile (155) in the presence of excess dimethylamine gave the amine, which was



Scheme 14.42



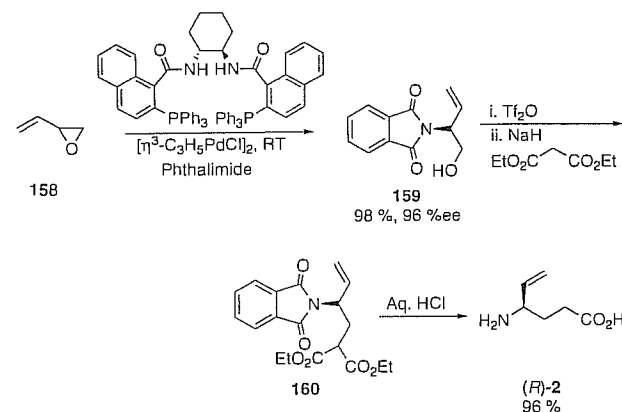
Scheme 14.43

oxidized to the *N*-oxide (156) (Scheme 14.44). Elimination to the alkene (157) and acid hydrolysis afforded an vigabatin (2) with an overall radiochemical yield of 22% and radiochemical purity greater than 98% [127].

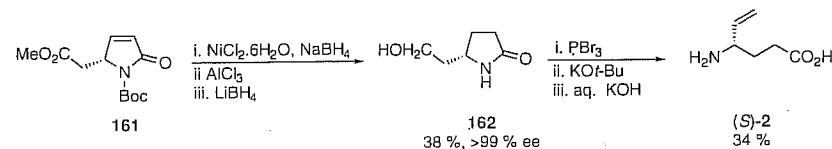
(*S*)-Vigabatin (*S*)-2 has been prepared in 38% overall yield and 90% enantiomeric purity via a Wittig reaction of the ω -aldehyde of glutamic acid and methyl triphenylphosphonium bromide [128]. Alternatively, both enantiomers of vigabatin have been prepared in five steps from (*R*)- or (*S*)-methionine, respectively, via a two-carbon homologation. Formation of the γ -lactam, oxidation of the thiol to the sulfoxide and thermal elimination afforded the 5-vinyl- γ -lactam, which was hydrolyzed to vigabatin [129].

Catalytic deracemization of butadiene monoepoxide (158) using a palladium catalyzed asymmetric allylic alkylation yields optically pure 2-phthalimido-but-3-en-ol (159) (Scheme 14.45). Conversion to the triflate and substitution with the anion of diethyl malonate yielded the diester (160). Deprotection and concomitant decarboxylation affords (*R*)-vigabatin (*R*)-2 in 59% overall yield and high enantiopurity. Use of the other enantiomer of the catalyst would afford (*S*)-vigabatin (*S*)-2 [130, 131].

Starting from inexpensive pyrrole, a four-step synthesis of both isomers of *N*-Boc-protected 3,4-didehydropyrrohomoglutamate (161) in 91% e.e., involving resolution by simulated moving bead chromatography, has been reported (Scheme 14.46). Conjugate reduction of the enone, deprotection of the amine, and subsequent reduction of the methyl ester gave the alcohol (162). The final transformation to (*S*)-vigabatin (*S*)-2 was carried out by a three-step protocol, forming first the



Scheme 14.45



Scheme 14.46

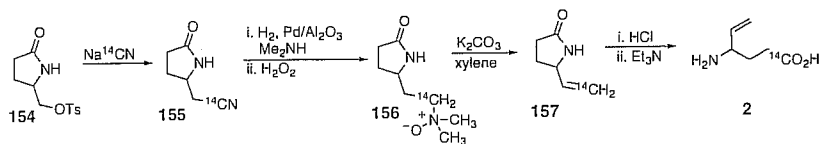
bromide, followed by dehydrobromination, and finally hydrolysis of the vinylpyrrolidinone to yield (*S*)-2 [132].

(*S*)-Vigabatin (*S*)-2 has been prepared via multistep syntheses employing Sharpless epoxidation of 5-phenylpent-2-en-1-ol [133] and Sharpless asymmetric aminohydroxylation of ethyl 6-hydroxyhex-2-enoate as the sole source of chirality [134], and the addition of alkyl 3-lithiopropiolates [135] or SmI_2 -catalyzed addition of methyl acrylate [136] to the nitron of *D*-glyceraldehyde. The cyclopropane analog of vigabatin, (\pm)- γ -amino- γ -cyclopropylbutanoic acid, has been prepared in six steps via a Mannich reaction of malonic acid, cyclopropanecarbaldehyde, and ammonium acetate, and subsequent Arndt-Eistert homologation [137].

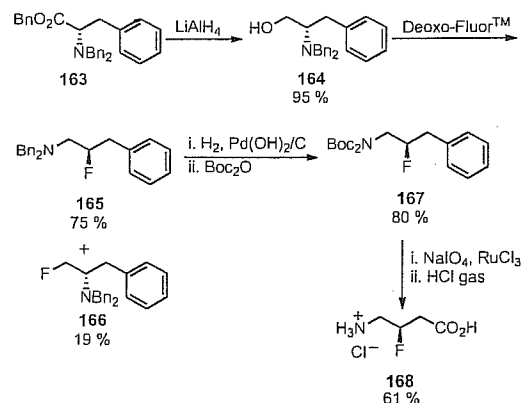
14.5

Halogenated γ -Amino Acids

γ -Amino- α -fluorobutanoic acid [(\pm)- α -fluoro-GABA] has been prepared by the addition of the sodium salt of diethylfluoromalonate to *N*-(*p*-nitrobenzoyl)aziridine yielding diethyl 2-(*p*-nitrobenzamido)ethylfluoromalonate, which undergoes acid hydrolysis to afford (\pm)- α -fluoro-GABA [138].



Scheme 14.44



Scheme 14.47

The synthesis of (*R*)- β - and (*S*)- β -fluoro-GABA (168) was initiated from (*R*)- or (*S*)-phenylalanine, respectively (Scheme 14.47). Tribenzyl protection of phenylalanine gave the *N,N*-dibenzyl benzyl ester (163), which was followed by reduction of the ester with LiAlH_4 to generate the *N,N*-dibenzyl alcohol (164). Treatment of the alcohol with Deoxo-Fluor gave rise to a 4:1 mixture of the separable regioisomeric products (165) and (166). Conversion of the dibenzyl amine moiety to the di-Boc-protected amine (167) allowed successful oxidation of the phenyl group and deprotection to afford the respective isomer as the hydrochloride salt (168) [139].

(\pm)- β -Chloro-GABA has been prepared by treatment of methyl β -hydroxy- γ -aminobutyrate with excess PCl_5 [140], and photochlorination of GABA using chlorine gas in concentrated HCl and photolysis with a mercury arc lamp [141].

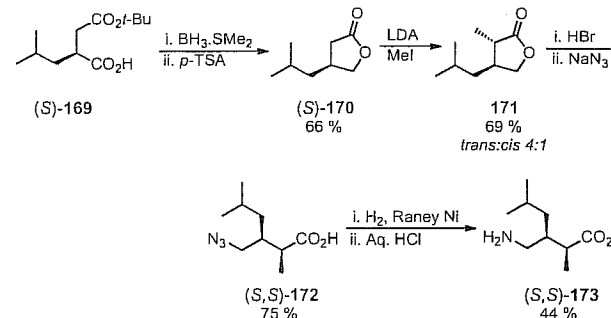
14.6

Disubstituted γ -Amino Acids

14.6.1

α,β -Disubstituted γ -Amino Acids

Only limited reports of α,β -substituted GABA analogs exist. A range of α,β -dialkyl substituted GABA derivatives were initially prepared by Raney nickel reduction of the corresponding γ -nitro acids [142]. The α -methyl analog of pregabalin has been reported [143]. Reduction of the carboxylic acid of (*S*)-169 and cyclization yields the γ -lactone (*S*)-170 (Scheme 14.48). Reaction of the lithium enolate of (*S*)-170 with methyl iodide results in a 4:1 mixture of *trans: cis* isomers (171). Separation of the *trans* isomer and conversion to the azide in two steps yields the azidoester (*S,S*)-172. Reduction of the azide and hydrolysis of the lactam affords (*S,S*)- α -methyl pregabalin (*S,S*)-173 [143].



Scheme 14.48

14.6.2

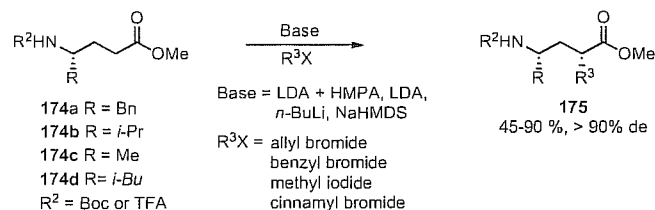
α,γ -Disubstituted γ -Amino Acids

Alkylation, under a range of conditions, of the enolates of methyl *N*-protected γ -amino esters (174) affords the *syn*-2,4-disubstituted products (175), through 1,3-asymmetric induction (Scheme 14.49) [144, 145].

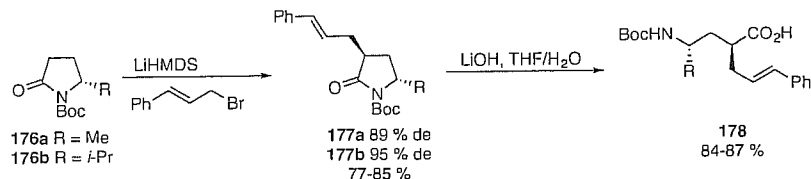
Alternatively, reaction of pyrrolidine-derived lithium enolates (176) with cinnamyl bromide yields the *anti*-disubstituted γ -lactams (177) with high diastereoselectivities (Scheme 14.50). Basic hydrolysis affords the *anti*-2,4-disubstituted *N*-Boc- γ -amino acids (178) [146].

(*R,S*)-Dimethyl-GABA has been prepared from *N*-Boc-L-alaninal (179) via a Horner-Emmons-Wadsworth reaction, yielding the unsaturated (*E*)-ester (180) as the major product (Scheme 14.51). Hydrogenation resulted in a 2:1 mixture of *anti: syn* products. However, conversion to the γ -lactam (181), subsequent hydrogenation, and hydrolysis yielded the *syn* compound (182) as the major product [147]. Coupling to L-serine methyl ester gave dipeptides that were readily separable by chromatography [148].

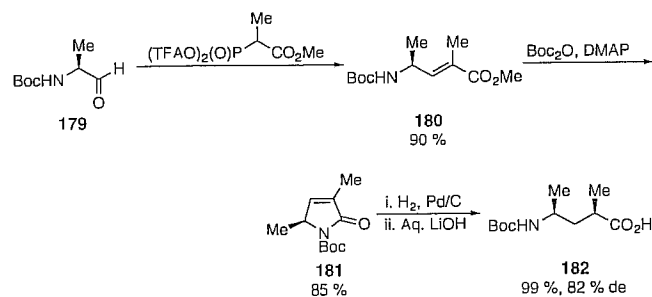
A highly diastereoselective manganese-mediated photolytic addition of alkyl iodides to the $\text{C}=\text{N}$ bond of chiral hydrazones (183), provides enantiomerically pure



Scheme 14.49



Scheme 14.50

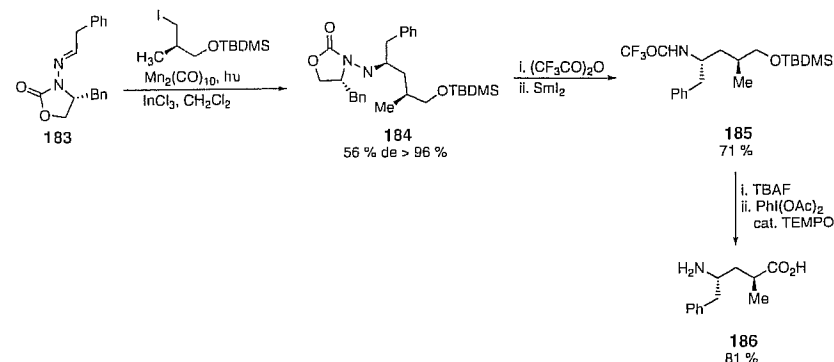


Scheme 14.51

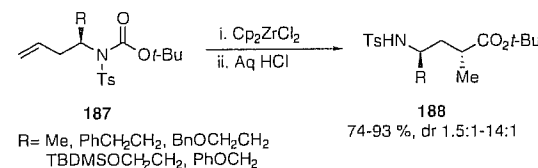
adducts (184) (Scheme 14.52). Reductive N–N bond cleavage yields the amine (185). Deprotection of the alcohol and then oxidation affords *anti*-2,4-disubstituted γ -amino acids such as tubuphenylalanine (186) [149].

Zirconium-mediated diastereoselective alkene–carbonyl coupling reactions using chiral *tert*-butyl 3-butenylcarbamates (187) having a substituent at the homoallylic position proceed in a highly diastereoselective manner to give α -methyl- γ -substituted γ -amino acid derivatives (188) (Scheme 14.53) [150].

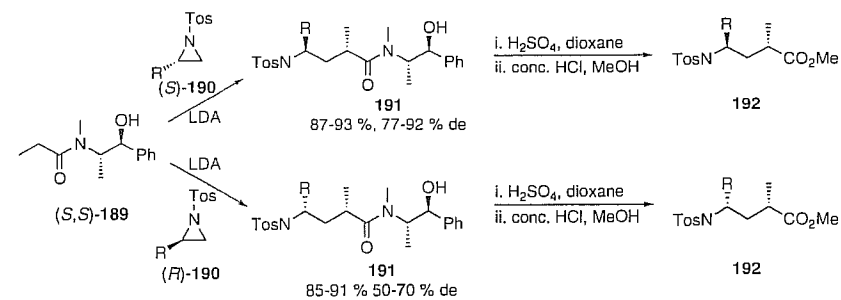
Stereocontrolled aziridine ring-opening reactions with chiral enolates derived from (*S,S*)-(+)-pseudoephedrine amides (189) lead to γ -amino amides in good yields (Scheme 14.54). The diastereoselectivity of the reaction is controlled by the presence of the chiral auxiliary on the enolate, although the stereogenic center contained in the structure of the aziridine has a strong influence on the stereochemical course of the reaction which results in matched and mismatched combinations. The enolates derived from (*S,S*)-(+)-pseudoephedrine propionamide (*S,S*)-(189) and (*S*)-aziridines (*S*)-(190) form a matched combination leading to γ -aminoamides with a 1,3-*syn* configuration (191) in good diastereomeric excess. On the contrary, the same enolate and (*R*)-aziridines (*R*)-(190) form a mismatched combination leading to the corresponding adducts (191) with a relative 1,3-*anti* configuration with moderate to poor diastereoselectivity. Hydrolysis and esterification affords the amino acid derivatives (192) [151].



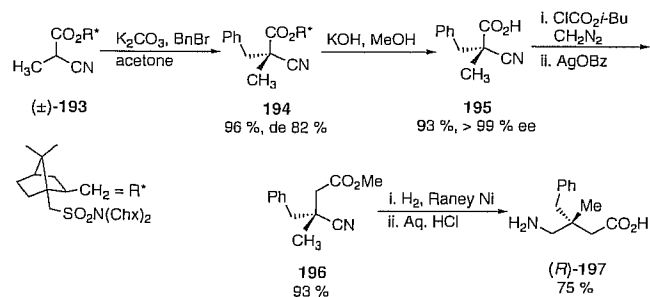
Scheme 14.52



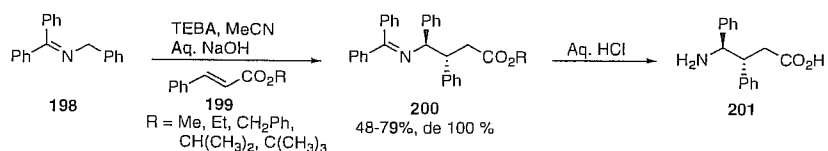
Scheme 14.53



Scheme 14.54



Scheme 14.55



Scheme 14.56

14.6.3

 β,β -Disubstituted γ -Amino Acids

Enantiomerically pure (*R*)- γ -amino- β -benzyl- β -methylbutyric acid (*R*)-197 has been efficiently synthesized using an Oppolzer chiral auxiliary derivative (193) (Scheme 14.55). Diastereoselective benzylation of the chiral enolate gives the product (194) in excellent yield and good diastereomeric excess. Isolation of the major isomer by recrystallization and cleavage of the chiral auxiliary yields the enantiomerically pure acid (195). Arndt-Eistert homologation yields the methyl ester (196). Reduction of the nitrile and acid hydrolysis afforded (*R*)-197 in 65% overall yield [152].

14.6.4

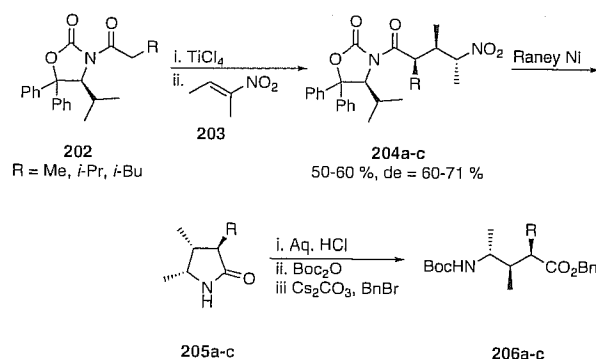
 β,γ -Disubstituted γ -Amino Acids

Phase-transfer catalyzed reaction of the Schiff's base *N*-(diphenylmethylene)benzylamine (198) with cinnamates (199) and hydrolysis of the resulting adduct (200) affords *threo*-4-amino-3,4-diphenylbutanoic acid (201) (Scheme 14.56) [153].

14.7

Trisubstituted γ -Amino Acids

(*R,R,R*)-Trialkyl- γ -amino acids have been prepared by the stereoselective Michael addition of modified Evans acyloxazolidinones with nitroolefins (Scheme 14.57).



Scheme 14.57

Reaction of the titanium enolate of the acyloxazolidinones (202) with (*E*)-2-nitro-2-butene (203) yielded the nitro derivatives (204a-c) in moderate diastereomeric excess, which were separable by chromatography. Raney nickel reduction which was accompanied by some epimerization, afforded the pyrrolidinones (205a-c), which were hydrolyzed and converted to the protected amino acid derivatives (206a-c) [154, 155].

14.8

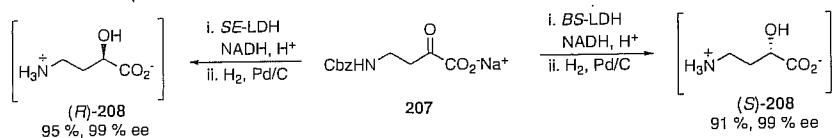
Hydroxy- γ -Amino Acids

14.8.1

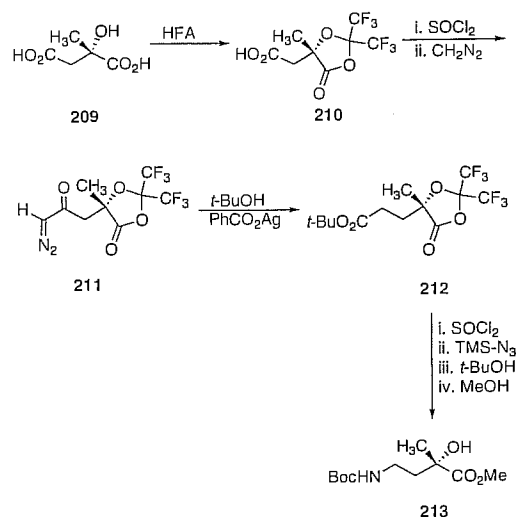
 α -Hydroxy- γ -Amino Acids

(\pm)- α -Hydroxy- γ -amino acid (homoisoserine, α -hydroxy-GABA) (208) was originally prepared by dehydration of L-2-hydroxysuccinamic acid and catalytic reduction of the ω -cyano acid [156] or by hydrogenolysis of a racemic isoxazolidine carboxylic acid [157]. A number of chemo-enzymatic syntheses of α -hydroxy-GABA have also been reported including reduction of *N*-(benzyloxycarbonyl) methyl 4-amino-2-oxobutanoate with baker's yeast [158] and various *Saccharomyces* sp. [159]. These reductions proceeded with poor yields and only moderate enantioselectivity. However, lactate dehydrogenase from *Bacillus stearothermophilus* and *Staphylococcus epidermidis* catalyzed reductions of the sodium 4-benzyloxycarbonylamino-2-oxobutanoate (207) have been used to prepare both (*S*)- and (*R*)-benzyloxycarbonylamino-2-hydroxybutanoic acids, respectively (Scheme 14.58). Deprotection affords the corresponding (*S*)- α -hydroxy-GABA (*S*)-208 and (*R*)- α -hydroxy-GABA (*S*)-208 [160].

Fully protected L- α -methyl-homoisoserine (α -hydroxy- α -methyl-GABA) (213) has been prepared in seven steps from L-citramalic acid (209), via protection of the α -hydroxyl and adjacent carboxylic acid as the 2,2-bis(trifluoromethyl)-1,3-dioxalane (210) (Scheme 14.59). Conversion to the diazoketone (211) and Wolff



Scheme 14.58



Scheme 14.59

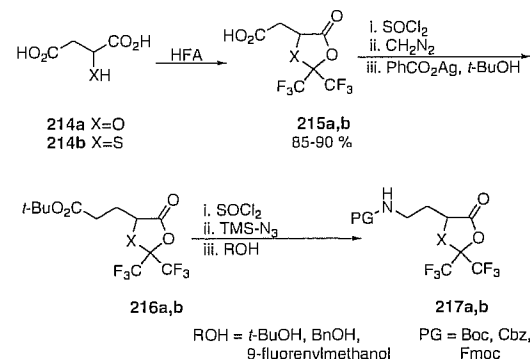
rearrangement yields the homolog (207). Curtius rearrangement and protection affords (213) [161].

α -Hydroxy and α -mercapto acids (214) react with hexafluoroacetone to give 2,2-bis(trifluoromethyl)-1,3-dioxolan-4-ones (215a) and 2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-ones (215b), respectively, in excellent yields (Scheme 14.60). Arndt-Eistert homologation yields the methyl esters (216). Treatment with thionyl chloride, reaction with trimethylsilyl azide, and Curtius rearrangement affords protected homoisoserine (217a) and homoisocysteine (217b) [18].

14.8.2

β -Hydroxy- γ -Amino Acids

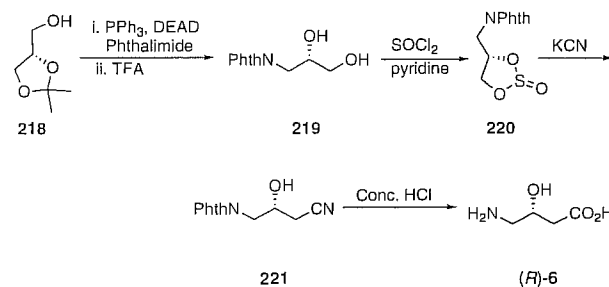
Enantiomerically pure (*R*)- and (*S*)-GABOB (6) have been prepared via chromatographic separation of the oxazolidin-2-ones formed from (*S*)-ethyl 4-(1-phenylethylamino)but-2-enoate [162]. Alternatively, reaction of trimethylamine and



Scheme 14.60

L-tartaric acid with epichlorohydrin yields the (3-chloro-2-hydroxypropyl)trimethylammonium tartrate salts which were resolved by crystallization and converted to enantiomerically pure (*R*)-carnitine in two steps [163].

GABOB and carnitine have been prepared from a wide variety of chiral starting materials. Both isomers of glycerol acetonide have been used in the syntheses of (*R*)-GABOB. (*R*)-Glycerol acetonide, prepared in two steps from ascorbic acid, was converted to (*R*)-GABOB in seven steps and 10% overall yield [164]. However, later reports suggest that a hydrolysis using 98% H₂SO₄ results in significant racemization [165]. Alternatively, (*S*)-glycerol acetonide (218) prepared from D-mannitol was transformed to (*R*)-GABOB (*R*)-(6) via conversion to the phthalimide (219) and subsequent formation of the cyclic sulfite (220) (Scheme 14.61). Reaction with potassium cyanide yielded the hydroxy nitrile (221) which was hydrolyzed to (*R*)-(6) in 37.5% overall yield [166].



Scheme 14.61

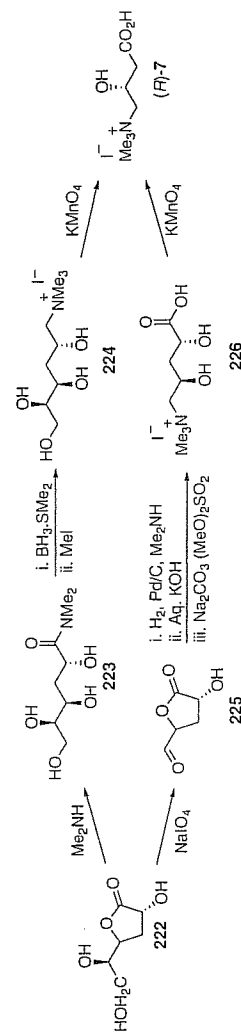
Bols *et al.* have described the use of 3-deoxy-D-galactono-1,4-lactone (222) in two simple syntheses of (*R*)-carnitine (*R*)-(7) (Scheme 14.62). In the first route, treatment of the lactone (222) with dimethylamine, reduction of the amide (223) with borane-dimethylsulfide and methylation yielded the trimethylammonium iodide (224) that underwent oxidative cleavage of the polyol chain with KMnO_4 to afford (*R*)-(7) in 58% overall yield. In the alternative approach, the C-5–C-6 bond of the diol (222) was cleaved with NaIO_4 , giving a quantitative yield of the aldehyde (225) that was hydrogenated in the presence of methylamine, hydrolyzed, and quarterized to the trimethylammonium salt (226), which then underwent oxidative cleavage to give (*R*)-(7) [167].

Chemoselective opening of (*R*)-3-hydroxy- γ -butyrolactone (*R*)-(227) with trimethylsilyl iodide, treatment of the resulting iodide (228) with sodium azide, ester hydrolysis, and reduction of the azide (229) afforded (*R*)-GABOB (*R*)-(6) in 56% overall yield and 99% e.e. (Scheme 14.63) [168]. Conversely, (*S*)-3-hydroxy- γ -butyrolactone (*S*)-(227) has been transformed into (*R*)-(6) via opening of (*S*)-(227) with HBr , conversion of the bromide (230) to the epoxide (231), and opening of the epoxide with cyanide to yield the cyano ester (215). Subsequently, (215) can be converted to (*R*)-(6) via a Curtius reaction of the ester and hydrolysis of the nitrile, resulting in a net inversion of stereochemistry to afford (*R*)-(6) [169].

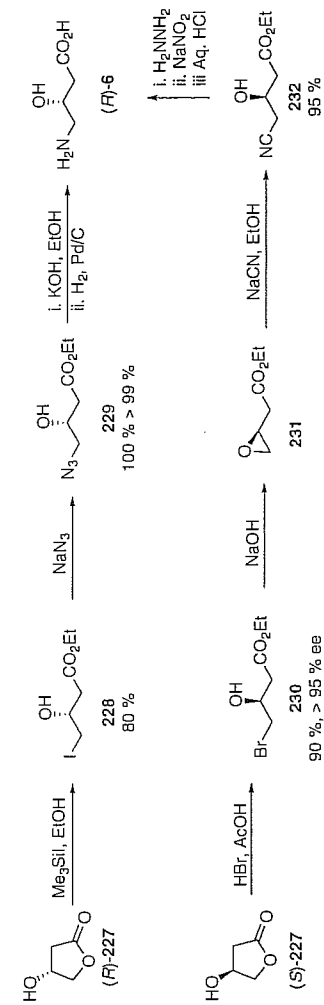
Commercially available (*R*)- and (*S*)-ethyl 4-chloro-3-hydroxybutyrate (233) are reacted with phenyl selenide anions to give the corresponding β -hydroxyalkyl phenylselenides (Scheme 14.64). Reaction with benzoyl isocyanate yields the *N*-benzoyl-carbamate derivative (234) that undergoes cyclization to the oxazolidin-2-one (235) on treatment with *m*-chloroperoxybenzoic acid. Hydrolysis affords optically pure (*R*)- or (*S*)-GABOB (6) [170].

A number of syntheses of enantiomerically pure GABOB (6) and carnitine (7) from malic acid (236) have been reported [171–174]. These include a seven-step synthesis via a cyclic anhydride [171], and a 13-step [172] and later six-step synthesis [173] via an oxazolidin-2-one. Both (*R*)- or (*S*)-carnitine (7) have been synthesized from the respective enantiomer of malic acid (236) (Scheme 14.65). Conversion to the dibenzyl ester (237) and chemoselective reduction of the α -hydroxyester group yielded a diol, which was converted to the monotosylate (238). Substitution with trimethylamine gave a carnitine derivative that was deprotected to afford the corresponding isomer of carnitine (7) in good overall yield [174].

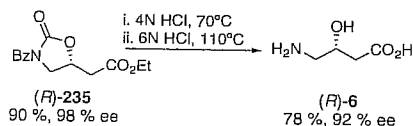
Epichlorohydrin has also proved a versatile starting material for the synthesis of β -hydroxy-GABA analogs. Ring opening of (*R*)-epichlorohydrin (*R*)-(66) with phenyl lithium/cuprous cyanide yields the alcohol (239) that was converted to the azide (240) and Sharpless oxidation yielded the acid (241) (Scheme 14.66). Reduction of the azide and alcohol deprotection afforded (*R*)-GABOB (*R*)-(6) in 57% overall yield [175]. Similarly, opening of the epoxide (*R*)-(66) with vinyl Grignard/cuprate and reaction of the resulting chloride (242) with trimethylamine yields the ammonium salt (243). Ozonolysis and oxidation produces enantiomerically pure (*R*)-(7) in 67% overall yield [176]. (*R*)-Glycidyl tosylate has also been converted in eight steps via the corresponding oxazoline to enantiopure (*R*)-GABOB (*R*)-(6) in good overall yield [177].



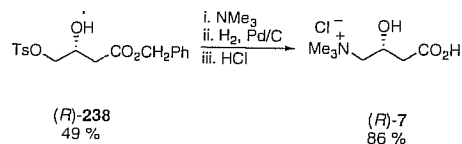
Scheme 14.62



Scheme 14.63



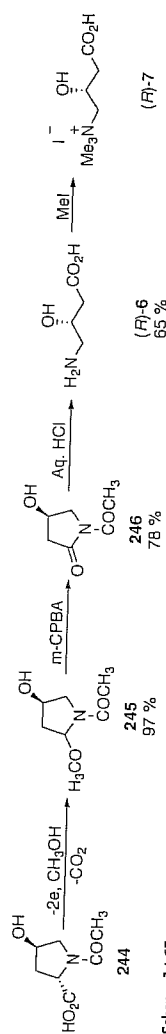
Scheme 14.64



Scheme 14.65

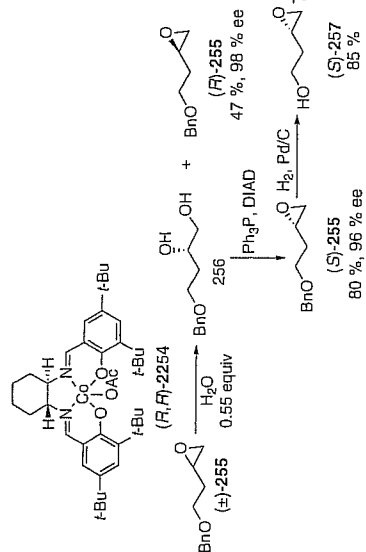
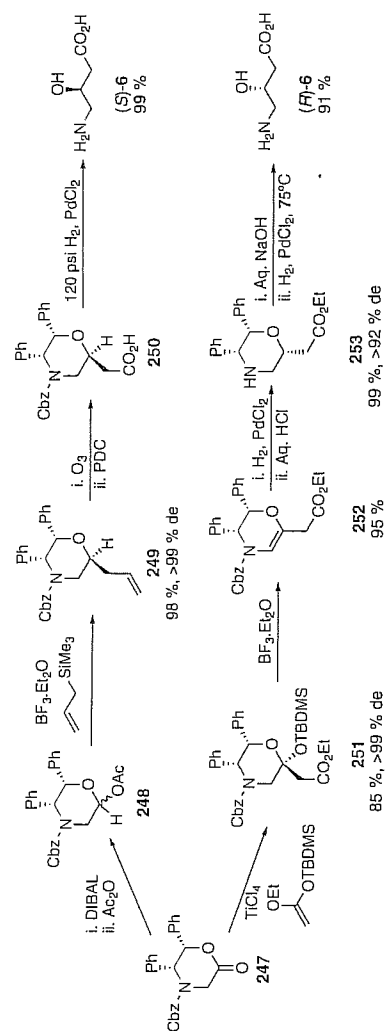
Amino acids have also been used as sources of chirality in the synthesis of (6) and (7). Enantiomerically pure (R)-2-*tert*-butyl-1,3-oxazoline prepared from serine has been converted to (S)-GABOB in six steps and 23% overall yield [178]. A novel procedure involving the electrochemical oxidation of (S,R)-N-acetyl-4-hydroxyproline (244) in methanol that yields the 2-methoxy derivative (240) as a mixture of diastereoisomers has been reported (Scheme 14.67). Oxidation of the amina and opening of the resulting lactam (246) affords optically pure (R)-(-)-6 in good overall yield that can be converted to (R)-(-)-7 [179].

The utility of the commercially available (*R,S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (247) in the synthesis of (*R*)- and (*S*)-(*6*) and (*R*)- and (*S*)-(*7*) and β -alkyl analogs has been demonstrated. The acetoxy hemiacetal (248) undergoes a stereoselective substitution reaction with allyltrimethylsilane (Scheme 14.68). Oxidative cleavage of (249) yields the acid (250) which was deprotected to afford (*S*)-(*6*) which can be converted to (*S*)-(*7*) in two steps [180]. A second route involves an asymmetric Mukaiyama-type aldol reaction on (247) providing the *tert*-butyldimethylsilyl (TBDMS)-protected hemiketal (251) which undergoes elimination to the alkene (252) and subsequent reduction to give the all *syn*-substituted oxazine (253). Deprotection affords (*R*)-(*6*) which can undergo conversion to (*R*)-(*7*) [181].



Scheme 14.66

Scheme 14.67

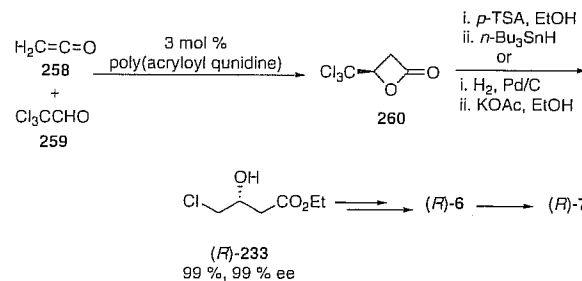


Only a limited number of GABOB and carnitine syntheses based on catalytic asymmetric reactions have been described, and these suffer from relatively low yields and/or low enantiomeric purities. Sharpless epoxidation of but-3-enol yields (*S*)-2-epoxyethanol that can undergo oxidation to the acid. Opening of the epoxide with ammonium hydroxide affords GABOB in 66% overall yield and 49% e.e., which can be improved by repeated crystallizations (95–95% e.e., 7.3% overall yield) [165]. Catalytic asymmetric dihydroxylation of allyl bromide provides access to (*S*)-3-bromopropane-1,2-diol in 74% yield and 72% e.e., which can be converted via a γ -chloro- β -hydroxy nitrile, hydrolysis, and recrystallization to afford (*R*)-GABOB in 90% e.e. Alternatively, treatment with methylamine, recrystallization, and hydrolysis affords (*R*)-carnitine in 95% e.e. [182]. Sharpless asymmetric aminohydroxylation of the 4-nitrophenyl ether of but-3-en-1-ol provides a mixture of 2-hydroxy and 4-hydroxy regioisomeric products in a 10:1 ratio. Separation, recrystallization, and oxidation to the acid affords the (*R*)-GABOB precursor in 23% overall yield and 96% e.e. [183].

Jacobsens' hydrolytic kinetic resolution technique using the cobalt chiral salen complex (*R,R*)-(254) has been used to prepare enantiomerically pure (*R*)- and (*S*)-[2-benzyloxy]ethyl]oxirane (255) (Scheme 14.69). Debenzylation of the (*S*)-isomer (*S*)-(255) yields (*S*)-(257), alcohol oxidation and opening of the epoxide with ammonia yields (*R*)-(6) and *N*-methylation affords (*R*)-(7) in high overall yield [184].

Enantiomerically pure (*R*)-4-(trichloromethyl)-oxetan-2-one (*R*)-(260) was obtained from the poly(acryloyl quinidine) catalyzed [2 + 2] cycloaddition of ketene (258) and chloral (259) (Scheme 14.70). Ethanolysis of (*R*)-(260) in the presence of catalytic amounts of *p*-toluenesulfonic acid and treatment with tributyltinhydride [185] or hydrogenation [186] yields ethyl (*R*)-3-hydroxy-4-chlorobutyrate (*R*)-(233) that can be transformed (*R*)-(6) and (*R*)-(7).

Condensation of 3-benzyloxycyclobutanone (261) with α -methylbenzylamine and oxidation yields the oxaziridine (262) as a mixture of stereoisomers that undergo a photochemical rearrangement to afford readily separable diastereoisomeric lactams (263) in 43 and 40% yields (Scheme 14.71). After chromatographic separation, removal of protecting groups gave (*R*)-4-hydroxypyrrolidin-2-one (264a) in 51% yield, which was converted to (*R*)-(6) and (*R*)-(7) [187].



resolution of (\pm)-2,3-dichloro-1-propanol using *Alcaligenes* sp. DS-K-S389 and converted to (*R*)-(7) [195].

Lipases have been used in both enantioselective hydrolyses and transesterification reactions of cyanohydrins. *Candida cylindracea* lipase (CCL) hydrolysis of *O*-acetyl cyanohydrin (\pm)-(277), prepared in three steps from (276), yields the (*R*)-cyanohydrin (*R*)-(278) (Scheme 14.75). Treatment of the residual *O*-acetyl cyanohydrin (*S*)-(277) with PPL gives the (*S*)-cyanohydrin (*S*)-(278). Reduction of the cyanohydrins affords enantiomerically pure (*R*)-(6) and (*S*)-(6) in good yields [196].

