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Enantioselective Preparation of β²-Amino Acid Derivatives for β-Peptide Synthesis

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Abstract: β-Amino acids with a single side chain in the α-position (β²-amino acids or H-β²hXaa(PG)-OH; i.e., homo-amino acids with proteinogenic side chains) have turned out to be important components in β-peptides. They contribute to unique secondary structures, they are required for mimicking the structure and the activity of β-turn-forming α-peptides, and they can be used for protecting α-peptides against attack by aminopeptidases. In contrast to β³-homo-amino acids, the β²-isomers cannot be obtained simply by enantiospecific homologation of the (natural) α-amino acids, but have to be prepared by enantioselective reactions or sequences of transformations, which are presented herein. The various preparative methods are ordered according to the bond at the stereogenic center, which is formed in the stereoselective step, with the four strategic bonds being the C(2)–C(3) backbone bond, the C(2)–side-chain bond, the C(2)–H bond, and the C(1)–C(2) bond between the carboxylate and the α-carbon. In the most frequently employed methods, a chiral auxiliary group is attached at the carboxyl C(1) atom or at the nitrogen in the 3-position, but there are also a number of enantioselective catalytic processes, including the hydrogenation of suitable acrylates. The alternative of stereoselective synthesis, namely resolution of racemic mixtures (for instance by biocatalysis), is also discussed. A critical comparison of the various methods and strategies is presented. For the peptide chemist, a list is included with the Cbz-, Boc-, and Fmoc-protected β²-amino acid building blocks, ready for peptide coupling. In addition, the search strategy for nonracemic β²-amino acids and their precursors from the databases is described in detail.

Key words: β²-amino acids, β-peptide, retrosynthetic analysis, overall enantioselective synthesis, chiral auxiliaries, enantioselective catalysis, database literature search strategies

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1 Introduction

Since the discovery[1] in 1996 that peptides consisting of homologated proteinogenic amino acids (Figure 1) form more stable secondary structures (helix, turn, sheet) than the natural counterpart, research on β-peptides has undergone an explosive development. This was not only caused by the variety of structures, which differ from, and at the same time are similar to, those of α-peptides, but by the findings that β-peptides (and mixed β/α-peptides) are generally proteolytically and metabolically stable *in vitro* and *in vivo*, and that they can be designed as to mimic biological activities of natural peptides, and thus are of interest for biomedical research. For an overview, we refer to review articles covering the field of β-peptides in general or special aspects of it.[2–4]

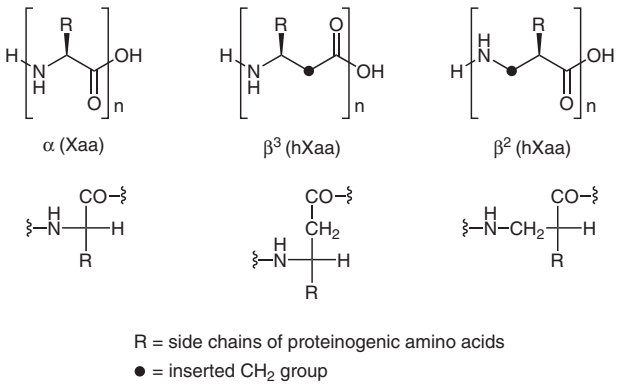


Figure 1 Strictly, the term β²-homo-amino acid (β²hXaa) should be used only for the homologated proteinogenic natural α-amino acids, while the more general term β²-amino acid for any β-amino acid that carries a side chain in the α-position. For the β-amino acids which do not have the absolute configuration derived from natural α-amino acids, as shown here, a stereochemical descriptor, preferably the CIP (*R*) or (*S*), should be used.

Biographical Sketches

Dieter Seebach received a Diploma in Chemistry and a PhD (Dr. rer. nat.) from the Universität Karlsruhe (TH), Germany (supervision by Rudolf Criegee). After a postdoctoral stay in Elias J. Corey's group and a Lectureship at Harvard University, he returned to the University of Karlsruhe for a Habilitation; he became a full Professor of Organic Chemistry at the Justus-Liebig-Universität in Giessen, Germany, in 1971. From 1977 until 2003 he was Professor of Chemistry at the Eidgenössische Technische Hochschule (ETH) in Zürich. Since 2003 he is officially retired; as Professor emeritus and Academic Guest of ETH he continues doing research with postdoctoral co-workers. His past and present research activities include the development of new synthetic methods (umpolung of reactivity, self-regeneration of chirality centers, the geminal-diaryl effect in stereoselective synthesis), natural product synthesis, structure determination, chiral dendrimers, the biopolymer PHB, and β-peptides.

Albert Karl Beck was born in 1947 in Karlsruhe (Germany). After completing a chemistry technician's apprenticeship at the Institute for Organic Chemistry of the University of Karlsruhe from 1963 to 1966, followed by 18 months of military service, he joined the Seebach research group at Karlsruhe in 1968. Between 1969 and 1972 he continued his education, obtaining official certification as a chemical technician (Chemotechniker) at the Fachschule für Chemotechnik in Karlsruhe. In 1971 he followed D. Seebach to the Institute for Organic Chemistry at the University of Giessen, and in 1974 he engaged in a six-month research visit to the California Institute of Technology in Pasadena (USA). Albert K. Beck has been an active part of the Laboratory for Organic Chemistry at the ETH in Zürich (Switzerland) since 1977, the time of Seebach's arrival there. During his long association with the Seebach research group he has participated in essentially all of the group research themes, as evidenced by his co-authorship of ca. 90 publications.

Stefania Capone was born in 1978 in Napoli (Italy). She graduated from Università di Napoli 'Federico II' in 2002. Her PhD work in the group of R. Caputo at Università di Napoli 'Federico II' was focused on the synthesis of modified amino acids and their application in peptidomimetics synthesis. She obtained her PhD in 2006. From 2006 to date she is a postdoctoral fellow in the group of D. Seebach at ETH Zürich (Switzerland). Her general research interests comprise β-peptide chemistry, drug delivery systems, and liposome technology.

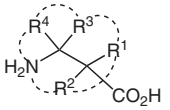
Gildas Deniau was born near Paris in 1979. He obtained his Diplôme d'Ingénieur Chimiste in 2002 from the Ecole Nationale Supérieure de Chimie de Lille. He also studied one semester at the University of Marburg (Germany) and completed his Diplomarbeit in Degussa AG (Hanau, Germany), under the supervision of H. Gröger. He then moved to the University of St Andrews to complete a PhD in the research group of D. O'Hagan, focusing on the synthesis and conformational behaviour of bioactive β-fluoroamines and, in particular, a fluorinated analogue of the neurotransmitter GABA. In 2007, he joined the group of D. Seebach for a postdoctoral stay. His research interests include peptide, fluorine, and small-ring chemistry.

Uroš Grošelj was born in 1975 in Kranj, Slovenia. He studied chemistry at the University of Ljubljana and received his BSc in 2000. He continued his studies under the supervision of J. Svete and received his PhD in 2004. His PhD work focused on the preparation of new camphor-derived heterocycles based on propenoate methodology. From 2004 he was employed as a researcher in the group of B. Stanovnik at the Faculty of Chemistry and Chemical Technology, University of Ljubljana. Currently he is a postdoctoral fellow in the group of D. Seebach at the ETH Zürich, Switzerland. His research interests encompass synthesis of heterocyclic compounds, stereoselective synthesis, chemistry of terpene enaminones, cycloadditions, and organocatalysis.

Engelbert Zass is head of the ETH Zürich Chemistry Biology Pharmacy Information Center. Trained as an organic chemist in Cologne (Diplom with E. Vogel) and at ETH Zürich (PhD with A. Eschenmoser in 1977), he specialized in chemical information, and accumulated more than 25 years experience in searching, operating and designing chemistry databases, as well as in support, training and education of users of chemical information. He has given numerous lectures and courses in Europe and the U.S.A., and published more than 50 papers on chemical information. Present activities include managing information services and user support, teaching courses at ETH Zürich, the Universities of Zürich and Berne, and design of multimedia material for chemical information instruction.

2 Why β²-Amino Acids?

There is an almost infinite number of β-amino acids (Figure 2)[5] that could become building blocks of β-peptides. Why do we show only the β²- and β³-homo-amino acid residues in Figure 1 and why did we decide to write a review article just on β²-amino acids?



- up to tetrasubstituted β-amino acids
- constitutional isomers
- chiral and nonchiral derivatives
- configurational isomers
- 5 types of cyclic β-amino acids

Figure 2

In our investigations of β-peptides we have almost exclusively kept the side chains (R in Figure 1) proteinogenic; that is, we used β³-homo-amino acids (CH_2 inserted between carbonyl and α-carbon) and β²-homo-amino acids (CH_2 inserted between α-carbon and nitrogen) as building blocks. This would guarantee that both intra- and intermolecular interactions between the side chains, or of the side chains with others molecules, are the same as they are with natural peptides. In hindsight this restriction turned out to be fortunate: there was more than enough to be discovered with the resulting β-peptides.[6] It turned out that the peptides consisting of β³-amino residues (β³hXaa) fold to a 3_{14}-helix (Figure 3, a and c). This helix was 'seen' by 2D-NMR analysis in the protic solvent methanol for β³-peptides ranging in length from 6[1] to 20 residues[7] (in aqueous solution, salt bridges[3k,8]or covalent-bond bridging[9] are required for stabilization of the 3_{14}-helix).

Even more stable was the helical conformation of a peptide consisting of *like*-2-methyl-3-amino acid residues[10] (Figure 3, b). When we started[11,12] incorporating β²-amino acid moieties (β²hXaa) into β-peptides, we were in for some surprises.

The β²-peptidic helix (Figure 3, d) is less stable than its β³ counterpart;[10,11] in spite of intense efforts, we were not able to find a secondary structure for a β²-eicosapeptide that consisted of the 20 homologated proteinogenic amino acid residues, and which had been synthesized using all our strengths (Figure 4).[3h] To put this in a positive way, β²-peptides have conformationally much more flexible backbones (than β³-peptides), a feature that is typical of the natural α-peptidic chains that fold to protein structures.

With a sequence consisting of alternating β²- and β³-homo-amino acids $(\beta^2hXaa\text{-}\beta^3hXaa)_n$ we discovered a novel type of helix (Figure 5).[10,12–14] The β²/β³-peptide does not fold to the 3_{14}-helix (Figure 3, e) but to a helix consisting of alternating 10- and 12-membered hydrogen-bonded rings, narrow and wide turns, steep and low pitches (Figure 5). Again, this helix is not as robust as the 3_{14}-helix but more flexible: depending on the chain length of the β²/β³- peptide and on the terminal protection, the folding is more or less pronounced, and there may even be a partial switch to a 3_{14}-helical conformation, as concluded from CD measurements.[15] There are two other peculiarities of the 10/12-helix: unlike all other α- and β-peptidic helices, it has no macrodipole, since the C=O bonds alternately point in opposite directions, and so, of course, do the N–H bonds (see Figure 5, a); furthermore, the surface of the helix is covered by substituents more densely on one side (see the view along the helix axis of a β²/β³-nonamer in Figure 5, c).

Inspection of the 12/10-helical structure reveals that the 10-membered hydrogen-bonded ring, that is, the β²hXaa-β³hXaa structural element, resembles a so-called β-turn in α-peptides and proteins (Figures 5 and 6, a); this led to the development of β-peptides folding to hairpin turns[16] (by choosing the right strategy, with as few as four β-amino acid residues, see Figure 6, b). Also, when we turned to investigations of 'mixed' β/α-peptides[17] (a recent focus in β-peptidic research[3o-q,16e]), incorporation of β²hXaa moieties uncovered a new type of hairpin structure, in which the actual turn section consists of a β²/α pair of residues (Figure 6, d).[16e]

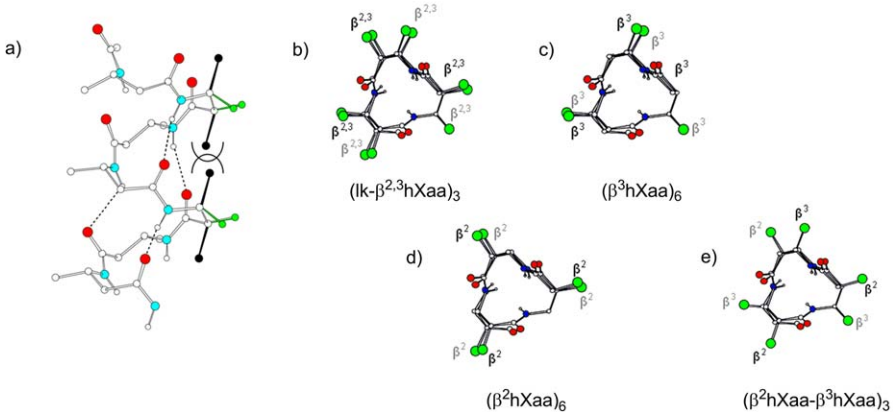


Figure 3 The 3_{14}*-helix of β-peptides*. (a) Left-handed (*M*) helix with lateral (green) and axial (black) position on the tetrahedral centers; pitch ca. 4.8 Å; macrodipole from C- to N-terminus; axial positions only for hydrogens. Distribution of the lateral substituents (green) with β²,³- (b), β³- (c) β²- (d) and β²/β³-amino acid residues. The stability of the helix decreases from (b) to (e). The β²/β³ sequence actually folds to a 10/12-helix (see Figure 5), and there is only weak evidence that it may adopt a 3_{14}-helical conformation with longer chain lengths.

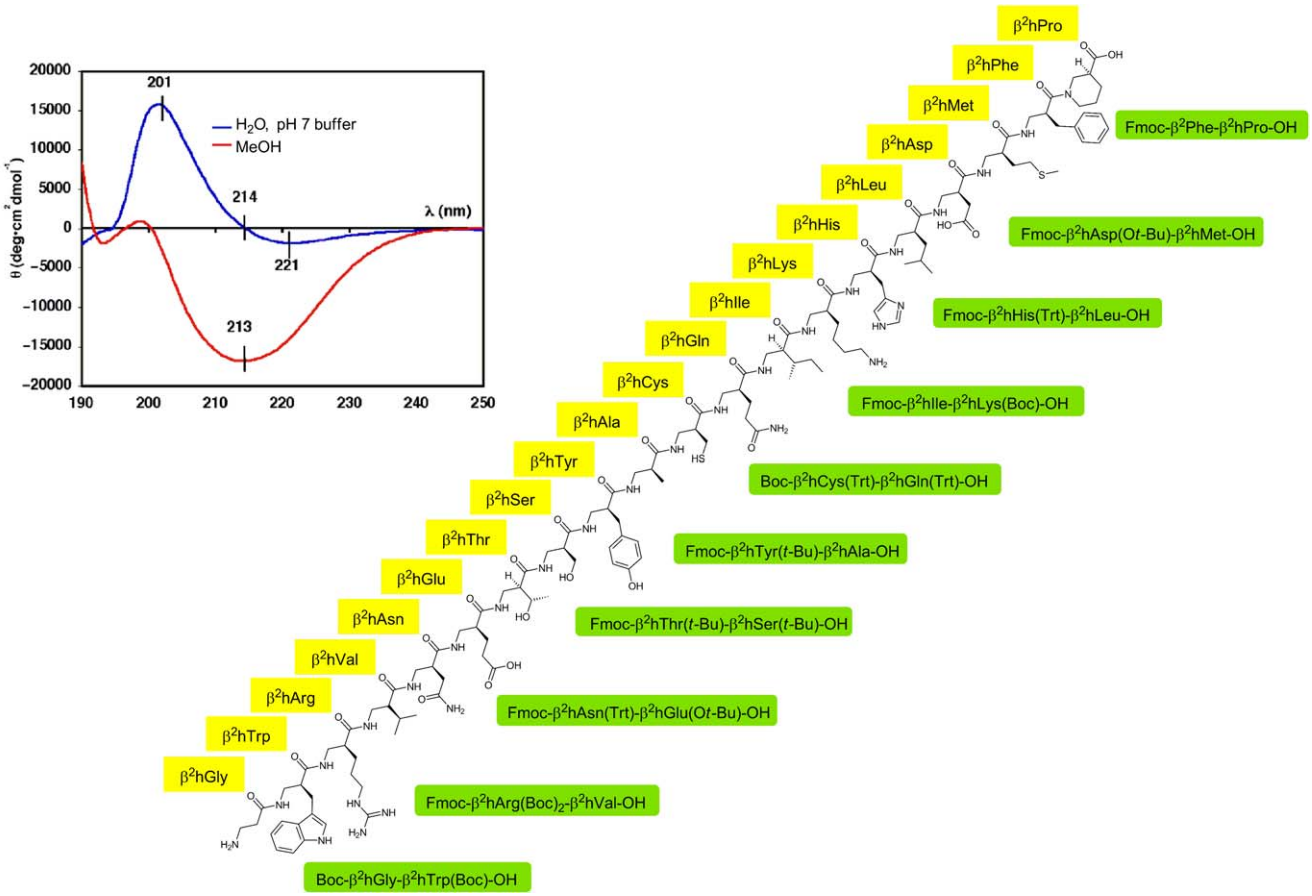


Figure 4 *β²-Eicosapeptide, consisting of the 20 homologated proteinogenic amino acids, synthesized in 159 steps.* This is one of 10^{18} possible sequences; for a rationale of synthesizing this particular peptide, see ref.[3h] The fundamentally different CD spectra in water and methanol indicate different structures in these solvents. It was not possible to find an NMR-solution structure in methanol, in spite of great efforts.

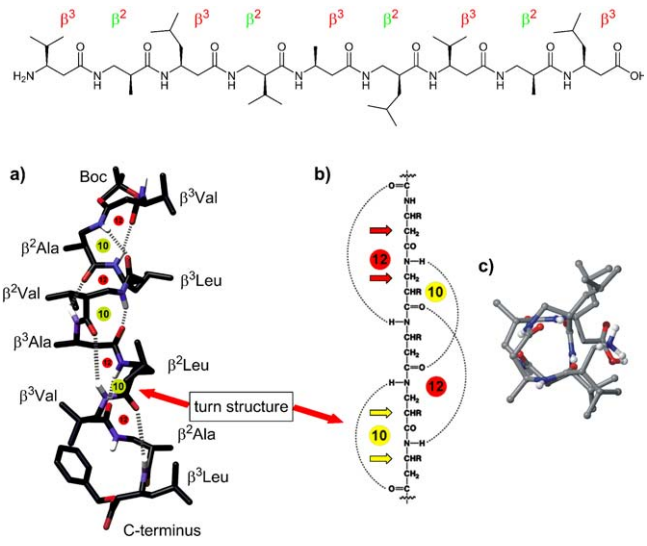


Figure 5 A right-handed (P) 10/12-helix of a β^3/β^2-*nonapeptide*. (a) Alternating 10- and 12-membered H-bonding rings; no macrodipole. (b) The 10-membered hydrogen-bonded rings form around CHR–CO–NH–CHR (β^3–β^2) moieties, in the central positions of the 12-membered hydrogen-bonded rings there are CH_2–CO–NH–CH_2 moieties; see the turn structure of the 10-membered ring and compare with Figure 6. (c) 'Uneven' distribution of substituents on the surface of the helix.

Not only in the realm of β-peptidic *structures* were β²-residues good for surprises. Of the numerous β-peptides (consisting of homologated proteinaceous amino acids) that were tested for hemolytic (*cf.* toxicity) and antibiotic activity (by N. Ryder and colleagues at Novartis[3j,18]), a β³/β²-nonapeptide was by far the most active (Figure 7, a). Since β³-peptidic analogues were inactive, the flexibility of the β³/β²-chain and, perhaps, the nonpolar character of the 10/12-helix, to which it can fold, may cause this toxic effect.

