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## $\beta^2$ -Amino Acids—Syntheses, Occurrence in Natural Products, and Components of $\beta$ -Peptides<sup>1,2</sup>

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**Abstract:** Although they are less abundant than their  $\alpha$ -analogues,  $\beta$ -amino acids occur in nature both in free form and bound to peptides. Oligomers composed exclusively of  $\beta$ -amino acids (so-called  $\beta$ -peptides) might be the most thoroughly investigated peptidomimetics. Beside the facts that they are stable to metabolism, exhibit slow microbial degradation, and are inherently stable to proteases and peptidases, they fold into well-ordered secondary structures consisting of helices, turns, and sheets. In this respect, the most intriguing effects have been observed when  $\beta^2$ -amino acids are present in the  $\beta$ -peptide backbone. This review gives an overview of the occurrence and importance of  $\beta^2$ -amino acids in nature, placing emphasis on the metabolic pathways of  $\beta$ -aminoisobutyric acid ( $\beta$ -Aib) and the appearance of  $\beta^2$ -amino acids as secondary metabolites or as components of more complex natural products, such as peptides, depsipeptides, lactones, and alkaloids. In addition, a compilation of the syntheses of both achiral and chiral  $\beta^2$ -amino acids is presented. While there are numerous routes to achiral  $\beta^2$ -amino acids, their EPC synthesis is currently the subject of many investigations. These include the diastereoselective alkylation and Mannich-type reactions of cyclic- or acyclic  $\beta$ -homoglycine derivatives containing chiral auxiliaries, the Curtius degradation, the employment of transition-metal catalyzed reactions such as enantioselective hydrogenations, reductions, C–H insertions, and Michael-type additions, and the resolution of rac.  $\beta^2$ -amino acids, as well as several miscellaneous methods. In the last part of the review, the importance of  $\beta^2$ -amino acids in the formation of  $\beta$ -peptide secondary structures is discussed. © 2004 Wiley Periodicals, Inc. *Biopolymers* (Pept Sci) 76: 206–243, 2004

**Keywords:**  $\beta$ -amino acids; stereoselectivity; 10/12-helix; hairpin turn; oxazolidinone; Evans auxiliary, Oppolzer sultam; N-methoxymethyl benzyl carbamate

### 1. INTRODUCTION

The chemistry of  $\beta$ -peptides was investigated intensively in the past decade.<sup>1–7</sup> Probably the most important results have been: (i) that  $\beta$ -peptides fold

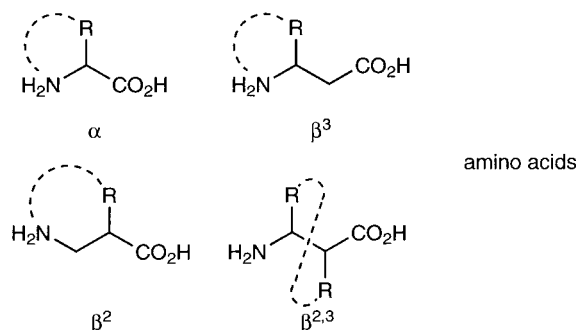
in a predictable way to form secondary structures in solution with short chain lengths; (ii) they are stable to cleavage by peptidases and to metabolic transformations; and (iii) they can mimic  $\alpha$ -peptides in peptide–protein and protein–protein inter-

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actions. The  $\beta$ -amino acids can be subdivided into  $\beta^3$ -,  $\beta^2$ -, and  $\beta^{2,3}$ -amino acids, depending upon the position of the side chain(s) on the 3-aminoalkanoic acid skeleton.



The most interesting secondary structures of  $\beta$ -peptides have only been observed when  $\beta^2$ -amino acids are built into the backbone: a  $\beta$ -peptidic hairpin turn and a novel type of helix consisting of 10- and 12-membered hydrogen-bonded rings. On the other hand,  $\beta^2$ -amino acids are not as readily available as their  $\beta^3$ -counterparts; almost all  $\beta^3$ -amino acids with proteinogenic side chains are now commercial (with *N*-Fmoc protection and acid labile side chain protection), while the  $\beta^2$ -amino acids must be prepared using multistep procedures.

For these reasons, a review article on naturally occurring  $\beta^2$ -amino acids, their syntheses, and their incorporation into  $\beta$ -peptides is appropriate.

## 2. $\beta$ -AMINOISOBUTYRIC ACID IN MAMMALIAN METABOLISM

Beside the proteinogenic amino acids aspartic (Asp) and glutamic acid (Glu) and their amides (Asn, Gln) that can be referred to simultaneously as  $\alpha$ - and  $\beta$ - or  $\alpha$ - and  $\gamma$ -aminocarboxylic acids, there are four other  $\beta$ -amino acids involved in mammalian metabolism. Among them, the so-called  $\beta$ -aminoisobutyric acid ( $\equiv$  3-amino-2-methyl propanoic acid,  $\beta$ -Aib, or  $\beta^2$ hAla)<sup>3</sup> represents the only example of a  $\beta^2$ -amino acid, and it is found in both enantiomeric forms:

<sup>1</sup> Taken in part from the Ph.D. thesis of G. Lelais, Dissertation No. 15429, ETH Zürich, 2004.

<sup>2</sup> Based on the 2004 Vincent duVigneand Swond Lecture of D. Seebach.

<sup>3</sup> In the notation  $\beta^n$ hXaa the number *n* indicates the position of the side chain in the  $\beta$ -amino acid, the prefix h stands for homo and relates to the extra methylene group, and Xaa is the three-letter code for the  $\alpha$ -amino acid with the same side chain. For brevity, the abbreviation  $\beta^n$ hXaa is used here for the corresponding amino acid; the correct but longer symbol is H- $\beta^n$ hXaa-OH.

(*R*)- $\beta^2$ hAla is a metabolite of thymine (Section 1.1, Scheme 1)<sup>8–11</sup> and (*S*)- $\beta^2$ hAla is a metabolite of valine<sup>4</sup> (Section 1.2, Scheme 2).<sup>11–13</sup> Early clinical studies<sup>17</sup> placed little emphasis on the sense of chirality; chromatographic resolution of the enantiomers shows that human urine contains H-(*R*)- $\beta^2$ hAla-OH almost exclusively, whereas the (*S*)-form is present in plasma.<sup>18</sup>

### 2.1. The (*R*)- $\beta^2$ hAla Metabolite

The natural occurrence of (*R*)-aminoisobutyric acid was first established in 1951 after its isolation from urine.<sup>19,20</sup> It was soon found that the characteristic of excreting this amino acid was inherited as a recessive trait.<sup>17,21</sup> Whereas most persons excrete little (*R*)- $\beta^2$ hAla in their urine (0–1.7  $\mu$ g/mg creatinine), some clinically normal persons are congenitally deficient in (*R*)- $\beta$ -aminoisobutyrate-pyruvate transaminase (cf. step 4 in Scheme 1) and excrete much larger amounts of this  $\beta^2$ -amino acid. This is called hyper- $\beta$ -aminoisobutyric aciduria (hyper- $\beta$ -Aiburia) and is referred to as a benign “metabolic polymorphism” present in human populations (5 to 10% of Caucasians and 40 to 95% of Asian populations). As shown in Scheme 1, (*R*)- $\beta^2$ hAla is a catabolite of thymine; dihydrothymine and  $\beta$ -ureidoisobutyrate are intermediates.<sup>22–24</sup> The first, second, and third steps of thymine catabolism, leading to (*R*)- $\beta^2$ hAla formation, correspond to the second, third, and fourth steps of cytosine/uracil catabolism yielding  $\beta$ -alanine (i.e.,  $\beta$ -homoglycine,  $\beta$ hGly).<sup>11</sup> Accordingly, the balance between the salvaging and catabolism of pyrimidines will influence the abundance of (*R*)- $\beta^2$ hAla.  $\beta$ -Ureidoisobutyric acid and its precursors must be transported to the liver to form (*R*)- $\beta^2$ hAla because  $\beta$ -ureidopropionase is active only in the liver. Early studies by Fink et al.<sup>10</sup> established that rat liver slices convert [ $\text{CH}_3$ -<sup>14</sup>C]thymine to radiolabeled glucose and alanine in addition to the expected intermediates of the thymine  $\rightarrow$  (*R*)- $\beta^2$ hAla pathway. (*R*)- $\beta^2$ hAla is thus a glycogenic amino acid. The first step of the  $\beta$ -aminoisobutyrate metabolism (cf. step 4 in Scheme 1) is a transamination reaction in which pyruvate is the acceptor. (*R*)-Methylmalonic acid semialdehyde ((*R*)-MMS) is then expected to be transformed to propionyl-CoA and finally to succinyl-CoA, but since this pathway has

<sup>4</sup> The other two natural  $\beta$ -amino acids are  $\beta$ -alanine (i.e.,  $\beta$ hGly) and (*R*)- $\beta$ -leucine (i.e., (*R*)- $\beta^3$ hVal) but they will not be taken into account in this article. For extensive referencing on the metabolic pathways of these two amino acids see Refs 11 and 14. For reasons of clarity it should be noted that (*R*)- $\beta^2$ hAla is referred to as (–)- $\beta^2$ hAla, or D- $\beta^2$ hAla<sup>15,16</sup> and that it is the homologue of  $\alpha$ -L-L-Ala!

only been well-established for the catabolism of (*S*)-MMS (cf. 8 in Scheme 2, Section 1.2), it may not apply to the (*R*)-enantiomer. If methylmalonate semialdehyde dehydrogenase, the enzyme catalyzing step 5 (Scheme 1), is specific for the (*S*)-enantiomer, two processes may possibly serve to racemise (*R*)-MMS; a nonenzymatic racemization of (*R*)-MMS<sup>5</sup> (step 9) or a reversible pathway through the nonchiral intermediate methylacryl-CoA (steps 10 to 13).

Although the synthesis of (*R*)- $\beta^2$ hAla is supposedly impaired in the face of dihydropyrimidine dehydrogenase (step 1), dihydropyrimidinase (step 2), and  $\beta$ -alanine synthase (step 3) deficiencies, it is not clear what consequence it might have on pathogenesis of the associated clinical phenotype. On the other hand it has been found that  $\beta$ -Aib excretion is increased by catabolism, in neoplastic states, in Down's syndrome, and when somatic growth increases the turnover of pyrimidines. In these circumstances, primarily the (*R*)-isomer is excreted.  $\beta$ -Aib excretion can, therefore, be used to monitor clinical progress and response to treatment of certain neoplasms.<sup>11</sup>

## 2.2. The (*S*)- $\beta^2$ hAla Metabolite

Some  $\beta$ -amino acids play also a role in the metabolism of  $\alpha$ -amino acids. L-Valine can, for example, be converted into (*S*)- $\beta^2$ hAla during its catabolism (Scheme 2). The initial step of this pathway involves a reversible transamination to the  $\alpha$ -ketoisovaleric acid followed by irreversible oxidative decarboxylation to form isobutyryl-CoA, which is then transformed to methacryl-CoA by the action of a dehydrogenase. The stereoselective hydration of the C=C double bond with subsequent hydrolysis of the thioester affords (*S*)- $\beta$ -hydroxyisobutyric acid. Oxidation of the hydroxy group to the aldehyde (*S*)-MMS followed by transamination leads to (*S*)- $\beta$ -aminoisobutyric acid. Due to the fact that (*S*)-MMS is mainly converted to propionyl-CoA (for further metabolism to succinyl-CoA) by an irreversible complex reaction catalyzed by methylmalonate semialdehyde dehydrogenase, the amount of (*S*)- $\beta^2$ hAla in plasma is usually kept low (1.8 to 4.5  $\mu$ M). An increase in its concentration (up to 30  $\mu$ M) has only been observed when the aforementioned dehydrogenase is defective.<sup>18,27,29–31</sup> In combination, an increase in the concentration of 3-hydroxyisobutyrate, 3-aminoisobutyrate, 3-hydroxypropanoate,  $\beta$ -alanine, and 2-ethyl-

3-hydroxybutyrate was also observed. Interestingly, in this case the  $\beta$ -Aib content in urine was about equally composed of the (*S*)- and (*R*)-isomers, while normally the *R/S* ratio is about 95:5.<sup>29</sup> 3-Hydroxyisobutyric acid was about 75% (*S*)- and 25% (*R*)-configuration, and all of the 2-ethyl-3-hydroxypropionic acid (i.e., a metabolite of the minor pathway of the isoleucine catabolism) was the (*S*)-isomer.<sup>27</sup> A defective methylmalonate semialdehyde dehydrogenase was proposed by studying the metabolism of valine in intact fibroblasts from a patient. The oxidation of [1-<sup>14</sup>C]valine to <sup>14</sup>CO<sub>2</sub> was normal, but the oxidation of [2-<sup>14</sup>C]valine to <sup>14</sup>CO<sub>2</sub> was undetectable, indicating a severe block in valine metabolism below the level of isobutyryl-CoA. The label in the 2-position of valine would be metabolized to the 1-position of MMS and would yield labeled carbon dioxide if methylmalonate semialdehyde dehydrogenase was active. Thus, the lack of production of labeled carbon dioxide from the substrate strongly indicates a deficiency of MMS dehydrogenase in the patient.<sup>28</sup>

## 3. $\beta^2$ -AMINO ACIDS AS A COMPONENT OF NATURAL PRODUCTS

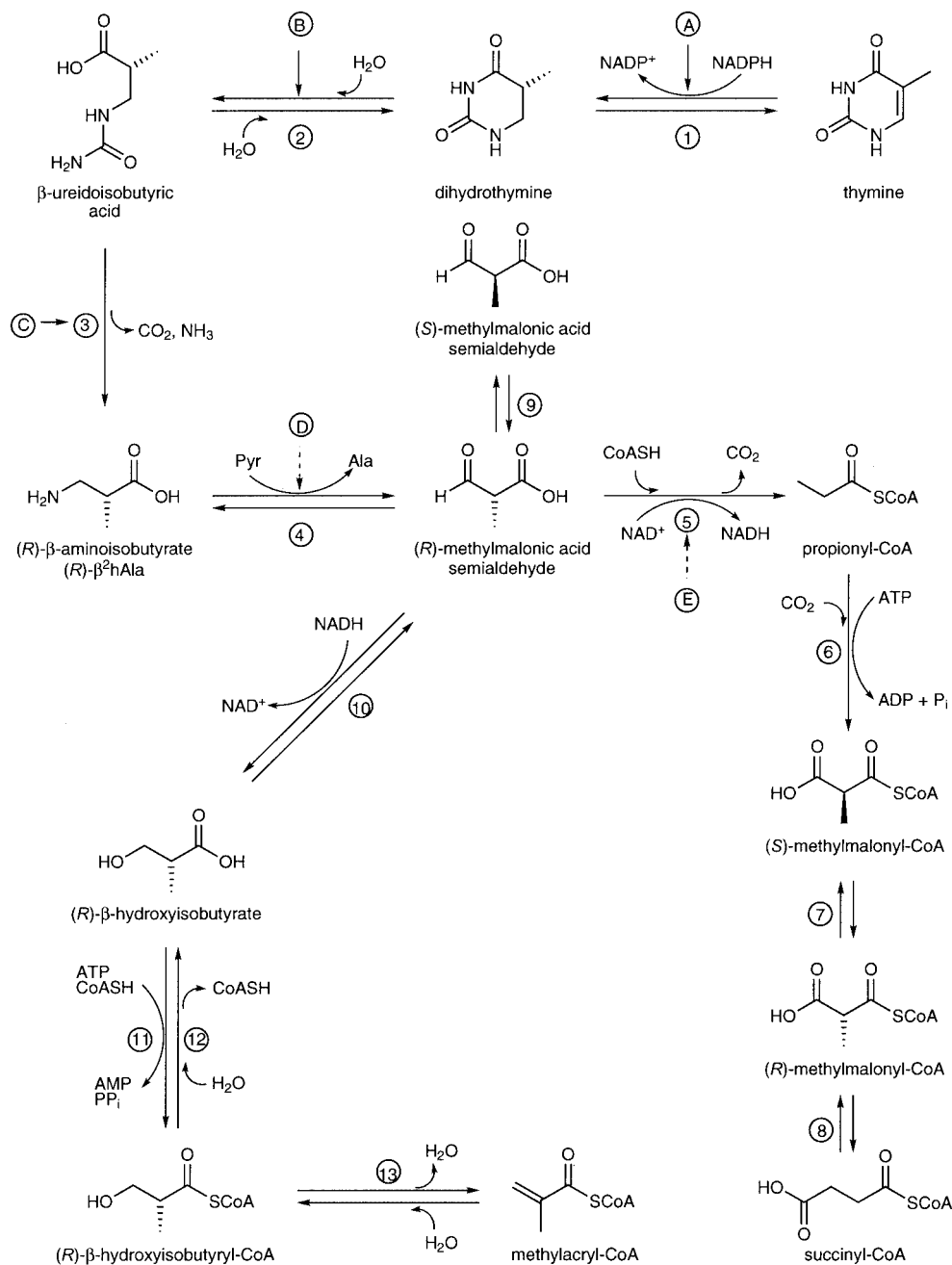
As for mammals, only  $\beta^2$ hAla seems to play a role as a primary metabolite in invertebrates (cf. Section 2.1). However, other  $\beta^2$ -amino acids are occasionally found in natural products. These secondary metabolites are either  $\beta^2$ -amino acid monomers or components of more complex structures like peptides, depsipeptides, lactones, and alkaloids. Often they have important pharmacological properties and are therefore of great interest.

### 3.1. Monomeric $\beta^2$ -Amino Acids

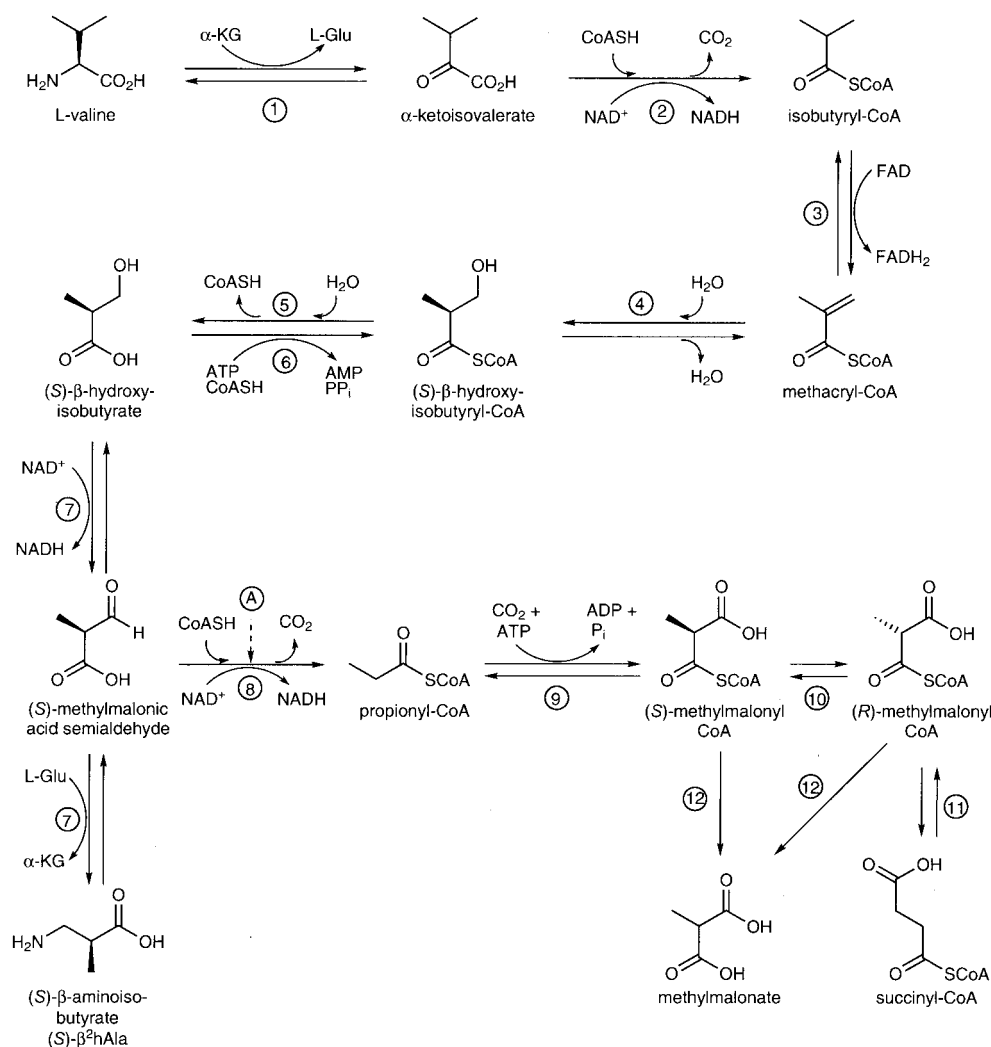
Only a few  $\beta^2$ -amino acids have been isolated from plants, bacteria, and invertebrates (Figure 1) and although their function is not known in all cases, they often exhibit interesting biological activities.

