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# Synthesis of Enantiopure *N*- and *C*-Protected *homo*-β-Amino Acids by Direct Homologation of α-Amino Acids¶,1

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**Abstract:** Enantiopure *N*- and/or *C*-protected *homo*-β-amino acids are prepared readily and in good yields from *N*-protected α-amino acids with the same side chain, *via* reduction of the carboxyl function and conversion of the resulting *N*-protected β-amino alcohol into the corresponding β-amino iodide and then β-amino cyanide. The key step of this strategy is represented by the synthesis of the enantiopure *N*-protected β-amino iodides **2** and **3** that are smoothly obtained from the parent amino alcohols **1** by polymer bound triarylphosphine-$I_2$ complex in anhydrous dichloromethane.

Design and synthesis of new, modified peptides depend largely upon the availability of uncommon amino acids, and in recent years β-amino acids (*homo*-β-amino acids[1]) have increased enormously their importance for the preparation of peptides with enhanced *in vivo* stability[1,2] as well as for the synthesis of β-lactam antibiotics[3]. Beside some early syntheses of racemic materials[2,4,5] a number of methods for the preparation of enantiopure β-amino acids and their derivatives already exist, and two excellent reviews on the topic have recently appeared[5,6]. Excepting the multi-step syntheses aimed at the preparation of individual β-amino acids[5] or particular classes of substituted β-amino acids[7], two main strategies are nowadays available to obtain *homo*-β-amino acids from their α-amino acid counterparts, namely a "true" homologation process of the carboxyl end of the latter, under the classical[8] or modified[9] Arndt-Eistert conditions, and a "formal" homologation process exploiting the preexistent β-amino carboxyl moiety of aspartic acid and its derivatives to build up the β-amino acid molecule[10-12]. Unfortunately, the Arndt-Eistert conditions of direct homologation are not suitable for large scale preparations and, besides, are not ideal for preserving the *N*-Fmoc protection of the starting α-amino acids. The formal homologation based on the use of aspartic acid derivatives, on the other hand, consists of the conversion of the α-carboxyl group into an amino acid side chain that sometimes may require several steps and is generally accomplished with rather low overall yield.

We have now devised a new process for the direct conversion of *N*-protected α-amino acids into their β-homologues under smooth, clean, quick, and large-scale applicable conditions. The key step of the whole conversion (Scheme 1) is represented by the synthesis of the enantiomerically pure *N*-protected β-amino iodides **2** and **3**. Based on our former experience in the use of polymer bound triarylphosphine-halogen complexes[14], the latter were in fact prepared by treatment of their corresponding *N*-protected β-amino alcohols

(obtained by *N*-protection[15,16] of commercially available β-amino alcohols, or by reduction of parent α-amino acid derivatives[17-18]) with polystyryl diphenylphosphine-iodine (PDPI) complex, in high yield and without any detectable epimerization of the chiral center. The subsequent replacement of the iodine atom in **2** and **3** by a cyano group, and hydrolysis (or alcoholysis) of the latter, then completed the synthetic sequence leading to *N*- and/or *C*-protected *homo*-β-amino acids. The extent of racemization at the chiral center of the starting α-amino acids and/or β-amino alcohols was checked at the various stages of the whole process by chiral column HPLC comparative analysis with specially prepared racemic intermediates. Under our conditions no traces of racemized products could be detected, even in the racemization prone[19] phenylglycine series.

It is noteworthy that, otherwise some reported procedures[20-22], the *N*-protected β-amino cyanides **4** and **5** (not **6**) may be obtained from their parent β-amino iodides **2** and **3** under experimental conditions that are compatible with the presence of the usual alkoxycarbonyl *N*-protecting groups currently utilized in peptide chemistry, namely *N*-Boc (*t*-butoxycarbonyl) and *N*-Cbz (benzyloxycarbonyl). *N*-Fmoc (9-fluorenylmethoxy carbonyl) derivatives **6**, due to their sensitivity to the basic treatments (*vide infra*), are however prepared *via* *N*-protection exchange from their *N*(Boc) analogs **5**.

The aspects that are peculiar of the various steps of the homologation process will be discussed in the following sections A-D.

## A. SYNTHESIS OF *N*-PROTECTED β-AMINO ALCOHOLS

*N*-Protected β-amino alcohols **1** were prepared either from commercial β-amino alcohols and *N*-urethane bond forming reagents, by modified literature procedures[15,16], or from *N*-protected α-amino acid mixed anhydrides by sodium borohydride reduction[17,18].

The free β-amino alcohols were treated with commercial reagents for selective *N*-protection, as di-*t*-butyl-dicarbonate [$(t\text{-Boc})_2O$] and *N*-(benzyloxycarbonyloxy)-succinimide [Cbz-OSu], in tetrahydrofuran at room temperature in the presence of triethylamine, the latter being conveniently replaced by diluted aq sodium carbonate when 9-fluorenylmethyl-succinimidyl carbonate [Fmoc-OSu] was used as the *N*-protection reagent. The *N*-protected β-amino alcohols thus obtained (Table 1)[23] were then crystallized from hexane-ethyl acetate (*N*-Boc) or hexane-dichloromethane (*N*-Cbz and *N*-Fmoc) mixtures.

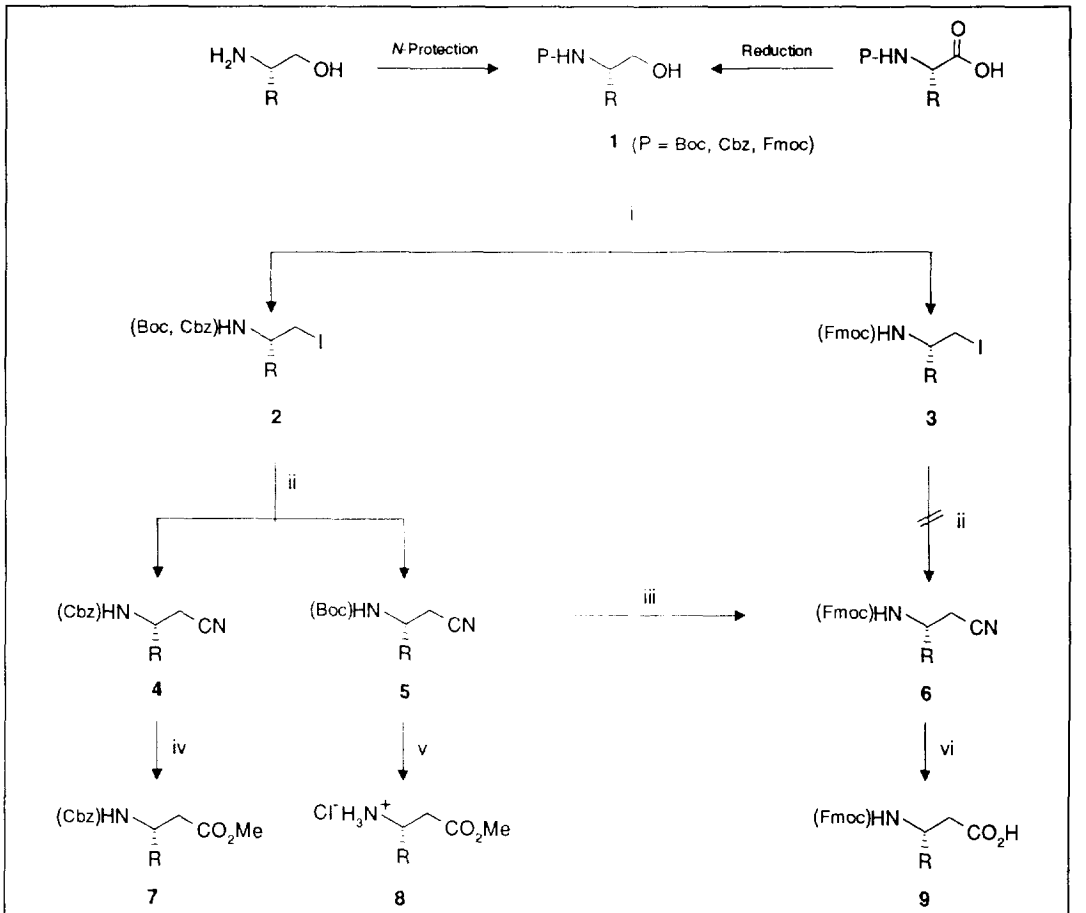
The reduction of *N*-protected α-amino acid mixed anhydrides was found very convenient for preparing *N*-protected β-amino alcohols from trifunctional α-amino acids carrying a further protective group on their side chain and was thus utilized successfully to synthesize the compounds **1g,h,n** (Table 1)[23].