β-Peptides are proteolytically[1,17,19](and metabolically[3n,20]) stable; that is, neither amino- nor carboxy- nor endopeptidases cleave them.[21] In order to protect a given α-peptide from N- and C-terminal cleavage by the most ubiquitous exopeptidases with minimal structural alteration, a β²-residue has to be introduced at the N-terminus and a β³-residue at the C-terminus[22] (Figure 7, b); β²- and β³-amino acids are actually on their way to becoming pharmacophores.[23]

The most extensive use of β²-amino acid residues in biological investigations has, so far, taken place in open-chain and cyclic mimics of the peptide hormone somatostatin.[3n,q] The dramatic affinity increase (for *one* of the G-protein coupled somatostatin receptors, $hsst_4$) of a β-tetrapeptide, when going from a β³-β³-β³-β³ to a turn-

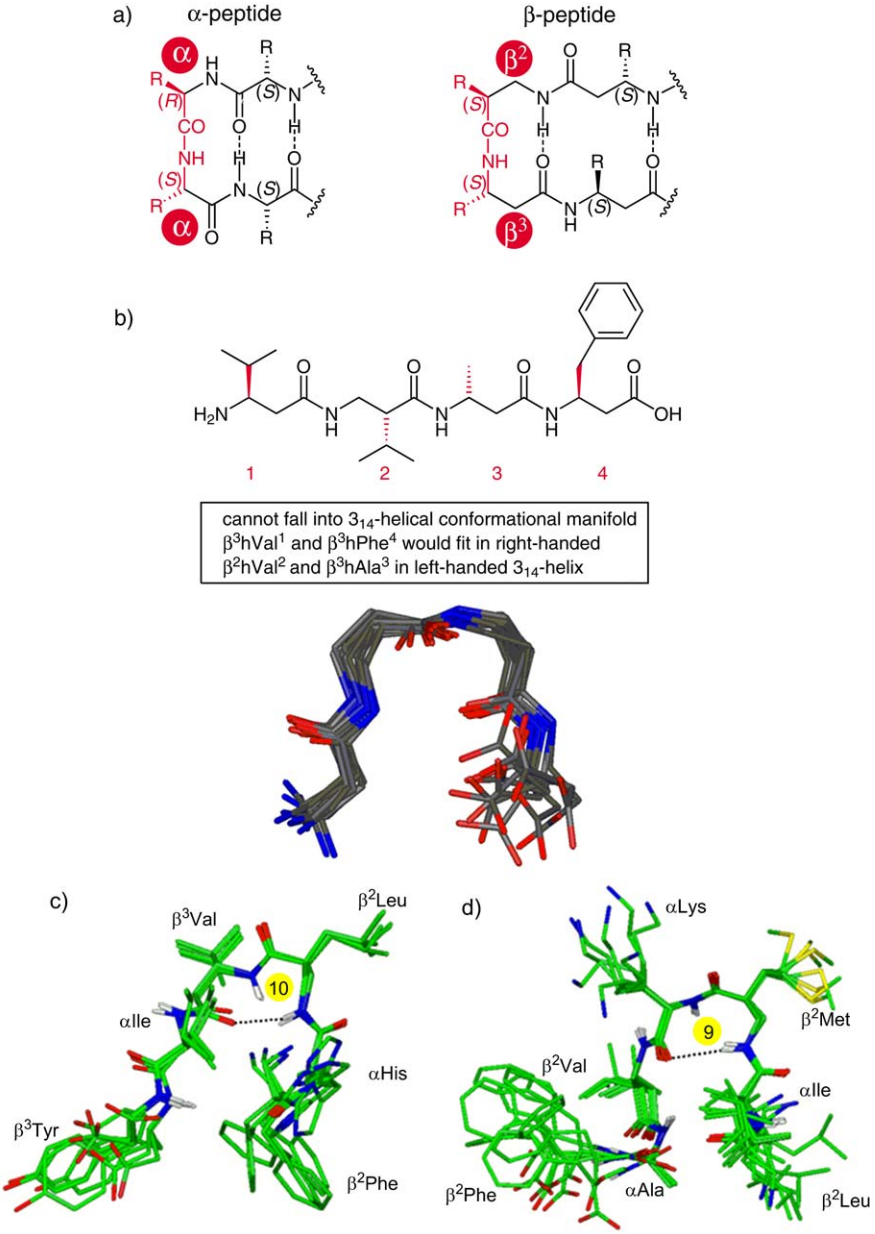


Figure 6 Hairpin turn structures of β-peptidic chains. (a) Structural similarity of an (*R*)Xaa-(*S*)Xaa 'β-turn' and an (*S*)β³hXaa-(*S*)β²hXaa turn; the RCH–CO–NH–CHR parts are actually superimposable (*cf.* the mimicking in Figure 7, c). (b) A β-tetrapeptide that folds to an especially stable turn. (c) and (d) Turns of mixed β/α-peptides with β²-amino acid residues in 'strategic' positions; these turn structures are minimally stabilized by hydrogen bonding, they result, rather, from preferred backbone conformations of the building blocks.

forming β³-β²-β³-β³ structure,[17,24] is demonstrated by the data given in Figure 7, c.

In conclusion, it appears appropriate to make the statement that the β²-amino acid residues play a special role in the chemistry and biology of β-peptides consisting of homologated proteinogenic α-amino acids. On the other hand, it is a fact that β²-, in contrast to β³-amino acids (Figure 8),[5a,b,25] *cannot* be prepared stereospecifically by a standard synthetic methodology from the corresponding readily available α-amino acids (see below, section 5.1). Furthermore, derivatives of β²-amino acids can undergo racemization or epimerization, while those of β³-amino acids cannot.

Thus, the β²-amino acids are of great interest for β-peptide structural design (and for biological and biomedical applications), and they are a challenge to prepare enantioselectively, good reasons to devote this account to preparative methods for making them.

3 Literature Search

Although we have followed the literature on β-amino acids for more than a decade, we wanted to make sure not to miss any principal method of building the β²-amino acid skeleton enantioselectively, keeping in mind that we eventually needed to have the orthogonal functionality

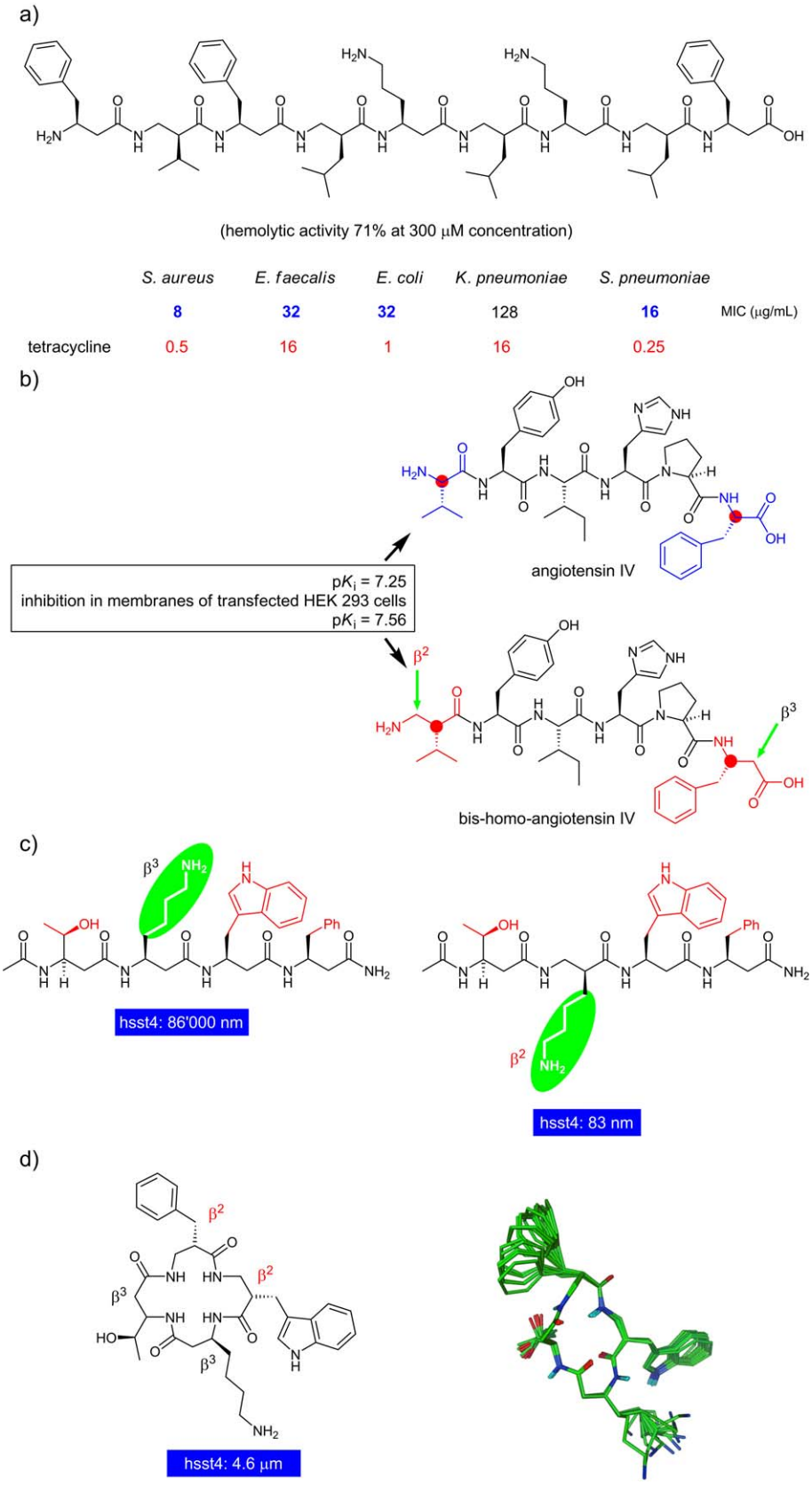


Figure 7 Peptides with β^2-*homo-amino acid residues in 'strategic' positions.* (a) A β^3/β^2-peptide with cytotoxic properties. (b) Protection of the termini of angiotensin IV against attack by exopeptidases by terminal homologation; at the N-terminus a β^2-homo-amino acid is required; the indicated activity is unchanged (*cf.* identical structure from red dot to red dot), but the β^2-α-α-α-β^3-peptide is proteolytically stable, whereas angiotensin IV is rapidly degraded. (c) The β^2-β^3-motif in hairpin turns allows for mimicking α-peptidic turns (*cf.* Figure 6); the all-β^3-tetrapeptide and the β^3-β^2-β^3-β^3-isomer differ by a factor of 10^3 in their affinity for the human somatostatin receptor hsst4. (d) A cyclic (β^2-β^2-β^3-β^3) peptide has micromolar affinity for this receptor.[3q]

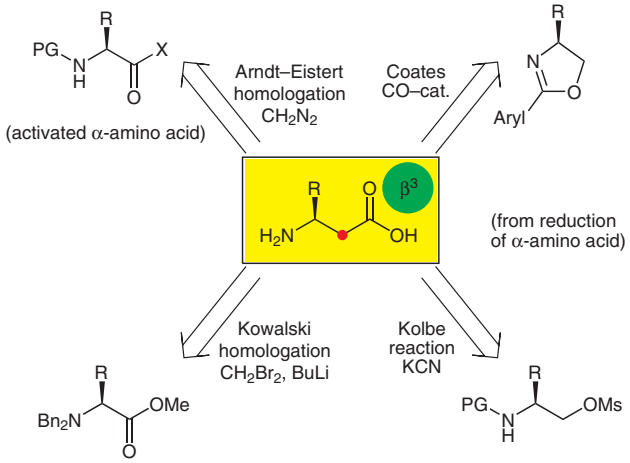


Figure 8 Homologation of α-amino acids to β³-*amino acids*. The Arndt–Eistert methodology is superior in effectiveness: two steps from a commercial Boc-, Cbz-, or Fmoc-protected α-amino acid with orthogonal protection of side-chain functionalities; diazomethane technology is now offered by companies, and the Wolff rearrangement is induced[25a] by catalytic CF_3CO_2Ag (4 mol%) in the presence of a tiny amount of SiO_2. The Kowalski homologation requires BuLi-stable protection on nitrogen and on side-chain functional groups,[25b] and the total number of steps leading to derivatives PG¹-β³hXaa(PG²)-OH used for peptide coupling is much larger. The new Coates[25c] and the old Kolbe homologation require a primary reduction of the α-amino acid to an amino alcohol; again, the number of steps leading from commercial starting materials to the building blocks of solid-phase or solution peptide coupling is greater than in the Arndt–Eistert homologation. To the best of our knowledge, all appropriately protected derivatives with proteinogenic side chains, with the exception of β³hHis, β³hCys and β³hSec,[25d,e] are now commercially available (we thank Fluka AG, CH-Buchs for discount prices). See also the discussion in the conclusion (Section 11).

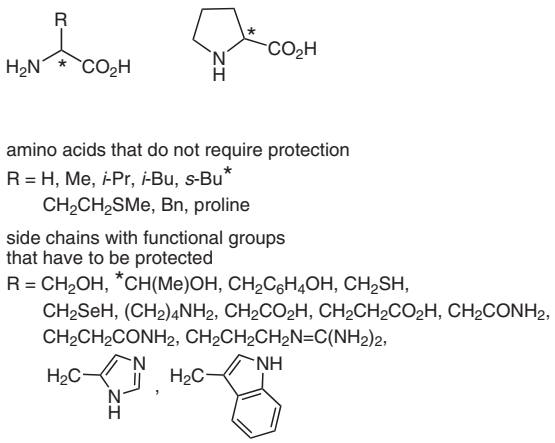


Figure 9

pattern for peptide assembly: a free carboxylic acid group, an Fmoc-, Boc- or Cbz-protected amino group and acid- or hydrogenolysis-labile protection of side-chain functional groups, which more than half of the proteinogenic amino acids actually have: hydroxy (Ser, Thr, Tyr), thiol (Cys), selenol (Sec), amino (Lys), heterocyclic (His, Trp), carboxyl (Asp, Glu), carboxamido (Asn, Gln), and guanidino (Arg) groups (Figure 9). An internal general search in a database system resulted in a shocking number of hits when we asked for β²-amino acids. What we wanted were those publications in which 'reasonable' precursors for the building blocks required in solution and solid-phase peptide synthesis are described (Figure 10).[26]

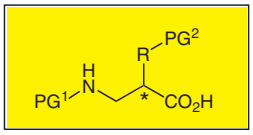
This was a challenging task even for the specialist in information retrieval. There were many pitfalls that had to be avoided, and weaknesses in the various databases and of the search strategies became evident. The details are described in section 10 of this article, and the lessons we learned will be of benefit for future searches of this type, both in our chemistry department and in others.

Eventually, we arrived at a trustworthy body of about 250 relevant publications, in which the preparations of non-racemic β²-amino acid derivatives or 'reasonable' precursors thereof were described. Without the specialized information-retrieval tool, we would have stood in front of a formidable mountain or have been totally lost. Still, we cannot be completely sure of not having missed a line of work in the literature on this subject – we are sorry if we did. The choice of particular examples to demonstrate a synthetic methodology for preparing β²-amino acids is, of course, subjective, and we apologize for that.

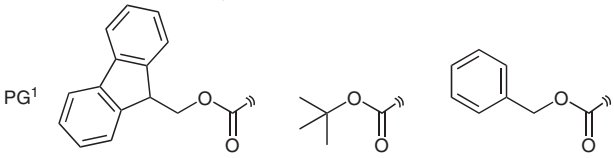
4 Retrosynthetic Analysis

When looking at the entire body of literature retrieved from the databases, it is, not surprisingly, evident that there are synthetic routes, leading to β²-amino acid derivatives, in which each and every bond of the parent skeleton is being formed (Figure 11, top). The bond-forming steps can be divided into two main categories: those in which bonds at the chirality center are created, and those in which bonds in the periphery around this center are generated. Since enantiopure β²-amino acids are the goal, the first category is going to be central to our discussion. We order the examples for the following chapters in four groups, namely stereoselective formation of (**a**) the C(2)–C(3) bond, (**b**) the C(2)–R bond, (**c**) the C(2)–H bond, and (**d**) the C(1)–C(2) bond. The second category of bond-forming steps includes the N–H, N–C(3), C(3)–H, C(1)–O or C(1)=O, and C(1′)–R′ bonds. Finally, there is a third category of bond formation: elaboration of the side chains (R, CH_2R'), functional-group interconversion or protective-group manipulations *in* the side chain, on nitrogen or on C(1) – not unimportant if we keep in mind that we eventually need to establish orthogonal protection of the amino group and the side-chain functional groups, and have a free carboxylic acid group of the β²-amino acids, in order to be able to carry out peptide syntheses.

In Figure 11 the types of synthetic operations are listed, by which the chirality center of β²-amino acids has been generated stereoselectively with formation of one of the strategic bonds (**a**)–(**d**). For bond (**a**) a des-amino acid, carrying the appropriate side chain or a precursor group thereof, is the starting material. For bond (**b**) the precursor of the side-chain R group is either an electrophilic (R–X)



building blocks for peptide synthesis

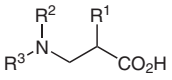


Fmoc Boc Cbz

PG^2 acid-labile for Fmoc solid-phase synthesis
or hydrogenolytically labile for Boc strategy

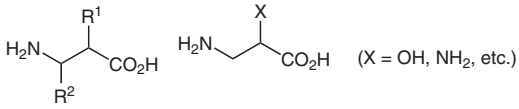
NOT INCLUDED

- β^2-amino acid derivatives which cannot be readily converted into the building blocks required for peptide synthesis, such as



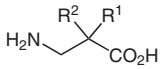
R^2, R^3 = alkyl
noncleavable aryl
hard to cleave SO_2-aryl

- preparation of racemic β^2-amino acids, unless resolution is reported (*cf.* ref. 5d and Section 9)
- β^2-amino acids with "exotic" side chains, such as heterocycles, carbohydrates (see ref. 2d and 31)
- $\beta^{2,3}$-amino acids and α-heterosubstituted β-amino acids



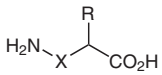
(X = OH, NH_2, etc.)

- $\beta^{2,2}$-amino acids such as β^2hAib (see ref. 3a)



R^1, $R^2 \neq H$

- 3-oxa- and 3-aza-β^2-amino acids (see ref. 2d, 26)



X = O, NH, NR

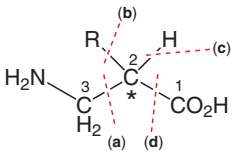
- extensive patent literature, mostly describing applications of the methods covered by journal literature
- discussions of the mechanisms or stereochemical courses of reactions

Figure 10

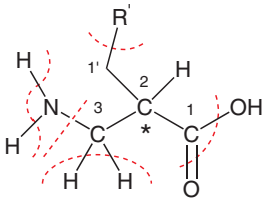
or a nucleophilic (R–metal) reagent. For bond (**c**) the *substrates* contain the entire skeleton of the β^2-amino acid, including the appropriate functionality patterns and a uniform *E*- or *Z*-configuration of their enolate or acrylate double bonds. For bond (**d**), the rarest case, a nucleophilic addition of, or a substitution by, a moiety, which eventually acts as precursor to the CO_2H group, is the key step.

With respect to these synthetic possibilities there are two fundamentally different types of β^2-amino acids: those in which the R group is a hydrocarbon residue (Figure 9, top), and those which contain a functional group in the side chain R (Figure 9, bottom); methionine is a 'borderline case'. β^2-Amino acids of the first type are far more easily prepared, because there is no reactivity conflict with the reagents employed in the construction of the strategic bonds (**a**)–(**d**): enolate generation with strong base or by Michael addition with in situ enolate trapping is possible; the side-chain R group can be introduced with R–X or with R–metal reagents, there is no problem with hydrogenation or oxidation steps (*cf.* the list of reactions in Figure 11). On the other hand, with functionalized side chains R there is not simply need for selective protection, but there may be bothersome neighboring-group effects, β-eliminations of leaving groups, competing reactivities, or catalyst poisoning (*cf.* Figure 9, bottom, and Figure 11).

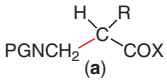
When comparing different routes, we also must take into account the number and the nature of reaction steps re-



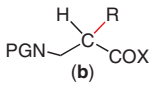
strategic bonds (category 1)



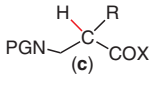
peripheral bonds (category 2)



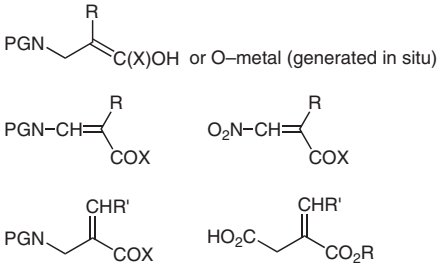
- aminomethylation of a desamino acid derivative (Mannich reaction)
- synthetically equivalent processes such as:
  - ▶ hydroxymethylation of desamino acid derivatives and OH/NH_2 substitution
  - ▶ alkylation with $RO_2C–CH_2X$ and Curtius degradation
  - ▶ carbene insertion into a $PGNCH_2$–H bond

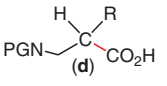


- alkylation or hydroxyalkylation with R–X or R'–CHO, respectively, of a 3-aminopropanoic acid enolate R = side chain of amino acid
- synthetically equivalent *umpolung*: $O_2N–CH=CH–CO_2R$ + R–metal (R = side chain of amino acid)



- the source of hydrogen may be:
  $H^{\oplus}$ (protonation of an enolate)
  H_2 (hydrogenation)
  $H^{\bullet}$ (radical reaction)
- synthetically equivalent precursors may be:





- a substituent is introduced, which is eventually converted into a CO_2H group
- precursors:

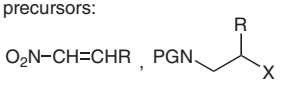


Figure 11

quired (i) to obtain the reactants and (ii) to arrive at the final target peptide building block (Figure 10, top), after the strategic bond has been formed. Thus, when the chirality center is created with formation of the C–H bond (**c**), the precursors are all acrylate derivatives, which have to be prepared by aldol, nitroaldol, Claisen, Knoevenagel, or Stobbe condensations, by Baylis-Hillman or Heck reactions, or by additions to acetylenes. In turn, the starting materials for these preparations are, again, often desamino acids (R–CH_2–CO_2H), α-keto carboxylic acids (R–CO–CO_2H), or synthetic equivalents thereof.

