Amino Acids (2007) 32: 401–404
DOI 10.1007/s00726-006-0384-0
Printed in The Netherlands

Amino Acids

Enantiopure β^3-amino acids-2,2-d_2 via homologation of proteinogenic α-amino acids

R. Caputo and **L. Longobardo**

Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Napoli, Italy

Received May 23, 2006
Accepted June 28, 2006
Published online September 15, 2006; © Springer-Verlag 2006

Summary. A procedure for the synthesis of enantiopure β^3-amino acids from proteinogenic α-amino acids, developed by our group a few years ago, has been modified to enable the production of *C*-2 fully deuterated, *C*-protected β^3-amino acids and, even more important, the synthesis of valuable deuterium labelled *N*(Boc)-protected chiral synthons, such as 2-aminoalcohols, 2-aminoiodides, and β^3-amino nitriles.

Keywords: β^3-amino acids – α-amino acid homologation – *C*-2-dideuterated amino acids – 2-aminoalcohols-d_2 – 2-aminoiodides-d_2 – β^3-amino nitriles-d_2

Introduction

Isotopically labelled molecules are important synthetic targets. Labelled α-amino acids bearing deuterium atoms (Lygo and Humphreys, 2002) at either α- or side-chain carbons have been used for the elucidation of several biosynthetic pathways (Church and Young, 1998; Brandl et al., 2005) as well as for the study of reaction mechanisms based on MS and/or NMR spectrometries. Most recently, deuterium labelled amino acids and their derivatives have been incorporated in reagents and auxiliaries of analytical interest: two important classes include ICAT (*Isotope Coded Affinity Tag*) reagents (Gygi et al., 1999; Schrimpf et al., 2005), used for accurate quantifications of individual proteins within complex mixtures, and SIDA (*Stable Isotope Dilution Assay*) auxiliaries, for the determination of trace compounds in foodstuffs (Rufián-Henares and Morales, 2006; Stark et al., 2006).

Incorporation of labelled α-amino acids into peptides and proteins often helps in the assignment of spectroscopic data and in the investigation of secondary and tertiary structures (Gardner and Kay, 1997; Sack et al., 2000).

Considering the interesting biological properties of β-amino acids and their role in natural product biosynthesis (Seebach et al., 2004), as well as the emerging properties of β-peptide oligomers in the field of foldamer chemistry (Cheng et al., 2001; Seebach et al., 2004), deuterium labelled β-amino acids are logical synthetic targets.

The simplest member in β-amino acid series is 3-aminopropanoic acid, better known as β-alanine, and several different approaches have been so far used for its stereocontrolled labelling, from biocatalysis to asymmetric synthesis (Basak, 1997). Other isotopically labelled β-amino acids have been used for revealing the role of the amino acidic moiety in natural product biosynthesis: they have mostly been prepared by either enzyme-mediated transformations or miscellaneous chemical methods (Sewald et al., 1995; Basak, 1997).

Following our interest in the synthesis of enantiopure β^3-amino acids[1)] from proteinogenic α-amino acids, by way of an efficient and scalable multi-step procedure developed by our group a few years ago (Caputo et al., 1995a, b), we are currently involved in the exploitation of the intermediates of such procedure as chiral synthons (Bolognese et al., 2006). Under these circumstances, we report now a simple modification of our procedure that enables the synthesis of unprecedented *C*-protected *C*-2-dideuterated β^3-amino acids and, possibly more significant, the production of valuable deuterium labelled *N*(Boc)-protected chiral synthons, like 2-aminoalcohols, 2-aminoiodides, and β^3-amino nitriles.

[1)] In β-amino acids, two carbon atoms separate carboxyl function and amino group. The number(s) on β indicates which of such carbons carries the amino acid side chain.