$\beta$ -Aminoisobutyric acid has been found in several invertebrates like mussels<sup>33</sup> and cestodes.<sup>34</sup> It has been established that, at least for the latter species, this amino acid is produced by thymine catabolism.<sup>35</sup> In addition,  $\beta$ -Aib has also been found in plants,<sup>36–40</sup> where its function is still unknown. It is interesting to note that  $\beta^2$ hAla and the homologous  $\beta^2$ hAbu ( $\alpha$ -ethyl- $\beta$ -alanine) have been extracted and characterized, together with other  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -amino acids, from the Murchison meteorite.<sup>41–43</sup> The fact

<sup>5</sup> The facile enolization of  $\beta$ -oxoacids and the relatively high acidity of their  $\alpha$ -protons is well-established, but the rate of racemization of (*R*)-MMS has apparently not been established.<sup>25,26</sup>



**SCHEME 1** Formation and metabolism of (R)- $\beta$ -aminoisobutyrate ((R)- $\beta$ -Aib or (R)- $\beta^2$ hAla).<sup>21</sup> The circled numbers indicate enzymes or metabolic processes: 1 = dihydropyrimidine dehydrogenase; 2 = dihydropyrimidinase; 3 =  $\beta$ -alanine synthase; 4 =  $\beta$ -aminoisobutyrate-pyruvate transaminase; 5 = methylmalonate semialdehyde dehydrogenase (acetylating) (?); 6 = propionyl-CoA carboxylase; 7 = methylmalonyl-CoA racemase; 8 = methylmalonyl-CoA mutase; 9 = nonenzymatic; 10 = 3-hydroxyisobutyrate dehydrogenase; 11 = an acyl-CoA synthetase (?); 12 = 3-hydroxyisobutyryl-CoA hydrolase; 13 = nonenzymatic for (R)-isomer (?). The circled letters indicate confirmed (solid arrows) and putative (interrupted arrows) enzyme deficiencies: A = dihydropyrimidine dehydrogenase deficiency; B = dihydropyrimidinase deficiency; C =  $\beta$ -alanine synthase deficiency; D = hyper- $\beta$ -Aiburia; E = a shared disorder of  $\beta$ -alanine and  $\beta$ -Aib catabolism.<sup>27,28</sup>

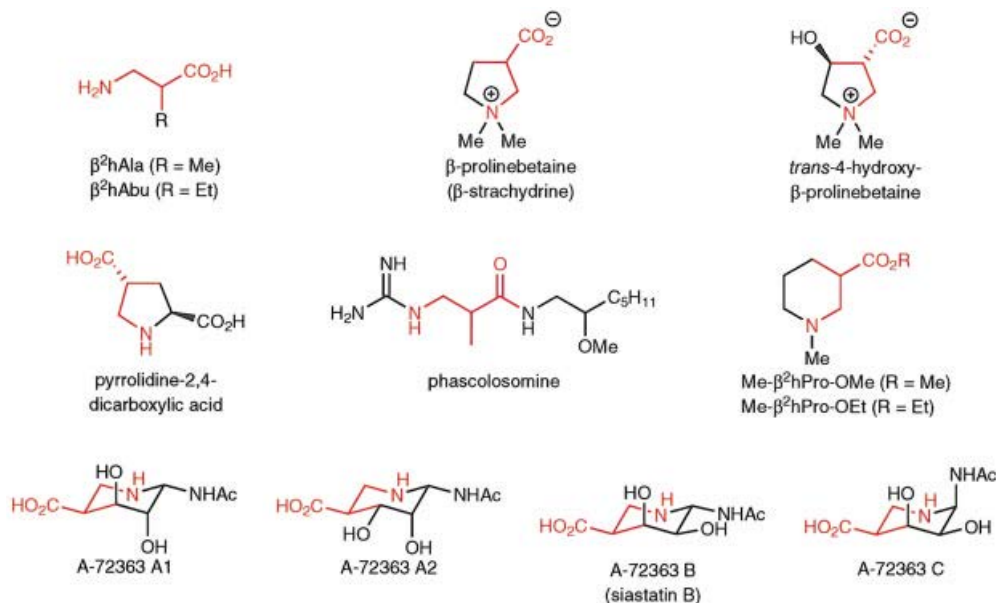


**SCHEME 2** Relationship between L-valine catabolism and (S)-β-aminoisobutyrate ((S)-β-Aib or (S)-β²Ala) metabolism.<sup>21</sup> The circled numbers indicate the following enzymes: 1 = branched-chain amino acid transaminase(s); 2 = branched-chain α-keto acid dehydrogenase; 3 = isobutyryl-CoA dehydrogenase; 4 = enoyl-CoA hydratase; 5 = 3-hydroxyisobutyryl-CoA hydrolase; 6 = an acyl-CoA synthetase (?); 7 = 3-hydroxyisobutyrate dehydrogenase; 8 = methylmalonate semialdehyde dehydrogenase (acylating); 9 = propionyl-CoA carboxylase; 10 = methylmalonyl-CoA racemase; 11 = methylmalonyl-CoA mutase; 12 = thiolester hydrolase (?); 13 = (S)-β-aminoisobutyrate-α-ketoglutarate transaminase. Disorders of valine oxidation (A)<sup>32</sup> may affect step 13.

that the meteorite contains all possible acyclic α-, β-, γ-, and δ-amino acids is consistent with a process of their formation involving a random combination of single C-precursors (e.g., radical species).

β-Prolinebetaine<sup>44,45</sup> and *trans*-4-hydroxy-β-prolinebetaine<sup>46</sup> could be considered cyclic β²-amino acids and have been found in many species of marine algae.<sup>47</sup> It would appear, therefore, that these compounds are a characteristic feature of such organisms. Betaines are thought to play a pivotal role in plant cytoplasmic osmotic adjustment in response to osmotic stress.<sup>48</sup> Some algae also contain *trans*-pyrro-

lidine-2,4-dicarboxylic acid,<sup>49</sup> a compound that selectively inhibits the transport of L-glutamate, one of the major excitatory neurotransmitters in the mammalian brain. The guanidino compound phascosomine was isolated from sipunculid worms<sup>50</sup> and was found to be mainly localized in the viscera of the worms. Usually, guanidino compounds are particularly abundant in muscle and were found to be the components of muscular phosphagens. Therefore, they play an important part in the energy processes of muscular contraction, and their function is similar to that of arginine in most invertebrates and to that of creatine in all



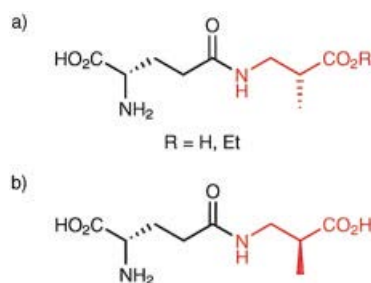
**FIGURE 1** Acyclic and cyclic  $\beta^2$ -amino acids found in nature as monomers.

vertebrate muscles. The concentration of phascolosomine is comparatively low in muscle, but exceptionally high in viscera (about 2 to 4 times the average concentration of the total guanidine bases used as phosphoryl acceptors in the body-wall muscle of these animals). Thus, phascolosomine exhibits unusual features with regard to its structure and distribution. The homologated proline esters Me- $\beta^2$ hPro-OMe and Me- $\beta^2$ hPro-OEt are volatile alkaloids found in the *Areca catechu* palmarum.<sup>51</sup> A more complex class of  $\beta^2$ -amino acids has been isolated from the culture filtrate of the bacterium *Streptomyces nobilis* SANK 60192.<sup>52</sup> They have been designated A-72363 A1, A2, B, and C and have been shown to inhibit several glycosidases. A-72363 B (i.e., siastatin B) is selective for neuraminidase and  $\beta$ -glucuronidase and A-72363 C for  $\beta$ -glucuronidase and heparanase, with the remaining two compounds exhibiting a weak inhibitory effect on the glycosidases tested.<sup>53</sup>

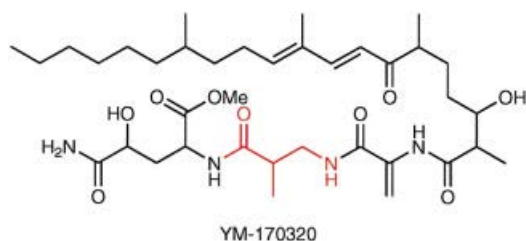
### 3.2. $\beta^2$ hAla Derivatives as Part of Peptides

Peptides containing  $\beta^2$ -amino acids occur rarely in nature. Moreover, they contain exclusively  $\beta^2$ hAla derivatives. The most simple structures isolated are represented by  $\gamma$ -L-glutamyl- $\beta$ -isobutyric acid, or ethyl ester, dipeptides (Figure 2). They have been found in several plants<sup>37–40</sup> and in bovine brain.<sup>54,55</sup> Whereas in plants the  $\beta^2$ hAla building block has the (*R*)-configuration, the enantiomer is present in bovine brain.

The physiological relevance of  $\gamma$ -glutamyl peptides is still not clear. It has been postulated<sup>55</sup> that the concentration of free  $\beta^2$ hAla as well as of other amino acids in the brain is regulated by reversible formation and hydrolysis of the corresponding  $\gamma$ -glutamyl dipeptide by action of a transferase, probably glutamyltransferase. This makes use of glutathione (i.e.,  $\gamma$ -glutamylcysteinylglycine tripeptide, also known as GSH) as a substrate to transfer the  $\gamma$ -glutamyl bond to new acceptors.<sup>56</sup> Such dipeptides could also be synthesized through the effect of  $\gamma$ -glutamylcysteine synthetase ( $\gamma$ -GCS), a mammalian enzyme that catalyzes the first step of glutathione synthesis, coupling L-glutamic acid and L-cysteine to form  $\gamma$ -glutamylcysteine. Rathbun<sup>57</sup> demonstrated the ability of this enzyme, isolated from bovine lens,<sup>58</sup> to catalyze the synthesis of  $\gamma$ -glutamyl dipeptides using several amino acids in place of cysteine. Moreover, he showed that both enantiomers of  $\beta^2$ hAla can substi-



**FIGURE 2**  $\gamma$ -Glutamyl dipeptides isolated from (a) plants and (b) bovine brain.



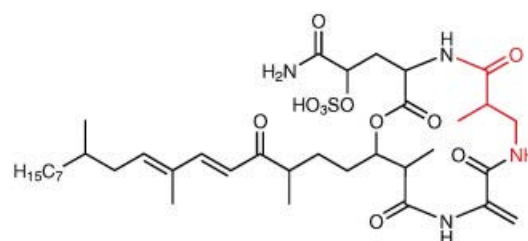
**FIGURE 3** The lipopeptide antibiotic YM-170320, an ergosterol-biosynthesis inhibitor.

tute L-cysteine in the  $\gamma$ -GCS reaction, although with different efficiency.<sup>59</sup> The enzyme can distinguish between these two isomers since (*S*)- $\beta^2$ hAla was consumed at a rate which was two or three times that of (*R*)- $\beta^2$ hAla. Whether these plant and bovine-brain peptides all arise from one of the mentioned reactions is still unknown.

A solid-state fermentation of vegetative mycelia of strain YL-03706F, a mutant of *Candida tropicalis* pK233, has produced a novel lipopeptide antibiotic designated YM-170320 (Figure 3).<sup>60</sup> YM-170320 belongs to a novel class of ergosterol-biosynthesis inhibitors,<sup>6</sup> and the mode of action is now under investigation.

Cryptophycins are potent antitumor and antifungal peptolides that are found in the blue-green alga (cyanobacteria) *Nostoc* sp. GSV 224.<sup>61–64</sup> The major nat-

<sup>6</sup> There is substantial interest in discovering inhibitors of ergosterol biosynthesis in fungi, since ergosterol is an essential constituent of the fungal cytoplasmic membrane.

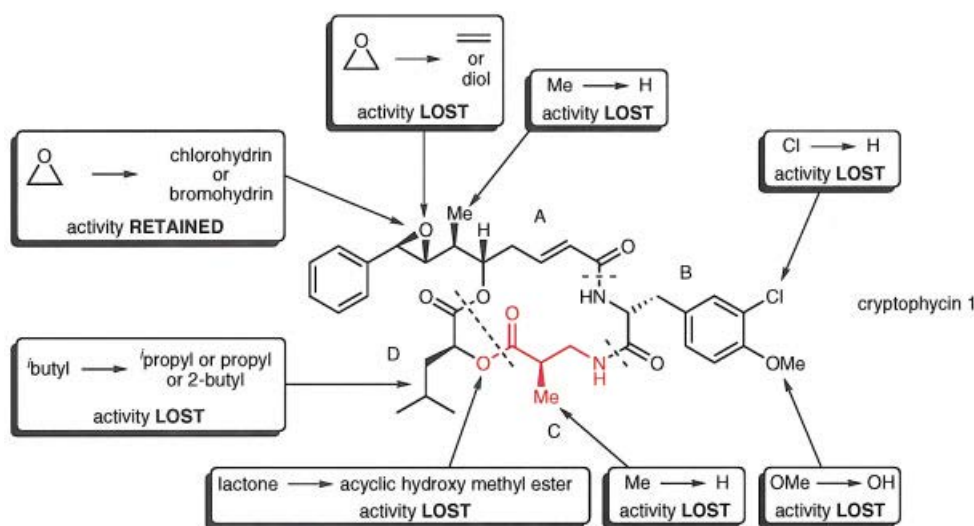


**FIGURE 5** Structure of topostatin, an inhibitor of topoisomerases I and II.

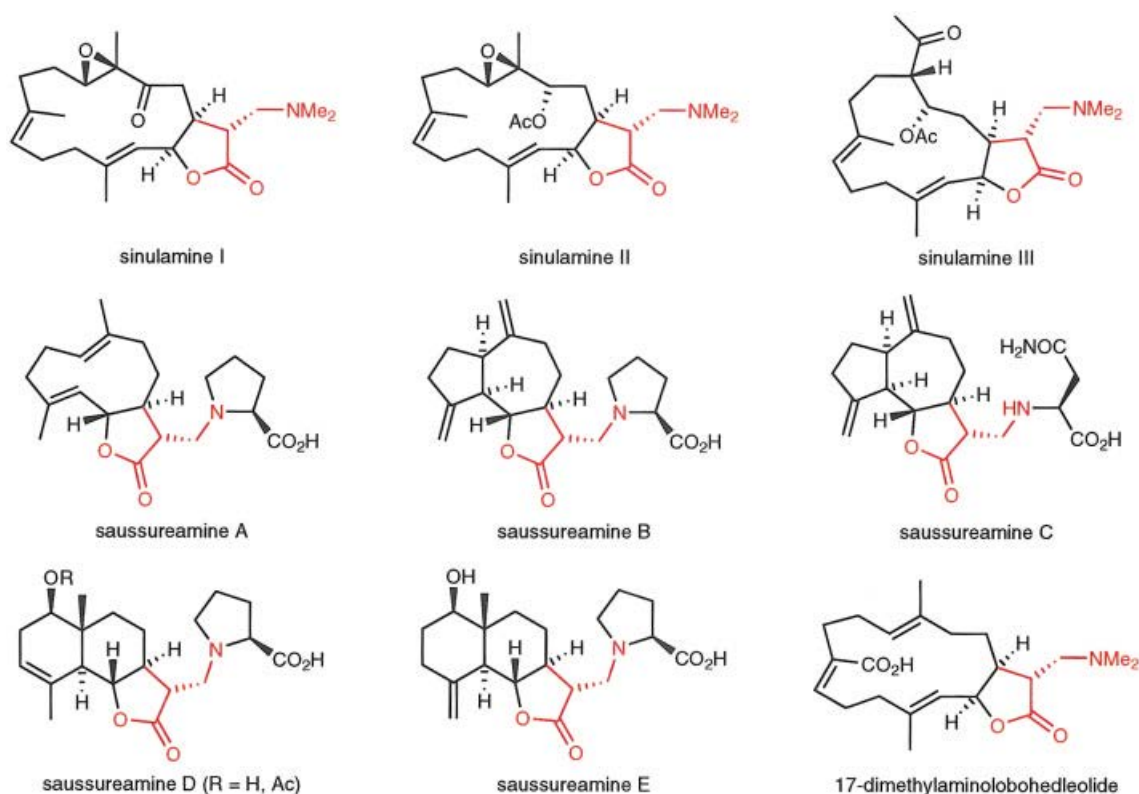
urally occurring representative of this class of cyclic depsipeptides, cryptophycin 1 (Figure 4), shows excellent activity against a broad spectrum of solid tumors, including drug-resistant ones, implanted in mice.<sup>61,65,66</sup> Structure-activity relationship (SAR) studies have shown that an intact 16-membered peptolide ring is essential for optimal cytotoxicity. Additionally, the (*R,R*)-epoxide ring, the chlorine substituent, and the methoxy group in unit B, the methyl groups in units A and C, and the isopropyl group in unit D are also necessary for activity.

Another example of a depsipeptide is represented by the topoisomerase inhibitor topostatin (Figure 5). This microbial antitumor compound was isolated from the culture filtrate of *Thermonospora alba* strain No. 1520<sup>67,68</sup> and was found to inhibit nuclear enzymes topoisomerases I and II, both responsible for the concerted breaking and rejoining of DNA strands.<sup>69</sup>

The enzymes are involved in producing the necessary topological and conformational changes in DNA



**FIGURE 4** Structure of cryptophycin 1 with the summary of in vivo structure-activity relationship (SAR) studies. It has been classified into four subunits: units A and D represent hydroxy acids, whereas units B and C are  $\alpha$ - and  $\beta^2$ -amino acids, respectively.



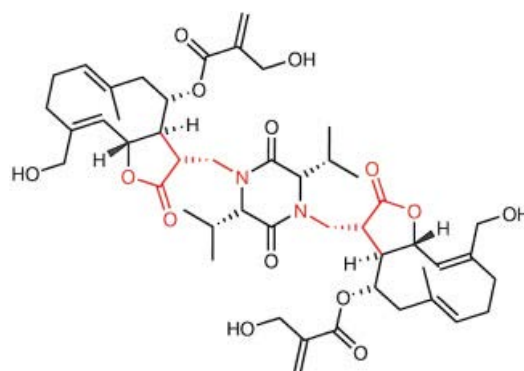
**FIGURE 6** Sinulamines (I–III), saussureamines (A–E), and 17-dimethylaminolobohedleolide are natural products isolated from soft coral species.

that are critical to many cellular processes such as replication, recombination, and transcription.<sup>70</sup> Topostatin is completely different from other anti-tumor drugs causing DNA damage, such as camptothecin and doxorubicin, which have so far been clinically tested. Topostatin is a topoisomerase inhibitor with no cytotoxicity against noncancerous human cells. Additionally, it shows a specific inhibition against the growth of SNB-75 and SNB-78, which are tumor cells of the central nervous system.

### 3.3. $\beta^2$ -Amino Acids as Part of Nonpeptidic Natural Products

Few nonpeptidic classes of natural products such as alkaloids, terpenes, and others possess a  $\beta^2$ -amino-acid moiety in their core system. These residues are often represented by  $\alpha$ -aminomethyl- $\gamma$ -butyrolactone moieties, which are potentially formed via a Michael-type addition to an  $\alpha$ -methylene- $\gamma$ -lactone by various *N*-nucleophiles. For example, several terpenes with such amino acid derivatives have been isolated from three soft coral species (Figure 6). All sinulamines<sup>71,72</sup> and the 17-dimethylaminolobohedleolide<sup>73</sup> are diterpenes containing an  $\alpha$ -dimethylamin-

omethyl- $\gamma$ -butyrolactone as the  $\beta^2$ -amino acid unit. These species have anti-cancer activities; the first group inhibits the proliferation of KB cells, and the second compound inhibits the cytopathic effect of in vitro HIV-1 infection. In contrast, the saussureamines are amino acid sesquiterpenes in which the amino group of the  $\beta^2$ -amino acid is also part of an  $\alpha$ -amino acid.<sup>74–76</sup> These natural products have been isolated from Chinese saussureae radix, the dried root of *Sau-*



**FIGURE 7** Germacranolide–valine adduct dimer isolated from *Centaurea aspera*.



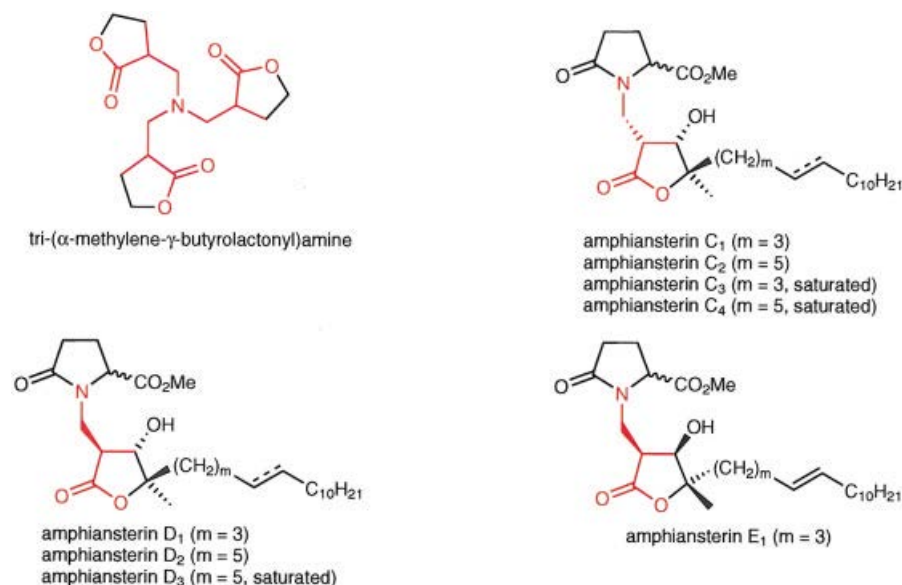


FIGURE 8 Other examples of natural products containing lactone-derived  $\beta^2$ -amino acids.

