Preparation of Achiral and of Enantiopure Geminally Disubstituted β-Amino Acids for β-Peptide Synthesis

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While geminally disubstituted α-amino acids are helix-inducing residues in α-peptides, *gem*-disubstituted β-amino acids are predicted not to fit into any of the three major secondary structures of β-peptides recognized to date [the 3_{14} helix, the 12/10/12 helix, and the pleated sheet (Figure 1)]. In order to be able to synthesize and structurally identify β-peptides containing such building blocks, or consisting entirely of them, and in order to establish the chirality of secondary structures they may form, achiral and chiral *gem*-disubstituted β-amino acids must be readily available. The methods of preparation of 3-amino carboxylic acids with two carbon substituents at the 2- or 3-position ($\beta^{2,2}$-/$\beta^{3,3}$-amino acids, Figure 2) are reviewed. While there are numerous essentially classical routes to achiral and *rac*-β-amino acids of this type (Schemes 1–4), their EPC synthesis is currently the subject of investigations. These include the nucleophilic addition to (*R*)- or (*S*)-*N*-sulfinimines (Schemes 6–10) and other Mannich-type transformations (Schemes 19–22), stereoselective alkylations of various chiral hydropyrimidines (Schemes 11, 12, 18), of esters or amides of 2-cyano-alkanoic acids (Schemes 13, 14, 16), and of Li_2 derivatives of non-racemic *N*-protected 3-amino-alkanoates (Scheme 17), as well as sequences of reactions involving enantiopure *gem*-disubstituted succinic acid derivatives and a Curtius degradation (Schemes 23–26). Oligomers of the achiral *gem*-disubstituted compounds 1-(aminomethyl)-cyclopropane and -cyclohexane carboxylic acid have already been shown to form 8- and 10-membered hydrogen-bonded rings, respectively (Figure 5), which provide novel motifs for the possible construction of turns, links, or steps in β-peptidic chains.

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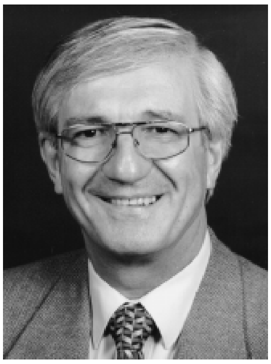
Dieter Seebach (right) was born in Karlsruhe, Germany, in 1937. He studied chemistry at the University of Karlsruhe and completed his Ph.D. thesis on small rings and peroxides under the supervision of Prof. R. Criegee in 1964. After a two-year stay at Harvard University as a postdoctoral coworker (with Prof. E. J. Corey) and lecturer, he returned to Karlsruhe, and, in 1969, completed his "habilitation" on the topic of S- and Se-stabilized carbanion and carbene derivatives. In 1971 he moved to the University of Giessen as a full professor and then in 1977 to the Eidgenössische Technische Hochschule (Swiss Federal Institute of Technology) in Zürich. He has been a visiting professor at the Universities of Wisconsin-Madison, Strasbourg, Munich (TU), and Kaiserslautern, and also at Caltech, Pasadena, and the Max Planck Institute in Mülheim. The main emphasis of his research lies in the development of new synthetic methods; in the last decade the self-regeneration of stereocenters (SRS) and the Ti-TADDOLates have been major interests. His work also involves mechanistic studies and the determination of structures. More recent research topics include chiral dendrimers, 3-hydroxyalkanoates, the biopolymer PHB, as well as β- and γ-peptides. – Stefan Abele (left) was born in Waiblingen, Germany, in 1970. He studied chemistry at the University of Konstanz, Germany, and the Université Joseph Fourrier, Grenoble, France. In 1996 he completed his Diploma at the University of Konstanz with research carried out in the group of Prof. R. R. Schmidt. Later that year, he joined Prof. D. Seebach's group at the ETH in Zürich, Switzerland, and completed his Ph.D. thesis in the summer of 1999. His research focused on the preparation of β-amino acids and the synthesis of β-peptides with novel secondary structures. He is now working at CarboGen Laboratories (Aarau) AG, Switzerland.



MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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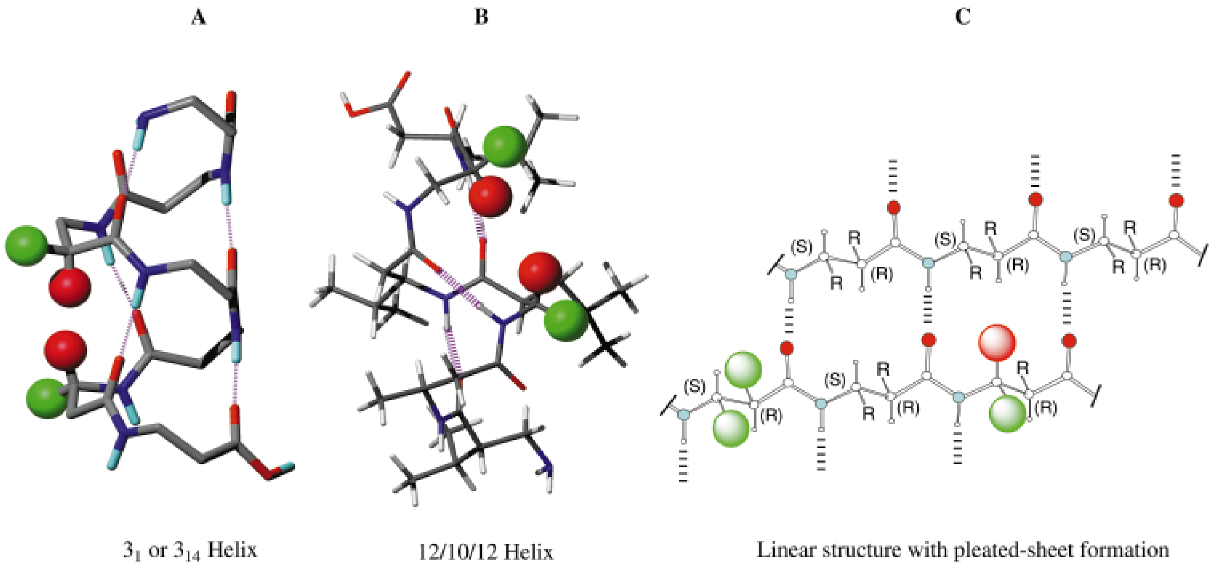
1. Introduction

In the course of our work on β-amino acid oligomers bearing proteinogenic side chains, we have identified two types of helices,[1][2] pleated sheets,[1,3,4] and turns.[4][5] These secondary structures can be formed by chains of as few as six residues.[6] Inspection of models (Figure 1) leads to the conclusion that geminally (*gem*) disubstituted $\beta^{2,2}$- and $\beta^{3,3}$-amino acids (Figure 2) ought not to fit into these secondary structures. Thus, we expect them to adopt hitherto unknown conformations of their backbones.

Open-chain and cyclic α,α-disubstituted or α-branched α-amino acids are among the most studied synthetic and naturally occurring non-coded amino acids. Their incorporation into peptides leads to a restricted conformational flexibility,[8] to stabilization of defined secondary structures in small peptides,[9−12] to increased lipophilicity,[13] as well as to higher resistance towards both enzymatic and chemical hydrolysis.[14] Moreover, some α,α-dialkylated α-amino acids have proved to be efficient enzyme inhibitors.[15−17] The preparation of enantiopure α,α-dialkylated α-amino acids has thus attracted considerable attention and has been described in several review articles.[18−21]

In contrast, there is no such compilation on the synthesis of chiral, geminally disubstituted β-amino acids. Since the far-reaching discovery that β-peptides form much more stable secondary structures in solution[1,22,23] than their α-peptidic natural counterparts, there has been an ever-growing interest in the synthesis of β-amino acids with various substitution patterns. Due to the increased number of possible constitutional and configurational isomers of β-amino acids, many more synthetic strategies are applicable.[24] Stereoselective syntheses of β-amino acids have already been extensively reviewed.[25−28] Many methods for the synthesis of β-amino acids are listed in the book "Methods of Non-α-Amino Acid Synthesis", edited by Smith.[29] The most recent and complete compilation of enantioselective syntheses of β-amino acids can be found in Juaristi's book.[30] However, among all the available methods for the preparation of β-amino acids (β^2- and β^3-amino acids[31]), only a few are suitable for the generation of a quaternary