Materials and methods

General

Melting points were measured on Kofler apparatus and are uncorrected. Optical rotations were measured on Jasco 1010 polarimeter (1.0 dm cell) in $CHCl_3$, unless otherwise specified. ^1H and ^{13}C NMR spectra were recorded on Varian Inova 500, Bruker DRX-400, Varian Gemini 300 and 200 spectrometers: chemical shifts are in ppm (δ); *J* coupling constants are in Hz; solvent $CDCl_3$, unless otherwise specified. GC/MS analyses were performed on Hewlett-Packard 6890 GC/5973*N* MS (column: HP-1 cross-linked methyl siloxane 25 m × 0.22 mm). Elemental analyses were performed on Perkin-Elmer Series II 2400, CHNS analyzer. TLC were carried out on silica gel Merck 60 F254 plates (0.2 mm layer thickness) and developed with ninhydrin (0.25% in MeOH) or UV visualized. Column chromatographies were run on Merck kieselgel 60 (70–230 mesh). Protected α-amino acids and other reagents, including $NaBD_4$ (98% D) and D_2O (99.9% D), were purchased from Aldrich, at the highest purity grade, and used without further purification. Dry solvents were distilled immediately before use.

Preparation of N(Boc)-protected 2-aminoalcohols-d_2

(*S*)-*tert*-Butyl 1-hydroxypropan-2-ylcarbamate-1,1-d_2 (**2b**). Typical procedure: to a solution of *N*-methyl morpholine (NMM) (2.6 ml, 23.3 mmol) and Boc-L-Ala-OH (4.0 g, 21.2 mmol) in anhydrous THF (70 ml), at 0 °C and under magnetic stirring, methyl chloroformate (1.8 ml, 23.3 mmol) was added dropwise. After 15 min, the solution was filtered and NMM·HCl salt was washed with anhydrous THF (3 × 20 ml). A solution of $NaBD_4$ (1.1 g, 26.5 mmol) in D_2O (8 ml) was then added dropwise to the filtrate, in ice bath and under magnetic stirring. The ice bath was removed and the mixture let rise to room temperature. After 10 min the solvent was evaporated under reduced pressure. The residue was redissolved in EtOAc (100 ml) and the solution washed with brine until neutral, then dried (Na_2SO_4). Evaporation of EtOAc in vacuo afforded the crude reaction product **2b** (3.47 g, 92%). One analytical sample was prepared by chromatography on silica gel (hexane/EtOAc, 7:3) and crystallization from hexane/EtOAc: m.p. 58.2–59.0 °C; $[\alpha]_D^{20}$ − 9.8 (*c* 1.32). ^1H NMR (300 MHz): δ 1.15 (d, *J* = 6.8, 3H, CH_3), 1.43 (s, 9H, *t*-Bu), 2.95 (bs, 1H, OH), 3.71 (dd, *J* = 6.6 and 6.8, 1H, CH), 4.75 (bd, *J* = 6.6, 1H, NHBoc). ^{13}C NMR (75 MHz): δ 17.1, 28.2, 48.3, 66.5, 79.5, 156.2. Anal. calcd for $C_8H_{15}D_2NO_3$ (177.13): C 54.21, H 10.80, N 7.90. Found: C 53.98, H 10.91, N 7.72.

tert-Butyl 2-hydroxyethylcarbamate-2,2-d_2 (**2a**): 82% from Boc-Gly-OH. One analytical sample: oil. ^1H NMR (200 MHz): δ 1.43 (s, 9H, *t*-Bu), 3.22 (d, *J* = 5.5, 2H, C*H*$_2$NH), 3.86 (bs, 1H, OH), 5.10 (bt, *J* = 5.5, 1H, NHBoc). ^{13}C NMR (50 MHz): δ 28.2, 29.5, 42.8, 79.6, 156.8. Anal. calcd for $C_7H_{13}D_2NO_3$ (163.12): C 51.51, H 10.50, N 8.58. Found: C 51.22, H 10.21, N 8.72.