*ssurea lappa* Clarke, which is known as an aromatic stomachic and frequently prescribed in Chinese and Japanese traditional medicine. Effectively, these compounds have a potent inhibitory effect on both acidified ethanol- and stress-induced gastric ulcer formation in rats.

Another sesquiterpene lactone has been isolated from *Centaurea aspera* and is shown in Figure 7.<sup>77</sup> This compound differs from the other amino acid sesquiterpene derivatives because it occurs in a dimeric form ("diketopiperazine").

Other derivatives with a  $\gamma$ -butyrolactone system were found in plants and marine sponges (Figure 8). For example, tri-( $\alpha$ -methylene- $\gamma$ -butyrolactonyl)amine was isolated from the Tasmanian endemic plant *Bellenden montana*,<sup>78</sup> whereas the amphiasterins C–E, a new family of cytotoxic secondary metabolites, were extracted from the marine sponge *Plakortis quasiamphiaster*.<sup>79</sup>

Natural products containing  $\beta^2$ -amino acids other than the lactone derivatives have also been found. An example is physarigin B,<sup>80</sup> a yellow pigment from a cultured myxomycete *Physarum rigidum*, an unusual

group of primitive organisms that may be assigned to one of the lowest classes of eukaryotes (Figure 9).

Other examples (Figure 10) include (+)-11-oxocystine, a lupin alkaloid with hallucinogenic activity isolated from the leaves of *Sophora secundiflora*,<sup>81</sup> and a group of ergot alkaloids isolated from *Claviceps purpurea*, a fungal parasite of grasses and cereals. The ergot alkaloids were the first  $\alpha$ -adrenergic antagonists discovered, but side effects generally prevent their administration in doses that would produce more than a minimal blockade in humans. In general, the effects of all these compounds appear to result from their actions as partial agonists or antagonists at adrenergic, dopaminergic, and serotonergic receptors. They have some clinical applications, notably in obstetrics and the treatment of migraines.<sup>82</sup>

The ergot alkaloids can be divided into four main structural groups: clavine alkaloids (which do not contain any  $\beta^2$ -amino acids); lysergic acid; simple lysergic acid amides (e.g., ergometrine); and peptide alkaloids or ergo-peptides (e.g., ergotamine). A further example of the occurrence of a  $\beta^2$ -amino acid as part of an alkaloid is shown in Figure 11. This steroidal

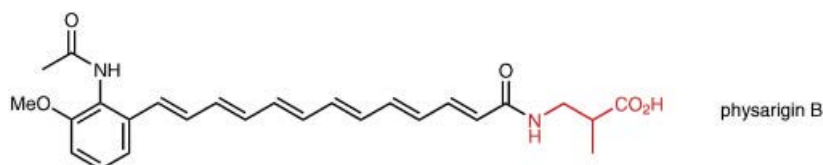
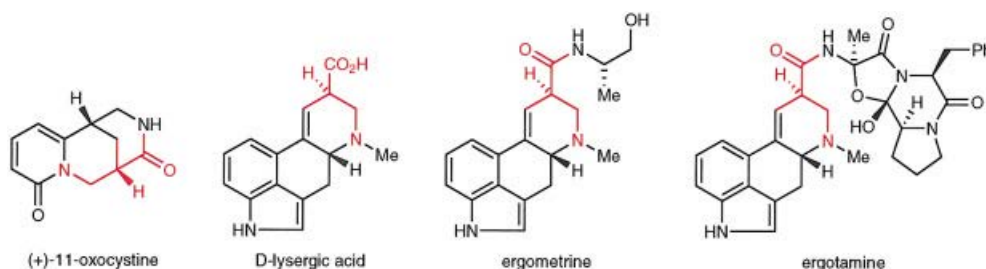


FIGURE 9 Physarigin B is a yellow pigment present in the myxomycetes of the *Physarum rigidum* species.

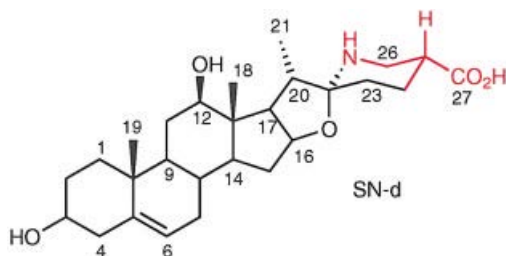


**FIGURE 10** Selection of alkaloids containing a  $\beta^2$ -amino-acid moieties. The (+)-11-oxocystine is a lupin alkaloid and the others are ergot alkaloids.

dal alkaloid (SN-d) has been characterized from the methanolic solution, kept for 2 years, of *Solanum nigrum* berries.<sup>83</sup> SN-d could never be isolated from fresh berries and it is, therefore, interesting that the ingredients of the fruits with unbroken pericarps soaked in MeOH for a long time were changed by a selective oxidation at C-12 and/or C-27 on the steroidal skeleton. This was apparently effected by the aid of enzymes included under the experimental conditions (in MeOH). Among the newly formed compounds in the culture, only SN-d contains a  $\beta^2$ -amino acid residue.

#### 4. METHODS FOR THE SYNTHESIS OF ACHIRAL $\beta^2$ -AMINO ACIDS

A first look into the Beilstein database with a search for simple or complex structures containing  $\beta^2$ -amino acids has, surprisingly, revealed that more than 15,000 different compounds have such residues in their core system. Among them, almost 2000 have biological activities and nearly 100 are present in nature. Racemic  $\beta^2$ -amino acids have been the subject of research since the early part of the 20th century. Most of the methods for their preparation rely on the use of acrylic, cyanoacetic, and malonic ester derivatives. Some examples are shown in Scheme 3.

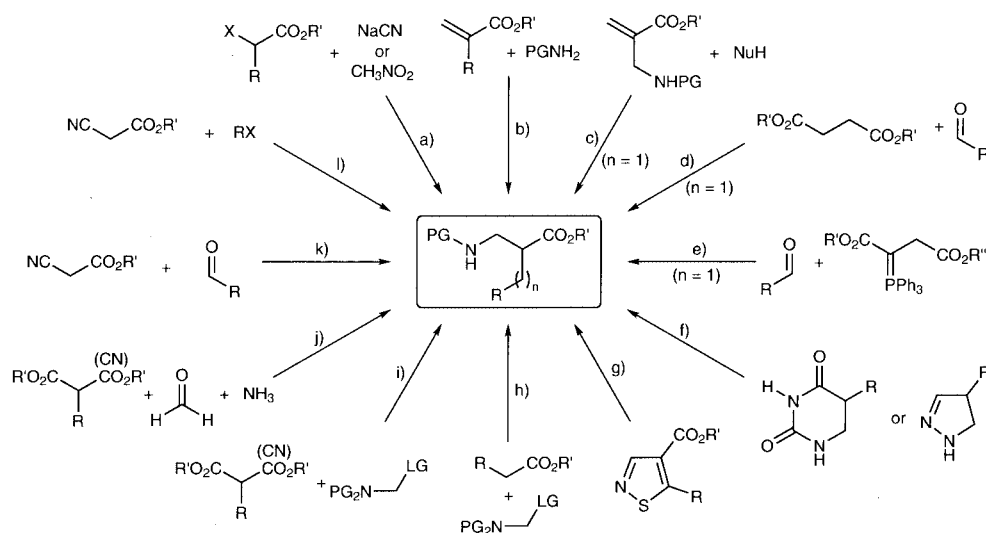


**FIGURE 11** SN-d, a steroidal alkaloid enzymatically derived from the original constituents of *Solanum nigrum* berries, immersed in MeOH for 2 years.

#### 5. METHODS FOR THE SYNTHESIS OF ENANTIOMERICALLY PURE $\beta^2$ -AMINO ACIDS (EPC SYNTHESIS)

The importance of  $\beta$ -amino acids and their derivatives in the field of pharmacology and in peptide chemistry is well represented by the multitude of papers that have been published in the past decades. Additionally, since the far-reaching discovery that  $\beta$ -peptides (i.e., oligomers derived from  $\beta$ -amino acids) form much more stable structures than their  $\alpha$ -peptidic natural counterparts,<sup>1–7</sup> there has been an ever-growing interest in synthesizing  $\beta$ -amino acids with various substitution patterns. In particular, the preparation of enantiomerically pure  $\beta$ -amino acids has become an important and challenging endeavor for organic chemists. Stereoselective syntheses of  $\beta$ -amino acids have already been extensively reviewed.<sup>112–123</sup> However, among all the methods for the preparation of  $\beta$ -amino acids, the synthesis of  $\beta$ -substituted  $\beta$ -amino acids (i.e.,  $\beta^3$ -amino acids) has been investigated most thoroughly. Several methodologies for the synthesis of  $\alpha$ -substituted  $\beta$ -amino acids ( $\beta^2$ -amino acids) have emerged recently; they include alkylation of a chiral cyclic or acyclic enolate, Mannich-type reactions of a chiral enolate, Curtius rearrangements, diastereoselective conjugate additions of an achiral amine to a chiral  $\alpha,\beta$ -unsaturated ester or of a chiral amine to an achiral enolate, metal-catalyzed reaction, and resolutions. These methods will be discussed in the following sections.<sup>7</sup>

<sup>7</sup> Throughout this article, we use % es and % ds to specify the selectivities of reactions where one of the enantiomers or one of the diastereomers is formed preferentially. The % ee present in the original literature has been converted to the corresponding % es value.



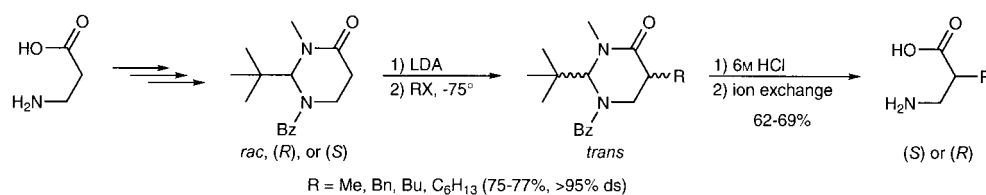
**SCHEME 3** Various methods for the preparation of racemic  $\beta^2$ -amino acids. (a) Nucleophilic attack of cyanide<sup>84,85</sup> or deprotonated nitromethane<sup>86</sup> on an  $\alpha$ -haloester followed by nitrile or nitro reduction.<sup>22,87–90</sup> (b) Michael addition of an amine to an acrylic ester derivative containing the side chain.<sup>22,87–90</sup> (c) 1,4-Addition of a nucleophile to an acrylic ester derivative containing the  $\beta$ -amino group.<sup>91</sup> (d) Stobbe condensation of a succinic ester<sup>92–95</sup> or (e) Wittig olefination of a succinic ester-derived phosphorane<sup>96,97</sup> with an aldehyde, followed by Curtius reaction and hydrogenation. (f) Hydrolysis of either 5-substituted dihydrouracils<sup>98–100</sup> or 4-substituted pyrazolines.<sup>101</sup> (g) Reductive desulphurisation of isothiazole derivatives.<sup>102</sup> (h) Amidomethylation of aryl acetic esters.<sup>103</sup> (i) Amidomethylation of monosubstituted malonic- or cyanoacetic esters.<sup>104–106</sup> (j) Three-component Mannich reaction of an aldehyde,  $\text{NH}_3$ , and a malonic- or cyanoacetic ester derivative.<sup>107</sup> (k) Knoevenagel condensation of a cyanoacetic ester with an aldehyde,<sup>108–110</sup> followed by hydrogenation or complete reduction with a borane reagent. (l) Alkylation of a cyanoacetic ester<sup>111</sup> followed by reduction. (LG = leaving group; PG = protecting group; Nu = nucleophile; X = halide; in all cases  $n = 0$ , unless indicated otherwise in the Scheme).

### 5.1. Enantioselective Synthesis of $\beta^2$ -Amino Acids via Chiral $\beta$ -Homoglycine Derivatives

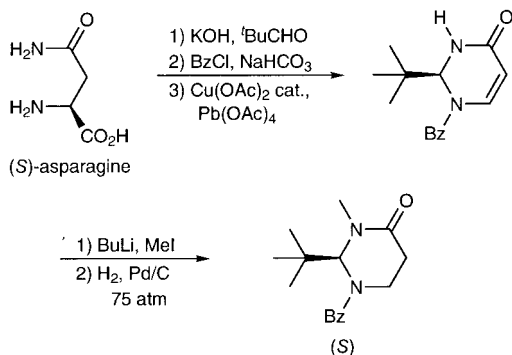
One of the best methods for introducing a substituent at the  $\alpha$ -position of a  $\beta$ -amino acid derivative is by far the diastereoselective alkylation of the corresponding enolates. Most of the examples described in the literature involve the use of either cyclic or acyclic  $\beta$ -homoglycine derivatives; cyclic ones often give better diastereoselectivities. The efficiency of this method has been demonstrated by Juaristi et al.,<sup>124,125</sup> em-

ploying a racemic or enantiomerically pure 2-*tert*-butylperhydropyrimidin-4-one derivative<sup>8</sup> that allows for excellent differentiation of the diastereotopic faces of the enolate plane (Scheme 4). The high *trans*-diastereoselectivity of the alkylation has been attributed to the axial orientation of the *tert*-butyl substituent in the sofa-conformation of the six-membered

<sup>8</sup> The enantiomeric pyrimidin-4-one derivatives were obtained via preparative resolution by recycling chromatography on a Chiraspher column.<sup>126</sup>



**SCHEME 4** Diastereoselective alkylation of *rac*-, (*R*)-, or (*S*)-1-benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one according to Juaristi.<sup>124,125</sup> The hydrolysis requires heating with 6 M HCl.



**SCHEME 5** Preparation of (S)-1-benzoyl-2-tert-butyl-3-methylperhydropyrimidin-4-one starting from (S)-asparagine.

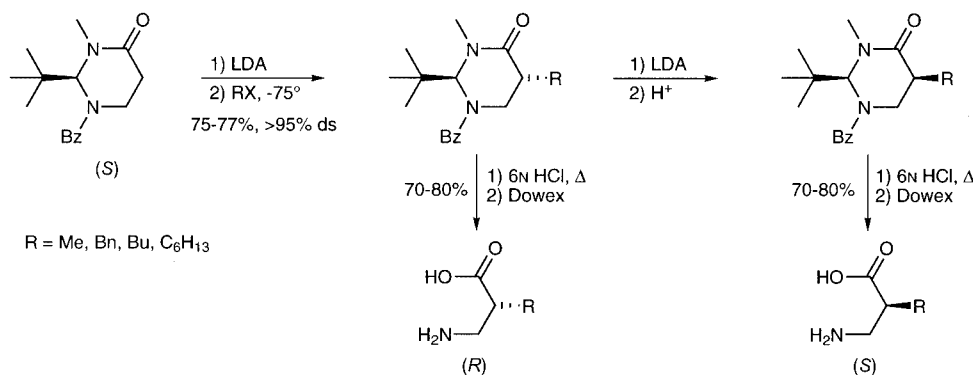
ring, being a classical manifestation of the so-called  $A^{1,3}$  effect exerted by an amide group. The corresponding  $\beta^2$ -amino acids are then obtained in good yields by acidic hydrolysis of the alkylated compound, followed by ion exchange chromatography.

The power of this method has been further improved by using (S)-asparagine for the synthesis of enantiomerically pure (S)-perhydropyrimidin-4-one.<sup>125,127,128</sup> Indeed, condensation of (S)-asparagine with pivalaldehyde according to the procedure described by Konopelski and co-workers,<sup>129,130</sup> followed by protection of the amino group, oxidative decarboxylation, and Pd-catalyzed hydrogenation, gives in good yield the chiral perhydropyrimidin-4-one (Scheme 5).

Diastereoselective alkylation of the (S)-perhydropyrimidin-4-one produces the 1,4-*trans*-product, which undergoes acidic hydrolysis to form the (R)- $\beta^2$ -amino acid with no loss of configurational integrity. It turns out that enolate formation of the 1,4-*trans*-adduct, followed by protonation (aqueous NH<sub>4</sub>Cl), can afford, with high stereoselectivity, the

1,4-*cis* diastereomer; the protonation takes place again from the face opposite to the *tert*-butyl group. In this way, a common precursor can be used for the preparation of either enantiomeric form of a  $\beta^2$ -amino acid (Scheme 6).

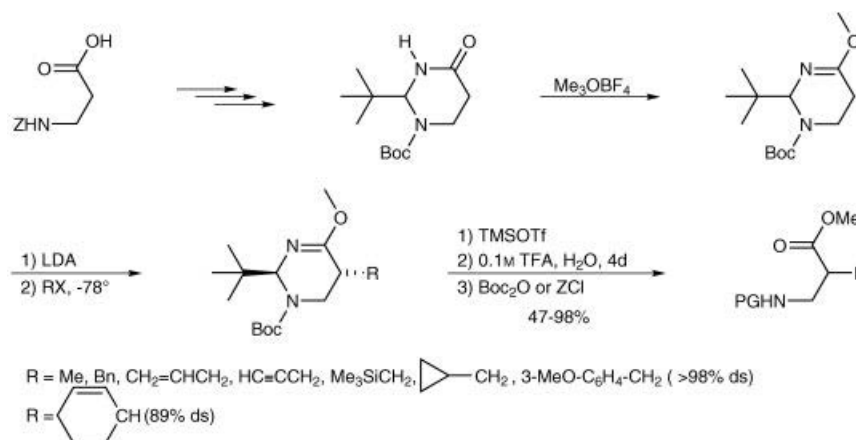
This route provides a classical example of the concept of “self-regeneration of a stereogenic center”<sup>131</sup>: the initial stereogenic center of asparagine induces the stereoselective formation of a new, temporary chirality center (i.e., carbon bearing the *tert*-butyl group), before being trigonalized by decarboxylation. A new ligand (i.e., *R*-group) is then introduced, again diastereoselectively, and the temporary center is finally removed. The major drawback of this method is the rather harsh condition needed for the release of the  $\beta^2$ -amino acids, hampering its application for the preparation of  $\beta^2$ -amino acids with functionalized side chains.<sup>9</sup> The introduction of 1-Boc-protected 2-*tert*-butyl-4-methoxytetrahydropyrimidine (BMP) for diastereoselective alkylation reactions by Seebach et al.<sup>132</sup> was an improvement. BMP has been prepared from *Z*-protected  $\beta$ -homoglycine by conversion to its amide and in situ reaction with pivalaldehyde to give the tetrahydropyrimidinone, the basic nitrogen of which was Boc-protected.<sup>10</sup> Treatment with Meerwein’s salt afforded racemic or enantiopure (after resolution) BMP. Alkylation of the Li-enaminate results in good yields (47–97%), and only the *trans* diastereoisomer is formed. Cleavage of the alkyl-substituted six-ring heterocycle can be accomplished by a two-step procedure: first, removal of the Boc-protecting group, and then cleavage of the ring



**SCHEME 6** Synthesis of either  $\beta^2$ -amino acid enantiomer starting from a common precursor.

<sup>9</sup> For solid phase synthesis by Fmoc-strategy, functionalized side chains must be protected with acid-cleavable protecting groups.

<sup>10</sup> Multigram amounts of nonracemic material can be obtained by preparative chromatographic resolution of the pyrimidinone precursor on a Chiralcel OD column.