## B. CONVERSION OF *N*-PROTECTED β-AMINO ALCOHOLS INTO *N*-PROTECTED β-AMINO IODIDES

*N*(Cbz)-Protected β-amino iodides **2i** and **2j** (Table 2)[23] were already reported to be intermediates in the synthesis of chiral *trans*-2,5-dimethylpyrrolidines[24] and of HIV-1 protease inhibitors[25] respectively. *N*(Cbz)-Protected β-*t*-butyl aspartate β'-amino iodide (paralleling **2g** in Table 2)[23] was also reported[10]. The preparation of such compounds is accomplished invariably in two steps by conversion of the parent β-amino alcohols into their tosyl or mesyl esters which in their turn lead to the iodides under the Finkelstein conditions (NaI in acetone).

The conditions we have devised for the preparation of *N*-protected β-amino iodides **2**, in only one step

**Scheme 1. Synthetic Pathways for *N*- and/or *C*-Protected *homo*-β-Amino Acid Preparation**




i. PDPI, imidazole, $CH_2Cl_2$, reflux 1 h; ii. $Et_4N^+CN^-$, $CH_2Cl_2$, reflux 4 h; iii. 30% TFA in $CH_2Cl_2$, 0° C, 0.5 h, then FmocOSu, 10% aq $Na_2CO_3$, THF, room temp. 1 h; iv. excess conc. HCl/MeOH, $Et_2O$, 4° C 12 h; v. as iv without $Et_2O$, room temp. 12 h; vi. excess conc. aq HCl, dioxane, reflux 8 h.

from their corresponding *N*-protected β-amino alcohols **1**, utilizes a triarylphosphine-iodine complex in the presence of imidazole[14] to accomplish the OH→I replacement in high yield and under very mild conditions (1 h reflux, in dichloromethane), suitable for the preservation of the commonly used *N*- and side chain-protecting groups and, at the same time, unaffecting the chiral center configuration. Imidazole should act as a proton trap for the hydrogen ions released during the reaction. Imidazole has been also suggested (although without experimental evidence[26]) to play an active role at least in some other reactions involving the triphenylphosphine-iodine reagent.

The choice of a polymer bound triarylphosphine, like polystyryl diphenylphosphine, to prepare the iodide ensures that the phosphine oxide, which is formed under our conditions as the only byproduct of the reaction, is linked to a polymeric matrix and, thus, can be separated by simple filtration. This avoids time consuming and circumstantial purification procedures to obtain the pure product that in fact can be directly

**Table 1.** ***N*-Protected β-Amino Alcohols**

| | *N*-Protection | R [a] | m.p. (°C) | $[\alpha]_D^{25}$ (*c*) [b] | Yield % [c] | Ref. |
|---|---|---|---|---|---|---|
| **1a** | Boc | Ala | 59-61 | -8.9 (1.01) | 92 | 28 |
| **1b** | Boc | Abu | 43-44 | -13.0 (0.73) | 93 | -- |
| **1c** | Boc | Val | oil | -17.0 (1.68) | 94 | 29[d] |
| **1d** | Boc | Leu | oil | -22.0 (1.66) | 90 | 29[d] |
| **1e** | Boc | Phe | 95-97 | -27.7 (1.11) | 90 | 17 |
| **1f** | Boc | Phg | 137-138 | +39.4 (1.67) | 96 | 30 |
| **1g** | Boc | Asp(OBn) | oil | -6.2 (1.08)[e] | 87 | 18 |
| **1h** | Boc | Tyr(Bn) | 107-109 | -17.2 (0.55) | 94 | 31 |
| **1i** | Cbz | Ala | 62-64 | -6.4 (1.00) | 92 | 30 |
| **1j** | Cbz | Phe | 90-91 | -42.5 (1.05)[e] | 95 | 30 |
| **1k** | Fmoc | Ala | 125-127 | -11.6 (1.02) | 92 | -- |
| **1l** | Fmoc | Leu | 136-137 | -24.6 (0.53) | 94 | -- |
| **1m** | Fmoc | Phe | 166-167 | -21.0 (1.03) | 96 | 16[f] |
| **1n** | Fmoc | D-Asp(O*t*Bu) | 95-96 | +20.0 (0.54) | 88 | 18[d] |

[a] Considered as the side chain of the α-amino acid indicated. [b] $CHCl_3$ solutions (1.0 dm cell). [c] Yield of pure crystallized product. [d] Enantiomer reported. [e] Measured in MeOH. [f] Rotation not reported.

**Table 2.** ***N*-Protected β-Amino Iodides from *N*-Protected β-Amino Alcohols**

| | *N*-Protection | R [a] | m.p. (°C) | $[\alpha]_D^{25}$ (*c*) [b] | Yield% [c] | Ref. |
|---|---|---|---|---|---|---|
| **2a** | Boc | Ala | 58-59 | -18.6 (0.99) | 90 | -- |
| **2b** | Boc | Abu | 51-52 | -36.7 (0.49) | 94 | -- |
| **2c** | Boc | Val | 48-51 | -18.7 (2.10) | 78 | -- |
| **2d** | Boc | Leu | 55-57 | -29.9 (1.30) | 90 | -- |
| **2e** | Boc | Phe | 110-111 | +1.3 (1.20) | 92 | -- |
| **2f** | Boc | Phg | 97-98 | +51.6 (0.88) | 91 | -- |
| **2g** | Boc | Asp(OBn) | 42-43 | +6.6 (1.08) | 82 | -- |
| **2h** | Boc | Tyr(Bn) | 117-118 | +21.2 (0.80) | 86 | -- |
| **2i** | Cbz | Ala | 96-97 | -11.2 (2.86)[d] | 89 | 24 |
| **2j** | Cbz | Phe | 92-93 | +8.2 (0.88) | 90 | 25 |
| **3k** | Fmoc | Ala | 127-128 | -11.3 (1.02) | 92 | -- |
| **3l** | Fmoc | Leu | 111-113 | -21.3 (1.20) | 94 | -- |
| **3m** | Fmoc | Phe | 148-149 | +2.7 (1.36) | 94 | -- |
| **3n** | Fmoc | D-Asp(O*t*Bu) | 145-146 | -9.4 (0.98) | 90 | -- |

[a] Considered as the side chain of the α-amino acid indicated. [b] $CHCl_3$ solutions (1.0 dm cell). [c] Yield of pure crystallized product. [d] Measured in $CH_2Cl_2$.

crystallized from a suitable solvent (hexane-dichloromethane). The *N*-protected β-amino iodides **2** and **3**, prepared under such conditions, are reported[23] in Table 2. Attempts to prepare some of them by using the dichloromethane soluble -and much less expensive- triphenylphosphine-iodine complex were also successful but the product yields were somewhat lower, in the range 70-75%.

It is also noteworthy that we did not observe any formation of aziridines that instead occurs in the reactions of either *N*-alkyl[27] or *N*-tosyl[20] β-amino alcohols with triphenylphosphine in carbon tetrachloride or carbon tetrabromide.

## C. *N*-PROTECTED β-AMINO CYANIDES

Preparations of chiral *N*-protected β-amino cyanides (as **4**, **5**, and **6**) have been very seldom reported. *N*-Tosyl β-amino cyanides were prepared[20] from *N*-tosyl aziridines by trimethylsilyl cyanide in the presence of lanthanoid cyanides as catalysts; *N,N*-dibenzyl β-amino cyanides have been also obtained by Barton deoxygenation[32] of *N,N*-dibenzyl-α-amino aldehyde cyanohydrins[21] or by an intriguing monosubstitution operated by LiCN in DMF onto the mesyl diester of the *N,N*-diprotected amino diol coming from aspartic acid reduction[22]. To the best of our knowledge, the conversion of *N*(Boc)-(*R*)-phenylglycinol tosyl ester into the corresponding β-amino cyanide by NaCN in DMSO (90° C, 1 h) represents (although questionable[33]) the only example of synthesis of *N*(alkoxycarbonylamino)-protected β-amino cyanides[34].