(*S*)-*tert*-Butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate-1,1-d_2 (**2c**): 90% from Boc-L-Phe-OH. One analytical sample: m.p. 97.3–98.9 °C (from hexane/EtOAc); $[\alpha]_D^{20}$ − 23.1 (*c* 1.15). ^1H NMR (300 MHz): δ 1.43 (s, 9H, *t*-Bu), 1.92 (bs, 1H, OH), 2.82 (d, *J* = 7.1, 2H, CH_2Ph), 3.78–3.92 (m, 1H, CH), 4.72 (bs, 1H, NHBoc), 7.18–7.28 (m, 5H, H-Ar). ^{13}C NMR (75 MHz): δ 28.2, 37.3, 49.1, 53.4, 79.6, 126.4, 128.4, 129.1, 137.6, 157.7. Anal. calcd for $C_{14}H_{19}D_2NO_3$ (253.16): C 66.37, H 9.15, N 5.53. Found: C 66.59, H 8.92, N 5.80.

(*R*)-*tert*-Butyl 1-(benzyloxy)-3-hydroxypropan-2-ylcarbamate 3,3-d_2 (**2d**): 84% from Boc-L-Ser(Bn)-OH. One analytical sample: mp 64.9–65.7 °C (from hexane/EtOAc); $[\alpha]_D^{20}$ + 14.8 (*c* 1.71). ^1H NMR (300 MHz): δ 1.45 (s, 9H, *t*-Bu), 2.60 (bs, 1H, OH), 3.67 (dd, *J* = 4.3 and 9.3, 1H, CH_aO), 3.71 (dd, *J* = 3.8 and 9.3, 1H, CH_bO), 3.80–3.90 (m, 1H, CH), 4.38 (d, *J* = 12.0, 1H, CH_aPh), 4.62 (d, *J* = 12.0, 1H, CH_bPh), 5.22 (bs, 1H, NHBoc), 7.27–7.42 (m, 5H, H-Ar). ^{13}C NMR (75 MHz): δ 28.8, 51.7, 63.1, 70.6, 73.4, 79.5, 127.0, 127.2, 127.8, 136.9, 155.1. Anal. calcd for $C_{15}H_{21}D_2NO_4$ (283.18): C 63.58, H 8.89, N 4.94. Found: C 63.75, H 8.91, N 4.72.

(*S*)-di-*tert*-Butyl 6-hydroxyhexane-1,5-diyldicarbamate-6,6-d_2 (**2e**): 86% from Boc-L-Lys(Boc)-OH. One analytical sample: oil; $[\alpha]_D^{20}$ − 10.1 (*c* 1.92, CH_3OH). ^1H NMR (200 MHz, C_6D_6): δ 0.93–1.32 (m, 6H, 3 × CH_2), 1.43 (s, 18H, 2 × *t*-Bu), 2.14 (bs, 1H, OH), 2.78–2.98 (m, 2H, C*H*$_2$NH), 3.43–3.58 (m, 1H, CH), 4.13 (bs, 1H, NHBoc), 4.51 (bs, NHBoc). ^{13}C NMR (125 MHz): δ 23.0, 28.7, 30.2, 30.9, 40.0, 52.6, 65.8, 79.4, 79.7, 156.6, 156.7. Anal. calcd for $C_{16}H_{30}D_2N_2O_5$ (334.24): C 57.46, H 10.25, N 8.38. Found: C 57.71, H 10.02, N 8.12.