5 β²-Amino Acids by Formation of the C(2)–C(3) Bond

There are several synthetically equivalent transformations by which this bond can be formed, whereby the H_2N–CH_2 synthon can be conceived of being realized in the form of a nucleophile (d^1-reactivity),[27] an electrophile (a^1-reactivity) or a carbenophile (Figure 12). The normal reactivity combination a^1/d^2 (Mannich transform)[28] is the most obvious.

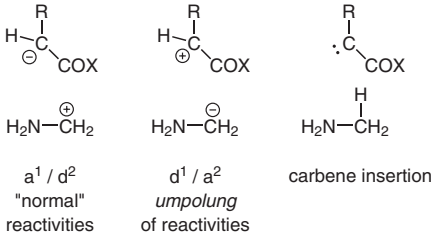
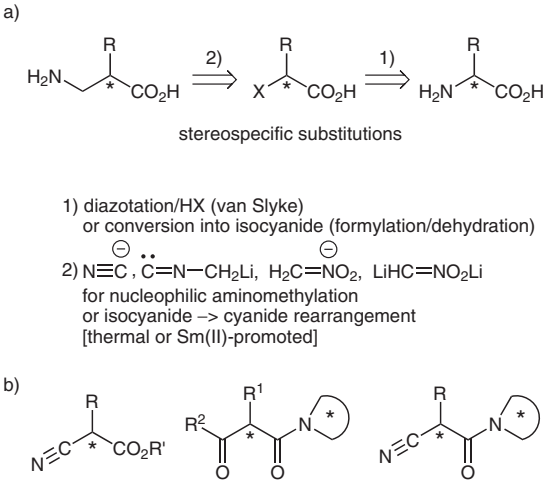


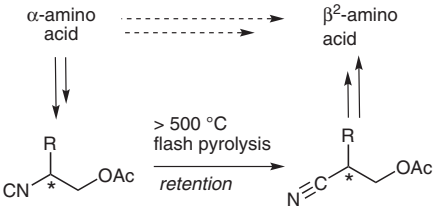
Figure 12

5.1 Is There a Stereospecific Route from α-Amino Acids?

The d^1/a^2 combination with *umpolung* of both reactants, on the other hand, is the most attractive transformation, since it could provide a stereospecific conversion of α- into β²-amino acids. Thus, the classical method of replacing the amino group of amino acids by OH or a halogen atom, most commonly Br, with retention of configuration, and a nucleophilic aminomethylation[27,29] with inversion of configuration would provide a β²-amino acid, as outlined (Scheme 1, a). Experiments along these lines have failed so far. It is, for instance, possible to convert α-halo esters into α-cyano esters,[30] but these are configurationally labile.[31] In certain derivatives of chiral heterocycles, α-substituted β-keto-carbonyl moieties are known to be configurationally stable,[32] but it appears that this is not true for corresponding cyano derivatives[33] (Scheme 1, b), otherwise analogous achiral heterocycles could be employed for the nucleophilic substitution process in Scheme 1, a (2). An intriguing reaction is the pyrolytic[34] or samarium-mediated[33a] rearrangement of isocyanides to cyanides with retention of configuration, through which α-amino acids have been stereospecifically converted into β²-amino acids[34b] (Scheme 2). The lability of the chirality center in substituted cyano acetates (malonitriles) prevents the direct application of this method to α-amino acid derived isocyanides and the high temperatures in the flash pyrolysis are prohibitive for practical purposes.

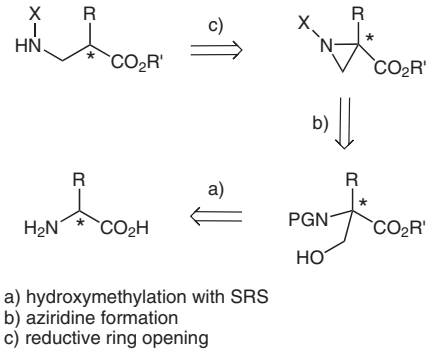


Scheme 1



Scheme 2

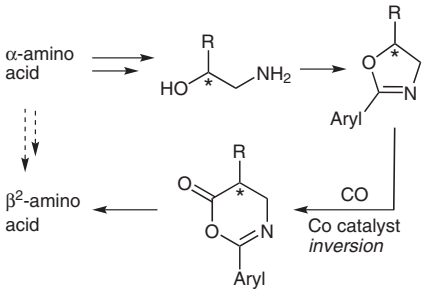
Another, more speculative, route for insertion of a CH_2 group between the nitrogen and the α-carbon of an amino acid, without racemization, might lead through intermediate aziridine derivatives[35] as outlined in Scheme 3. In this case the first step would be an electrophilic hydroxymethylation with self-regeneration of the chirality center (SRS).[36]



Scheme 3

Finally, the cobalt-catalysed insertion of carbon monoxide into the C–O bond of oxazolines (*cf.* Figure 8) could be elaborated to become an overall homologation of an α-amino to a β²-amino acid. Stereospecific conversion into

the α-hydroxy carboxylic acid amide, reduction to an amino alcohol[35g] and condensation with an aromatic carboxylic acid will provide the substrate for CO insertion, which has been shown[25c] to occur with inversion of configuration, see Scheme 4. The strategic bond formed here is actually bond (**d**)!



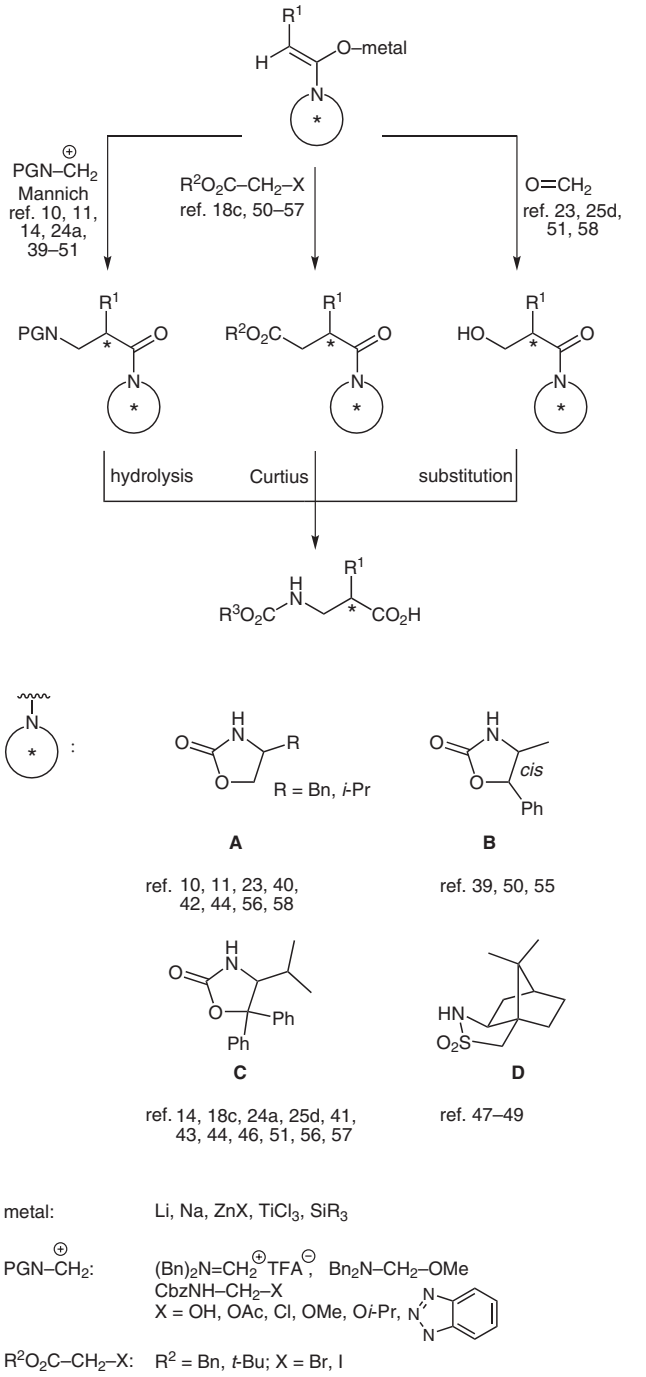
Scheme 4

At present, none of these transformations of α-amino acids seems to be of practical value, so that there is no way around using chiral auxiliaries, reagents, or catalysts for the preparation of the β²-amino acid building blocks for peptide synthesis.

5.2 Chiral Auxiliaries and Catalysts for C(2)–C(3) Bond Formation

β-Amino acid derivatives may be considered Mannich bases built of a carboxylic acid, formaldehyde, and ammonia. In fact, in 1922 Mannich made the following statement about β-amino acids: 'Im Gegensatz zu den wegen ihrer biologischen Bedeutung ausgiebig studierten α-Aminosäuren ist die Klasse der β-Aminosäuren weit weniger gründlich bearbeitet worden.'[37] In rough translation, Mannich was stating that in contrast to the α-amino acids, which have been extensively studied because of their biological importance, β-amino acids have been much less thoroughly investigated.

An overall enantioselective preparation of β-amino acids with stereoselective formation of the strategic bond (**a**), the 'Mannich C–C bond', can be envisioned by having (i) a chirality center in the group R, (ii) a removable chiral substituent on nitrogen, or (iii) a chiral auxiliary moiety on the carbonyl group. The first type of induction[38] is not of general importance since of the proteinogenic amino acids, only isoleucine and threonine have a stereocenter in the side chain. Amino groups with chiral substituents are employed directly (see below, organocatalysis) or indirectly [when their lithium amides are added to α-methylene esters, i.e. acrylates that can be prepared by aldol condensation between an ester and formaldehyde or by methylenation of an α-keto ester; in this case bonds (**b**) or (**c**) are the strategic bonds, see sections 6 and 7]. In the most commonly used method of stereoselective formation of bond (**a**), a chiral auxiliary is attached to the carbonyl carbon of the carboxylic acid and the aminomethylation is



Scheme 5

achieved in three synthetically equivalent ways[10,11,14,18c,23,24a,25d,39–58] as outlined in Scheme 5.

The starting material, generally a des-amino acid, may be commercially available, or may be prepared by reductive deamination of an α-amino acid, either directly (with H_2NOSO_3H[43,59] or with SmI_2[60]) or by first replacing NH_2 by Br (HNO_2/HBr or NOBr) and then removing Br with metals or hypophosphorous acid.[61] A chiral auxiliary is attached by acylation of a classical Evans oxazolidinone **A** or **B**, of the modified oxazolidinone DIOZ **C**, or of Oppolzer's sultam **D** (Scheme 5). The corresponding eno-

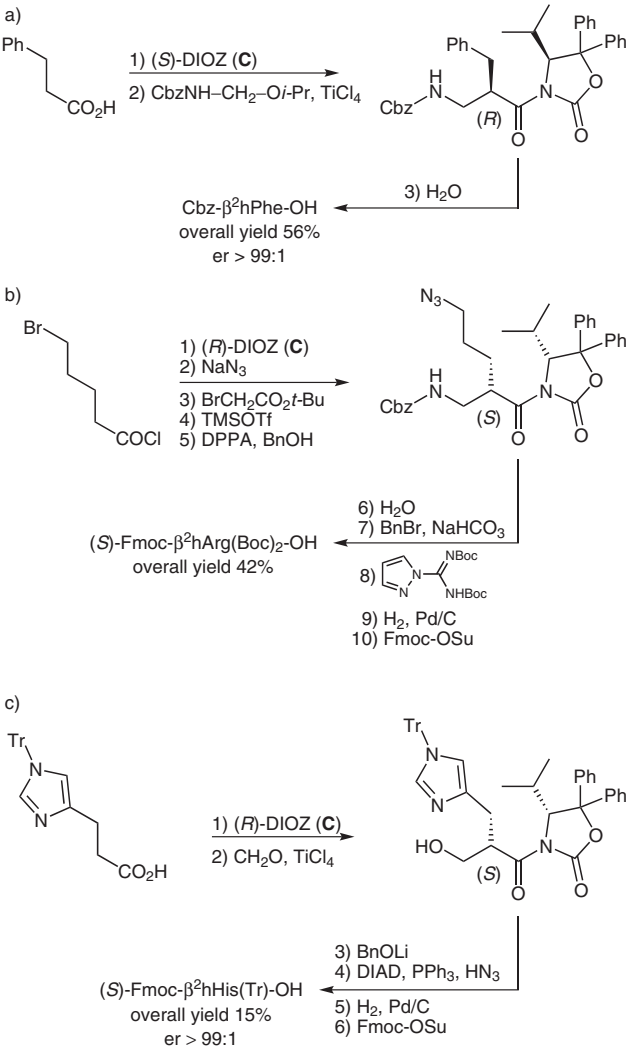
lates are generated by deprotonation. Alternatively, a sultam carrying an α-bromoacyl group is treated with zinc to produce a zinc enolate (Reformatsky reagent). There are three synthetically equivalent diastereoselective reactions of the chiral enolates, creating bond (**a**): (i) a 'real' Mannich reaction with an electrophilic aminomethylating compound (X–CH_2–NPG),[10,11,14,24a,39–51] (ii) the alkoxycarbonylmethylation (X–CH_2–CO_2R)[18c,50–57] with subsequent Curtius degradation, and (iii) the hydroxymethylation (CH_2O)[23,25d,51,58] followed by substitution of the OH by an NH_2 group (β-hydroxy acids[62] of any other origin may, of course, be employed as well).[63] Since all auxiliaries **A**–**D** are available in both enantiomeric forms, (*R*)- and (*S*)-β²-amino acids are accessible by these methods.

The most frequently used auxiliaries are the oxazolidinones **A**–**C**. Although there are claims of 'scalable' syntheses of β²-amino acids, using the sultam auxiliary **D** (compare β²hTrp in references 56 and 49), this alternative has yet to be applied with advantage (fewer steps, milder conditions, cheaper and safer[64] reagents, etc.) to the *more difficult*, side-chain-functionalized derivatives. In our work on β-peptides the diphenyl-substituted oxazolidinone **C** was used to prepare 16 of the β²-amino acids with proteinogenic side chains by one of the three synthetically equivalent routes shown in Scheme 5. For an example of each, see Scheme 6 and for the β²-eicosapeptide[3h] containing all of them, see Figure 4.

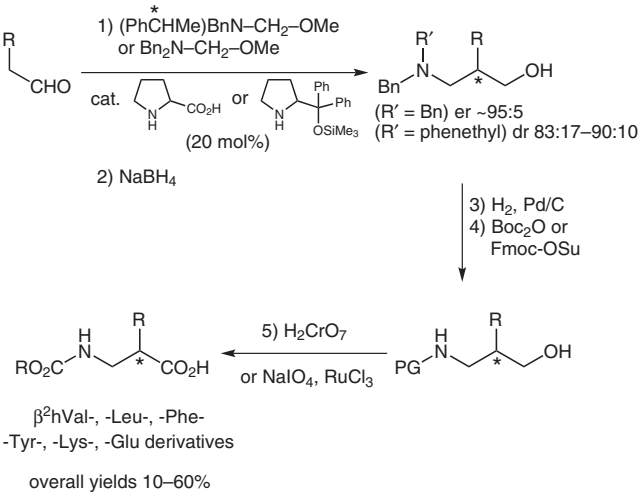
The aminomethylating agent now preferred by us[45] is Cbz–NH–CH_2–O*i*-Pr, the preparation and application of which for multigram-scale access to Cbz-β²hPhe-OH is described in recent *Organic Syntheses* procedures[46] (Scheme 6, a). The Curtius route was elaborated, for instance, in the preparation of Fmoc-β²hArg(Boc)$_2$-OH (Scheme 6, b).[18c] After testing several alternative sequences, Fmoc-β²hHis(Tr)-OH was obtained through the hydroxymethylated intermediate (Scheme 6, c).[25d] Other problematic cases, such as Fmoc-β²hAsn(Tr)-OH, were 'solved' along the same lines.[51,57] The superiority of the DIOZ ligand **C** is given (i) by its preparation from valine and PhMgBr (instead of complex hydride for **A**),[65] (ii) by the high diastereoselectivities with which its acyl derivatives react, (iii) by better regioselectivities between the two C=O groups in the acylated derivatives,[41] and (iv) by a high crystallization tendency of all DIOZ derivatives,[66] including the auxiliary itself (readily recovered, mp 254 °C).[65]

The Gellman group has chosen an *organocatalytic*[67,68] step to create the strategic bond (**a**) of β²-amino acids for their investigations of β-peptides[2b,3o] (Scheme 7).

Diphenylprolinol trimethylsilyl ether[67a] or proline[67b] were used as catalysts. It turned out that, in the proline catalysis, a chiral aminomethylating reagent gave the best results ('double stereodifferentiation', (*S*)-proline and (*S*)-benzyl(phenethyl)amine producing (*S*)-β²-amino acid derivatives).[67b] The sequence of steps starts with a Mannich reaction of an aldehyde (a *reduced* des-amino acid) and



Scheme 6

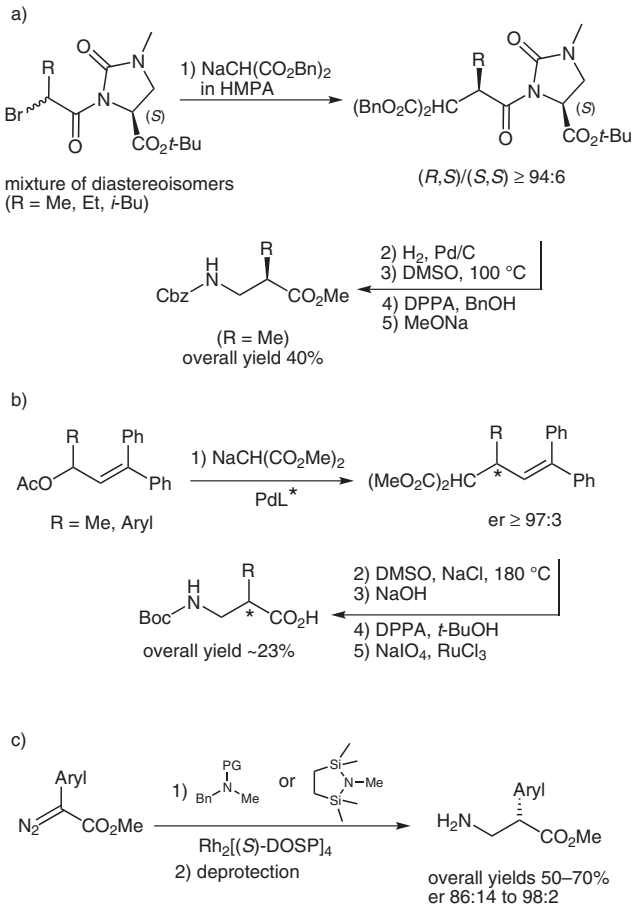


Scheme 7

involves a sodium borohydride reduction as well as an oxidation of a primary alcohol to a carboxylic acid. Of the β²-amino acids with functionalized side chains, Fmoc-

β²hGlu(*t*-Bu)-OH, -Tyr(*t*-Bu)-OH, and -Lys(Boc)$_2$-OH were reported. The chiral benzyl(phenethyl)amine is cheap enough to be sacrificed in the overall process, just like in other cases discussed below (see, for instance, Scheme 11), an event for which Mislow proposed the term *immolative asymmetric synthesis* in his famous textbook *Einführung in die Stereochemie* (1967) (Introduction to Stereochemistry, 1965).