In our hands *N*(Boc)- and *N*(Cbz)-protected β-amino iodides **2** were smoothly converted into their corresponding cyanides **4** and **5** by 4 h reflux with tetraethylammonium cyanide[35] in dichloromethane. Unfortunately *N*(Fmoc)-protected β-amino iodides **3** under these conditions undergo partial nitrogen

**Table 3. *N*-Protected β-Amino Cyanides from *N*-Protected β-Amino Iodides**

| | *N*-Protection | R [a] | m.p. (°C) | $[\alpha]_D^{25}$ (*c*) [b] | Yield% [c] | Ref. |
|---|---|---|---|---|---|---|
| **4i** | Cbz | Ala | 46-47 | -76.0 (0.50) | 84 | -- |
| **4j** | Cbz | Phe | 110-111 | -40.5 (0.24) | 78 | -- |
| **5a** | Boc | Ala | 69-71 | -87.0 (1.00) | 84 | -- |
| **5b** | Boc | Abu | 75-76 | -78.8 (0.23) | 83 | -- |
| **5c** | Boc | Val | 82-84 | -81.5 (0.65) | 82 | -- |
| **5d** | Boc | Leu | 75-77 | -83.2 (0.82) | 82 | -- |
| **5e** | Boc | Phe | 119-120 | -18.7 (0.48) | 83 | -- |
| **5f** | Boc | Phg | 112-113 | + 42.2 (0.45) [d,e] | 80 | 33,34 |
| **5h** | Boc | Tyr(Bn) | 113-114 | -11.5 (0.34) | 77 | -- |
| **6k** | Fmoc | Ala | 115-118 | -46.0 (0.42) | 95 [f] | -- |
| **6l** | Fmoc | Leu | 101-103 | -55.1 (0.63) | 94 [f] | -- |
| **6m** | Fmoc | Phe | 148-150 | -20.1 (0.81) | 91 [f] | -- |
| **6o** | Fmoc | Abu | 130-132 | -50.2 (0.55) | 95 [f] | -- |
| **6p** | Fmoc | Val | 127-128 | -55.4 (0.33) | 92 [f] | -- |

[a] Considered as the side chain of the α-amino acid indicated. [b] $CHCl_3$ solutions (1.0 dm cell). [c] Yield of pure crystallized product. [d] Measured in EtOH. [e] Enantiomer reported. [f] From their *N*(Boc)-analogues.

deprotection and, thus, the *N*(Fmoc)-protected β-amino cyanides **6** are better prepared from their *N*(Boc)-protected analogues **5** *via* Boc removal and Fmoc reprotection of the amino group by standard procedures.

The workup of the reaction with tetraethylammonium cyanide is also very simple and safe since, when the starting *N*-protected β-amino iodide **2** is fully consumed (TLC monitoring), silica gel is added to the reaction mixture and the solvent is evaporated under reduced pressure. The solid is then mechanically collected from the reaction flask walls and transferred directly onto a short silica gel column from which the product is eluted with light petrol-ethyl acetate and finally crystallized from dichloromethane-hexane. It is also noteworthy that this represents the only chromatographic purification throughout the whole process.

All the *N*-protected β-amino cyanides we have prepared are listed[23] in Table 3.

## D. HYDROLYSIS AND ALCOHOLYSIS OF *N*-PROTECTED β-AMINO CYANIDES

Only few examples of either hydrolysis or alcoholysis of *N*-protected β-amino cyanides are reported and include an alkaline hydrolysis (NaOH in EtOH, 90° C, 3 h) utilized[34] for the preparation of (*S*)-*N*(Boc-amino)-*homo*-β-phenylglycine and an acid catalyzed methanolysis representing the final step in the synthesis of chiral methyl 3-[*N*(Cbz-amino)]-2-hydroxy-4-phenylbutanoates[36].

We have focused our attention on the acid catalyzed conditions of hydrolysis, and alcoholysis as well, of the *N*-protected β-amino cyanides **4**, **5**, and **6**, i.e. conditions suitable to achieve *N*(Fmoc)-protected *homo*-β-amino acids which may find very broad utilization as such in solid phase peptide synthesis[37,38]. Under acid hydrolysis conditions, in fact, the *N*(Fmoc)-protected β-amino cyanide **6p** undergoes a ready and clean conversion -with full conservation of the *N*-Fmoc protection- into its corresponding *homo*-β-amino acid **9p** that is thus obtained in high purity and good yield.

The *N*(Boc) protection is removed under the acidic conditions and the *C*-protected *homo*-β-amino acids, as **8q**,**r**,**s**, obtained by acid catalyzed alcoholysis of *N*(Boc)-protected β-amino cyanides **5**, are suitable for peptide synthesis solution techniques. The possibility to synthesize *N*- and *C*-diprotected *homo*-β-amino acids -as **7j**, ready obtained by acid catalyzed alcoholysis of the *N*(Cbz)-protected β-amino cyanide **4j**- is also interesting in view of their further elaboration to prepare more complex α,β-substituted *homo*-β-amino acids.

In Table 4 we have summarized[23] a few examples of our results of acid catalyzed hydrolysis and alcoholysis reactions carried out on *N*(Cbz)-, *N*(Boc)-, and *N*(Fmoc)-protected β-amino cyanides **4**, **5**, and **6**, in order to put in evidence the flexibility of our synthetic procedure that leads to *homo*-β-amino acids in forms

**Table 4.** ***homo*-β-Amino Acid Derivatives from *N*-Protected β-Amino Cyanides**

| | *N*-Status | *C*-Status | R[a] | m.p. (°C) | $[\alpha]_D^{25}$ (*c*) | Yield%[b] |
|---|---|---|---|---|---|---|
| **7j** | Cbz-NH | $CO_2Me$ | Phe | 45-46 | -15.5 (0.40)[c] | 85 |
| **8q** | $^+NH_3$ $Cl^-$ | $CO_2Me$ | Val | 118-120 | +28.2 (0.48)[d] | 86 |
| **8r** | $^+NH_3$ $Cl^-$ | $CO_2Me$ | Leu | --[e] | --[e] | 88 |
| **8s** | $^+NH_3$ $Cl^-$ | $CO_2Me$ | Tyr(Bn) | 163-164 | +4.7 (0.32)[d] | 86 |
| **9p** | Fmoc-NH | $CO_2H$ | Val | 154-155 | -21.5 (0.46)[c] | 91 |

[a] Considered as the side chain of the α-amino acid indicated. [b] Yield of pure crystallized product. [c] $CHCl_3$ solutions (1.0 dm cell). [d] MeOH solutions (1.0 dm cell). [e] Highly hygroscopic, characterized as its *N*-(acetylamino) derivative.

already suitable for peptide as well as general purpose synthesis. Work is in fact in progress in our laboratory to optimize the alkaline hydrolysis conditions and to extend this strategy to more complex natural α-amino acids, also in view of the synthesis of α,β-substituted compounds.

In our opinion this homologation process of *N*-protected α-amino acids (in fact their β-amino alcohol derivatives) to *N*-protected, *C*-protected, *N*- and *C*-protected enantiopure *homo*-β-amino acids -as well as further forms which could also be envisaged as coming by other manipulations of the *N*-protected β-amino cyanides- does lead to a significant improvement of the present status of art in the field, and represents at the same time a powerful tool to synthesize new complex amino acids from low-cost, ready available compounds.

## EXPERIMENTAL SECTION

All chemicals were purchased (Aldrich, Fluka, Sigma) at the highest purity available and used without further purification. Solvents were dried and distilled ($CH_2Cl_2$ from $P_2O_5$, THF and $Et_2O$ from $LiAlH_4$, MeOH from metallic Mg) immediately before use. Melting points were determined in open capillary tubes and are uncorrected. TLCs were run on Merck silica gel 60 $F_{254}$ plates developed with ninhydrin (0.25% in MeOH) or UV visualized. Column chromatography was performed on Macherey-Nagel MN-kieselgel 60 (70-230 mesh). Polystyryl diphenylphosphine (Fluka, ~ 3 mmol P $g^{-1}$) and imidazole were dried before use, 3 h under vacuum respectively at 70° and 50° C. Optical rotations were measured on a Perkin-Elmer 141 polarimeter (1.0 dm cell) for chloroform solutions, unless otherwise specified. $^1$H NMR Spectra were recorded on a Bruker AC 270 instrument (270 MHz) on $CDCl_3$ solutions, unless otherwise specified. 400 MHz Spectra were recorded on a Bruker WH 400 instrument. Chemical shifts are given in ppm downfield from TMS internal standard; coupling constants are given in Hz. HPLC analyses were performed on a Gynkotek M 480 instrument equipped with UVD-160S detector, using reversed-phase Hypersil ODS 5 μm, 4.6x250 mm (Shandon Southern Ltd) and Chiralcel OD-R 10 μm, 4.6x250 mm (J.T. Baker) columns.

In order to get immediate translation from word to structure, chemical names are accompanied by an abbreviation we propose as an extension of ψ-peptide nomenclature[1], i.e. the use of the three letter code followed by the symbol ψ[ ] which signals the replacement of the amino acid α-carboxyl group by the structure contained within the brackets.