Alternatively, lipase-catalyzed esterification of (\pm)-*N*-(3-cyano-2-hydroxypropyl)phthalimide with *Pseudomonas cepacia* lipase (PS) supported on ceramic particles (PS-C) affords (*R*)-*N*-(3-cyano-2-acetoxypropyl)phthalimide (46%, 99% e.e.), which was converted to (*R*)-(6) and (*R*)-(7) in high yields and enantioselectivity [197]. Similarly, *P. cepacia* lipase supported on diatomite (PS-D)-catalyzed enantioselective esterification of (\pm)-3-hydroxy-4-(tosyloxy)butanenitrile provides optically pure (*R*)-3-(acetoxy)-4-(tosyloxy)-butanenitrile which was converted to (*R*)-(6) and (*R*)-(7) [198].

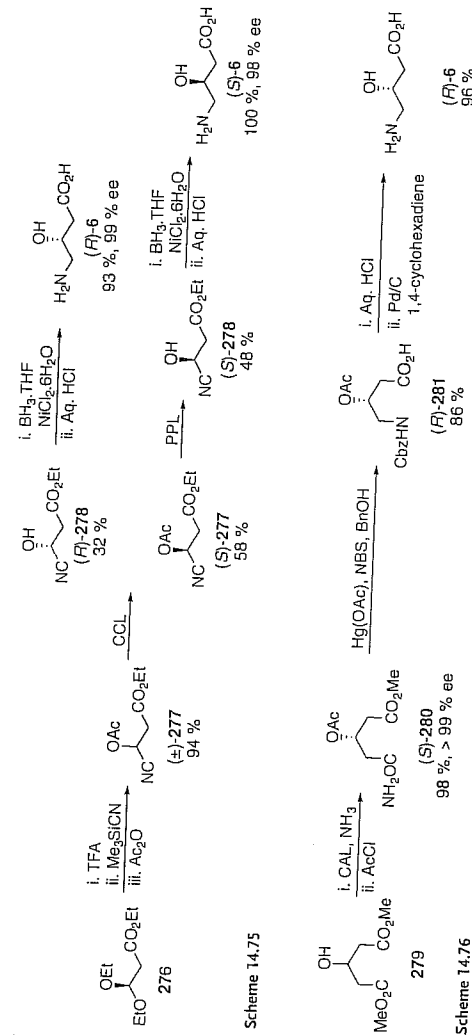
Candida antarctica lipase-catalyzed aminolysis of the prochiral diester dimethyl 3-hydroxyglutarate (279) affords the enantiopure monoamide (*S*)-(280) in high yield (Scheme 14.76). Conversion to the acetate and Hofmann rearrangement produced the protected amino acid (*R*)-(281), which was deprotected to afford a high yield of enantiopure (*R*)-(6) [199].

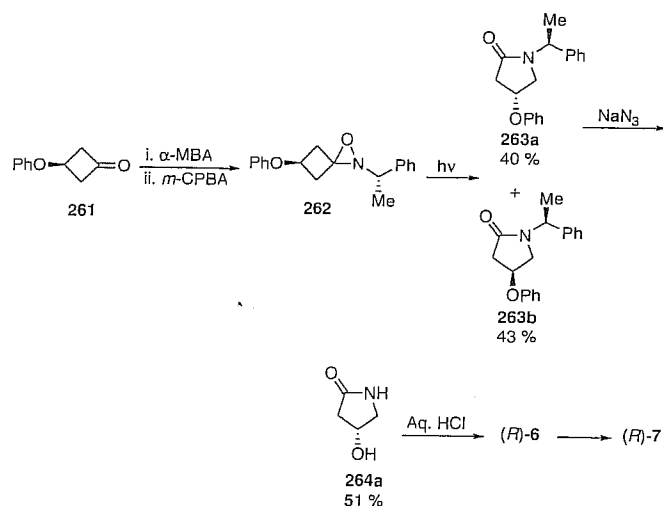
An alternative approach involves the enantioselective microbial hydrolysis of diethyl 3-hydroxyglutarate by *Corynebacterium equi* (IFO-3730). The resulting (*S*)-monoacid (97% e.e.) was transformed into (*R*)-GABOB and (*S*)-carnitine, via Curtius and Hunsdiecker rearrangements, respectively [200].

Bakers' yeast reductions have been employed to prepare a number of enantiomerically pure intermediates in the synthesis of GABOB and carnitine. Reduction of methyl 4-(*N*-Boc)-3-oxobutanoate (282) affords the (*R*)-hydroxy ester (*R*)-(283) in high yield and enantiomeric excess (Scheme 14.77). Deprotection affords (*R*)-(6) [201]. Ethyl 4-azido- and 4-bromo-3-oxobutanoate [202] and octyl 4-chloro-3-oxobutanoate [203] undergo similar reductions in good yields and enantiomeric excesses.

Both isomers of GABOB (6) and carnitine (7) have also been prepared by methods which have previously been described for the synthesis of β -substituted γ -amino acids such as the addition of chiral alkyl acetates to α -amino acids [204] and enantioselective di-Rh(II) catalyzed intramolecular C-H insertion of α -diazoacetamides [79, 205].

A number of syntheses of the phosphonic acid analogs of GABOB (GABOB^P; 290) and carnitine (phosphocarnitine; 287), including resolution of dimethyl (\pm)-3-(*N,N*-dibenzylamino)-2-hydroxypropylphosphonate with (*S*)-*O*-methylmandelic acid [206] and the conversion of (*R*)-epichlorohydrin (*R*)-(66) to (*R*)-phosphocarnitine (*R*)-(287), have been reported [207]. Compounds (*R*)- and (*S*)-(287) have been prepared by bakers' yeast reduction of diethyl 3-azido-2-oxopropanephosphonate in a similar method to that described above for the carboxylic compounds (Scheme 14.77) [208, 209]. Alternatively, resolution of diethyl 3-chloro-2-chloroacetoxypropanephosphonate (284) with *Mucor miehei* lipase provides access to both isomers of 3-chloro-2-

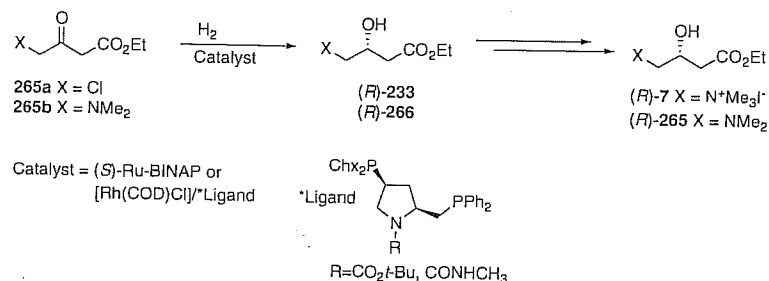




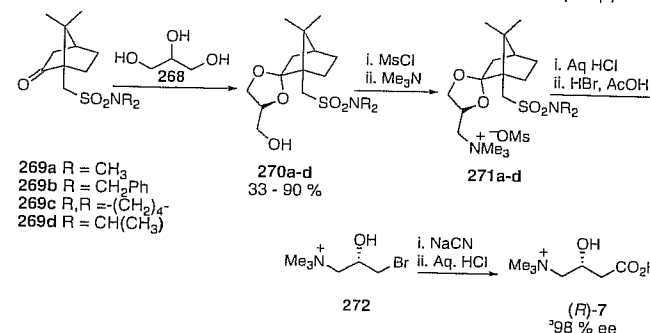
Scheme 14.71

Asymmetric hydrogenation of both ethyl 4-chloro-3-oxobutanoate (265a) with Ru-BINAP [188] and ethyl 4-(dimethylamino)-3-oxobutanoate (265b) with a range of chiral pyrrolidine-based rhodium catalysts [189, 190] affords the corresponding alcohol (266) that can be converted to (R)-7 [188–190] and (R)-norcarnitine (R)-267 (Scheme 14.72) [189, 190]. Highest yields (97%) and enantiomeric excess of 97% were obtained with Ru-BINAP catalyzed reactions, carried out on 100-g scale.

A low-cost, high-yielding seven-step synthesis of (R)-6 from glycerol (268) has been achieved through the use of the "Oppolzer" (1R)-(-)-10-camphorsulfonamide chiral auxiliary (269) to desymmetrize glycerol (Scheme 14.73). Reaction of (268) with the camphorsulfonamide (269) resulted in only one of the four possible spiro-acetals



Scheme 14.72

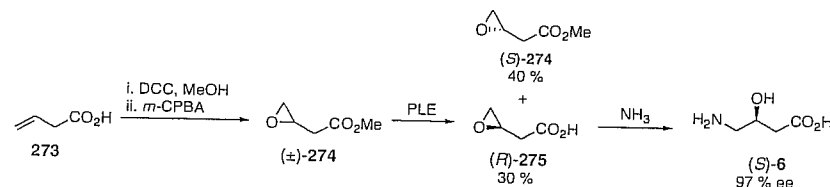


Scheme 14.73

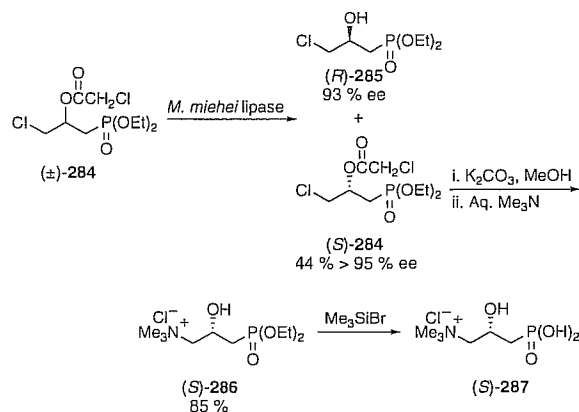
forming. Conversion of the alcohol (270) to the mesylate and reaction with trimethylamine yielded trimethylammonium salts (271). Cleavage of the chiral auxiliary and treatment with HBr gave exclusively the primary bromide (272), which was converted to the nitrile and hydrolyzed to afford (R)-7 in 56% overall yield and 98% e.e. or higher [191].

A wide range of chemo-enzymatic syntheses of GABOB and carnitine have been reported, with many of these based on the production of enantiomerically pure epoxides that can be further transformed into GABOB and carnitine. Enantioselective hydrolysis by PLE of (\pm)-methyl 3,4-epoxybutanoate (274), prepared from commercially available 3-butenic acid (273) in two steps, yielded 40% (R)-epoxy acid (R)-275 which was treated with ammonia and hydrolyzed to afford (S)-GABOB (S)-6 in 97% e.e. (Scheme 14.74) [192]. The effect of ester length and enzyme on the hydrolysis of a series of alkyl 3,4-epoxybutanoates has also been investigated, with good results being obtained with steapsin 700 hydrolysis of isopropyl and *n*-octyl esters (30 and 40% yield, respectively, and 95% e.e.) [193].

2,2,2-Trichloroethyl 3,4-epoxybutanoate has been resolved by enantioselective transesterification with polyethylene glycol using PPL in diisopropyl ether at 45 °C. The unchanged (R) enantiomer, isolated from the reaction mixture by cooling and filtration, was converted to (R)-7 (>96% e.e.) in two steps [194]. Optically pure (S)-epichlorohydrin (S)-66 (>99% e.e.) has also been obtained via microbial



Scheme 14.74



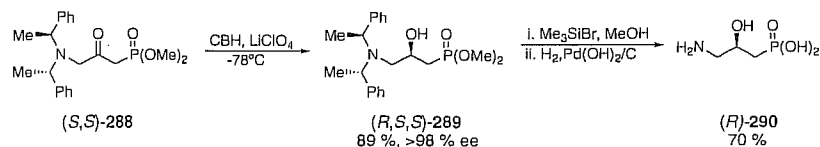
Scheme 14.78

hydroxypropanephosphonate (285) that can be converted to phosphocarnitine (287) in two steps via the ester (S) -286 in 45% overall yield (Scheme 14.78) [209].

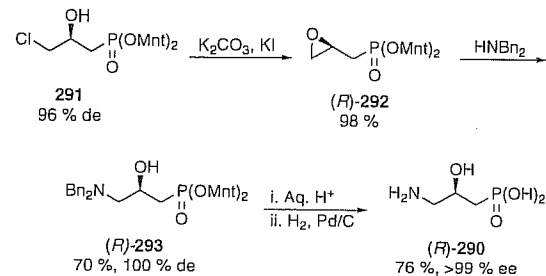
In an example of 1,4-induction, the diastereoselective reduction of (R,R) -dimethyl 3-*N,N*-di(α -methylbenzyl)amino-2-ketophosphonate (R,R) -(288) or (S,S) -(288) with catecholborane (CCB) at -78°C in the presence of LiClO_4 , yields and (S,R,R) - γ -amino- β -hydroxyphosphonate (S,R,R) -(289) and (R,S,S) -(289), respectively (Scheme 14.79). Solvolysis and hydrogenolysis afforded the corresponding isomers of (290) [210].

(S) -Dimethyl 3-chloro-2-hydroxyphosphonate (291) has been used to prepare the (R) -epoxide (R) -(292) without loss of enantiomeric purity (Scheme 14.80). Opening of the epoxide with dibenzylamine yields (R) -(293), which was deprotected to afford enantiomerically pure GABOB^P (R) -(290) [211].

Both enantiomers of β -trifluoromethyl- and β -difluoromethyl-GABOB (297) have been prepared by the addition of trimethylsilyl cyanide to the corresponding β -alkoxyvinyl polyfluoromethyl ketones (294) (Scheme 14.81). Reduction of the cyanohydrins (295) and treatment with phthalic anhydride yields the protected amine (296). Resolution with (S) -phenylethyl amine, deprotection of the aldehyde and oxidation to the carboxylic acid afforded the fluorinated GABOB derivatives (297) [212].



Scheme 14.79



Scheme 14.80

14.8.3

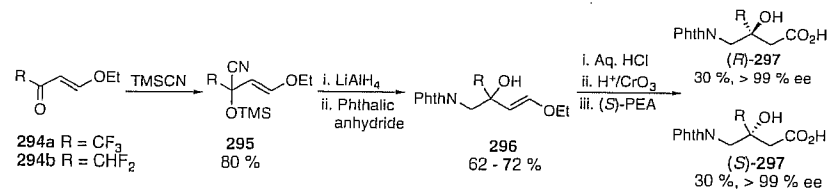
 α -Hydroxy- γ -Substituted γ -Amino Acids

The α -hydroxy γ -substituted amino acid (301) has been prepared as an intermediate in the synthesis of tubuvaline from the peptide tubulylin. Oxidation of *N*-Cbz- (S) -valinol (298) with 2,2,6,6-tetramethylpiperidinoxy (TEMPO) and homologation using a Wittig condensation gave the enoate (299) (Scheme 14.82). To prevent lactamization, the reduction was carried out with *rac*-BINAP, *t*BuONa, CuCl, and polymethylhydrosiloxane. Treatment of the resulting *N*-Cbz-protected γ -amino acid (300) with sodium hexamethyldisilazane in tetrahydrofuran (THF) at -78°C , followed by the achiral Davis reagent, gave the α -hydroxy derivative (301) as a single diastereoisomer. Finally, the hydroxyl group was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether, affording fully protected tubuvaline (302) in five steps and 31% yield from valinol [213].

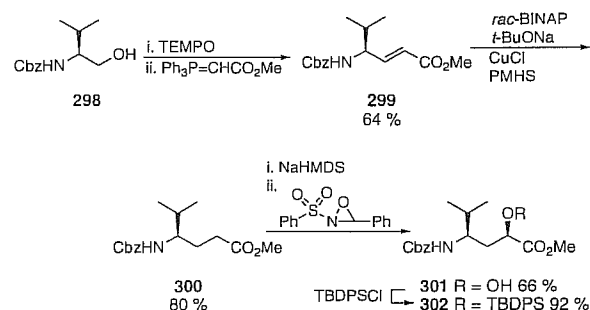
14.8.4

 β -Hydroxy- γ -Substituted γ -Amino Acids

Elongation of α -amino acids or α -amino aldehydes by a C-2 synthon has proved a versatile synthetic methodology in the preparation of γ -substituted β -hydroxy- γ -amino acids. The addition of achiral ester enolates to protected α -amino aldehydes and chromatographic isolation of the major product has routinely been used to



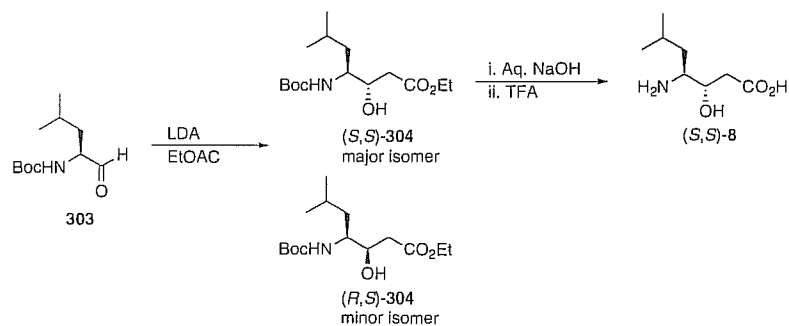
Scheme 14.81



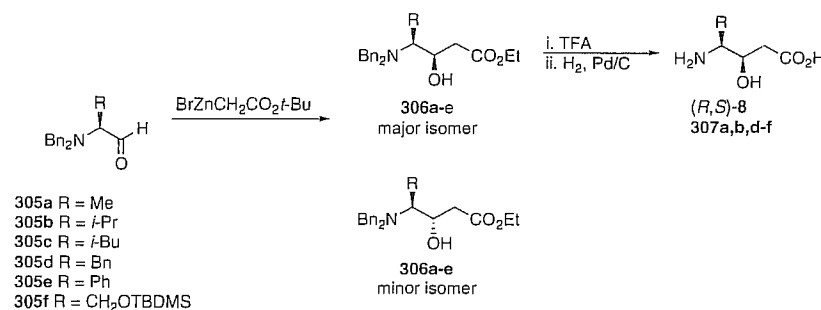
Scheme 14.82

prepare (*S,S*)-4-amino-3-hydroxy-6-methylheptanoic (statine) (*S,S*)-(8) [214, 215], (*R,S*)-Statine [216], and related analogs 4-amino-3-hydroxy-5-phenylpentanoate (AHPPA) [217] and (*S,S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACH-PA) [218], heterocyclic analogs [219], isostatine [220], all eight possible stereoisomers of isostatine from isoleucinal and *allo*-isoleucinal [221], (*R,S,S*)-dolaisoleuine [222], and phosphostatines [223, 224]. Treatment of isoleucinal (303) with ethyl lithioacetate yields the β -hydroxy acid as a 3 : 2 mixture of diastereoisomers (304) (Scheme 14.83). Chromatographic separation and hydrolysis affords (*S,S*)-(8) [214].

The lithium enolates of alkyl acetates add to Boc- and Cbz-protected amino aldehydes with *syn* selectivity [214], whereas the addition of the same enolates to *N,N*-dibenzyl aminoaldehydes afford the *anti* products [225]. Similarly, *N,N*-dibenzyl aminoaldehydes (305) treated with Reformatsky's reagent have also been reported to yield *anti*- γ -dibenzylamino- β -hydroxy esters (306) as the major diastereoisomer with moderate diastereoselectivity (3 : 2–5 : 1) in yields of 30–87% (Scheme 14.84). The diastereoisomers of most products can be easily separated by chromatography.



Scheme 14.83



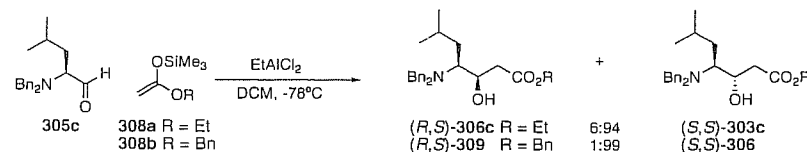
Scheme 14.84

Deprotection with trifluoroacetic acid (TFA) and hydrogenolysis afford the corresponding γ -amino- β -hydroxy acids (8, 307) [226].

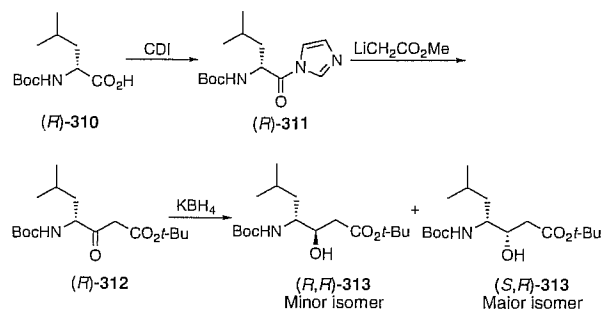
Alternatively, fully protected (*S,S*)-AHPPA has been prepared from (*S*)-*N*-Boc-phenylglycinal via Grignard reaction with allylmagnesium bromide that proceeds in moderate diastereoselectivity. Isolation of the major *syn* product by chromatography, protection of the amine and alcohol as the oxazolidine, and oxidation of the terminal olefin afforded the desired protected amino acid (*S,S*)-(307d) [227].

Another approach has been the highly diastereoselective addition of ketene silyl acetals to α -amino aldehydes in an aldol-type reaction catalyzed by Lewis acids [228–230]. Reaction of ketene silyl acetal (308) with *t*-leucinal (305c) in the presence of EtAlCl₂ affords the *anti* products (306, 309) as the major diastereoisomer (Scheme 14.85). The amino protecting group and the Lewis acid employed is of importance with addition to the *N*-Boc-protected compound in the presence of SnCl₄ giving the *syn* adduct [229].

An alternative amino acid based synthesis of statines and related compounds involves the addition of alkyl lithioacetates to activated carboxylic acids and subsequent reduction of the resulting β -keto ester. (*S,R*)-Statines and (*S,R,S*)-isostatine have been prepared by addition of alkyl lithioacetates to the imidazolide (311) (Scheme 14.86) [231, 232] or pentafluorophenyl esters [233–235] of *N*-protected *D*-leucine (*R*)-(310) and *D*-*allo*-isoleucine derivatives, respectively. Reduction of the β -keto ester (312) with KBH₄ or NaBH₄ affords the corresponding β -hydroxy esters (313) in good yield and high diastereomeric excess (up to 91%).



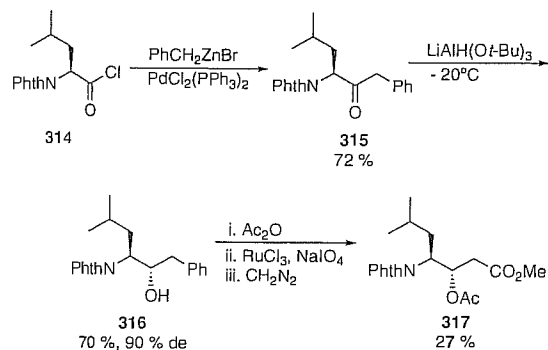
Scheme 14.85



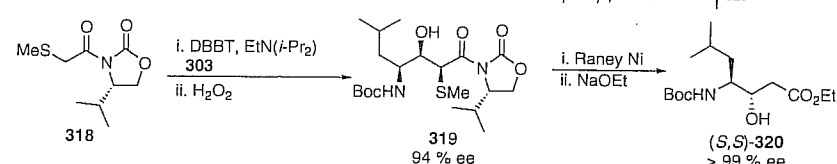
Scheme 14.86

Similarly, protected norstatine has been prepared from valine [236], (R,S,S) -dolaisoleucine from L -isoleucine [237], $(3R,4S)$ -AHPPA from L -phenylalanine [238–242], and (S,S) -ACHPA from the cyclohexyl amino acid prepared by PtO_2 -catalyzed hydrogenation of L -phenylalanine [243]. Acid chloride-activated N -Boc-protected [244] and N -Fmoc-protected [245] amino acids also yield β -hydroxy esters in high enantiomeric purity. The Fmoc protecting group allows for a final purification by crystallization to afford diastereomerically pure products [245]. Using this methodology, a variety of statine analogs, with both natural and unnatural configurations, and with branched and unbranched R groups, have been prepared in four steps from activated α -amino esters in excellent overall yields and diastereoselectivity [246].

$\text{Pd}(0)$ coupling of N -phthaloyl L -leucine acid chloride (314) with benzyl zinc bromide has also been used to prepare the ketone (315) that undergoes a *syn*-selective reduction with the bulky and chemoselective $\text{LiAlH}(\text{O}t\text{Bu})_3$ (Scheme 14.87). Protection of the alcohol (316), Sharpless oxidation of the phenyl ring and esterification afforded the fully protected statine (317) [247].



Scheme 14.87

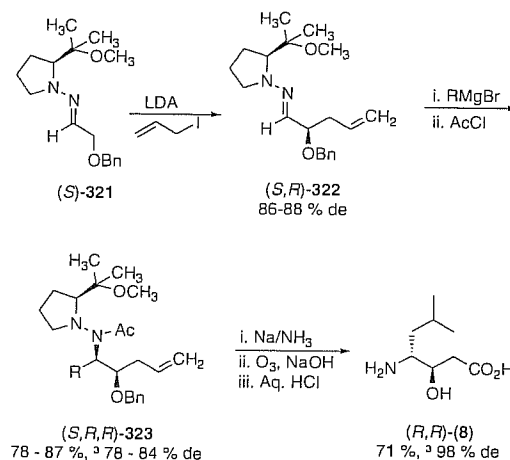


Scheme 14.88

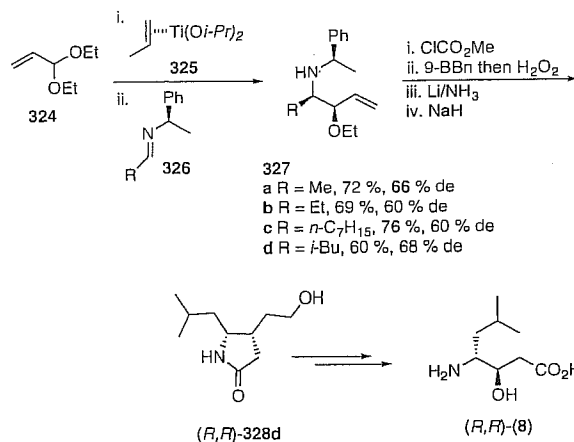
The use of an Evan's chiral auxiliary allows the two stereocenters of the target statines to be established by a single adol reaction. Treatment of the imide of (315) with dibutylboron triflate, reaction of the resulting enolate with N -Boc-leucinal (303), and oxidative decomposition of the boron complex yielded the trisubstituted product (319), which was purified chromatographically (Scheme 14.88). Desulfurization and cleavage of the oxazolidine afforded the product (S,S) -320 in 24% overall yield [248].

(S,S) -4-Amino-3-hydroxy-2-methylbutanoic acid [249], AHPPA (307e), N -MeAHPPA [250], and a range of statine analogs [251] have also been prepared using Evan's aldol methodology in multistep syntheses. Interestingly, increasing the amount of reagents has been reported to reverse the stereoselectivity of the aldol reaction albeit with lower yields and selectivity [252].

The highly *syn* diastereo- and enantioselective alkylation of the (S) -1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine hydrazone of protected glycol aldehydes (321) yields alkylated hydrazone (322) which has been used in the preparation of (R,R) -statine (R,R) -8 and analogs (Scheme 14.89). The hydrazone was prepared by condensation of the glycol aldehyde with the chiral auxiliary. α -Alkylation and



Scheme 14.89



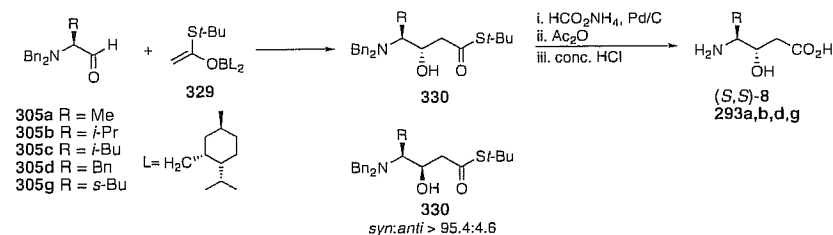
Scheme 14.90

subsequent reaction with excess Grignard reagent and the acetyl chloride gives the *N*-acetyl hydrazides (323). Removal of the chiral auxiliary with concomitant deprotection of the alcohol, ozonolysis of the terminal alkene, and hydrolysis of the acetamide affords (*R,R*)-8 in 38% overall yield [253, 254].

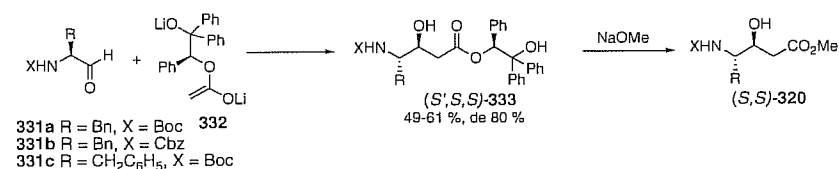
(γ -Alkoxyallyl)titaniums, generated by the reaction of acrolein diethyl acetals (324) and a divalent titanium reagent (η -propene)Ti(OiPr)₂ (325), react readily with chiral imines (326), in a regiospecific manner to give optically active *syn*-1-vinyl-2-amino alcohol derivatives (327) with moderate diastereoselectivity and yield (Scheme 14.90). Protection of the amine, hydroboration, debenzylolation, and subsequent cyclization affords the oxazolidine (328d), which was converted to (*R,R*)-8 in three steps [255].

The addition of menthone-derived chiral boron enolates of *tert*-butyl thioacetate (329) to amino acid-derived chiral α -amino aldehydes (305) yields either the 3,4-*anti* or the 3,4-*syn* adduct (330) with very high diastereoselectivity depending on the configuration of the chiral boron ligand (Scheme 14.91). This methodology has been used in the synthesis of (*S,S*)-statine (*S,S*)-8 and related analogs (307). The use of the other stereoisomer of the boron ligand yields the *anti* adducts as the major product with a ratio *syn* : *anti* > 1.8 : 98.2. The higher diastereoselectivities a result of “matched” stereochemistry between the aldehyde and the boron ligand [256, 257].

(*S*)- and (*R*)-2-Acetoxy-1,1,2-triphenylethanol has also been used as a chiral auxiliary in the addition of lithium enolates to various aldehydes in the synthesis of statine and its C-3 epimer [258], and a range of statine analogs [259], with good diastereoselectivity. Reaction of lithium enolate (332) with the protected aldehyde (331) affords the adduct (333) in moderate diastereomeric excess (Scheme 14.92). Chromatographic separation and removal of the chiral auxiliary by transesterification affords enantiomerically pure protected statine analogs (334) [259].



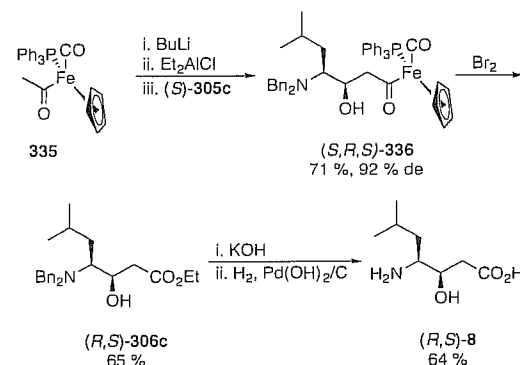
Scheme 14.91



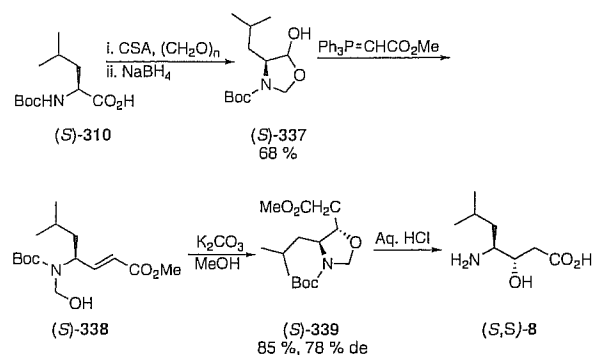
Scheme 14.92

A stereoselective synthesis of statine utilizing an iron acetyl complex as a chiral acetate enolate equivalent has been reported [260]. Diethylaluminum enolates derived from the iron acetyl complex (335) undergo highly diastereoselective aldol reactions with *N,N*-dibenzyl α -amino aldehydes (Scheme 14.93). Reaction of complex (335) with *N,N*-dibenzyl leucinal (*S*)-(305c) yields the adduct (*S,R,S*)-336. Decomplexation and deprotection affords (*R,S*)-statine (*R,S*)-8 [260].

An efficient synthesis of enantiomerically pure (*S,S*)-statine was achieved with the stereoselective intramolecular conjugate addition of a hydroxyl group tethered to the



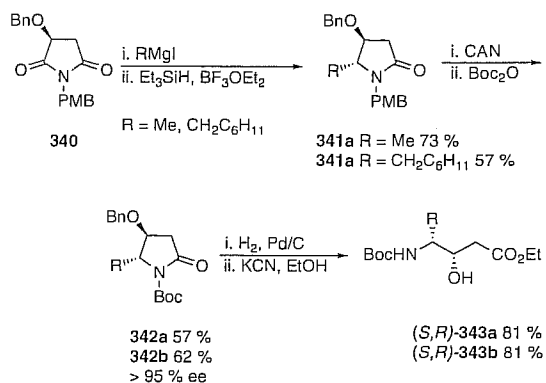
Scheme 14.93



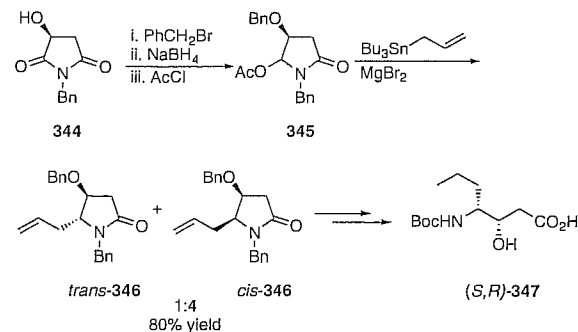
Scheme 14.94

amine of a configurationally stable *N*-Boc-L-leucinal derivative. Conversion of *N*-Boc-L-leucine (310) to the *N*-Boc-L-leucinal derivative (337) is achieved in two steps and Wittig olefination yields the α,β -unsaturated ester (S)-338 (Scheme 14.94). Intramolecular conjugate addition of the hydroxyl group was successful to give the expected oxazolidine (S)-339. Deprotection and recrystallization afforded enantiomerically pure (S,S)-(8) [261].

The development of flexible non-amino acid-based approaches to the synthesis of *anti*- γ -amino- β -hydroxy carboxylic acids has been explored. Malimides (340) derived from malic acid undergo regioselective alkylation at the C-2 position with good yields as a mixture of diastereoisomers (Scheme 14.95). Catalytic hydrogenation of the diastereomeric mixture gives the lactam as a 3:1 mixture of diastereoisomers [262], however Lewis acid mediated ionic hydrogenation yields only the *trans* isomer (341)



Scheme 14.95



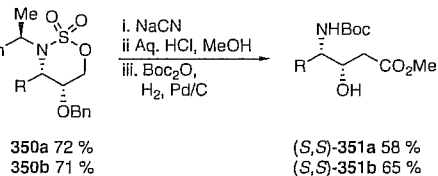
Scheme 14.96

indicating that the reaction proceeds through an *N*-acyliminium intermediate [263]. The pyrrolidin-2-ones (342) have been converted to the corresponding protected statine analogs (S,R)-(343a,b) in four steps [262, 263]. Similar methodology has been used to generate small libraries of β -hydroxy- α -amino acids used in a combinatorial synthesis of hapalosin analogs [264].

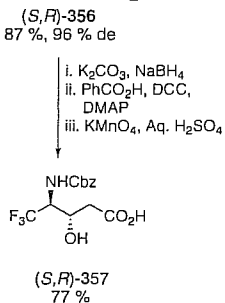
Statine analogs have also been synthesized from the malimide derivative (344) with diastereomeric ratios up to 4:11 via a *cis*-selective allylation of the α -alkoxy *N*-acyliminium intermediate of (345) (Scheme 14.96). Alkylation with allyl in the presence of MgBr_2 proceeds in high yield affording the lactam (346) as mixture of diastereoisomers which can be converted to the statine analog (347) in three steps [265]. A similar procedure has also been reported using methallyltrimethylsilane in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to facilitate the *trans*-selective alkylation (*cis*:*trans* 1:11) [266].

Several syntheses of statine or *syn* analogs starting from carbohydrates have been described. These include a multistep syntheses of statine from 3-deoxy-furanose derivatives [267, 268], AHPPA and statine from glucosamine [269, 270], and *N*-methyl AHPPA from (R)-cyclohexylidene glyceraldehydes [271]. One of the most versatile and efficient carbohydrate-based syntheses of statines is via the addition of Grignard reagents to the glyceraldehyde-derived chiral imine (348) (Scheme 14.97) [272]. The amine (349) is produced in high yields and diastereoselectivity, and converted to the amidosulfate (350). Displacement of the sulfate with cyanide, methanolysis, hydrogenolysis, and carbamoylation of the *N*-benzyl afforded the statine derivatives (351) [273].