The role of the electrophile N-CH_2^+ and the nucleophile $^-$CHR(COX) in the Mannich transformations are reversed (*umpolung*, *cf.* Figure 12) in the elaborations of the β²-amino acid skeleton shown in Scheme 8. In the first two transformations, (a) and (b),[52–54] malonate $(RO_2C)_2CH^-$ becomes synthetically equivalent to an aminomethyl anion (N-CH_2^-) and electrophilic character is imposed upon the α-carbonyl carbon atom. In the third case (c) a carbene inserts into an NCH_2–H bond.[69] The imidazolidinone chiral auxiliary shown in Scheme 8 a (a 2,3-diaminopropanoic acid derivative) causes the α-bromo carbonyl compound of *R*,*S*-configuration to undergo Br/CH$(CO_2Bn)_2$ nucleophilic substitution (with inversion) faster than the *S*,*S*-diastereoisomer; under appropriate conditions, the two diastereomeric starting materials equilibrate by epimerization at the Br-substituted carbon, so that a 1:1 mixture gives rise to an 80% yield of *R*,*S*-product (*cf.* the discussion in section 5.1 and Scheme 1); the subsequent conversion of the malonate unit to CbzNH-CH_2 is straightforward.[54] In the second equation (b) of Scheme 8, an application of the enantioselective palladium-catalyzed allylation to the preparation of a β²-amino acid is shown.[52,53] The construction principle for β²-homo-arylglycines by carbene insertion, invented by Huw Davies[69] (Scheme 8, c), comes closest to that of a Mannich reaction. While chemically and mechanistically intriguing, the reactions in Scheme 8 do not appear to lend themselves to a more general access to the kind of β²-amino acid derivatives required for β-peptide synthesis.



Scheme 8

6 β²-Amino Acids by Formation of the C(2)–R Bond

By the classical Mannich transform, discussed in the previous section, the side chain R is part of a carboxylic acid derivative ('des-amino' acid), the enolate of which is aminomethylated; natural (proteinogenic), as well as unnatural and nonproteinogenic side chains thus become part of the resulting β²-amino acid. In contrast, the side chain is attached to a 3-amino acid derivative by a, likewise classical, enolate alkylation with RX (an electrophile) when the strategic bond (**b**) is formed. In this case, the amino group must be protected in such a way that it does not become a leaving group[70] at the enolate stage[71] (Mannich bases are, after all, precursors to α,β-unsaturated carbonyl compounds!). As with the Mannich reaction, there are several routes with *umpolung* of reactivity, in which the side chain is introduced with R–metal (a nucleophile) that adds to an enolate cation equivalent (a²-reactivity,[27] see section 6.2). With functionalized side chains R, the functional group has to be protected to be compatible either with an alkylating site (C–X) or with an organometallic center (C–metal) in the same molecule.

6.1 α-Alkylations of Chiral Enolates Derived from β-Aminopropanoic Acid

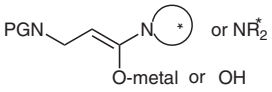
The most commonly used derivatives for enolate generation are, again, *N*-acyloxazolidinones or analogues thereof – see the auxiliary column in Table 1 and the corresponding references.[5e,25d,44,72–84]

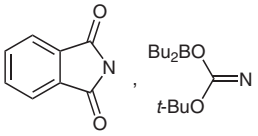
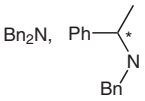
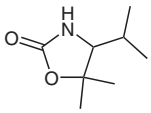
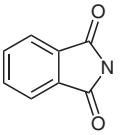
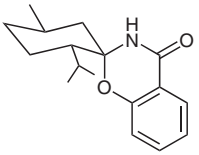
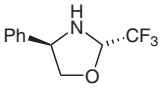
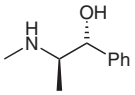
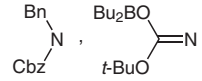
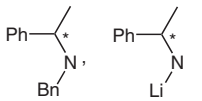
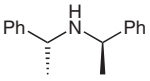
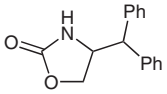
Besides the free NH_2 (entry 7) and benzylated amino groups (entries 1, 3, 6, 8) there are deprotonated carbamoyl groups (entries 2, 8), as well as phthalimido (entries 2, 5) and imido groups (entry 4); in two cases (entries 9, 10) the amino group is a 'hidden' functionality on the corresponding enolate ($CO_2R \rightarrow NH_2$ or $CH{=}CH_2 \rightarrow CO_2H \rightarrow NH_2$). In all but one case, the enolate is generated with base. Davies et al. (entry 3) use an in situ enolate-trapping[85] procedure, in which Bn_2NLi, (PhMeCH*)BnNLi or $(PhMeCH^*)_2NLi$ (*cf.* entry 8) was added to an acryloyl oxazolidinone with enolate formation.[86] Note that in this and other cases (entries 3, 8) there is a 'double stereodifferentiation', with a chiral auxiliary

group on the carbonyl carbon and a chiral alkylamino group in the β-position, which must 'match'[87] for optimal results, *cf.* immolation and Scheme 7, above. Other chiral (heterocyclic) compounds derived from 3-aminopropanoic acid,[82d,88–91] that have been used for enolate generation and preparation of β²-amino acid derivatives, are shown in Scheme 9.

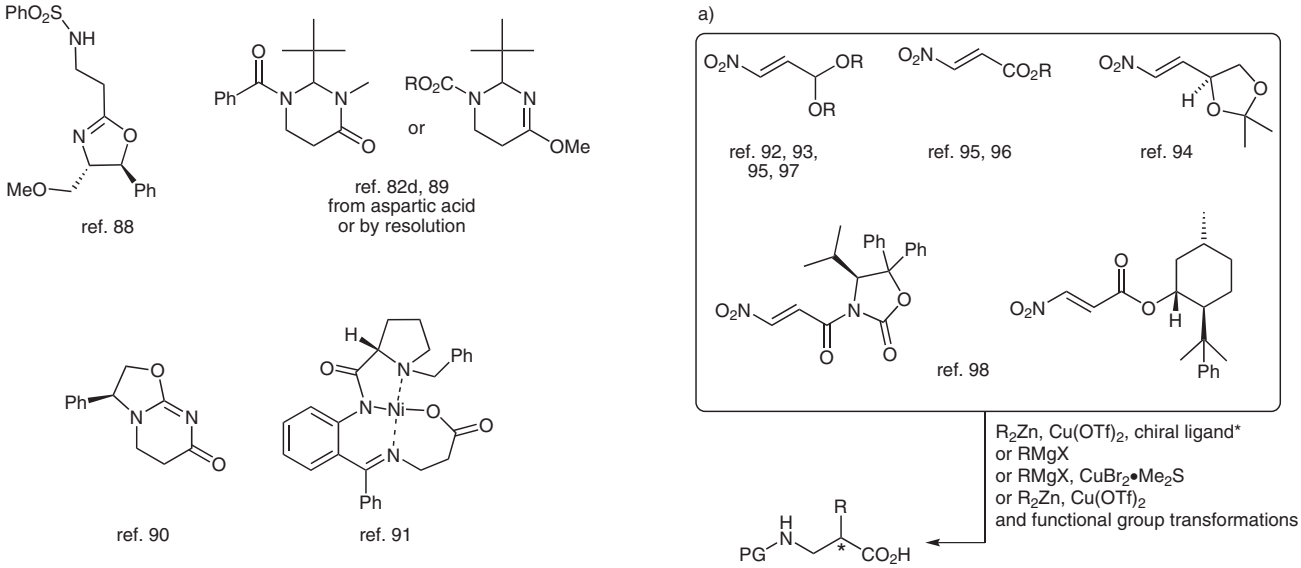
As can be concluded by inspection of the β²hXaa column in Table 1, 'simple' electrophiles (R–CH_2–X, CH_2O, MeCHO, RO_2C–CH_2–X) are used for enolate alkylations and hydroxyalkylations; of course, many nonproteinogen-

Table 1 Chiral Enolates Derived from 3-Aminopropanoic Acid for Alkylations and Hydroxyalkylations with Formation of the Strategic Bond (**b**)[a,b]



Entry	PGN	Auxiliary	β²hXaa	Ref.[c]
1		**A**, R = Bn	β²hAsp	74
2		**C**	β²hSer β²hCys β²hThr	25d, 44, 75
3			β²hAla β²hPhe β²hThr	5e, 76
4	$Ph_2C{=}N$ $(MeS)_2C{=}N$	**D**	β²hAla β²hLeu β²hPhe	77, 78
5			β²hThr	79
6	Bn_2N		β²hAla β²hPhe β²hVal β²hLeu	80
7	H_2N		β²hAla	81
8	 		β²hAla β²hPhe	72, 82
9	RO_2C/Curtius degradation (*cf.* the Curtius route in Scheme 5)	 **A**, R = Bn	β²hAla β²hPhe β²hSer β²hAsp	73 83
10	$H_2C{=}CH/NaIO_4$–$RuCl_3$ then Curtius degradation (*cf.* Scheme 8, b)	**B**	β²hAsp	84

[a] The metal can be Li, Na, BR_2.
[b] For specification of **A**–**D** see Scheme 5.
[c] There may be one or more than one of the defined amino acids described in one of the references.



Scheme 9

ic side chains of this type were introduced (such as primary alkyl, allylic, and benzylic substituents R, not shown here); the same is true of the reactions of the 3-aminopropanoic acid derivatives shown in Scheme 9. Furthermore, there are auxiliaries (entries 7, 8 in Table 1) and heterocycles (hydropyrimidinones in Scheme 9) that are difficult to cleave. Whenever an amide group CO–NH_2, CO–NHMe, CO–N(alkyl)$_2$ has to be hydrolyzed to produce the desired free carboxylic acid, rather harsh acidic (or basic) conditions are required, which may lead to racemizations, or may be otherwise incompatible with other functional groups in the molecule.

6.2 C(2)–R Bond Formation by Nucleophilic Addition and Substitution

The *umpolung* of enolate alkylation of a 3-aminopropanoic acid moiety can be accomplished by nucleophilic addition to a 3-nitroacrylate or its synthetic equivalent (Scheme 10).[92–99]

The nitro group determines the regioselectivity of addition.[100] With the achiral nitroacrylate and nitroacrolein acetals, enantioselective additions of dialkylzinc reagents in the presence of catalytic amounts of copper triflate and a chiral ligand are used. With the chiral precursors (acetonide, acryloyloxazolidinone, phenylmenthol ester) shown (Scheme 10, a), diastereoselective additions of Grignard and zinc reagents occur. After more or less simple functional-group manipulations, β^2-amino acids are obtained. So far, the reactions have been carried out mainly with dialkylzinc reagents. Considering the fact that organozinc compounds may contain functional groups, this approach to β^2-amino acids has the potential of becoming widely applicable, if not in large-scale production (low-molecular-weight nitro compounds and pyrophoric dialkyl zinc compounds!), at least for laboratory use. In Scheme 10 b, another enantioselectively catalyzed nu-

Scheme 10

cleophilic attachment[99] of the side chain of a β^2-amino acid is illustrated.

7 β^2-Amino Acids by Stereoselective Formation of the C(2)-H Bond

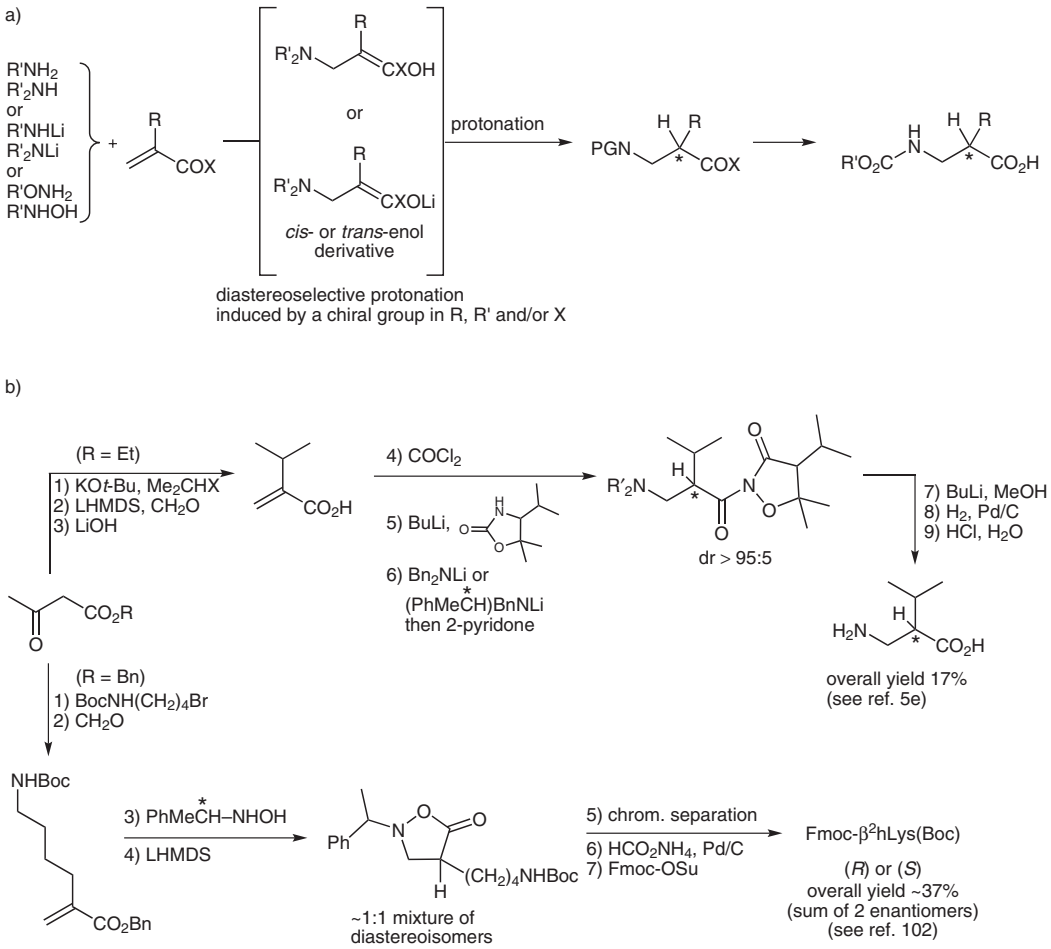
The smallest substituents H on the chirality center of β^2-amino acids can be introduced by protonation (H^+), hydrogenation (H–H) or hydrogen-atom transfer ($H^{\cdot}$), see Figure 11. Except for hydrogenations, which can be carried out enantioselectively with a chiral catalyst, the substrate must be a chiral molecule, so that a diastereoselective H-addition can take place.

7.1 Protonation of Enols or Enolates Derived from 3-Aminopropanoic Acid

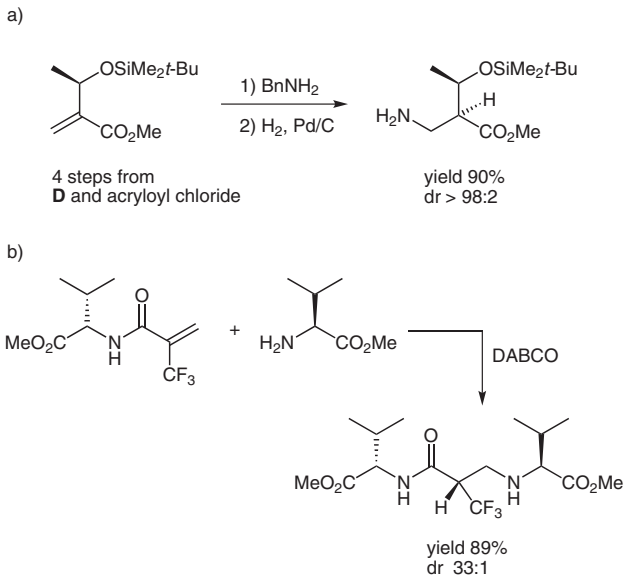
For diastereoselective protonations to occur, a chiral enol derivative is generated in situ, by addition of an N-nucleophile to an acrylate carrying the side chain R in the α-carbonyl position, formally an overall hydroamination of the acryloyl C=C bond. The same kind of enolate derivative (without a side chain R in the α-position) is formed in the addition of R_2NLi to acrylate ester (Table 1, entry 3), but, rather than by a proton, it is trapped by an alkyl halide (formally an overall alkylative amination of the C=C bond). The process is related to the first two steps of a Morita–Baylis–Hillman reaction[101] (formally an electro-

philic substitution of the hydrogen in the acrylate α-carbonyl position), when, for instance, a tertiary amine is adding to acrylate, and the resulting enolate is trapped by an electrophile. *Chiral enols or enolates* for the protonation may be generated in three ways (see Scheme 11, a): (i) by adding to an acrylate ester an amine, a lithium amide[5e] or a hydroxylamine[102] nucleophile carrying a removable chiral group R′, (ii) by having a chirality center in the R group of the acrylate (*cf.* the threonine side chain),[103,104] or (iii) by attaching the acryloyl group to a chiral auxiliary X.[5e,23,105] Stereoselective protonation is also observed with an *achiral enolate* either in the presence of chiral additives (such as amines or lithium amides[89h,106]) or by using a chiral proton source (for instance a phenol derivative[89h]).[107] As in previous sections of this article, there are cases in which more than one type of stereoinduction is at work, for instance a chiral substituent on nitrogen *and* a chiral X group[5e,108] on the enol or enolate shown in brackets in Scheme 11, a; this enol derivative contains yet another stereogenic unit, the C=C bond, which can have *cis*- or *trans*-configuration. Especially when amines or hydroxylamines are applied as N-nucleophiles it is conceivable that equilibria are established – between the acrylate and the enol, between enols, and even between enols and the corresponding carbonyl compounds – so that the observed overall diastereoselective addition of R_2N and H to the acrylate double bond might become the result of thermodynamic, rather than kinetic control (*cf.* the diastereoisomerization occurring in the Br/malonate substitution outlined above in Scheme 8, a).

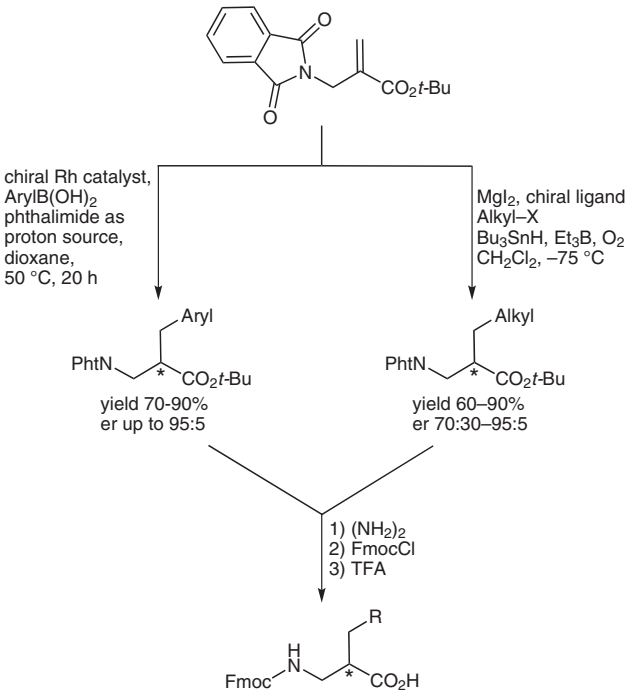
In spite of the potential complexity of the processes involved, the method of adding R_2N–H to acrylate double bonds can be quite useful for the preparation of β^2-amino acids, see the examples in Scheme 11, b and in Scheme 12. The addition of benzylic lithium amides to an *N*-acryloyloxazolidinone and protonation with pyridone is highly diastereoselective.[5e] On the other hand, *N*-phenethylhydroxylamine adds with poor selectivity to α-substituted acrylates, but the isoxazolidinones resulting from base treatment of the primary adducts are readily separated; this provides, eventually, both enantiomeric β^2-amino acids,[102] a useful aspect for a research group actively engaged in investigations of β-peptides, in which (*R*)- and (*S*)-PG^1-β^2hXaa(PG^2)-OH are welcome building blocks (vide supra, section 2). In Scheme 12, a and b, two highly diastereoselective hydroaminations are presented, the addition of benzylamine to (*R*)-2-methylene-3-silyloxy butanoate (→ a β^2hThr derivative)[104] and the 'coupling' of valine ester with *N*-(trifluoromethacryloyl)valine ester (→ a peptide containing a β^2hAla(F_3) residue).[108]



Scheme 11



Scheme 12



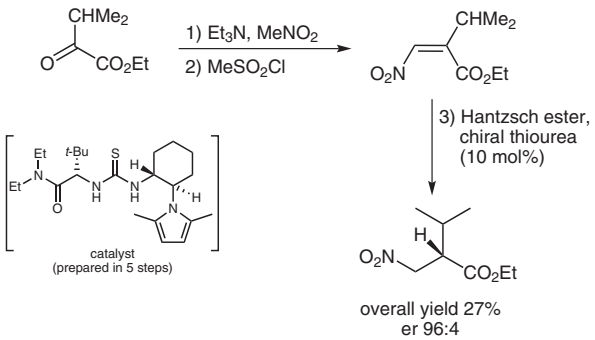
Scheme 13

A fundamentally different approach to β^2-amino acid derivatives was taken by Sibi et al. (Scheme 13),[109,110] in the form of an overall R/H addition to the C=C bond of *tert*-butyl 2-(phthalimidomethyl)acrylate. Thus, besides the strategic C–H bond (**c**), a 'peripheral' C–C bond R′–CH_2 (Figure 11, top right) is formed. Under one set of conditions, an arylborane adds, catalyzed by a chiral rhodium–phosphane complex, where phthalimide is used to protonate a supposed[111] rhodium-enolate intermediate.[110] Alternatively, an alkyl radical adds, in the presence of a chiral Lewis acid (MgI_2·bisoxazoline), and the resulting enoyl radical is trapped by tributyltin hydride.[109] The products can be converted into Fmoc-β^2hXaa-OH in three steps.