3_1 or 3_{14} Helix

12/10/12 Helix

Linear structure with pleated-sheet formation

Figure 1. Three secondary structures of β-peptides; green spheres indicate tetrahedral backbone positions that may be occupied by non-hydrogen atoms in the corresponding secondary structure; positions marked by red spheres can only be occupied by hydrogen atoms; A: left-handed or (*M*) 3_1 or 3_{14} helix; B: right-handed or (*P*) 12/10/12 helix; C: parallel pleated sheet

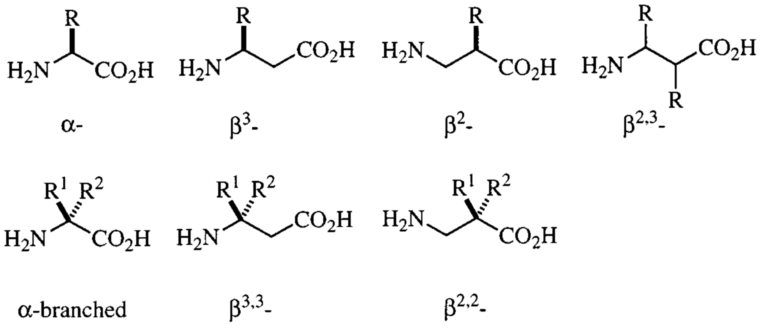


Figure 2. Designation of β-amino acids; superscripts indicate positions of side chains on the 3-aminopropanoic acid backbone; for comparison, the corresponding α-amino acids are included; where R is a proteinaceous side chain, the three-letter code designating the amino acid residue is used: β^3 with $R = CH_3$ is thus H-β^3-HAla-OH[1,2,7]

carbon at the α-position or of a tertiary carbon at the β-position. In the following chapters, we have collected the methods for the preparation of both achiral and chiral *geminally disubstituted* β-amino acids. Furthermore, new strategies for the synthesis of enantiopure derivatives of this class of compounds are discussed.

2. Methods for the Synthesis of Achiral Geminally Disubstituted β-Amino Acids

Some methods for the preparation of achiral β-amino acids, disubstituted at the β-carbon ($\beta^{3,3}$), are shown in Scheme 1. Methods that have been used for the preparation of achiral α,α-disubstituted β-amino acids ($\beta^{2,2}$) are summarized in Scheme 2.

$\beta^{2,2,3,3}$-Amino Acids

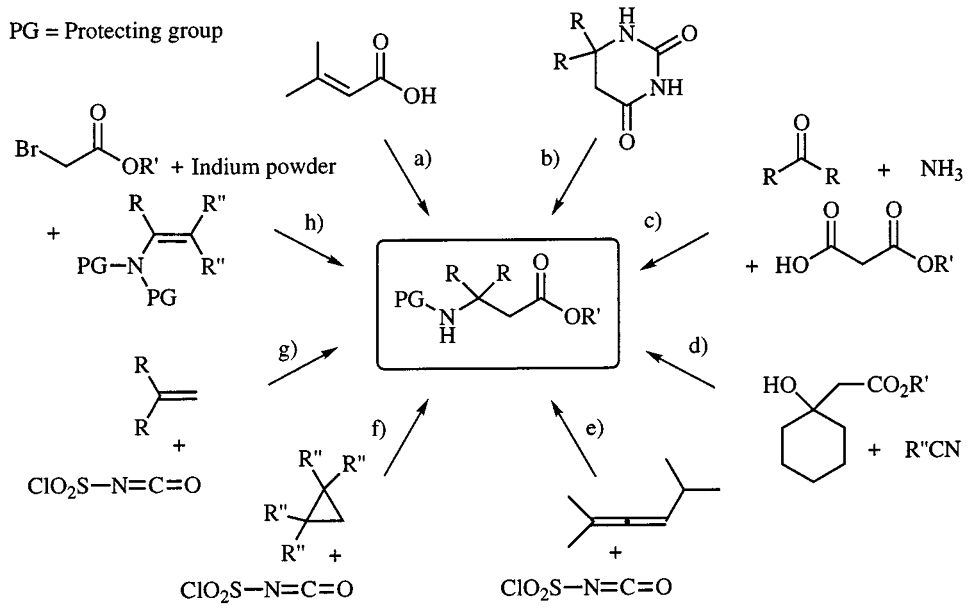
Tetrasubstituted $\beta^{2,2,3,3}$-amino acids represent interesting building blocks for testing the efficiency of coupling reagents in amide-bond formation, since both the amino and carboxy group are sterically hindered. Moreover, they may be capable of acting as secondary-structure breakers if incorporated into β-peptides. Some of the methods presented above can also be applied to the synthesis of $\beta^{2,2,3,3}$-amino acids.

Tetramethyl- and di-pentamethylene-substituted β-lactams can be prepared in quantitative yield by reaction of chlorosulfonyl isocyanate with tetrasubstituted olefins in diethyl ether or liquid SO_2 (Scheme 3).[47] The chlorosulfonyl-β-lactams can easily be hydrolyzed to the corresponding $\beta^{2,2,3,3}$-amino acids.[43−45] Olefins bearing electron-withdrawing substituents are not tolerated.

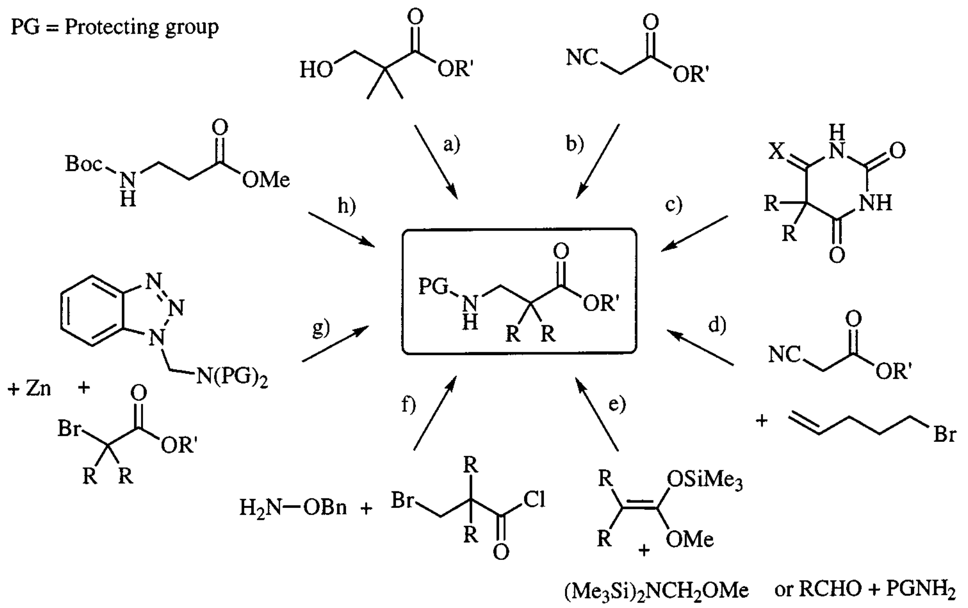
Another approach uses methyl 2,2,3,3-tetramethylsuccinate[64] as starting material for a Curtius rearrangement.[65] Treatment of the intermediate isocyanate with benzyl alcohol and hydrolysis with NaOH afforded the *N*-(*Z*)-protected 2,2,3,3-tetramethyl-β-alanine in 28% yield (Scheme 4).