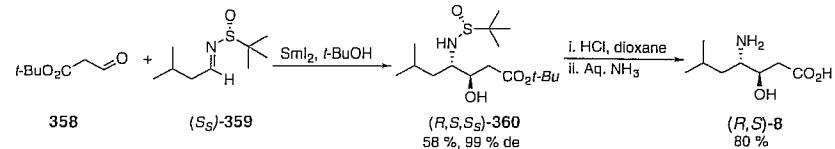
The stereocontrolled elaboration of various chiral auxiliaries has provided access to a range of γ -substituted β -hydroxy- γ -amino acids and related analogs. Chiral sulfoxides have been used as a chiral auxiliary in the synthesis of (S,R)-4-amino-5,5,5-trifluoro-3-hydroxypentanoic acid [(S,R)- γ -Tfm-GABOB] (S,R)-(357) (Scheme 14.98). Addition of lithiated (R)-*p*-tolyl- γ -butenyl sulfoxide (S)-(352) to *N*-*p*-methoxyphenyl imine (353) affords the adduct (354) with poor diastereomeric excess. After cleavage of *N*-*p*-methoxyphenyl group the major (S,R,*R*_S) isomer (355) was isolated by chromatography. Conversion of the amine, to the *N*-Cbz derivative,



Scheme 14.97



Scheme 14:98



Scheme 14.99

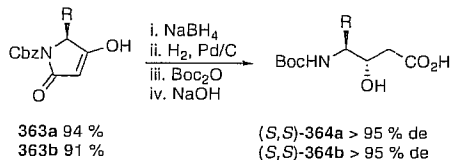
a nonoxidative Pummerer reaction, and reduction of the sulfenamide intermediate affords (*S,R*)-356, which was converted to orthogonally protected enantiomerically pure (*S,R*)- γ -Tfm-GABOB (*S,R*)-357. The synthesis of (*R,S*)-357 from the *N,S*-thioaminal of (*R*)-trifluoropyruvaldehyde has also been reported [274].

Alternatively, chiral *N*-*tert*-butanesulfinyl imine of 3-methylbutanal (359) undergoes a samarium diiodide catalyzed cross-coupling reaction with *tert*-butyl 3-oxopropanoate (Scheme 14.99). The corresponding β -amino alcohol (360) is attained in 58% yield with 99% d.e. Cleavage of the *tert*-butyl ester and *N*-sulfinyl group in one step by acid hydrolysis affords optically pure (*R,S*)-statine (*R,S*)-8 in high yield [275].

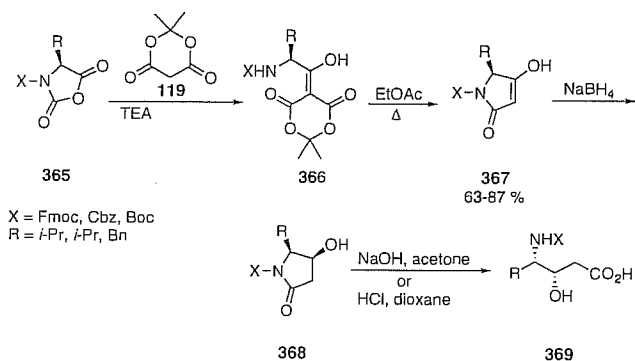
Stereospecific synthesis of *N*-Boc-(*S,S*)-statine (*S,S*)-(364a) and *N*-Boc-(*S,S*)-AHP-PA (*S,S*)-(364b) was achieved via a novel Wittig reaction of oxazolidinones (361) derived from *N*-Cbz- α -amino acids (Scheme 14.100). Treatment of the oxazolidinones (362) with HCl yields the tetramic acids (363) that can be converted to (*S,S*)-(364a) and (*S,S*)-(364b) in four steps with high enantioselectivity and good yields [276, 277].

A range of optically pure tetramic acid (367) derivatives have also been prepared in high yields by reaction of urethane-*N*-carboxyanhydrides (362) from protected α -amino acids, with Meldrum's acid (119) and subsequent cyclization (Scheme 14.101). Reduction to the alcohol (368) and hydrolysis affords the statine derivatives (369) in high overall yields and diastereomeric purity [278].

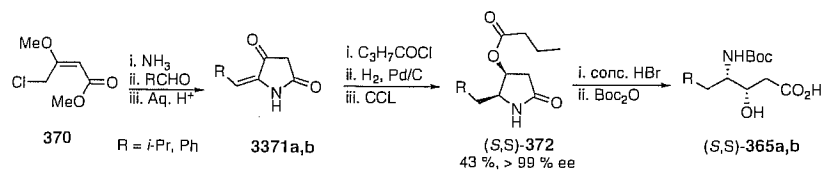
Reaction of (*E*)-methyl 4-chloro-3-methoxybut-2-enoate (370) with ammonia, direct condensation with the appropriate aldehyde, and subsequent hydrolysis yields



Scheme 14.100



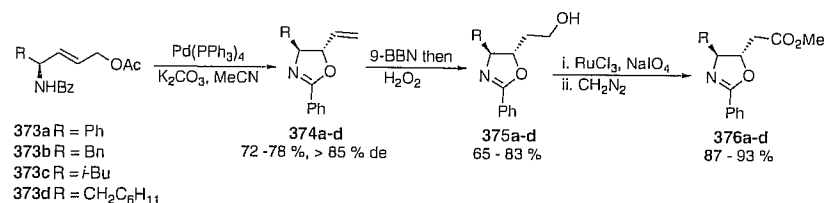
Scheme 14.101



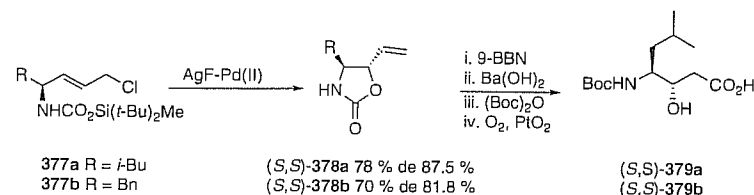
Scheme 14.102

the 5-substituted tetramic acid (371) (Scheme 14.102). Conversion to the enol butyrate, hydrogenation, and crystallization afforded the racemic *cis* butyrates which were resolved via a kinetic resolution catalyzed by CCL to provide (*S,S*)-372. Acid hydrolysis and protection of the amine affords the *N*-Boc derivatives (*S,S*)-365 [279].

Intramolecular Pd(0)-catalyzed reaction of the *O*-acetyl 4-amino-2-alken-1-ols (373), prepared in four steps from α -amino acids, affords the *trans* oxazolines (374) in good yield and high diastereoselectivity (Scheme 14.103). A hydroboration sequence yields the alcohol (375), which was oxidized and esterified to afford the oxazoline protected γ -amino- β -hydroxy esters (376). Deprotection to the corresponding γ -amino- β -hydroxy acids can be achieved using known methodology [280].



Scheme 14.103

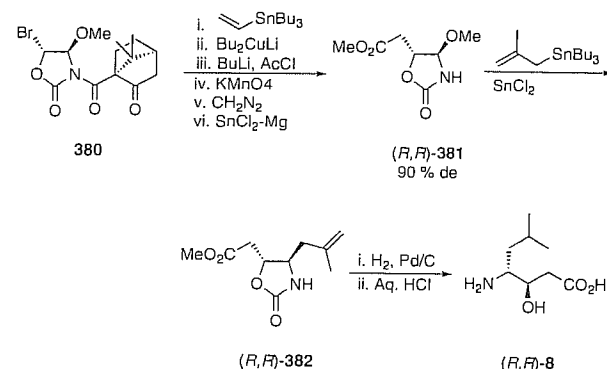


Scheme 14.104

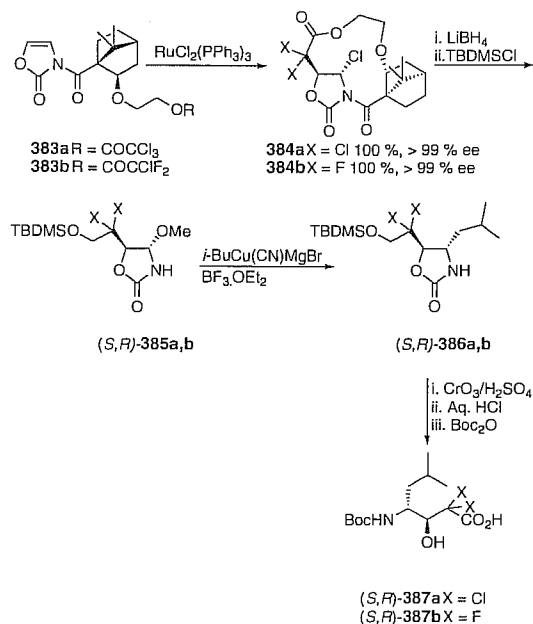
Stereoselective S_N2' cyclic carbamate formation [initiated by AgF or AgF-Pd(II)] of the *tert*-butyldimethyl silyl carbamate of 4-amino-6-methylhept-2-enyl chloride (377a) yields the oxazolidone (378a) (Scheme 14.104). Hydroboration of the terminal alkene, cleavage of the oxazolidone, protection of the amine, and oxidation affords the *N*-Boc-protected statine (*S,R*)-379a. AHPPA (*S,R*)-379a) was also prepared by this method [281, 282].

The stereodefined functionalization of oxazolones (380) results in the highly diastereoselective formation of substituted oxazolidinone derivatives, which are versatile chiral synthons for vic-amino hydroxy compounds (Scheme 14.105). Allylation at the 5-position and oxidative cleavage of the allyl group yields the ester (381). Stereospecific displacement of the 4-methoxy group with a methallyl group afforded the oxazolidinone (382), which was converted to (*R,R*)-statine (*R,R*)-8 [283]. In a similar synthesis, all four stereoisomers of statine have been prepared from oxazolidinones derived from (*R*)- and (*S*)-methyl α -hydroxyphenylpropanoate via a highly diastereoselective isobutenylation [284].

A novel intramolecular Ru(II)-catalyzed cyclization of the chiral oxazolones (383) results in the exclusive formation of the 12-membered cycloadducts (384) with complete diastereoselectivity (Scheme 14.106). Reductive cleavage of the adducts



Scheme 14.105

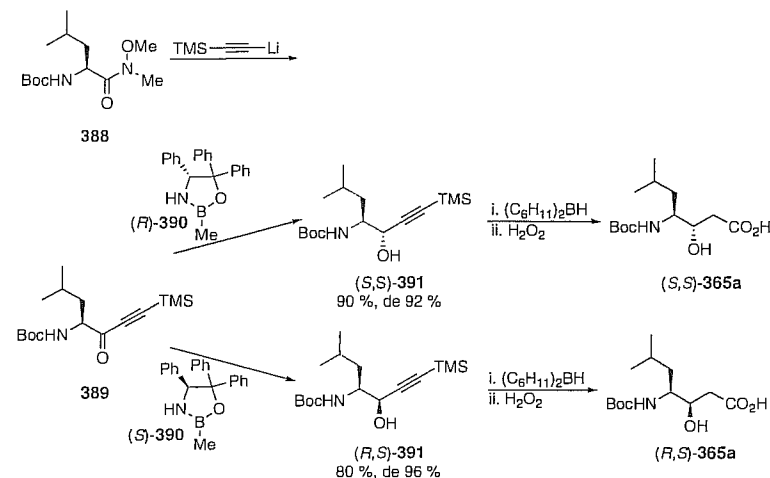


Scheme 14.106

affords the oxazolidinones (*S,R*)-(385) which can be alkylated and converted to enantiomerically pure dichloro and difluoro statine analogs (*S,R*)-(387) [285].

All four isomers of statine [286] and a range of analogs [287] have been prepared via a tandem stereoselective reduction/hydroboration strategy. 1-Trialkylsilyl acetylenic ketones (389) were derived from the appropriate α -amino acid by reaction of the Weinreb amide (388) with the lithium acetylide (Scheme 14.107). Reduction of the ketones with the chiral oxazaborolidine (390) afforded the corresponding alcohol (391) in good yields and high diastereoselectivity. Oxidative hydroboration yields the *N*-Boc-statine (365a) [286, 288].

The reduction of *N*-protected γ -amino- β -ketophosphonates derived from α -amino acids has been thoroughly investigated as a route to phosphostatines. Reaction of protected α -amino acids yields the protected γ -amino- β -ketophosphonates (392) (Scheme 14.108). Reduction of (*S*)-(393) with CCB affords the *syn* product (*R,S*)-(394) [289, 290], whereas the reduction of (*S*)-*N*-benzylamino- β -ketophosphonates with Zn(BH₄)₂ yields the (*S,S*) or *anti* product through chelation control [290]. In both cases the reduction proceeds with good chemical yields and high diastereoselectivity. Hydrolysis and hydrogenolysis affords the corresponding aminohydroxyphosphonic acids (395). However, protection as the *N*-*p*-toluenesulfonamide is reported to result

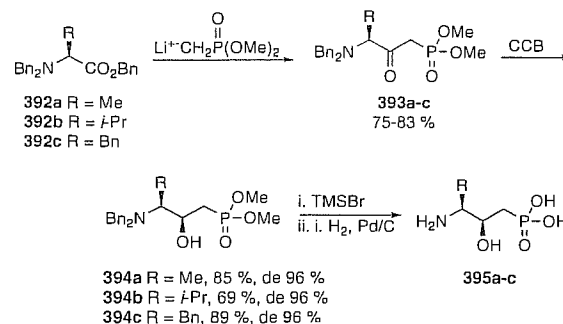


Scheme 14.107

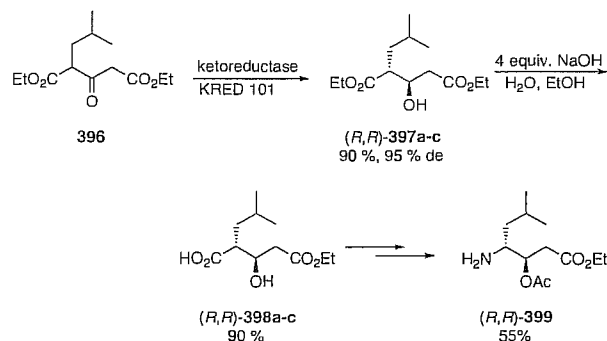
in good yields but poor diastereoselectivity on reduction with a range of hydrides [291].

Both (*R,S*)- and (*S,S*)-*N*-Boc-statine have also been synthesized in high diastereomeric purity from the readily available β -keto sulfoxide by a stereodivergent sequence involving reduction of the keto sulfoxide with diisobutylaluminum hydride (DIBAH) or DIBAH/ZnBr₂, respectively [292].

Statine and statine analogs with natural and unnatural side chains have been prepared via a diastereoselective reduction of a 2-alkyl-substituted 3-ketoglutarate (396) by an NADPH-dependent ketoreductase (Scheme 14.109). Various enzymes



Scheme 14.108

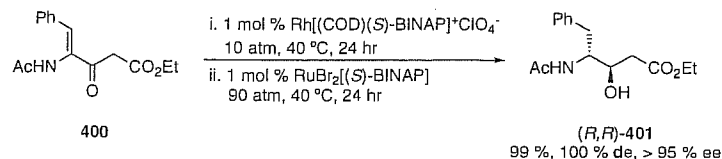


Scheme 14.109

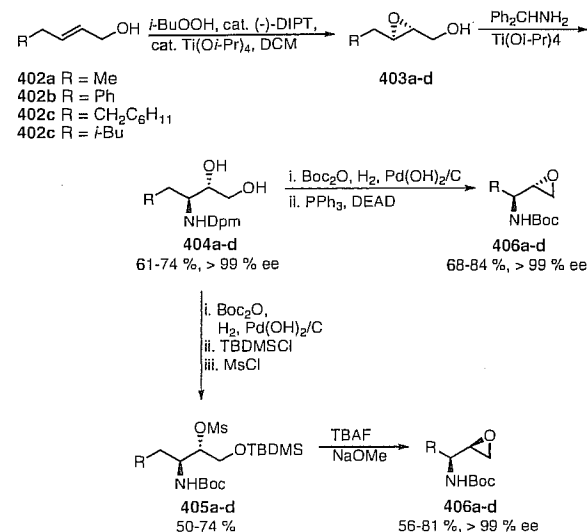
were evaluated for stereoselectivity, with the enzyme KRED 101 found to have the highest stereoselectivity in the reduction of (396). Due to the rapid isomerization of (396) the two chiral centers of (397) are generated in one step with high yields of a single stereoisomer obtained. Subsequent chemical or enzymatic regioselective hydrolysis to the mono-acid followed by rearrangement under Curtius or Hofmann conditions generates the final statine protected (*R,R*)-399 [293, 294].

The diastereoselective hydrogenation of *N*-protected γ -keto esters catalyzed by BINAP-Ru(II) complexes has also been reported to provide an efficient entry to the statine series with high enantiomeric purities [295]. The protected (*R,R*)-AHPPA derivative (*R,R*)-401 has been prepared in high yields and enantiomeric purity by a one-pot, two-catalyst sequential reduction of γ -(acylamino)- γ,δ -unsaturated- β -keto esters (400) using a combination of Rh(I) and Ru(II) catalysts (Scheme 14.110) [296]. However, these reactions also require high pressures (90 atm) over extended periods of time.

Sharpless catalytic asymmetric functionalization of allylic alcohols affords a convenient entry to enantiopure *syn* or *anti* β -hydroxy- γ -amino acids. Sharpless epoxidation of 4-substituted (*E*)-but-2-en-1-ols (402) provides the epoxide (403) that is converted to the enantiomerically enriched *anti*-3-amino-1,2-diols (404) and subsequently transformed through a stereodivergent sequence to both *N*-Boc-aminoalkyl epoxides (406) (Scheme 14.111) [297].



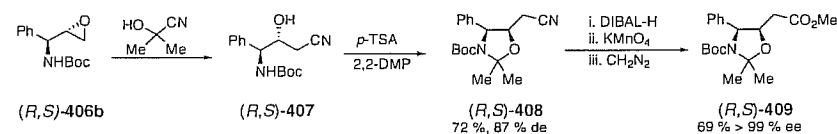
Scheme 14.110



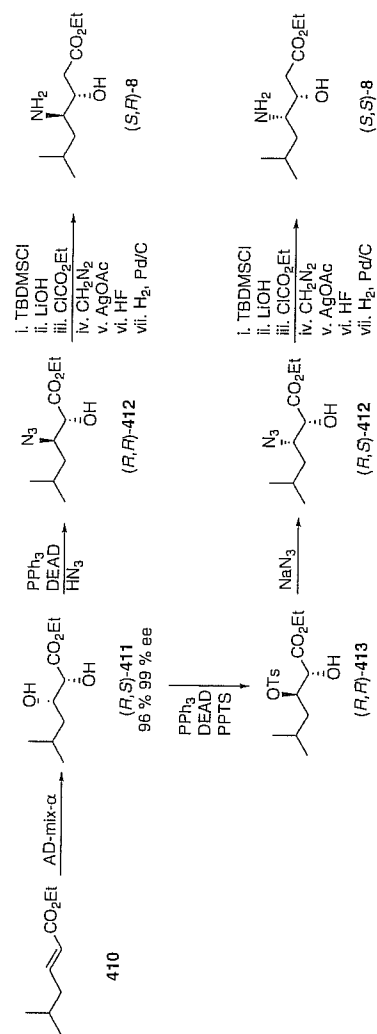
Scheme 14.111

Subsequent regioselective ring-opening of the epoxide (406b) with cyanide yields the nitrile (407), formation of the oxazolidine (408) and nitrile to carboxyl conversion afford, in good yields, protected γ -hydroxy- β -amino acids (409) belonging to either the *anti* or *syn* series, depending on the stereochemistry of the epoxide (406b) (Scheme 14.112) [298]. Similar methodology has been used in the synthesis of (*R,S*)-MeAHPPA [299]. Statine and its 3-epimer have also been prepared by the regioselective epoxide opening of the 2,3-epoxy-1-alkanols (400d) by azide [300].

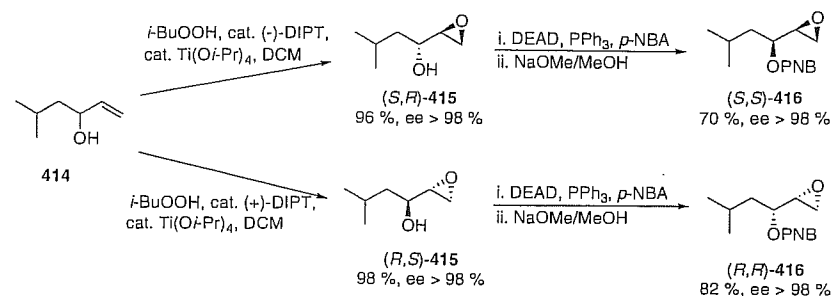
Asymmetric dihydroxylations have also been employed as the sole source of chirality in the synthesis of statines. *N*-MeAHPPA has been prepared in an 11-step synthesis from (*E*)-5-(benzyloxy)pent-2-en-1-ol [301]. Reaction of (*E*)-ethyl 5-methylhex-2-enoate (410) under Sharpless asymmetric dihydroxylation conditions yields the *syn*-2,3-dihydroxy ester (411) which was converted to the γ -azide (412) either directly or via the tosylate (413), providing access to both diastereoisomers (Scheme 14.113). Arndt-Eistert homologation and deprotection yielded the *anti*-statine (*S,R*)-8 and



Scheme 14.112



Scheme 14.113



Scheme 14.114

the natural *syn*-statine (*S,S*)-(8), respectively. The other two stereoisomers are attainable by the use of AD-mix- β [302].

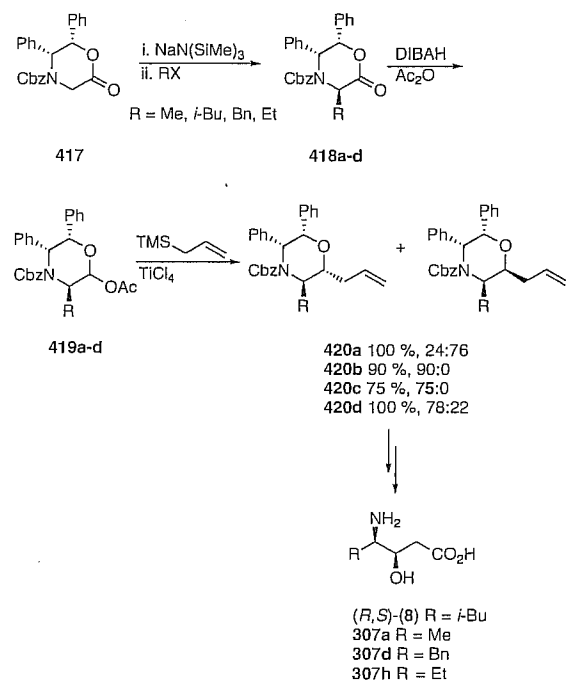
All four stereoisomers of statine amide (*S,S*)-4-amino-3-hydroxy-6-methylheptanamide have been synthesized via a kinetic resolution using the Sharpless asymmetric epoxidation of a racemic 3-hydroxy-5-methyl-1-hexene (414) (Scheme 14.114). Epoxidation with diisopropyl *D*-tartrate gave (*R,S*)-(415) and diisopropyl *L*-tartrate gave (*S,R*)-(415). The *anti* compounds (*S,S*)- and (*R,R*)-(416) were prepared through inversion of the C-2 hydroxyl under Mitsunobu conditions. The epoxides (416) were converted to the corresponding statine amides via conversion to the azide and opening of the epoxide with cyanide [303].

AHPPA has also been prepared via Sharpless asymmetric aminohydroxylation of ethyl cinnamate with *N*-bromoacetamide as the nitrogen source. The *N,O*-protected aminohydroxyl ester was afforded in moderate yield as a 10:1 mixture of regioisomers and 89% e.e. [304].

The phenyl glycine-derived alkylated oxazinone (417) was alkylated to yield (418) and reduced to the lactol acetate (419), which undergoes coupling with the ketene silyl acetals or allyl silanes [305] in the presence of a Lewis acid to afford the corresponding product (420) (Scheme 14.115). In the case of the allyl silanes, the reaction proceeds with good to excellent stereoselectivity and yields. The smaller methyl substituent results in the reverse stereoselectivity. However, a substantial amount of a rearrangement product, resulting from a 1,2-alkyl migration, was formed in a number of cases. These coupling products are easily converted to the β -hydroxy- γ -amino acids (307) by oxidation to the carboxylic acid and deprotection [306].

Other methods have also been used to prepare statine and related analogs, such as chromatographic resolution of α -methoxyphenylacetates [307], the cycloaddition of chiral enol ethers with dichloroketene coupled with the Beckmann ring expansion [308, 309], and the addition of cyanide to 4-alkoxy-trichloro-but-3-en-2-ones which occurs with poor diastereoselectivity [310].

A novel protected α -methylene-statine (424) has been prepared as an intermediate in the synthesis of epopromycin B (Scheme 14.116). Baylis–Hillman reaction of (*S*)-*N*-Fmoc-leucinal (422) with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (423)



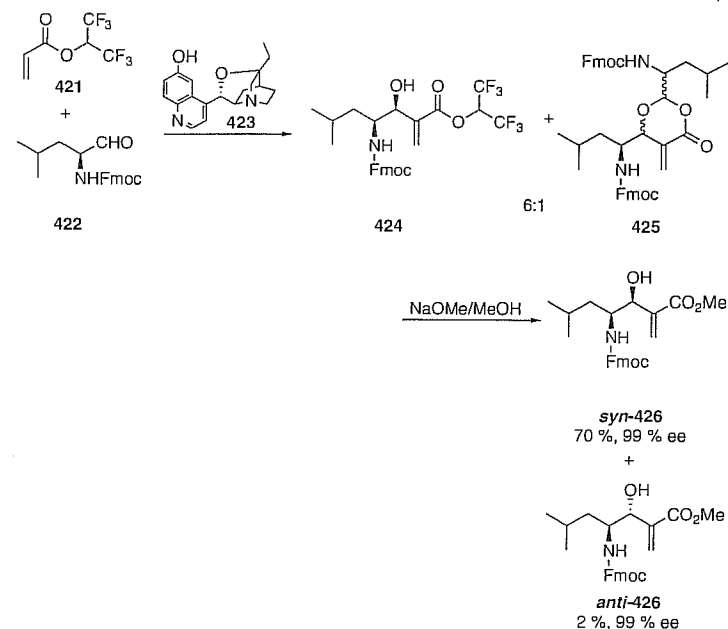
Scheme 14.115

catalyzed by a stoichiometric amount of the *Cinchona* alkaloid proceeded smoothly to yield a mixture of the ester (424) and the dioxanone (425). Methanolysis of the mixture afforded the *syn* diastereoisomer (426) as the major product [311].

14.8.5

 β -Hydroxy-Disubstituted γ -Amino Acids

Many of the standard synthetic methods used for the synthesis of β -hydroxy-substituted γ -amino acids have also been used in the synthesis of β -hydroxy-disubstituted derivatives. The 2,3-*anti*-2-isobutyl statines were prepared by the addition of achiral ester enolates to *N*-Boc-leucinal and the 2,3-*syn* isomers via a β -keto ester reduction [312]. Evan's aldol methodology has been employed in the synthesis of β -hydroxy-disubstituted γ -amino acids (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (AHMPA) subunit of bleomycin A₂ [313, 314] and a 2-substituted analog of ACHPA [315]. (2*S*,3*S*,4*R*)-AHMPA has been prepared via a nonstereoselective NaBH₄ reduction of the corresponding 3-keto derivative [316],

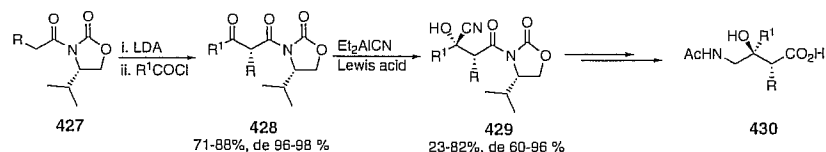


Scheme 14.116

and from *D*-rhamnose via a multistep synthesis resulting in a low overall yield [317]. A more facile synthesis of (2*S*,3*S*,4*R*)-AHMPA, was achieved through a stereoselective aldol condensation of protected *D*-alaninal and chiral (*E*)-vinylxyboranes. Highest diastereoselectivity (35:1) was achieved by the addition of phenylthio (*E*)-vinylxyborane to the protected alaninal [318]. The addition of ethyl lithioacetate to the α -amino acid-derived methyl ketones affords 3-methyl-statine and AHPPA derivatives. Coupling of the diastereoisomers to alanine isomylamide facilitated chromatographic separation [319].

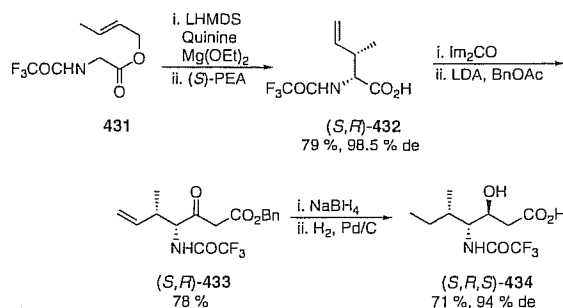
A range of α -methyl- β -substituted β -hydroxy- γ -amino acids (430) have been prepared using a two-step Evans chiral auxiliary methodology. The addition of Et₂AlCN in the presence of ZnBr₂ or Et₂AlCl to 1,3-dicarbonyl compounds (428) derived from (*S*)-4-isopropyl-2-oxazolidinone (427), proceeds with good to excellent diastereoselectivity and good yields (Scheme 14.117). This type of addition to chiral-dicarbonyl substrates represents a new synthetic methodology leading to the formation of enantiomerically pure cyanohydrins (429) which can be converted in a three-step procedure to the α -methyl- β -methyl- β -hydroxy- γ -amino acid (430) [320].

The achiral TFA-protected glycine crotyl ester (431) has been converted to *N*-protected isostatine in four steps via an ester enolate Claisen rearrangement



R = H, Me
R¹ = Me, Ph, *p*-Cl-Ph, *p*-MeO-Ph, *p*-Me-Ph

Scheme 14.117



Scheme 14.118

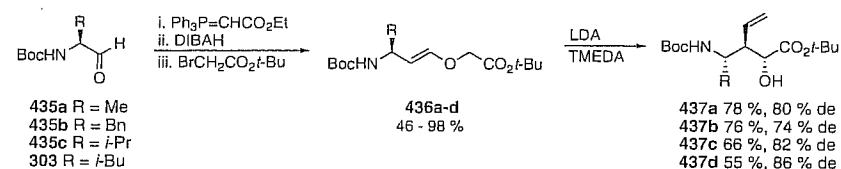
(Scheme 14.118). Deprotonation of the achiral glycine crotyl ester (431) in the presence of quinine affords (S,R)-432 in near quantitative yield and 88% e.e. A single recrystallization with (S)-phenylethylamine provides (S,R)-432 in high enantiomeric purity. Claisen condensation with the imadazolidine and conversion to the benzyl ester yields the β -keto ester (S,R)-433 which is reduced and deprotected to afford (S,R,S)-434 [321].

Enantiomerically pure 4-amino-allyloxyacetates (436), prepared from α -amino aldehydes (300, 435), undergo a stereoselective Wittig rearrangement in the presence of *N,N,N',N'*-tetramethylethylenediamine (Scheme 14.119). The *anti*- α -hydroxy- β , γ -substituted γ -amino acid esters (437) are produced as the major diastereoisomer in good yield [322].

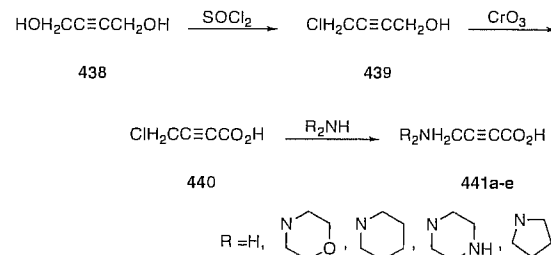
14.9

Unsaturated γ -Amino Acids

A range of 4-aminobut-2-ynoic acids (4-aminotetrolic acid) (441) (Scheme 14.120), the alkyne analog of GABA, have been prepared by direct nucleophilic attack of the appropriate amine on 4-chlorotetrolic acid (440), which was prepared via oxidation of 4-chlorobut-2-yn-1-ol (439) [323]. More recently, γ -substituted α,β -acetylenic γ -amino



Scheme 14.119



Scheme 14.120

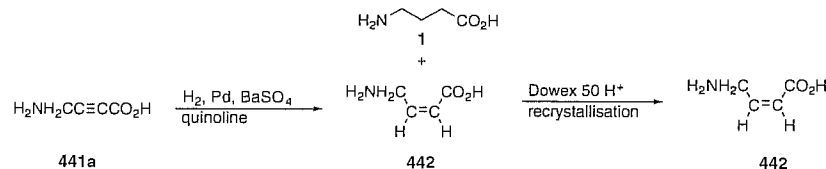
esters were obtained in moderate yields (30–40%) by a two-step procedure involving formation and flash vacuum pyrolysis of chiral aminoacyl phosphorus ylides [324, 325].

Hydrogenation of 4-aminotetrolic acid (441a) over 10% palladium-on-barium sulfate catalyst in the presence of quinoline afforded a mixture of GABA (1) and *cis*-4-aminocrotonic acid (442) that was purified by ion-exchange chromatography and recrystallization (Scheme 14.121). The *trans* isomer of 4-aminocrotonic acid has been prepared by dehydration of 3-hydroxy-4-aminobutyric acid (6) [326].

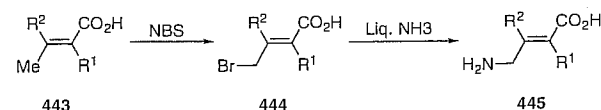
14.9.1

Unsaturated Substituted γ -Amino Acids

Allan and Twitchin have prepared a range of substituted *trans*-4-aminocrotonic acids (445) via amination of the allylic bromides (444) (Scheme 14.122). The configuration of (443) was found not to be important as the allylic bromination resulted in



Scheme 14.121



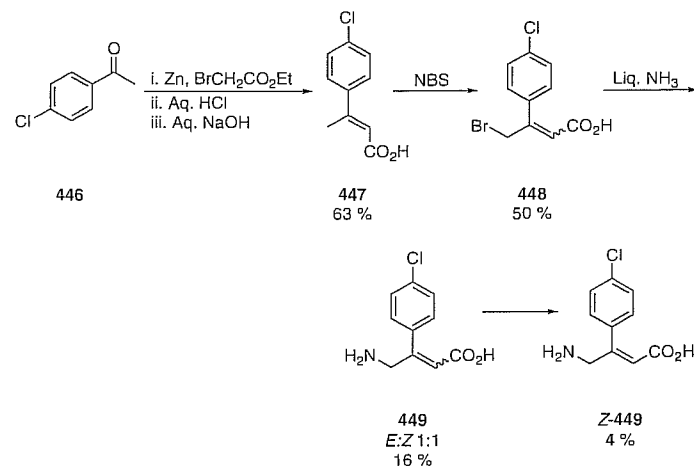
R¹ = H, Me, Cl, Br
R² = H, Me, Br

Scheme 14.122

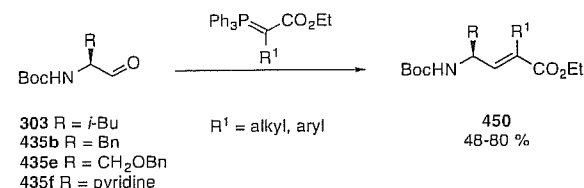
isomerization to equilibrium mixtures. The reactions proceed in low to moderate yields and also resulted in the formation of vinyl glycine analogs [327, 328]. 4-Amino-3-halogenobut-2-enoic acids were prepared by *trans* addition of HX to 4-chlorotetrolac acid (440) and subsequent amination [329].

The preparation of the *cis* isomer of the unsaturated baclofen analog (449) from 4-chloroacetophenone (446) via a Reformatsky reaction has been reported (Scheme 14.123) [330]. The α,β -unsaturated acid (447) which was isolated by crystallization from a mixture with the alternative α,β -unsaturated acid. Allylic bromination gave a 12:1 mixture of monobrominated derivatives (448) with the (*Z*) product predominating. Treatment of the (*Z*) isomer with liquid ammonia gave (*Z*)- and (*E*)-4-amino-3-(4-chlorophenyl)but-2-enoic acids (449) as a 1:1 mixture from which the (*Z*) isomer could be isolated in low yield [330].

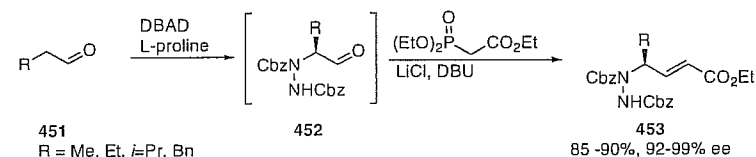
γ -Amino- α,β -unsaturated esters have been prepared by Horner–Wadsworth–Emmons olefination of a range of aldehydes. *N*-Boc-protected α -amino aldehydes (303, 435b, e and f) react smoothly with a variety of ylides and in general without racemization to afford 2,4-disubstituted α,β -unsaturated γ -amino acids (450) (Scheme 14.124). Racemization was reported to occur with (435e) [331].



Scheme 14.123



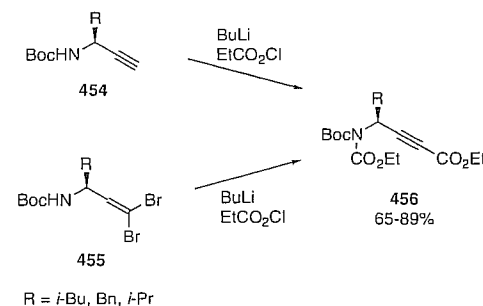
Scheme 14.124



Scheme 14.125

Similar methodology has been used in the solid-phase preparation of olefin-containing protease inhibitors [332]. A one-pot tandem proline-catalyzed direct α -amination/Horner–Wadsworth–Emmons olefination of aldehydes has also been described. Reaction of the aldehydes (451) and trapping of the intermediate (452) with diethyl phosphonacetate affords the γ -amino- α,β -unsaturated esters (453) (Scheme 14.125) [333].

Protected chiral γ -amino acetylenic esters have been synthesized using naturally occurring amino acids as the chiral source. Enantiomerically enriched propargylamines (454) [334, 335] or vinyl dibromides (455) [334] were treated with BuLi at low temperature affording, after alkoxy carboxylation and carbamoylation, enantiomerically enriched derivatives of alkynologous amino esters (456) (Scheme 14.126). Cyclopentadienylruthenium (1,4-cyclooctadiene [COD]) chloride-catalyzed reaction



Scheme 14.126

of the γ -amino acetylenic esters with alkenes affords a convenient synthesis of α -alkylated- γ -amino- α -alkenoates [335].

γ -Substituted γ -amino α,β -unsaturated esters have also been prepared by the nucleophilic reaction of a planar chiral allyl η^3 -allyldicarbonylnitrosyliron complex with benzylamine [336], the flash vacuum pyrolysis of α -aminoacyl-stabilized phosphorus ylides [324, 325], and the reaction of nitrones with the alkyl lithiopropiolates and subsequent reduction [337].