7.2 Enantioselective Hydrogenation of Acrylates and Nitroolefins with Formation of β^2-Amino Acid Derivatives

As compared to the (stoichiometric) use of a chiral auxiliary, enantioselective catalytic hydrogenation appears to be much more attractive (in previous sections there were only three examples of catalytic processes – Schemes 7, 8, 13). The apparent simplicity of the hydrogenation must, of course, be paid for: the substrate must contain the entire skeleton of the target β^2-amino acid, with its functional groups or immediate precursors thereof, and its double bond must generally have a uniform geometry. The types of hydrogenation precursors are listed in Table 2, together with information about their origins and specification of the side chains (only hydrocarbon!), with which the reactions have been carried out so far.[112–127] Selected information about the access to the substrates, the catalysts employed, the N-protection, the scope, and references are also given. For high enantioselectivities, the 3-aminoacrylates, the benzylidene succinic acid half-esters and the nitroacrylates must be configurationally uniform; in the dihydropyrimidinone the *Z*-configuration is fixed.

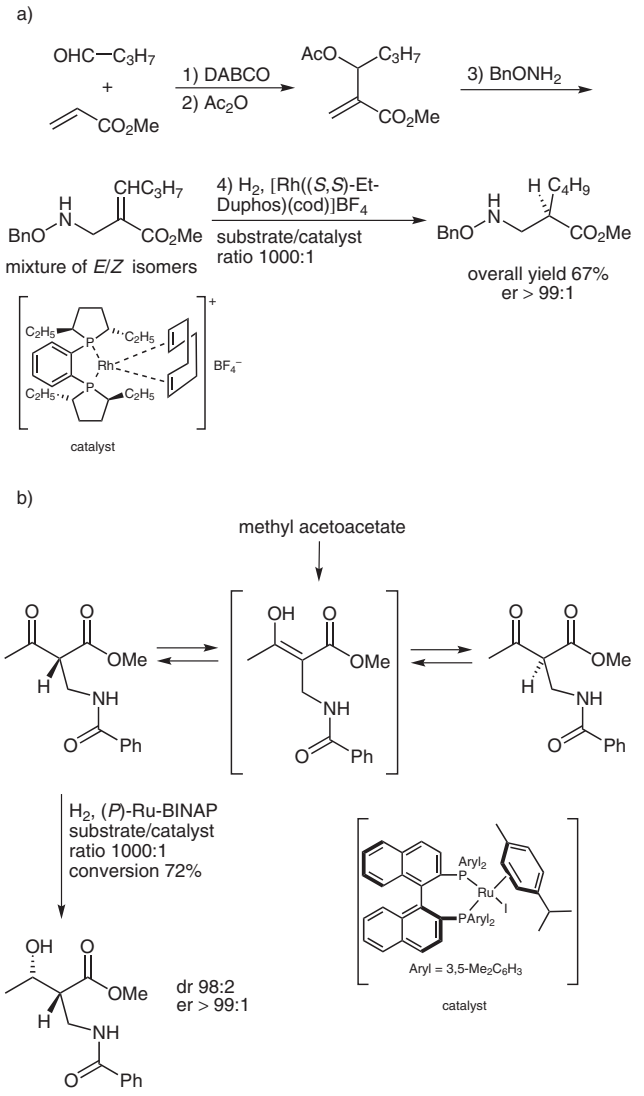
In Scheme 14 and Scheme 15, three specific examples are outlined. An organocatalytic nitroolefin reduction with Hantzsch ester[120] is shown in Scheme 14. The 2-keto ester, formally derived from valine, is converted into the (*Z*)-2-isopropylnitroacrylate, to which hydride is transferred from the dihydropyridine system under the influence of a Jacobsen thiourea (a so-called hydrogen-bond catalyst), to give a β-nitro ester with excellent enantioselectivity. The conditions are mild enough to prevent otherwise facile HNO_2 elimination[100] from the product, which itself is a potential precursor to a β^2hVal building block for peptide synthesis.



Scheme 14

In Scheme15, two special reactions are shown in which a mixture of two equilibrating stereoisomeric precursors gives rise to a single stereoisomer of a product: a process, which, in the case of enantiomers, is commonly referred to as dynamic resolution. Thus, the *E*/*Z* mixture of

methyl-2-(benzylhydroxylaminomethyl)hex-2-enoate is hydrogenated to a β²-amino acid derivative in almost complete enantioselectivity with a Rh-Duphos catalyst (Scheme 15, a).[116] Likewise, racemic mixtures of α-substituted β-keto esters are known to be reduced to single stereoisomers of 2-substituted 3-hydroxy esters with hydrogen and Ru-BINAP catalyst (Noyori's method[121a,b]) or with yeast[62b,121c–k]; the enantiomers equilibrate through the achiral enol form, and the keto group of essentially only one of the enantiomers is reduced diastereoselectively (kinetic resolution with in situ recycling). Applied to a 2-aminomethyl-3-ketobutanoate, this process provides a diastereomerically and enantioselectively pure derivative of H-β²Thr-OH (Scheme 15, b).[121l] For peptide synthesis, Bz-NH would have to be converted into Fmoc-, Boc- or Cbz-NH, the OH group will have to be orthogonally protected, and the methyl ester group hydrolyzed. Note that, in this case, the strategic C–H bond (**c**) is not formed by hydrogenation but rather in a keto–enol equilibrium step; the chiral catalyst 'picks' the (*R*)-β-keto ester for hydrogen transfer to the O=C bond.



Scheme 15

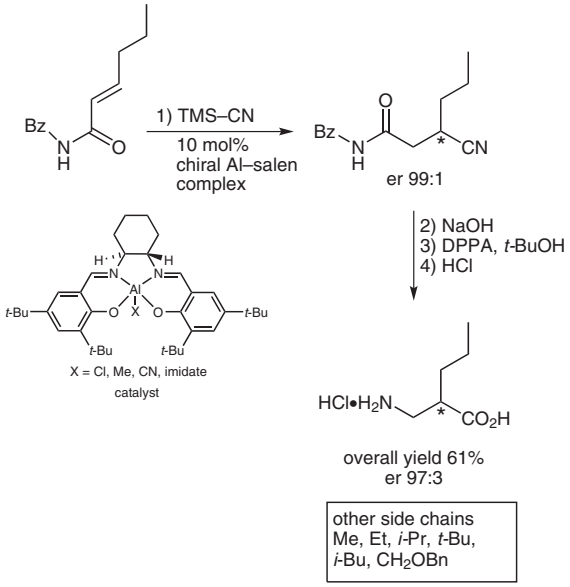
8 Preparation of β²-Amino Acids with Formation of the Strategic C(1)–C(2) Bond

The C–C bond between the chirality center and the CO_2H group has been created stereoselectively in three mechanistically different ways; remarkably, all of them use a catalyst. The cobalt-catalyzed *CO insertion* into the O–C(5) bond of an enantiopure oxazoline was discussed in a previous section (see 5.1, Scheme 4),[25c] as a possibility of enantiospecifically converting an α-amino acid into a β²-amino acid. *Conjugate additions* of carbon nucleophiles, that are synthetically equivalent to HO_2C^-, to the C=C bond of α,β-unsaturated carboxylic acid derivatives or of nitroolefins provide a second route to the β²-amino acid skeleton; these reactions have been catalyzed by a chiral Lewis acid or a thiourea-type organocatalyst (*cf.* Scheme 14). A third avenue that has been used in one case is the palladium-catalyzed allylation of a malonate anion, which acts as the HO_2C^- equivalent in an enantioselective *substitution reaction*. Again, these processes have, so far, been applied only to the formation of potential β²-amino acid precursors with nonfunctionalized side chains, mostly aryl (→ β²hPhg and analogues).

In Scheme 16, a four-step sequence from benzoylhex-2-enoyl imide to the β²-amino acid with a propyl side chain is illustrated.[128a] The starting material was prepared by the authors[128b] from an epoxide that was opened with CO/$BzNH_2$ (a cobalt-catalyzed amidocarbonylation), and H_2O elimination from the resulting β-hydroxyacid derivative; of course, there would be many other ways of preparing this type of compound. The strategic bond (**d**) is formed by cyanide addition in the presence of an aluminum–salen complex, and the enantiopurity (99:1) is almost completely preserved in the three following steps (imide cleavage with base, Curtius degradation, nitrile hydrolysis) to the amino acid hydrochloride (er = 97:3).

Three synthetically equivalent nucleophiles, hydroxyacetophenone,[129] acetylacetone,[130] or 2-methoxyfuran,[131] are used as masked HO_2C^- in Michael additions to nitroolefins (mostly nitrostyrenes), see Scheme 17. The enantioselectivities are induced by chiral Lewis acid complexes (Mg^{2+}, Zn^{2+}) or a binaphthyl-derived thiourea. All reactions are highly enantioselective (generally 95:5), and in two cases[129,130] the conversion of primary adducts into β²-homophenylglycine by oxidative degradation (Oxone®, $KMnO_4$, $NaIO_4/RuCl_3$) and nitro-group reduction (H_2 and Pd/C, LAH) has been demonstrated.

A rather laborious enantioselective synthesis of nipecotic acid (H-β²hPro-OH) is shown in Scheme 18, where the key step is a palladium-catalyzed allylation; the acetoxymalonate moiety thus introduced is converted into a CO_2H group by decarboxylative hydrolysis and sodium periodate oxidation.[132] β²-Homoproline is normally prepared from nicotinic acid by hydrogenation and resolution.[133]



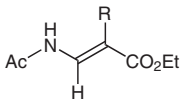
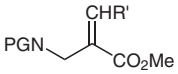
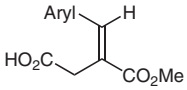
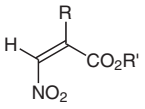
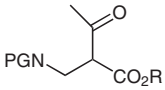
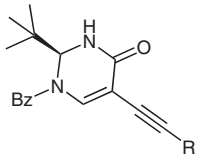
Scheme 16

9 β²-Amino Acids by Resolution?

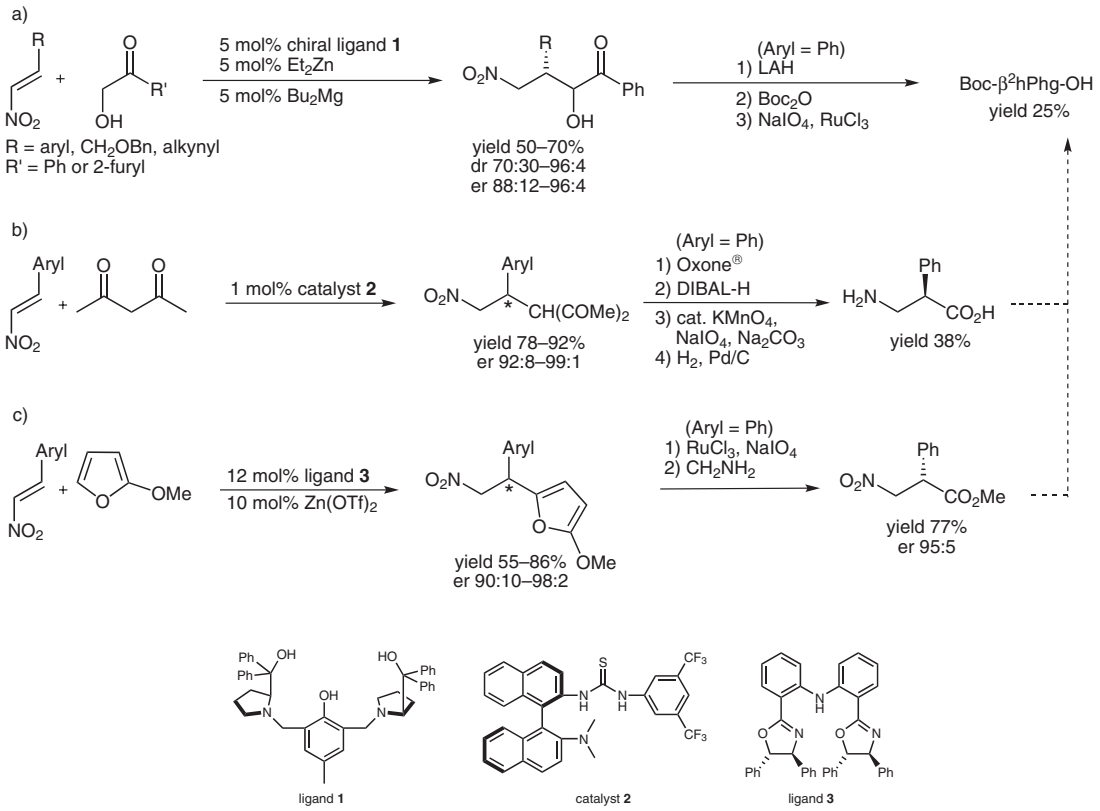
In sections 5 through 8, we restricted the discussion (*cf.* Figure 10) to cover exclusively reactions (enantioselective) or series of reactions (involving a diastereoselective step), in which one of the strategic bonds (**a**)–(**c**) at the chirality center of the target molecule, a β²-amino acid, is formed stereoselectively, so that eventually enantiopure[134] building blocks for peptide synthesis could, at least in principle,[135] be prepared. Some routes are cumbersome, involve expensive, dangerous or toxic reagents, require elaborate reaction conditions, or are applicable only to β²-amino acids with 'simple' (hydrocarbon) side chains (*cf.* Figure 9).

Thus, the question appears appropriate and fair, whether it would not be easier to prepare racemic β²-amino acid derivatives by simple methods and carry out resolutions. Especially for the purposes of an academic and, even more so, of an industrial research laboratory, this procedure could be doubly advantageous: (a) simpler chemistry is involved and (b) *both* enantiomers become available.[136]

Table 2 Substrates Used in Catalytic Enantioselective Hydrogenations for the Preparation of β²-Amino Acids[a]

Substrate	Details	Ref.
	*E*-configuration from 2-formyl ester and $MeCONH_2$ H_2/RhL* catalyst R = Me, *i*-Pr, *i*-Bu, Ph	112
	*E*- or *Z*-configuration or mixtures thereof through Baylis–Hillman reaction or from phthalimidomethyl alkynes + HCN H_2/RhL* catalyst R′ = H, alkyl, aryl PGN = BnNH, BnO-NH, PhtN, AcNH	113–117 (see Scheme 15a)
	*E*-configuration by Stobbe condensation H_2/RhL* catalyst subsequent Curtius degradation	118
	*Z*-configuration (chromatographically separated from *E*-isomer) by Henry reaction from 2-keto esters and nitromethane Hantzsch ester/thiourea organocatalyst or enzyme/NADPH R = alkyl, aryl R′ = Me, Et, Bn, *t*-Bu	119, 120
	by aminomethylations of acetoacetate H_2/RhL* or RuL* catalyst or enzyme/NADH or plant-cell culture R = Me, Et PGN = BzNH, PhthN product is PG-β²hThr-OR	121a,b,l, 122–126 (see Scheme 15b)
	from 5-iododihydropyrimidinone by Sonogashira coupling H_2/Raney Ni	127

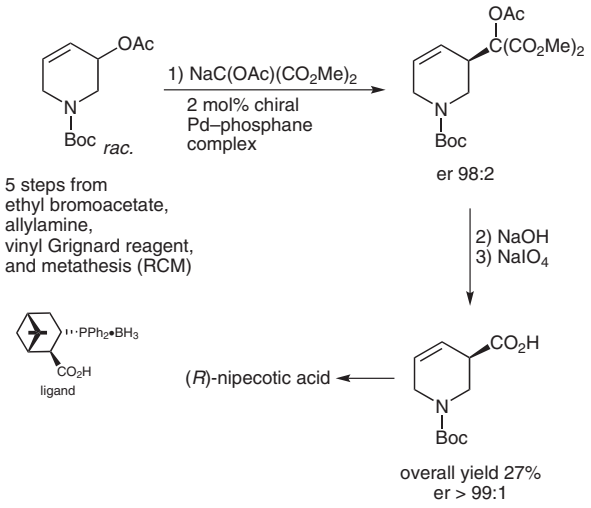
[a] The hydrogenation of the hydropyrimidinone is diastereoselective (achiral catalyst).



Scheme 17

The pharmaceutical companies nowadays have facilities dedicated to routine chromatographic resolution with chiral column materials.[137] When we searched for β²-amino acids, without specifying that they had to be enantiomerically pure, the databases provided tens of thousands of hits (*cf.* section 10). This is not surprising, since, after all, β-amino acids have the functionality pattern of classical Mannich bases, a 1,3-relationship[27] of the two functional groups, and thus are formed by the classical textbook reactions of organic chemistry: acetoacetate, malonate, malonitrile, cyanoacetate, succinate, and acrylate ester syntheses, keto-cleavage, decarboxylation, see the name reactions associated with Claisen, Curtius, Henry, Knoevenagel, Mannich, Morita–Baylis–Hillman, Stobbe. These methods can provide racemic β²-amino acids, see the indications made in Figure 13, with some references.[138] Classical resolutions by attachment to a chiral compound and diastereoisomer separation[102] or by formation and crystallization of diastereoisomeric salts with chiral amines or chiral acids could be used to obtain enantiopure β²-amino acids (*cf.* nipecotic acid[133]). Unfortunately, application of these methods cannot be rationally designed like a stereoselective synthesis. In fact, attempts with *N*-Boc-β²-homovaline and the Aldrich ChiroSolv® kit for crystallizing resolutions (32 different chiral bases) were unsuccessful.[139]

The preparation of *β³-amino acids* by enzymatic kinetic resolution, with isolated immobilized enzymes or with cell cultures, has been thoroughly studied and reviewed in an article entitled 'Biocatalysis as a profound tool in the



Scheme 18

preparation of highly enantiopure β-amino acids.'[5d] A large variety of different types of enzymes was employed successfully, including chymotrypsin, β-lactamases, nitrilases, hydantoinases, lipases, transferases and isomerases. The examples[140–143] for β²-amino acids that we found in the databases are shown in Scheme 19. In an ideal case (Scheme 19, d) an almost theoretical yield of two different derivatives of the enantiomers of a β²-amino acid can be obtained.[143]

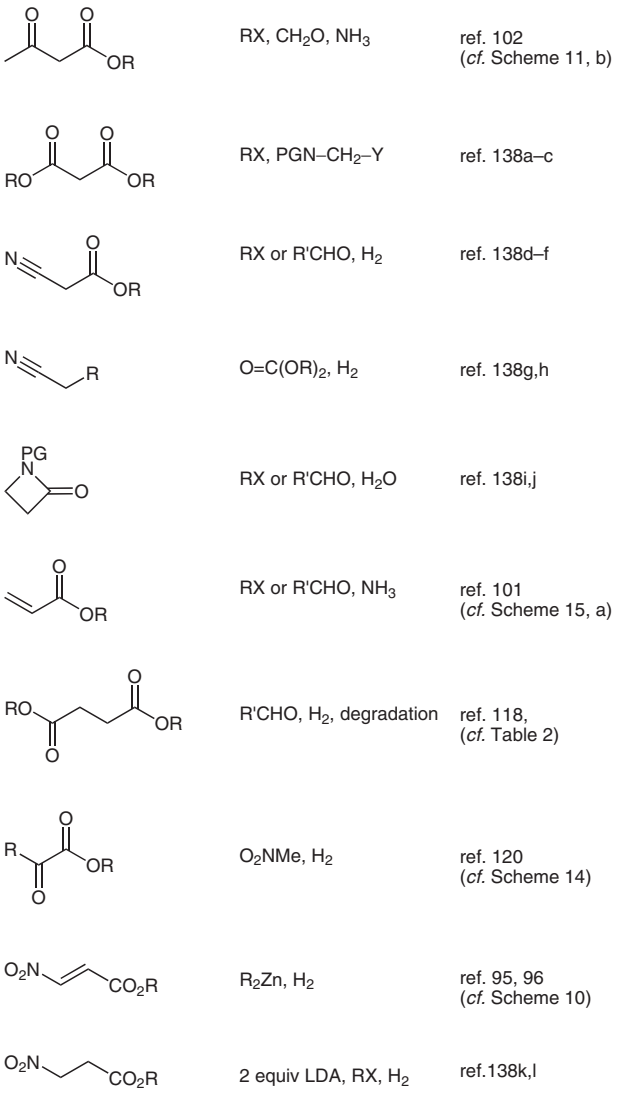
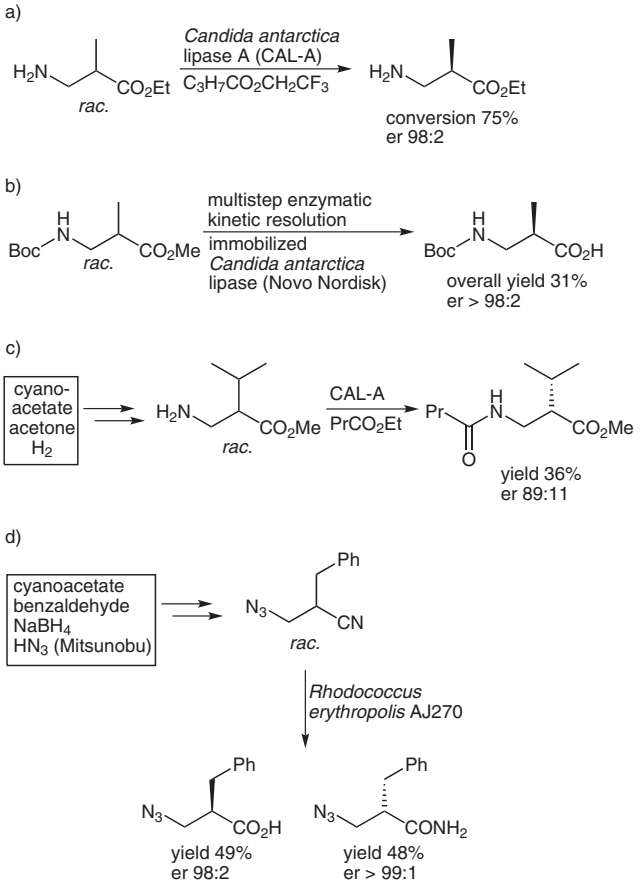


Figure 13 More or less classical sequences of reactions leading to racemic mixtures of β^2-amino-acids derivatives. Starting materials, reactants and/or reagents and leading references are given.