Preparation of N(Boc)-protected β^3-amino nitriles-d_2

(*S*)-*tert*-Butyl 1-cyanopropan-2-ylcarbamate-1,1-d_2 (**4b**). Typical procedure: to a solution of triphenylphosphine (2.8 g, 10.6 mmol) in anhydrous CH_2Cl_2 (70 ml), iodine (2.7 g, 10.8 mmol) was added at room temperature, under argon atmosphere and magnetic stirring. After 15 min imidazole (1.4 g, 21.2 mmol) was also added and the mixture was stirred for additional 15 min. The alcohol **2b** (1.5 g, 8.5 mmol), dissolved in the same solvent (20 ml), was finally added and the reaction mixture refluxed until consumption of **2b** (∼1 h, TLC monitoring). The mixture was then cooled, diluted with CH_2Cl_2 (100 ml), and washed with 10% aq $Na_2S_2O_4$ (40 ml) and brine (2 × 50 ml). The organic layer was finally dried (Na_2SO_4) and the solvents were evaporated in vacuo to give the crude iodide **3b**, in mixture with some white solid Ph_3PO. The crude iodide was dissolved in anhydrous DMSO (30 ml) and solid KCN (1.1 g, 17.0 mmol) was added in one portion. The mixture was kept under magnetic stirring at 50 °C for ∼3 h (TLC monitoring) and then carefully evaporated in vacuo. The residue, redissolved in ethyl acetate (120 ml), was washed with brine until neutral. The organic layer was finally dried (Na_2SO_4) and the solvents were evaporated to give a whitish solid which was eventually purified by chromatography (hexane/EtOAc; 8:2) to give **4b** as a white solid (1.3 g, 80%). One analytical sample: m.p. 68.2–70.0 °C (from hexane/Et_2O); $[\alpha]_D^{20}$ − 83.1 (*c* 0.35). ^1H NMR (400 MHz): δ 1.33 (d, *J* = 6.8, 3H, CH_3), 1.43 (s, 9H, *t*-Bu), 3.95–4.15 (m, 1H, CH), 4.69 (bd, *J* = 7.05, 1H, NHBoc). No evidences of signals in the region δ 2.50–2.75 which are shown by its non-deuterated analog (Caputo et al., 1995b). ^{13}C NMR (75 MHz): δ 19.4, 25.0, 28.3, 43.0, 80.1, 117.4, 154.8. Anal. calcd for $C_9H_{14}D_2N_2O_2$ (186.13): C 58.04, H 9.74, N 15.04. Found: C 58.31, H 9.62, N 14.92.

tert-Butyl 2-cyanoethylcarbamate-2,2-d_2 (**4a**): 69% from **2a**. One analytical sample: m.p. 42.4–43.5 °C (from hexane/Et_2O). ^1H NMR (200 MHz): δ 1.45 (s, 9H, *t*-Bu), 3.38 (d, *J* = 6.3, 2H, C*H*$_2$NH), 4.90 (bs, 1H, NHBoc). ^{13}C NMR (50 MHz): δ 28.1, 29.5, 36.5, 80.1, 118.0, 155.0. Anal. calcd for $C_8H_{12}D_2N_2O_2$ (172.12): C 55.79, H 9.36, N 16.27. Found: C 55.47, H 9.51, N 16.52.

(*S*)-*tert*-Butyl 1-cyano-3-phenylpropan-2-ylcarbamate-1,1-d_2 (**4c**): 77% from **2c**. One analytical sample: m.p. 123.8–125.0 °C (from hexane/Et_2O); $[\alpha]_D^{20}$ − 18.2 (*c* 1.15). ^1H NMR (200 MHz): δ 1.43 (s, 9H, *t*-Bu), 2.86 (dd, *J* = 7.8 and 13.6, 1H, CH_aPh), 2.99 (dd, *J* = 5.8 and 13.6, 1H, CH_bPh), 4.00–4.17 (m, 1H, CH), 4.72 (bs, 1H, NHBoc), 7.18–7.28 (m, 5H, H-Ar). ^{13}C NMR (75 MHz): δ 28.2, 29.9, 39.3, 48.3, 79.6, 117.3, 126.4, 128.4, 129.1, 137.6, 154.8. No evidences of signals in the region δ 2.40–2.70 which are shown by its non-deuterated analog (Caputo et al., 1995b). Anal. calcd for $C_{15}H_{18}D_2N_2O_2$ (262.17): C 68.67, H 8.45, N 10.68. Found: C 68.39, H 8.28, N 10.91.