3. Methods of EPC Synthesis of Geminally Disubstituted Amino Acids

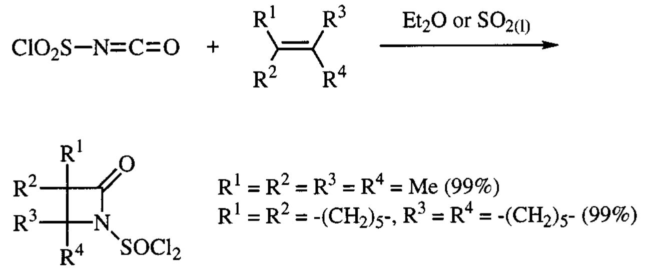
Stereogenic tertiary and quaternary centers occur frequently in natural products.[66−68] The control of stereoselectivity in reactions generating such "per-substituted" centers still represents a synthetic challenge.[19,69−71] To date, only a few methods for the preparation of enantiopure



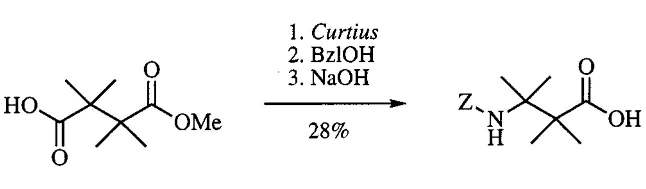
Scheme 1. Various methods for the preparation of achiral $\beta^{3,3}$-amino acids: (a) Michael addition of ammonia to 3-methylbut-2-enoic acid derivatives (senecioic acid).[5,32−34] (b) Hydrolysis of 6,6-disubstituted dihydrouracils,[35] followed by acidic work-up.[36][37] (c) Three-component Mannich reaction of a ketone, NH_3, and a malonic acid derivative.[38][39] (d) Ritter transformation[40] of 3-hydroxycarboxylates with nitriles in the presence of conc. H_2SO_4 to give the *N*-acyl-β-amino acid.[41][42] (e) Cycloaddition of chlorosulfonyl isocyanate with allenes to give an alkylidene β-lactam, which can be hydrolyzed and hydrogenated to give the corresponding β-amino acid.[43] (f) Reaction of substituted cyclopropanes with chlorosulfonyl isocyanate to yield β-lactams that can be transformed as described in (e).[44] (g) Cycloaddition of disubstituted alkenes and chlorosulfonyl isocyanate, reductive cleavage of the chlorosulfonyl group, followed by protection of the β-lactam N atom and β-lactam opening,[45][46] providing the desired β-amino acid.[47][48] (h) Indium-mediated reaction of enamines with methyl bromoacetate in the presence of acid[49]



Scheme 2. Various methods for the preparation of achiral $\beta^{2,2}$-amino acids: (a) Nucleophilic displacement of the hydroxy group in hydroxypivalic acid by PBr_5 followed by treatment with ethanolic NH_3.[50] (b) Dialkylation of methyl cyanoacetate with alkyl halides[51] or various dibromides[52][53] to yield α,α-disubstituted methyl cyanoacetates (which can alternatively be prepared by Mitsunobu reaction of diols with methyl cyanoacetate[54]); selective reduction of the cyanoesters,[5,34,55] *N*-protection, and saponification of the ester group affords the $\beta^{2,2}$-amino acid derivatives. (c) Hydrolytic cleavage of 5,5-diethylbarbituric acid,[56] obtained by desulfurization[35] of 5,5-diethyl-4-thiobarbituric acid.[57] (d) Alkylation of cyanoacetate with 5-bromo-1-pentene, followed by radical cyclization.[58] (e) Aminomethylation of silyl ketene acetals with *N*,*N*-bis[(trimethylsilyl)methoxy]methylamine;[59] a one-pot Mannich-type condensation of aldehydes, primary amines, and silyl ketene acetals in H_2O in the presence of $InCl_3$[60] or a Ti-catalyzed reaction of phenethyl-protected imines with silyl ketene acetals to give the β-lactam, which is then hydrolyzed and hydrogenated to give the free β-amino acid.[61] (f) Ring-closure of benzyl-protected hydroxylamines with β-bromopropionyl chlorides to give β-lactams and subsequent hydrolysis.[62] (g) Reformatzky reaction of an appropriate benzotriazole derivative with a 2-bromoalkanoate.[63] (h) Dialkylation of Boc-protected methyl 3-aminopropanoate via a doubly lithiated species[5][34]



Scheme 3. Reaction of chlorosulfonyl isocyanate with tetrasubstituted olefins according to Graf[47]



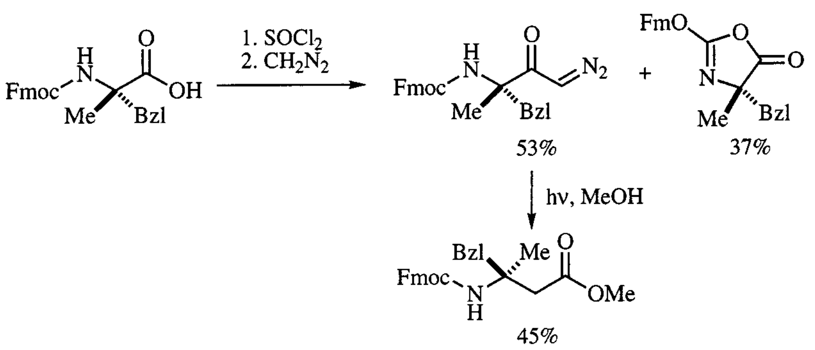
Scheme 4. Curtius rearrangement of methyl 2,2,3,3-tetramethylsuccinate, followed by treatment with benzyl alcohol and alkaline hydrolysis according to Shadbolt[65]

geminally disubstituted β-amino acids have been described, which are the subject of the following sections.[72] All three methods for synthesizing enantiopure compounds (EPC; resolution, use of the pool of chiral building blocks, overall enantioselective transformations) have been applied. Throughout this article, we use % *es* and % *ds* to specify the selectivities of reactions where one of the enantiomers or one of the diastereoisomers is formed preferentially. To specify enantiopurity of a product, we use % *ep*. These specifications take into account the fact that the ratios of stereoisomers are now being determined almost exclusively by chromatographic or NMR-spectroscopic methods, and not by measurement of optical rotation!

3.1 Chiral $\beta^{3,3}$-Amino Acids

At first sight, the Arndt−Eistert homologation, routinely applied in our group for the preparation of β^3-amino acids,[73][74] appears to be an ideal method for the synthesis of chiral β,β-disubstituted β-amino acids from enantiopure α,α-disubstituted α-amino acids since the latter are readily available (vide supra). However, both the preparation of the appropriate diazo ketones and their subsequent decomposition and rearrangement turn out to have severe problems associated with them.[75] Treatment[76] of the acid chloride derived from an Fmoc-protected α,α-disubstituted α-amino acid[77][78] with diazomethane afforded a mixture (*ca.* 1.4:1) of the desired diazo ketone and the corresponding oxazolone (Scheme 5).[79] The highly substituted diazo ketones rearrange in poor yields in the presence of Ag^+/triethylamine in methanol. However, initiation of the rearrangement by photolysis in methanol yielded the Fmoc-protected $\beta^{3,3}$-amino acid in 45% yield (Scheme 5).

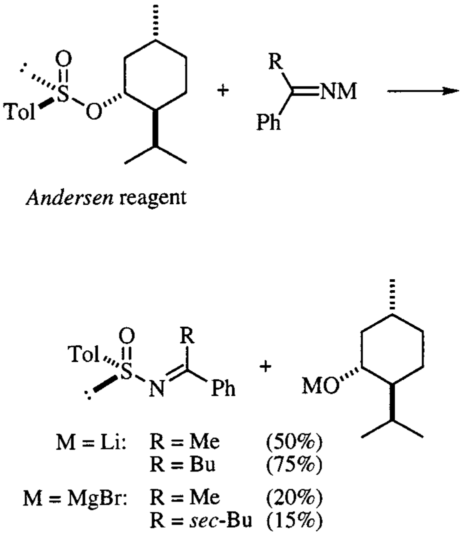
Recently, enantiopure *N*-*p*-toluenesulfinimines have been successfully used for the asymmetric synthesis of azirid-



Scheme 5. Formation of the diazo ketone from an enantiomerically pure benzyl-methyl-substituted α-amino acid and subsequent Wolff rearrangement upon irradiation, as described by Seebach et al.[75]

ines,[80][81] α-branched amines,[82][83] and β-amino acids.[84–87] The pioneering work of Davis on *p*-toluenesulfinimines[88] demonstrates that the sulfinyl group serves as an ideal activator, enabling the C=N group to undergo nucleophilic addition with high diastereofacial selectivity. Moreover, it is easily removed by hydrolysis under mildly acidic conditions.