14.10

Cyclic γ -Amino Acids

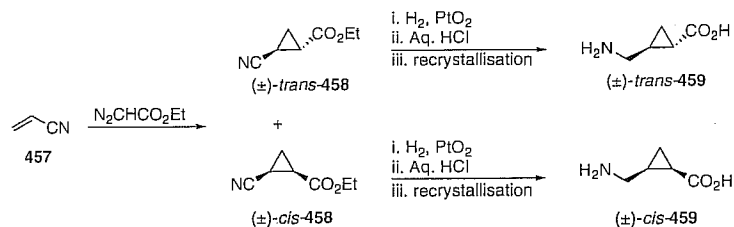
14.10.1

Cyclopropyl γ -Amino Acids

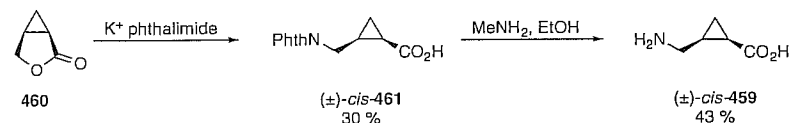
Ethyl 2-cyanocyclopropanecarboxylate (458) was initially prepared by cyclopropanation of acrylonitrile (457) (Scheme 14.127). The *trans* and *cis* isomers of the cyanoester were separated by fractional distillation. Hydrogenation of the *trans* cyanoester (\pm)-*trans*-(458) in acetic acid, hydrolysis of the resulting amide, and recrystallization yielded *trans*-2-(aminomethyl)cyclopropanecarboxylic acid (\pm)-*trans*-(459) [338]. Hydrogenation of the less-stable *cis* isomer (\pm)-*cis*-(458) was accompanied by isomerism to the *trans* isomer; however, pure *cis*-2-(aminomethyl)cyclopropanecarboxylic acid (\pm)-*cis*-(459) could be isolated after hydrolysis of the amide by repeated slow recrystallizations [339]. All four enantiomers of 2-(aminomethyl)-1-carboxycyclopropane prepared as described above, have also been resolved by chromatographic separation of the diastereomeric (*R*)-pantolactone esters [340].

The (\pm)-*cis*-(459) has also been achieved by reaction of the cyclopropyl lactone (460) with potassium phthalimide to give the *cis* acid (461), overcoming the problems of racemization (Scheme 14.128). Dephthaloylation was accomplished in ethanolic methylamine solution and the *cis* amino acid was obtained as a crystalline solid. The *trans*-(459) was also prepared by Gabriel synthesis of *trans*-ethyl 2-(bromomethyl)cyclopropanecarboxylate and subsequent hydrolysis [341].

Polymer-supported PLE has been used for the resolution of the *meso* diester *cis*-(462) to yield the enantiopure monoacid (*R,S*)-(463) (Scheme 14.129). Borane



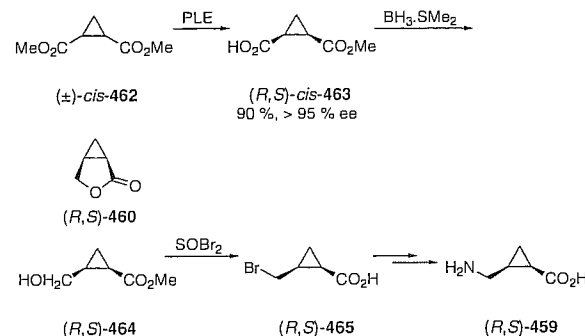
Scheme 14.127



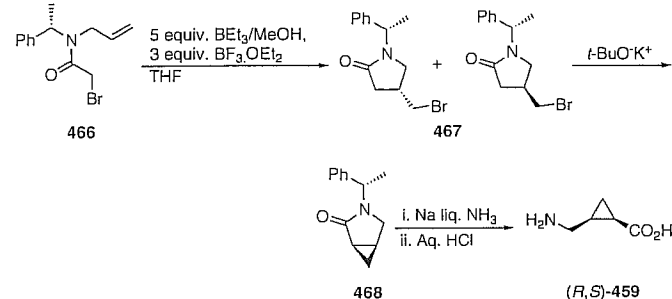
Scheme 14.128

reduction of the carboxylic acid and removal of boric acid with a borane-specific resin yielded a mixture of alcohol (*R,S*)-(464) and lactone (*R,S*)-(460), which were both transformed to the bromide (*R,S*)-(465). Conversion of (*R,S*)-(465) to (*R,S*)-(459) was carried out, either via reaction with azide or phthalimide [342].

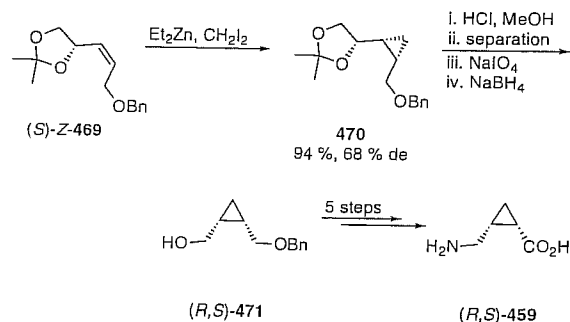
(*R,S*)-(459) has also been prepared by a novel tin-free chemo- and stereoselective radical protocol (Scheme 14.130) [343]. The 4-alkyl-pyrrolin-2-ones (467) were synthesized from chiral *N*-allyl- α -bromoacetamides (466), via a sequential 5-*exo*-trig radical cyclization-hydrogen or bromine atom-transfer process, and the major isomer isolated by chromatography. Formation of the cyclopropane (468) and deprotection afforded (*R,S*)-(459) in high yield and enantiopurity [343].



Scheme 14.129



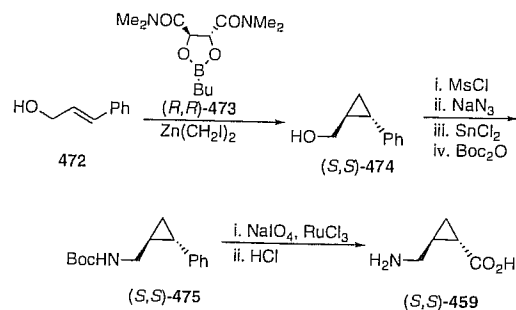
Scheme 14.130



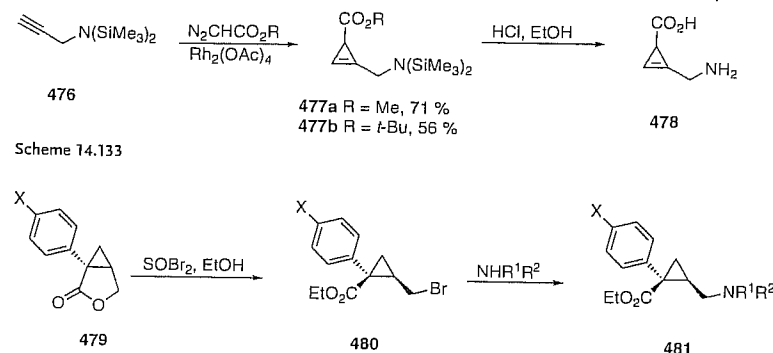
Scheme 14.131

All four enantiomers of (**459**) are available from Simmons–Smith reactions of (*Z*)- and (*E*)-allyl alcohol derivatives (**469**), respectively, obtained from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde (Scheme 14.131). The cyclopropane (**470**) was afforded in good yields. Cleavage of the chiral auxiliary, chromatographic separation, and oxidation provided access to the desymmetrized diol (**471**), which could be converted to the corresponding isomer of (**459**) in five steps. The terminal allylic hydroxyl protecting group was found to greatly influence the diastereoselectivity of the cyclopropanation, with the TBDMS ether affording a single diastereoisomer [344].

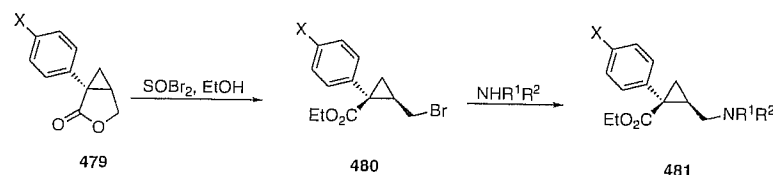
An efficient synthesis of (*S,S*)-(**459**) has been achieved via asymmetric cyclopropanation of *trans*-cinnamyl alcohol (**472**) in the presence of the (+)-tartaric acid-derived chiral dioxaborolane chiral ligand (*R,R*)-(**473**) (Scheme 14.132). The (*S,S*)-cyclopropyl alcohol (**474**) was obtained in high enantiomeric excess and good yield. Conversion of the alcohol to the azide via the mesylate and reduction with Sn(II) chloride followed by Boc protection yields the *N*-protected amine (**475**). Oxidative degradation of the phenyl moiety to a carboxylic acid and deprotection completed the synthesis of (*S,S*)-(**459**) [345].



Scheme 14.132



Scheme 14.133



X = H, Cl, F, CH₃, OCH₃.

R¹ = H, Me, CH₂CH₂OH, *i*-Pr
R² = H, CH₃, Bn, CH₂CH₂OH, *i*-Pr, *n*-Bu

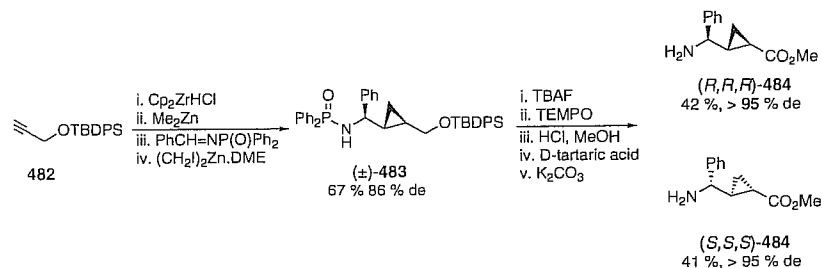
Scheme 14.134

Treatment of *N*-silylated propargylamine (**476**) with alkyl diazoacetates in the presence of rhodium acetate affords the cyclopropene (**477**) in good yields (Scheme 14.133). Hydrolysis yields racemic 2-(aminomethyl)cyclopropanecarboxylic acid (**478**) [346]. Similarly, β,γ -unsaturated, *N*-silylated amines undergo reaction with diazoacetates to afford 1-substituted 2-(aminomethyl)cyclopropanecarboxylic acids [347] and *N*-silylated allyl amines react with substituted methyl diazoacetate to yield 2-substituted 2-(aminomethyl)cyclopropanecarboxylic acids [348].

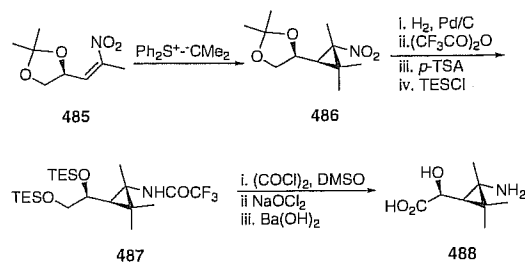
(*S,R*)-2-(Aminomethyl)cyclopropanecarboxylic acid [349] and a series of (*Z*)-2-substituted 2-(aminomethyl)cyclopropanecarboxylic acids have also been prepared from the appropriately substituted lactones [350]. Reaction of (**479**) with thionyl bromide affords the bromo ester (**480**) which can be converted to the disubstituted amine (**481**) (Scheme 14.134). Alternatively, reaction with phthalimide and hydrolysis with methylamine affords the primary amine (R¹ = R² = H) [350, 351].

The multicomponent condensation of organozirconocene, an aldimine, and a zinc carbenoid has been applied to the stereoselective synthesis of γ -substituted α,β -cyclopropane amino acid derivatives. Reaction of the organozirconocene with propargylic ethers (**482**) or homopropargylic ethers, followed by sequential transmetalation to dimethylzinc, addition to *N*-diphenylphosphinylimine, and treatment with bis(iodomethyl)-zinc/dimethoxy ether (DME) complex afforded the desired amide (\pm)-(**483**) (Scheme 14.135). Removal of the TBDPS group and oxidation of the resulting alcohol afforded the carboxylic acid, which could be converted into the methyl ester. Hydrolysis of the amide and resolution as the tartrate salts afforded diastereomerically pure amino acids (**484**) [352]. Homopropargylic ethers have also been converted to γ -substituted α,β -cyclopropane amino acids [353].

Cyclopropanation of optically active nitroalkenes (**485**) with sulfur ylides or dibromocarbene affords nitrocyclopropanes (**586**) in a diastereoselective manner (Scheme 14.136). Reduction of the nitro group, protection as the *N*-trifluoroacetyl



Scheme 14.135



Scheme 14.136

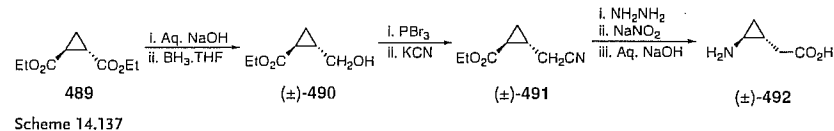
derivative, and replacement of the dioxolane protecting group yields the bistriethylsilyloxy ether (487). Selective oxidation of the primary triethylsilyl ether and subsequent deprotection afforded 2,3,3-trisubstituted (2-aminocyclopropyl)-2-hydroxyacetic acid (488) [354].

The *cis*- and *trans*-2-aminocyclopropylacetic acids have been prepared in seven steps starting from the corresponding diethyl cyclopropane-1,2-dicarboxylic ester (489) (Scheme 14.137). Partial hydrolysis yielded the monoacid, which was reduced to the alcohol (490). Conversion to the bromide and treatment with sodium cyanide yielded the nitrile (491). Curtius rearrangement of the acid hydrazide and hydrolysis afforded the desired *trans* amino acid (492). In the case of the *cis* isomer, conversion to the acid hydrazide was carried out at 0°C to control racemization and required purification by high-performance chromatography (HPLC) to remove the *trans* isomer was required [355].

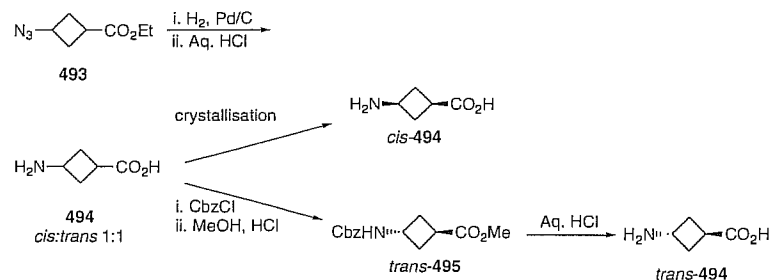
14.10.2

Cyclobutyl γ -Amino Acids

Ethyl 3-azidoocyclobutane-1-carboxylate (493) was synthesized from epibromohydrin and diethyl malonate in seven steps. Catalytic reduction to the amine and ester hydrolysis gave an approximately 1:1 mixture of *cis*- and *trans*-3-aminocyclobutane-1-carboxylic acids (494) that on careful crystallization yielded the pure *cis*-(494)



Scheme 14.137

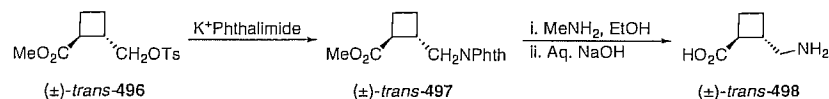


Scheme 14.138

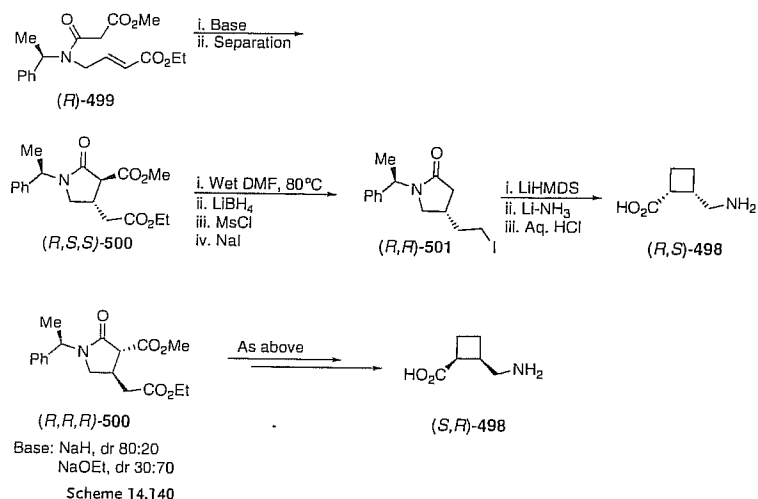
(Scheme 14.138). The *trans* isomer *trans*-(494) was obtained by chromatography of the *N*-benzyloxycarbonyl methyl esters *trans*-(495) of the residual mixture and subsequent hydrolysis and crystallization. The *cis* isomer *cis*-(494) was also prepared by reaction of cyclobutane cyclic anhydride with an equivalent of trimethylsilyl azide followed by hydrolysis and Curtius rearrangement of the resulting isocyanate [356].

The (±)-*trans*-2-(aminomethyl)cyclobutanecarboxylic acid (±)-*trans*-(498) has been prepared by Gabriel synthesis of (±)-*trans*-2-(bromomethyl)cyclobutanecarboxylic acid (±)-*trans*-(496) and hydrolysis of the protected intermediate *trans*-(497) (Scheme 14.139). The *cis*-(498) was prepared by opening of the cyclobutane lactone with phthalimide as described above for the cyclopropyl analog (Scheme 14.128) [341].

Both diastereoisomers of *cis*-(498) have been prepared by a stereodivergent synthesis that is dependent on the conditions used for the intramolecular cyclization of (R)-499 (Scheme 14.140). The use of NaH in THF leads to (R,S,S)-(500) and NaOEt in EtOH (R,R,R)-(500). Demethoxycarboxylation of (500), reduction of the alcohol, and conversion to the iodide affords (501). Reaction with lithium hexamethyldisilazane provides the β -lactam in good yield as a sole diastereoisomer and deprotection affords the corresponding isomer of (498) in 30% overall yield [357].



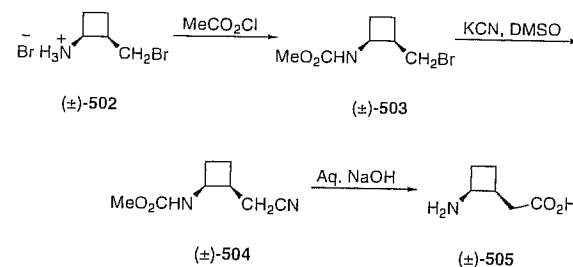
Scheme 14.139



A number of methodologies used for the synthesis of the cyclopropane compounds are also applicable to the synthesis of cyclobutane γ -amino acids. Both (\pm)-*cis*- and (\pm)-*trans*-(498) have also been prepared by opening of the cyclobutyl lactone with potassium phthalimide and a Gabriel synthesis on the tosylate, respectively, in a manner identical to that described for the corresponding cyclopropyl compounds [341]. The (\pm)-*trans*-(498) has also been prepared by conversion of the tosylate to the azide and subsequent reduction to the amine [358]. The (*S,R*)-(498) has also been obtained by a PPL resolution of the *meso* diester as described above for the cyclopropyl analog [342].

Likewise, the synthesis of (\pm)-*trans*-2-aminocyclobutylacetic acid (\pm)-*trans*-(505) in seven steps from the corresponding cyclobutyl-1,2-dicarboxylic acid, in a method analogous to that described above for the 2-aminocyclopropylacetic acids, has been reported [355]. The (\pm)-*cis*-2-aminocyclobutylacetic acid (\pm)-*cis*-(505) has been prepared from the readily available (\pm)-*cis*-(502) (Scheme 14.141) [359]. Conversion to the methyl carbamate (\pm)-*cis*-(503) prior to reaction with cyanide prevents the ring-opening side-reaction from occurring, yielding (\pm)-*cis*-(504) in good yield. Hydrolysis affords (\pm)-*cis*-(505) (Scheme 14.141) [355].

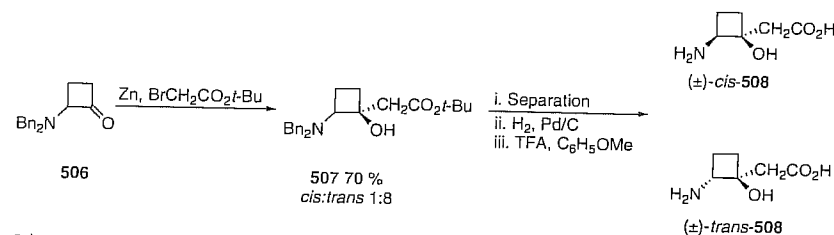
A cyclobutane analog of GABOB has been obtained via reaction of 2-(dibenzylamino)cyclobutanone (506) with *tert*-butylbromoacetate under Reformatsky conditions (Scheme 14.142). Both (\pm)-*cis*- and (\pm)-*trans*-(507) were readily separated by flash chromatography on silica gel. Debenzylation of each product gave the racemic amino alcohols, which upon treatment with TFA/anisole and subsequent purification by ion-exchange chromatography and HPLC gave the (\pm)-1-hydroxy-2-



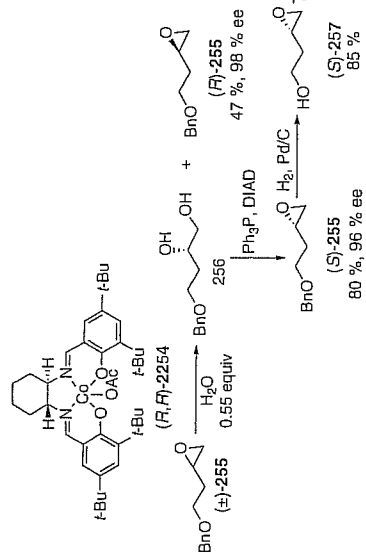
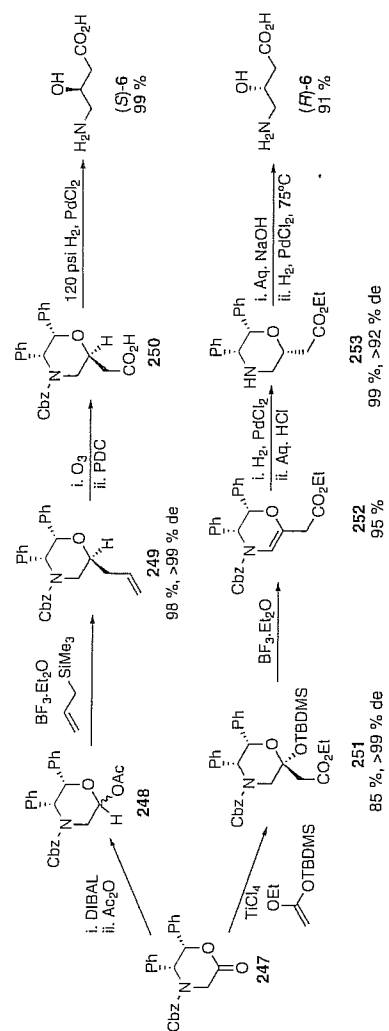
Scheme 14.141

aminocyclobutaneacetic acids (508). The *trans*-(*R,R*)- and (*S,S*)-1-hydroxy-2-aminocyclobutane-1-acetic acid were resolved by HPLC or by coupling to *N*-*tert*-butoxycarbonyl-(*S*)-valine and recrystallization [360].

Pinene has proved to be a versatile substrate in the synthesis of 2,2-dimethyl-substituted cyclobutane γ -amino acid derivatives. Oxidative cleavage of (*R*)-verbenone (*R*)-(509), available from the allylic oxidation of (+)- α -pinene, produced (+)-pinonic acid (*S,R*)-(510) with concomitant loss of CO₂ (Scheme 14.143). The (*S,R*)-(510) was converted to both isomers of *cis*-3-amino-2,2-dimethylcyclobutanecarboxylic acid (512) by a stereodivergent synthesis. Benzylation of (*S,R*)-(510) and subsequent haloform reaction yields the acid (511) which undergoes a Curtius rearrangement in *tert*-butanol to give the protected amino ester. Cleavage of the benzyl ester by hydrogenolysis affords (*R,S*)-3-(Boc-amino)-2,2-dimethylcyclobutanecarboxylic acid (*R,S*)-(512) in good yield. The (*S,R*)-(512) is available by Curtius rearrangement to give the keto-acid (513) and subsequent haloform reaction [361]. Similar syntheses of (512) have also been reported from (*S*)-verbenone [362] and (+)-(*R*)- α -pinene [363]. The highly stereoselective conjugate addition of nitromethane to α,β -unsaturated cyclobutyl esters derived from (–)-(*S*)-verbenone furnishes 3-substituted cyclobutyl gabapentin analogs [364].



Scheme 14.142

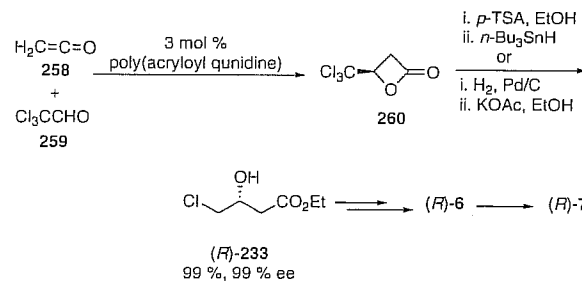


Only a limited number of GABOB and carnitine syntheses based on catalytic asymmetric reactions have been described, and these suffer from relatively low yields and/or low enantiomeric purities. Sharpless epoxidation of but-3-enol yields (*S*)-2-epoxyethanol that can undergo oxidation to the acid. Opening of the epoxide with ammonium hydroxide affords GABOB in 66% overall yield and 49% e.e., which can be improved by repeated crystallizations (95–95% e.e., 7.3% overall yield) [165]. Catalytic asymmetric dihydroxylation of allyl bromide provides access to (*S*)-3-bromopropane-1,2-diol in 74% yield and 72% e.e., which can be converted via a γ -chloro- β -hydroxy nitrile, hydrolysis, and recrystallization to afford (*R*)-GABOB in 90% e.e. Alternatively, treatment with methylamine, recrystallization, and hydrolysis affords (*R*)-carnitine in 95% e.e. [182]. Sharpless asymmetric aminohydroxylation of the 4-nitrophenyl ether of but-3-en-1-ol provides a mixture of 2-hydroxy and 4-hydroxy regioisomeric products in a 10:1 ratio. Separation, recrystallization, and oxidation to the acid affords the (*R*)-GABOB precursor in 23% overall yield and 96% e.e. [183].

Jacobsens' hydrolytic kinetic resolution technique using the cobalt chiral salen complex (*R,R*)-(254) has been used to prepare enantiomerically pure (*R*)- and (*S*)-[2-benzyloxy]ethyl]oxirane (255) (Scheme 14.69). Debenzylation of the (*S*)-isomer (*S*)-(255) yields (*S*)-(257), alcohol oxidation and opening of the epoxide with ammonia yields (*R*)-(6) and *N*-methylation affords (*R*)-(7) in high overall yield [184].

Enantiomerically pure (*R*)-4-(trichloromethyl)-oxetan-2-one (*R*)-(260) was obtained from the poly(acryloyl quinidine) catalyzed [2 + 2] cycloaddition of ketene (258) and chloral (259) (Scheme 14.70). Ethanolysis of (*R*)-(260) in the presence of catalytic amounts of *p*-toluenesulfonic acid and treatment with tributyltinhydride [185] or hydrogenation [186] yields ethyl (*R*)-3-hydroxy-4-chlorobutyrate (*R*)-(233) that can be transformed (*R*)-(6) and (*R*)-(7).

Condensation of 3-benzyloxycyclobutanone (261) with α -methylbenzylamine and oxidation yields the oxaziridine (262) as a mixture of stereoisomers that undergo a photochemical rearrangement to afford readily separable diastereoisomeric lactams (263) in 43 and 40% yields (Scheme 14.71). After chromatographic separation, removal of protecting groups gave (*R*)-4-hydroxypyrrolidin-2-one (264a) in 51% yield, which was converted to (*R*)-(6) and (*R*)-(7) [187].



resolution of (\pm)-2,3-dichloro-1-propanol using *Alcaligenes* sp. DS-K-S389 and converted to (*R*)-(**7**) [195].

Lipases have been used in both enantioselective hydrolyses and transesterification reactions of cyanohydrins. *Candida cylindracea* lipase (CCL) hydrolysis of *O*-acetyl cyanohydrin (\pm)-(**277**), prepared in three steps from (**276**), yields the (*R*)-cyanohydrin (*R*)-(**278**) (Scheme 14.75). Treatment of the residual *O*-acetyl cyanohydrin (*S*)-(**277**) with PPL gives the (*S*)-cyanohydrin (*S*)-(**278**). Reduction of the cyanohydrins affords enantiomerically pure (*R*)-(**6**) and (*S*)-(**6**) in good yields [196].

Alternatively, lipase-catalyzed esterification of (\pm)-*N*-(3-cyano-2-hydroxypropyl)phthalimide with *Pseudomonas cepacia* lipase (PS) supported on ceramic particles (PS-C) affords (*R*)-*N*-(3-cyano-2-acetoxypropyl)phthalimide (46%, 99% e.e.), which was converted to (*R*)-(**6**) and (*R*)-(**7**) in high yields and enantioselectivity [197]. Similarly, *P. cepacia* lipase supported on diatomite (PS-D)-catalyzed enantioselective esterification of (\pm)-3-hydroxy-4-(tosyloxy)butanenitrile provides optically pure (*R*)-3-(acetoxy)-4-(tosyloxy)-butanenitrile which was converted to (*R*)-(**6**) and (*R*)-(**7**) [198].

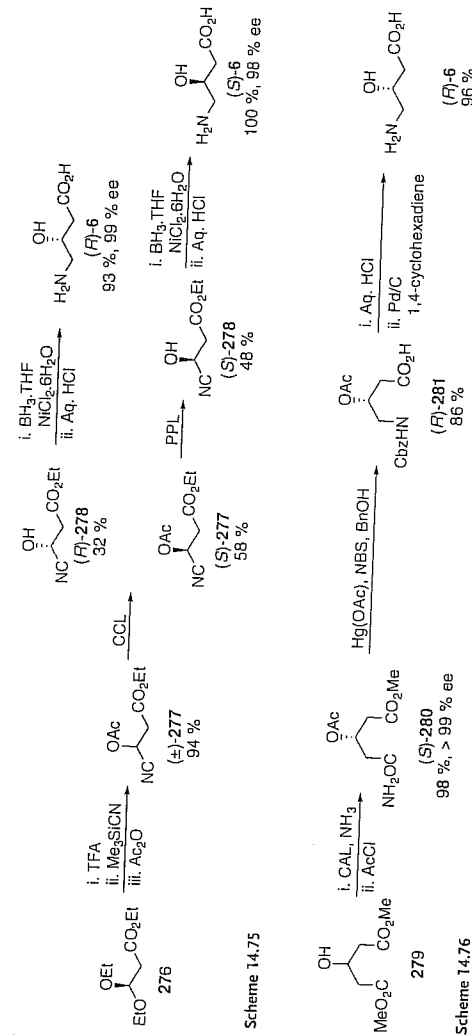
Candida antarctica lipase-catalyzed aminolysis of the prochiral diester dimethyl 3-hydroxyglutarate (**279**) affords the enantiopure monoamide (*S*)-(**280**) in high yield (Scheme 14.76). Conversion to the acetate and Hofmann rearrangement produced the protected amino acid (*R*)-(**281**), which was deprotected to afford a high yield of enantiopure (*R*)-(**6**) [199].

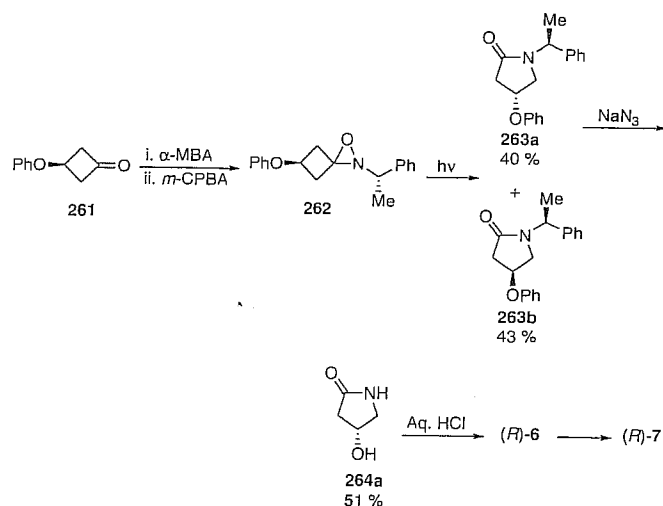
An alternative approach involves the enantioselective microbial hydrolysis of diethyl 3-hydroxyglutarate by *Corynebacterium equi* (IFO-3730). The resulting (*S*)-monoacid (97% e.e.) was transformed into (*R*)-GABOB and (*S*)-carnitine, via Curtius and Hunsdiecker rearrangements, respectively [200].

Bakers' yeast reductions have been employed to prepare a number of enantiomerically pure intermediates in the synthesis of GABOB and carnitine. Reduction of methyl 4-(*N*-Boc)-3-oxobutanoate (**282**) affords the (*R*)-hydroxy ester (*R*)-(**283**) in high yield and enantiomeric excess (Scheme 14.77). Deprotection affords (*R*)-(**6**) [201]. Ethyl 4-azido- and 4-bromo-3-oxobutanoate [202] and octyl 4-chloro-3-oxobutanoate [203] undergo similar reductions in good yields and enantiomeric excesses.

Both isomers of GABOB (**6**) and carnitine (**7**) have also been prepared by methods which have previously been described for the synthesis of β -substituted γ -amino acids such as the addition of chiral alkyl acetates to α -amino acids [204] and enantioselective di-Rh(II) catalyzed intramolecular C-H insertion of α -diazoacetamides [79, 205].

A number of syntheses of the phosphonic acid analogs of GABOB (GABOB^P; **290**) and carnitine (phosphocarnitine; **287**), including resolution of dimethyl (\pm)-3-(*N,N*-dibenzylamino)-2-hydroxypropylphosphonate with (*S*)-*O*-methylmandelic acid [206] and the conversion of (*R*)-epichlorohydrin (*R*)-(**66**) to (*R*)-phosphocarnitine (*R*)-(**287**), have been reported [207]. Compounds (*R*)- and (*S*)-(**287**) have been prepared by bakers' yeast reduction of diethyl 3-azido-2-oxopropanephosphonate in a similar method to that described above for the carboxylic compounds (Scheme 14.77) [208, 209]. Alternatively, resolution of diethyl 3-chloro-2-chloroacetoxypropanephosphonate (**284**) with *Mucor miehei* lipase provides access to both isomers of 3-chloro-2-

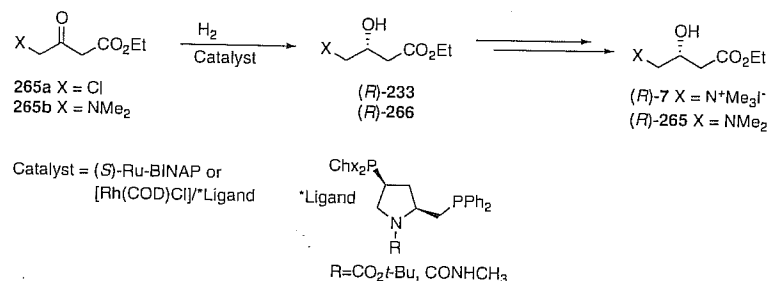




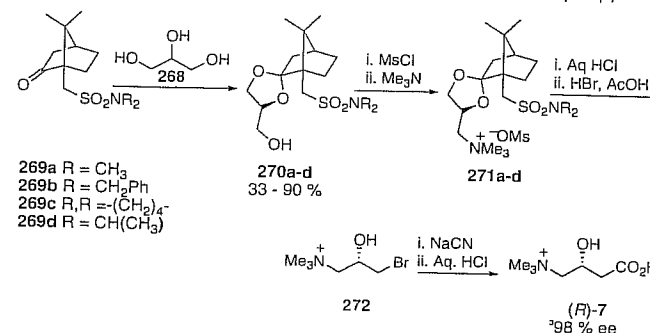
Scheme 14.71

Asymmetric hydrogenation of both ethyl 4-chloro-3-oxobutanoate (265a) with Ru-BINAP [188] and ethyl 4-(dimethylamino)-3-oxobutanoate (265b) with a range of chiral pyrrolidine-based rhodium catalysts [189, 190] affords the corresponding alcohol (266) that can be converted to (R)-7 [188–190] and (R)-norcarnitine (R)-267 (Scheme 14.72) [189, 190]. Highest yields (97%) and enantiomeric excess of 97% were obtained with Ru-BINAP catalyzed reactions, carried out on 100-g scale.

A low-cost, high-yielding seven-step synthesis of (R)-6 from glycerol (268) has been achieved through the use of the "Oppolzer" (1R)-(-)-10-camphorsulfonamide chiral auxiliary (269) to desymmetrize glycerol (Scheme 14.73). Reaction of (268) with the camphorsulfonamide (269) resulted in only one of the four possible spiro-acetals



Scheme 14.72

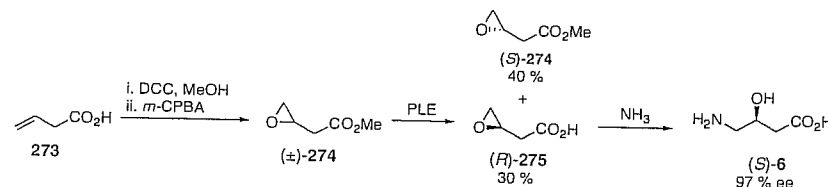


Scheme 14.73

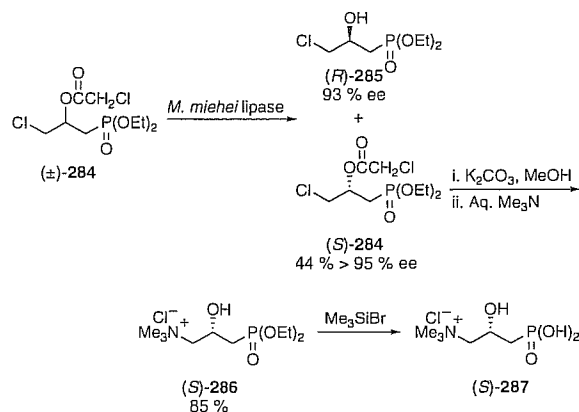
forming. Conversion of the alcohol (270) to the mesylate and reaction with trimethylamine yielded trimethylammonium salts (271). Cleavage of the chiral auxiliary and treatment with HBr gave exclusively the primary bromide (272), which was converted to the nitrile and hydrolyzed to afford (R)-7 in 56% overall yield and 98% e.e. or higher [191].