(*R*)-*tert*-Butyl 1-(benzyloxy)-3-cyanopropan-2-ylcarbamate-3,3-d_2 (**4d**): 72% from **2d**. One analytical sample: oil; $[\alpha]_D^{20}$ − 9.7 (*c* = 1.62). ^1H NMR (300 MHz): δ 1.50 (s, 9H, *t*-Bu), 3.60 (dd, *J* = 4.9 and 9.6, 1H, CH_aO), 3.70 (dd, *J* = 3.8 and 9.6, 1H, CH_bO), 4.05–4.18 (m, 1H, CH), 4.58 (s, 2H, CH_2Ph), 5.10 (bd, *J* = 6.4, 1H, NHBoc), 7.31–7.40 (m, 5H, H-Ar). ^{13}C NMR (75 MHz): δ 28.1, 29.6, 46.8, 69.5, 73.4, 80.1, 117.1, 127.6, 127.9, 128.4, 137.1, 154.8. Anal. calcd for $C_{16}H_{20}D_2N_2O_3$ (292.18): C 65.73, H 8.27, N 9.58. Found: C 65.48, H 8.02, N 9.67.

(*S*)-*tert*-Butyl 6-cyanohexane-1,5-diyldicarbamate-6,6-d_2 (**4e**): 70% from **2e**. One analytical sample: m.p. 60.7–64.0 °C; $[\alpha]_D^{20}$ − 45.2 (*c* = 0.57). ^1H NMR (200 MHz, C_6D_6): δ 1.10–1.60 (m, 6H, 3 × CH_2), 1.38 (s, 18H,

$2 \times$ *t*-Bu), 2.96–3.10 (m, 2H, CH_2NH), 3.60–3.72 (m, 1H, CH), 4.42 (bs, 1H, NHBoc), 4.65 (bs, 1H, NHBoc). ^{13}C NMR (50 MHz): δ 23.0, 28.5, 28.6, 29.9, 30.0, 33.1, 40.0, 47.3, 79.5, 80.3, 117.5, 155.4, 156.4. Anal. calcd for $C_{17}H_{29}D_2N_3O_4$ (343.24): C 59.45, H 9.68, N 12.23. Found: C 59.67, H 9.72, N 11.98.

Preparation of methyl β^3-amino esters-d_2 hydrochlorides

(*S*)-Methyl 3-aminobutanoate-2,2-d_2 hydrochloride (**5b**). Typical procedure: to solid *N*(Boc)-β^3-amino nitrile **4b** (0.36 g, 1.95 mmol) a standard solution (5 ml) of dry HCl (g) in anhydrous methanol (~12 M) was added in one portion at 0 °C. The flask was then sealed and let reach room temperature. After 12 h, 1–2 drops of D_2O were added to the solution and, within 20 min, the solvent was co-evaporated with anhydrous Et_2O (3×25 ml) under reduced pressure, to give the final product **5b** as a crystalline solid (0.3 g, 91%). After recrystallization from MeOH/Et_2O: m.p. 250 °C (*dec.*); $[\alpha]_D^{20} + 0.19$ (*c* 2.5, CH_3OH). ^{1}H NMR (200 MHz; CD_3OD): δ 1.47 (d, $J = 6.8$, 3H, CH_3), 3.48 (t, $J = 6.8$, 1H, CH), 3.72 (s, 3H, OCH_3). ^{13}C NMR (50 MHz; CD_3OD): δ 18.3, 38.2, 44.7, 52.2, 170.8.

Methyl 3-aminopropanoate-2,2-d_2 hydrochloride (**5a**): 90% from **4a**. One analytical sample: m.p. 102.4–104.6 °C (from MeOH/Et_2O). ^{1}H NMR (200 MHz; CD_3OD): δ 3.18 (bs, 2H, CH_2NH), 3.73 (s, 3H, OCH_3). ^{13}C NMR (50 MHz; CD_3OD): δ 32.1, 36.4, 52.7, 172.6.