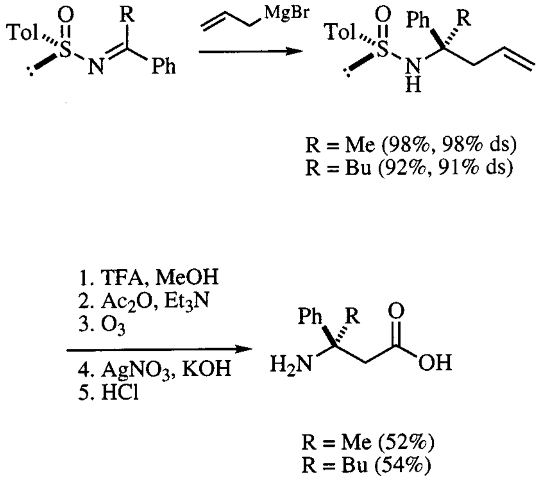
Enantiomerically pure sulfinimines (also called thiooxime *S*-oxides) derived from ketones are versatile precursors for the synthesis of $\beta^{2,2}$-amino acids – by nucleophilic addition of an appropriate d^2 reagent.[89] A general approach to chiral sulfinimines is outlined in Scheme 6. It is based on the asymmetric iminolysis of the Andersen reagent[90–92] (*R*)- or (*S*)-menthyl *p*-toluenesulfinate.[93] The reaction is stereospecific.[94]



Scheme 6. S$_N$2 displacement of metal menthoxide from the Andersen reagent by metal ketimines (derived from phenones) to provide enantiopure *p*-toluenesulfinimines according to Hua[85] and Cinquini[82]

Metal ketimines[95] are obtained by the reaction of a Grignard[82] or an alkyllithium reagent with benzonitrile.[85] The yields are much higher with lithium than with magnesium imino derivatives. These Andersen-type syntheses[96] are limited to aromatic nitriles.[97] Alternatively, the sulfinimines can be prepared by enantiomer-differentiating oxidation of racemic sulfenimines using chiral oxaziridines derived from camphor.[98–100] The enantiopurities of the sulfinimines thus formed (> 90% *es*) can be further increased by recrystallization from hexane. However, the major drawback of this procedure is that the enantiopurities of non-crystalline derivatives (i.e. most aliphatic compounds) cannot be improved in this way.

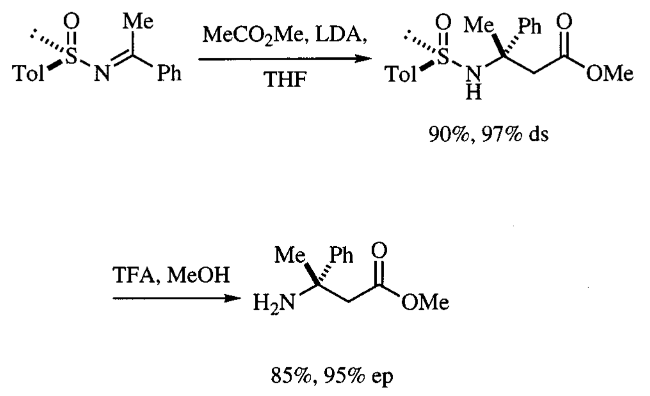
The chiral sulfinimines react smoothly with allylmagnesium bromide with high diastereoselectivity (Scheme 7). The diastereoisomers can be readily separated by chromatography and then converted to the corresponding free $\beta^{3,3}$-amino acids in a five-step sequence.[85]



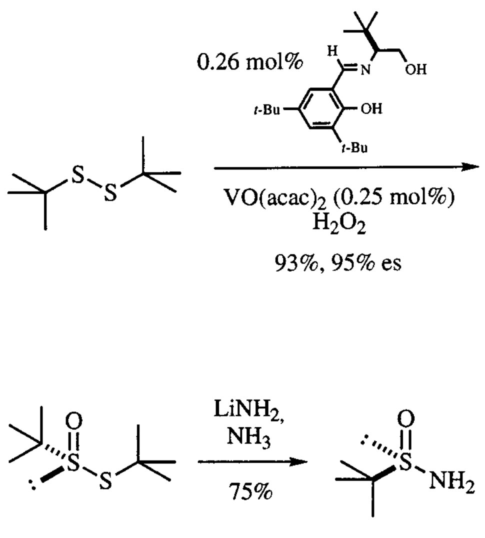
Scheme 7. Diastereoselective addition of allylmagnesium bromide to enantiopure sulfinimines according to Hua[85]

The number of steps leading to $\beta^{3,3}$-amino acids can in fact be reduced by adding the lithium enolate of methyl acetate to enantiopure sulfinimines (Scheme 8). Mild hydrolysis of the sulfinamide S,N bond at 0°C affords chiral $\beta^{3,3}$-amino acid esters in high yield and with excellent enantioselectivity.[86]

Recently, a new approach to enantiomerically pure sulfinimines has been developed by Ellman et al.[87] The key step is an asymmetric catalytic oxidation of di-*tert*-butyl disulfide with a catalyst derived from *tert*-leucinol[101] to provide *tert*-butyl *tert*-butanethiosulfinate in high yield and with high enantioselectivity (Scheme 9). Enantiopure *tert*-butanesulfinamides are then formed by nucleophilic cleavage of the S,S bond with lithium amide.[102]



Scheme 8. Diastereoselective addition of enolates to enantiopure sulfinimines according to Davis[86]

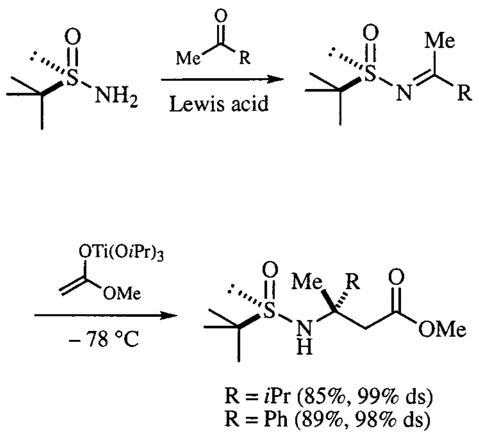


Scheme 9. Enantioselective catalytic oxidation of di-*tert*-butyl disulfide, followed by reaction with lithium amide to provide enantiopure *tert*-butanesulfinamide according to Ellman[101][102]

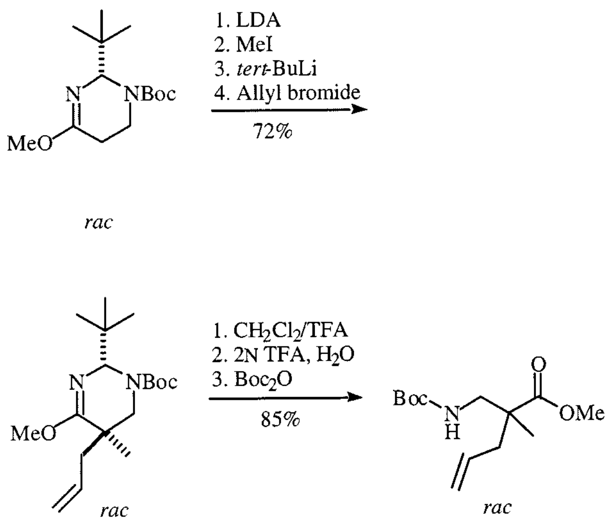
Enantiopure sulfinimines derived from *aliphatic* carbonyl compounds are now available in high yields[103] (Scheme 10) by condensation of the *tert*-butanesulfinamide with aldehydes[102] or ketones.[104] Finally, addition of the titanium enolate of methyl acetate, prepared by transmetallation from the corresponding Li enolate with ClTi(O*i*Pr)$_3$ and subsequent cleavage provides $\beta^{3,3}$-amino esters.[105]