A wide range of chemo-enzymatic syntheses of GABOB and carnitine have been reported, with many of these based on the production of enantiomerically pure epoxides that can be further transformed into GABOB and carnitine. Enantioselective hydrolysis by PLE of (\pm)-methyl 3,4-epoxybutanoate (274), prepared from commercially available 3-butenic acid (273) in two steps, yielded 40% (R)-epoxy acid (R)-275 which was treated with ammonia and hydrolyzed to afford (S)-GABOB (S)-6 in 97% e.e. (Scheme 14.74) [192]. The effect of ester length and enzyme on the hydrolysis of a series of alkyl 3,4-epoxybutanoates has also been investigated, with good results being obtained with steapsin 700 hydrolysis of isopropyl and *n*-octyl esters (30 and 40% yield, respectively, and 95% e.e.) [193].

2,2,2-Trichloroethyl 3,4-epoxybutanoate has been resolved by enantioselective transesterification with polyethylene glycol using PPL in diisopropyl ether at 45 °C. The unchanged (R) enantiomer, isolated from the reaction mixture by cooling and filtration, was converted to (R)-7 (>96% e.e.) in two steps [194]. Optically pure (S)-epichlorohydrin (S)-66 (>99% e.e.) has also been obtained via microbial



Scheme 14.74



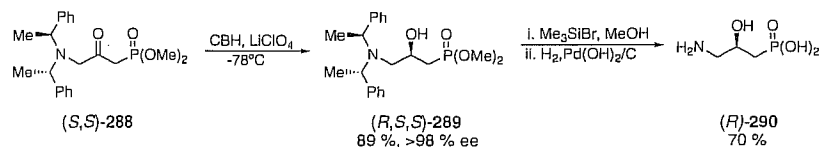
Scheme 14.78

hydroxypropanephosphonate (285) that can be converted to phosphocarnitine (287) in two steps via the ester (S) -286 in 45% overall yield (Scheme 14.78) [209].

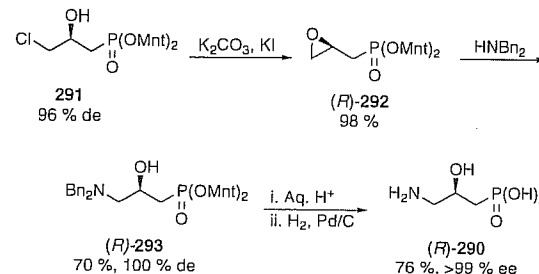
In an example of 1,4-induction, the diastereoselective reduction of (R,R) -dimethyl 3-*N,N*-di(α -methylbenzyl)amino-2-ketophosphonate (R,R) -(288) or (S,S) -(288) with catecholborane (CCB) at -78°C in the presence of LiClO_4 , yields and (S,R,R) - γ -amino- β -hydroxyphosphonate (S,R,R) -(289) and (R,S,S) -(289), respectively (Scheme 14.79). Solvolysis and hydrogenolysis afforded the corresponding isomers of (290) [210].

(S) -Dimethyl 3-chloro-2-hydroxyphosphonate (291) has been used to prepare the (R) -epoxide (R) -(292) without loss of enantiomeric purity (Scheme 14.80). Opening of the epoxide with dibenzylamine yields (R) -(293), which was deprotected to afford enantiomerically pure GABOB^P (R) -(290) [211].

Both enantiomers of β -trifluoromethyl- and β -difluoromethyl-GABOB (297) have been prepared by the addition of trimethylsilyl cyanide to the corresponding β -alkoxyvinyl polyfluoromethyl ketones (294) (Scheme 14.81). Reduction of the cyanohydrins (295) and treatment with phthalic anhydride yields the protected amine (296). Resolution with (S) -phenylethyl amine, deprotection of the aldehyde and oxidation to the carboxylic acid afforded the fluorinated GABOB derivatives (297) [212].



Scheme 14.79



Scheme 14.80

14.8.3

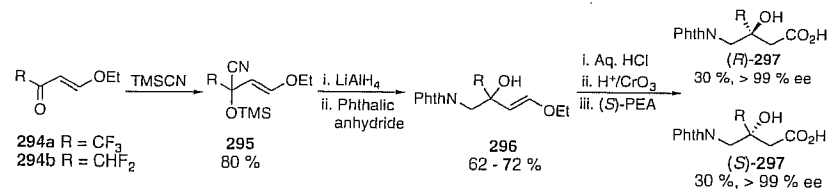
 α -Hydroxy- γ -Substituted γ -Amino Acids

The α -hydroxy γ -substituted amino acid (301) has been prepared as an intermediate in the synthesis of tubuvaline from the peptide tubulylin. Oxidation of *N*-Cbz- (S) -valinol (298) with 2,2,6,6-tetramethylpiperidinoxy (TEMPO) and homologation using a Wittig condensation gave the enoate (299) (Scheme 14.82). To prevent lactamization, the reduction was carried out with *rac*-BINAP, *t*BuONa, CuCl, and polymethylhydrosiloxane. Treatment of the resulting *N*-Cbz-protected γ -amino acid (300) with sodium hexamethyldisilazane in tetrahydrofuran (THF) at -78°C , followed by the achiral Davis reagent, gave the α -hydroxy derivative (301) as a single diastereoisomer. Finally, the hydroxyl group was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether, affording fully protected tubuvaline (302) in five steps and 31% yield from valinol [213].

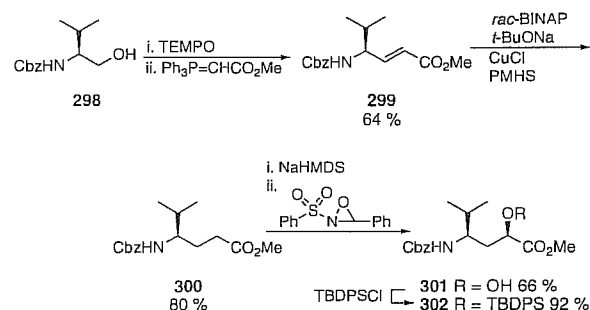
14.8.4

 β -Hydroxy- γ -Substituted γ -Amino Acids

Elongation of α -amino acids or α -amino aldehydes by a C-2 synthon has proved a versatile synthetic methodology in the preparation of γ -substituted β -hydroxy- γ -amino acids. The addition of achiral ester enolates to protected α -amino aldehydes and chromatographic isolation of the major product has routinely been used to



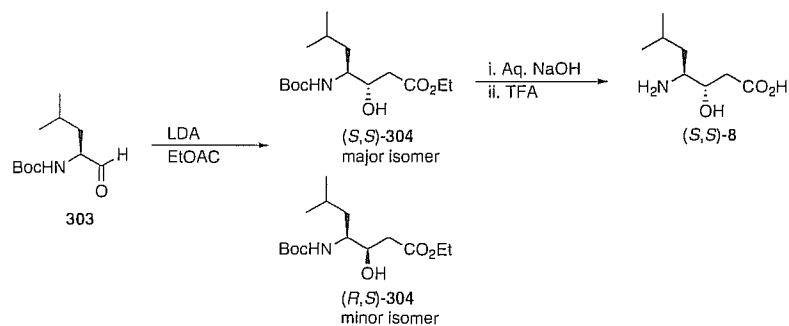
Scheme 14.81



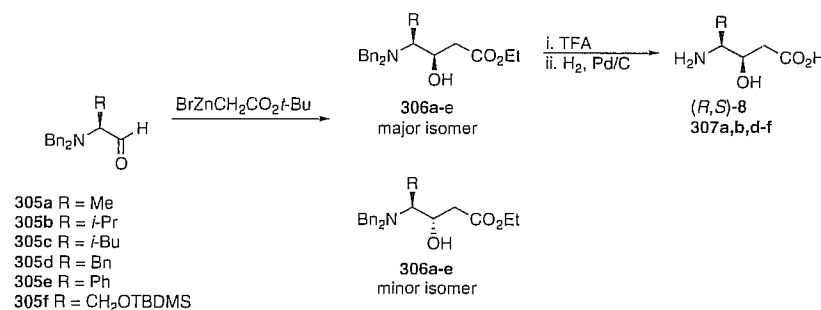
Scheme 14.82

prepare (*S,S*)-4-amino-3-hydroxy-6-methylheptanoic (statine) (*S,S*)-(8) [214, 215], (*R,S*)-Statine [216], and related analogs 4-amino-3-hydroxy-5-phenylpentanoate (AHPPA) [217] and (*S,S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACH-PA) [218], heterocyclic analogs [219], isostatine [220], all eight possible stereoisomers of isostatine from isoleucinal and *allo*-isoleucinal [221], (*R,S,S*)-dolaisoleuine [222], and phosphostatines [223, 224]. Treatment of isoleucinal (303) with ethyl lithioacetate yields the β -hydroxy acid as a 3 : 2 mixture of diastereoisomers (304) (Scheme 14.83). Chromatographic separation and hydrolysis affords (*S,S*)-(8) [214].

The lithium enolates of alkyl acetates add to Boc- and Cbz-protected amino aldehydes with *syn* selectivity [214], whereas the addition of the same enolates to *N,N*-dibenzyl aminoaldehydes afford the *anti* products [225]. Similarly, *N,N*-dibenzyl aminoaldehydes (305) treated with Reformatsky's reagent have also been reported to yield *anti*- γ -dibenzylamino- β -hydroxy esters (306) as the major diastereoisomer with moderate diastereoselectivity (3 : 2–5 : 1) in yields of 30–87% (Scheme 14.84). The diastereoisomers of most products can be easily separated by chromatography.



Scheme 14.83



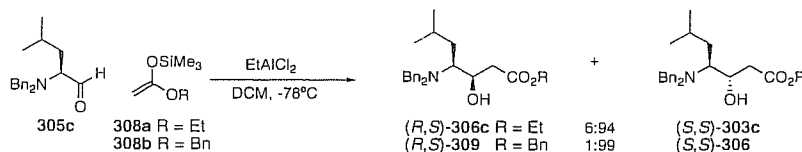
Scheme 14.84

Deprotection with trifluoroacetic acid (TFA) and hydrogenolysis afford the corresponding γ -amino- β -hydroxy acids (8, 307) [226].

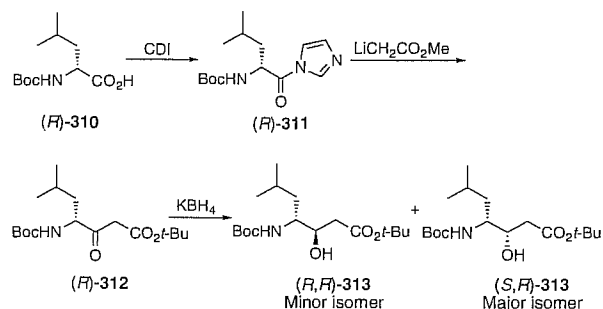
Alternatively, fully protected (*S,S*)-AHPPA has been prepared from (*S*)-*N*-Boc-phenylglycinal via Grignard reaction with allylmagnesium bromide that proceeds in moderate diastereoselectivity. Isolation of the major *syn* product by chromatography, protection of the amine and alcohol as the oxazolidine, and oxidation of the terminal olefin afforded the desired protected amino acid (*S,S*)-(307d) [227].

Another approach has been the highly diastereoselective addition of ketene silyl acetals to α -amino aldehydes in an aldol-type reaction catalyzed by Lewis acids [228–230]. Reaction of ketene silyl acetal (308) with *t*-leucinal (305c) in the presence of EtAlCl₂ affords the *anti* products (306, 309) as the major diastereoisomer (Scheme 14.85). The amino protecting group and the Lewis acid employed is of importance with addition to the *N*-Boc-protected compound in the presence of SnCl₄ giving the *syn* adduct [229].

An alternative amino acid based synthesis of statines and related compounds involves the addition of alkyl lithioacetates to activated carboxylic acids and subsequent reduction of the resulting β -keto ester. (*S,R*)-Statines and (*S,R,S*)-isostatine have been prepared by addition of alkyl lithioacetates to the imidazolide (311) (Scheme 14.86) [231, 232] or pentafluorophenyl esters [233–235] of *N*-protected *D*-leucine (*R*)-(310) and *D*-*allo*-isoleucine derivatives, respectively. Reduction of the β -keto ester (312) with KBH₄ or NaBH₄ affords the corresponding β -hydroxy esters (313) in good yield and high diastereomeric excess (up to 91%).



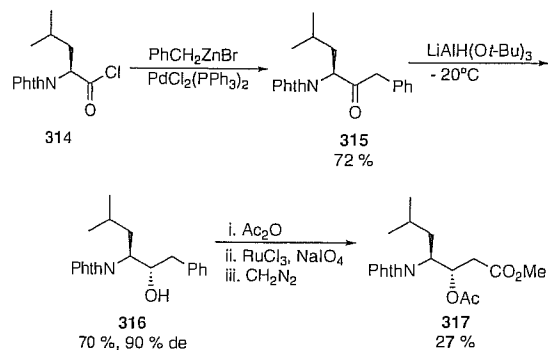
Scheme 14.85



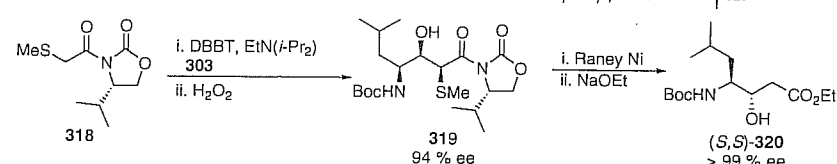
Scheme 14.86

Similarly, protected norstatine has been prepared from valine [236], (R,S,S) -dolaisoleucine from L -isoleucine [237], $(3R,4S)$ -AHPPA from L -phenylalanine [238–242], and (S,S) -ACHPA from the cyclohexyl amino acid prepared by PtO_2 -catalyzed hydrogenation of L -phenylalanine [243]. Acid chloride-activated N -Boc-protected [244] and N -Fmoc-protected [245] amino acids also yield β -hydroxy esters in high enantiomeric purity. The Fmoc protecting group allows for a final purification by crystallization to afford diastereomerically pure products [245]. Using this methodology, a variety of statine analogs, with both natural and unnatural configurations, and with branched and unbranched R groups, have been prepared in four steps from activated α -amino esters in excellent overall yields and diastereoselectivity [246].

$\text{Pd}(0)$ coupling of N -phthaloyl L -leucine acid chloride (314) with benzyl zinc bromide has also been used to prepare the ketone (315) that undergoes a *syn*-selective reduction with the bulky and chemoselective $\text{LiAlH}(\text{O}t\text{Bu})_3$ (Scheme 14.87). Protection of the alcohol (316), Sharpless oxidation of the phenyl ring and esterification afforded the fully protected statine (317) [247].



Scheme 14.87

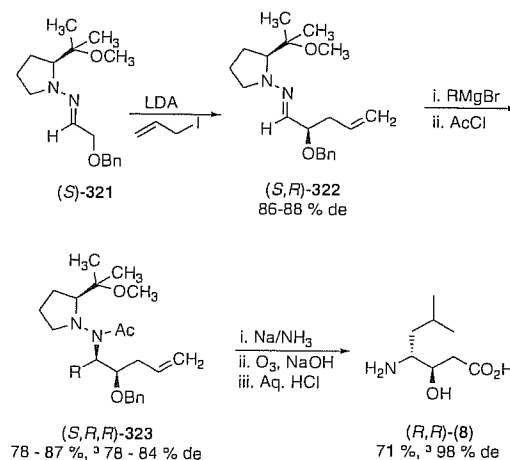


Scheme 14.88

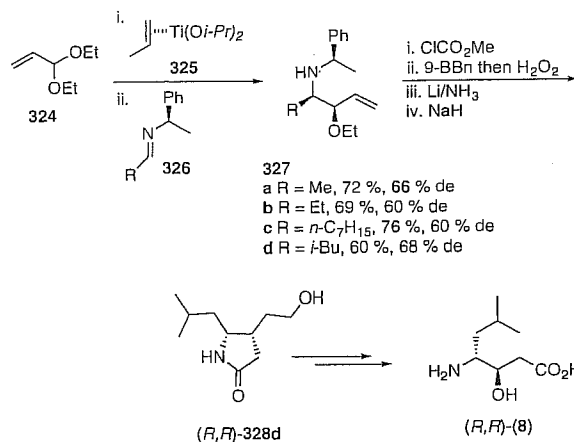
The use of an Evan's chiral auxiliary allows the two stereocenters of the target statines to be established by a single adol reaction. Treatment of the imide of (315) with dibutylboron triflate, reaction of the resulting enolate with N -Boc-leucinal (303), and oxidative decomposition of the boron complex yielded the trisubstituted product (319), which was purified chromatographically (Scheme 14.88). Desulfurization and cleavage of the oxazolidine afforded the product (S,S) -320 in 24% overall yield [248].

(S,S) -4-Amino-3-hydroxy-2-methylbutanoic acid [249], AHPPA (307e), N -MeAHPPA [250], and a range of statine analogs [251] have also been prepared using Evan's aldol methodology in multistep syntheses. Interestingly, increasing the amount of reagents has been reported to reverse the stereoselectivity of the aldol reaction albeit with lower yields and selectivity [252].

The highly *syn* diastereo- and enantioselective alkylation of the (S) -1-amino-2-(1-methoxy-1-methylethyl)pyrrolidine hydrazone of protected glycol aldehydes (321) yields alkylated hydrazone (322) which has been used in the preparation of (R,R) -statine (R,R) -8 and analogs (Scheme 14.89). The hydrazone was prepared by condensation of the glycol aldehyde with the chiral auxiliary. α -Alkylation and



Scheme 14.89



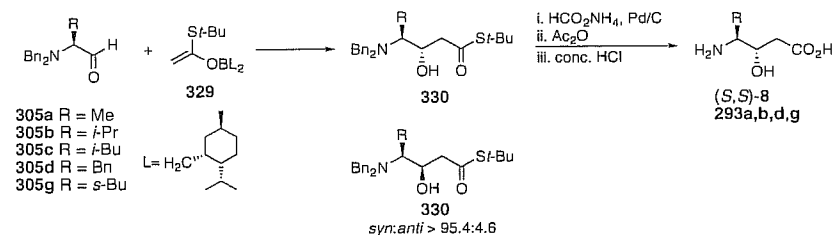
Scheme 14.90

subsequent reaction with excess Grignard reagent and the acetyl chloride gives the *N*-acetyl hydrazides (323). Removal of the chiral auxiliary with concomitant deprotection of the alcohol, ozonolysis of the terminal alkene, and hydrolysis of the acetamide affords (*R,R*)-8 in 38% overall yield [253, 254].

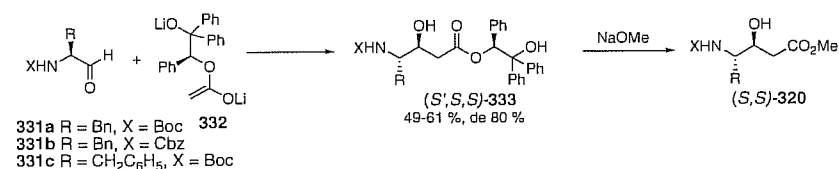
(γ -Alkoxyallyl)titaniums, generated by the reaction of acrolein diethyl acetals (324) and a divalent titanium reagent (η -propene)Ti(OiPr)₂ (325), react readily with chiral imines (326), in a regiospecific manner to give optically active *syn*-1-vinyl-2-amino alcohol derivatives (327) with moderate diastereoselectivity and yield (Scheme 14.90). Protection of the amine, hydroboration, debenzoylation, and subsequent cyclization affords the oxazolidine (328d), which was converted to (*R,R*)-8 in three steps [255].

The addition of menthone-derived chiral boron enolates of *tert*-butyl thioacetate (329) to amino acid-derived chiral α -amino aldehydes (305) yields either the 3,4-*anti* or the 3,4-*syn* adduct (330) with very high diastereoselectivity depending on the configuration of the chiral boron ligand (Scheme 14.91). This methodology has been used in the synthesis of (*S,S*)-statine (*S,S*)-8 and related analogs (307). The use of the other stereoisomer of the boron ligand yields the *anti* adducts as the major product with a ratio *syn* : *anti* > 1.8 : 98.2. The higher diastereoselectivities a result of “matched” stereochemistry between the aldehyde and the boron ligand [256, 257].

(*S*)- and (*R*)-2-Acetoxy-1,1,2-triphenylethanol has also been used as a chiral auxiliary in the addition of lithium enolates to various aldehydes in the synthesis of statine and its C-3 epimer [258], and a range of statine analogs [259], with good diastereoselectivity. Reaction of lithium enolate (332) with the protected aldehyde (331) affords the adduct (333) in moderate diastereomeric excess (Scheme 14.92). Chromatographic separation and removal of the chiral auxiliary by transesterification affords enantiomerically pure protected statine analogs (334) [259].



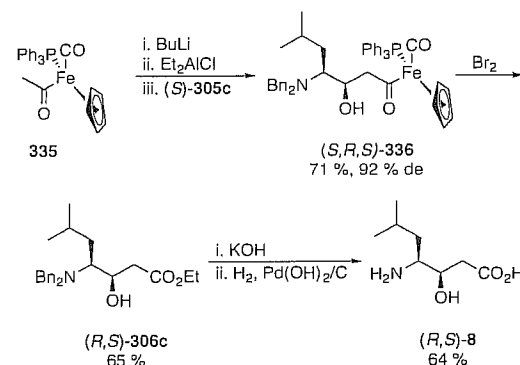
Scheme 14.91



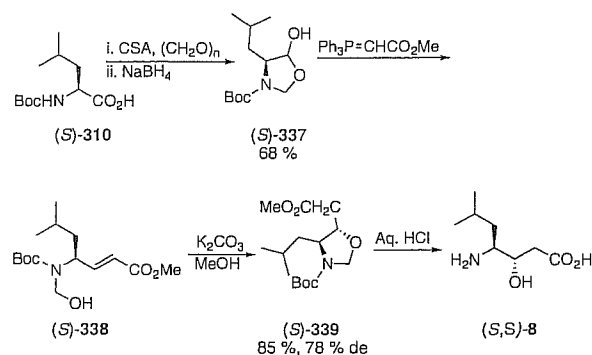
Scheme 14.92

A stereoselective synthesis of statine utilizing an iron acetyl complex as a chiral acetate enolate equivalent has been reported [260]. Diethylaluminum enolates derived from the iron acetyl complex (335) undergo highly diastereoselective aldol reactions with *N,N*-dibenzyl α -amino aldehydes (Scheme 14.93). Reaction of complex (335) with *N,N*-dibenzyl leucinal (*S*)-(305c) yields the adduct (*S,R,S*)-336. Decomplexation and deprotection affords (*R,S*)-statine (*R,S*)-8 [260].

An efficient synthesis of enantiomerically pure (*S,S*)-statine was achieved with the stereoselective intramolecular conjugate addition of a hydroxyl group tethered to the



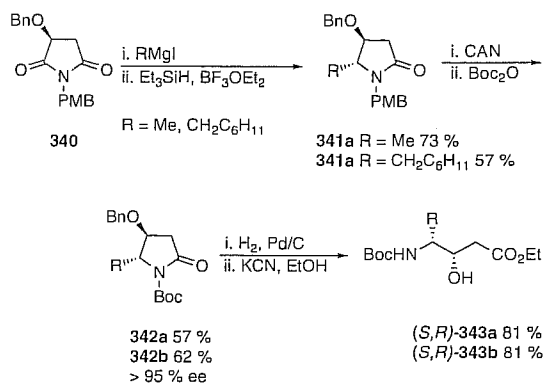
Scheme 14.93



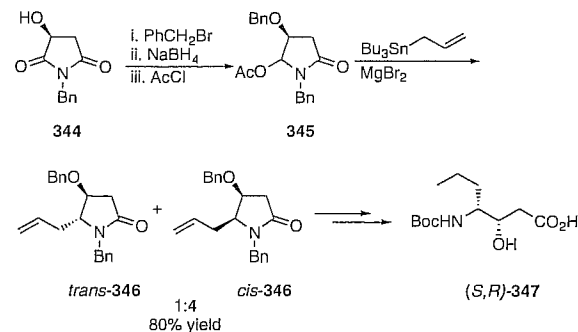
Scheme 14.94

amine of a configurationally stable *N*-Boc-L-leucinal derivative. Conversion of *N*-Boc-L-leucine (310) to the *N*-Boc-L-leucinal derivative (337) is achieved in two steps and Wittig olefination yields the α,β -unsaturated ester (S)-338 (Scheme 14.94). Intramolecular conjugate addition of the hydroxyl group was successful to give the expected oxazolidine (S)-339. Deprotection and recrystallization afforded enantiomerically pure (S,S)-(8) [261].

The development of flexible non-amino acid-based approaches to the synthesis of *anti*- γ -amino- β -hydroxy carboxylic acids has been explored. Malimides (340) derived from malic acid undergo regioselective alkylation at the C-2 position with good yields as a mixture of diastereoisomers (Scheme 14.95). Catalytic hydrogenation of the diastereomeric mixture gives the lactam as a 3:1 mixture of diastereoisomers [262], however Lewis acid mediated ionic hydrogenation yields only the *trans* isomer (341)



Scheme 14.95



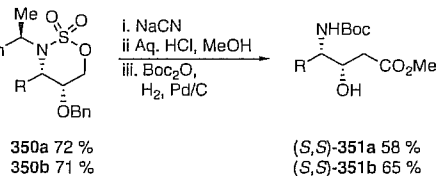
Scheme 14.96

indicating that the reaction proceeds through an *N*-acyliminium intermediate [263]. The pyrrolidin-2-ones (342) have been converted to the corresponding protected statine analogs (S,R)-(343a,b) in four steps [262, 263]. Similar methodology has been used to generate small libraries of β -hydroxy- α -amino acids used in a combinatorial synthesis of hapalosin analogs [264].

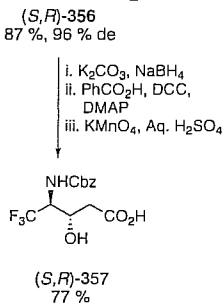
Statine analogs have also been synthesized from the malimide derivative (344) with diastereomeric ratios up to 4:1:1 via a *cis*-selective allylation of the α -alkoxy *N*-acyliminium intermediate of (345) (Scheme 14.96). Alkylation with allyl in the presence of MgBr_2 proceeds in high yield affording the lactam (346) as mixture of diastereoisomers which can be converted to the statine analog (347) in three steps [265]. A similar procedure has also been reported using methallyltrimethylsilane in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to facilitate the *trans*-selective alkylation (*cis*:*trans* 1:11) [266].

Several syntheses of statine or *syn* analogs starting from carbohydrates have been described. These include a multistep syntheses of statine from 3-deoxy-furanose derivatives [267, 268], AHPPA and statine from glucosamine [269, 270], and *N*-methyl AHPPA from (R)-cyclohexylidene glyceraldehydes [271]. One of the most versatile and efficient carbohydrate-based syntheses of statines is via the addition of Grignard reagents to the glyceraldehyde-derived chiral imine (348) (Scheme 14.97) [272]. The amine (349) is produced in high yields and diastereoselectivity, and converted to the amidosulfate (350). Displacement of the sulfate with cyanide, methanolysis, hydrogenolysis, and carbamoylation of the *N*-benzyl afforded the statine derivatives (351) [273].

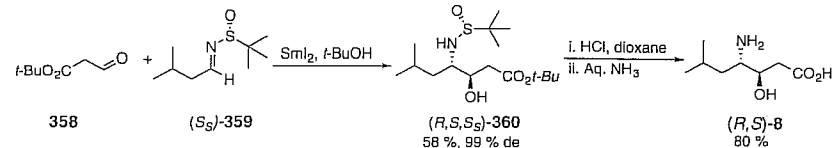
The stereocontrolled elaboration of various chiral auxiliaries has provided access to a range of γ -substituted β -hydroxy- γ -amino acids and related analogs. Chiral sulfoxides have been used as a chiral auxiliary in the synthesis of (S,R)-4-amino-5,5,5-trifluoro-3-hydroxypentanoic acid [(S,R)- γ -Tfm-GABOB] (S,R)-(357) (Scheme 14.98). Addition of lithiated (R)-*p*-tolyl- γ -butenyl sulfoxide (S)-(352) to *N*-*p*-methoxyphenyl imine (353) affords the adduct (354) with poor diastereomeric excess. After cleavage of *N*-*p*-methoxyphenyl group the major (S,R,*R*_s) isomer (355) was isolated by chromatography. Conversion of the amine, to the *N*-Cbz derivative,



Scheme 14.97



Scheme 14:98



Scheme 14.99

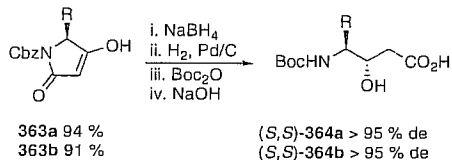
a nonoxidative Pummerer reaction, and reduction of the sulfenamide intermediate affords (*S,R*)-356, which was converted to orthogonally protected enantiomerically pure (*S,R*)- γ -Tfm-GABOB (*S,R*)-357. The synthesis of (*R,S*)-357 from the *N,S*-thioaminal of (*R*)-trifluoropyruvaldehyde has also been reported [274].

Alternatively, chiral *N*-*tert*-butanesulfinyl imine of 3-methylbutanal (359) undergoes a samarium diiodide catalyzed cross-coupling reaction with *tert*-butyl 3-oxopropanoate (Scheme 14.99). The corresponding β -amino alcohol (360) is attained in 58% yield with 99% d.e. Cleavage of the *tert*-butyl ester and *N*-sulfinyl group in one step by acid hydrolysis affords optically pure (*R,S*)-statine (*R,S*)-8 in high yield [275].

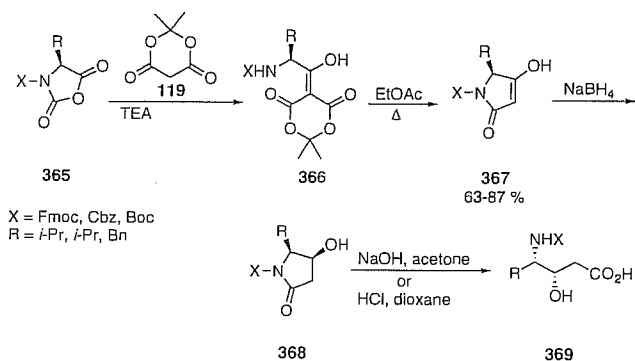
Stereospecific synthesis of *N*-Boc-(*S,S*)-statine (*S,S*)-(364a) and *N*-Boc-(*S,S*)-AHP-PA (*S,S*)-(364b) was achieved via a novel Wittig reaction of oxazolidinones (361) derived from *N*-Cbz- α -amino acids (Scheme 14.100). Treatment of the oxazolidinones (362) with HCl yields the tetramic acids (363) that can be converted to (*S,S*)-(364a) and (*S,S*)-(364b) in four steps with high enantioselectivity and good yields [276, 277].

A range of optically pure tetramic acid (367) derivatives have also been prepared in high yields by reaction of urethane-*N*-carboxyanhydrides (362) from protected α -amino acids, with Meldrum's acid (119) and subsequent cyclization (Scheme 14.101). Reduction to the alcohol (368) and hydrolysis affords the statine derivatives (369) in high overall yields and diastereomeric purity [278].

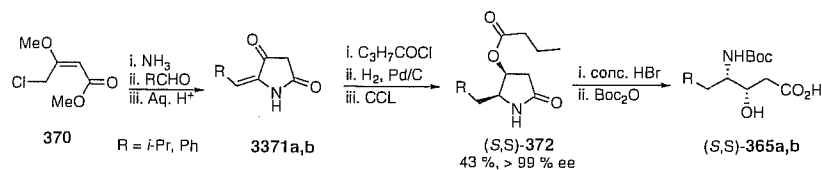
Reaction of (*E*)-methyl 4-chloro-3-methoxybut-2-enoate (370) with ammonia, direct condensation with the appropriate aldehyde, and subsequent hydrolysis yields



Scheme 14.100



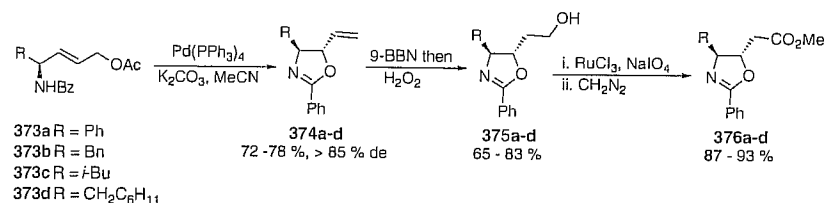
Scheme 14.101



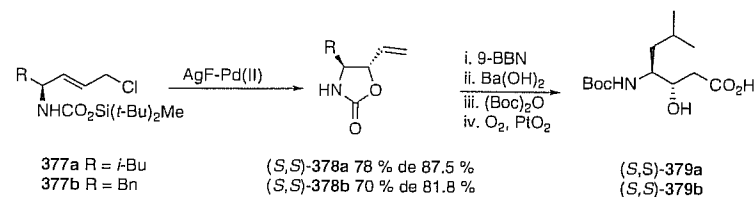
Scheme 14.102

the 5-substituted tetramic acid (371) (Scheme 14.102). Conversion to the enol butyrate, hydrogenation, and crystallization afforded the racemic *cis* butyrates which were resolved via a kinetic resolution catalyzed by CCL to provide (*S,S*)-372. Acid hydrolysis and protection of the amine affords the *N*-Boc derivatives (*S,S*)-365 [279].

Intramolecular Pd(0)-catalyzed reaction of the *O*-acetyl 4-amino-2-alken-1-ols (373), prepared in four steps from α -amino acids, affords the *trans* oxazolines (374) in good yield and high diastereoselectivity (Scheme 14.103). A hydroboration sequence yields the alcohol (375), which was oxidized and esterified to afford the oxazoline protected γ -amino- β -hydroxy esters (376). Deprotection to the corresponding γ -amino- β -hydroxy acids can be achieved using known methodology [280].



Scheme 14.103

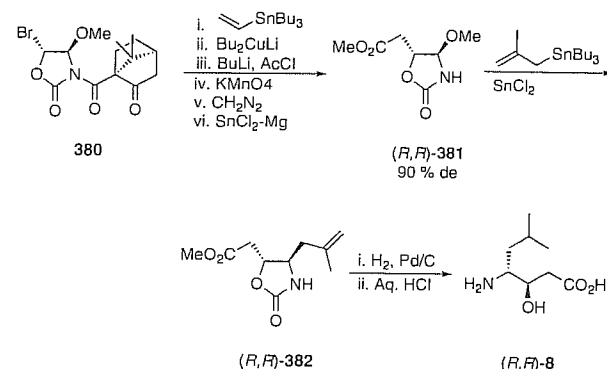


Scheme 14.104

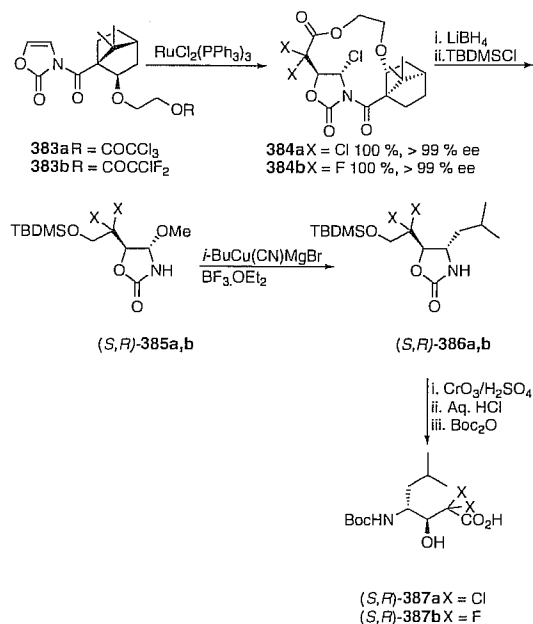
Stereoselective S_N2' cyclic carbamate formation [initiated by AgF or AgF-Pd(II)] of the *tert*-butyldimethyl silyl carbamate of 4-amino-6-methylhept-2-enyl chloride (377a) yields the oxazolidone (378a) (Scheme 14.104). Hydroboration of the terminal alkene, cleavage of the oxazolidone, protection of the amine, and oxidation affords the *N*-Boc-protected statine (*S,R*)-379a. AHPPA (*S,R*)-379a) was also prepared by this method [281, 282].

The stereodefined functionalization of oxazolones (380) results in the highly diastereoselective formation of substituted oxazolidinone derivatives, which are versatile chiral synthons for vic-amino hydroxy compounds (Scheme 14.105). Allylation at the 5-position and oxidative cleavage of the allyl group yields the ester (381). Stereospecific displacement of the 4-methoxy group with a methallyl group afforded the oxazolidinone (382), which was converted to (*R,R*)-statine (*R,R*)-8 [283]. In a similar synthesis, all four stereoisomers of statine have been prepared from oxazolidinones derived from (*R*)- and (*S*)-methyl α -hydroxyphenylpropanoate via a highly diastereoselective isobutenylation [284].