(*S*)-Methyl 3-amino-4-phenylbutanoate-2,2-d_2 (**5c**): 85% from **4c**. One analytical sample: m.p. 255.0 °C (*dec.*) (from MeOH/Et_2O); $[\alpha]_D^{20} + 4.28$ (*c* 1.38, CH_3OH). ^{1}H NMR (500 MHz; CD_3OD): δ 2.94 (dd, $J = 8.3$ and 14.16, 1H, CH_aPh), 3.79 (dd, $J = 6.35$ and 14.16, 1H, CH_bPh), 3.70 (s, 3H, OCH_3), 3.82 (t, $J = 7.32$, 1H, CH), 7.05–7.38 (m, 5H, H-Ar). ^{13}C NMR (75 MHz; CD_3OD): δ 39.5, 48.3, 50.3, 52.8, 128.7, 129.4, 130.1, 136.7, 173.1.

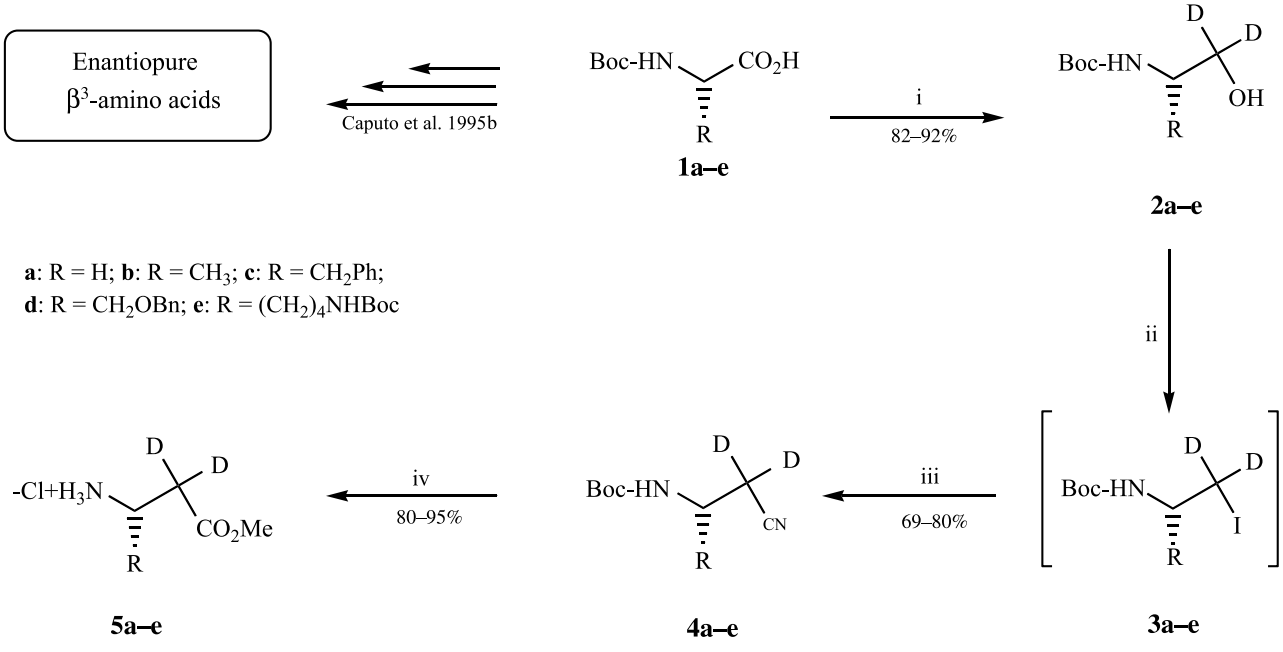
(*R*)-Methyl 3-amino-4-(benzyloxy)butanoate-2,2-d_2 (**5d**): 80% from **4d**. One analytical sample: oil; $[\alpha]_D^{20} + 0.68$ (*c* 0.74, CH_3OH). ^{1}H NMR (300 MHz; CD_3OD): δ 3.63–3.78 (m, 2H, CH_2O), 3.63 (s, 3H, OCH_3), 4.48 (d, $J = 12.0$, 1H, CH_aPh), 4.54 (d, $J = 12.0$, 1H, CH_bPh), 4.78 (m, 1H, CH), 7.31–7.40 (m, 5H, H-Ar). ^{13}C NMR (75 MHz): δ 37.0, 48.0, 51.8, 72.4, 73.1, 127.2, 127.5, 127.8, 138.2, 171.1.