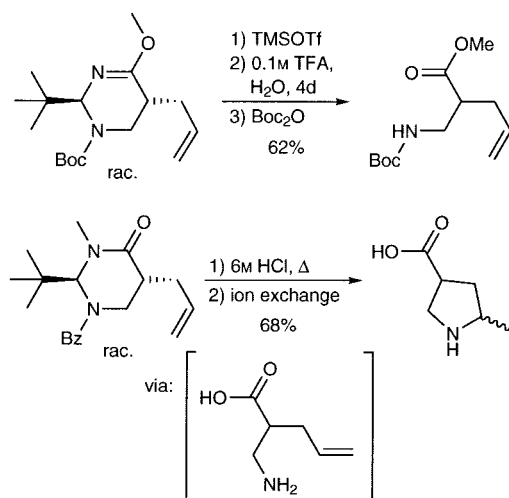


**SCHEME 7** Boc-Protected BMP as a precursor for diastereoselective alkylations, which lead to the formation of racemic or enantiopure Boc- or Z-protected  $\beta^2$ -amino acid methyl esters upon acidic hydrolysis under mild conditions. Only one enantiomer of the trans-adduct is shown.

under acidic conditions (TFA in water at 0°C) to give the methyl esters of the  $\beta$ -amino acids (Scheme 7).

The use of milder conditions for the cleavage of the Boc-protected alkylated BMP is well demonstrated by the successful isolation of an  $\alpha$ -allyl- $\beta$ -amino acid derivative, which could not be obtained by cleavage of the corresponding perhydropyrimidin-4-one with 6 M HCl<sup>124</sup> (Scheme 8).

As already mentioned above, acyclic  $\beta$ -homoglycine derivatives have also been successfully employed in the enantioselective preparation of  $\beta^2$ -amino acids.



**SCHEME 8** Hydrolysis of the allylated BMP derivative for the formation of the Boc-protected  $\alpha$ -allyl- $\beta$ -amino acid methyl ester. Cleavage of the corresponding perhydropyrimidin-4-one compound caused cyclization of the intermediate  $\beta^2$ -amino acid, so that a mixture of *cis*- and *trans*-5-methyl- $\beta$ -proline was isolated.

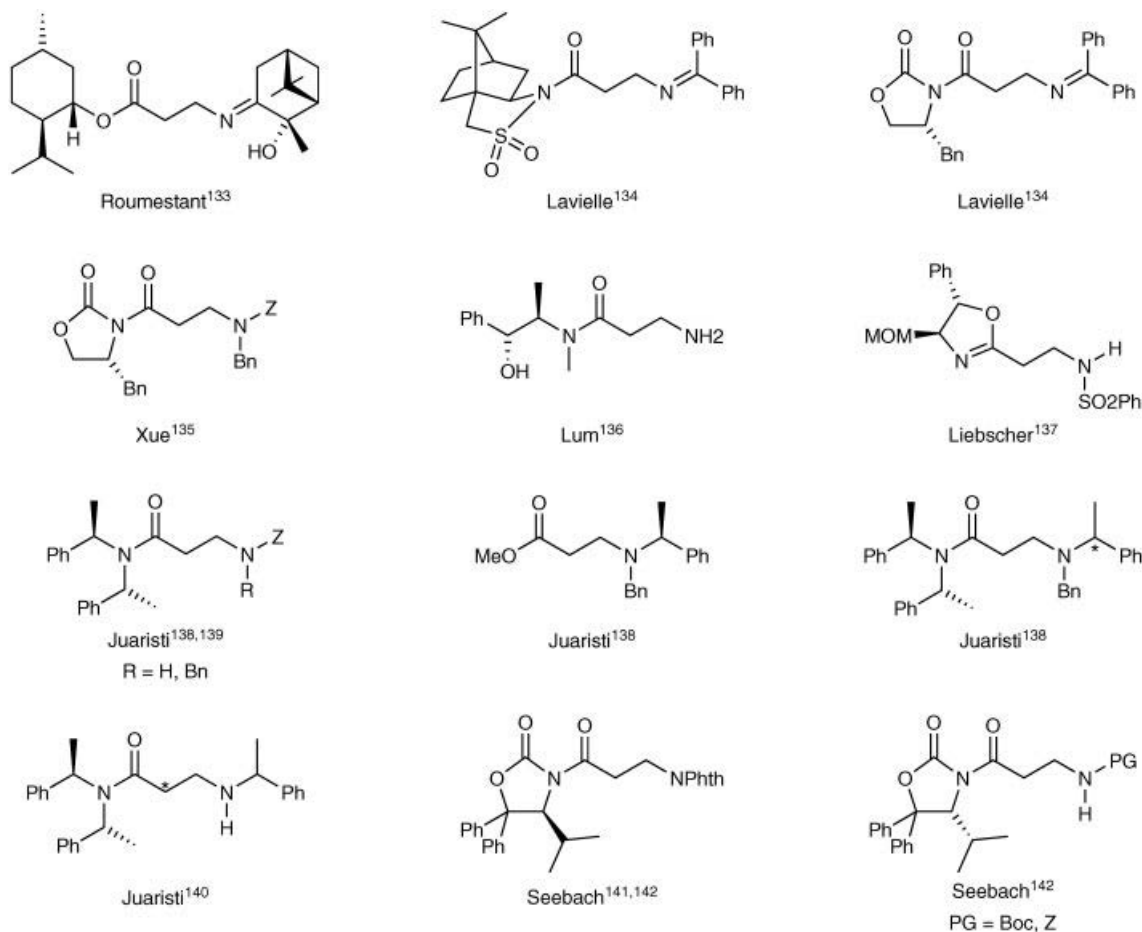
For this approach several chiral auxiliaries have provided good selectivities. A collection of chiral  $\beta$ -aminopropionic acid derivatives, which have been successfully adopted for diastereoselective alkylations or aldol reactions, is presented in Figure 12.

The first example of chiral induction by acyclic homoglycine derivatives was achieved in 1994 when Roumestant and co-workers<sup>133</sup> performed a diastereoselective methylation reaction on a  $\beta$ -homoglycine derivative with two chiral handles (i.e., (1*S*,2*R*,5*S*)-menthyl-*N*-[(1*S*,2*S*,5*S*)-2-hydroxypinan-3-ylidene]- $\beta$ -alaninate). Although alkylation of the Li-enolate with methyl iodide occurred with poor conversion, addition of hexamethylphosphoramide (HMPA) as cosolvent afforded the alkylation product in 86% yield and 92% ds. Separation of the mixture by column chromatography, followed by acidic hydrolysis of both auxiliaries, gave the pure (*S*)- $\beta^2$ hAla in good yield (Scheme 9).

Interestingly, the use of (–)-menthol instead of (+)-menthol ester for alkylation under the same conditions gives better yields of the methylated compound but poorer diastereoselectivity (cf. “double stereoinduction” or “matched/mismatched pairs”)<sup>143</sup>.

Lavielle and co-workers<sup>134</sup> reported the use of chiral imine derivatives for the enantioselective preparation of  $\beta^2$ -amino acids. The sultam-derived  $\beta$ -homoglycine imine, easily obtained from Boc- $\beta$ -homoglycine and the corresponding sultam, is lithiated by means of LDA or BuLi in a THF/DMPU<sup>11</sup>-solution at –78°C and then alkylated to give the (*R*)-product as a single diastereoisomer. The  $\beta^2$ -amino acids are ob-

<sup>11</sup> DMPU, *N,N*-dimethylpropylene urea.<sup>144</sup>

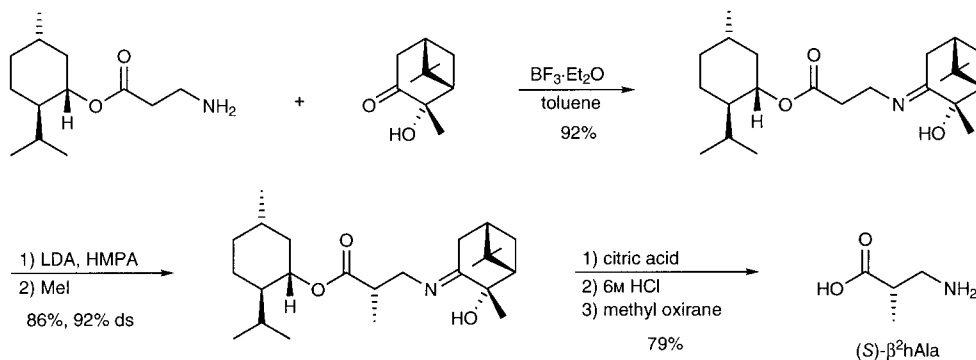


**FIGURE 12** Examples of chiral  $\beta$ -homoglycine derivatives employed in the synthesis of  $\beta^2$ -amino acids. It should be mentioned that the likelihood of eliminating the protected  $\beta$ -amino moiety upon treatment with base can depend on the protecting groups that are used.

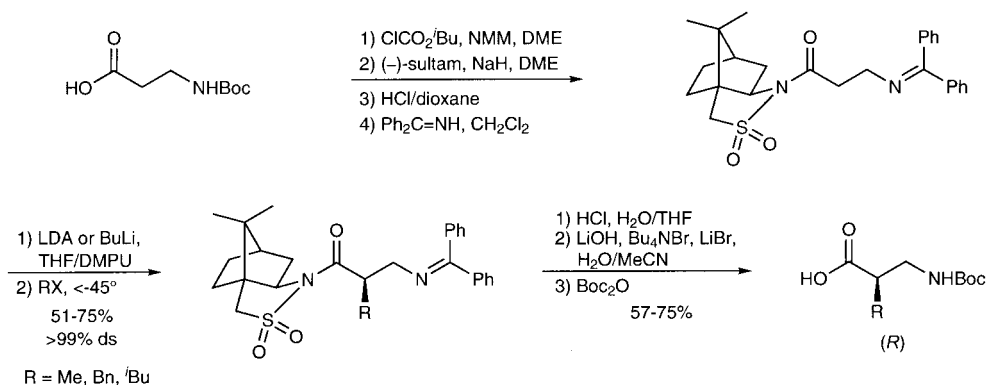
tained in 57–75% yield after acidic hydrolysis and Boc-protection (Scheme 10).

The use of (–)-sultam as chiral auxiliary yields the (*R*)- $\beta^2$ -amino acid precursors, conversely, (+)-sultam leads to the (*S*)- $\beta^2$ -amino acid derivatives. The alky-

lation step must be performed at a temperature of less than  $-45^\circ\text{C}$  to avoid competitive elimination with ketene formation, which leads to the alkylated sultam as the main product. By comparison, the analogous imine precursor using Evans' benzyl oxazolidinone as



**SCHEME 9** Diastereoselective alkylation of a chiral  $\beta$ -homoglycine.<sup>133</sup>



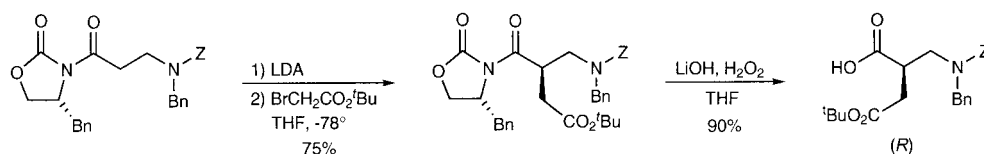
**SCHEME 10** Enantioselective synthesis of  $\beta^2$ -amino acids according to Lavielle and co-workers.<sup>134</sup>

the chiral moiety (cf. Figure 12) has also been tested for stereoselective alkylations, albeit with lower diastereoselectivities obtained: alkylation with benzyl bromide afforded the product with 90% diastereoselectivity, whereas with *iso*-butyl iodide a racemic mixture was obtained, even at  $-78^\circ\text{C}$ . A better result for the diastereoselective alkylation of a *Z*- and benzyl-protected  $\beta$ -homoglycine with Evans' benzyl oxazolidinone as chiral auxiliary has been described by Xue and co-workers,<sup>135</sup> who synthesized an enantiopure (*R*)- $\beta^2$ -homoaspartate derivative through stereoselective alkylation with *tert*-butyl bromoacetate (Scheme 11).

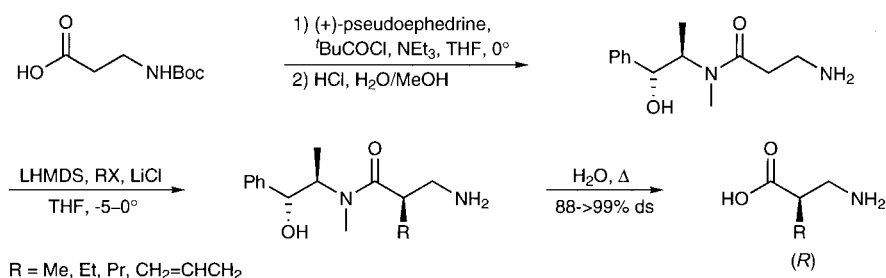
Another chiral auxiliary that has been successfully used for the synthesis of  $\alpha$ -substituted  $\beta$ -amino acids is pseudoephedrine (Myers method<sup>145-147</sup>). Lum and

co-workers<sup>136</sup> coupled Boc- $\beta$ -homoglycine and (+)-pseudoephedrine to give the corresponding derivative, which was Boc-deprotected to afford the chiral  $\beta$ -aminopropanoic amide precursor. Lithiation with lithium hexamethyldisilazide (LHMDS) in the presence of LiCl followed by alkylation with several electrophiles can provide the alkylated products as a mixture of diastereoisomers and in good yields (Scheme 12). Unfortunately, no separation of diastereoisomers could be achieved by chromatography and no determination of the alkylation selectivities was possible by either NMR or HPLC. Cleavage of the auxiliary provided enantiomerically enriched fully deprotected  $\beta^2$ -amino acids (88–>99% es).

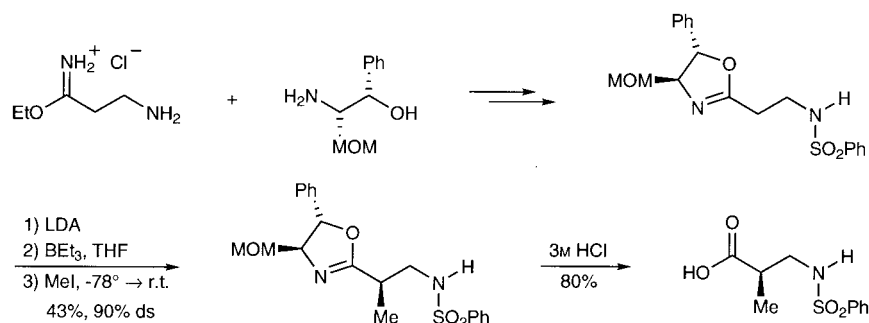
For the preparation of a  $\beta^2$ -homoolanine derivative, Liebscher and co-workers<sup>137</sup> employed a chiral



**SCHEME 11** Synthesis of an (*R*)- $\beta^2$ -homoaspartate derivative via diastereoselective alkylation of a chiral  $\beta$ -alanyloxazolidinone precursor according to Xue and co-workers.<sup>135</sup>



**SCHEME 12** Synthesis of  $\beta^2$ -amino acids using pseudoephedrine as a chiral auxiliary according to Lum and co-workers.<sup>136</sup>



**SCHEME 13** Preparation of a  $\beta^2$ -homoalanine derivative by diastereoselective alkylation of a chiral oxazoline derivative according to Liebscher.<sup>137</sup>

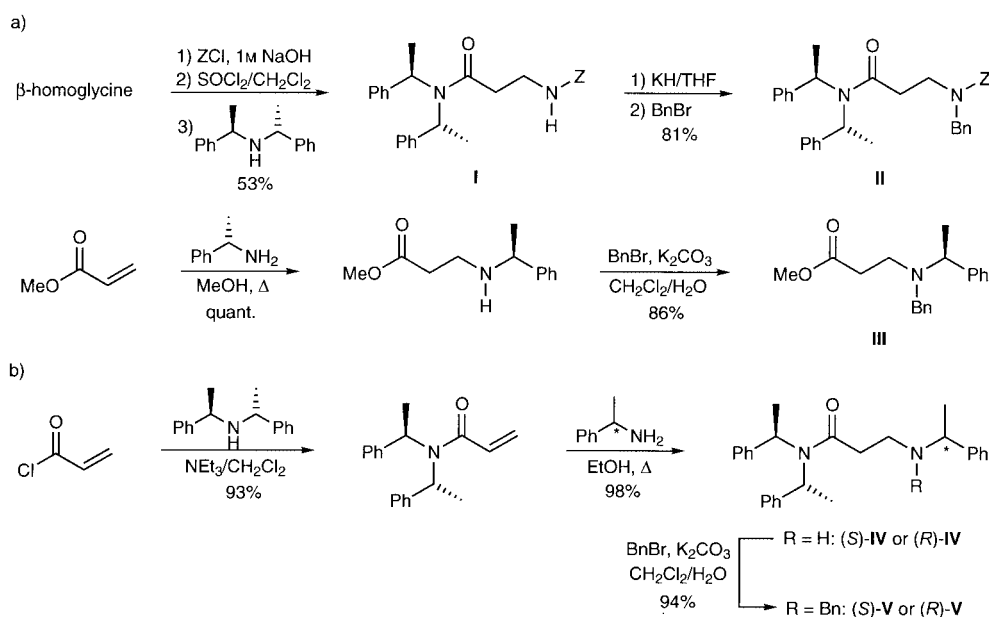
2-( $\beta$ -aminoethyl)oxazoline for achieving diastereoselective methylations (Meyers' method<sup>148,149</sup>). This precursor was prepared by adapting the known synthesis of oxazolines<sup>150</sup> from the corresponding imido ester and chiral amino alcohol, followed by benzene sulfonylation. Methylation of the Li-enolate in the presence of  $\text{BEt}_3$  afforded the  $\alpha$ -methyl derivative in only 43% yield but 90% diastereoselectivity. In the absence of  $\text{BEt}_3$  both the yield and the selectivity dropped to 20 and 64%, respectively. The *N*-protected  $\beta^2$ -homoalanine can be obtained in good yield after hydrolytic removal of the chiral auxiliary (Scheme 13).

A whole series of  $\beta$ -homoglycine derivatives (**I–V**) containing an  $\alpha$ -phenethyl group as the chiral inductor have recently been the subject of research in

Juaristi's group;<sup>138–140</sup> the preparation of these derivatives is shown in Scheme 14.

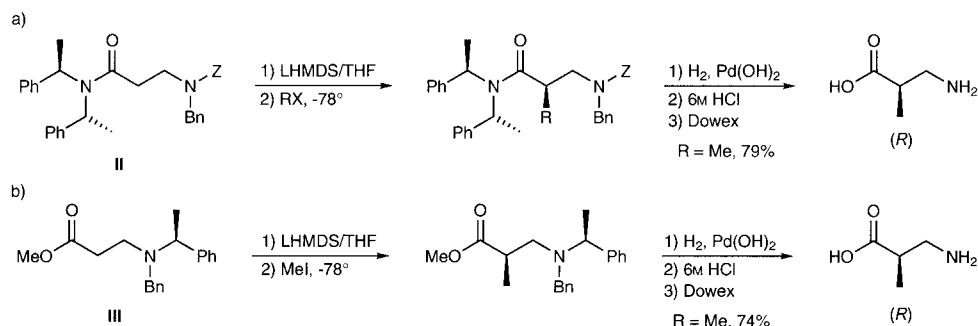
In most cases, the selectivities of subsequent alkylation reactions are only moderate and are sometimes influenced by the addition of cosolvents (i.e., DMPU, or HMPA) or "inert" salts (e.g., LiCl). In the case of compound **II**, for example, neither the addition of LiCl nor that of one of the cosolvents had any beneficial effects. In contrast, with compound **III** the selectivity of the alkylation, as well as the yield, increased by the addition of either DMPU or HMPA, but decreased when LiCl was used as the additive (Scheme 15).