Scheme 19

10 Detailed Search Strategy

Information retrieval in chemistry and related sciences has been dominated for some time by end-user searching, that is, chemists searching databases themselves at their workplace, without specialist intermediaries, using database systems like *SciFinder/SciFinder Scholar*, *CrossFire*, *DiscoveryGate*, *Web of Knowledge*, etc. This has been facilitated, or rather made feasible at all, by graphic user interfaces, and also by flat-fee licenses for such commercial systems. In contrast, the first two decades of online (database) searching for chemical information were dominated by information specialists doing the searches as intermediaries, this being necessitated by the complex nature of the text-based, command-driven retrieval systems and interfaces, as well as by the pay-per-use license model with an underlying complex cost structure, charging for connect time, searches, and results displayed in a manner often hard to predict.

What is often overlooked, however, are the limitations of these modern database systems: ease of use (handling) cannot be equated with overall utility when large, complex databases like those produced by *Chemical Abstracts Service* (*CAS*), *Beilstein*, or *Gmelin* are involved. For the large majority of the database systems mentioned above and the databases thus accessible, the 'traditional' host-based versions of the same databases are still available, using complex, but powerful command-driven retrieval languages.[144] This is important with regard to the fact that many end-user systems were designed only for routine searches. *SciFinder Scholar*[145] is an important example in this respect: for practical and for teaching purposes, we classify chemical information retrieval problems into four categories with regard to this database system:

(1) queries for which the search method is obvious in *SciFinder Scholar*

(2) queries for which the search method is *not* obvious to an average user in *SciFinder Scholar* (a clear case for support and training)

(3) queries for which the *SciFinder Scholar* user interface is not suitable, but the desired information is retrievable from *CAS* databases using other interfaces; these would include complex topic searches, searches for all com-

pounds having a certain number of elements in any stoichiometric ratio, searches for sequence fragments of biopolymers

(4) searches for which databases other than those produced by *CAS* look more promising, or are at least as important as these

This situation has prompted us to use *SciFinder Scholar* for routine access to the *CAS* databases, but still keep access to the *CAS* databases at the host *STN International*[146] via the powerful retrieval language *STN Messenger.*[147] This is important not only for the searches in category 3 above; quite a number of substructure and reaction searches which are in principle amenable to be searched via *SciFinder Scholar* (category 1 or 2) hit an internal system limit called 'Auto Fix'. This 'fixing' prevents acyclic parts of the substructure searched for (i.e., those not explicitly in rings) from being in a ring, and excludes further ring annellation (but not other substitution) to cyclic parts of the substructure. This limitation imposed by *SciFinder Scholar* may sometimes be acceptable or even desired by users, but often it is not. For the latter cases, we turn to substructure searches in *STN Registry*[148] for compounds, or *STN CASREACT*[149] for reactions.[150] Some substructure searches in *SciFinder Scholar* will not even run within the limitations imposed by AutoFix, they demand further limitations via molecular weight, or formal restrictions ('filters') like excluding mixtures, restricting to polymers, etc.

For a question as complex as a search for all β²-amino acids and the corresponding literature about methods for their preparation, one would assume, based both on our previous experience with this type of search (dating back for more than 25 years), and on the limitations mentioned for *SciFinder Scholar*, that a substructure search in *STN Registry* would be the indispensable key step. In the course of extensive orientational searches we learned, however, that this kind of search is also amenable to be solved by *SciFinder Scholar*. This has not only economic advantages – using *SciFinder Scholar* with its fixed price already paid for versus *STN* with costs incurred for database connect times, searches and items displayed – it also reduces the necessary intervention of an information specialist to consulting in the steps of the search process instead of executing all the searches oneself. Command-driven searches in *CAS* databases with *STN Messenger*[147] for structures, reactions, and literature require knowledge of search features, *CAS* indexing policies, and cost control measures beyond the experience of most users.

The first step in complex, rather comprehensive substructure search for an entire compound class like β²-amino acids is the definition of border conditions in the substructure query at hand; this is traditionally done with so-called 'sample searches' in *STN Registry* (for which only connect charges, but no search or display charges, are incurred if executed in the proper way). In our example, we decided to try *SciFinder Scholar* searches for this preliminary query optimization.

The particular questions to answer for β-amino acids were:

(1) C-terminus: include, besides free acid, esters, amides, also protecting groups not in this class of derivatives, or even acid chlorides, aldehydes (R = H), or corresponding alcohols (CH_2OH instead of C=O-R)?

(2) topology: entire fragment shown in Figure 14 also in a ring – either in its entirety, or only the terminal N, R at the C-terminus, or substituent R* part of a ring?

(3) substitution pattern: chiral center at α-carbon; no substituent, mono, or disubstitution at α-carbon/β-carbon; type of substituent R*: H, C, heteroatom?

(4) N-terminus: free amino group, protection with acyclic or cyclic protecting group (i.e., N either part of a ring or not)?

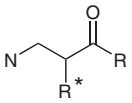


Figure 14 Basic structure of β²-amino acids

In these test searches, features and limitations were determined or ascertained, many of which are to our knowledge not documented for *SciFinder Scholar*. As in many routine cases, AutoFix was the first stumbling block, limiting retrieval to amino acids with the query fragment not being part of a ring. The only way to overcome this limit was to 'slice' the search domain by ranges of molecular weight in such a way as to bypass the limits of *SciFinder Scholar*, and finally then recombine all these partial (saved) result sets. Fortunately, we did not need to use this rather tedious search tactic (see below).

When limiting searches to 'return single components only', the (in our search) undesired and often very common mixtures are eliminated, but so are also salts of amino acids; this limit was therefore not acceptable here.

Two further problems had to be decided upon which relate not to the user interface *SciFinder Scholar*, but to the underlying content of the *CAS* databases. In the beginnings of the *CAS Registry System*,[151] stereochemical information was only present in stereodescriptors as part of the name. Only later on, absolute or relative configuration of chiral centers was made structure-searchable. Whenever a query with one or several chiral centers is searched in *SciFinder Scholar*, all stereoisomers are retrieved, and then grouped into categories according to their matching properties with the query structure: absolute stereo match, absolute stereo mirror image, relative stereo match, stereo that does not match query, no stereo in answer structure. The last category includes those compounds where stereochemical information was not present in the structure; that is, either present only in textual stereodescriptors not searchable via *SciFinder Scholar*, or unknown. Because of the relatively large number of compounds retrieved in this category in our searches (8323), we decided to ex-

clude these from our results, as we were interested in chiral compounds with known stereochemistry and from a time period where this information was structure-searchable in *CAS Registry*.

Retrieving the desired β²-amino acids was only the first step in our search, the final goal being methods for their synthesis. When indexing the literature, *CAS* assigns the term 'preparation' for compounds in a very generous way, including also formations of the compound (or of unspecified derivatives) which most chemists would not classify as synthesis. With the interface *SciFinder Scholar*, narrowing down the large amount of publications for 'preparation' is not possible in the same way as it is in using the *STN* version of the *CAS* literature databases (e.g., using the more specific role SPN = synthetic preparation), and even these features in *STN* are considered insufficient. We therefore decided to limit ourselves to preparations of the retrieved β-amino acids in the *CASREACT* reaction database[152] and the corresponding references; this reduced the literature references for preparation of 2441 β²-amino acids from 479 'references associated with preparation' in *CAplus*[153] to only 183 references for 'reaction role: product' of these compounds.

As a result of the extensive test searches and discussions, we came up with the query shown in Figure 15. This query is characterized by the following key features:

(1) C-terminus: free acid or ester

(2) AutoFix: entire fragment not in ring (except terminal atoms!)

(3) β-**un**substituted/α-**mono**substituted

(4) N-terminus free or protected (also permitted in a ring)

(5) stereochemistry: only absolute or relative stereochemistry, 'no match' or 'no stereo' excluded

(6) only preparations from reaction database CASREACT

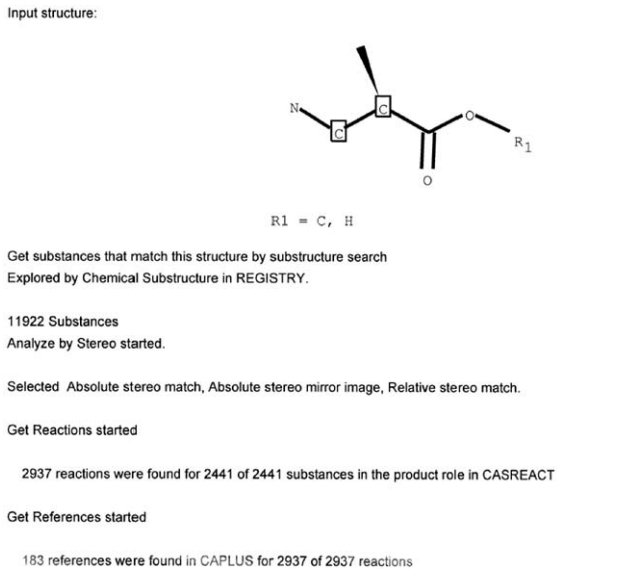


Figure 15 Query for β²-amino acids (© reprinted with permission of American Chemical Society)

When the literature thus retrieved was compared with references already known to us from the work on an earlier publication,[2d] and with additional references quoted in those found in the search, 23 journal articles considered of interest were found missing from our search result. For every one of these, the *CAS* indexing was examined to determine the following reasons for the retrieval failure:[154]

(1) no indexing of individual compounds and reactions in reviews: 3 publications

(2) no reactions indexed at all: 4 publications

(3) stereochemistry not matching/not present: 4 publications

(4) different C-terminus (i.e., not acid or ester): 4 publications

(5) query fragment in ring: 1 publication

(6) different substitution pattern on α- or β-carbon: 12 publications

(7) no β-amino acid indexed: 1 publication (azides only indexed)

Two special cases deserve mentioning in this context: for one publication[72] missed, the compound indexing had been complete at the date of search (April 18, 2008), and therefore the compound itself was retrieved, but not the literature about its preparation via the *CASREACT* database, as the indexing in this database was only completed after our first search on May 3, 2008. In another case,[73] compounds with the desired substitution pattern were indexed in the literature database *CAplus*, but only those with a different, undesired pattern in *CASREACT* for the same publication. This demonstrates, together with other missed articles in category 2, the dangers of restricting oneself to *CASREACT* for syntheses.

This investigation shows the difficulty in navigating between a search result as precise as possible (given a limited amount of time to examine the retrieved literature), and missing important information for a review article such as this. We re-examined all restrictions agreed upon in the original search on the basis of these results, and decided to repeat the original structure search with an enhanced query (amides also possible at C-terminus, see Figure 15), but leave all other restrictions in force.

As we had stored the result from the search on April 18, 2008, we were able to extend this search on June 15, 2008, both for the amides of β-amino acids not retrieved in the previous search, as well as for additional β-amino acids registered by *CAS* in the meantime. This second search provided 43 additional references about the synthesis.

Although *SciFinder Scholar*[145] was primarily designed for routine searches by end-users, this example shows that it is also a valuable tool for at least some of the searches that so far were considered to belong to the domain of information specialists and powerful (but complex) command-driven interfaces like that provided by *STN International*.[146] Key aspects in this context were the ability to store and logically combine answer sets in *SciFinder Scholar*, a

feature which became available only with the recent version 2007, and the fact that AutoFix, a limiting factor also in this as in many other searches, still permits the terminal atoms of an acyclic query fragment to be also in a ring.

11 Conclusions and a Table with β²-Amino Acid Building Blocks for Peptide Synthesis

The intriguing chemical, structural, biological and physiological[3n] properties of β-peptides[2] have triggered extensive activity towards the preparation of their building blocks, namely the β-amino acids. For research purposes, the β³-amino acids (with proteinogenic or nonproteinogenic side chains) are readily obtained by direct Arndt–Eistert homologation of the α-amino acid building blocks used for peptide synthesis by the Boc or Fmoc strategy. The commercial availability[155] of these β³-amino acid derivatives is due to the fact that there are companies which offer diazomethane technology even on large industrial scale.[156] For the β²-amino acids, no such generally applicable method of preparation from α-amino acids exists (*cf.* Section 5.1). The survey, presented here, about the preparation of β²-amino acids is evidence for the wonderful complexity of organic synthesis: a multitude of possibilities to prepare such seemingly simple compounds with only two or three functional groups (*cf.* Figure 9) and a single stereocenter.[157] A wealth of highly original, imaginative, innovative and creative routes has been designed in a worldwide competition between many groups (*cf.* references list).

There is no single best synthetic route for all types of β²-amino acids. In our own work we needed to have access to the (*R*)- and (*S*)-β²-amino acids with the 20 proteinogenic side chains,[3h] in sufficient quantities and in a short period of time, in order to be able to elucidate the properties of peptides containing these building blocks. The auxiliary DIOZ (**C**) served us well to reach this goal – by one and the same methodology (*cf.* Scheme 6).[3h,25d,51,57,66] For a particular type of β²-amino acid, for instance with a hydrocarbon RCH_2 side chain or with the threonine side chain (*cf.* Schemes 12, a, and 15, b), there may be a single 'best' method not applicable to other derivatives with functionalized side chains, and each of these 'ideal' methods may require particular experience on the part of the experimentalist, or special equipment in a laboratory or in the process development division or plant facility of a company. The shortest and most suitable route will also depend upon whether a Boc- or Fmoc-β²hXaa(PG)-OH – for solution- or solid-phase peptide synthesis or for creating a large library of β-peptidic compounds – is required, or whether a particular β²-amino acid is to be incorporated into a small-molecule drug candidate.[23,105,116]

For the peptide chemist we have collected the Cbz- Boc-, and Fmoc-β²-amino acids, with proper side-chain protections in Table 3. The database search strategy described in Section 10 allowed us to choose only those references in which detailed experimental procedures, with characterization of the compounds, are given. For other targets requiring access to β²-amino acids, inspection of the schemes in sections 5 through 9 will allow the synthetic chemist to choose the most appropriate method.

The purpose of this review article was dual: to give an overview of the procedures which have hitherto been employed for the preparation of β²-amino acids, and to challenge synthetic organic chemists to search for new, practical avenues to these valuable building blocks for peptide synthesis and for incorporation in pharmaceutical drug candidates.

Table 3 List of *N*-Fmoc-, *N*-Boc-, and *N*-Cbz-Protected β²-Amino Acids with the Proteinogenic and Some Nonproteinogenic Side Chains[a–d]

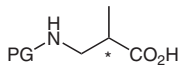
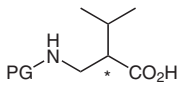
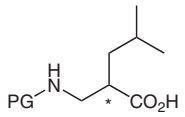
β²-Amino acid	Reference PG = Fmoc	PG = Boc	PG = Cbz
Proteinogenic side chains Xaa			
Ala 	158 (*S*) 63i (*R*)	48, 52, 63a, 63h, 68, 77, 97, 78, 83 (*R*)	
Val 	158 (*S*) 102 (*R*)	67b (*S*) 10, 48 (*R*)	
Leu 	102, 158 (*S*)	67b (*S*) 47, 48, 77 (*R*)	

Table 3 List of *N*-Fmoc-, *N*-Boc-, and *N*-Cbz-Protected β²-Amino Acids with the Proteinogenic and Some Nonproteinogenic Side Chains[a–d] (continued)

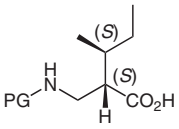
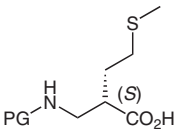
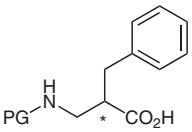
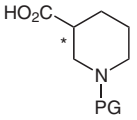
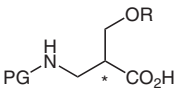
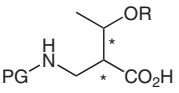
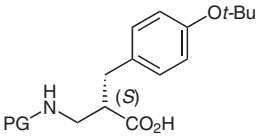
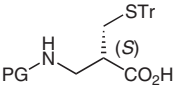
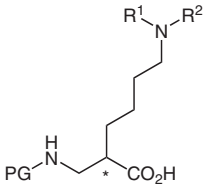
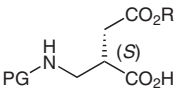
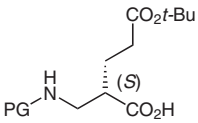
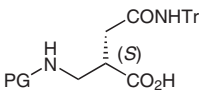
β²-Amino acid		Reference PG = Fmoc	PG = Boc	PG = Cbz
Ile		43		43
Met		43		43
Phe		102, 158 (*S*)	67b, 110 (*S*) 48, 77, 78, 80 (*R*)	50 (*R*)
Pro		44 (*S*)	44 (*S*) 133b (*R*)	
Ser		25d (*R*); R = *t*-Bu 75 (*S*); R = *t*-Bu	83 (*S*); R = Bn	
Thr			63k (2*S*,3*R*); R = $SiMe_2$*t*-Bu	44 (2*R*,3*S*); R = *t*-Bu
Tyr		43, 67b		43
Cys			25d	
Lys		24a (*S*); R^1 = H, R^2 = Boc 67b (*S*); R^1 = R^2 = Boc 102 (*R*); R^1 = H, R^2 = Boc		
Asp		57; R = *t*-Bu		57, 83; R = *t*-Bu 84; R = H
Glu		57, 67b		57
Asn		57		57

Table 3 List of *N*-Fmoc-, *N*-Boc-, and *N*-Cbz-Protected β²-Amino Acids with the Proteinogenic and Some Nonproteinogenic Side Chains[a–d] (continued)

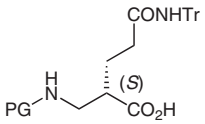
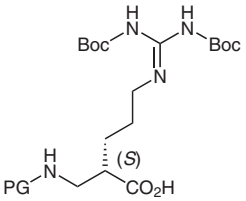
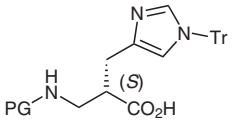
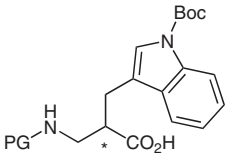
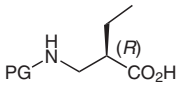
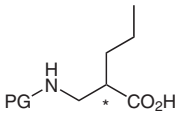
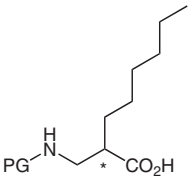
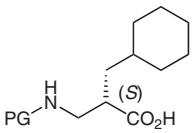
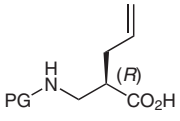
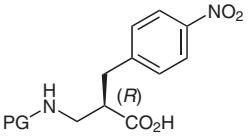
β²-Amino acid	Reference PG = Fmoc	PG = Boc	PG = Cbz
Gln 	57		57
Arg 	18c		18c
His 	25d		
Trp 	44 (*S*) 56 (*R*)		44 (*S*) 56 (*R*)
Nonproteinogenic side chains			
		94, 95b, 95c	
		67b (*S*) 67a (*R*)	
		67b (*S*) 48 (*R*)	
		67b	
		78	
		78	

Table 3 List of *N*-Fmoc-, *N*-Boc-, and *N*-Cbz-Protected β²-Amino Acids with the Proteinogenic and Some Nonproteinogenic Side Chains[a–d] (continued)

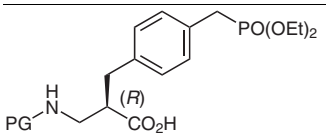
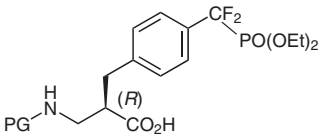
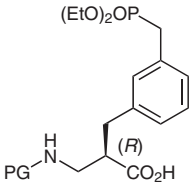
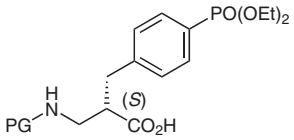
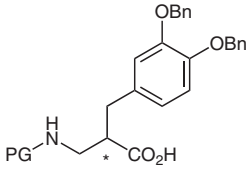
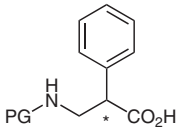
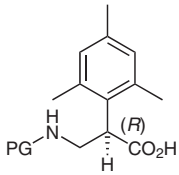
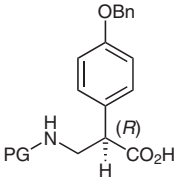
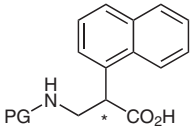
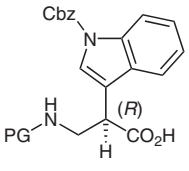
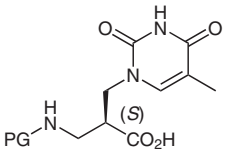
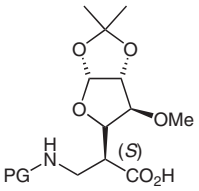
β²-Amino acid	Reference PG = Fmoc	PG = Boc	PG = Cbz
		63d	
		63d	
		63d	
	55		55
			82d (*S*) 82d (*R*)
		33b, 129 (*S*) 52 (*R*)	50 (*R*)
		52	
			50
		159 (*S*) 52 (*R*)	
			50

Table 3 List of *N*-Fmoc-, *N*-Boc-, and *N*-Cbz-Protected β²-Amino Acids with the Proteinogenic and Some Nonproteinogenic Side Chains[a–d] (continued)

β²-Amino acid	Reference PG = Fmoc	PG = Boc	PG = Cbz
		160	
		161	

[a] Side-chain functional groups are protected orthogonally.
[b] In the references given, the compound's preparation and characterization are described, either in the paper directly or in supplementary material.
[c] If no configuration is specified in the formula, both enantiomers are described.
[d] *R*-Configuration corresponds to β²hXaa, *S*-configuration to *ent*-β²hXaa (except with Ser, Thr, Cys, where it is the other way around), see the definitions in Figure 1.