***N-protection of the free β-amino alcohols. General procedure.***

To a magnetically stirred solution of triethylamine (1.4 $cm^3$, 10.0 mmol) and a pure β-amino alcohol (10.0 mmol) in THF (30 $cm^3$) in ice bath, solid $Boc_2O$ (or CbzOSu) (10.0 mmol) is added in one portion. The clear solution is then let to reach room temperature and the starting free β-amino alcohol is completely consumed (TLC monitoring) within 2 h. The reaction mixture is then evaporated under reduced pressure and the residue collected with ethyl acetate (100 $cm^3$) and water (50 $cm^3$). The organic layer is separated, washed with water until neutral, dried ($Na_2SO_4$), and evaporated under reduced pressure. The crude *N*(Boc)-protected β-amino alcohols are finally crystallized from hexane-ethyl acetate, whereas the *N*(Cbz)-protected β-amino alcohols are crystallized from hexane-dichloromethane. *N*(Fmoc)-Protected β-amino alcohols are prepared under the same conditions, by using FmocOSu as the *N*-protection reagent and replacing triethylamine with 10% aq $Na_2CO_3$ (5 $cm^3$, added dropwise to maintain pH ≅ 9). The crude *N*(Fmoc)-protected β-amino alcohols are finally crystallized from hexane-dichloromethane.

All the *N*-protected β-amino alcohols **1** reported in Table 1 (but the compounds **1g,h,n**, obtained according to literature procedures[18,31]) were prepared under the above conditions and their m.p.s, rotations, and yields are shown in the table. $^1$H NMR assignments and elemental analyses are reported below for the new compounds only (the reported[16,18] spectra for compounds **1m** and **1n** were not considered significant):

***(S)-2-(N-t-Butoxycarbonylamino)-butanol, Boc-Abuψ[CH$_2$OH], (1b)***: $\delta_H$ 0.94 (*t*, 3H, *J*=7.4, $CH_3$), 1.44 (*s*, 9H,

H Boc), 1.51-1.58 (*m*, 2H, 2xH-3), 3.48-3.72 (*m*, 3H, H-2 and 2xH-1), 4.52-4.68 (*m*, 1H, NH). (Found: C, 56.99; H, 10.21; N, 7.38. $C_9H_{19}NO_3$ requires C, 57.11; H, 10.11; N, 7.40%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-propanol, Fmoc-Alaψ[CH$_2$OH], (1k)***: $\delta_H$ 1.17 (*d*, 3H, *J*=6.8, $CH_3$), 3.50-3.75 (*m*, 2H, 2xH-1), 3.76-3.94 (*m*, 1H, H-2), 4.22 (*t*, 1H, *J*=6.8, CH-Fmoc), 4.45 (*d*, 2H, *J*=6.8, $CH_2$-Fmoc), 4.78-4.90 (*m*, 1H, NH), 7.31-7.79 (*m*, 8H, H Ar). (Found: C, 72.51; H, 6.50; N, 4.52. $C_{18}H_{19}NO_3$ requires C, 72.70; H, 6.44; N, 4.71%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-4-methylpentanol, Fmoc-Leuψ[CH$_2$OH], (1l)***: $\delta_H$ 0.92 (*d*, 6H, *J*=6.3, 2x$CH_3$), 1.20-1.40 (*m*, 2H, H-3), 1.66 (*m*, 1H, H-4), 3.45-3.58 (*m*, 1H, H-1a), 3.60-3.85 (*m*, 2H, H-1b and H-2), 4.21 (*t*, 1H, *J*=6.8, CH-Fmoc), 4.45 (*d*, 2H, *J*=6.8, $CH_2$-Fmoc), 4.65-4.80 (*m*, 1H, NH), 7.25-7.82 (*m*, 8H, H Ar). (Found: C, 74.41; H, 7.40; N, 4.22. $C_{21}H_{25}NO_3$ requires C, 74.30; H, 7.42; N, 4.12%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-3-phenylpropanol, Fmoc-Pheψ[CH$_2$OH], (1m)***: $\delta_H$ 2.87 (br *d*, 2H, *J*=5.5, H-3), 3.58-3.82 (*m*, 2H, 2xH-1), 3.90-3.96 (*m*, 1H, H-2), 4.18 (*t*, 1H, *J*=6.8, CH-Fmoc), 4.41 (*d*, 2H, *J*=6.8, $CH_2$-Fmoc), 4.90-5.02 (*m*, 1H, NH), 7.10-7.77 (*m*, 13H, H Ar). (Found: C, 77.27; H, 6.11; N, 3.79. $C_{24}H_{23}NO_3$ requires C, 77.18; H, 6.20; N, 3.75%)

***t-Butyl (R)-3-(N-Fluorenylmethoxycarbonylamino)-4-hydroxybutanoate, Fmoc-D-Asp(OtBu)ψ[CH$_2$OH], (1n)***:
$\delta_H$ 1.48 (*s*, 9H, H *t*-Bu), 2.52-2.64 (*m*, 2H, 2xH-2), 3.69-3.80 (*m*, 2H, 2xH-4), 3.95-4.12 (*m*, 1H, H-3), 4.23 (*t*, 1H, *J*=6.6, CH-Fmoc), 4.38-4.50 (*m*, 2H, $CH_2$-Fmoc), 5.43-5.55 (*m*, 1H, NH), 7.30-7.82 (*m*, 8H, H Ar). (Found: C, 69.62; H, 6.66; N, 3.40. $C_{29}H_{31}NO_5$ requires C, 69.50; H, 6.84; N, 3.52%)

***Conversion of N-protected β-amino alcohols 1 into N-protected β-amino iodides 2 and 3. General procedure.***
To a magnetically stirred suspension of polystyryl diphenylphosphine (4.1 g, ~ 11 mmol) in anhydrous $CH_2Cl_2$ (100 $cm^3$) at room temperature and under argon (or nitrogen) atmosphere, solid $I_2$ (2.8 g, 11.0 mmol) is added in one portion and, after 15 min, solid imidazole (0.8 g, 12.5 mmol) is also added, stirring being gently continued for additional 15 min. A solution of a pure *N*-protected β-amino alcohol **1** (5.0 mmol) in the same solvent (20 $cm^3$) is then added in one portion to the suspension and the resulting reaction mixture is refluxed 1 h, i.e. until complete consumption (TLC monitoring) of the starting *N*-protected β-amino alcohol. Filtration of the polymeric phase on Celite and washing with small portions of $CH_2Cl_2$ gives a clear solution that is shaken with 5 mol $dm^{-3}$ aq $Na_2S_2O_3$ (50 $cm^3$) and then water until neutral. Evaporation of the dried ($Na_2SO_4$) organic layer under reduced pressure affords the *N*-protected β-amino iodide, **2** or **3**, which is directly crystallized from hexane-dichloromethane.
M.p.s, rotations, and yields of the *N*-protected β-amino iodides **2** and **3**, prepared under these conditions from their corresponding *N*-protected β-amino alcohols **1**, are reported in Table 2. $^1$H NMR assignments and elemental analyses are reported below for the new compounds:

***(S)-2-(N-t-Butoxycarbonylamino)-iodopropane, Boc-Alaψ[CH$_2$I], (2a)***: $\delta_H$ 1.20 (*d*, 3H, *J*=6.5, $CH_3$), 1.45 (*s*, 9H, H Boc), 3.29 (*dd*, 1H, *J*= 8.7, *J*=9.9, H-1a), 3.45-3.47 (*m*, 1H, H-2), 3.48-3.60 (*m*, 1H, H-2), 4.50-4.63 (*m*, 1H, NH). (Found: C, 33.62; H, 5.61; N, 4.59. $C_8H_{16}NO_2I$ requires C, 33.70; H, 5.65; N, 4.91%)

***(S)-2-(N-t-Butoxycarbonylamino)-iodobutane, Boc-Abuψ[CH$_2$I], (2b)***: $\delta_H$ 0.93 (*t*, 3H, *J*=7.4, $CH_3$), 1.40-1.60 (*m*, 11H, 2xH-3 and H Boc), 3.20-3.38 (*m*, 2H, H-2 and H-1a), 3.45 (*dd*, 1H, *J*= 3.8, *J*=14.0, H-1b), 4.48-4.60 (*m*, 1H, NH). (Found: C, 36.31; H, 6.11; N, 4.72. $C_9H_{18}NO_2I$ requires C, 36.13; H, 6.06; N, 4.68%)