(*S*)-Methyl 3,7-diaminoheptanoate-2,2-d_2 dihydrochloride (**5e**): 84% from **4e**. One analytical sample: oil; $[\alpha]_D^{20} + 8.49$ (*c* 0.56, CH_3OH). ^{1}H NMR (500 MHz; CD_3OD): δ 1.48–1.58 (m, 4H, $2 \times CH_2$), 1.68–1.72 (m, 2H, CH_2CH), 2.93 (t, $J = 7.8$, 2H, CH_2NH), 3.57 (t, $J = 6.8$, 1H, CH), 3.75 (s, 3H, OCH_3). ^{13}C NMR (75 MHz): δ 22.3, 27.9, 32.2, 38.3, 40.2, 44.0, 51.9, 173.2.

Results

The key step of the procedure, which is outlined in Fig. 1, consisted of the preparation of *N*(Boc)-protected 2-aminoalcohols-1,1-d_2, **2a–e**, by sodium borodeuteride reduction of the parent *N*(Boc)-protected α-amino acid mixed anhydrides, prepared in situ from *N*(Boc)-L-amino acids.

Deuterated *N*(Boc)-protected 2-aminoalcohols were then converted into the corresponding 2-aminoiodides, **3a–e**, by reaction with triphenylphosphine-iodine (TPP-I_2) complex, in the presence of imidazole (Caputo et al., 1995a). Aminoiodides **3a–e** were not isolated, in order to avoid time-consuming and circumstantial chromatographic separations of triphenylphosphine oxide that may also affect the rather sensitive iodides. Should their purification be necessary, the conversion of the parent alcohols into iodides may be better performed using polystyryl diphenylphosphine-iodine complex: under such conditions, phosphine oxide comes out



i: NMM, MeOCOCl, THF, 0 °C, then $NaBD_4$, D_2O; ii: TPP-I_2, ImH, CH_2Cl_2, reflux, 1h;
iii: KCN, DMSO, 50 °C, 3h; iv: HCl-MeOH, 0 °C to r.t., 12h

Fig. 1. Multi-step conversion of α-amino acids into enantiomerically pure β^3-amino esters-2,2-d_2 hydrochlorides

being linked to the polymeric matrix and can be separated by simple filtration.

Therefore, aminoiodides **3a**–**e** were treated directly with potassium cyanide, in anhydrous DMSO at 50 °C, to afford smoothly their corresponding β^3-amino nitriles **4a**–**e**. The replacement of tetraethylammonium cyanide in dichloromethane (Caputo et al., 1995b) with potassium cyanide in DMSO was recently devised in our lab as a significant improvement of our original procedure, entailing more confortable workup of the reaction and, as a consequence, better yields of β^3-amino nitriles from iodides.

The final methanolysis (HCl, >10 M in MeOH, 12 h, room temperature) of *N*(Boc)-protected β^3-amino nitriles **4a**–**e** afforded the expected *C*-2 fully deuterated methyl β^3-amino ester hydrochlorides **5a**–**e**. Despite the harsh methanolysis conditions, no exchange of ^{2}H by ^{1}H could be appreciated. The need of high HCl concentration is accounted for by the co-occurrence of both cyano group transformation and removal of amino group protection.

The incorporation of deuterium atoms into the target molecules was excellent (>97.5%), as confirmed by ^{1}H NMR spectrometry.

To the best of our knowledge *C*-2-dideuterated β^3-amino acids have not been so far reported. The entire process for their synthesis described by this paper is simple and general, characterized by ready-to-handle, easily scalable reactions, and excellent yields of the target products. It is also far reaching for the significance of the intermediates in the general organic synthesis.