3.2 Chiral $\beta^{2,2}$-Amino Acids

The diastereoselective introduction of two substituents at the α-carbon atom of chiral 3-amino alkanoates seems to be the method of choice for the preparation of chiral α,α-disubstituted β-amino acids. However, a literature search (Beilstein Crossfire) revealed that there is as yet no published procedure for the diastereoselective α-*di*alkylation of open-chain 3-aminopropanoic acid derivatives. Better stereoselectivities are often obtained using cyclic derivatives, which allow excellent differentiation of the diastereotopic faces of enolate planes.[19] Indeed, high diastereoselectivities are observed with two types of geminally disubstituted cyclic derivatives (Schemes 11 and 12). In Scheme 11, the use of chiral cyclic methyl iminoesters for the preparation of α,α-disubstituted β-amino acids is outlined.[106][107] The chiral building block, Boc-protected 2-*tert*-butyl-4-methoxytetrahydropyrimidine, is easily prepared in three steps (56% yield) from (*Z*)-protected 3-aminopropionic acid and can be resolved by chromatography on a chiral column.[107][108] The Li enaminate of this heterocycle reacts smoothly with iodomethane and, in a second step, with allyl bromide to give the geminally disubstituted product.[108] In both alkylation steps only *one* diastereoisomer is formed. A two-step cleavage under mild conditions converts the heterocycle to the corresponding enantiopure $\beta^{2,2}$-amino acid methyl esters.[109]



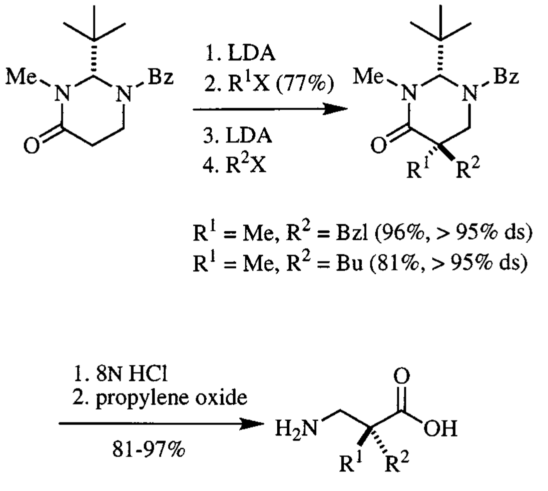
Scheme 10. Preparation of enantiopure *tert*-butanesulfinimines for an asymmetric Mannich reaction according to Ellman et al.[87]



Scheme 11. Highly diastereoselective dialkylation of *rac* 1-Boc-protected 2-*tert*-butyl-4-methoxytetrahydropyrimidine and subsequent hydrolysis to the $\beta^{2,2}$-amino acid methyl ester according to Seebach and Boog; only one enantiomer is shown; using enantiopure starting material, the corresponding (*R*)- or (*S*)-$\beta^{3,3}$-amino acid esters are accessible[107–109]

Another cyclic derivative of 3-aminopropanoic acid, (*S*)- or (*R*)-1-benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-

one,[110] has been shown to be dialkylated with comparable yields and diastereoselectivities (Scheme 12).[111]

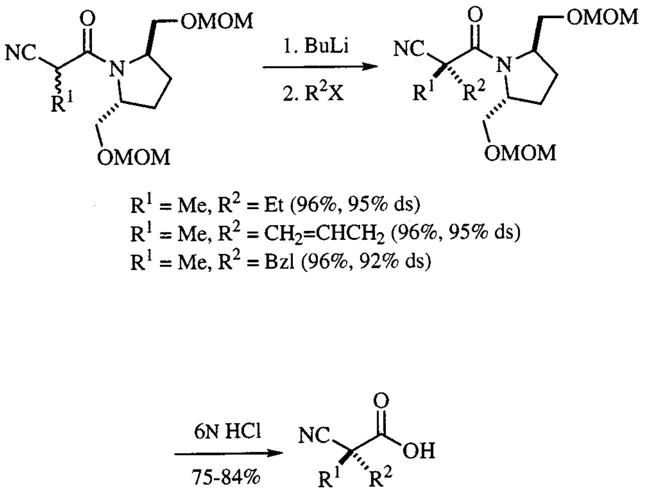


Scheme 12. Diastereoselective double alkylation of (*S*)-1-benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one and hydrolysis to afford the free enantiopure $\beta^{2,2}$-amino acids according to Juaristi;[110][111] the diastereoselectivities refer to the second alkylation step

Whereas the dialkylation of non-cyclic 3-aminopropanoic acid derivatives has not been reported, the diastereoselective alkylation of chiral α-cyanoacetic acid ester-[112] or α-cyanoacetamide enolates[113] has been used to prepare α,α-disubstituted α-cyanoacetic acid derivatives, precursors to $\beta^{2,2}$-amino acids by way of nitrile reduction.

The chiral auxiliary for the diastereoselective alkylation depicted in Scheme 13 is an isoborneol derivative. The alkylated cyanoacetates are employed as epimeric mixtures. Various substituents R^1 and R^2 are compatible with this method.[112] Reduction of the cyano group provides the diastereomerically pure $\beta^{2,2}$-amino esters.[114] Using similar derivatives, Cativiela has shown that the chiral auxiliary can be removed by saponification with 10% KOH in methanol.[115][116]

In a procedure devised by Katsuki, the chiral *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine moiety accounts for high diastereoselectivity in the alkylation of the Li amide enolates[117] derived from α-cyanoalkanoic acid (Scheme 14).[113] The chiral auxiliary was cleaved by treatment with 6 N HCl to give α,α-disubstituted α-cyanoacetic acid, which could be transformed into the corresponding $\beta^{2,2}$-amino acid in one step by hydrogenation according to known procedures.[5][112]



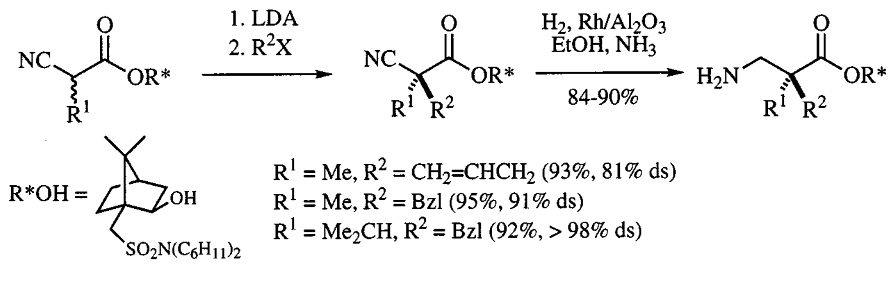
Scheme 14. Double alkylation of α-cyano-carboxamide enolates bearing the (2*R*,5*R*)-2,5-bis(methoxymethoxymethyl)pyrrolidine moiety as chiral auxiliary and subsequent acidic cleavage to give α,α-disubstituted α-cyanoacetic acids, according to Katsuki[113]

An enantioselective synthesis of $\beta^{2,2}$-amino acids following an entirely different strategy is shown in Scheme 15. The highly diastereoselective Diels–Alder reaction of 1,3-butadiene with the (*E*)-2-cyanocinnamate of (*S*)-ethyl lactate[118] is the key step. After removal of the lactic acid moiety and esterification, the C,C double bond is hydrogenated and the cyano group is reduced with Raney nickel to give the corresponding $\beta^{2,2}$-amino acid methyl ester in enantiomerically pure form.[119]

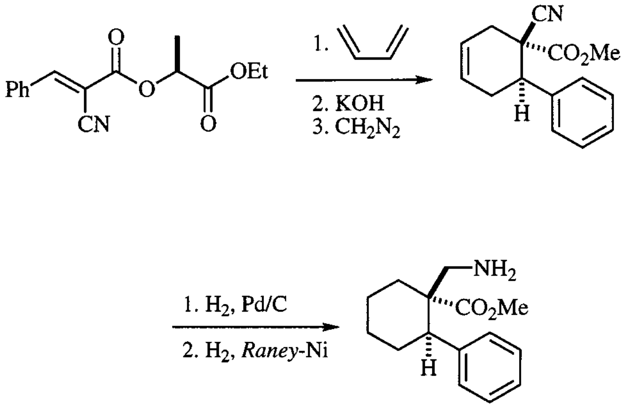
In yet another synthesis (Scheme 16), enantiopure[120] 2,2′-bis(bromomethyl)-1,1′-binaphthyl acts as a double alkylating reagent towards ethyl cyanoacetate.[121] Selective cobalt boride reduction[122][123] of the cyano group and protection/deprotection manipulations lead to axially chiral $\beta^{2,2}$-amino acids.