Due to the fact that both compounds **II** and **III** in Scheme 15 favored addition of the electrophile with formation of an (*R*) stereogenic center, the influence



**SCHEME 14** Preparation of the  $\beta$ -homoglycine derivatives containing (a) one chiral-auxiliary (**I–III**) or (b) two chiral-auxiliary groups (**IV**, **V**), according to Juaristi and co-workers.<sup>138–140</sup>



Diastereoselectivity of enolate **II**-Li alkylation with RX; first step in a):

entry	RX	additive, equiv.	ds (%)	yield (%)
1	MeI	—	80	65
2	MeI	LiCl, 6	79	60
3	MeI	DMPU, 6	76	65
4	MeI	HMPA, 1	80	49
5	BnBr	—	66	50
6	BnBr	LiCl, 6	67	28
7	BnBr	DMPU, 6	56	50
8	BnBr	HMPA, 1	60	43

Diastereoselectivity of enolate **III**-Li alkylation with iodomethane; first step in b):

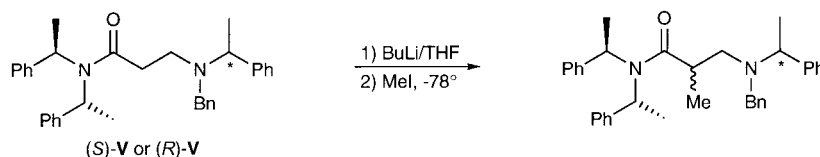
entry	additive, equiv.	ds (%)	yield (%)
1	—	65	68
2	HMPA, 1	72	77
3	HMPA, 3	81	87
4	HMPA, 6	70	95
5	DMPU, 1	71	68
6	DMPU, 3	77	91
7	DMPU, 6	75	95
8	LiCl, 6	60	64

**SCHEME 15** Diastereoselectivities of enolate **II**-Li and **III**-Li alkylations and subsequent cleavage of the auxiliaries by  $R = \text{Me}$  to afford the fully deprotected (*R*)- $\beta^2$ -homoalanine.<sup>138</sup>

of “double induction” was tested. It was discovered that precursor (*S*)-**V** gives, in the absence of additives, slightly lower selectivity than that observed in the methylation of **II**, but significantly higher selectivity than that obtained from the methylation of **III**. Additionally, the highest selectivity is reached in the presence of 3 equivalents of HMPA. In contrast, precursor (*R*)-**V** affords low selectivity in the absence of additives and complete inversion of selectivity in the presence of 3 equivalents of HMPA (Scheme 16).

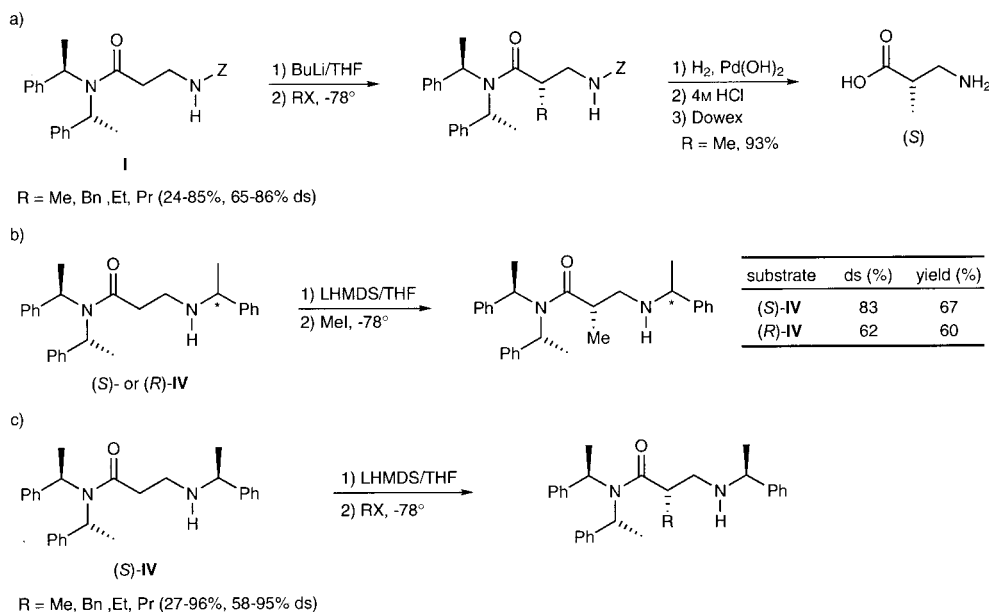
As a further extension toward the preparation of enantiopure  $\beta^2$ -amino acids, the stereoselective alkylation of  $\beta$ -homoglycine dianion derivatives **I**-2Li<sup>139</sup> and **IV**-2Li<sup>140</sup> has also been tested (Scheme 17). Previous work of several groups has, indeed, demonstrated that alkylation of chiral dianion derivatives proceeds with high stereoselectivity.<sup>151–160</sup>

In general, both higher yields and better stereoselectivities are observed in the alkylation reaction of the dilithio-derivative **I**-2Li compared with the enolate **II**-Li. In addition, the alkylation products show opposite diastereoselectivities; compounds derived from **I** are of (*S*)-configuration, whereas the ones derived from **II** are of (*R*)-configuration. The effect of LiCl or HMPA additive on the diastereoselectivity of the alkylation reaction is negligible, although yields generally improved. In the methylation of **IV**, the (*S*)-derivative is more selective than the (*R*)-derivative (i.e., “matched” versus “mismatched” compound), and for the alkylation of (*S*)-**IV**, the addition of LiCl salts to the reaction medium causes an increase in diastereoselectivity. At the same time, both methylation and benzylation proceed in higher yields, whereas the reaction with EtI and PrI gives lower yields.



entry	precursor	additive, equiv.	dr ( <i>R</i> ):( <i>S</i> )	yield (%)
1	( <i>S</i> )- <b>V</b>	—	75:25	73
2	( <i>S</i> )- <b>V</b>	HMPA, 3	89:11	73
3	( <i>R</i> )- <b>V</b>	—	66:33	89
4	( <i>R</i> )- <b>V</b>	HMPA, 3	36:64	47

**SCHEME 16** Diastereoselectivity of enolate **V**-Li methylation.<sup>138</sup>



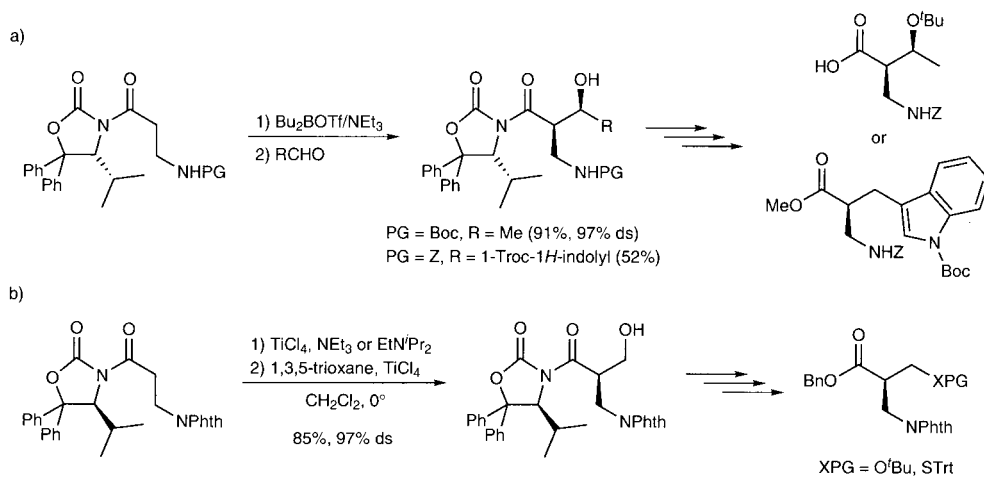
**SCHEME 17** Stereoselective alkylation of  $\beta$ -homoglycine derivatives containing  $\alpha$ -phenethyl groups as the chiral auxiliary. (a) Alkylation of compound **I** followed by cleavage of the auxiliary when  $R = \text{Me}$ . (b) Comparison of methylation selectivity of “matched and mismatched” compounds **IV**. (c) Diastereoselective alkylations of (S)-**IV**.

Finally, in our group,<sup>141,142</sup> the use of chiral diphenyloxazolidinone-containing  $\beta$ -alanine derivatives for aldol reactions was explored, allowing for introduction at the  $\alpha$ -position the side chains of serine, cysteine, threonine, and tryptophan on the  $\beta$ -amino acid backbone (Scheme 18).

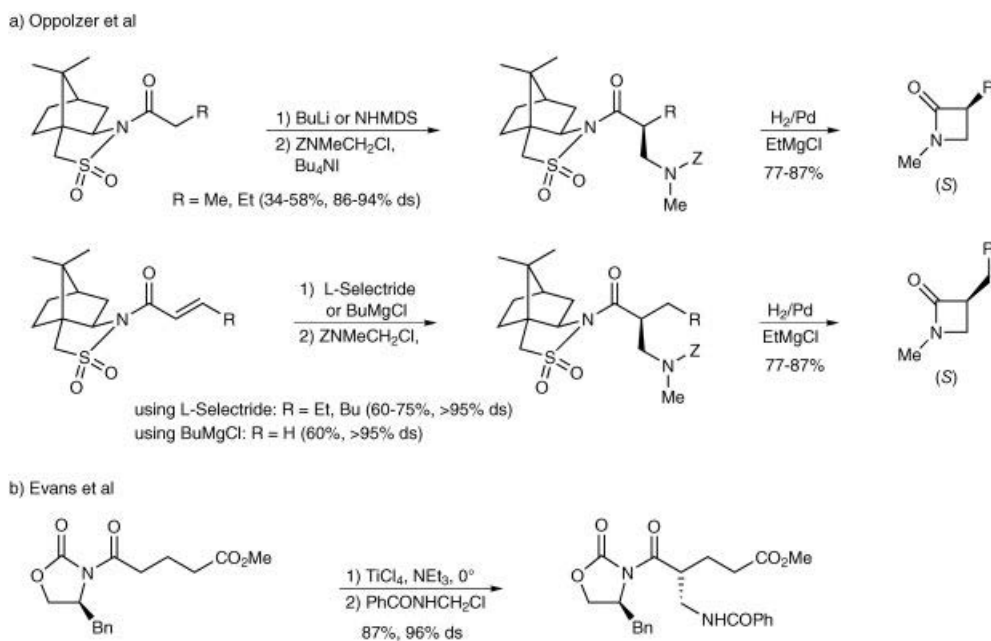
In the case of serine/cysteine and threonine derivatives, the aldol reaction proceeded with almost com-

plete diastereoselectivity, whereas with tryptophan a mixture of diastereomers was observed (ca. 6:4). Complete selectivity has only been achieved when the original Evans auxiliary was employed.<sup>12</sup>

<sup>12</sup> T. Kimmerlin and D. Seebach, unpublished results.



**SCHEME 18** Diastereoselective aldol reaction of  $\beta$ -homoglycine precursors using Seebach's chiral auxiliary; for the preparation of (a)  $\beta^2$ -homothreonine- and  $\beta^2$ -homotryptophan-<sup>142</sup> or (b)  $\beta^2$ -homoserine- and  $\beta^2$ -homocysteine derivatives.<sup>141,142</sup>



**SCHEME 19** Diastereoselective amidomethylation of chiral (a) *N*-acyl-sultam and (b) *N*-acyl-oxazolidinone derivatives.

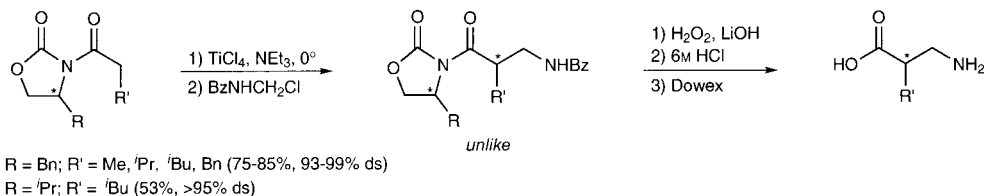
## 5.2. Diastereoselective Addition of Chiral Enolates to Acyliminium Salts: The Amidomethylation Reaction

Although less explored than the alkylation, the Mannich-type reaction with chiral enolate derivatives provides a general route to enantiopure  $\beta^2$ -amino acids. It involves the condensation of a chiral acid derivative with a reagent that is synthetically equivalent with a formyl imine. The independent pioneering work by Oppolzer and colleagues<sup>161,162</sup> and that of Evans et al.<sup>163</sup> has demonstrated the feasibility of this method by coupling aminomethyl compounds with a chiral *N*-acyl-sultam or *N*-acyl-benzyloxazolidinone, respectively (Scheme 19).

(*Z*)-Enolate formation with metal chelation and electrophilic attack from the less hindered faces of the enolates gives, in moderate to good diastereoselectivities, the amino-alkylated products, which can be easily isolated as single diastereoisomers after flash chro-

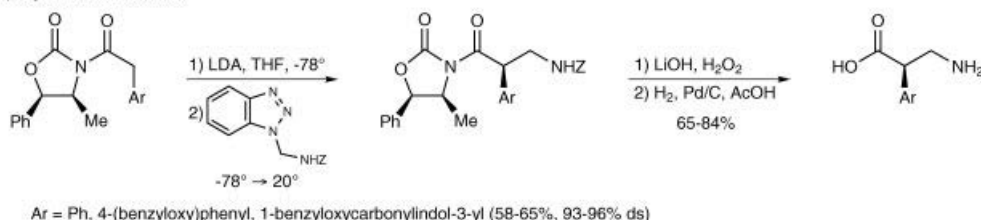
matography and crystallization. The Evans method is by far the best in terms of yield and selectivity and has been successfully adopted by Seebach and colleagues<sup>164,165</sup> and Roberts and co-workers<sup>166</sup> for the preparation of  $\beta^2$ -amino acids (Scheme 20).

There are, however, drawbacks relating to the use of *N*-chloromethylbenzamide as the amidomethylating reagent, such as degradation of the reagent on storage and the need for harsh conditions (i.e., heating in 6 *M* HCl) for the final removal of the *N*-benzoyl group. Thus, this method can only be used to prepare a limited number of  $\beta$ -amino acids. Following improvements in this field with the introduction of amidomethylating agents bearing *N*-protecting groups that are cleavable under milder conditions by Wyatt and co-workers<sup>167</sup> and Evans and colleagues<sup>168</sup> (i.e., 1-(*N*-benzyloxycarbonylaminoethyl)benzotriazole and *N*-methoxymethyl benzyl carbamate, respectively), the synthesis of a wide range of  $\beta^2$ -amino acid

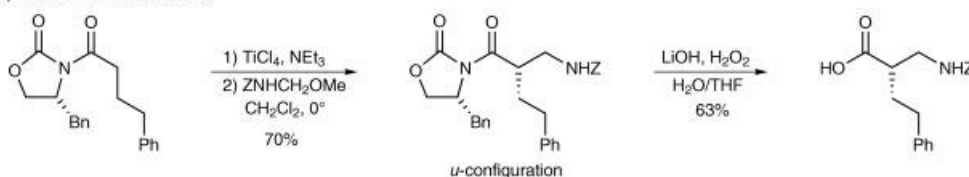


**SCHEME 20** Preparation of (*R*)- and (*S*)- $\beta^2$ -amino acid derivatives by amidomethylation of acyl-oxazolidinones.

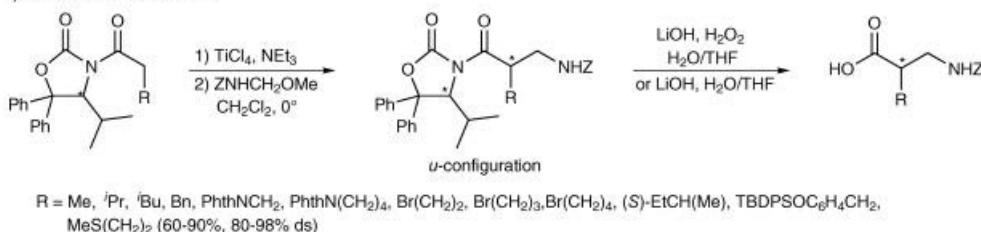
a) Wyatt and co-workers:



b) Seebach and co-workers:



c) Seebach and co-workers:



**SCHEME 21** Preparation of  $\beta^2$ -amino acids by amidomethylation using electrophiles that contain protecting groups cleavable under mild conditions. (a) According to Wyatt,<sup>167,169</sup> (b) with Evans' benzyl-oxazolidinone auxiliary,<sup>168,170</sup> and (c) with Seebach's oxazolidinone auxiliary.<sup>141,142,171,172</sup>

derivatives by means of this methodology was made possible (Scheme 21). As with the previous examples, several auxiliaries can be employed, affording the products with *unlike* relative configurations in good to complete diastereoselectivities. The use of the benzotriazole derivative as the electrophile (cf. (a) in Scheme 21) is limited to Li- and Na-enolates, since Ti-enolates are unreactive. The best yields have been obtained by warming up the reaction mixture to room temperature before quenching, although the formation of ca. 30% of deacylated chiral auxiliary as a major by-product is observed.

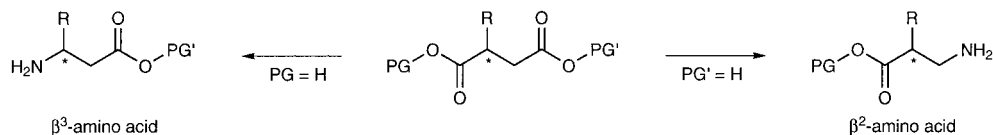
Wyatt and co-workers<sup>169</sup> have also attempted the use of *N*-acetoxymethyl benzyl carbamate (ZNHCH<sub>2</sub>OAc) for the Mannich reaction under Ti-enolate conditions. However, only moderate to low yields have been obtained when *R* is either aryl or alkyl, with much of the

starting material remaining. On the other hand, *N*-methoxymethylbenzyl carbamate (ZNHCH<sub>2</sub>OMe) shows enhanced reactivity under Ti-enolate conditions, permitting the isolation of alkylated products in 60–90% yield, making this method suitable for the multigram<sup>13</sup> preparation of a wide variety of  $\beta^2$ -amino acids.<sup>141,142,171,172</sup>

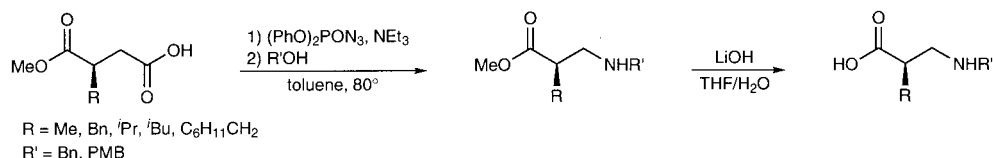
### 5.3. Curtius Degradation

Another route for the incorporation of an aminomethyl group is based on the Curtius rearrangement of enantiomerically pure and regioselectively protected monosubstituted succinates, a route that can lead to either  $\beta^2$ - or  $\beta^3$ -amino acids<sup>173,174</sup> (Scheme 22).

<sup>13</sup> A large-scale synthesis of ZNHCH<sub>2</sub>OMe performed by Novartis has highlighted some purification issues.



**SCHEME 22** Curtius rearrangement of succinic acid derivatives for the selective preparation of  $\beta^2$ - or  $\beta^3$ -amino acids.



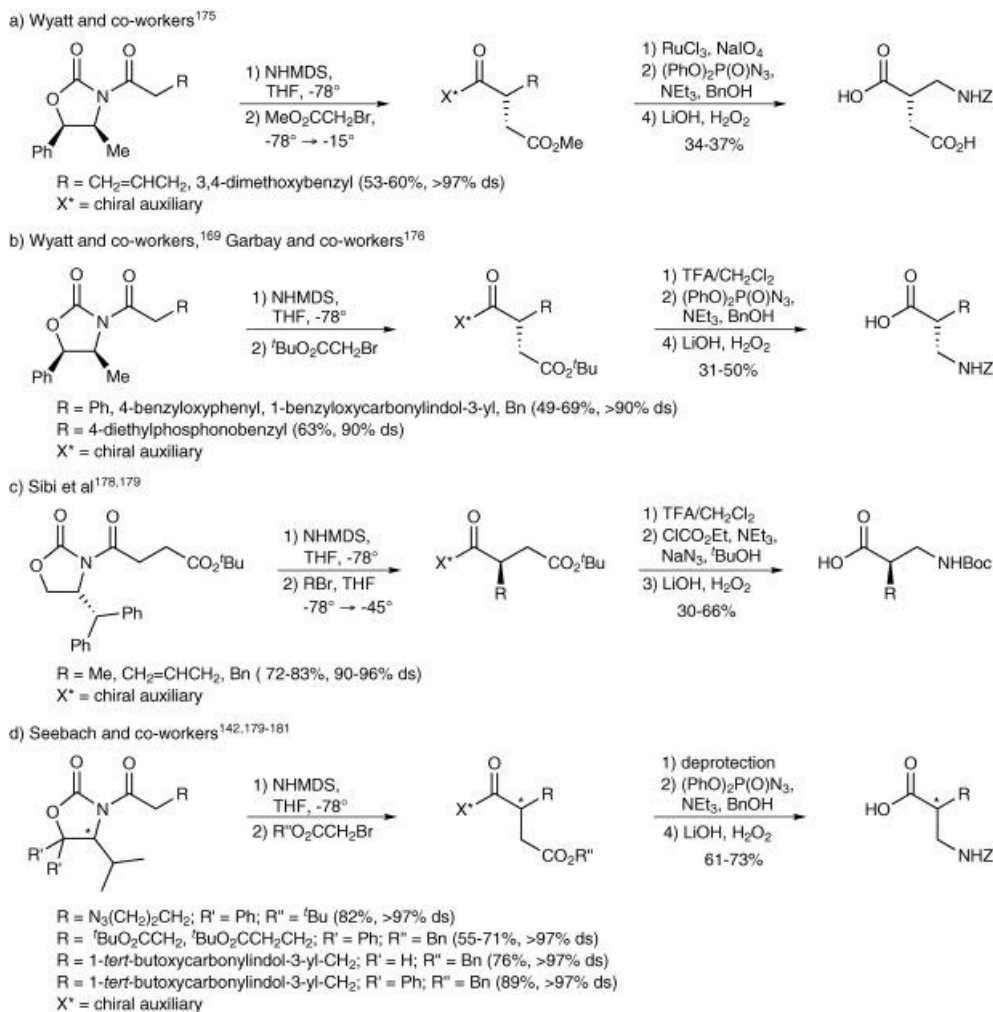
**SCHEME 23** Curtius rearrangement of (*R*)-monosubstituted succinates for the preparation of  $\beta^2$ -amino acids.