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References

(1) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B. *Helv. Chim. Acta* **1996**, *79*, 913.
(2) General review articles on β-peptides: (a) *β-Peptides: A surprise at every turn*: Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (b) *β-Peptides: From Structure to Function*: Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (c) Seebach, D. *Homologs of Amino Acids and Explorations into the Worlds of β- and γ-Peptides,* In *Chemistry of Crop Protection Progress and Prospects in Science and Regulation*; Voss, G.; Ramos, G., Eds.; Wiley-VCH: Weinheim, **2003**, 17–29. (d) *The World of β- and γ-Peptides Comprised of Homologated Proteinogenic Amino Acids and Other Components*: Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111. (e) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Die Welt der β- und γ-Peptide aus homologisierten proteinogenen Aminosäuren und anderen Bausteinen*; VHCA: Zürich, **2004**. (f) Gelman, M. A.; Gellman, S. H. *Using Constrained β-Amino Acid Residues to Control β-Peptide Shape and Function,* In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E.; Soloshonok, V. A., Eds.; John Wiley & Sons: Hoboken NJ, **2005**, Chap. 22, 527–591.
(3) Review articles covering special aspects of β-peptide chemistry structure and biology: (a) *Preparation of Achiral and of Enantiopure Geminally Disubstituted β-Amino Acids for β-Peptide Synthesis*: Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (b) *Excursions of Synthetic Organic Chemists to the World of Oligomers and Polymers*: Seebach, D.; Beck, A. K.; Rueping, M.; Schreiber, J. V.; Sellner, H. *Chimia* **2001**, *55*, 98. (c) *From the Biopolymer PHB to Biological Investigations of Unnatural β- and γ-Peptides*: Seebach, D.; Albert, M.; Arvidsson, P. I.; Rueping, M.; Schreiber, J. V. *Chimia* **2001**, *55*, 345. (d) *From Synthetic Methods to γ-Peptides – From Chemistry to Biology*: Seebach, D.; Beck, A. K.; Brenner, M.; Gaul, C.; Heckel, A. *Chimia* **2001**, *55*, 831. (e) *A Field Guide to Foldamers*: Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (f) Matthews, J. L. *Synthesis of Peptides Based on β-Amino Acids,* In *Synthesis of Peptides and Peptidomimetics,* In *Houben-Weyl*, Vol. E22c; Felix, A.; Moroder, L.; Toniolo, C., Eds.; Georg Thieme Verlag: Stuttgart, **2003**, Chap. 10-12, 552–569. (g) *Side-chain control of β-peptide secondary structures. Design principles*: Martinek, T. A.; Fülöp, F. *Eur. J. Biochem.* **2003**, *270*, 3657. (h) *How we drifted into peptide chemistry and where we have arrived at*: Seebach, D.; Kimmerlin, T.; Šebesta, R.; Campo, M. A.; Beck, A. K. *Tetrahedron* **2004**, *60*, 7455. (i) *100 years of peptide synthesis: ligation methods for peptide and protein synthesis with applications to β-peptide assemblies*: Kimmerlin, T.; Seebach, D. *J. Pept. Res.* **2005**, *65*, 229. (j) *Exploring the Antibacterial and Hemolytic Activity of Shorter- and Longer-Chain β-, α,β-, and γ-Peptides and of β-Peptides from β² -3-Aza- and β³-2-Methylidene-amino Acids Bearing Proteinogenic Side Chains – A Survey*: Arvidsson, P. I.; Ryder, N. S.; Weiss, H. M.; Hook, D. F.; Escalante, J.; Seebach, D. *Chem. Biodiversity* **2005**, *2*, 401. (k) *β-Peptides as inhibitors of protein–protein interactions*: Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.* **2005**, *13*, 11. (l) *Helices and Other Secondary Structures of β- and γ-Peptides*: Seebach, D.; Hook, D. F.; Glättli, A. *Biopolymers* **2006**, *84*, 23. (m) *Bacterial β-peptidyl aminopeptidases: on the hydrolytic degradation of β-peptides*: Geueke, B.;

Kohler, H.-P. E. *Appl. Microbiol. Biotechnol.* **2007**, *74*, 1197. (n) *β-Peptidic Peptidomimetics*: Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366. (o) *Foldamers with Heterogeneous Backbones*: Horne, W. S.; Gellman, S. H. *Acc. Chem. Res.* **2008**, *41*, 1399. (p) *Interplay among side chain sequence backbone composition and residue rigidification in polypeptide folding and assembly*: Horne, W. S.; Price, J. L.; Gellman, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 9151. (q) *New Open-Chain and Cyclic Tetrapeptides Consisting of α-, β²- and β³-Amino-Acid Residues as Somastotatin Mimics – A Survey*: Seebach, D.; Dubost, E.; Mathada, R. I.; Jaun, B.; Limbach, M.; Löweneck, M.; Flögel, O.; Gardiner, J.; Capone, S.; Beck, A. K. *Helv. Chim. Acta* **2008**, *91*, 1736.

(4) Review articles on β²-peptides: (a) *β²-Amino Acids – Syntheses, Occurrence in Natural Products and Components of β-Peptides*: Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206. (b) Campo, M. A.; Escalante, J.; Šebesta, R. *β-Amino acids with proteinogenic side chains and corresponding peptides: synthesis secondary structure and biological activity,* In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E.; Soloshonok, V. A., Eds.; John Wiley & Sons: Hoboken NJ, **2005**, Chap. 23, 593–618.

(5) Books and review articles on β-amino acids: (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; John Wiley & Sons: New York, **1997**. (b) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E.; Soloshonok, V. A., Eds.; John Wiley & Sons: Hoboken NJ, **2005**. (c) *Synthesis of fluorinated amino acids*: Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711. (d) *Biocatalysis as a profound tool in the preparation of highly enantiopure β-amino acids*: Liljeblad, A.; Kanerva, L. T. *Tetrahedron* **2006**, *62*, 5831. (e) *Asymmetric synthesis of β²-amino acids: 2-substituted-3-aminopropanoic acids from N-acryloyl SuperQuat derivatives*: Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biol. Chem.* **2007**, *5*, 2812.

(6) Others groups studied β-peptides with 'unnatural' side chains or with cyclic β-amino acids as building blocks (see section 8 in an extensive review article on β-peptides[2d,e] and references 2b and 2f).

(7) (a) Kimmerlin, T.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 2098. (b) Seebach, D.; Mathad, R. I.; Kimmerlin, T.; Mahajan, Y. R.; Bindschädler, P.; Rueping, M.; Jaun, B.; Hilty, C.; Etezady-Esfarjani, T. *Helv. Chim. Acta* **2005**, *88*, 1969.

(8) (a) Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2141. (b) Arvidsson, P. I.; Rueping, M.; Seebach, D. *Chem. Commun.* **2001**, 649.

(9) (a) Jacobi, A.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1150. (b) Rueping, M.; Jaun, B.; Seebach, D. *Chem. Commun.* **2000**, 2267. (c) Vaz, E.; Brunsveld, L. *Org. Lett.* **2006**, *8*, 4199.

(10) Seebach, D.; Abele, S.; Gademann, K.; Guichard, G.; Hintermann, T.; Jaun, B.; Matthews, J. L.; Schreiber, J. V.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1998**, *81*, 932.

(11) Hintermann, T.; Seebach, D. *Synlett* **1997**, 437.

(12) Seebach, D.; Gademann, K.; Schreiber, J. V.; Matthews, J. L.; Hintermann, T.; Jaun, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1997**, *80*, 2033.

(13) Rueping, M.; Schreiber, J. V.; Lelais, G.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 2577.

(14) Arvidsson, P. I.; Frackenpohl, J.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 1522.

(15) See Figure 4c in reference 10.

(16) (a) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1595; *Angew. Chem.* **1999**, *111*, 1700. (b) Daura, X.; Gademann, K.; Schäfer, H.; Jaun, B.; Seebach, D.; van Gunsteren, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 2393. (c) Peter, C.; Rueping, M.; Wörner, H. J.; Jaun, B.; Seebach, D.; van Gunsteren, W. F. *Chem. Eur. J.* **2003**, *9*, 5838. (d) Lelais, G.; Seebach, D.; Jaun, B.; Mathad, R. I.; Flögel, O.; Rossi, F.; Campo, M.; Wortmann, A. *Helv. Chim. Acta* **2006**, *89*, 361. (e) Seebach, D.; Jaun, B.; Šebesta, R.; Mathad, R. I.; Flögel, O.; Limbach, M.; Sellner, H.; Cottens, S. *Helv. Chim. Acta* **2006**, *89*, 1801. (f) Flögel, O.; Codée, J. D. C.; Seebach, D.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7000; *Angew. Chem.* **2006**, *118*, 7157. (g) Mathad, R. I.; Jaun, B.; Flögel, O.; Gardiner, J.; Löweneck, M.; Codée, J. D. C.; Seeberger, P. H.; Seebach, D.; Edmonds, M. K.; Graichen, F. H. M.; Abell, A. D. *Helv. Chim. Acta* **2007**, *90*, 2251.

(17) Seebach, D.; Rueping, M.; Arvidsson, P. I.; Kimmerlin, T.; Micuch, P.; Noti, C.; Langenegger, D.; Hoyer, D. *Helv. Chim. Acta* **2001**, *84*, 3503.

(18) (a) Arvidsson, P. I.; Frackenpohl, J.; Ryder, N. S.; Liechty, B.; Petersen, F.; Zimmermann, H.; Camenisch, G. P.; Woessner, R.; Seebach, D. *ChemBioChem* **2001**, *2*, 771. (b) Arvidsson, P. I.; Ryder, N. S.; Weiss, H. M.; Gross, G.; Kretz, O.; Woessner, R.; Seebach, D. *ChemBioChem* **2003**, *4*, 1345. (c) Seebach, D.; Namoto, K.; Mahajan, Y. R.; Bindschädler, P.; Sustmann, R.; Kirsch, M.; Ryder, N. S.; Weiss, M.; Sauer, M.; Roth, C.; Werner, S.; Beer, H.-D.; Munding, C.; Walde, P.; Voser, M. *Chem. Biodiversity* **2004**, *1*, 65.

(19) (a) Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445. (b) Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691. (c) Hook, D. F.; Bindschädler, P.; Mahajan, Y. R.; Šebesta, R.; Kast, P.; Seebach, D. *Chem. Biodiversity* **2005**, *2*, 591.

(20) (a) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.; Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734. (b) Stoeckli, M.; Staab, D.; Schweitzer, A.; Gardiner, J.; Seebach, D. *J. Am. Soc. Mass Spectrom.* **2007**, *18*, 1921. (c) Weiss, H. M.; Wirz, B.; Schweitzer, A.; Amstutz, R.; Rodriguez Perez, M. I.; Andres, H.; Metz, Y.; Gardiner, J.; Seebach, D. *Chem. Biodiversity* **2007**, *4*, 1413.

(21) Only recently have we discovered three microbial enzymes which curiously can cleave *only* β-peptidic bond ('β-aminopeptidases'), see reference 3m and: (a) Geueke, B.; Heck, T.; Limbach, M.; Nesatyy, V.; Seebach, D.; Kohler, H.-P. E. *FEBS J.* **2006**, *273*, 5261. (b) Heck, T.; Limbach, M.; Geueke, B.; Zacharias, M.; Gardiner, J.; Kohler, H.-P. E.; Seebach, D. *Chem. Biodiversity* **2006**, *3*, 1325. (c) Heck, T.; Kohler, H.-P. E.; Limbach, M.; Flögel, O.; Seebach, D.; Geueke, B. *Chem. Biodiversity* **2007**, *4*, 2016.

(22) Lukaszuk, A.; Demaegdt, H.; Szemenyei, E.; Tóth, G.; Tymecka, D.; Misicka, A.; Karoyan, P.; Vanderheyden, P.; Vauquelin, G.; Tourwé, D. *J. Med. Chem.* **2008**, *51*, 2291.

(23) For a recent example, see: Liu, Y.; Prashad, M.; Ciszewski, L.; Vargas, K.; Repič, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2008**, *12*, 183.

(24) (a) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. *J. Med. Chem.* **2001**, *44*, 2460. (b) Nunn, C.; Rueping, M.; Langenegger, D.; Schuepbach, E.; Kimmerlin, T.; Micuch, P.; Hurth, K.; Seebach, D.; Hoyer, D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2003**, *367*, 95.

(25) (a) Koch, K.; Podlech, J. *Synth. Commun.* **2005**, *35*, 2789. (b) Gray, D.; Concellón, C.; Gallagher, T. *J. Org. Chem.* **2004**, *69*, 4849. (c) Byrne, C. M.; Church, T. L.; Kramer, J. W.; Coates, G. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 3979; *Angew. Chem.* **2008**, *120*, 4043. (d) Lelais, G.; Micuch, P.; Josien-Lefebvre, D.; Rossi, F.; Seebach, D. *Helv. Chim. Acta* **2004**, *87*, 3131. (e) Flögel, O.; Casi, G.; Hilvert, D.; Seebach, D. *Helv. Chim. Acta* **2007**, *90*, 1651.

(26) For two recent papers on peptides consisting of such building blocks, see: (a) Salaün, A.; Potel, M.; Roisnel, T.; Gall, P.; Le Grel, P. *J. Org. Chem.* **2005**, *70*, 6499. (b) Li, X.; Yang, D. *Chem. Commun.* **2006**, 3367.

(27) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239; *Angew. Chem.* **1979**, *91*, 259.

(28) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, **1989**.

(29) (a) Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* **1975**, *14*, 15; *Angew. Chem.* **1975**, *87*, 1. (b) Seebach, D.; Lubosch, W.; Enders, D. *Chem. Ber.* **1976**, *109*, 1309. (c) Schlecker, R.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1459. (d) Schöllkopf, U. *Angew. Chem. Int. Ed.* **1977**, *16*, 339; *Angew. Chem.* **1977**, *89*, 351. (e) Marti, R. E.; Seebach, D. *Encyclopedia of Reagents for Organic Synthesis*, Vol. 5; John Wiley & Sons: New York, **2001**, 3138–3140. (f) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206; *Angew. Chem.* **2004**, *116*, 2256.

(30) (a) Pollack, M. A. *J. Am. Chem. Soc.* **1943**, *65*, 1335. (b) Lukas, J. H.; Gerber, G. B. *J. Labelled Compds.* **1965**, *1*, 229. (c) Hultin, P. G.; Jones, J. B. *Bioorg. Chem.* **1992**, *20*, 30.

(31) (a) For a recent example, see: Inaba, Y.; Yano, S.; Mikata, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 606. (b) Exception: Pirrung, M. C.; Brown, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 6388.

(32) (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015. (c) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961. (d) Oppolzer, W.; Rodriguez, I.; Starkemann, C.; Walther, E. *Tetrahedron Lett.* **1990**, *31*, 5019. (e) Blank, S.; Seebach, D. *Liebigs Ann. Chem.* **1993**, 889.

(33) (a) Kang, H.-Y.; Pae, A. N.; Cho, Y. S.; Koh, H. Y.; Chung, B. Y. *Chem. Commun.* **1997**, 821. (b) Ponsinet, R.; Chassaing, G.; Lavielle, S. *Tetrahedron: Asymmetry* **1998**, *9*, 865.

(34) (a) Haaf, K.; Rüchardt, C. *Chem. Ber.* **1990**, *123*, 635; and references cited therein. (b) Rüchardt, C.; Meier, M.; Haaf, K.; Pakusch, J.; Wolber, E. K. A.; Müller, B. *Angew. Chem. Int. Ed. Engl.* **1991**, *29*, 893; *Angew. Chem.* **1991**, *103*, 907.

(35) (a) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1852. (b) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (c) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887. (d) Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 5739. (e) Kedrowski, B. L.; Heathcock, C. H. *Heterocycles* **2002**, *58*, 601. (f) Nishikawa, T.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Synthesis* **2002**, 1658. (g) Métro, T.-X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2007**, *72*, 6556.

(36) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed.* **1997**, *35*, 2708; *Angew. Chem.* **1997**, *108*, 2881.

(37) Mannich, C.; Ganz, E. *Ber. Dtsch. Chem. Ges. B* **1922**, *55*, 3486.

(38) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *J. Org. Chem.* **1999**, *64*, 3790.

(39) D'Souza, A. A.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1.

(40) Barnett, C. J.; Wilson, T. M.; Evans, D. A.; Somers, T. C. *Tetrahedron Lett.* **1997**, *38*, 735.

(41) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093.

(42) Coffey, P. E.; Drauz, K.-H.; Roberts, S. M.; Skidmore, J.; Smith, J. A. *Chem. Commun.* **2001**, 2330.

(43) Šebesta, R.; Seebach, D. *Helv. Chim. Acta* **2003**, *86*, 4061.

(44) Gessier, F.; Schaeffer, L.; Kimmerlin, T.; Flögel, O.; Seebach, D. *Helv. Chim. Acta* **2005**, *88*, 2235.

(45) Meyer, H.; Beck, A. K.; Šebesta, R.; Seebach, D. *Org. Synth.* **2008**, *85*, 287.

(46) Müller-Hartwieg, J. C. D.; LaVecchia, L.; Meyer, H.; Beck, A. K.; Seebach, D. *Org. Synth.* **2008**, *85*, 295.

(47) Moumné, R.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2006**, *71*, 3332.

(48) Moumné, R.; Denise, B.; Guitot, K.; Rudler, H.; Lavielle, S.; Karoyan, P. *Eur. J. Org. Chem.* **2007**, 1912.

(49) Moumné, R.; Larregola, M.; Boutadla, Y.; Lavielle, S.; Karoyan, P. *Tetrahedron Lett.* **2008**, *49*, 4704.

(50) Arvanitis, E.; Ernst, H.; Ludwig, A. A.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 521.