***(S)-2-(N-t-Butoxycarbonylamino)-3-methyl-iodobutane, Boc-Valψ[CH$_2$I], (2c)***: $\delta_H$ (400 MHz) 0.92 (*d*, 3H, *J*= 6.5,

$CH_3$), 0.96 (*d*, 3H, *J*= 6.5, $CH_3$), 1.45 (*s*, 9H, H-Boc), 1.70-1.82 (*m*, 1H, H-3), 3.06-3.16 (*m*, 1H, H-2), 3.32 (*dd*, 1H, *J*=4.1, *J*=10.8, H-1a), 3.40 (*dd*, 1H, *J*=3.5, *J*=10.8, H-1b), 4.58 (br *d*, 1H, *J*=5.0, NH). (Found: C, 38.42; H, 6.31; N, 4.29. $C_{10}H_{20}NO_2I$ requires C, 38.35; H, 6.43; N, 4.47%)

***(S)-2-(N-t-Butoxycarbonylamino)-4-methyl-iodopentane, Boc-Leuψ[CH$_2$I], (2d)***: $\delta_H$ 0.92 (*d*, 3H, *J*=6.7, $CH_3$), 0.93 (*d*, 3H, *J*=6.7, $CH_3$), 1.30-1.37 (*m*, 2H, 2xH-3), 1.45 (*s*, 9H, H Boc), 1.53-1.68 (*m*, 1H, H-4), 3.28 (*dd*, 1H, *J*=2.7, *J*=9.2, H-1a), 3.35-3.45 (*m*, 1H, H-2), 3.47 (*dd*, 1H, *J*=3.7, *J*=9.2, H-1b), 4.52 (br *d*, 1H, *J*=6.0, NH). (Found: C, 40.41; H, 6.72; N, 4.35. $C_{11}H_{22}NO_2I$ requires C, 40.37; H, 6.77; N, 4.28%)

***(S)-2-(N-t-Butoxycarbonylamino)-3-phenyl-iodopropane, Boc-Pheψ[CH$_2$I], (2e)***: $\delta_H$ 1.42 (*s*, 9H, H Boc), 2.76 (*dd*, 1H, *J*=6.7, *J*=13.4, H-3a), 2.90 (*dd*, 1H, *J*=5.0, *J*=13.4, H-3b), 3.16 (*dd*, 1H, *J*=3.3, *J*=10.0, H-1a), 3.38 (br *dd*, 1H, *J*=4.0, *J*=10.0, H-1b), 3.45-3.70 (*m*, 1H, H-2), 4.57-4.72 (*m*, 1H, NH), 7.20-7.40 (*m*, 5H, H Ar). (Found: C, 46.32; H, 5.52; N, 3.94. $C_{14}H_{20}NO_2I$ requires C, 46.55; H, 5.58; N, 3.87%)

***(S)-2-(N-t-Butoxycarbonylamino)-2-phenyl-iodoethane, Boc-Phgψ[CH$_2$I], (2f)***: $\delta_H$ 1.48 (*s*, 9H, H Boc), 3.45-3.60 (*m*, 2H, 2xH-1), 4.73-4.86 (*m*, 1H, H-2), 5.06-5.16 (*m*, 1H, NH), 7.22-7.40 (*m*, 5H, H Ar). (Found: C, 45.02; H, 5.31; N, 4.12. $C_{13}H_{18}NO_2I$ requires C, 44.97; H, 5.22; N, 4.03%)

***Benzyl (S)-3-(N-t-Butoxycarbonylamino)-4-iodobutanoate, Boc-Asp(OBn)ψ[CH$_2$I], (2g)***: $\delta_H$ (400 MHz) 1.45 (*s*, 9H, H Boc), 2.67 (*dd*, 1H, *J*=6.2, *J*=16.2, H-2a), 2.81 (*dd*, 1H, *J*=5.4, *J*=16.2, H-2b), 3.35-3.48 (*m*, 2H, 2xH-4), 3.89-3.98 (*m*, 1H, H-3), 5.02-5.12 (*m*, 1H, NH), 5.14 (*s*, 2H, $CH_2$-Ph), 7.36 (*s*, 5H, H Ar). (Found: C, 45.66; H, 5.12; N, 3.23. $C_{16}H_{22}NO_4I$ requires C, 45.83; H, 5.28; N, 3.34%)

***(S)-2-(N-t-Butoxycarbonylamino)-3-(4'-benzyloxyphenyl)-iodopropane, Boc-Tyr(Bn)ψ[CH$_2$I], (2h)***: $\delta_H$ 1.45 (*s*, 9H, H Boc), 2.72 (*dd*, 1H, *J*=7.8, *J*=13.5, H-3a), 2.85 (*dd*, 1H, *J*=5.3, *J*=13.5, H-3b), 3.17 (*dd*, 1H, *J*=3.4, *J*=10.1, H-1a), 3.38 (br *dd*, 1H, *J*=4.5, *J*=10.1, H-1b), 3.46-3.62 (*m*, 1H, H-2), 4.60-4.75 (*m*, 1H, NH), 5.05 (*s*, 2H, $OCH_2$-Ph), 6.93 (*d*, 2H, *J*=8.5, H-3' and H-5'), 7.18 (*d*, 2H, *J*=8.5, H-2' and H-6'), 7.32-7.48 (*m*, 5H, H Ar). (Found: C, 53.69; H, 5.42; N, 3.07. $C_{21}H_{26}NO_3I$ requires C, 53.97; H, 5.60; N, 2.99%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-iodopropane, Fmoc-Alaψ[CH$_2$I], (3k)***: $\delta_H$ 1.23 (*d*, 3H, *J*=7.1, $CH_3$), 3.22-3.35 (*m*, 1H, H-1a), 3.36-3.52 (*m*, 1H, H-1b), 3.53-3.70 (*m*, 1H, H-2), 4.22 (*t*, 1H, *J*=6.4, CH-Fmoc), 4.30-4.52 (*m*, 2H, $CH_2$-Fmoc), 4.73-4.90 (*m*, 1H, NH), 7.25-7.78 (*m*, 8H, H Ar). (Found: C, 53.36; H, 4.36; N, 3.61. $C_{18}H_{18}NO_2I$ requires C, 53.08; H, 4.45; N, 3.43%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-4-methyl-iodopentane, Fmoc-Leuψ[CH$_2$I], (3l)***: $\delta_H$ 0.93 (*d*, 6H, *J*=5.7, 2x$CH_3$), 1.30-1.47 (*m*, 2H, 2xH-3), 1.47-1.72 (*m*, 1H, H-4), 3.20-3.33 (*m*, 1H, H-1a), 3.37-3.50 (*m*, 2H, H-1b and H-2), 4.23 (*t*, 1H, *J*=6.4, CH-Fmoc), 4.38-4.48 (*m*, 2H, $CH_2$-Fmoc), 4.67-4.78 (*m*, 1H, NH), 7.25-7.82 (*m*, 8H, H Ar). (Found: C, 55.94; H, 5.22; N, 3.33. $C_{21}H_{24}NO_2I$ requires C, 56.13; H, 5.38; N, 3.11%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-3-phenyl-iodopropane, Fmoc-Pheψ[CH$_2$I], (3m)***: $\delta_H$ 2.76 (*dd*, 1H, *J*=4.7, *J*=9.3, H-3a), 2.89 (*dd*, 1H, *J*=4.0, *J*=9.3, H-3b), 3.12 (*dd*, 1H, *J*=2.3, *J*=7.0, H-1a), 3.35 (*dd*, 1H, *J*=3.5, *J*=7.0, H-1b), 3.60-3.70 (*m*, 1H, H-2), 4.15 (*t*, 1H, *J*=6.6, CH-Fmoc), 4.38-4.42 (*m*, 2H, $CH_2$-Fmoc), 4.88 (br *d*, 1H, *J*=5.6, NH), 7.17-7.75 (*m*, 13H, H Ar). (Found: C, 59.42; H, 4.64; N, 2.98. $C_{24}H_{22}NO_2I$ requires C, 59.63; H, 4.58; N, 2.89%)

***t-Butyl (R)-3-(N-fluorenylmethoxycarbonylamino)-4-iodobutanoate, Fmoc-D-Asp(OtBu)ψ[CH$_2$I], (3n)***: $\delta_H$ 1.46 (*s*, 9H, H *t*-Bu), 2.50-2.72 (*m*, 2H, 2xH-2), 3.35-3.48 (*m*, 2H, 2xH-4), 3.87-4.02 (*m*, 1H, H-3), 4.22 (*t*, 1H, *J*=6.7, CH-Fmoc), 4.30-4.55 (*m*, 2H, $CH_2$-Fmoc), 5.34 (br *d*, 1H, *J*=6.0, NH), 7.20-7.83 (*m*, 8H, H Ar). (Found: C, 54.61;

H, 5.00; N, 2.84. $C_{23}H_{26}NO_4I$ requires C, 54.44; H, 5.16; N, 2.76%)

***Conversion of N(Cbz)- and N(Boc)-protected β-amino iodides 2 into N(Cbz)- and N(Boc)-protected β-amino cyanides 4 and 5. General procedure.***

To a magnetically stirred solution of a pure *N*(Cbz)- or *N*(Boc)-protected β-amino iodide **2** (5.0 mmol) in anhydrous dichloromethane (75 $cm^3$), at room temperature and under argon (or nitrogen) atmosphere, solid tetraethylammonium cyanide (1.0 g, 6.5 mmol) is added in one portion. The mixture is refluxed 4 h, until complete consumption of the starting *N*-protected β-amino iodide (TLC monitoring), then cooled and, after addition of silica gel (10 g), evaporated under reduced pressure. The solid residue is removed mechanically from the flask walls and transferred onto a short silica gel (40 g) column. Elution with light petrol-ethyl acetate (5→20%) affords the *N*-protected β-amino cyanide, **4** or **5**, as a crystalline white solid that can be recrystallized from dichloromethane-hexane.