A novel intramolecular Ru(II)-catalyzed cyclization of the chiral oxazolones (383) results in the exclusive formation of the 12-membered cycloadducts (384) with complete diastereoselectivity (Scheme 14.106). Reductive cleavage of the adducts



Scheme 14.105

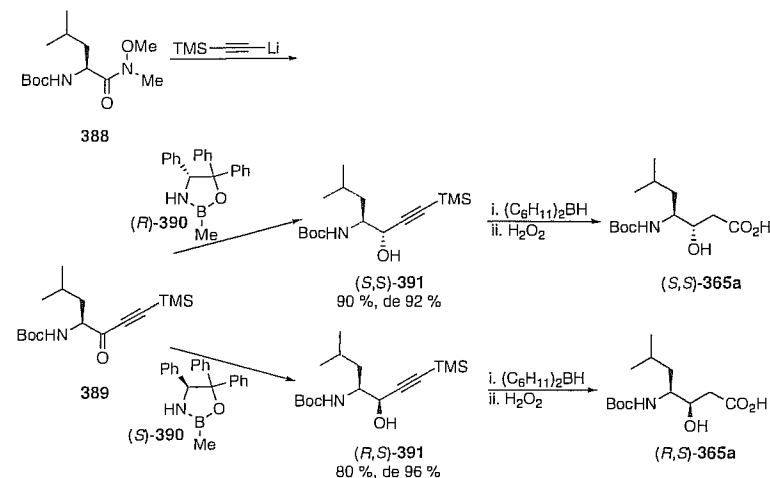


Scheme 14.106

affords the oxazolidinones (*S,R*)-(385) which can be alkylated and converted to enantiomerically pure dichloro and difluoro statine analogs (*S,R*)-(387) [285].

All four isomers of statine [286] and a range of analogs [287] have been prepared via a tandem stereoselective reduction/hydroboration strategy. 1-Trialkylsilyl acetylenic ketones (389) were derived from the appropriate α -amino acid by reaction of the Weinreb amide (388) with the lithium acetylide (Scheme 14.107). Reduction of the ketones with the chiral oxazaborolidine (390) afforded the corresponding alcohol (391) in good yields and high diastereoselectivity. Oxidative hydroboration yields the *N*-Boc-statine (365a) [286, 288].

The reduction of *N*-protected γ -amino- β -ketophosphonates derived from α -amino acids has been thoroughly investigated as a route to phosphostatines. Reaction of protected α -amino acids yields the protected γ -amino- β -ketophosphonates (392) (Scheme 14.108). Reduction of (*S*)-(393) with CCB affords the *syn* product (*R,S*)-(394) [289, 290], whereas the reduction of (*S*)-*N*-benzylamino- β -ketophosphonates with Zn(BH₄)₂ yields the (*S,S*) or *anti* product through chelation control [290]. In both cases the reduction proceeds with good chemical yields and high diastereoselectivity. Hydrolysis and hydrogenolysis affords the corresponding aminohydroxyphosphonic acids (395). However, protection as the *N*-*p*-toluenesulfonamide is reported to result

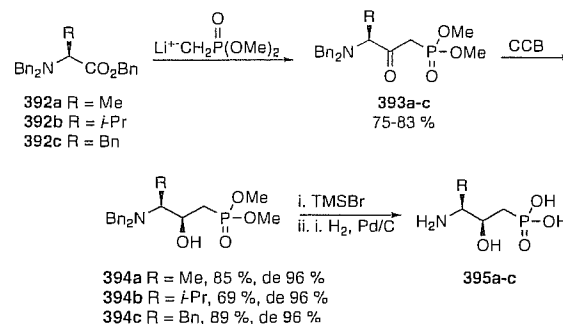


Scheme 14.107

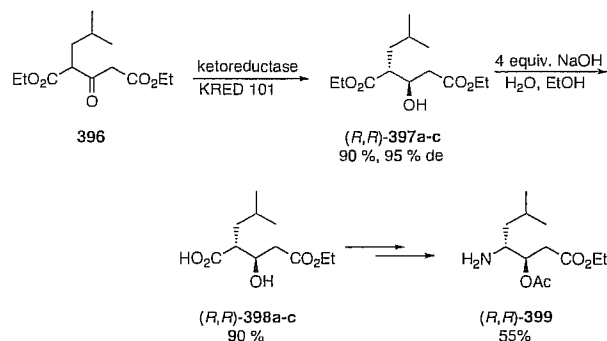
in good yields but poor diastereoselectivity on reduction with a range of hydrides [291].

Both (*R,S*)- and (*S,S*)-*N*-Boc-statine have also been synthesized in high diastereomeric purity from the readily available β -keto sulfoxide by a stereodivergent sequence involving reduction of the keto sulfoxide with diisobutylaluminum hydride (DIBAH) or DIBAH/ZnBr₂, respectively [292].

Statine and statine analogs with natural and unnatural side chains have been prepared via a diastereoselective reduction of a 2-alkyl-substituted 3-ketoglutarate (396) by an NADPH-dependent ketoreductase (Scheme 14.109). Various enzymes



Scheme 14.108

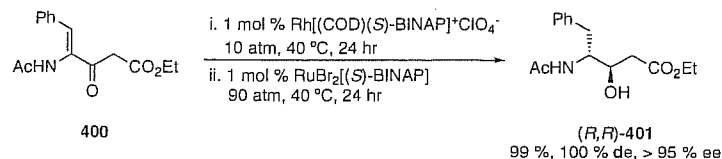


Scheme 14.109

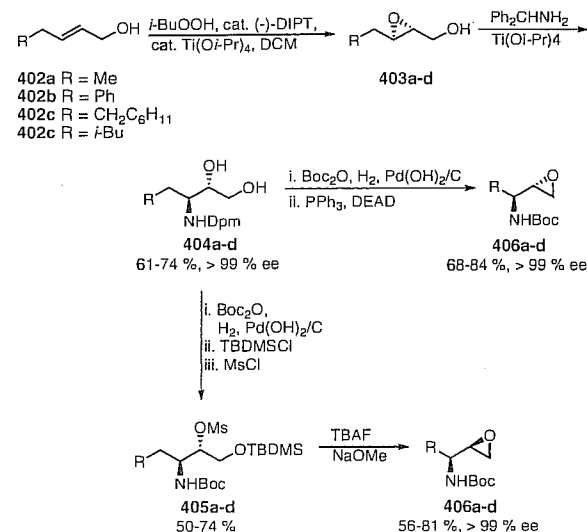
were evaluated for stereoselectivity, with the enzyme KRED 101 found to have the highest stereoselectivity in the reduction of (396). Due to the rapid isomerization of (396) the two chiral centers of (397) are generated in one step with high yields of a single stereoisomer obtained. Subsequent chemical or enzymatic regioselective hydrolysis to the mono-acid followed by rearrangement under Curtius or Hofmann conditions generates the final statine protected (*R,R*)-399 [293, 294].

The diastereoselective hydrogenation of *N*-protected γ -keto esters catalyzed by BINAP-Ru(II) complexes has also been reported to provide an efficient entry to the statine series with high enantiomeric purities [295]. The protected (*R,R*)-AHPPA derivative (*R,R*)-401 has been prepared in high yields and enantiomeric purity by a one-pot, two-catalyst sequential reduction of γ -(acylamino)- γ,δ -unsaturated- β -keto esters (400) using a combination of Rh(I) and Ru(II) catalysts (Scheme 14.110) [296]. However, these reactions also require high pressures (90 atm) over extended periods of time.

Sharpless catalytic asymmetric functionalization of allylic alcohols affords a convenient entry to enantiopure *syn* or *anti* β -hydroxy- γ -amino acids. Sharpless epoxidation of 4-substituted (*E*)-but-2-en-1-ols (402) provides the epoxide (403) that is converted to the enantiomerically enriched *anti*-3-amino-1,2-diols (404) and subsequently transformed through a stereodivergent sequence to both *N*-Boc-aminoalkyl epoxides (406) (Scheme 14.111) [297].



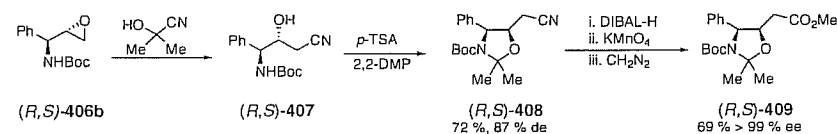
Scheme 14.110



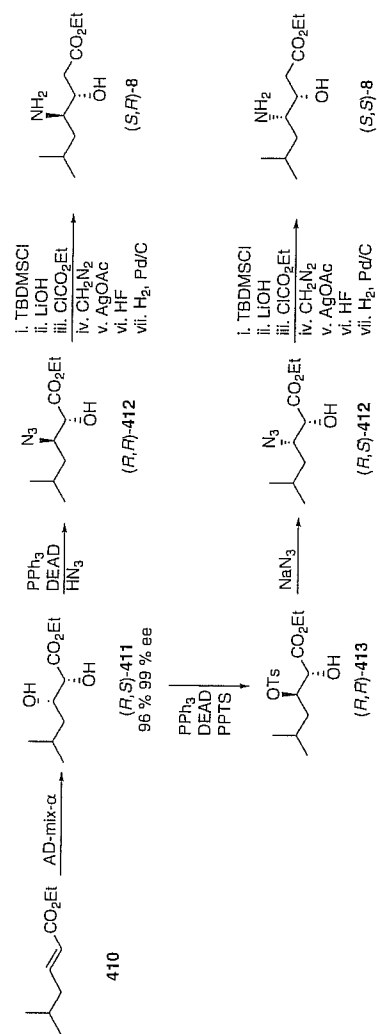
Scheme 14.111

Subsequent regioselective ring-opening of the epoxide (406b) with cyanide yields the nitrile (407), formation of the oxazolidine (408) and nitrile to carboxyl conversion afford, in good yields, protected γ -hydroxy- β -amino acids (409) belonging to either the *anti* or *syn* series, depending on the stereochemistry of the epoxide (406b) (Scheme 14.112) [298]. Similar methodology has been used in the synthesis of (*R,S*)-MeAHPPA [299]. Statine and its 3-epimer have also been prepared by the regioselective epoxide opening of the 2,3-epoxy-1-alkanols (400d) by azide [300].

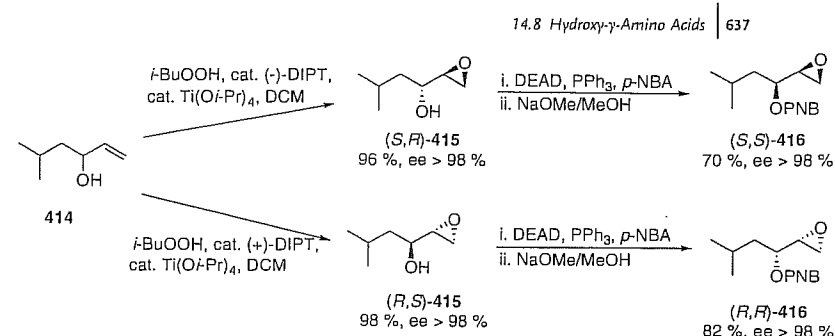
Asymmetric dihydroxylations have also been employed as the sole source of chirality in the synthesis of statines. *N*-MeAHPPA has been prepared in an 11-step synthesis from (*E*)-5-(benzyloxy)pent-2-en-1-ol [301]. Reaction of (*E*)-ethyl 5-methylhex-2-enoate (410) under Sharpless asymmetric dihydroxylation conditions yields the *syn*-2,3-dihydroxy ester (411) which was converted to the γ -azide (412) either directly or via the tosylate (413), providing access to both diastereoisomers (Scheme 14.113). Arndt-Eistert homologation and deprotection yielded the *anti*-statine (*S,R*)-8 and



Scheme 14.112



Scheme 14.113



Scheme 14.114

the natural *syn*-statine (*S,S*)-(8), respectively. The other two stereoisomers are attainable by the use of AD-mix- β [302].

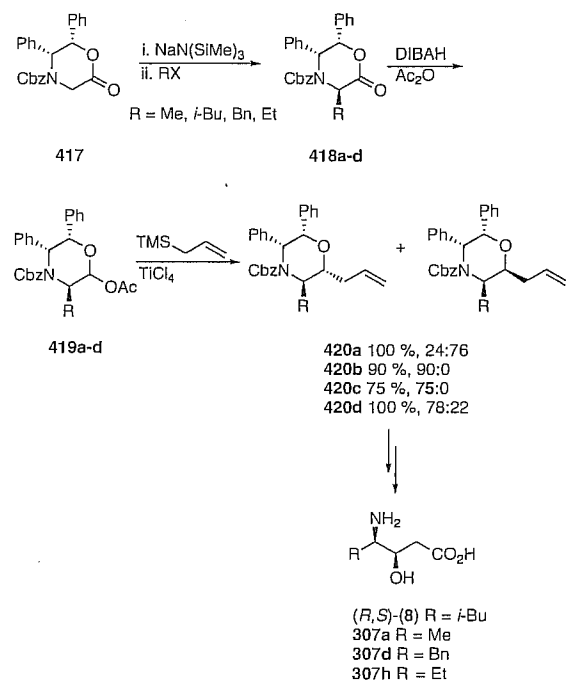
All four stereoisomers of statine amide (*S,S*)-4-amino-3-hydroxy-6-methylheptanamide have been synthesized via a kinetic resolution using the Sharpless asymmetric epoxidation of a racemic 3-hydroxy-5-methyl-1-hexene (414) (Scheme 14.114). Epoxidation with diisopropyl *D*-tartrate gave (*R,S*)-(415) and diisopropyl *L*-tartrate gave (*S,R*)-(415). The *anti* compounds (*S,S*)- and (*R,R*)-(416) were prepared through inversion of the C-2 hydroxyl under Mitsunobu conditions. The epoxides (416) were converted to the corresponding statine amides via conversion to the azide and opening of the epoxide with cyanide [303].

AHPPA has also been prepared via Sharpless asymmetric aminohydroxylation of ethyl cinnamate with *N*-bromoacetamide as the nitrogen source. The *N,O*-protected aminohydroxyl ester was afforded in moderate yield as a 10:1 mixture of regioisomers and 89% e.e. [304].

The phenyl glycine-derived alkylated oxazinone (417) was alkylated to yield (418) and reduced to the lactol acetate (419), which undergoes coupling with the ketene silyl acetals or allyl silanes [305] in the presence of a Lewis acid to afford the corresponding product (420) (Scheme 14.115). In the case of the allyl silanes, the reaction proceeds with good to excellent stereoselectivity and yields. The smaller methyl substituent results in the reverse stereoselectivity. However, a substantial amount of a rearrangement product, resulting from a 1,2-alkyl migration, was formed in a number of cases. These coupling products are easily converted to the β -hydroxy- γ -amino acids (307) by oxidation to the carboxylic acid and deprotection [306].

Other methods have also been used to prepare statine and related analogs, such as chromatographic resolution of α -methoxyphenylacetates [307], the cycloaddition of chiral enol ethers with dichloroketene coupled with the Beckmann ring expansion [308, 309], and the addition of cyanide to 4-alkoxy-trichloro-but-3-en-2-ones which occurs with poor diastereoselectivity [310].

A novel protected α -methylene-statine (424) has been prepared as an intermediate in the synthesis of epopromycin B (Scheme 14.116). Baylis–Hillman reaction of (*S*)-*N*-Fmoc-leucinal (422) with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (423)



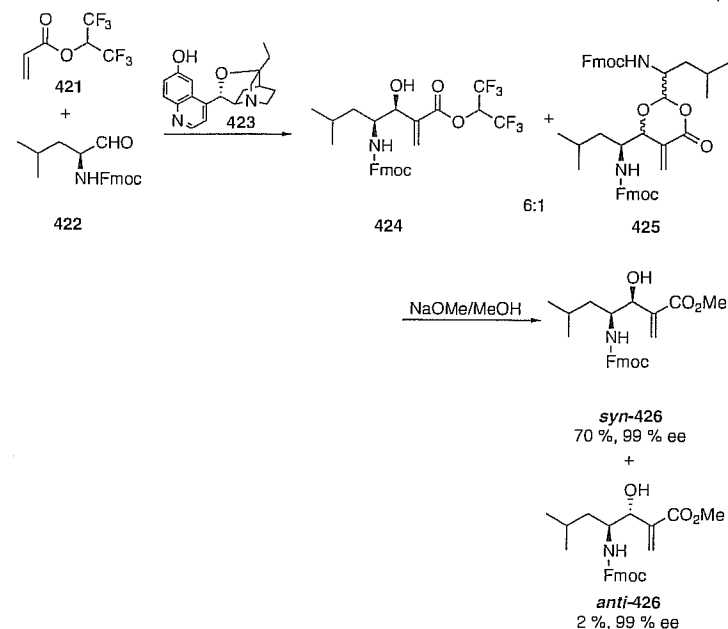
Scheme 14.115

catalyzed by a stoichiometric amount of the *Cinchona* alkaloid proceeded smoothly to yield a mixture of the ester (424) and the dioxanone (425). Methanolysis of the mixture afforded the *syn* diastereoisomer (426) as the major product [311].

14.8.5

 β -Hydroxy-Disubstituted γ -Amino Acids

Many of the standard synthetic methods used for the synthesis of β -hydroxy-substituted γ -amino acids have also been used in the synthesis of β -hydroxy-disubstituted derivatives. The 2,3-*anti*-2-isobutyl statines were prepared by the addition of achiral ester enolates to *N*-Boc-leucinal and the 2,3-*syn* isomers via a β -keto ester reduction [312]. Evan's aldol methodology has been employed in the synthesis of β -hydroxy-disubstituted γ -amino acids (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (AHMPA) subunit of bleomycin A₂ [313, 314] and a 2-substituted analog of ACHPA [315]. (2*S*,3*S*,4*R*)-AHMPA has been prepared via a nonstereoselective NaBH₄ reduction of the corresponding 3-keto derivative [316],

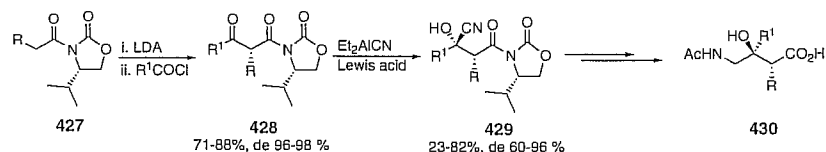


Scheme 14.116

and from *D*-rhamnose via a multistep synthesis resulting in a low overall yield [317]. A more facile synthesis of (2*S*,3*S*,4*R*)-AHMPA, was achieved through a stereoselective aldol condensation of protected *D*-alaninal and chiral (*E*)-vinylxyboranes. Highest diastereoselectivity (35:1) was achieved by the addition of phenylthio (*E*)-vinylxyborane to the protected alaninal [318]. The addition of ethyl lithioacetate to the α -amino acid-derived methyl ketones affords 3-methyl-statine and AHPPA derivatives. Coupling of the diastereoisomers to alanine isomylamide facilitated chromatographic separation [319].

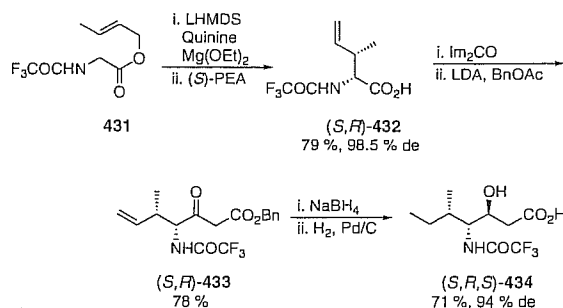
A range of α -methyl- β -substituted β -hydroxy- γ -amino acids (430) have been prepared using a two-step Evans chiral auxiliary methodology. The addition of Et₂AlCN in the presence of ZnBr₂ or Et₂AlCl to 1,3-dicarbonyl compounds (428) derived from (*S*)-4-isopropyl-2-oxazolidinone (427), proceeds with good to excellent diastereoselectivity and good yields (Scheme 14.117). This type of addition to chiral-dicarbonyl substrates represents a new synthetic methodology leading to the formation of enantiomerically pure cyanohydrins (429) which can be converted in a three-step procedure to the α -methyl- β -methyl- β -hydroxy- γ -amino acid (430) [320].

The achiral TFA-protected glycine crotyl ester (431) has been converted to *N*-protected isostatine in four steps via an ester enolate Claisen rearrangement



R = H, Me
R¹ = Me, Ph, *p*-Cl-Ph, *p*-MeO-Ph, *p*-Me-Ph

Scheme 14.117



Scheme 14.118

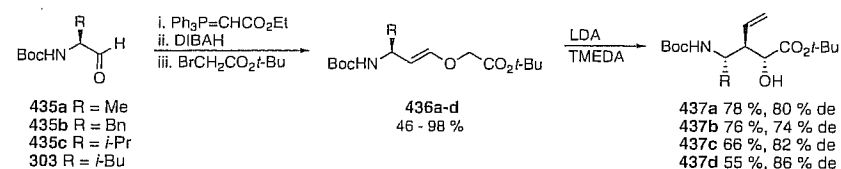
(Scheme 14.118). Deprotonation of the achiral glycine crotyl ester (431) in the presence of quinine affords (S,R)-432 in near quantitative yield and 88% e.e. A single recrystallization with (S)-phenylethylamine provides (S,R)-432 in high enantiomeric purity. Claisen condensation with the imadazolidine and conversion to the benzyl ester yields the β -keto ester (S,R)-433 which is reduced and deprotected to afford (S,R,S)-434 [321].

Enantiomerically pure 4-amino-allyloxyacetates (436), prepared from L- α -amino aldehydes (300, 435), undergo a stereoselective Wittig rearrangement in the presence of *N,N,N',N'*-tetramethylethylenediamine (Scheme 14.119). The *anti*- α -hydroxy- β , γ -substituted γ -amino acid esters (437) are produced as the major diastereoisomer in good yield [322].

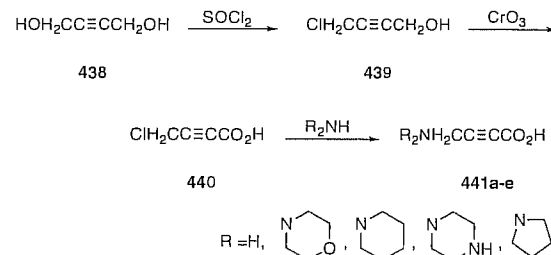
14.9

Unsaturated γ -Amino Acids

A range of 4-aminobut-2-ynoic acids (4-aminotetrolic acid) (441) (Scheme 14.120), the alkyne analog of GABA, have been prepared by direct nucleophilic attack of the appropriate amine on 4-chlorotetrolic acid (440), which was prepared via oxidation of 4-chlorobut-2-yn-1-ol (439) [323]. More recently, γ -substituted α,β -acetylenic γ -amino



Scheme 14.119



Scheme 14.120

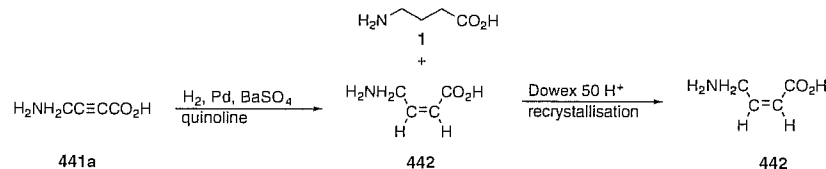
esters were obtained in moderate yields (30–40%) by a two-step procedure involving formation and flash vacuum pyrolysis of chiral aminoacyl phosphorus ylides [324, 325].

Hydrogenation of 4-aminotetrolic acid (441a) over 10% palladium-on-barium sulfate catalyst in the presence of quinoline afforded a mixture of GABA (1) and *cis*-4-aminocrotonic acid (442) that was purified by ion-exchange chromatography and recrystallization (Scheme 14.121). The *trans* isomer of 4-aminocrotonic acid has been prepared by dehydration of 3-hydroxy-4-aminobutyric acid (6) [326].

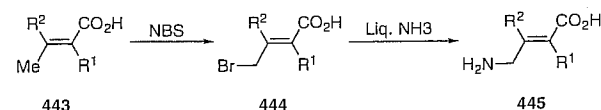
14.9.1

Unsaturated Substituted γ -Amino Acids

Allan and Twitchin have prepared a range of substituted *trans*-4-aminocrotonic acids (445) via amination of the allylic bromides (444) (Scheme 14.122). The configuration of (443) was found not to be important as the allylic bromination resulted in



Scheme 14.121



R¹ = H, Me, Cl, Br

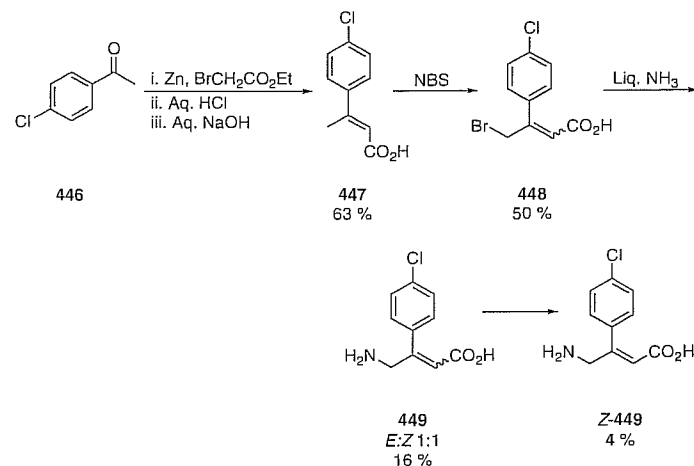
R² = H, Me, Br

Scheme 14.122

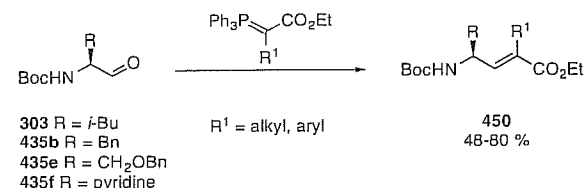
isomerization to equilibrium mixtures. The reactions proceed in low to moderate yields and also resulted in the formation of vinyl glycine analogs [327, 328]. 4-Amino-3-halogenobut-2-enoic acids were prepared by *trans* addition of HX to 4-chlorotetrolac acid (440) and subsequent amination [329].

The preparation of the *cis* isomer of the unsaturated baclofen analog (449) from 4-chloroacetophenone (446) via a Reformatsky reaction has been reported (Scheme 14.123) [330]. The α,β -unsaturated acid (447) which was isolated by crystallization from a mixture with the alternative α,β -unsaturated acid. Allylic bromination gave a 12:1 mixture of monobrominated derivatives (448) with the (*Z*) product predominating. Treatment of the (*Z*) isomer with liquid ammonia gave (*Z*)- and (*E*)-4-amino-3-(4-chlorophenyl)but-2-enoic acids (449) as a 1:1 mixture from which the (*Z*) isomer could be isolated in low yield [330].

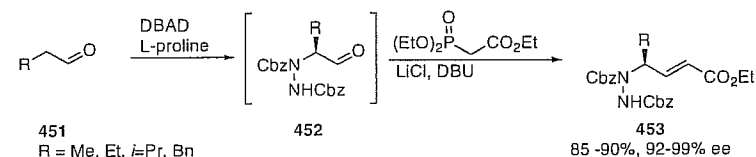
γ -Amino- α,β -unsaturated esters have been prepared by Horner–Wadsworth–Emmons olefination of a range of aldehydes. *N*-Boc-protected α -amino aldehydes (303, 435b, e and f) react smoothly with a variety of ylides and in general without racemization to afford 2,4-disubstituted α,β -unsaturated γ -amino acids (450) (Scheme 14.124). Racemization was reported to occur with (435e) [331].



Scheme 14.123



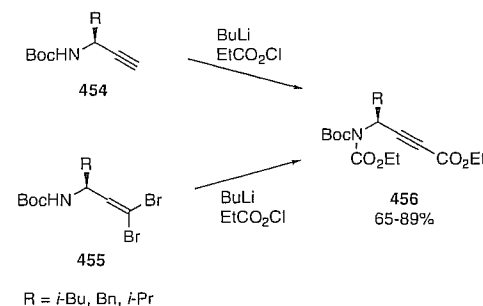
Scheme 14.124



Scheme 14.125

Similar methodology has been used in the solid-phase preparation of olefin-containing protease inhibitors [332]. A one-pot tandem proline-catalyzed direct α -amination/Horner–Wadsworth–Emmons olefination of aldehydes has also been described. Reaction of the aldehydes (451) and trapping of the intermediate (452) with diethyl phosphonacetate affords the γ -amino- α,β -unsaturated esters (453) (Scheme 14.125) [333].

Protected chiral γ -amino acetylenic esters have been synthesized using naturally occurring amino acids as the chiral source. Enantiomerically enriched propargylamines (454) [334, 335] or vinyl dibromides (455) [334] were treated with BuLi at low temperature affording, after alkoxy carboxylation and carbamoylation, enantiomerically enriched derivatives of alkynologous amino esters (456) (Scheme 14.126). Cyclopentadienylruthenium (1,4-cyclooctadiene [COD]) chloride-catalyzed reaction



R = *i*-Bu, Bn, *i*-Pr

Scheme 14.126

of the γ -amino acetylenic esters with alkenes affords a convenient synthesis of α -alkylated- γ -amino- α -alkenoates [335].

γ -Substituted γ -amino α,β -unsaturated esters have also been prepared by the nucleophilic reaction of a planar chiral allyl η^3 -allyldicarbonylnitrosyliron complex with benzylamine [336], the flash vacuum pyrolysis of α -aminoacyl-stabilized phosphorus ylides [324, 325], and the reaction of nitrones with the alkyl lithiopropiolates and subsequent reduction [337].

14.10

Cyclic γ -Amino Acids

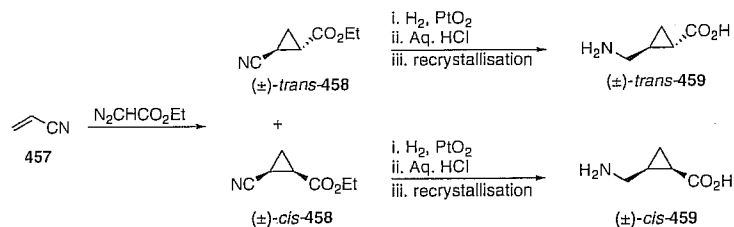
14.10.1

Cyclopropyl γ -Amino Acids

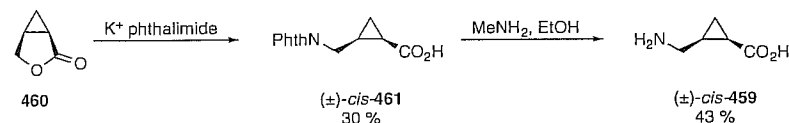
Ethyl 2-cyanocyclopropanecarboxylate (458) was initially prepared by cyclopropanation of acrylonitrile (457) (Scheme 14.127). The *trans* and *cis* isomers of the cyanoester were separated by fractional distillation. Hydrogenation of the *trans* cyanoester (\pm)-*trans*-(458) in acetic acid, hydrolysis of the resulting amide, and recrystallization yielded *trans*-2-(aminomethyl)cyclopropanecarboxylic acid (\pm)-*trans*-(459) [338]. Hydrogenation of the less-stable *cis* isomer (\pm)-*cis*-(458) was accompanied by isomerism to the *trans* isomer; however, pure *cis*-2-(aminomethyl)cyclopropanecarboxylic acid (\pm)-*cis*-(459) could be isolated after hydrolysis of the amide by repeated slow recrystallizations [339]. All four enantiomers of 2-(aminomethyl)-1-carboxycyclopropane prepared as described above, have also been resolved by chromatographic separation of the diastereomeric (*R*)-pantolactone esters [340].

The (\pm)-*cis*-(459) has also been achieved by reaction of the cyclopropyl lactone (460) with potassium phthalimide to give the *cis* acid (461), overcoming the problems of racemization (Scheme 14.128). Dephthaloylation was accomplished in ethanolic methylamine solution and the *cis* amino acid was obtained as a crystalline solid. The *trans*-(459) was also prepared by Gabriel synthesis of *trans*-ethyl 2-(bromomethyl)cyclopropanecarboxylate and subsequent hydrolysis [341].

Polymer-supported PLE has been used for the resolution of the *meso* diester *cis*-(462) to yield the enantiopure monoacid (*R,S*)-(463) (Scheme 14.129). Borane



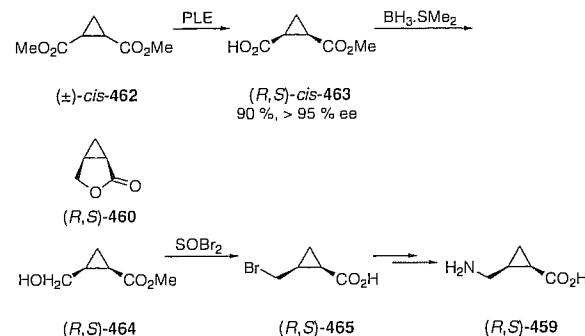
Scheme 14.127



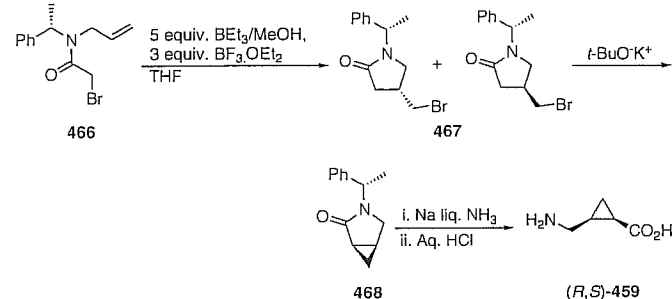
Scheme 14.128

reduction of the carboxylic acid and removal of boric acid with a borane-specific resin yielded a mixture of alcohol (*R,S*)-(464) and lactone (*R,S*)-(460), which were both transformed to the bromide (*R,S*)-(465). Conversion of (*R,S*)-(465) to (*R,S*)-(459) was carried out, either via reaction with azide or phthalimide [342].

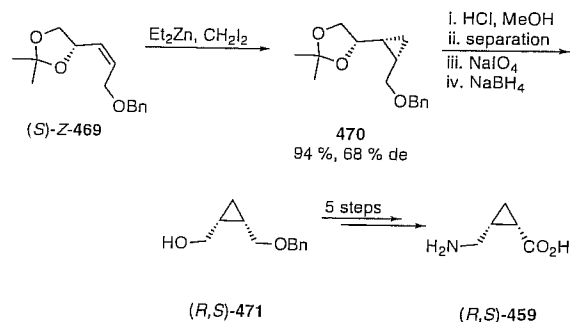
(*R,S*)-(459) has also been prepared by a novel tin-free chemo- and stereoselective radical protocol (Scheme 14.130) [343]. The 4-alkyl-pyrrolin-2-ones (467) were synthesized from chiral *N*-allyl- α -bromoacetamides (466), via a sequential 5-*exo*-trig radical cyclization-hydrogen or bromine atom-transfer process, and the major isomer isolated by chromatography. Formation of the cyclopropane (468) and deprotection afforded (*R,S*)-(459) in high yield and enantiopurity [343].



Scheme 14.129



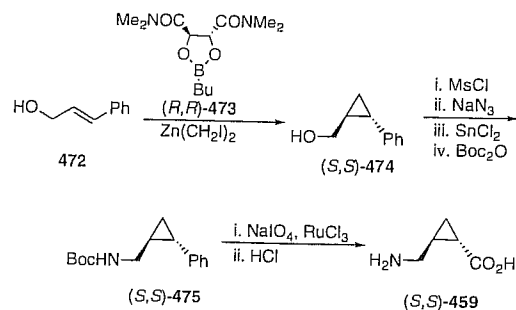
Scheme 14.130



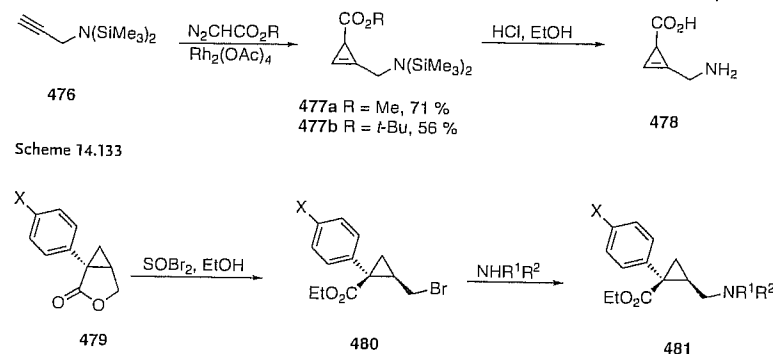
Scheme 14.131

All four enantiomers of (**459**) are available from Simmons–Smith reactions of (*Z*)- and (*E*)-allyl alcohol derivatives (**469**), respectively, obtained from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde (Scheme 14.131). The cyclopropane (**470**) was afforded in good yields. Cleavage of the chiral auxiliary, chromatographic separation, and oxidation provided access to the desymmetrized diol (**471**), which could be converted to the corresponding isomer of (**459**) in five steps. The terminal allylic hydroxyl protecting group was found to greatly influence the diastereoselectivity of the cyclopropanation, with the TBDMS ether affording a single diastereoisomer [344].

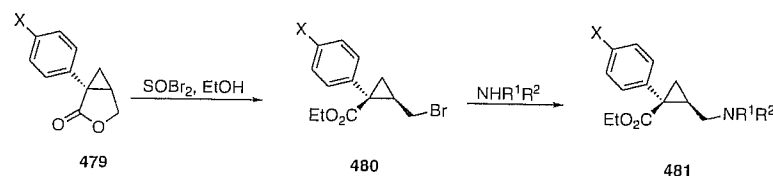
An efficient synthesis of (*S,S*)-(**459**) has been achieved via asymmetric cyclopropanation of *trans*-cinnamyl alcohol (**472**) in the presence of the (+)-tartaric acid-derived chiral dioxaborolane chiral ligand (*R,R*)-(**473**) (Scheme 14.132). The (*S,S*)-cyclopropyl alcohol (**474**) was obtained in high enantiomeric excess and good yield. Conversion of the alcohol to the azide via the mesylate and reduction with Sn(II) chloride followed by Boc protection yields the *N*-protected amine (**475**). Oxidative degradation of the phenyl moiety to a carboxylic acid and deprotection completed the synthesis of (*S,S*)-(**459**) [345].



Scheme 14.132



Scheme 14.133



X = H, Cl, F, CH₃, OCH₃.