3.3 Chiral $\beta^{2,2,3}$-Amino Acids

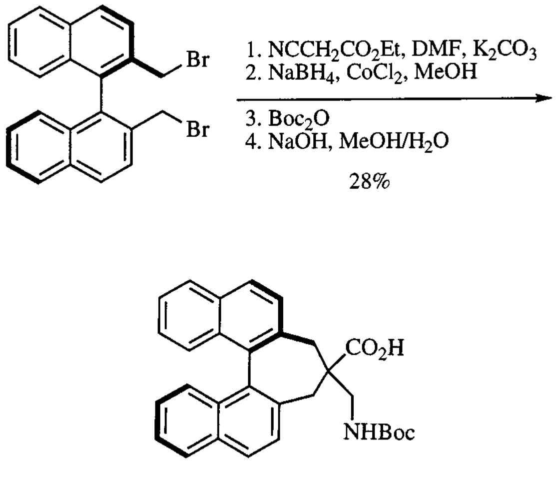
This kind of β-amino acid can be prepared either through α-branched β-amino acid precursors or intermediates, or alternatively by a variety of Mannich-type reactions.



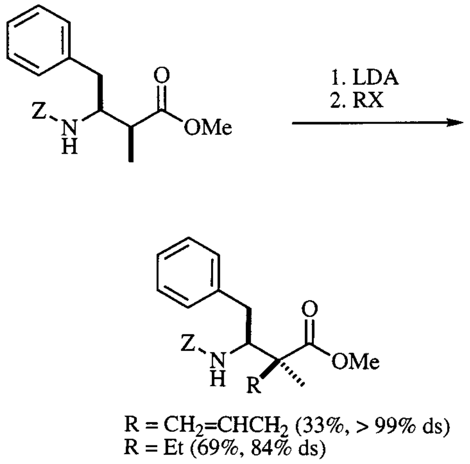
Scheme 13. Diastereoselective alkylation of the enolate of (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)isobornyl-2-alkyl-2-cyanoacetates and hydrogenation of the nitrile group according to Cativiela[112,114–116]



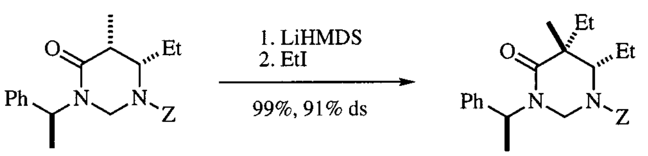
Scheme 15. Diels−Alder cycloaddition of an (*S*)-lactate ester to 1,3-butadiene and subsequent functional group transformations leading to an enantiopure $\beta^{2,2}$-amino acid methyl ester according to Cativiela[118][119]



Scheme 16. Synthesis of an α,α-disubstituted β-amino acid with a chirality axis, starting with a dialkylation of ethyl cyanoacetate using enantiomerically pure 2,2′-bis(bromomethyl)-1,1′-binaphthyl according to Mazaleyrat[121]



Scheme 17. Alkylation of α-methyl-β^3-homophenylalanine with iodoethane or allyl bromide to give α,α,β-trisubstituted β-amino acid derivatives according to Seebach and Podlech[73]



Scheme 18. Diastereoselective ethylation of a vicinally dialkylated perhydropyrimidin-4-one to give a derivative of an enantiopure $\beta^{2,2,3}$-amino acid according to Cardillo[128]

For instance, the Seebach method for α-alkylation of β-aminoalkanoates[124][125] has also been applied to α,β-disubstituted β-amino acid esters and was shown to occur with *lk*-1,2-induction[126] (Scheme 17).[73]

Davies obtained enantiopure $\beta^{2,2,3}$-amino acid *tert*-butyl esters by quenching the enolate derived from the conjugate addition of a chiral Li amide to an α,β-unsaturated ester with alkyl halides.[127] However, this reaction is very sensitive to steric hindrance (no reaction with EtI) and gives only moderate yields.

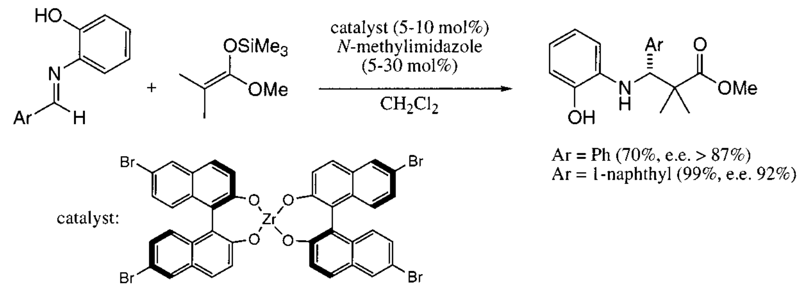
Cardillo reported on the alkylation of vicinally dialkylated perhydropyrimidin-4-ones (Scheme 18).[128] The (*S*)-phenethyl-substituted perhydropyrimidin-4-one was ethylated in high yield and with high diastereoselectivity. Hydrolysis[129] of the resulting pentasubstituted heterocycle can be expected to provide the corresponding free $\beta^{2,2,3}$-amino acid.

The following transformations leading to $\beta^{2,2,3}$-amino acid derivatives are all Mannich-type reactions. Stereoselectivity arises either from a chiral catalyst or from a chiral substrate (for uses of the term "substrate control", see refs.[130−133]).

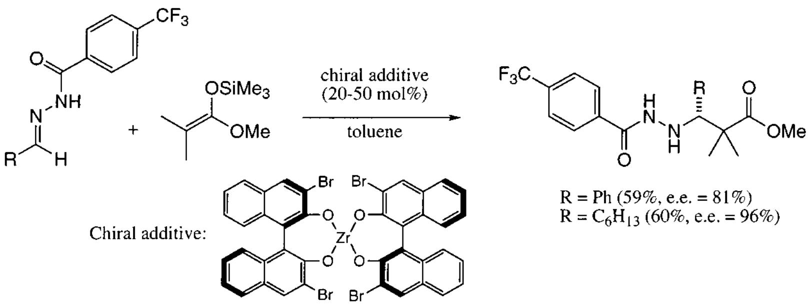
In one approach, Kobayashi has recently reported a catalytic enantioselective Mannich-type reaction of aldimines with silyl enol ethers[134] using a novel chiral Zr catalyst (Scheme 19).[135] The catalyst was formed by treatment of two equivalents of (*M*)-6,6′-dibromo-1,1′-bi-2-naphthol with one equivalent of Zr(O*t*Bu)$_4$ and was employed at a level of 5−10 mol%. Good yields and % *es* are obtained for imines derived from aromatic aldehydes. Removal of the 2-hydroxyphenyl group by *O*-methylation and oxidative cleavage with cerium ammonium nitrate provided the corresponding $\beta^{2,2,3}$-amino acid methyl esters.[136]

A variation of this method is the use of suitably protected *N*′-acylhydrazones as electrophiles (Scheme 20).[137] Moderate yields and good enantioselectivities are obtained using a catalyst (20 mol%) prepared from (*M*)-3,3′-dibromo-1,1′-bi-2-naphthol and Zr(O*t*Bu)$_4$. Aliphatic imines are also tolerated. However, large amounts of catalyst are necessary; the reaction with the benzaldehyde-derived imine required "50 mol% of catalyst". The $\beta^{2,2,3}$-amino acid methyl ester was liberated by reductive cleavage of the nitrogen−nitrogen bond of the hydrazino compound with samarium diiodide.[137][138]