M.p.s, rotations, and yields of the *N*(Cbz)- and *N*(Boc)-protected β-amino cyanides, **4** and **5**, prepared under these conditions are reported in Table 3. Their $^1H$ NMR assignments and microanalyses are reported below:

***(S)-2-(N-Benzyloxycarbonylamino)-propyl cyanide, Cbz-Alaψ[CH₂CN], (4i)***: $\delta_H$ (400 MHz) 1.35 (*d*, 3H, *J*=6.8, $CH_3$), 2.55 (*dd*, 1H, *J*=3.9, *J*=16.7, H-1a), 2.78 (*dd*, 1H, *J*=5.2, *J*=16.7, H-1b), 3.92-4.03 (*m*, 1H, H-2), 4.80 (br *s*, 1H, NH), 5.02 (*d*, 1H, *J*=12.0, OCHaPh), 5.09 (*d*, 1H, *J*=12.0, OCHbPh), 7.28 (*s*, 5H, H Ar). (Found: C, 66.21; H, 6.29; N, 12.92. $C_{12}H_{14}N_2O_2$ requires C, 66.03; H, 6.46; N, 12.83%)

***(S)-2-(N-Benzyloxycarbonylamino)-3-phenylpropyl cyanide, Cbz-Pheψ[CH₂CN], (4j)***: $\delta_H$ 2.46 (*dd*, 1H, *J*=4.3, *J*=16.8, H-1a), 2.72 (*dd*, 1H, *J*=4.8, *J*=16.8, H-1b), 2.89 (*dd*, 1H, *J*=8.0, *J*=13.8, H-3a), 3.02 (*dd*, 1H, *J*=6.7, *J*=13.8, H-3b), 4.08-4.22 (*m*, 1H, H-2), 4.95 (br *d*, J=5.6, 1H, NH), 5.09 (*s*, 2H, $CH_2$-Cbz), 7.19-7.40 (*m*, 10H, H Ar). (Found: C, 73.27; H, 6.30; N, 9.34. $C_{18}H_{18}N_2O_2$ requires C, 73.44; H, 6.16; N, 9.51%)

***(S)-2-(N-t-Butoxycarbonylamino)-propyl cyanide, Boc-Alaψ[CH₂CN], (5a)***: $\delta_H$ (400 MHz) 1.32 (*d*, 3H, *J*=6.8, $CH_3$), 1.45 (*s*, 9H, H Boc), 2.53 (*dd*, 1H, *J*=4.0, *J*=16.7, H-1a), 2.73 (br *d*, 1H, *J*=16.7, H-1b), 3.90-4.01 (*m*, 1H, H-2), 4.58-4.70 (*m*, 1H, NH). (Found: C, 58.50; H, 8.61; N, 15.32. $C_9H_{16}N_2O_2$ requires C, 58.67; H, 8.75; N, 15.20%)

***(S)-2-(N-t-Butoxycarbonylamino)-butyl cyanide, Boc-Abuψ[CH₂CN], (5b)***: $\delta_H$ 0.98 (*t*, 3H, *J*=7.4, $CH_3$), 1.45 (*s*, 9H, H Boc), 1.55-1.71 (*m*, 2H, 2xH-3), 2.52 (*dd*, 1H, *J*=3.6, *J*=16.8, H-1a), 2.75 (br *dd*, 1H, *J*=4.3, *J*=16.8, H-1b), 3.65-3.82 (*m*, 1H, H-2), 4.62-4.75 (*m*, 1H, NH). (Found: C, 60.66; H, 9.27; N, 13.98. $C_{10}H_{18}N_2O_2$ requires C, 60.58; H, 9.15; N, 14.12%)

***(R)-2-(N-t-Butoxycarbonylamino)-3-methylbutyl cyanide, Boc-Valψ[CH₂CN], (5c)***: $\delta_H$ 0.97 (*d*, 6H, *J*=6.8, 2x$CH_3$), 1.45 (*s*, 9H, H Boc), 1.76-1.96 (*m*, 1H, H-3), 2.55 (*dd*, 1H, *J*=4.5, *J*=15.4, H-1a), 2.68 (*dd*, 1H, *J*=5.7, *J*=15.4, H-1b), 3.52-3.66 (*m*, 1H, H-2), 4.65 (br *d*, 1H, *J*=6.8, NH). (Found: C, 62.02; H, 9.58; N, 13.26. $C_{11}H_{20}N_2O_2$ requires C, 62.23; H, 9.49; N, 13.19%)

***(S)-2-(N-t-Butoxycarbonylamino)-4-methylpentyl cyanide, Boc-Leuψ[CH₂CN], (5d)***: $\delta_H$ 0.92 (*d*, 6H, *J*=6.3, 2x$CH_3$), 1.34-1.78 (*m*, 12H, H Boc, 2xH-3, and H-4), 2.45 (*dd*, 1H, *J*=4.1, *J*=16.8, H-1a), 2.76 (*dd*, 1H, *J*=5.1, *J*=16.8, H-1b), 3.78-3.87 (*m*, 1H, H-2), 4.60 (br *d*, 1H, *J*=7.2, NH). (Found: C, 63.50; H, 9.91; N, 12.19. $C_{12}H_{22}N_2O_2$ requires C, 63.68; H, 9.79; N, 12.37%)

***(S)-2-(N-t-Butoxycarbonylamino)-3-phenylpropyl cyanide, Boc-Pheψ[CH₂CN], (5e)***: $\delta_H$ (400 MHz) 1.43 (*s*, 9H, H Boc), 2.42 (*dd*, 1H, *J*=3.6, *J*=16.4, H-1a), 2.69 (br *dd*, 1H, *J*=2.9, *J*=16.4, H-1b), 2.83 (*dd*, 1H, *J*=7.2, *J*=14.5, H-3a), 3.07 (*dd*, 1H, *J*=5.4, *J*=14.5, H-3b), 4.02-4.16 (*m*, 1H, H-2), 4.89 (br *d*, 1H, J=7.3, NH), 7.20-7.38 (*m*, 5H, H Ar).

(Found: C, 69.38; H, 7.61; N, 10.92. $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.74; N, 10.76%)

***(R)-2-(N-t-Butoxycarbonylamino)-2-phenylethyl cyanide, Boc-Phgψ[CH$_2$CN], (5f)***: $\delta_H$ 1.46 (*s*, 9H, H Boc), 2.88 (*dd*, 1H, *J*=5.0, *J*=16.4, H-1a), 3.00 (*dd*, 1H, *J*=6.2, *J*=16.4, H-1b), 4.90-5.07 (*m*, 1H, H-2), 5.18 (br *d*, 1H, *J*=5.7, NH), 7.33-7.44 (*m*, 5H, H Ar). (Found: C, 68.07; H, 7.29; N, 11.49. $C_{14}H_{18}N_2O_2$ requires C, 68.26; H, 7.36; N, 11.37%)