R¹ = H, Me, CH₂CH₂OH, *i*-Pr
R² = H, CH₃, Bn, CH₂CH₂OH, *i*-Pr, *n*-Bu

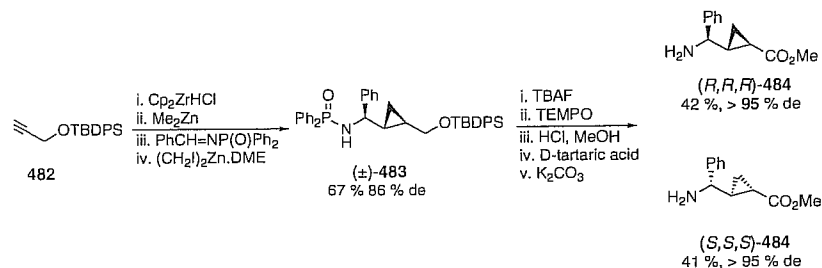
Scheme 14.134

Treatment of *N*-silylated propargylamine (**476**) with alkyl diazoacetates in the presence of rhodium acetate affords the cyclopropane (**477**) in good yields (Scheme 14.133). Hydrolysis yields racemic 2-(aminomethyl)cyclopropanecarboxylic acid (**478**) [346]. Similarly, β,γ -unsaturated, *N*-silylated amines undergo reaction with diazoacetates to afford 1-substituted 2-(aminomethyl)cyclopropanecarboxylic acids [347] and *N*-silylated allyl amines react with substituted methyl diazoacetate to yield 2-substituted 2-(aminomethyl)cyclopropanecarboxylic acids [348].

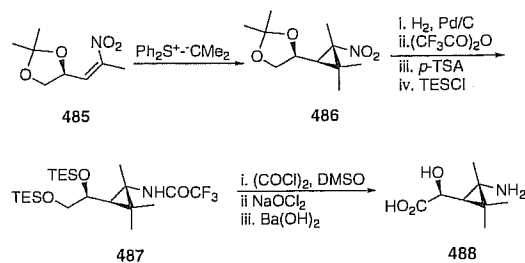
(*S,R*)-2-(Aminomethyl)cyclopropanecarboxylic acid [349] and a series of (*Z*)-2-substituted 2-(aminomethyl)cyclopropanecarboxylic acids have also been prepared from the appropriately substituted lactones [350]. Reaction of (**479**) with thionyl bromide affords the bromo ester (**480**) which can be converted to the disubstituted amine (**481**) (Scheme 14.134). Alternatively, reaction with phthalimide and hydrolysis with methylamine affords the primary amine (*R*¹ = *R*² = H) [350, 351].

The multicomponent condensation of organozirconocene, an aldimine, and a zinc carbenoid has been applied to the stereoselective synthesis of γ -substituted α,β -cyclopropane amino acid derivatives. Reaction of the organozirconocene with propargylic ethers (**482**) or homopropargylic ethers, followed by sequential transmetalation to dimethylzinc, addition to *N*-diphenylphosphinylimine, and treatment with bis(iodomethyl)-zinc/dimethoxy ether (DME) complex afforded the desired amide (\pm)-(**483**) (Scheme 14.135). Removal of the TBDPS group and oxidation of the resulting alcohol afforded the carboxylic acid, which could be converted into the methyl ester. Hydrolysis of the amide and resolution as the tartrate salts afforded diastereomerically pure amino acids (**484**) [352]. Homopropargylic ethers have also been converted to γ -substituted α,β -cyclopropane amino acids [353].

Cyclopropanation of optically active nitroalkenes (**485**) with sulfur ylides or dibromocarbene affords nitrocyclopropanes (**586**) in a diastereoselective manner (Scheme 14.136). Reduction of the nitro group, protection as the *N*-trifluoroacetyl



Scheme 14.135



Scheme 14.136

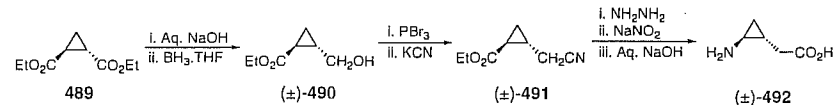
derivative, and replacement of the dioxolane protecting group yields the bistriethylsilyloxy ether (487). Selective oxidation of the primary triethylsilyl ether and subsequent deprotection afforded 2,3,3-trisubstituted (2-aminocyclopropyl)-2-hydroxyacetic acid (488) [354].

The *cis*- and *trans*-2-aminocyclopropylacetic acids have been prepared in seven steps starting from the corresponding diethyl cyclopropane-1,2-dicarboxylic ester (489) (Scheme 14.137). Partial hydrolysis yielded the monoacid, which was reduced to the alcohol (490). Conversion to the bromide and treatment with sodium cyanide yielded the nitrile (491). Curtius rearrangement of the acid hydrazide and hydrolysis afforded the desired *trans* amino acid (492). In the case of the *cis* isomer, conversion to the acid hydrazide was carried out at 0°C to control racemization and required purification by high-performance chromatography (HPLC) to remove the *trans* isomer was required [355].

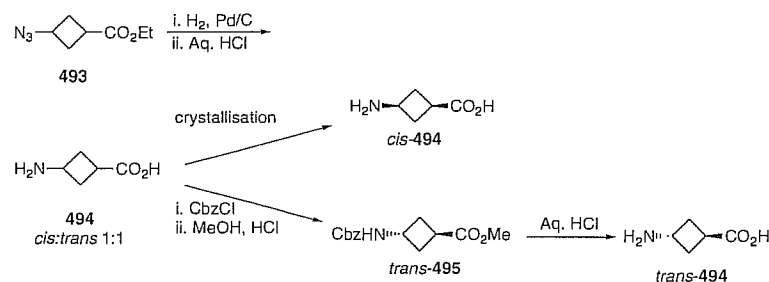
14.10.2

Cyclobutyl γ -Amino Acids

Ethyl 3-azidoocyclobutane-1-carboxylate (493) was synthesized from epibromohydrin and diethyl malonate in seven steps. Catalytic reduction to the amine and ester hydrolysis gave an approximately 1:1 mixture of *cis*- and *trans*-3-aminocyclobutane-1-carboxylic acids (494) that on careful crystallization yielded the pure *cis*-(494)



Scheme 14.137

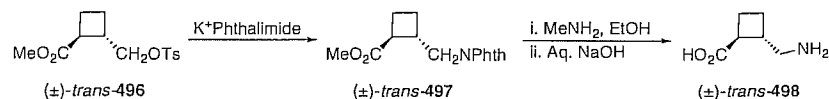


Scheme 14.138

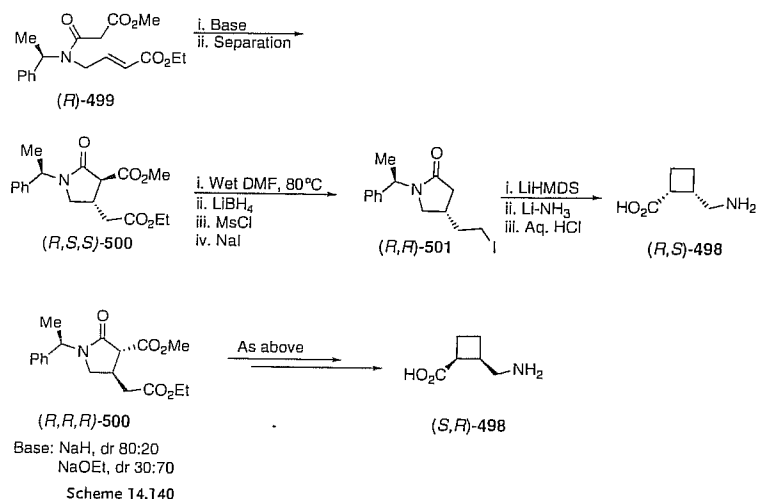
(Scheme 14.138). The *trans* isomer *trans*-(494) was obtained by chromatography of the *N*-benzyloxycarbonyl methyl esters *trans*-(495) of the residual mixture and subsequent hydrolysis and crystallization. The *cis* isomer *cis*-(494) was also prepared by reaction of cyclobutane cyclic anhydride with an equivalent of trimethylsilyl azide followed by hydrolysis and Curtius rearrangement of the resulting isocyanate [356].

The (±)-*trans*-2-(aminomethyl)cyclobutanecarboxylic acid (±)-*trans*-(498) has been prepared by Gabriel synthesis of (±)-*trans*-2-(bromomethyl)cyclobutanecarboxylic acid (±)-*trans*-(496) and hydrolysis of the protected intermediate *trans*-(497) (Scheme 14.139). The *cis*-(498) was prepared by opening of the cyclobutane lactone with phthalimide as described above for the cyclopropyl analog (Scheme 14.128) [341].

Both diastereoisomers of *cis*-(498) have been prepared by a stereodivergent synthesis that is dependent on the conditions used for the intramolecular cyclization of (R)-(499) (Scheme 14.140). The use of NaH in THF leads to (R,S,S)-(500) and NaOEt in EtOH (R,R,R)-(500). Demethoxycarboxylation of (500), reduction of the alcohol, and conversion to the iodide affords (501). Reaction with lithium hexamethyldisilazane provides the β -lactam in good yield as a sole diastereoisomer and deprotection affords the corresponding isomer of (498) in 30% overall yield [357].



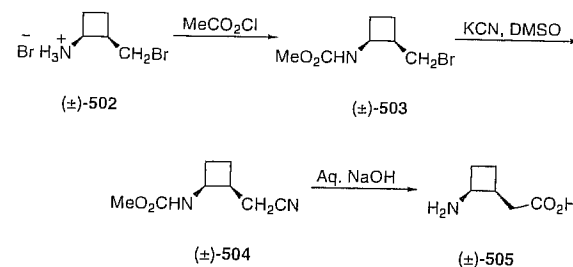
Scheme 14.139



A number of methodologies used for the synthesis of the cyclopropane compounds are also applicable to the synthesis of cyclobutane γ -amino acids. Both (\pm)-*cis*- and (\pm)-*trans*-(498) have also been prepared by opening of the cyclobutyl lactone with potassium phthalimide and a Gabriel synthesis on the tosylate, respectively, in a manner identical to that described for the corresponding cyclopropyl compounds [341]. The (\pm)-*trans*-(498) has also been prepared by conversion of the tosylate to the azide and subsequent reduction to the amine [358]. The (*S,R*)-(498) has also been obtained by a PPL resolution of the *meso* diester as described above for the cyclopropyl analog [342].

Likewise, the synthesis of (\pm)-*trans*-2-aminocyclobutylacetic acid (\pm)-*trans*-(505) in seven steps from the corresponding cyclobutyl-1,2-dicarboxylic acid, in a method analogous to that described above for the 2-aminocyclopropylacetic acids, has been reported [355]. The (\pm)-*cis*-2-aminocyclobutylacetic acid (\pm)-*cis*-(505) has been prepared from the readily available (\pm)-*cis*-(502) (Scheme 14.141) [359]. Conversion to the methyl carbamate (\pm)-*cis*-(503) prior to reaction with cyanide prevents the ring-opening side-reaction from occurring, yielding (\pm)-*cis*-(504) in good yield. Hydrolysis affords (\pm)-*cis*-(505) (Scheme 14.141) [355].

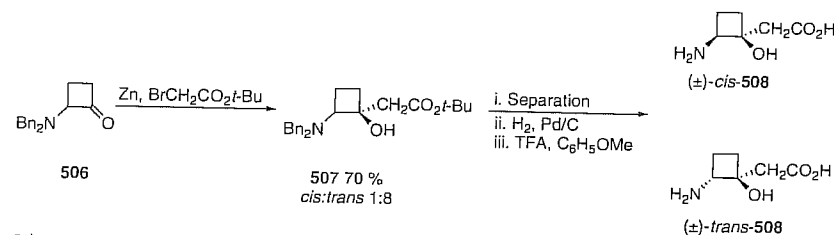
A cyclobutane analog of GABOB has been obtained via reaction of 2-(dibenzylamino)cyclobutanone (506) with *tert*-butylbromoacetate under Reformatsky conditions (Scheme 14.142). Both (\pm)-*cis*- and (\pm)-*trans*-(507) were readily separated by flash chromatography on silica gel. Debenzylation of each product gave the racemic amino alcohols, which upon treatment with TFA/anisole and subsequent purification by ion-exchange chromatography and HPLC gave the (\pm)-1-hydroxy-2-



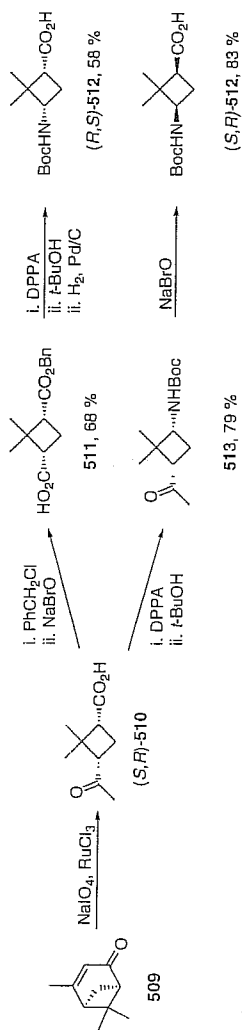
Scheme 14.141

aminocyclobutanecarboxylic acids (508). The *trans*-(*R,R*)- and (*S,S*)-1-hydroxy-2-aminocyclobutane-1-acetic acid were resolved by HPLC or by coupling to *N*-*tert*-butoxycarbonyl-(*S*)-valine and recrystallization [360].

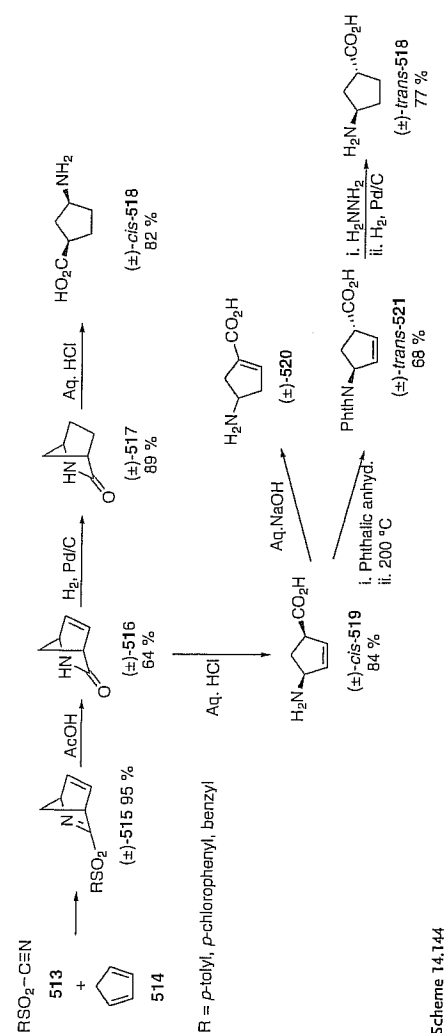
Pinene has proved to be a versatile substrate in the synthesis of 2,2-dimethyl-substituted cyclobutane γ -amino acid derivatives. Oxidative cleavage of (*R*)-verbenone (*R*)-(509), available from the allylic oxidation of (+)- α -pinene, produced (+)-pinonic acid (*S,R*)-(510) with concomitant loss of CO₂ (Scheme 14.143). The (*S,R*)-(510) was converted to both isomers of *cis*-3-amino-2,2-dimethylcyclobutanecarboxylic acid (512) by a stereodivergent synthesis. Benzylation of (*S,R*)-(510) and subsequent haloform reaction yields the acid (511) which undergoes a Curtius rearrangement in *tert*-butanol to give the protected amino ester. Cleavage of the benzyl ester by hydrogenolysis affords (*R,S*)-3-(Boc-amino)-2,2-dimethylcyclobutanecarboxylic acid (*R,S*)-(512) in good yield. The (*S,R*)-(512) is available by Curtius rearrangement to give the keto-acid (513) and subsequent haloform reaction [361]. Similar syntheses of (512) have also been reported from (*S*)-verbenone [362] and (+)-(*R*)- α -pinene [363]. The highly stereoselective conjugate addition of nitromethane to α,β -unsaturated cyclobutyl esters derived from (–)-(*S*)-verbenone furnishes 3-substituted cyclobutyl gabapentin analogs [364].



Scheme 14.142



Scheme 14.143



Scheme 14.144

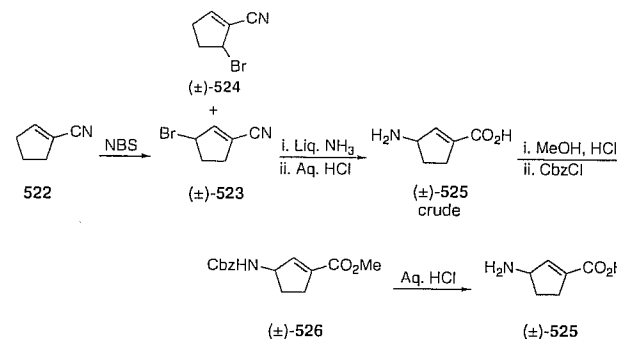
14.10.3

Cyclopentyl γ -Amino Acids

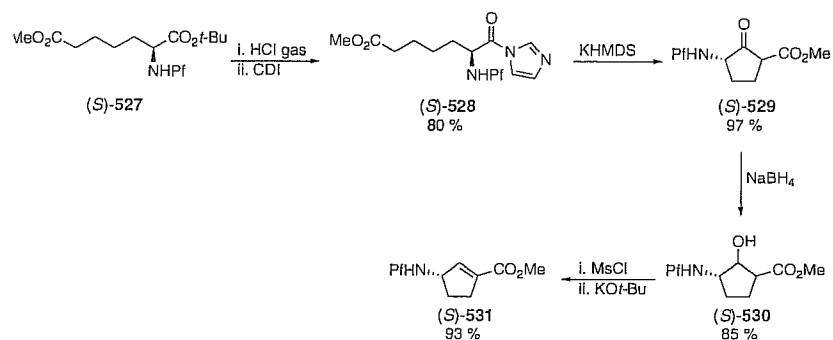
Diels-Alder cycloaddition of tosyl cyanide (513) to cyclopentadiene (514) at room temperature produces 3-tosyl-2-azabicyclo[2.2.1]hepta-2,5-diene (±)-(515) (Scheme 14.144). Hydrolysis yields the unsaturated lactam (±)-(516). Catalytic reduction to the saturated lactam (±)-(517) and acid-catalyzed hydrolysis affords (±)-*cis*-3-aminocyclopentanecarboxylic acid (±)-*cis*-(518) [365]. Hydrolysis of the unsaturated lactam affords 4-aminocyclopent-2-enecarboxylic acid (±)-*cis*-(519) [366], which undergoes isomerization to give 4-aminocyclopent-1-ene-1-carboxylic acid (±)-(520) on treatment with 2 M NaOH [367]. Thermal *cis-trans* isomerization of (±)-*cis*-(519) yields (±)-*trans*-4-aminocyclopent-2-ene-1-carboxylic acid (±)-*trans*-(521) [368]. Resolution of (±)-(521) was achieved by crystallization of isopropylideneribonolactone esters or pantolactone esters of the phthalimido-protected intermediates to afford (+)-(S)-(521) and (-)-(R)-(521) [368].

Reduction of 3-(hydroxyamino)cyclopentanecarboxylic acid or its ethyl ester has also been used in the preparation of (518). Hydrogenation over platinum oxide in ethanolic HCl provided a mixture of isomeric amino esters, which on distillation afforded the *cis* lactam and the *trans* amino ester. Hydrolysis afforded the (±)-*cis*-(518) and (±)-*trans*-(518), respectively [355]. All four stereoisomers of 3-aminocyclopentanecarboxylic acid have also been prepared via reduction of the oximes prepared from optically pure (R)- and (S)-ethyl 3-oxocyclopentanecarboxylates. Reduction using sodium/ammonia/methanol yielded a separable mixture (*cis:trans* 55:45) of the desired amino acids. However, reduction using zinc in HCl proceeded stereoselectively to the *cis* amino acids in low yield to afford after crystallization (R,S)-*cis*-(518) and (S,R)-*cis*-(518) [369].

Allylic bromination of the cyclopentene nitrile (522) gave a 3:1 mixture of the desired product (±)-(523) and 5-bromo regioisomer (±)-(524) (Scheme 14.145). Amination of the crude mixture in liquid ammonia and immediate hydrolysis



Scheme 14.145



Scheme 14.146

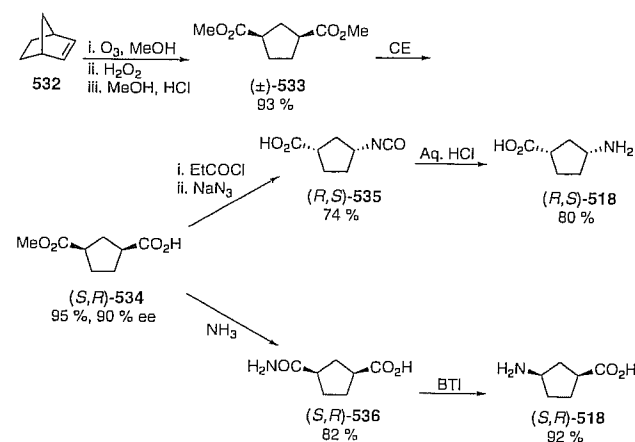
yielded the desired amino acid (\pm)-(525); however, the 5-bromo byproduct hindered purification. Derivatization as the *N*-benzyloxycarbonyl methyl ester (\pm)-(526) facilitated purification by chromatography and crystallization. Regeneration of the amino acid by hydrolysis afforded pure (\pm)-3-aminocyclopent-1-enecarboxylate derivative (\pm)-(525) [367].

Dieckmann cyclization of the *N*-(9-phenylfluoren-9-yl)-protected (*S*)-2-aminoadipic acid derivative (*S*)-(527), activated by conversion to the imidazolide (*S*)-(528) yields the cyclopentane keto ester (*S*)-(529) (Scheme 14.146). Reduction of the keto ester to the hydroxy ester (*S*)-(530) and subsequent elimination affords enantiomerically pure 3-aminocyclopent-1-enecarboxylate derivative (*S*)-(531) in high overall yield. Hydrogenation of the double bond under a variety of conditions gave *cis*:*trans* ratios of 1:1 to 1:5.[370]

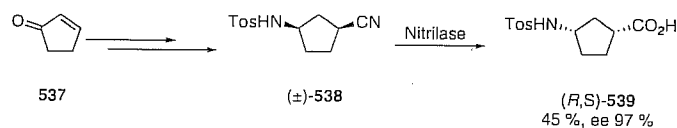
Enzymatic resolution of the racemic diester (\pm)-(533), prepared via ozonolysis of norbornylene (532), with cholesterol esterase yields the mono-ester (*S,R*)-(534) in high yield and enantiopurity (Scheme 14.147). Conversion of the isocyanate (*R,S*)-(535) and subsequent Curtius rearrangement afforded (*R,S*)-(518). Alternatively, ammonolysis of the monoester and subsequent Hofmann rearrangement of the amide (*S,R*)-(536) using bis(trifluoroacetoxy)iodobenzene afforded the amino acid (*S,R*)-(518) [371].

Nitrilase-mediated hydrolysis of *N*-protected *cis*- or *trans*-3-aminocyclopentane carbonitriles (538), prepared via Michael addition of cyanide to α,β -unsaturated cyclic ketone (537), has been reported as an efficient method for the enantioselective synthesis of *cis*-(*R,S*)-3-aminocyclopentanecarboxylic acid in high optical purity (Scheme 14.148). In contrast, the nitrilase-mediated hydrolysis of the *trans* isomer resulted in much lower optical purity (55% e.e.). A range of enzymes and *N*-protecting groups were investigated, with the *N*-tosyl moiety found to be optimal for both yield and stereoselectivity [372].

Enzymatic hydrolysis of (\pm)-4-acetamido-cyclopent-2-enecarboxylates (\pm)-(540) has been investigated as a route to enantiomerically pure cyclopentene/ane γ -amino



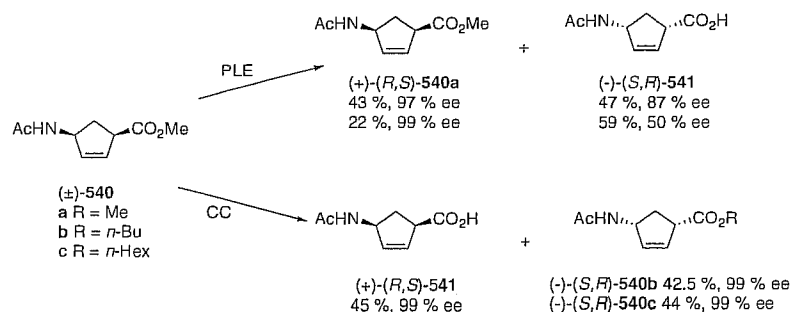
Scheme 14.147



Scheme 14.148

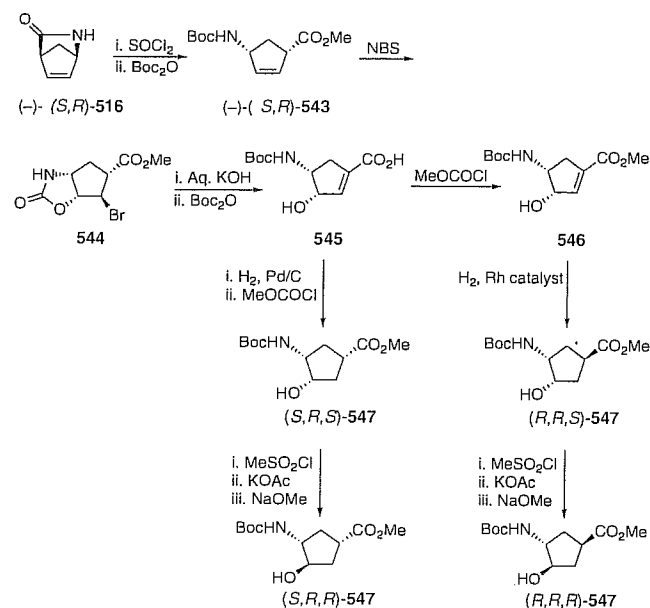
acid analogs. Hydrolysis of (\pm)-(540a) by PLE was originally reported to afford high yields and moderate to high enantiopurities of both (+)-(540) and (-)-(541) (Scheme 14.149) [373]. However, a later study reported much lower yields and enantioselectivity for this enzymatic hydrolysis [374]. Alternatively, CCL-catalyzed hydrolysis of (\pm)-(540b,c) afforded enantiopure (+)-(540b,c) and (-)-(541) [374].

The lactam (\pm)-(516), undergoes enantiospecific and enantiocomplementary hydrolyses using whole cell catalysts or immobilized enzyme to give enantiopure lactams and *cis*-4-aminocyclopent-2-enecarboxylic acid (Scheme 14.150). The use of *Rhodococcus equi* NCIB 40 213 (ENZA 1) or *Aureobacterium* sp. (ENZA 25) affords (+)-lactam (+)-(R,S)-516 and the (-)-acid (-)-(S,R)-519, while the use of *Pseudomonas solanacearum* NCIB 40 249 (ENZA 20) and *Pseudomonas fluorescens* (ENZA 22) affords the (-)-lactam (-)-(S,R)-516 and the (+)-acid (+)-(R,S)-519 [375, 376]. Treatment of the lactam (-)-(S,R)-516 with bromine gave the adduct (-)-(542) that, through rearrangement of the bromonium ion intermediate, undergoes a net "inversion" of the carbocyclic skeleton. Reduction of the dibromo compound with tributyltin hydride gave the saturated lactam (+)-(R,S)-517, which on hydrolysis of gave the (+)-(S,R)-518 [377].

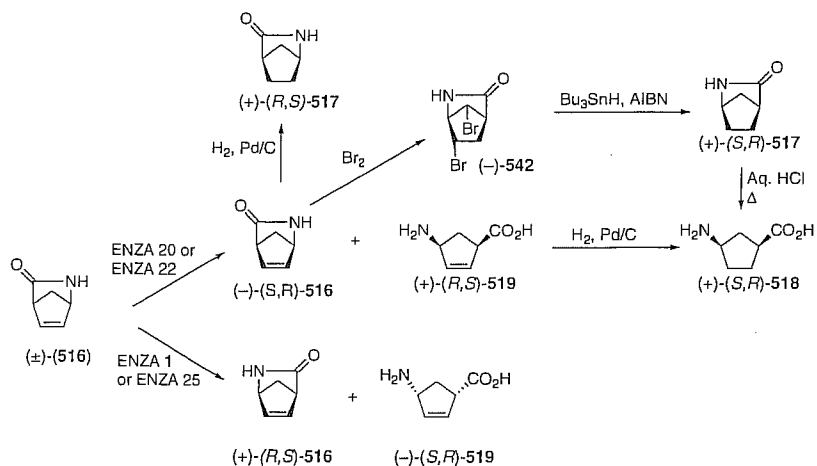


Scheme 14.149

The enantiomerically pure lactams (–)-(*S,R*)-(**516**) and (+)-(*R,S*)-(**516**), which can be prepared on a multitonne scale, have been used in the synthesis of all eight stereoisomers of 3-(*tert*-butoxycarbonylamino)-4-hydroxycyclopentanecarboxylic acid methyl ester (**548**) (Scheme 14.151). Treatment of (–)-(*S,R*)-(**516**) with thionyl chloride in methanol and subsequent reaction with Boc-anhydride yielded (–)-(*S,R*)-(**543**). The protected cyclopentene (–)-(*S,R*)-(**543**) was subjected to an NBS-promoted bromocyclization, forming the cyclic carbamate (**544**) in high yield and introducing an oxygen atom with defined stereochemistry. Elimination of HBr, hydrolysis, and reprotection of the amine as the *N*-Boc-carbamate yielded (**545**). Hydrogenation



Scheme 14.151

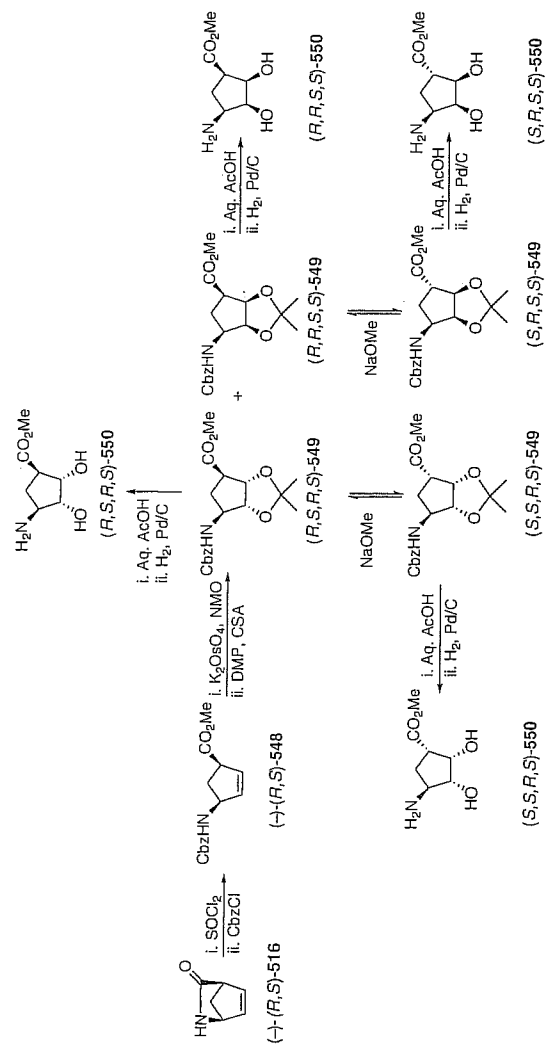


Scheme 14.150

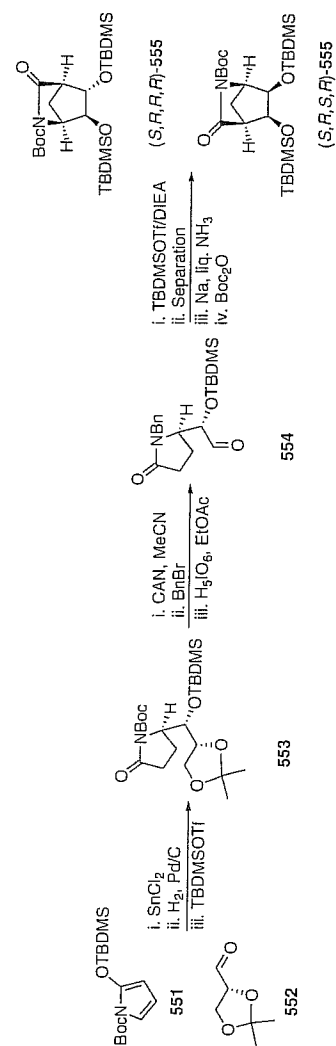
provided the all-*cis* stereoisomer, which was esterified to yield (*S,R,S*)-(541). Alternatively, esterification to afford (540) and homogeneous hydrogenation in the presence of (*R,R*)-[MeDuPhos]-Rh(COD)]BF₄ [378] gave (*R,R,S*)-(547). Inversion of the hydroxyl of both (*S,R,S*)-(547) and (*R,R,S*)-(547) afforded (*S,R,R*)-(547) and (*R,R,R*)-(547), respectively. An analogous process starting from the (+)-(*R,S*)-(516) afforded the enantiomeric products [379]; (547) has also been formed via epoxidation of (543) and treatment with base [378].

The lactam (–)-(R,S)-516 has also been used in the preparation of the dihydroxy-γ-amino esters (550) (Scheme 14.152). Treatment of (–)-(R,S)-516 with thionyl chloride and subsequent reaction with benzyl chloroformate provides the fully protected (–)-(R,S)-548. Dihydroxylation gave two diastereomeric *cis* diols in a 1 : 1 ratio that could be separated by column chromatography after conversion to the acetonides (549). Deprotection afforded the dihydroxy-γ-amino esters (R,S,R,S)-550 and (R,R,S,S)-550. Epimerization of (R,S,R,S)-549 and (R,R,S,S)-549 and deprotection afford (S,S,R,S)-550 and (S,R,S,S)-550, respectively [380].

The (S,R,S,R)- and (S,R,R,R)-4-amino-2,3-dihydroxycyclopentanecarboxylic acids are available by hydrolysis of (S,R,S,R)- and (S,R,R,R)-555 (Scheme 14.153). The



Scheme 14.152



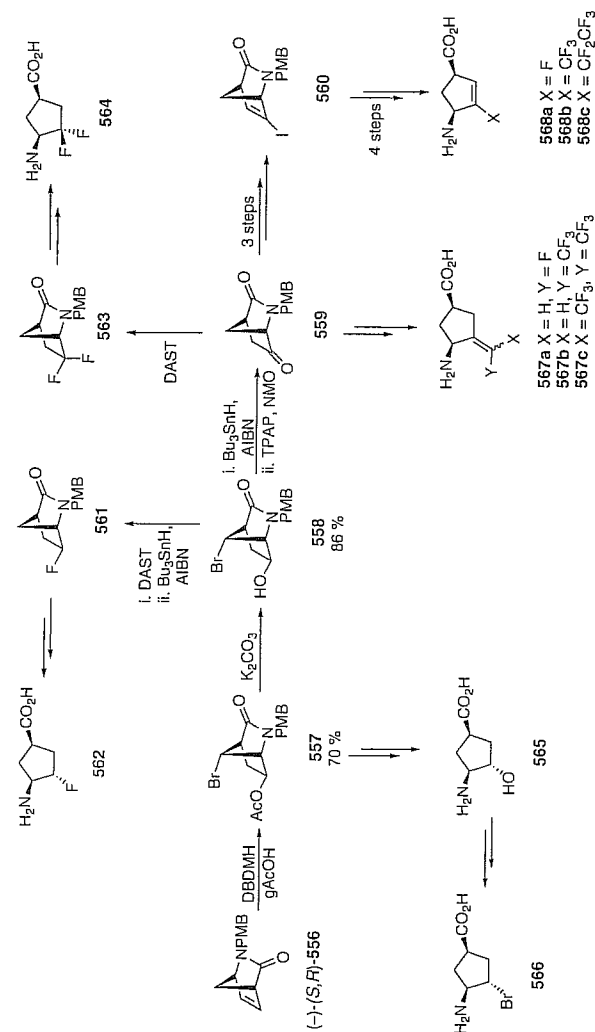
Scheme 14.153

dihydroxy lactams are prepared as a separable mixture of *trans*:*cis* (8:2) isomers in a multistep synthesis via a diastereoselective crossed vinylogous Mukaiyama aldol coupling of the pyrrole (551) and 2,3-*O*-isopropylidene-D-glyceraldehyde (552). Reduction and *O*-protection yields (553), which can be converted to the aldehyde (554) in four steps. A high-yielding silylative cycloaldolization of (554), chromatographic separation, and conversion of the *N*-benzyl to the *N*-Boc-carbamate affords enantiomerically pure (*S*,*R*,*S*,*R*)- and (*S*,*R*,*R*,*R*)-555 [381, 382].