The first examples of enantiomerically pure  $\beta^2$ -amino acids prepared by this method were summarized in a patent of the Monsanto Company in 1990,<sup>173</sup> in which chiral monosubstituted succinates are degraded to *N*-protected  $\beta^2$ -amino acids by the action of diphenylphosphoryl azide (i.e., (PhO)<sub>2</sub>PON<sub>3</sub>) and triethylamine, with quenching of the intermediate isocyanate by primary alcohols (Scheme 23).

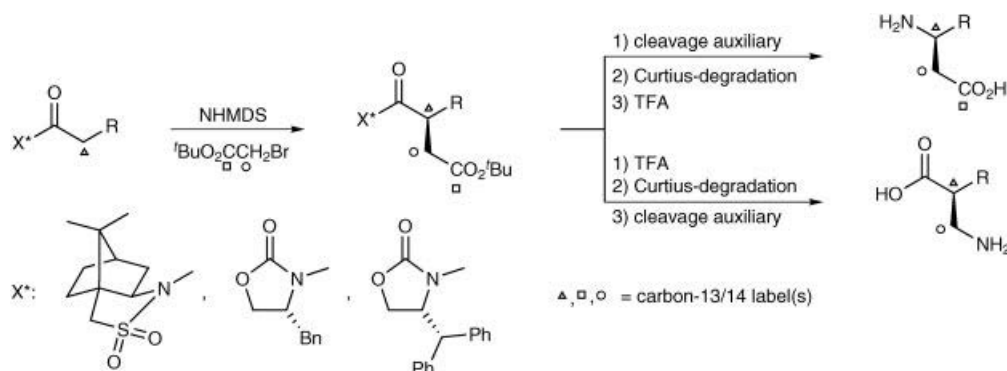
Other groups have also applied the Curtius protocol for the preparation of  $\beta^2$ -amino acids. In addition,

they have utilized such a transformation with the asymmetric multistep synthesis of succinate derivatives, including a diastereoselective alkylation reaction of acyl oxazolidinones (Scheme 24).

For the preparation of chiral succinate derivatives, essentially two routes have been adopted: the first one involves diastereoselective alkylation of chiral succinyl oxazolidinones with alkyl or benzyl halides (cf. (c) in Scheme 24), whereas the second one includes an alkylation of acyloxazolidinones with XCH<sub>2</sub>CO<sub>2</sub>R



**SCHEME 24** Approaches for the preparation of chiral succinate derivatives and the subsequent Curtius rearrangement toward the preparation of  $\beta^2$ -amino acids.



**SCHEME 25** Preparation of isotopically labeled  $\beta^2$ - and  $\beta^3$ -amino acids by alkylation and subsequent Curtius rearrangement.

(cf. (a), (b), and (d) in Scheme 24).<sup>14</sup> All these examples give high yields and diastereoselectivities and have recently permitted the preparation of  $\beta^2$ -amino acids with functionalized side chains<sup>142,180,181</sup> (i.e.,  $\beta^2$ hTrp-,  $\beta^2$ hArg-,  $\beta^2$ hOrn-,  $\beta^2$ hAsx-, and  $\beta^2$ hGlx derivatives). Alternatively, Voges and Metz applied similar methodology to the synthesis of isotopically labeled  $\beta^2$ - and  $\beta^3$ -amino acids using the Oppolzer or Evans methodology<sup>187</sup> (Scheme 25).

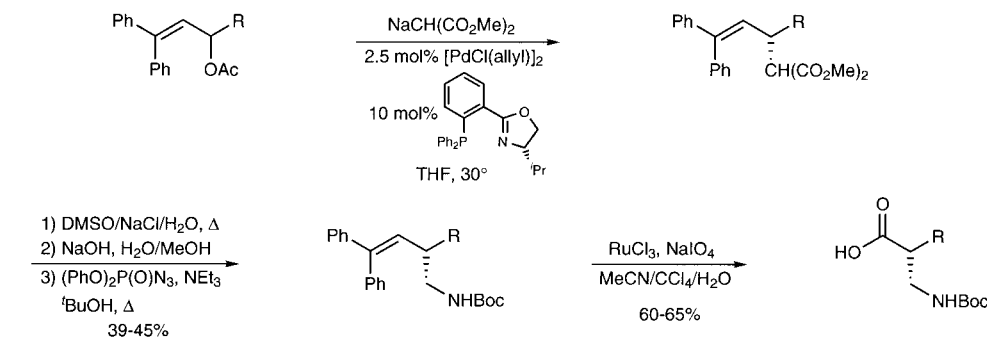
Another method for the construction of  $\beta^2$ -amino acid derivatives was explored by Williams and co-workers,<sup>188,189</sup> applying palladium catalyzed asymmetric allylic substitutions followed by a Curtius rearrangement (Scheme 26). The first step leads, very cleanly, to the corresponding malonate substituted product in high yield, with complete regiocontrol and excellent enantioselectivity. The following decarboxylation, Curtius rearrangement, and oxidation steps

lead to the isolation of the corresponding  $\beta^2$ -amino acids, without loss of enantiopurity.

#### 5.4. Preparation of $\beta^2$ -Amino Acids by Transition-Metal Catalyzed Reactions

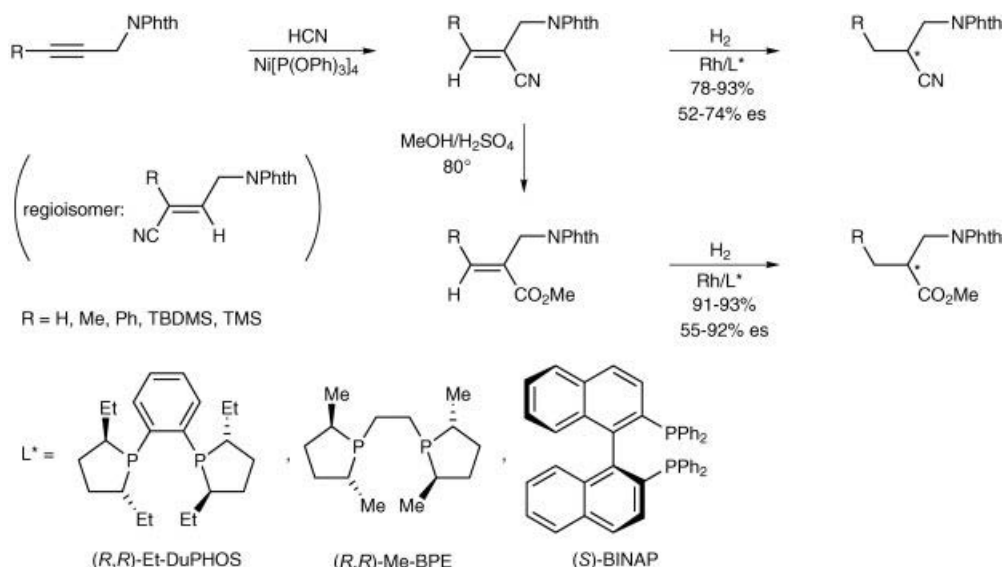
Apart from the aforementioned example, which could also have been included in this section, only a few other methods relying on the use of chiral metal complexes for the enantioselective synthesis of  $\beta^2$ -amino acids have been reported. All of them have been introduced very recently and are still in their seminal phase, showing good selectivities only sporadically and with only restricted diversity. One of the most attractive approaches toward enantiopure  $\beta^2$ -amino acids is, by far, the enantioselective hydrogenation of readily available  $\alpha,\beta$ -unsaturated amino acid precursors (cf. Scheme 3, above). This approach has been investigated by Jackson and co-workers<sup>190</sup> in pursuing the enantioselective hydrogenation of  $\alpha,\beta$ -unsaturated nitrile and methyl ester derivatives (Scheme 27). The corresponding nitriles can be pre-

<sup>14</sup> The high regioselectivity observed in the enolate generation of acyloxazolidinones that also contain an ester group must be attributed to the increased acidity (or deprotonation rate) of the  $\alpha$ -hydrogen adjacent to the imide over the ester group.<sup>163,182–186</sup>



R = Me, Ph, mesityl, 1-naphthyl (86-97%, >97% es)

**SCHEME 26** Palladium catalyzed asymmetric allylic substitution followed by Curtius rearrangement for the preparation of enantiomerically pure  $\beta^2$ -amino acids.



**SCHEME 27** Enantioselective hydrogenation of  $\alpha,\beta$ -unsaturated nitrile and ester derivatives for the preparation of  $\beta^2$ -amino acids.

pared by Ni-catalyzed hydrocyanation, although as a mixture of two regioisomers, in which the desired  $\alpha$ -phthalimidomethyl cyanide is the major product. Methanolysis of the latter affords the corresponding methylacrylate. Both compounds have been subjected to enantioselective hydrogenation with Rh DuPHOS, Rh BPE, and Rh BINAP chiral catalysts to give the  $\beta^2$ -amino acids in good yields and with es values ranging from 50 to 92%. The best result was obtained by hydrogenation of the phthalimido ester precursor of  $\beta^2$ hAla ( $R = H$ ). It is noteworthy that, depending on both the chiral ligand and the substrate, enantioenriched  $\beta^2$ -amino acids of (*R*)- or (*S*)-configuration could be obtained.

Better results, applying a similar approach, have been documented by Li and co-workers.<sup>191</sup> They accomplished the synthesis of enantiopure  $\alpha,\beta$ -diaminopropanoic acid derivatives<sup>15</sup> by Rh DuPHOS-catalyzed asymmetric hydrogenation of  $\alpha,\beta$ -diamidoacrylates (Scheme 28). It is not clear whether the high selectivity is due to the effect of the  $\alpha$ -amino group, the  $\beta$ -amino group, or both.

An important industrial transformation, which produces 100 ton/year of almost enantiomerically pure

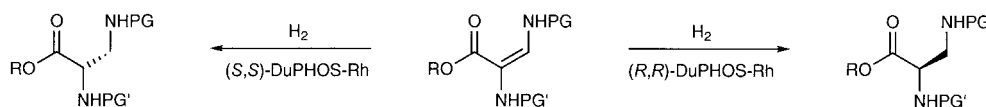
compound, is the asymmetric ketone hydrogenation of methyl ( $\pm$ )-2-(benzamidomethyl)-3-oxobutanoate (Scheme 29). The resulting *syn*-(2*S*,3*R*)- $\beta^2$ -homothreonine derivative is obtained with optimal diastereo- and enantioselectivities, making use of several chiral complexes,<sup>192-197</sup> and can be transformed to the  $\beta$ -lactam key intermediate of carbapenem antibiotics.<sup>198,199</sup>

Another example of a catalytic enantioselective reaction for the preparation of  $\beta^2$ -amino acids was reported by Davies and Venkataramani.<sup>200</sup> The crucial reaction is an asymmetric C–H activation of *N*-Boc-protected methylamines by means of a  $[\text{Rh}_2((S)\text{-DOSP})_4]$  induced C–H insertion (Scheme 30).

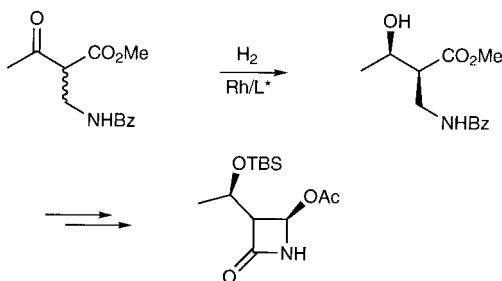
It has been postulated that the cause of the selective insertion into the *N*-methyl group over electronically much more favorable sites (e.g., an allylic site:  $R = \text{trans-MeCH=CHCH}_2$ ) is due to the sterically demanding nature of the Rh complex.

Alternatively, Wendisch and co-workers applied Cu(I)-mediated Michael-type additions of alkyl zinc<sup>201</sup> or alkyl aluminium<sup>202</sup> reagents to nitro acrylates to obtain  $\beta^2$ -amino acids, thus demonstrating the feasibility of the alkylation process with *umpolung* (compare Scheme 31 (a) with Section 4.1). The use of copper catalysts increases the regioselectivity of the

<sup>15</sup> These derivatives are at the same time  $\alpha$ - and  $\beta$ -amino acids.



**SCHEME 28** Rh-Catalyzed asymmetric hydrogenation of  $\alpha,\beta$ -diamidopropenoates.

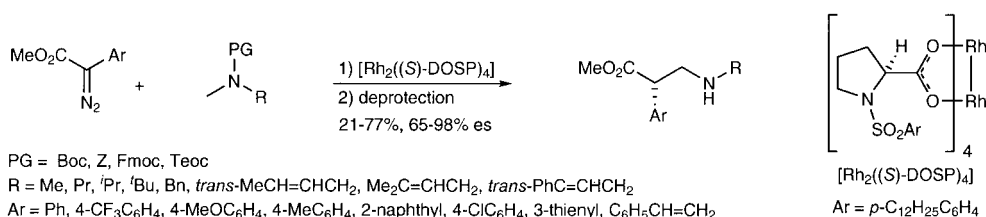


**SCHEME 29** Diastereo- and enantioselective hydrogenation for the preparation of a  $\beta$ -homothreonine derivative—a precursor of a key intermediate for carbapenem antibiotics production.

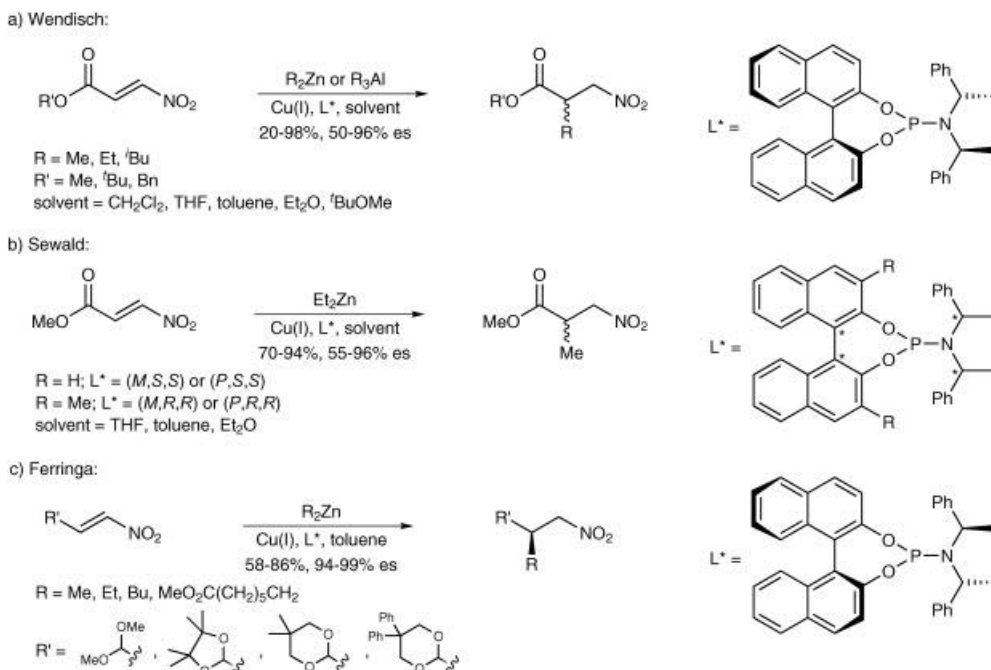
reaction but most of the chiral ligands screened gave only moderate enantioselectivities. Only the Feringa-type BINOL-based ligand shown in Scheme 31 gave rise to high enantioselectivities up to 94%. It has been

found that solvents lacking electron donating atoms lead to low es, and as a result  $t$ BuOMe is the solvent of choice. Moreover, it could be confirmed that the nature of the ester group ( $R'$ ) does not influence the yield or the enantioselectivity of the reaction. On the other hand, a difference in selectivity was observed with different organometal compounds. Diethyl and di-*tert*-butyl zinc give better results than their aluminium analogs, but the opposite is found when  $R$  is methyl. Independently, Rimkus and Sewald<sup>203</sup> also explored the potential application of diethyl zinc additions to 3-nitromethylacrylate and similar conclusions have been drawn (Scheme 31(b)).

At the same time, Feringa and co-workers<sup>204</sup> (Scheme 31(c)) applied the conjugate addition of dialkyl zinc reagents to nitropropene acetals using several chiral catalysts providing enantioselective reactions. In this case the best es values were also ob-



**SCHEME 30** C–H insertion of N-protected methylamines for the construction of  $\beta^2$ -amino acids.



**SCHEME 31** Stereoselective synthesis of  $\beta^2$ -amino acids by Michael-type addition of diorgano zinc reagents to nitro acrylates ((a), (b)) or nitropropene acetals ((c)).



tained with the BINOL-based ligand. In contrast to Wendisch's results, the reaction with methyl zinc gave the desired product with 99% enantioselectivity.

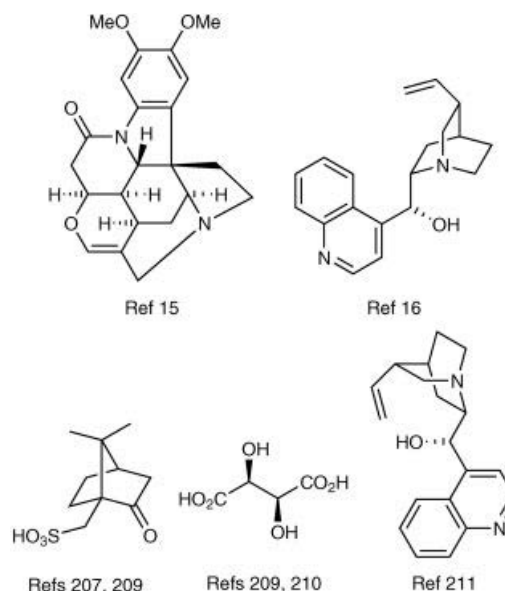
Organometallic reagents have also been applied by Baldwin and co-workers<sup>205,206</sup> in their experiments devoted to the selective ring opening of aziridines toward the formation of  $\alpha$ - and  $\beta$ -amino acids. Unfortunately, organocuprates and methyl-Grignard reagents led to nonselective opening of chiral aziridine-2-carboxylate esters to give mixtures of  $\alpha$ - and  $\beta^2$ -amino acids, together with plenty of other compounds.

### 5.5. Resolutions of Racemic $\beta^2$ -Amino Acids

The easiest method to separate a racemic mixture into its enantiomeric constituents is resolution, in other words converting a racemic mixture into a diastereoisomeric mixture by means of a chiral compound. Most of the time, this reaction is used with formation of diastereoisomeric salts, permitting separation by crystallization (due to a difference in solubility in a suitable solvent), or by chromatography. After separation, the resulting diastereomerically pure salts can be easily "cleaved" to give the desired enantiomerically pure compound. For the resolution of  $\beta^2$ -amino acids only a few examples have so far been described, and they involve the resolution of  $\beta^2$ -homoalanine<sup>15,16</sup>  $\beta^2$ -homophenylglycine,<sup>207,208</sup>  $\beta^2$ -homoproline,<sup>209</sup> and  $\beta^2$ -iso-proline.<sup>210,211</sup> The chiral reagents used for these purposes are shown in Figure 13.