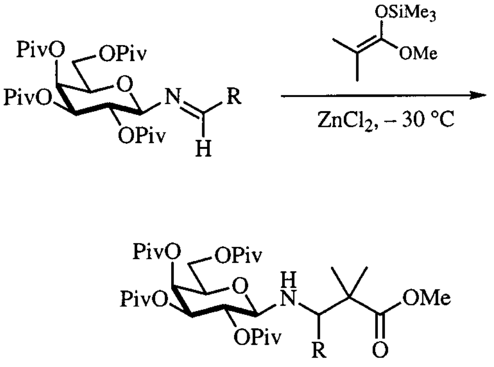
Kunz et al. employed the same silyl ketene acetal in a highly diastereoselective Mannich reaction with aldimines of per-pivaloylated β-D-galactopyranosylamine (Scheme 21).[139] The β-amino acid esters were released from the carbohydrate auxiliary in almost quantitative yield upon treatment with methanolic HCl.[140]



Scheme 19. Catalytic asymmetric Mannich-type reaction of the silyl ketene acetal derived from methyl 2-methylpropanoate with a suitably protected arylimine according to Kobayashi[135]



Scheme 20. Asymmetric Mannich-type reaction using sub-stoichiometric amounts of a zirconate, employing acylhydrazones as imine equivalents according to Kobayashi[137]



Scheme 21. Diastereoselective Mannich reaction of a β-D-galactosylamine-derived aldimine according to Kunz[139][140]

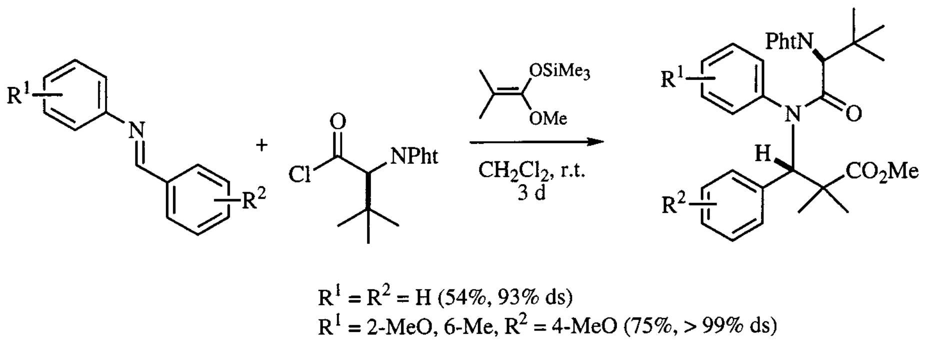
In situ generated chiral acyliminium ions derived from *N*,*N*-phthaloylamino acids have been successfully used in the preparation of $\beta^{2,2,3}$-amino acid derivatives (Scheme 22).[141] The reaction is highly diastereoselective and tolerates a wide range of aromatic substituents. A two-step procedure involving removal of the phthaloyl group and Edman degradation furnished the *N*-arylated $\beta^{2,2,3}$-amino acid esters.[141]

4. New Routes to Enantiopure $\beta^{2,2}$-and $\beta^{3,3}$-Amino Acids

Most of the methods for the enantioselective synthesis of geminally disubstituted β-amino acids presented so far are limited to specific residues and give either $\beta^{2,2}$- or $\beta^{3,3}$-amino acids. This inspired us to look for a more general approach allowing access to either substitution pattern. Eventually, a route was envisaged and realized, the key step of which is the enantioselective synthesis of geminally disubstituted succinates. This approach is outlined in the following section.

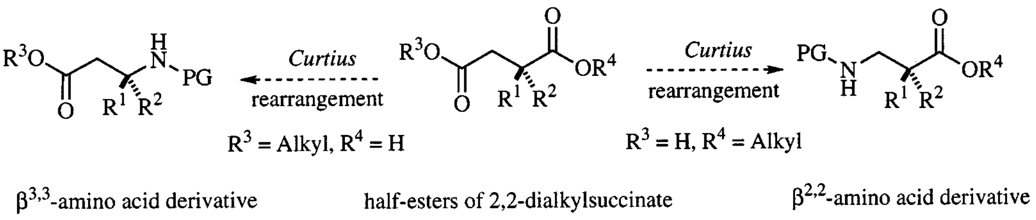
4.1 Chiral 2,2-Dialkyl Succinates: Versatile Precursors to Geminally Disubstituted β-Amino Acids

The solution to this problem emanates from research carried out in our laboratory dealing with the diastereoselective alkylation of β-hetero-substituted carbonyl compounds via dianionic derivatives.[142–147] Both β-hydroxycarboxylic esters[148–153] and β-aminocarboxylic esters[154][155] were alkylated with high diastereoselectivities.[156] In the course of



Scheme 22. One-pot Mannich reaction according to Waldmann et al.[141]

these studies, a convenient method for the synthesis of enantiopure geminally disubstituted malates and succinates was developed.[150][155] These can be transformed into either $\beta^{2,2}$- and $\beta^{3,3}$-amino acids by means of a Curtius rearrangement (Scheme 23).

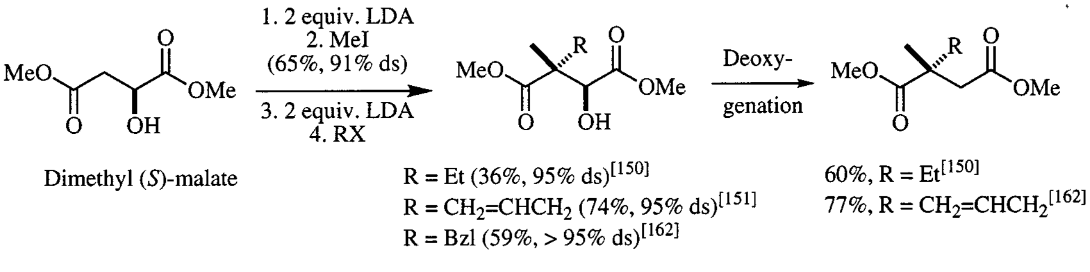


Scheme 23. Monoalkyl esters of geminally dialkylated succinates as versatile precursors of $\beta^{2,2}$- or $\beta^{3,3}$-amino acids

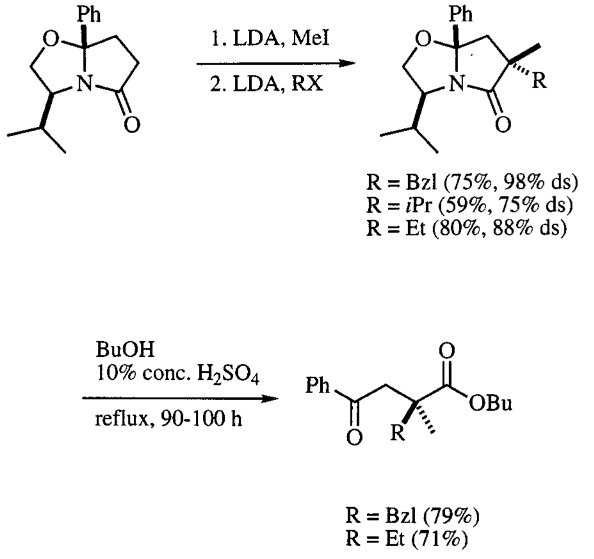
The first step of the synthesis of a dialkyl succinate is the highly diastereoselective methylation of the enolate derived from dimethyl (*S*)-malate, which proceeds in 65% yield (Scheme 24).[150,151,157] A second alkylation step using either ethyl iodide or allyl bromide provided a geminally dialkylated dimethyl malate with excellent diastereoselectivity.[158] Both alkylation steps proceed with relative topicity *ul*.[126] The product can be deoxygenated either by reduction of the corresponding xanthate ester in 60% yield,[150][159] or by hydroxy/chloride substitution and reductive halide removal using zinc in acetic acid.[160] Alkaline hydrolysis of the *gem*-disubstituted dimethyl succinate affords preferentially the half-ester containing an α,α-disubstituted ester, in accordance with similar hydrolyses reported in the literature.[161] This half-ester represents a direct precursor to $\beta^{2,2}$-amino acid derivatives, as outlined in Scheme 23.[162]

Meyers devised another enantioselective synthesis of 2,2-dialkyl carboxylic esters,[163–164] which is depicted in Scheme 25. The 2,2-dialkyl-4-oxocarboxylic esters shown can be smoothly transformed into the corresponding succinates by ozonolysis followed by basic work-up using hydrogen peroxide.[165] The synthesis starts with the alkylation of a chiral bicyclic lactam, which was prepared in 85% yield by condensing (*S*)-valinol with 3-benzoylpropionic acid. Enolate formation with LDA and subsequent addition of various alkyl halides gave good yields of the 2-alkyl derivatives. Treatment of the resulting mixture of diastereoisomers with LDA and a further alkyl halide provided the α,α-dialkylated lactam unit in good yields and with good diastereoselectivities. Acidic hydrolysis gave the 2,2-dialkyl 4-phenyl-4-oxocarboxylates.