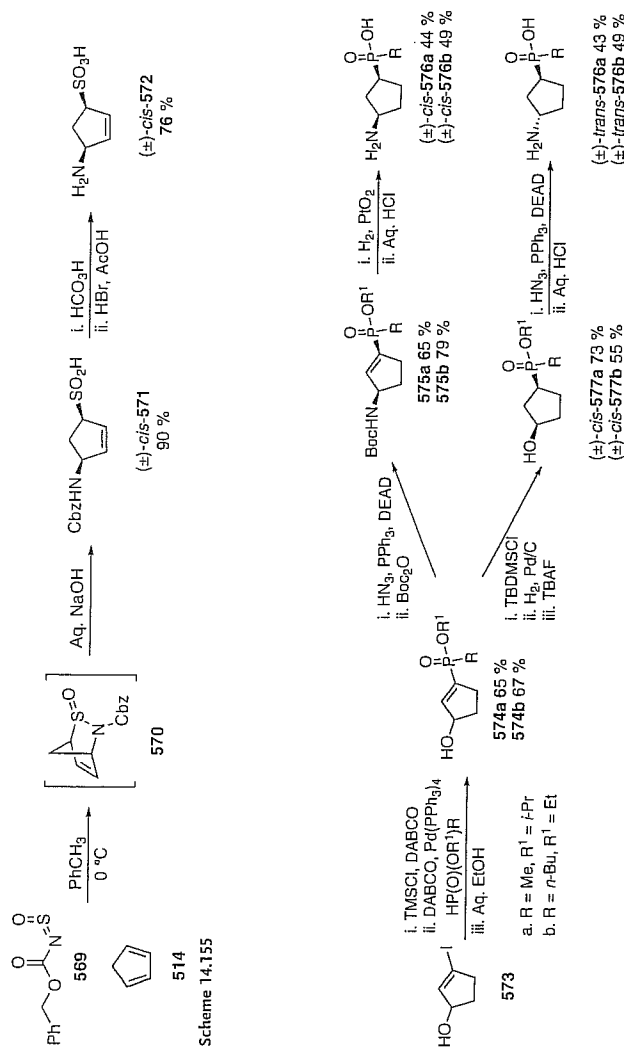
Modifications of the rearrangement of (–)-(*S*,*R*)-516 to (–)-542 (Scheme 14.150) or derivatives have been used to prepare versatile 5,7-substituted 2-azabicycloheptan-3-ones, which can be converted to a range of 3-substituted cyclopentene/ane γ -amino acids. Reaction of *N*-PMB protected lactam (556) with 1,3-dibromo-5,5-dimethylhydantoin in glacial acetic acid afforded the bromoacetate (557) (Scheme 14.154). Hydrolysis of the acetate furnished alcohol (558) [383]. Reaction of (558) with (diethylamino)sulfur trifluoride (DAST) and debromination yields the monofluoro compound (561), which can be deprotected and hydrolyzed to afford the monofluoro amino acid (562). Alternatively, debromination and oxidation of (558) to the ketone (559) and treatment with DAST affords the difluoro derivative (564) and the corresponding difluoro amino acid (564) [384]. Conversion of (559) to the iodo derivative (560) facilitates the synthesis of 3-fluoro-cyclopentene and 3-fluoroalkyl-cyclopentene amino acids (568a–c) [385]. Debromination and hydrolysis of (557) furnishes the 3-hydroxy derivative (565) which can be converted to the 3-bromo amino acid (566) [384]. Finally the ketone (559) can be converted to alkenes by reaction with fluoromethyl phenylsulfone to yield (567a) [386] or via Horner–Wadsworth–Emmons reactions to yield (567b and c) [387].

The cycloaddition of cyclopentadiene (514) and the *N*-sulfinyl carbamate (569) afforded the bicyclic 3,6-dihydrothiazine oxide (570) (Scheme 14.155). Base hydrolysis afforded the carbamate protected sulfinic acid (571). Oxidation and hydrolysis gave (±)-*cis*-4-aminocyclopent-2-ene-1-sulfonic acid (±)-572 [388].

A stereodivergent synthesis of the alkyl phosphinate cyclopentane γ -amino acid analogs (±)-*cis*- and (±)-*trans*-(576) has been reported. Both (±)-*cis*- and (±)-*trans*-(576) were obtained in five steps from the key (±)-(3-hydroxycyclopent-1-ene)alkylphosphinate esters (574) which are prepared via a Pd(0)-catalyzed C–P bond-forming reaction between trimethylsilyl-protected 3-iodocyclopent-2-enol (573) and alkylphosphinate esters (Scheme 14.156). Protection of (574) as the sterically demanding TBDMS ether and hydrogenation yielded the *cis* alcohols (±)-*cis*-(577) that were converted to (±)-*trans*-(576) via a Staudinger–Mitsunobu reaction and subsequent hydrolysis. Alternatively, conversion of (574) to the amine and protection as the *N*-Boc-carbamate yields (575). Hydrogenation and subsequent hydrolysis affords (±)-*cis*-(576). Both reaction pathways proceed in moderate to good overall yield and high diastereomeric excess [389]. Similar methodology has been used for the enantioselective synthesis of the 4-amino-cyclopent-1-enyl phosphinic acid analogs from (*R*)- and (*S*)-4-*tert*-butyldimethylsilyloxy)cyclopent-1-enyl trifluoromethanesulfonate [390].

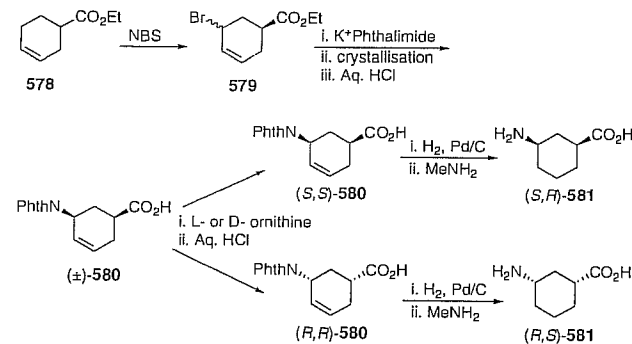


Scheme 14.154



Scheme 14.156

3



Scheme 14.157

14.10.4

Cyclohexyl γ -Amino Acids

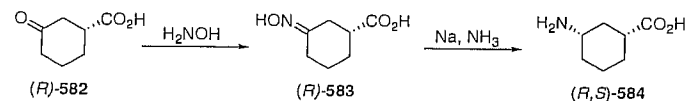
Allylic bromination of ethyl cyclohex-3-ene-1-carboxylate (578) gave the unsaturated bromo ester (579) (Scheme 14.157). Reaction of this crude product with potassium phthalimide gave ethyl 5-phthalimidocyclohex-3-ene-1-carboxylate as a mixture of isomers from which the major product, (\pm)-*cis*-(580), was purified by crystallization. Hydrolysis of the ester and resolution via crystallization with L- or D-ornithine yielded enantiomerically pure (*S,S*)- and (*R,R*)-580. Catalytic reduction and removal of the phthaloyl protecting group produced (*S,R*)- and (*R,S*)-581, respectively, in high optical purity [391].

Birch reduction of (*R*)-583, prepared from (*R*)-582, yields a mixture from which enantiomerically pure (*R*)-584 is obtained, after recrystallization (Scheme 14.158) [391].

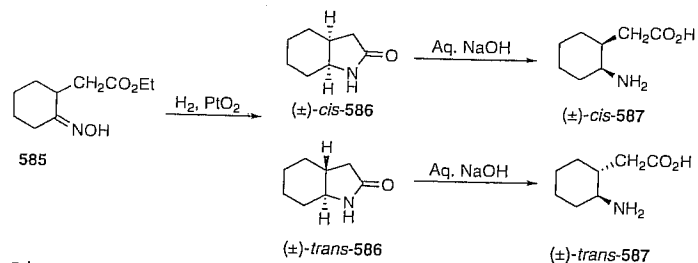
Oxime reduction has also been used in the synthesis of (\pm)-*trans*- and (\pm)-*cis*-2-(2-aminocyclohexyl)acetic acids. Hydrogenation of (585) and distillation of the crude product gave a mixture of the *cis* and *trans* lactams (586) that were separated by HPLC (Scheme 14.159). Hydrolysis afforded pure (\pm)-*cis*- and (\pm)-*trans*-(587) [355].

The preparation of (\pm)-*trans*-(592) was carried out by $\text{S}_{\text{N}}2$ azide substitution of the lactam (\pm)-(590) which had been prepared from (588) via the iodolactam (\pm)-(589) (Scheme 14.160). Reduction of the azide afforded (\pm)-(592) [392].

The (\pm)-*cis*- and (\pm)-*trans*-5-amino-2-methylenecyclohexanecarboxylic acids (\pm)-*cis*- and (\pm)-*trans*-(597) have both been prepared from ethyl 4-oxocyclohexanecarboxylate



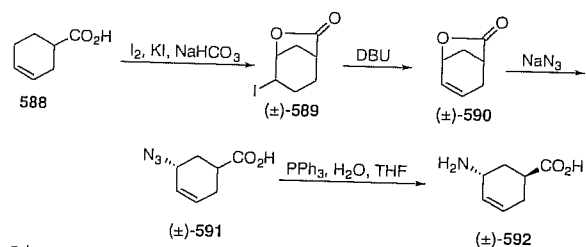
Scheme 14.158



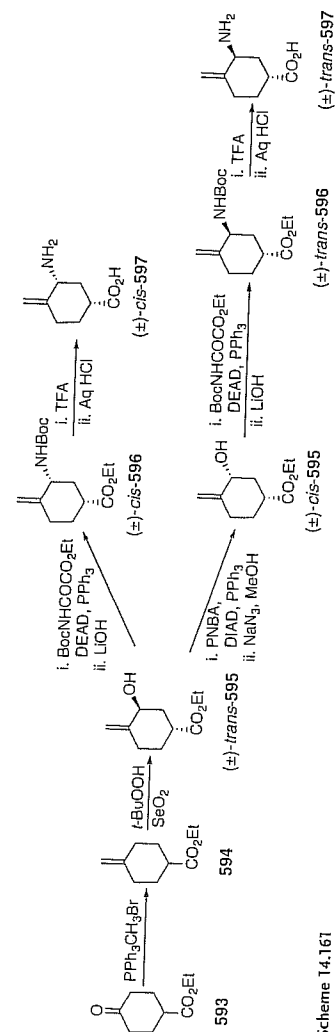
Scheme 14.159

(593) in a divergent synthesis (Scheme 14.161). Conversion of (593) to the alkene (594) by Wittig reaction and oxidation yielded the *trans* allylic alcohol (±)-*trans*-(595) as the major product. Mitsunobu reaction with *N*-Boc-ethyl oxamate and hydrolysis furnished the protected *cis* amino acid (±)-*cis*-(596) that can be deprotected to (±)-*cis*-(597). Mitsunobu reaction of the alcohol (±)-*trans*-(595), followed by methanolysis in the presence of sodium azide gave the *cis* alcohol (±)-*cis*-(595). This alcohol was converted to (±)-*trans*-(596) and hydrolyzed to (±)-*trans*-(597) as described above [386].

Hydrogenation of *m*-substituted benzoic acid derivatives affords a convenient synthesis of cyclohexane γ -amino acid analogs. Hydrogenation of the sodium salt of *m*-aminobenzoic acid in the presence of alkaline Raney nickel at 90–100 atm and 150 °C followed by treatment with Boc-anhydride provides (±)-*cis*-cyclohexane amino acid. Resolution by successive recrystallizations from chloroform containing one equivalent of (+)-1-phenylethanamine gave (*R,S*)-*N*-Boc-3-aminocyclohexanecarboxylic acid with an enantiomeric purity greater than 95% [393]. Similarly, substituted cyclohexane γ -amino acid analogs have been prepared by hydrogenation of 3-amino-4-hydroxybenzoic acid over Rh/Al₂O₃ and treatment with DAST to yield 4-fluorocyclohexane amino acid in low yield or hydrogenation of (±)-3-amino-5-hydroxybenzoic acid and subsequent Dess–Martin oxidation and reaction with DAST to afford (±)-*cis*-3-amino-2,2-difluorocyclohexanecarboxylic acid [394]. Nitration of 5-chlorosalicylic acid, esterification, and then hydrogenation over PtO₂ affords the



Scheme 14.160



Scheme 14.161

cyclohexane analog of GABOB as a mixture of diastereoisomers that can be separated by chromatography of the benzyl carbamate derivatives [395].

The camphorsultam-derived dienophile (598) was reacted with 1-acetoxy-1,3-diene (599) to yield two products in a ratio of 96:4, in which the desired *endo* product (*S,R*)-(600) predominated (Scheme 14.162). The (*S,R*)-(600) was hydrolyzed to give the intermediate hydroxy acid (*S,R*)-(601) in nearly quantitative yield. Iodination gave the iodolactone and removal of the iodine under radical conditions yielded the lactone (*S,S,R*)-(602). Transesterification of the lactone to the methyl ester and conversion of the hydroxyl to the triflate provided (*S,S,R*)-(603). Displacement of the triflate using buffered tetramethylguanidinium azide and subsequent deprotection afforded the enantiomerically pure GABOB analog (*S,S,R*)-3-amino-2-hydroxycyclohexanecarboxylic acid (*S,S,S*)-(604) [396, 397].

A number of substituted cyclohexane γ -amino acid analogs have been recently prepared via a [3 + 3] ring-forming strategy between the nitro phosphonate (605) and unsaturated aldehydes (606) (Scheme 14.163). Reaction in the presence of 2 equiv. 1,8-diazabicyclo[5.4.0]undec-7-ene produces the cyclic nitro ester (607) in moderate yields predominantly as a single diastereoisomer. Reduction of the nitro group with Raney nickel in ethanol afforded the cyclohexene amino esters (608) [398].

14.11

Conclusions

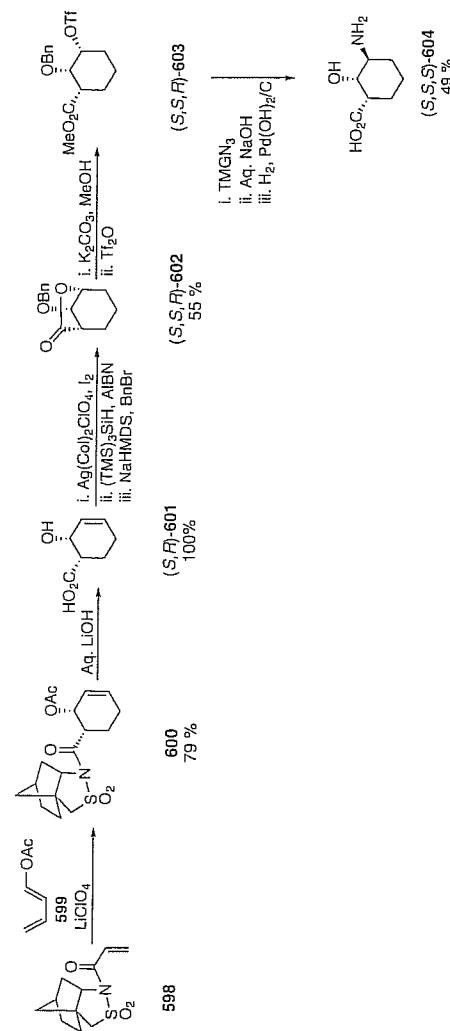
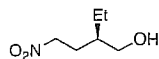
Interest in the synthesis of new analogs of GABA will continue to develop in view of the increasing range of targets associated with the GABA structural motif. These targets include not only subtypes of ionotropic (GABA_A and GABA_C) and metabotropic (GABA_B) receptors, GABA transporters (GAT1–4), and metabolizing enzymes (glutamic acid decarboxylase and GABA-T), but also voltage-gated calcium channels and non-neuronal sites in the immune system. In addition to their use in the treatment of epilepsy and other neurological disorders, GABA analogs may have future roles in the treatment of disorders such as asthma, cancer and diabetes. The GABA motif is also found as a component of many peptide antibiotics and may be used to construct peptidomimetics. The continued development of new synthetic routes to GABA analogs is important in order to increase the availability of new agents for evaluation and to provide procedures for the larger-scale synthesis of analogs of commercial interest.

14.12

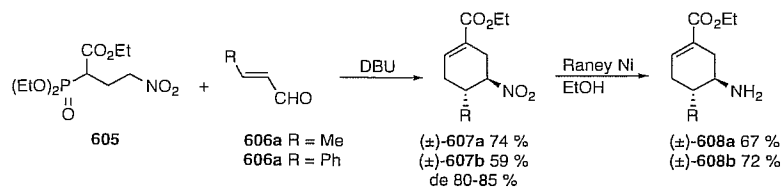
Experimental Procedures

14.12.1

(*R*)-2-Ethyl-4-nitrobutan-1-ol (36c) (Scheme 14.8 [39])



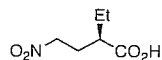
Scheme 14.162



Scheme 14.163

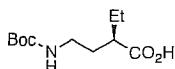
To an 8-ml vial equipped with a small magnetic stir bar was added dry toluene (1.2 ml), (*S*)-diphenylprolinol silyl ether (2 mol%, 0.4 ml stock solution in toluene, 0.05 M), butyraldehyde (2.0 mmol, neat), and 3-nitrobenzoic acid (33.4 mg, 0.2 mmol). The mixture was stirred in an ice bath for 5 min and then nitroethylene (1 mmol, 0.2 ml stock solution in toluene) was added. The mixture was stirred at 3 °C and the reaction progress was monitored by ¹H-nuclear magnetic resonance analysis of the crude reaction mixture. After the reaction was complete, excess NaBH₄ (3.4 mmol, 128.5 mg) was added, followed by MeOH (10 ml), and the mixture was stirred for a few minutes. The mixture was then slowly poured into a 100-ml beaker containing aqueous NH₄Cl (15 ml, 1 M) at 0 °C and the resulting mixture was extracted with EtOAc (3 × 10 ml). The EtOAc layers were collected, washed with brine (20 ml), dried over MgSO₄, and filtered. The filtrate was concentrated to give the crude alcohol product, which was purified via silica gel column chromatography (EtOAc/hexane) to yield (*R*)-2-ethyl-4-nitrobutan-1-ol (96%, 99% e.e.).

(*R*)-2-Ethyl-4-nitrobutanoic Acid



To the alcohol (1.0 mmol) dissolved in acetone (10 ml) at 0 °C was added H₂Cr₂O₇ (3 ml, 1.5 mmol). The mixture was stirred for 5 h, during which time the mixture warmed to room temperature. Excess isopropanol was added and the mixture was stirred for 10 min. The mixture was filtered, and the solution was diluted with aqueous HCl (2 ml, 2 N) and extracted with Et₂O. Complete extraction of the product into the Et₂O phase was monitored by thin-layer chromatography (TLC). The organic layers were washed with saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to give a viscous oil, from which the desired nitrobutanoic acid was purified via column chromatography eluting with EtOAc/hexane (1 : 10 to 1 : 3; v/v) to give pure product (92%, >95% e.e.).

(*R*)-4-(*tert*-Butoxycarbonylamino)-2-ethylbutanoic Acid

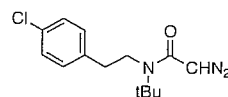


A mixture of (*R*)-2-ethyl-4-nitrobutanoic acid (0.36 g, 2.2 mmol), ammonium formate (0.70 g, 11 mmol), and 10% Pd/C (dry, 0.21 g) in anhydrous MeOH (10 ml) was

refluxed overnight under an atmosphere of N₂ until the starting material disappeared as indicated by TLC analysis. The mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was collected and concentrated to give the crude amine, which was dissolved in CH₂Cl₂ (10 ml) containing *N,N*-diisopropylethylamine (0.6 ml, 3.3 mmol) and Boc₂O (0.7 g, 3.3 mmol) was added. The mixture was stirred at room temperature for 2 h and then it was concentrated to give the crude product, which was purified by silica gel chromatography EtOAc/hexane to yield pure (*R*)-4-(*tert*-butoxycarbonylamino)-2-ethylbutanoic acid (71%).

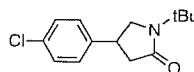
14.12.2

N-*tert*-Butyl-*N*-(*p*-chlorophenylethyl) α -Diazoacetamide (Scheme 14.25 [79])



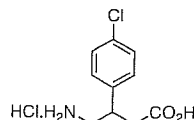
To *N*-*tert*-butyl-*N*-(*p*-chlorophenylethyl)amine (5.29 g, 25 mmol) in THF (30 ml) was added diketene (2 ml, 25 mmol). The mixture was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature and stirred overnight. To the resulting reaction mixture was added 4-acetamidobenzene sulfonyl azide (7.3 g, 29 mmol), followed by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (4.4 ml, 29 mmol). The resulting solution was stirred at room temperature for 8 h. An aqueous solution of lithium hydroxide (50 ml, 95 mmol) was added and the resulting orange-brown mixture was stirred vigorously for 8 h. The reaction mixture was diluted with ethyl acetate (60 ml), and the organic layer was washed with water (2 × 30 ml) and dried over anhydrous MgSO₄. Solvent was removed under reduced pressure to yield a red-brown mixture. Silica gel column chromatography petroleum ether/ethyl acetate (5 : 1 v/v), afforded the product as a yellow solid in 84% yield.

N-*tert*-Butyl- β -*p*-chlorophenyl- γ -lactam



To a solution of Rh₂(cap)₄ (1 mol%) in the CH₂Cl₂ (5 ml) at reflux was added the α -diazoacetamide (1.0 mmol) in the CH₂Cl₂ (5 ml) via a syringe pump over a 2 h period. After the addition was complete, the reaction mixture was stirred for an additional 30 min and then the solvent was removed under reduced pressure. Silica gel column chromatography purification (petroleum ether/ethyl acetate, 3 : 1 v/v) yielded the γ -lactam as a pale yellow (or colorless) oil (77% yield).

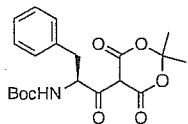
(±)-Baclofen Hydrochloride



A mixture of the γ -lactam (0.85 mmol) in aqueous HCl (6 ml, 25–28%) was heated at 90–120 °C for 18 h. After cooling to room temperature, the solution was extracted with diethyl ether (3 \times 20 ml). The water was removed under reduced pressure to give the desired product (as the corresponding hydrochloride salt) in 95% yield.

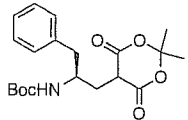
14.12.3

(*R*)-5-[(1-Oxo-2-(*tert*-butoxycarbonylamino)-3-phenyl)-propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (Scheme 14.34 [113])



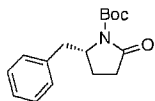
N-Boc-protected L-phenylalanine (5.3 g, 20 mmol) was dissolved with 2,2-dimethyl-1,3-dioxane-4,6-dione (3.02 g, 22 mmol) and 4-(dimethylamino)pyridine (3.85 g, 31 mmol) in CH₂Cl₂ (100 ml). The reaction mixture was cooled to –5 °C and a solution of dicyclohexylcarbodiimide (4.74 g, 22 mmol) in CH₂Cl₂ (50 ml) was added dropwise over 1 h. The mixture was left at below 0 °C overnight, during which time dicyclohexylurea precipitated. After filtration the reaction mixture was washed 4 times with aqueous 5% KHSO₄ and once with brine, and dried in the refrigerator with MgSO₄ for 5 h. This solution was used in the second step without further purification.

(*R*)-5-[(2-*tert*-Butoxycarbonylamino-3-phenyl)-propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione



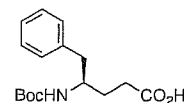
The solution of (*R*)-5-[(1-oxo-2-(*tert*-butoxycarbonylamino)-3-phenyl)-propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione from the previous reaction was cooled to –5 °C and 98% AcOH (13.3 ml, 220 mmol) was added. Then, NaBH₄ (1.85 g, 50 mmol) was added in small portions while stirring over 1 h. The reaction mixture was left in the refrigerator overnight, and then washed 3 times with brine and 2 times with water. The organic phase was dried with MgSO₄, filtered, evaporated to dryness, and purified by column chromatography with hexane/ethyl acetate (1:1) to afford the desired product (76% yield).

(*R*)-(*tert*-Butoxycarbonyl)-5-benzyl-2-pyrrolidinone



Pure (*R*)-5-[(2-*tert*-butoxycarbonylamino-3-phenyl)-propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione was refluxed in toluene (50 ml). TLC in ethyl acetate/hexane 2:1 indicated complete conversion after 3 h. After evaporation of solvent, the compound was isolated in 96% yield and used without further purification.

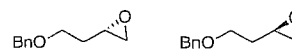
(*R*)-4-(*tert*-Butoxycarbonylamino)-5-phenyl-pentanoic Acid



The pyrrolidinone (8 mmol) was dissolved in acetone (15 ml) and aqueous NaOH (1 M, 24 ml) was added. The reaction mixture was stirred at 22 °C for 30 min. Acetone was removed under reduced pressure and the reaction mixture was acidified to pH 2 (6 M HCl). The desired product precipitated and was filtered, washed twice with water, and recrystallized from a mixture of ethyl acetate/hexane to afford (*R*)-4-(*N*-*tert*-butoxycarbonylamino)-5-phenyl-pentanoic acid in 72% yield.

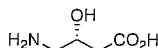
14.12.4

(*R*)- and (*S*)-[2-(Benzyloxy) ethyl]oxirane (Scheme 14.69 [184])



A stirred solution of (\pm)-[2-(benzyloxy)ethyl]oxirane (8.0 g, 44.9 mmol) and (*R,R*)-(salen)Co(III)-OAc catalyst (145 mg, 0.22 mmol) was cooled to 0 °C, then H₂O (0.45 ml, 25.0 mmol) was added dropwise over a period of 45 min. The reaction mixture was stirred at room temperature for 5 h, diluted with EtOAc, dried over anhydrous Na₂SO₄, and concentrated at reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexane, 1:9). The first fraction contained (*R*)-(benzyloxy)ethyl]oxirane and the second fraction afforded (*S*)-4-(benzyloxy)butane-1,2-diol (3.8 g, 43%). The diol (3.5 g, 17.8 mmol), Ph₃P (7.0 g, 26.7 mmol), and diisopropylazodicarboxylate (5.16 ml, 26.8 mmol) in benzene (50 ml) were heated under reflux for 20 h. The solvent was removed under reduced pressure and Et₂O (80 ml) added precipitating the Ph₃P=O which was removed by filtration. The filtrate was concentrated and the resulting residue was purified by column silica gel chromatography (EtOAc/hexane, 1:9) to afford (*S*)-(benzyloxy)ethyl]oxirane (2.55 g, 80%).

(3*R*)-CABOB

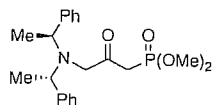


A stirred solution of (*R*)-(benzyloxy)ethyl]oxirane (1.5 g, 8.4 mmol) in ethanol (10 ml) was hydrogenated over 5% Pd/C (150 mg) under an atmosphere of H₂ (1 atm). After 5 h the reaction mixture was filtered through Celite and the filtrate was concentrated

to afford (*S*)-2-(2-(hydroxy)ethyl)oxirane (630 mg, 85%), which was used without further purification. The alcohol (0.5 g, 5.7 mmol) was added slowly to a vigorously stirred solution of sodium periodate (3.33 g 15.5 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{CCl}_4$ (1:1:1, 10 ml) and $\text{RuCl}_3 \cdot 5\text{H}_2\text{O}$ (8.0 mg). The reaction mixture was stirred for 1 h, filtered, and the heterogeneous mixture partitioned. The aqueous phase was extracted with THF (3 \times 5 ml). The combined organic phases were treated with excess concentrated NH_4OH (2 ml) and the reaction mixture was warmed on a steam bath for 24 h. The solution was evaporated under reduced pressure to give a tan solid which was purified on Dowex 50W-X8 (H^+ form) to yield GABOB as a white crystalline solid (400 mg, 60%).

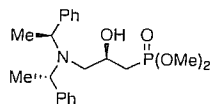
14.12.5

Dimethyl (*S,S*)-(-)-3-*N,N*-bis(α -Methylbenzyl)-amino-2-oxopropylphosphonate (Scheme 14.79 [210])



A solution of dimethyl methylphosphonate (1.43 g, 11.6 mmol) in anhydrous THF (20 ml) was cooled to -78°C before the slow addition of $n\text{BuLi}$ (0.56 g, 3.61 ml of 2.4 M solution in hexanes, 8.7 mmol). The resulting solution was stirred at -50°C for 1.5 h, and then the solution cooled to -78°C and slowly added to a solution of ethyl glycinate (0.9 g, 2.9 mmol) in anhydrous THF (20 ml). The reaction mixture was stirred at -78°C for 4 h, quenched with aqueous NH_4Cl solution (10 ml), and extracted with EtOAc (3 \times 20 ml). The combined organic extracts were washed with brine solution (2 \times 10 ml), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane 70:30) to afford 0.98 g, 87% yield of the desired product as a colorless oil.

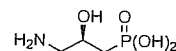
Dimethyl (*S,S*)-(-)-3-*N,N*-bis(α -Methylbenzyl)-amino-2-hydroxypropylphosphonate



To a solution of the β -ketophosphonate (100 mg, 0.26 mmol) and LiClO_4 (69 mg, 0.65 mmol) in dry THF (20 ml) cooled at -78°C was added 124 mg, 1.1 ml, 1.04 mmol of CCB 1 M in THF. The reaction mixture was stirred at -78°C for 4 h, and at room temperature for 10 h. The reaction was quenched with aqueous

NH_4Cl solution. The solvent was evaporated in vacuum and the residue dissolved in water (10 ml) and extracted with ethyl acetate (3 \times 20 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude β -hydroxyphosphonates were purified by flash chromatography to afford dimethyl 3-[(*R,R*)-*N,N*-bis(α -methylbenzylamino)]-(2*S*)-hydroxypropylphosphonate as a white solid (88 mg, 87%).

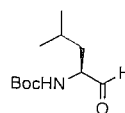
(*R*)-3-Amino-2-hydroxypropylphosphonic Acid



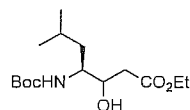
Dimethyl 3-[(*S,S*)-*N,N*-bis(α -methylbenzylamino)]-(2*R*)-hydroxypropylphosphonate (228 mg, 0.58 mmol) in CH_2Cl_2 (5 ml) was treated under a nitrogen atmosphere with bromotrimethylsilane (178 mg, 0.15 ml, 1.16 mmol). The reaction mixture was stirred at room temperature for 6 h, and after this period of time the volatiles materials were removed under reduced pressure and water was added. After 4 h under stirring, the solvents were removed *in vacuo* to give 3-[(*S,S*)-*N,N*-bis(α -methylbenzylamino)]-(2*R*)-hydroxypropylphosphonic acid, which without isolation was treated with PdOH/C (22 mg, 20 wt%) in methanol (20 ml) and five drops of $\text{HCl}/i\text{PrOH}$ (20%), and stirred for 48 h under hydrogen gas at 60°C and 60 psi. The mixture was filtered through a pad of Celite and the solvent removed under reduced pressure. The residue was treated with propylene oxide (3 ml) to afford (*R*)-3-amino-2-hydroxypropylphosphonic acid as a white solid (63 mg, 70%).

14.12.6

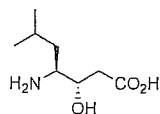
Boc-L-leucinal (Scheme 14.83 [214])



To a stirred solution of Boc-L-leucine methyl ester (4.0 g, 16.3 mmol) in dry toluene (70 ml) was added a hexane solution of DIBALH (40.8 mmol) at -78°C under a nitrogen atmosphere. After 6 min, the reaction was quenched with methanol (4 ml) and Rochelle salt solution was added immediately. The mixture was allowed to warm to 25°C and ether (100 ml) was added. The ethereal layer was separated and combined with ether extracts of the aqueous layer. The combined layers were dried (MgSO_4) and concentrated under reduced pressure. The crude oil was passed through a short pad of silica gel, eluting with 4% ethyl acetate in benzene to remove the alcohol side-product to yield Boc-leucinal (2.98 g, 85%), which was used without further purification.

(3*R*,4*S*)-Ethyl *N*-Boc-4-amino-3-hydroxy-6-methylheptanoate

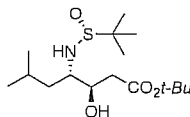
To dry THF (5 ml) cooled in dry ice/ CCl_4 was added diisopropylamine (15 mmol) under a nitrogen atmosphere, followed by a solution of $n\text{BuLi}$ in hexane (15 mmol). After 1 h, the bath temperature was lowered to -78°C and dry EtOAc (15 mmol) was added via syringe and stirred for 15 min. Boc-leucinal (2.15 g, 10 mmol) in THF (10 ml) was added and the reaction mixture was stirred for 5 min before 1 N HCl was added. The flask was warmed to room temperature and the reaction mixture acidified with cold 1 N HCl to pH 2–3, and then extracted with EtOAc 3 times. The organic layer was washed with saturated NaCl and dried (MgSO_4). Evaporation under reduced pressure gave an oil which after silica gel column chromatography gave Boc-Sta-OEt (2.42 g, 80%) as a mixture of diastereomers. Chromatography of the mixture on silica gel eluting with a gradient of 10% ethyl acetate in benzene to 50% ethyl acetate in benzene afforded pure (3*S*,4*S*)-ethyl *N*-Boc-4-amino-3-hydroxy-6-methylheptanoate (38–40%) and (3*R*,4*S*)-ethyl *N*-Boc-4-amino-3-hydroxy-6-methylheptanoate.

(3*S*,4*S*)-*N*-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid

A solution of the ester (548 mg, 1.8 mmol) in aqueous dioxane was maintained at pH 10 for 30 min. The solution was acidified (pH 2.5) with cold HCl (1 N) and the aqueous layer was washed with EtOAc. The organic layer was dried over MgSO_4 and evaporated to give the desired acid (428 mg, 86%).

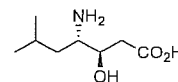
14.12.7

Cross-Coupling of *N*-*tert*-Butylsulfinyl Imine and *tert*-Butyl 3-oxopropanoate (Scheme 14.99 [275])



A freshly prepared solution of samarium diiodide (1.0 mmol) in THF (5 ml) was cooled to -78°C under an atmosphere of nitrogen. A mixture of *tert*-butyl alcohol (1.0 mmol), *tert*-butyl 3-oxopropanoate (1.0 mmol), and chiral *N*-*tert*-butylsulfinyl imine (0.5 mmol) in THF (6 ml) was added dropwise. The reaction was monitored

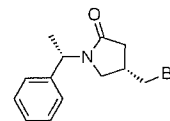
by TLC and quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml) when the reaction had gone to completion. Extraction with ethyl acetate and purification by flash column chromatography afforded the cross-coupling product in 58% yield.

(*R*,*S*)-Statine

To the solution of HCl in dioxane (5.8 N, 0.5 ml) was added the β -amino alcohol (42 mg, 0.125 mmol) and stirred at room temperature for 5 h. The reaction solution was washed with ether; the separated aqueous layer was neutralized with ammonia. After concentration under reduced pressure, the resulting residue was purified by preparative TLC (silica gel) to give (*R*,*S*)-statine (18 mg, 80%).

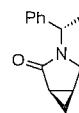
14.12.8

(1'*S*,4*S*)-4-Bromomethyl-1-(1-phenyleth-1-yl)-pyrrolidin-2-one (Scheme 14.130 [343])



To a solution of (*S*)-*N*-allyl-2-bromo-*N*-(1-phenylethyl)-acetamide (0.27 g, 0.9 mmol) in dry toluene (50 ml) at -78°C were added triethylborane (0.4 g, 2.8 mmol) of a 1 M solution in hexane and $\text{BF}_3\cdot\text{OEt}_2$ (0.5 g, 5.6 mmol). The resulting solution was stirred for 15 min before adding methanol (0.8 ml, 2.8 mmol). Then, an air balloon was placed on the reaction flask and the reaction was stirred for 6 h to ensure completion. Finally, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel) eluting with hexane/EtOAc (45:1) giving the (1'*S*,4*S*) product as the major diastereoisomer (0.23 g, 86%) and the (1'*S*,4*R*) product as the minor diastereoisomer (0.04 g, 4%), both as colorless oils.

(1'*S*,1*R*,5*S*)-3-(1-Phenyleth-1-yl)-3-aza-bicyclo[3.1.0] hexane-2-one



To a solution of the (1'*S*,4*S*) product (0.34 g, 1.2 mmol) in dry THF (30 ml) at 0°C was added a solution of potassium *tert*-butoxide (2.4 mmol, 1 M solution in THF). The resulting solution was stirred for 1 h. The reaction mixture was quenched with water (30 ml) and extracted with EtOAc (3 \times 30 ml). The organic layer was dried

with NaSO_4 , evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel) eluting with hexane/EtOAc (8:1) to give the desired product as a colorless oil (0.24 g, 98%).

(1*R*,5*S*)-3-Aza-bicyclo[3.1.0] hexan-2-one



A solution of (1'*S*,1*R*,5*S*)-3-(1-phenyleth-1-yl)-3-aza-bicyclo[3.1.0]hexane-2-one (0.38 g, 1.90 mmol) in THF (30 ml) was added dropwise to a deep blue solution of Li (0.1 g) in liquid NH_3 (20 ml) at -78°C . The reaction mixture was allowed to stir for 1 h at -78°C before the addition of an aqueous solution of NH_4Cl (40 ml), then the reaction mixture was neutralized with dilute aqueous HCl, extracted with EtOAc, dried over Na_2SO_4 , and evaporated under reduced pressure. The reaction was purified by column chromatography through silica gel eluting with hexane/EtOAc (1:1) to give (1*R*,5*S*)-3-aza-bicyclo[3.1.0]hexan-2-one as a white solid (0.2 g, 96%).

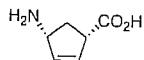
(1*R*,2*S*)-2-(Aminomethyl) cyclopropanecarboxylic Acid



A solution of (1*R*,5*S*)-3-aza-bicyclo[3.1.0]hexan-2-one (0.15 g, 2.1 mmol) in HCl (20 ml, 1 M) was stirred at 70°C for 8 h. The resulting solution was evaporated under reduced pressure and the residue was crystallized from EtOAc/methanol (1:5) to give (1*R*,2*S*)-2-(aminomethyl)cyclopropanecarboxylic acid as a white solid (0.12 g, 80%).

14.12.9

(+)-(1*R*,5*S*)-4-Amino-2-cyclopentene-1-carboxylic Acid (Scheme 14.150 [376])



(\pm)-2-Azabicyclo[2.2.1] hept-5-en-3-one was dissolved to 10 g/l in a whole-cell suspension of ENZA 20. The cultures were incubated on orbital shakers (350 rpm) at 30°C in conical flasks. Biotransformations were monitored by HPLC, following the disappearance of 2-azabicyclo[2.2.1]hept-5-en-3-one and appearance of 4-amino-2-cyclopentenecarboxylic acid. The cells were first removed by centrifugation then ($-$)-(1*S*,*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one continuously extracted from the bio-transformation culture into CH_2Cl_2 for 48 h. The dichloromethane solutions were concentrated under reduced pressure, ($-$)-(1*S*,*R*)-2-Azabicyclo[2.2.1]hept-5-en-3-one was recrystallized by addition of *n*-hexane. The aqueous solution after extraction of the residual lactam was concentrated to 150 g/l and diluted with an equal volume of acetone. (+)-(1*R*,5*S*)-4-Amino-2-cyclopentene-1-carboxylic acid crystallized.

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