However, there are also other methods for obtaining enantiopure amino acids, for example, attempting "diastereoselective" reactions for the construction of  $\beta^2$ -amino acid scaffolds, which are deliberately modified to give only racemic mixtures of diastereoisomers, but in very high yields. Subsequent crystallization or chromatography produces either diastereoisomer as single compound. Indeed, Shustov and Rauk<sup>212</sup> and Gellman and co-workers<sup>213</sup> applied this methodology by treating chiral amines with achiral acrylate derivatives at high temperatures. The so-formed 1:1 mixtures of diastereoisomers were obtained in almost quantitative yield and could easily be separated by crystallization and chromatography, respectively (Scheme 32). Subsequent cleavage of the chiral "protecting group" afforded the enantiopure  $\beta^2$ -amino acids in good yields.

In a similar approach, Kim and co-workers<sup>214</sup> coupled racemic  $\beta$ -hydroxyacids with (*S*)-phenethyl amine. After chromatographic separation they converted both diastereoisomers into the  $\beta^2$ -amino acid enantiomers (Scheme 33).

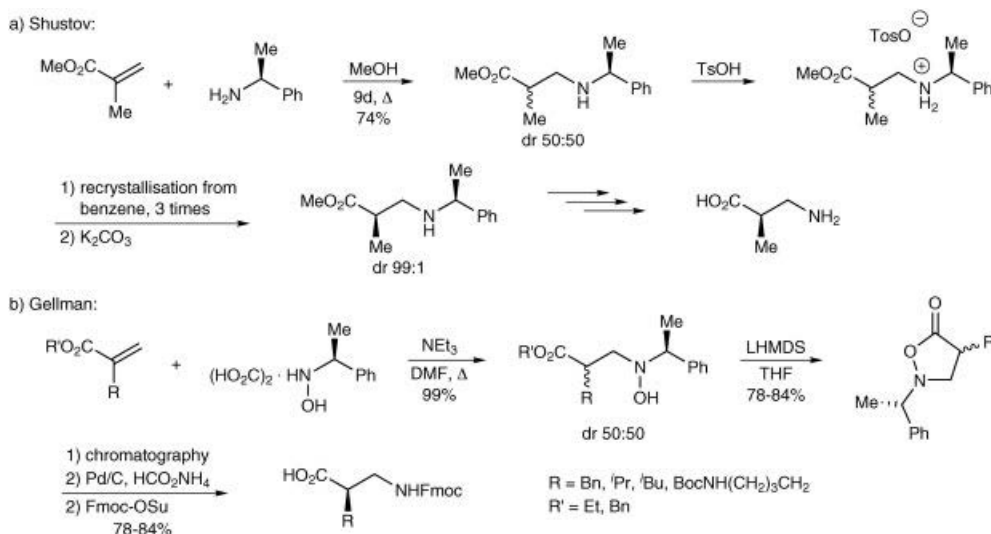


**FIGURE 13** Some chiral compounds, which have been used for diastereoisomeric salt formation with  $\beta^2$ -amino acid racemates.

Enzymatic resolution has also been applied to the preparation of  $\beta^2$ -amino acid, but it plays a less important role in comparison with the production of  $\alpha$ - and  $\beta^3$ -analogues. The ability of hydrolytic enzymes to act as asymmetric catalysts for the Michael addition reaction has been explored by Kitazume et al.<sup>215–217</sup> in order to prepare enantioenriched  $\alpha$ -trifluoromethyl- $\beta$ -alanines (Scheme 34). In most examples, only moderate enantioselectivities (up to 86% es) were observed, but a drastic improvement (>99% es) was achieved using chiral esters of menthol as the Michael acceptors.

Kanerva and co-workers<sup>218</sup> studied the enzymatic resolution of racemic  $\beta^2$ -homoalanine ethyl ester by *N*-propionylation with *Candida antarctica* lipase A and B (i.e., CAL-A and CAL-B) using neat ethyl-, butyl-, and 2,2,2-trifluoroethyl butanoate as organic solvents. The two enzymes displayed opposite and low enantioselectivities, but allowed for the preparation of the two enantiomers in a two-step resolution protocol (Scheme 35).

The efficiency of lipases in catalysing the asymmetric acylation of 2-substituted 1,3-propanediols has also been explored. Yokomatsu et al.<sup>219</sup> employed this technique for the preparation of an enantiopure  $\beta^2$ -peptide nucleic acid (PNA) having a (thymine-1-yl) methyl side chain ( $n = 1$ ). The synthesis was based on a "chemoenzymatic" route, which is shown in Scheme 36. It should be noted that elongation of the side chain by another  $\text{CH}_2$ -group ( $n = 2$ ) causes a drastic decrease in the efficiency of the enzymatic



**SCHEME 32** Michael-type reactions to form 1:1 mixtures of diastereoisomers for resolution. Only one enantiomer is shown.

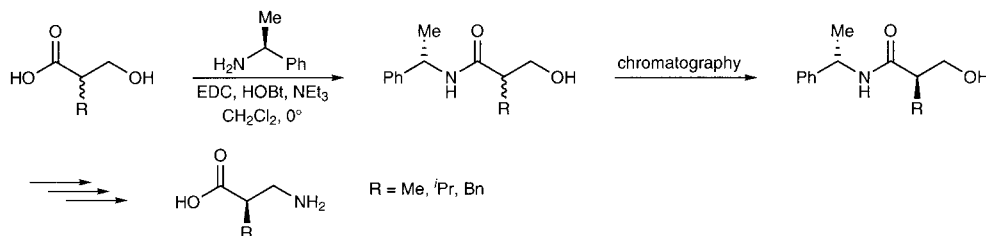
reaction, allowing for the isolation of the acetate derivative in only 57% enantiopurity.

In one of the routes for the enantioselective preparation of either (*R*)- or (*S*)- $\beta^2$ -*iso*-proline, Furstoss and co-workers<sup>220</sup> used a microbial stereoselective Baeyer–Villiger oxidation for the synthesis of a common chiral starting material. Thus, oxidation of an achiral cyclobutanone derivative with the fungus *Cunninghamella echinulata* NRRL 3655 afforded in good yield and very high enantiopurity (60%, >98% es) the (–)-benzyloxymethyl- $\gamma$ -butyrolactone, which was

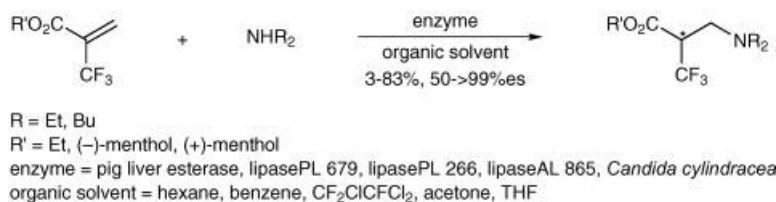
subsequently converted to either (*R*)- or (*S*)- $\beta^2$ -*iso*-proline (Scheme 37).

## 5.6. Miscellaneous Methods

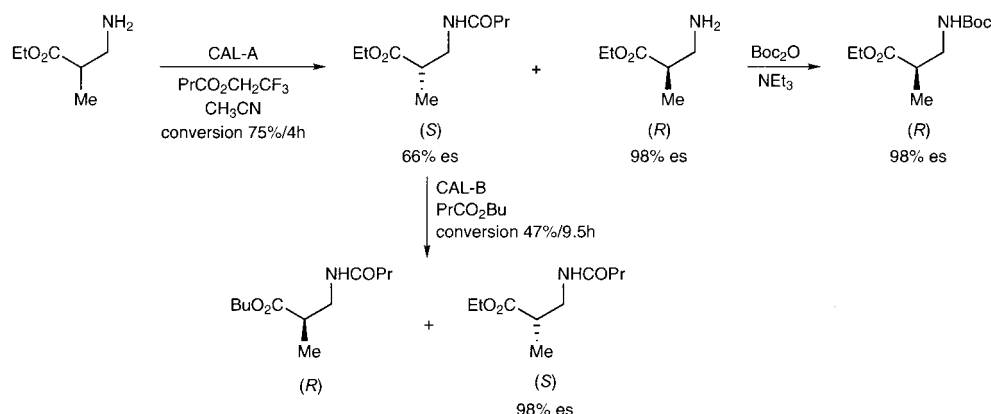
Some other approaches have been successfully applied for the preparation of specific  $\beta^2$ -amino acid derivatives. For example, stereoselective Michael-addition reactions of benzylamine to a chiral substrate have been investigated by Perlmutter and Tabone for the preparation of  $\beta^2$ -homothreonine and its ana-



**SCHEME 33** Racemic  $\beta$ -hydroxyacids as starting materials for the preparation of enantiopure  $\beta^2$ -amino acids. Only one enantiomer is shown.



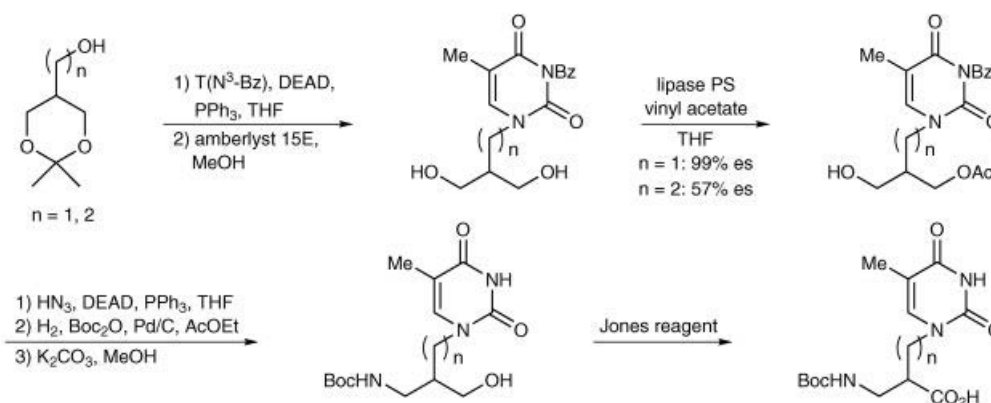
**SCHEME 34** Enzyme-assisted Michael addition of alkyl amines to 2-trifluoromethylpropenoic acid esters.



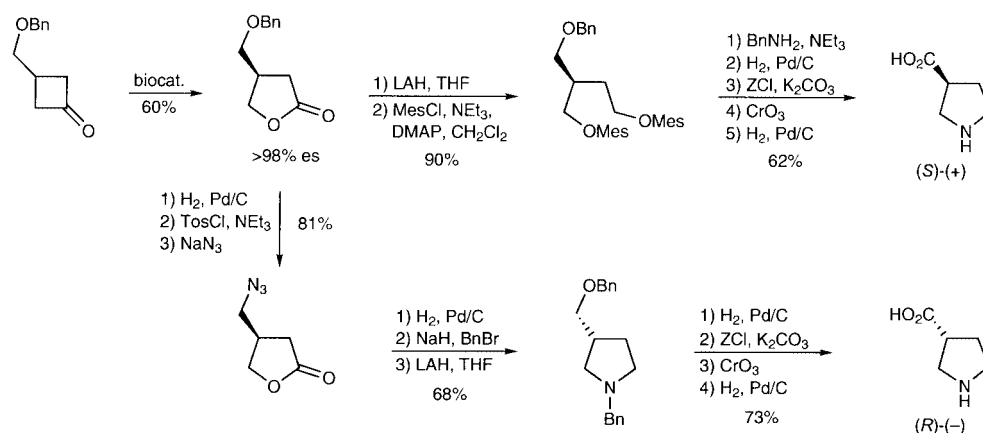
**SCHEME 35** Two-step resolution protocol for the preparation of enantiomerically pure  $\beta^2$ -homoalanine derivatives.

logues.<sup>221,222</sup> Addition of benzylamine to enantiopure methyl 2-methylene-3-hydroxy or -silyloxy-alkanoates proceeds with excellent yields, but modest diastereoselectivities are observed when the hydroxy group

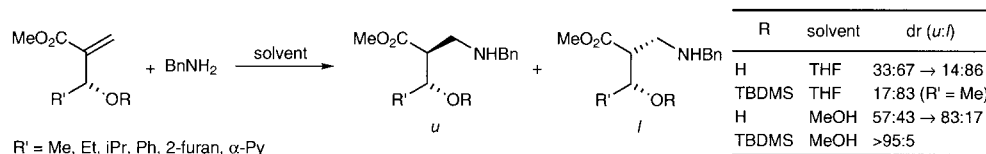
is unprotected. Remarkably, protection of this group as a *tert*-butyldimethylsilyl (TBDMS) ether causes the addition to be diastereoselective, yielding only the *u*-product (Scheme 38). When THF is used as solvent,



**SCHEME 36** "Chemoenzymatic" approach for the preparation of a  $\beta^2$ -PNA with a (thymine-1-yl)methyl side chain.

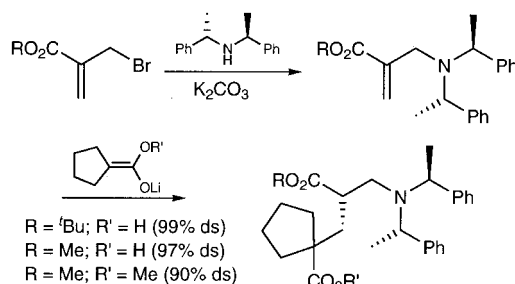


**SCHEME 37** Preparation of  $\beta^2$ -iso-proline according to Furstoss.

**SCHEME 38** Addition of benzylamine to propenoate derivatives.

protonation takes place preferentially from the *Si*-face; on the other hand when MeOH is used the selectivity is reversed in favor of *Re*-attack.

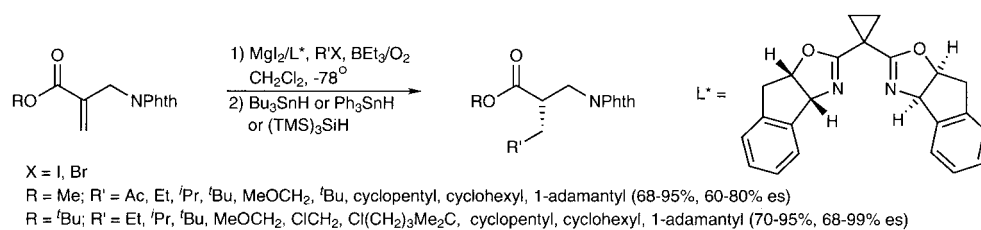
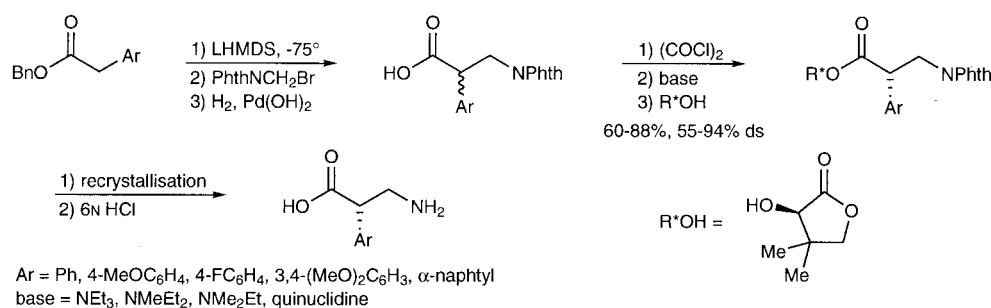
The 1,4-addition of a lithium enolate to chiral aminomethylacrylates has also been demonstrated to proceed with excellent diastereoselectivities (up to 99% ds), providing an expeditious synthesis of  $\beta^2$ -homoglutarate derivatives for the construction of neutral endopeptidase inhibitors in multi gram scale (up

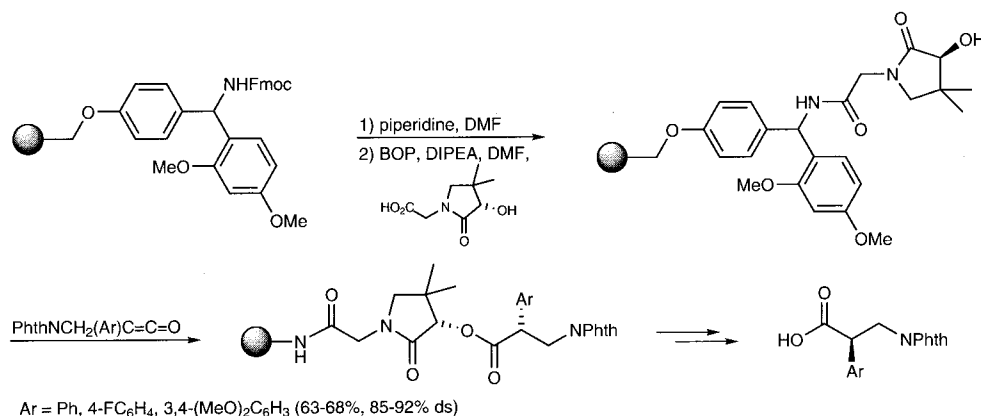
**SCHEME 39** 1,4-Addition of enolates to chiral  $\alpha$ -(aminomethyl)acrylates for the preparation of  $\beta^2$ -amino acids.

to 500 g)<sup>223</sup> (Scheme 39). Thus, condensation of 2-bromomethylacrylic esters with commercially available  $C_2$ -symmetrical (*S,S*)-bis-phenethylamine in the presence of potassium carbonate gives the chiral acrylates, which are subsequently treated with the enolates of cyclopentanecarboxylic acid or methyl ester to afford the corresponding  $\beta^2$ -amino acids with almost complete diastereoselectivity.

Recently, Sibi and Kalyani<sup>224</sup> applied a new methodology relying on enantioselective H-atom transfer reactions for the preparation of  $\beta^2$ -amino acids. Thus, radical 1,4-addition of alkyl groups to  $\beta$ -amino acryl ester derivatives followed by reaction with either  $R_3SnH$  or  $(TMS)_3SiH$ , in the presence of a chiral Lewis acid, permitted the isolation of  $\beta^2$ -amino acid esters with alkyl side chains in good yields and selectivity (Scheme 40).

Using a different approach, Calmès and co-workers<sup>103,225</sup> have prepared enantiomerically pure (*S*)- $\beta^2$ -homoarylglycines *via* asymmetric transformation of the corresponding racemic *N*-phthaloyl derivatives, conveniently obtained from benzyl aryl acetates and

**SCHEME 40** Enantioselective H-atom transfer reactions for the preparation of  $\beta^2$ -amino acids.**SCHEME 41** Stereoselective synthesis of (*S*)- $\beta^2$ -homoarylglycines.



**SCHEME 42** Solid-support asymmetric synthesis of  $\beta^2$ -homoarylglycines according to Calmès.

*N*-bromomethyl phthalimide. These achiral  $\beta$ -amino acids are precursors to the *N*-phthalyl-3-aminomethyl-2-aryl ketenes by treatment with oxalyl chloride, followed by dehydrochlorination and trapping with a chiral alcohol (i.e., (*R*)-pantolactone), which leads to the corresponding diastereoisomeric mixtures, with the (*S,R*)-products being the major isomers (Scheme 41).

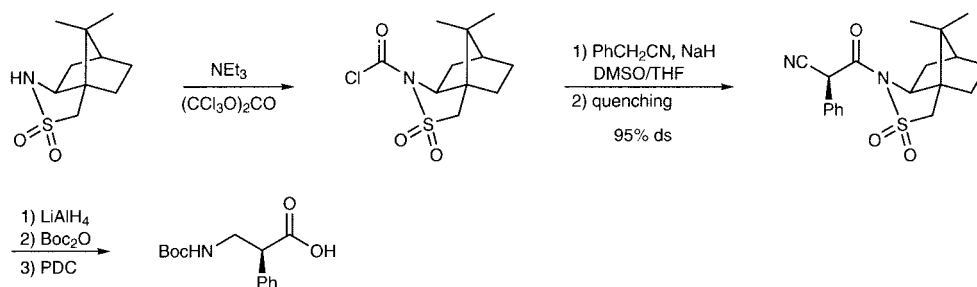
In an extension to this methodology, an enantiopure pantolactone derivative was recently attached to a solid support and the asymmetric preparation of  $\beta^2$ -amino acids was undertaken.<sup>226</sup> After Fmoc-deprotection of the *Rink* amide resin and attachment of the chiral auxiliary, diastereoselective addition of the supported alcohol to the ketene was accomplished. Acid hydrolysis of both the ester and phthalimido groups gave the enantiomerically enriched  $\beta^2$ -homoarylglycines in good yields and comparable selectivities to that obtained in solution (Scheme 42).