***(S)-2-(N-t-Butoxycarbonylamino)-3-(4'-benzyloxyphenyl)-propyl cyanide, Boc-Tyr(Bn)ψ[CH$_2$CN], (5h)***: $\delta_H$ 1.45 (*s*, 9H, H Boc), 2.40 (*dd*, 1H, *J*=4.4, *J*=17.4, H-1a), 2.69 (*dd*, 1H, *J*=5.3, *J*=17.4, H-1b), 2.78 (*dd*, 1H, *J*=8.0, *J*=13.4, H-3a), 2.93 (*dd*, 1H, *J*=6.3, *J*=13.4, H-3b), 3.92-4.11 (*m*, 1H, H-2), 4.58-4.75 (*m*, 1H, NH), 5.07 (*s*, 2H, $OCH_2Ph$), 6.94 (*d*, 2H, *J*=8.6, H-3' and H-5'), 7.13 (*d*, 2H, *J*=8.6, H-2' and H-6'), 7.32-7.48 (*m*, 5H, H Ar). (Found: C, 72.31; H, 7.01; N, 7.59. $C_{22}H_{26}N_2O_3$ requires C, 72.10; H, 7.15; N, 7.64%)

***Preparation of N(Fmoc)-protected β-amino cyanides 6 from their N(Boc)-protected analogues 5. General procedure.*** To a solution of a pure *N*(Boc)-protected β-amino cyanide **5** (5.0 mmol) in dichloromethane (15 $cm^3$), magnetically stirred in an ice bath, TFA (5 $cm^3$) is added dropwise. After the addition the clear solution is let to reach room temperature and within 1 h the starting *N*(Boc)-protected β-amino cyanide is completely consumed (TLC monitoring). The solution is then evaporated under reduced pressure by adding from time to time ethyl ether for steam removal of the residual TFA. The solid residue is dissolved by tetrahydrofuran (20 $cm^3$), 10% aq $Na_2CO_3$ (until the pH ≅ 9) and then FmocOSu (5.0 mmol) being added to the resulting solution under magnetic stirring and in ice bath. The latter is then removed and the reaction mixture is kept at room temperature for 1 h. Workup and purification of the *N*(Fmoc)-protected β-amino cyanide **6** are those already described in the general procedure for the *N*(Fmoc) protection of the free β-amino alcohols.

M.p.s., rotations, and yields of the *N*(Fmoc)-protected β-amino cyanides **6k,l,m,o,p**, prepared under these conditions, are reported in Table 3. Their $^1$H NMR assignments and elemental analyses are reported below:

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-propyl cyanide, Fmoc-Alaψ[CH$_2$CN], (6k)***: $\delta_H$ 1.35 (*d*, 3H, *J*=5.2, $CH_3$), 2.50 (br *d*, 1H, *J*=16.0, H-1a), 2.75 (br *d*, 1H, *J*=16.0, H-1b), 3.92-4.10 (*m*, 1H, H-2), 4.21 (*t*, 1H, *J*=6.7, CH-Fmoc), 4.35-4.52 (*m*, 2H, $CH_2$-Fmoc), 4.83 (br *s*, 1H, NH), 7.29-7.84 (*m*, 8H, H Ar). (Found: C, 74.52; H, 5.76; N, 9.18. $C_{19}H_{18}N_2O_2$ requires C, 74.48; H, 5.92; N, 9.14%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-4-methylpentyl cyanide, Fmoc-Leuψ[CH$_2$CN], (6l)***: $\delta_H$ 0.93 (*d*, 6H, *J*=5.6, 2x$CH_3$), 1.41-1.71 (*m*, 3H, 2xH-3 and H-4), 2.47 (*dd*, 1H, *J*=3.2, *J*=16.2, H-1a), 2.73 (*dd*, 1H, *J*=5.3, *J*=16.2, H-1b), 3.82-4.05 (*m*, 1H, H-2), 4.21 (*t*, 1H, *J*=6.5, CH-Fmoc), 4.40-4.55 (*m*, 2H, $CH_2$-Fmoc), 4.80 (br *d*, 1H, *J*=8.9, NH), 7.25-7.82 (*m*, 8H, H Ar). (Found: C, 75.72; H, 6.81; N, 8.20. $C_{22}H_{24}N_2O_2$ requires C, 75.83; H, 6.94; N, 8.03%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-3-phenylpropyl cyanide, Fmoc-Pheψ[CH$_2$CN], (6m)***: $\delta_H$ 2.47 (br *d*, 1H, *J*=15.7, H-1a), 2.72 (br *d*, 1H, *J*=15.7, H-1b), 2.93 (*dd*, 1H, *J*=7.8, *J*=15.6, H-3a), 3.00 (*dd*, 1H, *J*=5.9, *J*=15.6, H-3b), 4.10-4.19 (*m*, 1H, H-2), 4.21 (*t*, 1H, *J*=6.7, CH-Fmoc), 4.38-4.50 (*m*, 2H, $CH_2$-Fmoc), 4.94 (br *s*, 1H, NH), 7.23-7.79 (*m*, 13H, H Ar). (Found: C, 78.62; H, 5.68; N, 7.14. $C_{25}H_{22}N_2O_2$ requires C, 78.51; H, 5.79; N, 7.32%)

***(S)-2-(N-Fluorenylmethoxycarbonylamino)-butyl cyanide, Fmoc-Abuψ[CH$_2$CN], (6o)***: $\delta_H$ 0.98 (*t*, 3H, *J*=6.2, $CH_3$), 1.55-1.78 (*m*, 2H, 2xH-3), 2.53 (br *d*, 1H, *J*=16.2, H-1a), 2.73 (*dd*, 1H, *J*=3.8, *J*=16.2, H-1b), 3.68-3.87 (*m*, 1H, H-2), 4.22 (*t*, 1H, *J*=6.6, CH-Fmoc), 4.39-4.56 (*m*, 2H, $CH_2$-Fmoc), 4.73-4.88 (*m*, 1H, NH), 7.26-7.82 (*m*, 8H, H Ar). (Found: C, 74.82; H, 6.18; N, 8.61. $C_{20}H_{20}N_2O_2$ requires C, 74.97; H, 6.29; N, 8.74%)

***(R)-2-(N-Fluorenylmethoxycarbonylamino)-4-methylbutyl cyanide, Fmoc-Valψ[CH$_2$CN], (6p)***: $\delta_H$ 0.98 (*d*, 6H, *J*=5.6, 2x$CH_3$), 1.80-2.00 (*m*, 1H, H-3), 2.58 (*dd*, 1H, *J*=3.2, *J*=12.1, H-1a), 2.67 (*dd*, 1H, *J*=2.5, *J*=12.1, H-1b), 3.53-3.72 (*m*,

1H, H-2), 4.22 (*t*, 1H, *J*=6.5, CH-Fmoc), 4.45 (*d*, 2H, *J*=6.8, $CH_2$-Fmoc), 4.84 (br *d*, 1H, *J*=6.8, NH), 7.25-7.82 (*m*, 8H, H Ar). (Found: C, 75.27; H, 6.48; N, 8.16. $C_{21}H_{22}N_2O_2$ requires C,75.42; H, 6.63; N, 8.37%)

***Acid catalyzed alcoholysis of the N(Cbz)-protected β-amino cyanide 4j.***

To a magnetically stirred solution of (*S*)-2-(*N*-benzyloxycarbonylamino)-3-phenylpropyl cyanide, Cbz-Phe$\psi$[$CH_2CN$], **4j** (1.0 g; 3.4 mmol) in anhydrous $Et_2O$ (15 $cm^3$) at 4° C, cold hydrogen chloride saturated (~ 14 mol $dm^{-3}$) anhydrous methanol (5 $cm^3$) is added in one portion, and the clear solution is kept overnight at the same temperature. Then few drops af water are added to the reaction mixture and the solvent is coevaporated several times with anhydrous $Et_2O$ under reduced pressure. The solid residue is eventually dissolved in ethyl acetate (50 $cm^3$) and the solution is washed with water until neutral, dried ($Na_2SO_4$), and evaporated under reduced pressure. The crystalline crude product, by crystallization from hexane-ethyl acetate (80:20), affords the pure:

***Methyl (S)-3-(N-benzyloxycarbonylamino)-4-phenylbutanoate, Cbz-Phe$\psi$[$CH_2CO_2Me$], Cbz-homo-β-Phe-OMe, (7j)***: yield, m.p., $[\alpha]_D^{25}$, see Table 4; $\delta_H$ 2.48 (*dd*, 1H, *J*=5.4, *J*=13.9, H-2a), 2.55 (*dd*, 1H, *J*=5.3, *J*=13.9, H-2b), 2.83 (*dd*, 1H, *J*=7.7, *J*=12.4, H-4a), 2.96 (*dd*, 1H, *J*=6.3, *J*=12.4, H-4b), 3.68 (*s*, 3H, $OCH_3$), 4.12-4.30 (*m*, 1H, H-3), 5.08 (*s*, 2H, $OCH_2$), 5.22-5.43 (*m*, 1H, NH), 7.08-7.45 (*m*, 10H, H Ar). (Found: C, 69.51; H, 6.62; N, 4.33. $C_{19}H_{21}NO_4$ requires C, 69.70; H, 6.46; N, 4.27%)