Ideally, both succinate half-esters (see Scheme 23) should be available from the same precursor. There is literature precedent for regioselective nucleophilic ring-opening of unsymmetrical cyclic anhydrides (Figure 3). Hydride ions are reported to attack preferentially at the carbonyl adjacent to the disubstituted carbon.[166] However, *O*-[167–173] and *N*-nucleophiles[174][175] give rise to the regioisomeric products; heating cyclic geminally disubstituted anhydrides in absolute alcohol or in alcohol containing catalytic amounts of concentrated sulfuric acid[161] gives the monoester with high regioselectivity as a result of an attack at the carbonyl ad-



Scheme 24. Diastereoselective α-dialkylation of dimethyl (*S*)-malate with relative topicity *ul* and subsequent deoxygenation to give enantiopure geminally disubstituted dimethyl succinates, according to Seebach and Wasmuth[148,150,162]



Scheme 25. Diastereoselective dialkylation of a chiral bicyclic lactam and subsequent hydrolysis to give 2,2-dialkylcarboxylates according to Meyers[163]

jacent to the methylene group.[176] Treatment of the cyclic anhydride with ammonia or an ethereal solution of an amine gives the α,α-disubstituted amino acid.[174] Ring-opening by sodium methoxide is less regioselective, resulting in a mixture of both half-esters.[177] According to theoretical studies of regioselectivity in metal hydride reductions of unsymmetrical cyclic anhydrides,[166][178] the LUMO coefficient on the carbon of the carbonyl group next to the disubstituted carbon is considerably larger than that on the other carbonyl carbon atom.[166][179] This is in agreement with the experimental findings. This same type of regioselectivity has been predicted previously[180][181] on the basis of a non-perpendicular approach along the Bürgi−Dunitz trajectory.[182−185] In contrast, the opposite regioselectivity observed for anhydride opening by alcohols or amines is not yet understood.[186]

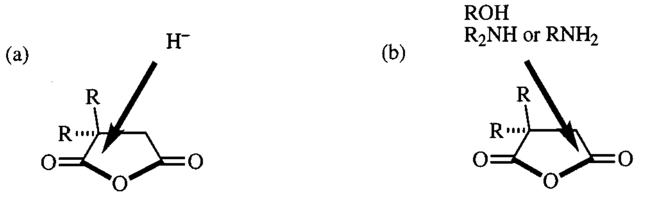
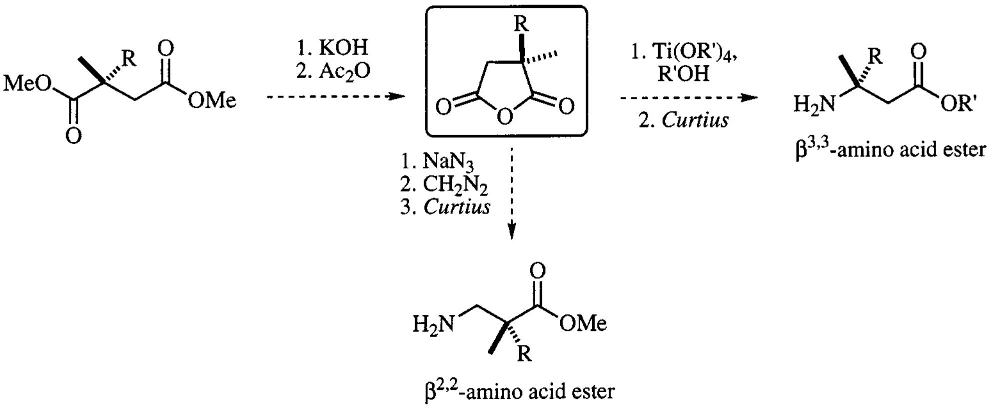


Figure 3. Observed regioselectivity in nucleophilic ring-opening of unsymmetrical cyclic anhydrides; direction of the approach of hydride ions (a) and of *O*- or *N*-nucleophiles (b)

On the basis of these precedents, the following path to either $\beta^{2,2}$- or $\beta^{3,3}$-amino acids can be envisaged (Scheme 26). Cyclization of the α,α-disubstituted succinic acids (Scheme 24) should be possible by treatment with acetic anhydride,[170][171] with acetyl chloride,[187][188] or with thionyl chloride.[161] The regioselectivity of anhydride opening with alcohols can be expected to be improved by using titanates.[189][190] The free acid may then be subjected to a Curtius rearrangement to give the enantiopure $\beta^{3,3}$-amino acid ester.[191] On the other hand, treatment of the chiral anhydride with azide should furnish the corresponding α,α-disubstituted acid, which may then be esterified and rearranged to give the enantiomerically pure $\beta^{2,2}$-amino acid ester.

5. First Structural Investigations of β-Peptides from Achiral $\beta^{2,2}$- and $\beta^{3,3}$-Geminally Disubstituted Amino Acids

The incorporation of β-amino acids with geminal disubstitution, as described herein, into β-peptides promises to provide exciting new secondary structures: previous work in our group[5][192] has led to the production of a number



Scheme 26. *gem*-Disubstituted cyclic anhydrides as possible precursors of enantiopure $\beta^{2,2}$- and $\beta^{3,3}$-amino acids

of β-peptides consisting of up to twelve achiral *gem*-disubstituted β-amino acids (Figure 4).

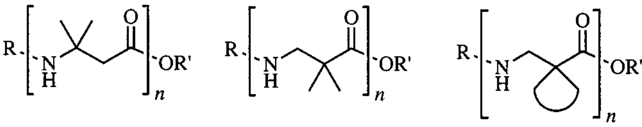


Figure 4. $\beta^{3,3}$- and $\beta^{2,2}$-Peptides consisting of geminally disubstituted β-amino acids that we have synthesized to date[5]

To date, structural investigations have focused on crystal structures. It has been found that the cyclohexane derivative (n = 3) forms 10-membered hydrogen-bonded rings (also present in a 12/10/12 helix[2] and in a β-peptidic hairpin turn[4]). Surprisingly, the oligomers of 1-(aminomethyl)cyclopropanecarboxylic acid form 8-membered hydrogen-bonded rings, which arrange to stair-like or U-shaped structures in the crystalline state (see Figure 5; X-ray analyses of the dimer, trimer, and tetramer[5b]). It will be interesting to see what chiral supramolecular structures are produced as a result of the chirality of building blocks with geminal disubstitution! Synthetic and structural investigations along these lines are currently in progress.

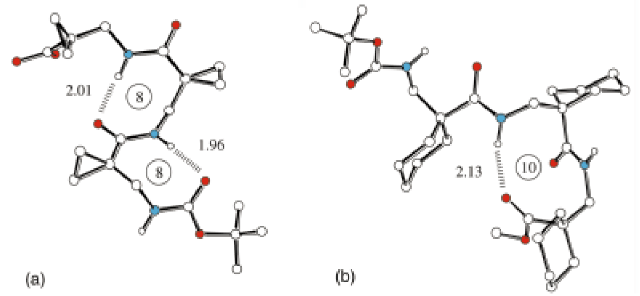


Figure 5. X-ray structures of $\beta^{2,2}$-tripeptides consisting (a)[5b] of 1-(aminomethyl)cyclopropanecarboxylic acid, and (b)[5a] of 1-(aminomethyl)cyclohexanecarboxylic acid; intramolecular H-bonds (N−H···O in [Å]) are indicated with a standard N−H bond length of 1.00 Å)

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