Among all  $\beta^2$ -homoarylglycine derivatives, the synthesis of  $\beta^2$ -homophenylglycine (i.e.,  $\beta^2$ hPhg) has drawn the interest of many groups, probably due to the fact that the ( $\pm$ )-ethyl ester has neuro-

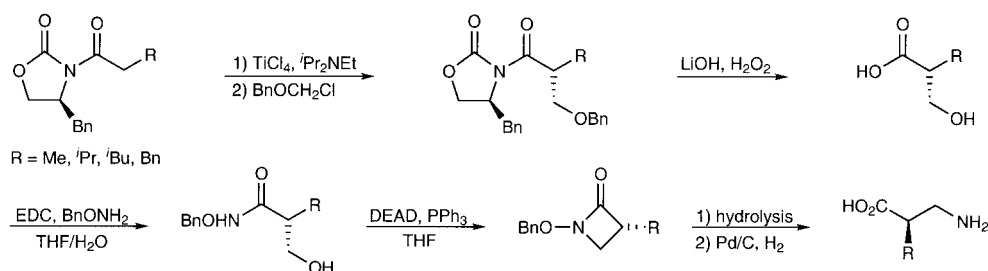
logical activity<sup>227</sup> and (*S*)- $\beta^2$ hPhg is part of the side chain of the semisynthetic penicillin betacin.<sup>207</sup> An approach toward its preparation in enantiopure form was explored by Lavielle and co-workers<sup>228</sup>: acylation of phenylacetonitrile with a chiral electrophilic sultam carbonyl chloride leads selectively to one diastereoisomer, which can be transformed by reduction, *N*-Boc protection, and oxidation, to afford *N*-Boc- $\beta^2$ -homophenylglycine as a single enantiomer (Scheme 43).

$\beta$ -Hydroxy carboxylic acids are interesting precursors for conversion to  $\beta^2$ -amino acids. First, they are easily obtained by diastereoselective hydroxymethylation using Evans' methodology, and second, they react under Mitsunobu conditions to form the  $\beta^2$ -amino acids (Scheme 44). This method has been successfully applied by Kim and co-workers<sup>229,230</sup> for the preparation of  $\beta^2$ -amino acids with methyl, *iso*-propyl, *iso*-butyl, and benzyl side chains.

$\beta^2$ -*iso*-Proline, a cyclic  $\beta^2$ -amino acid, is a potent agonist at the strychnine-sensitive glycine receptor.<sup>231</sup> It serves as a building block for the preparation of novel inhibitors of bacterial DNA gyrase<sup>232</sup> and forms the central moiety of a conformationally restricted,



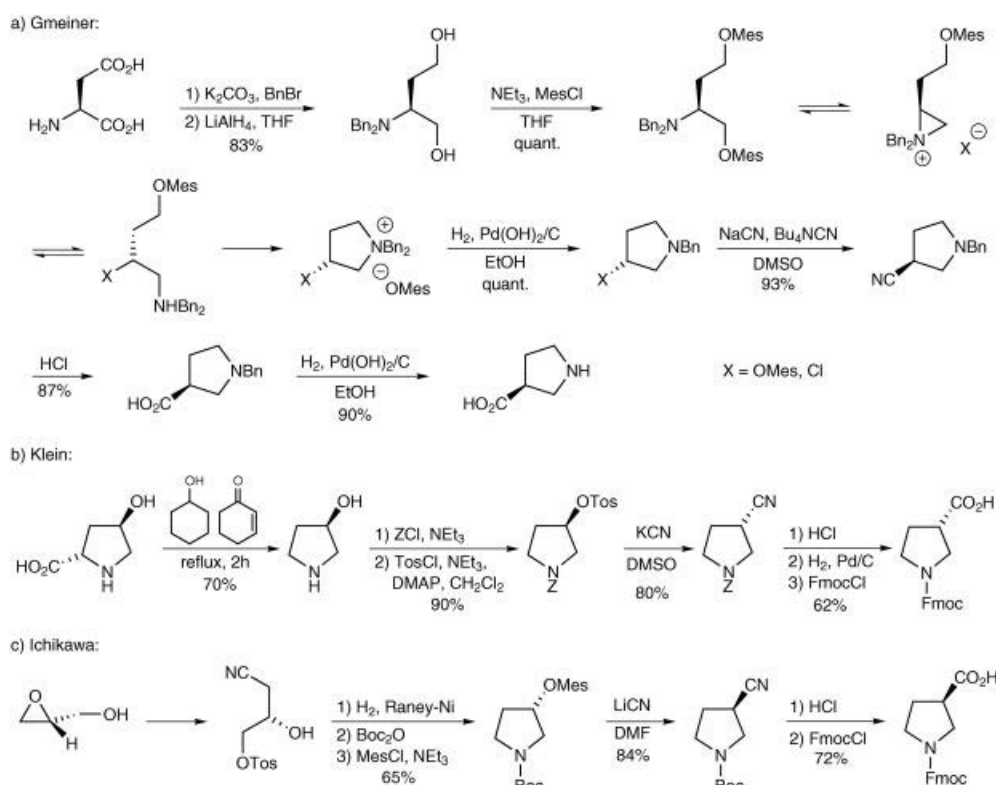
**SCHEME 43** Preparation of enantiopure Boc- $\beta^2$ hPhg-OH according to Lavielle



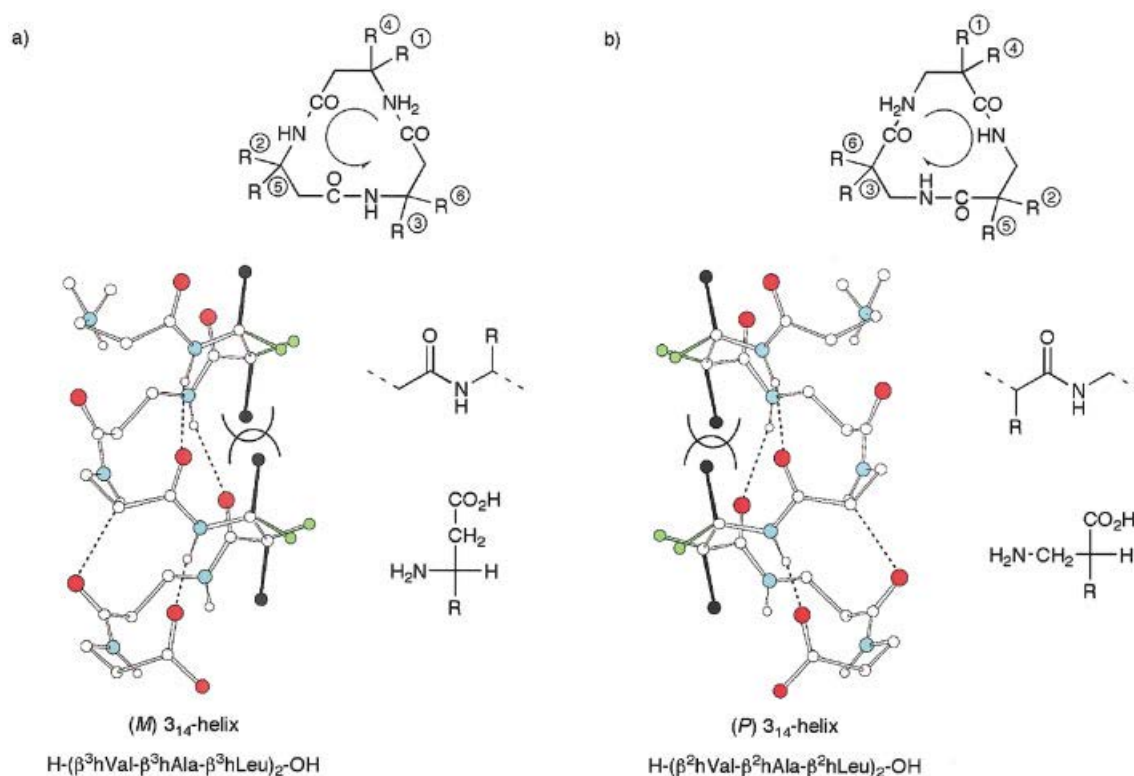
**SCHEME 44** Synthesis of chiral  $\beta$ -hydroxy acids and the subsequent conversion to  $\beta^2$ -amino acids.

highly potent fibrinogen receptor antagonist.<sup>233</sup> For this reason, several groups became interested in its preparation (Scheme 45). In a first approach, Gmeiner and co-workers<sup>234,235</sup> made use of aspartate as the starting material. This natural  $\alpha$ -amino acid is transformed in high yield to a *N,N*-dibenzyl-protected amino-1,4-diol, which is subsequently converted to a 1,4-hydroxyamino-derivative by equilibrating rearrangement of the dibenzylamino group. Cyclization, substitution by cyanide, and hydrolysis give the  $\beta^2$ -iso-proline as single enantiomer. The second route, proposed by Klein and co-workers<sup>233</sup> and also used by Gellman and colleagues<sup>236</sup>, starts

from 4-hydroxyproline. Decarboxylation followed by hydroxy activation and displacement by cyanide affords a compound with the desired  $\beta$ -amino-acid backbone, which is hydrolyzed to give the *N*-protected  $\beta$ -amino acid. In another approach, Ichikawa and co-workers<sup>237</sup> employed commercially available (*R*)-glycidol as the starting material. Conversion to a nitrile derivative, followed by reductive cyclization and displacement of the activated hydroxy group by cyanide, gives the  $\beta^2$ -iso-proline core system, which by hydrolysis and Fmoc-protection is converted to the desired  $\beta^2$ -amino acid derivative.



**SCHEME 45** Synthetic approaches for the preparation of  $\beta^2$ -iso-proline according to (a) Gmeiner, (b) Klein, and (c) Ichikawa.



**FIGURE 14** (a) (*M*)-Helix of a peptide of  $L$ - $\beta^3$ -amino acid residues and (b) (*P*)-helix of a peptide consisting of (*R*)- $\beta^2$ -amino acids. Assignment by the Fisher nomenclature must be used for the  $\beta^3$ -amino acids, because the “systematic” CIP specification of configuration is conflicting in this case.<sup>7</sup> The green circles indicate “allowed” positions for nonhydrogen substituents; in the positions labelled by black circles only hydrogen and fluorine atoms have been shown to be tolerated (F. Gessier, C. Noti, R. Mathad, B. Jaun, D. Seebach, unpublished results, ETH-Zürich).

## 6. $\beta^2$ -AMINO ACIDS IN $\beta$ -PEPTIDES

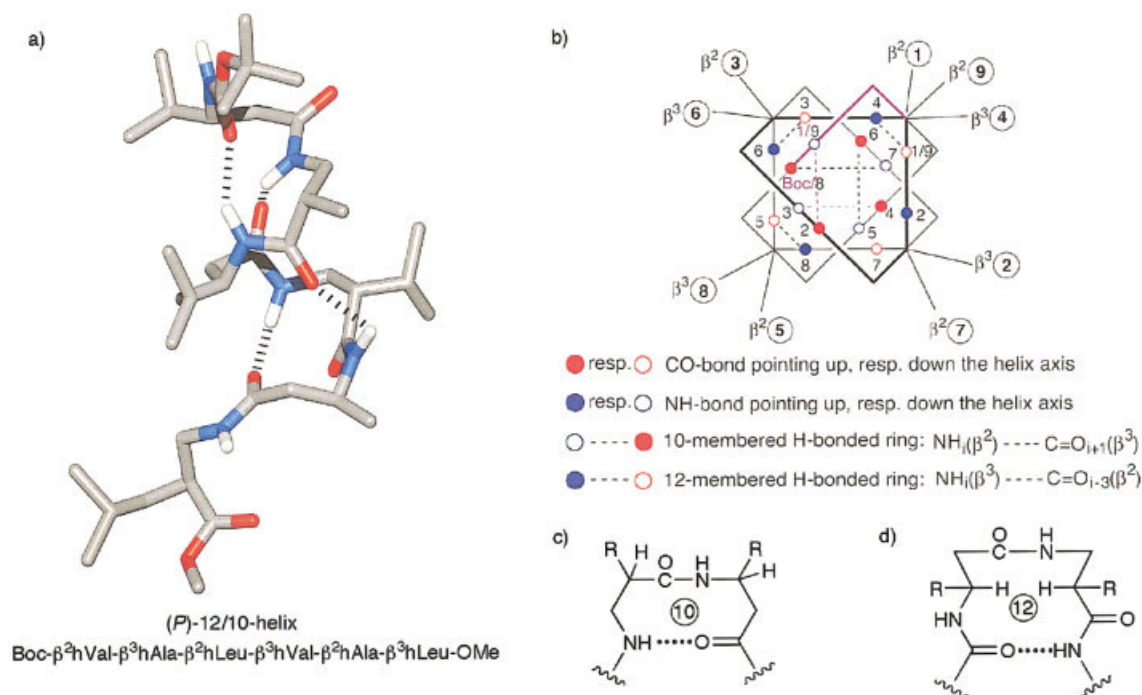
$\beta$ -Peptides composed entirely of homochiral  $\beta^2$ - or  $\beta^3$ -amino acids with proteinogenic side chains have, so far, only been found to form the  $3_{14}$ -helical secondary structure in solution (Figure 14).

From the few examples of  $\beta^2$ -peptides investigated,<sup>164,165,238,239</sup> it can be concluded that they form somewhat less stable  $3_{14}$ -helices than their  $\beta^3$  counterparts. For example, in order to observe a  $3_{14}$ -helical CD-pattern of comparable intensity, the MeOH solution of the  $\beta^2$ -hexapeptide shown in Figure 14 had to be cooled to  $-20^\circ\text{C}$ .

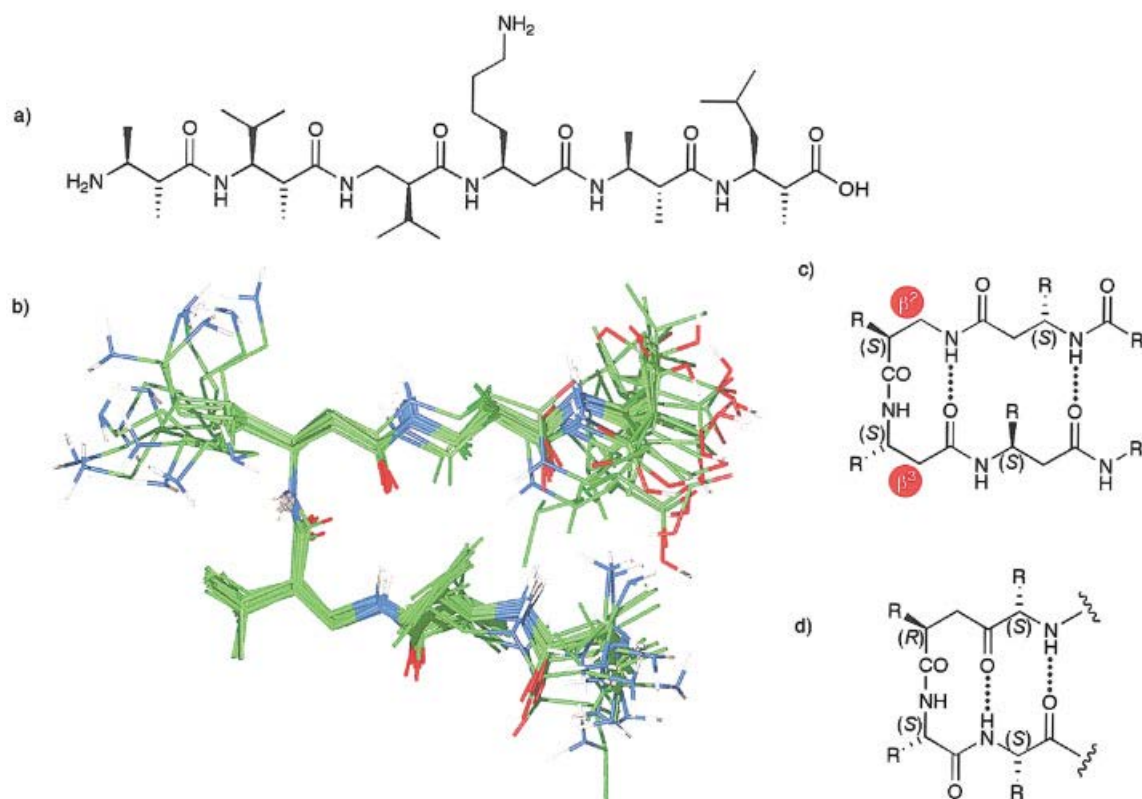
A unique helical secondary structure is observed with  $\beta$ -peptides built of alternating  $L$ - $\beta^3$ - and (*S*)- $\beta^2$ -amino acids.<sup>165,240–243</sup> A chain constructed in this way could very well fold to a left-hand  $3_{14}$ -helix, with all substituents in the allowed, lateral positions labeled with green circles in Figure 14. However, several  $\beta^2/\beta^3$ -peptides of this type have been shown to fold to a (*P*)-10/12-helix, comprised of alternating 10-

and 12-membered hydrogen-bonded rings (Figure 15).

The *N*-terminal Boc-protecting groups participate in the folding process and, depending on whether the chain begins with a  $\beta^2$ - or a  $\beta^3$ -amino acid moiety, the helix starts with a 10- or a 12-membered hydrogen-bonded ring.<sup>243</sup> The consequence is that the  $\beta^2$ - $\beta^3$ -segments in the helix become part of the 10- and the  $\beta^3$ - $\beta^2$ -segments part of the 12-membered H-bonded rings (Figure 15(b) and (c)). Besides the unusual fact that it is held together by two types of H-bonded rings, the 10/12-helix has another exceptional property: the  $\text{C}=\text{O}$  dipoles are alternatively pointing in opposite directions with respect to the helix axis, resulting in no macrodipole. It is this feature that may be responsible for the nonpolar properties of  $\beta^2/\beta^3$ -peptides. The compounds are soluble in organic solvents, such as  $\text{CH}_2\text{Cl}_2$  or AcOEt, which allows for the preparation of a nonamer from the hexamer shown in Figure 15(a) by fragment coupling in solution. This would not be possible with an *all*- $\beta^3$ -peptide carrying



**FIGURE 15** (a) The 10/12-helix in side-view; (b) in a schematic presentation looking down the helix axis, and its (c) 10- and (d) 12-membered hydrogen-bonded-ring components.



**FIGURE 16** (a) Formula and (b) NMR-solution structure in MeOH of a  $\beta$ -hexapeptide forming a hairpin turn with adjacent antiparallel sheet. (c) Schematic presentation of a hairpin turn of an *N*-acyl- $\beta$ -tetrapeptide amide and, for comparison, (d) section of an  $\alpha$ -peptidic  $\beta$ -turn with a D-amino acid residue.



the same aliphatic side chains of Val, Ala, and Leu, for reasons of poor solubility. In fact, larger  $\beta^3/\beta^2$ -oligomers run faster on a silica gel plate than shorter ones. When looking down the 10/12-helix axis (Figure 15(b)), the surface of the helix is covered by more substituents than in a  $3_{14}$ -helix (cf. Figure 14) and sequential *R*-groups alternatively adopt diagonal and adjacent positions with respect to one another.<sup>243</sup> The better “wrapping” of the helix by aliphatic side chains may be another reason for the nonpolar properties of this particular type of  $\beta^2/\beta^3$ -peptides. The 10/12-helix is more stable with terminal protection than without.<sup>165,243</sup> Also, NMR analysis and molecular-modeling calculations using GROMOS lead to the conclusion that the  $\beta^2/\beta^3$ -peptidic 10/12-helix of the hexapeptide shown in Figure 15 is in equilibrium with a smaller fraction of the  $3_{14}$ -helix.<sup>165,240–242</sup>

Knowing that a  $\beta^2$ - $\beta^3$ -segment has a tendency to form a 10-membered H-bonded ring, as outlined above, and that  $\beta$ -peptides built from  $\beta^{2,3}$ -disubstituted amino acids of unlike-configuration<sup>244</sup> are forced to adopt a linear conformation and can therefore form  $\beta$ -peptidic pleated-sheet structures,<sup>244</sup> a  $\beta$ -peptidic hairpin turn has been constructed from six noncyclic  $\beta$ -amino acids as detected by NMR spectroscopy in MeOH solution<sup>244,245</sup> (Figure 16).

Again, besides the turn conformer there seems to be a smaller fraction of molecules that form a 10/12-helix, according to MD calculations.<sup>246</sup> Shorter  $\beta$ -peptides possessing a  $\beta^2$ - $\beta^3$ -segment consisting of only four or even two  $\beta$ -amino acid residues may also, at least partially, adopt a turn structure.<sup>171,247</sup> In agreement with these structural investigations are the results of biological tests, in which it was shown that  $\beta$ -peptides of the type discussed here can mimic the  $\alpha$ -peptidic hormone somatostatin as potent and highly specific agonists:<sup>171,248</sup> somatostatin is known to contain a  $\beta_{II}$ -type turn as a key recognition motif for the five human membrane-bound SRIF-receptor subtypes.<sup>249</sup>

Thus, there is ample evidence for the statement made in the Introduction:  $\beta^2$ -amino acids as residues in  $\beta$ -peptides of designed structures and physiological activities are most important!

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