Acknowledgment

This work was a partial fulfilment of the research project accomplished for "Dottorato di Ricerca" in Biotechnological Sciences (University of Napoli, Federico II) by S. Capone (2006).

References

Basak A (1997) Enantioselective preparation of deuterated β-alanines. In: Juaristi E (ed) Enantioselective synthesis of β-amino acids. Wiley VCH, New York, pp 465–480

Bolognese A, Fierro O, Guarino D, Longobardo L, Caputo R (2006) One-pot synthesis of orthogonally protected enantiopure *S*-(aminoalkyl)-cysteine derivatives. Eur J Org Chem, 169–173

Brandl M, Kozhushkov SI, Zlatopolskiy BD, Alvermann P, Geers B, Zeeck A, de Meijere A (2005) The biosynthesis of 3-(*trans*-2-nitrocyclopropyl)alanine, a constituent of the signal metabolite hormaomycin. Eur J Org Chem, 123–135

Caputo R, Cassano E, Longobardo L, Palumbo G (1995a) Chiral *N*-protected β-iodoamines from α-aminoacids: a general synthesis. Tetrahedron Lett 36: 167–168

Caputo R, Cassano E, Longobardo L, Palumbo G (1995b) Synthesis of enantiopure *N*- and *C*-protected *homo*-β-amino acids by direct homologation of α-amino acids. Tetrahedron 51: 12337–12550

Cheng RP, Gellman SH, DeGrado WF (2001) β-Peptides: from structure to function. Chem Rev 101: 3219–3232

Church NJ, Young DW (1998) Synthesis of the suicide substrate D-propargylglycine stereospecifically labelled with deuterium and investigation of its oxidation by D-amino acid oxidase. J Chem Soc Perkin Trans 1: 1475–1482

Gardner KH, Kay LE (1997) Production and incorporation of ^{15}N, ^{13}C, ^{2}H (^{1}H-δ1 methyl) isoleucine into proteins for multidimensional NMR studies. J Am Chem Soc 119: 7599–7600

Gygi SP, Rist B, Gerber SA, Turecek F, Gelb MH, Aebersold R (1999) Quantitative analysis of complex protein mixtures using isotope-coded affinity tags. Nat Biotechnol 17: 994–996

Lygo B, Humphreys LD (2002) Enantioselective synthesis of α-carbon deuterium-labelled L-α-amino acids. Tetrahedron Lett 43: 6677–6679

Rufián-Henares JA, Morales FJ (2006) Determination of acrylamide in potato chips by a reversed-phase LC-MS method based on a stable isotope dilution assay. Food Chem 97: 555–562

Sack I, Balazs YS, Rahimipour S, Vega S (2000) Solid-state NMR determination of peptide torsion angles: applications of ^{2}H-dephased REDOR. J Am Chem Soc 122: 12263–12269

Schrimpf SP, Meskenaite V, Brunner E, Rutishauser D, Walther P, Eng J, Aebersold R, Sonderegger P (2005) Proteomic analysis of synaptosomes using isotope-coded affinity tags and mass spectrometry. Proteomics 5: 2531–2541

Seebach D, Beck A, Bierbaum DJ (2004) The world of β- and γ-peptides comprised of homologated proteinogenic amino acids and other components. Chem Biodiv 1: 1111–1239 (and literature cited therein)

Sewald N, Hiller KD, Helmreich B (1995) Asymmetric synthesis of β-amino acids and α-deuterated β-amino acids *via* conjugate addition of homochiral amidocuprates. Liebigs Ann, 925–928

Stark T, Justus H, Hofmann T (2006) Quantitative analysis of *N*-phenylpropenoyl-L-amino acids in roasted coffee and cocoa powder by means of a stable isotope dilution assay. J Agric Food Chem 54: 2859–2867

Authors' address: R. Caputo, Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Montesantangelo, Via Cynthia 4, I-80126 Napoli, Italy,
Fax: +39 081 674117; E-mail: rocaputo@unina.it