***Acid catalyzed alcoholysis of the N(Boc)-protected β-amino cyanide 5c. Typical procedure.***

(*R*)-2-(*N*-*t*-Butoxycarbonylamino)-3-methylbutyl cyanide, Boc-Val$\psi$[$CH_2CN$], **5c** (1.0 g, 4.7 mmol) is dissolved in hydrogen chloride saturated (~14 mol $dm^{-3}$) anhydrous methanol (10 $cm^3$), in ice bath and under magnetic stirring. The solution is then let to reach room temperature and stirred gently overnight. Few drops of water are eventually added to the solution and the solvent is coevaporated several times with anhydrous $Et_2O$ under reduced pressure. The solid residue is dissolved in 10% aq $Na_2CO_3$ (20 $cm^3$) and the resulting solution is extracted with $Et_2O$ (3x50 $cm^3$). The organic layer, after drying on $Na_2SO_4$, is acidified by dropwise addition of hydrogen chloride saturated anhydrous $Et_2O$ (0.5 $cm^3$) to precipitate the pure:

***Methyl (R)-3-amino-4-methylpentanoate hydrochloride, H-Val$\psi$[$CH_2CO_2Me$]·HCl, H-homo-β-Val-OMe·HCl, (8q)***: yield, m.p., $[\alpha]_D^{25}$, see Table 4; $\delta_H$ ($CH_3OH$-$d_4$, 400 MHz) 1.00 (*d*, 3H, *J*=6.7, $CH_3$), 1.04, (*d*, 3H, *J*=6.7, $CH_3$), 1.95-2.08 (*m*, 1H, H-4), 2.62 (*dd*, 1H, *J*=8.7, *J*=17.5, H-2a), 2.81 (*dd*, 1H, *J*=4.0, *J*=17.5, H-2b), 3.41-3.55 (*m*, 1H, H-3), 3.76 (*s*, 3H, $OCH_3$). (Found: C, 46.32; H, 8.21; N, 7.54. $C_7H_{15}NO_2Cl$ requires C, 46.54; H, 8.36; N, 7.75%)

Under the same conditions the following *C*-protected *homo*-β-amino acids were also prepared:

***Methyl (S)-3-amino-5-methylesanoate hydrochloride, H-Leu$\psi$[$CH_2CO_2Me$]·HCl, H-homo-β-Leu-OMe·HCl, (8r)***: yield, see Table 4: $\delta_H$ ($CH_3OH$-$d_4$) 0.96 (*d*, 3H, *J*=6.5, $CH_3$), 0.97 (*d*, 3H, *J*=6.5, $CH_3$), 1.50-1.62 (*m*, 2H, 2xH-4), 1.65-1.80 (*m*, 1H, H-5), 2.63 (*dd*, 1H, *J*=7.6, *J*=17.5, H-2a), 2.80 (*dd*, 1H, *J*=4.7, *J*=17.5, H-2b), 3.61(2 *dd*, 1H, *J*=4.7, *J*=7.6, *J*=4.7, *J*=8.3, H-3), 3.75 (*s*, 3H, $OCH_3$). Due to its highly hygroscopic nature, **8r** was characterized as its *N*-(acetylamino) derivative: oil; $[\alpha]_D^{30}$ = -42.0 (c=0.94); $\delta_H$ 0.90 (*d*, 3H, *J*=6.6, $CH_3$), 0.91 (*d*, 3H, *J*=6.6, $CH_3$), 1.21-1.35 (*m*, 2H, 2xH-4), 1.41-1.70 (*m*, 1H, H-5), 1.96 (*s*, 3H, $COCH_3$), 2.47 (*dd*, 1H, *J*=5.5, *J*=16.1, H-2a), 2.56 (*dd*, 1H, *J*=5.1, *J*=16.1, H-2b), 3.67 (*s*, 3H, $OCH_3$), 4.22-4.40 (*m*, 1H, H-3). 6.26 (br *d*, 1H, *J*=9.1, NH). (Found: C, 59.82; H, 9.35; N, 6.80. $C_{10}H_{19}NO_3$ requires C, 59.67; H, 9.51; N, 6.95%)

***Methyl (S)-3-amino-4-(4'-benzyloxyphenyl)-butanoate hydrochloride, H-Tyr(Bn)$\psi$[$CH_2CO_2Me$]·HCl, H-homo-β-Tyr(Bn)-OMe·HCl, (8s)***: $\delta_H$ ($CH_3OH$-$d_4$) 2.58 (*dd*, 1H, *J*=7.5, *J*=17.3, H-2a), 2.70 (*dd*, 1H, *J*=4.7, *J*=17.3, H-2b), 2.84 (*dd*, 1H, *J*=8.0, *J*=13.9, H-4a), 2.98 (*dd*, 1H, *J*=6.3, *J*=13.9, H-4b), 3.68 (*s*, 3H, $OCH_3$), 3.70-3.92 (*m*, 1H,

H-3), 5.08 (*s*, 2H, $OCH_2$-Ph), 6.98 (*d*, 2H, *J*=8.5, H-3' and H-5'), 7.18 (*d*, 2H, *J*=8.5, H-2' and H-6'), 7.24-7.50 (*m*, 5H, H Ar). (Found: C, 64.11; H, 6.79; N, 4.25. $C_{18}H_{22}NO_3Cl$ requires C, 64.37; H, 6.60; N, 4.17%)

***Acid catalyzed hydrolysis of the N(Fmoc)-protected β-amino cyanide 6p.***

A solution of (*R*)-2-(*N*-fluorenylmethoxycarbonylamino)-4-methylbutyl cyanide, Fmoc-Valψ[$CH_2CN$], **6p** (0.6 g, 1.8 mmol) in dioxane (10 $cm^3$) and conc. aq hydrogen chloride (10 $cm^3$) is gently refluxed for 8 h. After cooling, the solution is diluted with water (30 $cm^3$) and extracted with ethyl acetate (3x50 $cm^3$). The organic layer is then washed with water until neutral, dried ($Na_2SO_4$), and evaporated under reduced pressure. The crude reaction product is crystallized from hexane-dichloromethane (80:20) to afford the pure:

***(R)-3-(N-Fluorenylmethoxycarbonylamino)-4-methylpentanoic acid, Fmoc-Valψ[$CH_2CO_2H$], Fmoc-homo-β-Val-OH, (9p)***: yield, m.p., $[\alpha]_D^{25}$, see Table 4; $\delta_H$ 0.92 (*d*, 6H, *J*=6.0, 2x$CH_3$), 1.78-1.95 (*m*, 1H, H-4), 2.50-2.80 (*m*, 2H, 2xH-2), 3.73-3.92 (*m*, 1H, H-3), 4.22 (*t*, 1H, *J*=6.6, CH-Fmoc), 4.40 (br *d*, 2H, *J*=7.1, $CH_2$-Fmoc), 5.15 (br *d*, 1H, *J*=9.8, NH), 7.23-7.83 (*m*, 8H, H Ar). (Found: C, 71.17; H, 6.64; N, 4.08. $C_{21}H_{23}NO_4$ requires C, 71.36; H, 6.55; N, 3.96%)

***HPLC Analysis of compounds 1f, 5f, 6p, and 9p on chiral column.***

Pure samples (~ 0.002 g) of the compounds under investigation were dissolved in methanol (3 $cm^3$), 20 μL aliquots of the resulting solutions being injected into a HPLC system (see general experimental) and analyzed in comparison with sample solutions of specially prepared racemic mixtures of the same compounds (flow rate 1.0 $cm^3$ $min^{-1}$, UV 215 nm):

- Compound **1f** (0.01% TFA in water plus $CH_3CN$ 20%→90% in 25.0 min): retention time 13.22 min; racemic **1f**: 12.77 and 13.21 min.
- Compound **5f** (0.01% TFA in water plus $CH_3CN$ 10%→30% in 5.0 min; 30% for 5.0 min→40% in 8.0 min; 40% for 7.0 min→60% in 6.0 min): retention time 23.48 min; racemic **5f**: 23.47 and 23.90 min.
- Compound **6p** (0.01% TFA in water plus $CH_3CN$ 30%→100% in 15.0 min): retention time 17.37 min; racemic **6p**: 17.35 and 18.50 min.
- Compound **9p** (as for compound **6p**): retention time 15.38 min; racemic **9p**: 15.34 and 16.26 min.

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