(51) Seebach, D.; Schaeffer, L.; Gessier, F.; Bindschädler, P.; Jäger, C.; Josien, D.; Kopp, S.; Lelais, G.; Mahajan, Y. R.; Micuch, P.; Šebesta, R.; Schweizer, B. W. *Helv. Chim. Acta* **2003**, *86*, 1852.

(52) Bower, J. F.; Williams, J. M. J. *Synlett* **1996**, 685.

(53) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411.

(54) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K.-I. *J. Org. Chem.* **1997**, *62*, 5830.

(55) Liu, W.-Q.; Olszowy, C.; Bischoff, L.; Garbay, C. *Tetrahedron Lett.* **2002**, *43*, 1417.

(56) Micuch, P.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1567.

(57) Lelais, G.; Campo, M. A.; Kopp, S.; Seebach, D. *Helv. Chim. Acta* **2004**, *87*, 1545.

(58) Hu, X.; Nguyen, K. T.; Verlinde, C. L. M. J.; Hol, W. G. J.; Pei, D. *J. Med. Chem.* **2003**, *46*, 3771.

(59) (a) Doldouras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *100*, 341. (b) Shier, W. T.; Abbas, H. K.; Badria, F. A. *Tetrahedron Lett.* **1995**, *36*, 1571.

(60) (a) Honda, T.; Ishikawa, F. *Chem. Commun.* **1999**, 1065. (b) Katoh, M.; Inoue, H.; Suzuki, A.; Honda, T. *Synlett* **2005**, 2820.

(61) (a) Spatola, A. F.; Bettag, A. L. *J. Org. Chem.* **1981**, *46*, 2393; and references cited therein. (b) Jang, D. O. *Tetrahedron Lett.* **1996**, *37*, 5367. (c) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Kutsuna, T.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 1203. (d) Park, L.; Keum, G.; Kang, S. B.; Soo Kim, K.; Kim, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4462. (e) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R.; Romera, J. L. *Synlett* **2001**, 485. (f) Li, J.; Ye, D.; Liu, H.; Luo, X.; Jiang, H. *Synth. Commun.* **2008**, *38*, 567.

(62) (a) Fischli, A. *Chiral building blocks in enantiomer synthesis using enzymic transformations,* In *Modern Synthetic Methods 1980*, Vol. 2; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt a. M., **1980**, 269–350. (b) Seebach, D.; Roggo, S.; Zimmermann, J. *Biological-Chemical Preparation of 3-Hydroxycarboxylic Acids and Their Use in EPC-Syntheses,* In *Stereochemistry of Organic and Bioorganic Transformations*, Vol. 17; Bartmann, W.; Sharpless, K. B., Eds.; Workshop Conferences Hoechst Verlag Chemie: Weinheim, **1987**, 85–126.

(63) (a) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*,

2479. (b) Jin, Y.; Kim, D. H. *Synlett* **1998**, 1189. (c) Jin, Y. H.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3515. (d) Yokomatsu, T.; Minowa, T.; Murano, T.; Shibuya, S. *Tetrahedron* **1998**, *54*, 9341. (e) Ghosh, A. K.; Bischoff, A. *Org. Lett.* **2000**, *2*, 1573. (f) Walz, A. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 2047. (g) Lee, H. S.; Park, J. D.; Kim, D. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 467. (h) Ghosh, A. K.; Bischoff, A. *Eur. J. Org. Chem.* **2004**, 2131. (i) Danner, P.; Bauer, M.; Phukan, P.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 317. (j) Maibaum, J.; Stutz, S.; Göschke, R.; Rigollier, P.; Yamaguchi, Y.; Cumin, F.; Rahuel, J.; Baum, H.-P.; Cohen, N.-C.; Schnell, C. R.; Fuhrer, W.; Gruetter, M. G.; Schilling, W.; Wood, J. M. *J. Med. Chem.* **2007**, *50*, 4832. (k) Ham, W.-H.; Oh, C.-Y.; Lee, Y.-S.; Jeong, J.-H. *J. Org. Chem.* **2000**, *65*, 8372.

(64) The sultam **D** is an irritant which may prevent its application on large scale or in an industrial process.

(65) Brenner, M.; La Vecchia, L.; Leutert, T.; Seebach, D. *Org. Synth.* **2003**, *80*, 57.

(66) Gaul, C.; Schweizer, B. W.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1546.

(67) (a) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (b) Chi, Y.; English, E. P.; Pomerantz, W. C.; Horne, W. S.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6050.

(68) The Córdova group has also studied the aminomethylation of aldehydes but have actually prepared only a single β^2-amino acid derivative (Boc-β^2hAla-OH): Ibrahem, I.; Zhao, G.-L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 683.

(69) (a) Davies, H. M. L.; Venkataramani, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 2197; *Angew. Chem.* **2002**, *114*, 2301. (b) Davies, H. M. L.; Ni, A. *Chem. Commun.* **2006**, 3110.

(70) See, for instance, the discussions in: (a) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103. (b) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824; and references cited therein.

(71) An amino group itself is a poor leaving group (R_2N^-) from an enolate. On the other hand, phthalimido or sulfonylamido groups [R(R'SO_2)N^-] would be expected to be good leaving groups.

(72) Guzmán-Mejía, R.; Reyes-Rangel, G.; Juaristi, E. *Nat. Protoc.* **2007**, *2*, 2759.

(73) Sibi, M. P.; Deshpande, P. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1461.

(74) Xue, C.-B.; He, X.; Roderick, J.; Corbett, R. L.; Decicco, C. P. *J. Org. Chem.* **2002**, *67*, 865.

(75) Zhang, X.; Ni, W.; van der Donk, W. A. *J. Org. Chem.* **2005**, *70*, 6685.

(76) Beddow, J. E.; Davies, S. G.; Smith, A. D.; Russell, A. J. *Chem. Commun.* **2004**, 2778.

(77) Ponsinet, R.; Chassaing, G.; Vaissermann, J.; Lavielle, S. *Eur. J. Org. Chem.* **2000**, 83.

(78) Woźniak, D.; Szymańska, A.; Oldziej, S.; Łankiewicz, L.; Grzonka, Z. *Pol. J. Chem.* **2006**, *80*, 265.

(79) (a) Seki, M.; Furutani, T.; Miyake, T.; Yamanaka, T.; Ohmizu, H. *Tetrahedron: Asymmetry* **1996**, *7*, 1241. (b) Seki, M.; Miyake, T.; Yamanaka, T.; Ohmizu, H. *Synlett* **1996**, 455.

(80) Tessier, A.; Lahmar, N.; Pytkowicz, J.; Brigaud, T. *J. Org. Chem.* **2008**, *73*, 3970.

(81) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527.

(82) (a) Gutiérrez-García, V. M.; López-Ruiz, H.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2001**, *57*, 6487. (b) Gutiérrez-García, V. M.; Reyes-Rangel, G.; Muñoz-Muñiz, O.; Juaristi, E. *J. Braz. Chem. Soc.* **2001**, *12*, 652. (c) Gutiérrez-García, V. M.; Reyes-Rangel, G.; Muñoz-Muñiz, O.; Juaristi, E. *Helv. Chim. Acta* **2002**, *85*, 4189. (d) Avila-Ortiz, C. G.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2005**, *61*, 8372.

(83) Stončius, A.; Nahrwold, M.; Sewald, N. *Synthesis* **2005**, 1829.

(84) Arvanitis, E.; Motevalli, M.; Wyatt, P. B. *Tetrahedron Lett.* **1996**, *37*, 4277.

(85) (a) Stork, G. *Pure Appl. Chem.* **1968**, *17*, 383. (b) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682.

(86) Previously phenylethylamine was added directly to α,β-unsaturated esters with poor stereoselectivities; the diastereoisomers formed were separated, so that eventually both enantiomeric products were isolated. For examples, see reference 70 and: (a) Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1319. (b) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650.

(87) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1; *Angew. Chem.* **1985**, *97*, 1.

(88) (a) Meyers, A. I. *General Heterocyclic Chemistry Series: Heterocycles in Organic Synthesis*; Wiley-Interscience: New York, **1974**. (b) Rottmann, A.; Bartoczek, M.; Liebscher, J. *Synthesis* **1997**, 313.

(89) (a) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355. (b) Lakner, F. J.; Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *Org. Synth.* **1996**, *73*, 201. (c) Kinkel, J. N.; Gysel, U.; Blaser, D.; Seebach, D. *Helv. Chim. Acta* **1991**, *74*, 1622. (d) Seebach, D.; Boog, A.; Schweizer, W. B. *Eur. J. Org. Chem.* **1999**, 335. (e) Juaristi, E.; Quintana, D. *Tetrahedron: Asymmetry* **1992**, *3*, 723. (f) Juaristi, E.; Quintana, D.; Balderas, M.; García-Peréz, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233. (g) Juaristi, E.; Balderas, M.; López-Ruiz, H.; Jiménez-Pérez, V. M.; Kaiser-Carril, M. L.; Ramírez-Quirós, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 3493. (h) Muñoz-Muñiz, O.; Juaristi, E. *Tetrahedron* **2003**, *59*, 4223.

(90) Agami, C.; Cheramy, S.; Dechoux, L. *Synlett* **1999**, 1838.

(91) Belokon, Y. N.; Mociskite, S.; Maleev, V. I.; Orlova, S. A.; Ikonnikov, N. S.; Shamuratov, E. B.; Batsanov, A. S.; Struchkov, Y. T. *Mendeleev Commun.* **1992**, 89.

(92) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341.

(93) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579.

(94) Hübner, J.; Liebscher, J.; Pätzel, M. *Tetrahedron* **2002**, *58*, 10485.

(95) (a) Sewald, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5794; *Angew. Chem.* **2003**, *115*, 5972. (b) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79. (c) Rimkus, A.; Sewald, N. *Synthesis* **2004**, 135.

(96) Eilitz, U.; Leßmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189.

(97) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700.

(98) Seebach, D.; Marti, R.; Beck, A. K.; Sprecher, H.; Pletscher, S.; Möri, M. *hitherto unpublished results*; ETH Zürich and Zürcher Hochschule für Angewandte Wissenschaften 2006–2008.

(99) van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558.

(100) (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1. (b) Ono, N. *The Nitro Group in Organic Synthesis*; John Wiley & Sons: New York, **2001**.

(101) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481. (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; *Angew. Chem.* **2007**, *119*, 4698.
(102) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575.
(103) (a) Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949. (b) Perlmutter, P.; Tabone, M. *J. Org. Chem.* **1995**, *60*, 6515.
(104) Singh, S. K.; Singh, G. B.; Byri, V. K.; Satish, B.; Dhamjewar, R.; Gopalan, B. *Synth. Commun.* **2008**, *38*, 456.
(105) (a) Pratt, L. M.; Beckett, R. P.; Davies, S. J.; Launchbury, S. B.; Miller, A.; Spavold, Z. M.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2585. (b) Jiang, X.; Prasad, K.; Prashad, M.; Slade, J.; Repič, O.; Blacklock, T. J. *Synlett* **2006**, 3179.
(106) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624; *Angew. Chem.* **1988**, *100*, 1685. (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.
(107) A special case is the Et_3N-catalyzed addition of the hydroxy group of a rather complex, polymer-bound chiral molecule to the ketene derived from 2-aryl-3-phthalimidopropanoic acid; after hydrolysis, β^2Phg derivatives are isolated: Akkari, R.; Calmés, M.; Di Malta, D.; Escale, F.; Martinez, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1223.
(108) (a) Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2060; *Angew. Chem.* **2003**, *115*, 2106. (b) Volonterio, A.; Chiva, G.; Fustero, S.; Piera, J.; Rosello, M. S.; Sani, M.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 7019. (c) Fustero, S.; Garcia Sancho, A.; Chiva, G.; Sanz-Cervera, J. F.; Del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 3299. (d) Fustero, S.; Chiva, G.; Piera, J.; Volonterio, A.; Zanda, M.; González, J.; Ramallal, A. M. *Chem. Eur. J.* **2007**, *13*, 8530.
(109) Sibi, M. P.; Patil, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1235; *Angew. Chem.* **2004**, *116*, 1255.
(110) Sibi, M. P.; Tatamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571.
(111) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2004**, *43*, 719; *Angew. Chem.* **2004**, *116*, 737.
(112) Elaridi, J.; Thaqi, A.; Prosser, A.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1309.
(113) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869.
(114) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657.
(115) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359.
(116) Qiu, L.; Prashad, M.; Hu, B.; Prasad, K.; Repič, O.; Blacklock, T. J.; Kwong, F. Y.; Kok, S. H. L.; Lee, H. W.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 16787.
(117) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015.
(118) Tanaka, T.; Muto, T.; Maruoka, H.; Imajo, S.; Fukami, H.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3431.
(119) Swiderska, M. A.; Stewart, J. D. *Org. Lett.* **2006**, *8*, 6131.
(120) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862.
(121) (a) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008; *Angew. Chem.* **2002**, *114*, 2108. (b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 34; *Angew. Chem.* **1991**, *103*, 34. (c) Züger, M. F.; Giovannini, F.; Seebach, D. *Angew. Chem. Int. Ed.* **1983**, *22*, 1012; *Angew. Chem.* **1983**, *95*, 1024. (d) Seebach, D.; Renaud, P.; Schweizer, W. B.; Züger, M. F.; Brienne, M. J. *Helv. Chim. Acta* **1984**, *67*, 1843. (e) Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. *Org. Synth.* **1985**, *63*, 1. (f) Ehrler, J.; Giovannini, F.; Lamatsch, B.; Seebach, D. *Chimia* **1986**, *40*, 172. (g) Seebach, D.; Eberle, M. *Synthesis* **1986**, 37. (h) Seebach, D.; Herradon, B. *Tetrahedron Lett.* **1987**, *28*, 3791. (i) Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta* **1987**, *70*, 1605. (j) Herradon, B.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690. (k) Haag, T.; Arslan, T.; Seebach, D. *Chimia* **1989**, *43*, 351. (l) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.
(122) Mashima, K.; Matsumura, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1991**, 609.
(123) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2309.
(124) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 2043.
(125) Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Kim, W. H.; Han, Y. S.; Yun, H.-C.; Lee, J.; Koh, H. Y.; Lee, E. *Biotechnol. Lett.* **2002**, *24*, 1695.
(126) Shimoda, K.; Kubota, N.; Hamada, H.; Hamada, H. *Tetrahedron Lett.* **2006**, *47*, 1541.
(127) Díaz-Sánchez, B. R.; Iglesias-Arteaga, M. A.; Melgar-Fernández, R.; Juaristi, E. *J. Org. Chem.* **2007**, *72*, 4822.
(128) (a) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (b) Goodman, S. N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 4703; *Angew. Chem.* **2002**, *114*, 4897.
(129) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003.
(130) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.
(131) Liu, H.; Xu, J.; Du, D.-M. *Org. Lett.* **2007**, *9*, 4725.
(132) Schleich, S.; Helmchen, G. *Eur. J. Org. Chem.* **1999**, 2515.
(133) (a) Zheng, X.; Day, C.; Gollamudi, R. *Chirality* **1995**, *7*, 90. (b) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthäuser, S.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995.
(134) For a reliable determination of the enantiopurity of β^2-, β^3- and γ-amino acids by NMR analysis of diastereoisomeric Pd complexes see: Böhm, A.; Seebach, D. *Helv. Chim. Acta* **2000**, *83*, 3262.
(135) In many cases, the reported preparations ended with 'reasonable' precursors to properly protected β^2-amino acids for peptide synthesis.
(136) In one case discussed (Scheme 11, c), an approximately 1:1 mixture of diastereoisomers was actually separated chromatographically to eventually provide the enantiomeric β^2-amino acid derivatives.[102]
(137) For a large-scale production of an enantiopure drug or pesticide, on the other hand, it is not acceptable to lose 50% of material through resolution, after a multistep synthesis.

(138) (a) Hellmann, H.; Haas, G. *Chem. Ber.* **1957**, *90*, 1357. (b) Böhme, H.; Broese, R.; Eiden, F. *Chem. Ber.* **1959**, *92*, 1258. (c) Tan, C. Y. K.; Wainman, D.; Weaver, D. F. *Bioorg. Med. Chem.* **2003**, *11*, 113. (d) Hessler, J. C. *J. Am. Chem. Soc.* **1913**, *35*, 990. (e) Gardner, P. D.; Brandon, R. L. *J. Org. Chem.* **1957**, *22*, 1704. (f) Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060. (g) Albarella, J. P. *J. Org. Chem.* **1977**, *42*, 2009. (h) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (i) Romanova, N. N.; Budylin, V. A.; Grishina, G. V.; Potapov, V. M.; Demchuk, M. L.; Sivkova, I. Y.; Bundel, Y. G. *Chem. Heterocycl. Compd.* **1986**, *22*, 495. (j) Urbach, A.; Muccioli, G. G.; Stern, E.; Lambert, D. M.; Marchand-Brynaert, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4163. (k) Seebach, D.; Henning, R.; Lehr, F.; Gonnermann, J. *Tetrahedron Lett.* **1977**, 1161. (l) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705.

(139) Lukaszuk, A.; Tourwé, D. *hitherto unpublished results*; Department of Organic Chemistry Vrije Universiteit Brussel, Belgium.

(140) Salamonczyk, G. M.; Han, K.; G uo, Z.-w.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893.

(141) Solymár, M.; Liljeblad, A.; Lázár, L.; Fülöp, F.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2002**, *13*, 1923.

(142) Fitz, M.; Forró, E.; Vigóczki, E.; Lázár, L.; Fülöp, F. *Tetrahedron: Asymmetry* **2008**, *19*, 1114.

(143) Ma, D.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Tetrahedron: Asymmetry* **2006**, *17*, 2366.

(144) A notable exception is *Gmelin*, for which the version available at the host *STN International* has not been updated since 1997. For other databases, there may be significant differences in item coverage; for example, the *Science Citation Index* database version available under *Web of Knowledge/Web of Science* goes back to 1900, while the same database at the host *STN International* extends only back to 1974.

(145) Ridley, D. D. *Information Retrieval: SciFinder and SciFinder Scholar*; John Wiley & Sons: Chichester UK, **2002**.

(146) *STN International*: http://www.stn-international.de/ (last accessed 27.8.2008).

(147) *STN Messenger Commands*: http://www.stn-international.de/training_center/rl/commands/Contents.htm (last accessed 27.8.2008).

(148) *STN Registry*: http://www.stn-international.de/stndatabases/databases/registry.html (last accessed 27.8.2008).

(149) *STN CASREACT*: http://www.stn-international.de/stndatabases/databases/casreact.html html (last accessed 27.8.2008).

(150) So far, for any such 'AutoFix' problem in *SciFinder Scholar* referred to us, the undesired limit could be eliminated by searching in *STN*, but at the extra cost involved in those 'pay-per-use' searches at this host.

(151) (a) Weisgerber, D. W. *J. Am. Soc. Inf. Sci.* **1997**, *48*, 349. (b) Buntrock, R. E. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 259. (c) Blackwood, J. E.; Blower, P. E. Jr.; Layten, S. W.; Lillie, D. H.; Lipkus, A. H.; Peer, J. P.; Qian, C.; Staggenborg, L. M.; Watson, C. E. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 204.

(152) This reliance on *CASREACT* is not without problems, both regarding reaction selection policies of *CAS*, and particularly the time coverage of this database: specified by *CAS* as covering the literature back to 1840 (http://www.cas.org/expertise/cascontent/casreact.html), full coverage provided by *CAS* literature exception starts only in 1985 (for reactions from patents, only in 1991). Before that time, coverage is almost entirely provided by non-*CAS* sources: *ZIC/VINITI*, and *INPI* (French Patent Office).

(153) *CAplus*: http://www.cas.org/expertise/cascontent/caplus/index.html (last accessed 27.8.2008).

(154) Some publications appear in more than one of the categories shown.

(155) *SciFinder* search (as of November 2008) provides more than 500 hits of commercially available enantiopure β^2-amino acids, but only 16 hits for β^2-amino acids, which are offered up to the 10-kg scale.

(156) For instance, Phoenix Chemicals or Novasep.

(157) …compare with total syntheses of complex natural products! (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44; *Angew. Chem.* **2000**, *112*, 46. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; Wiley-VCH: Weinheim, **1996**. (c) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed the World: A Brief History of the Art and Science of Synthesis and Its Impact on Society*; Wiley-VCH: Weinheim, **2008**.

(158) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187.

(159) Calmés, M.; Escale, F.; Glot, C.; Rolland, M.; Martinez, J. *Eur. J. Org. Chem.* **2000**, 2459.

(160) Yokomatsu, T.; Takada, K.; Yasumoto, A.; Yuasa, Y.; Shibuya, S. *Heterocycles* **2002**, *56*, 545.

(161) Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Ravi, R.; Kunwar, A. C. *J. Org. Chem.* **2006**, *71*, 3967.