SYNTHESIS OF (2R)- AND (2S)-[3-^{2}H]-VALINE

Christopher J. Easton and Nicola G. Findlay
Department of Chemistry
University of Canterbury
Christchurch, New Zealand

SUMMARY

(2R)-Valine and the (2S)-isomer were esterified and benzoylated. The derivatives were chlorinated at C-3 by treatment with sulphuryl chloride, reduced to the 3-^{2}H derivatives by reaction with triphenyltin deuteride, then hydrolysed to give (2R)- and (2S)-[3-^{2}H]-valine. The labelling is achieved with complete retention of optical purity.

Key Words: (2R)-[3-^{2}H]-valine, (2S)-[3-^{2}H]-valine, deuterium, triphenyltin deuteride.

INTRODUCTION

In order to study aspects of valine metabolism we required a simple, high yield synthesis of (2R)- and (2S)-[3-^{2}H]-valine. Syntheses of (2R,S)-[3-^{2}H]- and [3-^{3}H]-valines have been reported (1-3). In the most recent work (3) (2R)-[3-^{2}H]- and [3-^{3}H]-valines were obtained by enzymic resolution of (R,S)-mixtures. The synthesis of (2S)-[3-^{2}H]- or [3-^{3}H]-valine has never been reported, although conceivably these compounds could also be prepared by enzymic resolution of (R,S)-mixtures. This paper describes a synthesis of (2R)- and (2S)-[3-^{2}H]-valine that circumvents the need for resolution of (R,S)-mixtures.

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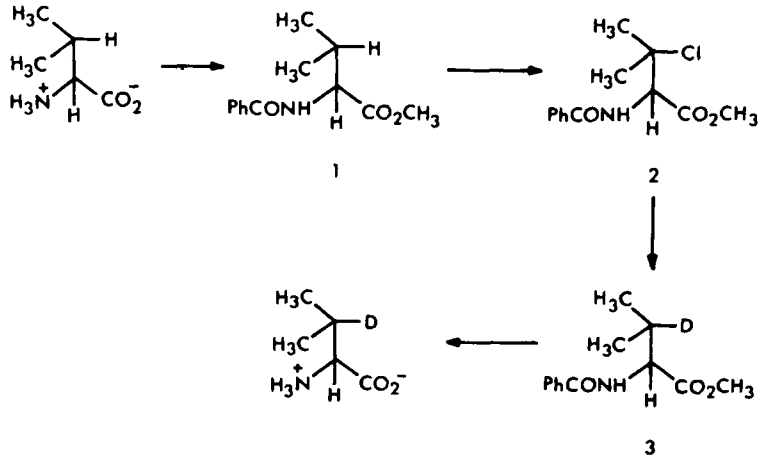
RESULTS AND DISCUSSION

Reaction of (2R)- and (2S)-valine with thionyl chloride in methanol, followed by treatment with benzoyl chloride, afforded (2R)- and (2S)-N-benzoylvaline methyl ester, 1a and 1b. Reaction of these valine derivatives with sulphuryl chloride in benzene (4) afforded the respective 3-chlorovaline derivatives 2a and 2b as the principal products, the yields being solvent dependent as well as dependent on the concentration of the substrates 1a and 1b (5). The chlorides 2a and 2b were purified by HPLC or column chromatography. Reduction of the chlorides 2a and 2b by reaction with triphenyltin deuteride afforded (2R)- and (2S)-[3-^{2}H]-N-benzoylvaline methyl ester, 3a and 3b. Analysis of these compounds by GLC established their chiral integrity. Hydrolysis of the labelled valine derivatives 3a and 3b in refluxing hydrochloric acid afforded (2R)- and (2S)-[3-^{2}H]-valine.



a = (2R), b = (2S)

Thus (2R)- and (2S)-[3-^{2}H]-valine were prepared from (2R)- and (2S)-valine, in 32% and 27% yield, respectively. Because the valine structure is retained throughout the synthesis, the method should be suitable for synthesis of double-labelled valines for use in cotracer experiments.

EXPERIMENTAL

General ^{1}H NMR spectra were recorded on a Varian T60 spectrometer and ^{13}C NMR spectra were recorded on a Varian CFT20 spectrometer. Analytical GLC was carried out using a Chrompack XE-60-S-VAL-S-X-PEA column (50 m x 0.22 mm i.d.), for analysis of chiral compounds.

(2R)-N-Benzoylvaline methyl ester, 1a.(2R)-Valine (3.0 g, 0.025 mole) was added to a stirred solution of thionyl chloride (3.7 ml) in methanol (25 ml). After 3 h the solvent was removed under reduced pressure. The crystalline residue was added to a stirred mixture of potassium carbonate (1.7 g), water (50 ml), and ethyl acetate (50 ml). Benzoyl chloride (10 ml) was then added dropwise with stirring. After 4 h the organic layer was separated, the aqueous layer was extracted with ethyl acetate (2 x 50 ml), and the combined ethyl acetate solutions were washed with 5% aqueous potassium bicarbonate, dried ($MgSO_4$), and concentrated. The residue recrystallised from ethyl acetate - light petroleum to give needles of (2R)-N-benzoylvaline methyl ester, 1a (4.9 g, 83%):m.p. 109-111° [lit.(6) 110.5-111.0°]; ^{1}H NMR (CCl_4) δ1.01 (6H, d, J = 7 Hz), 2.2 (1H, m), 3.73 (3H, s), 4.70 (1H, dd, J = 4 and 9 Hz), 6.54 (1H, broad d, J = 9 Hz), and 7.2-8.0 (5H, m). Chiral purity was established by GLC comparison with an (R,S)- mixture of 1a and 1b.

(2S)-N-Benzoylvaline methyl ester, 1b, was prepared as described above for the (2R)-isomer, 1a : 78% yield; m.p. 108-110° [lit.(7)111°]; ^{1}H NMR as for 1a; optically pure by GLC.

(2R)-N-Benzoyl-3-chlorovaline methyl ester, 2a. (2R)-N-Benzoylvaline methyl ester, 1a (2.0 g, 0.0085 mole), sulphuryl chloride (4 ml), and benzoyl peroxide (30 mg) in benzene (150 ml) were heated under reflux for 1 h. The mixture was concentrated and chromatographed on silica. Elution with ethyl acetate - dichloromethane (1:19) afforded (2R)-N-benzoyl-3-chlorovaline methyl ester, 2a, as an oil (1.4 g, 61%) : ^{1}H NMR (CCl_4) δ1.63 (3H, s), 1.77 (3H, s), 3.77 (3H, s), 4.87 (1H, d, J = 9 Hz), 6.80 (1H, broad d, J = 9 Hz), and 7.1-8.0 (5H, m). Alternatively the chloride 2a was purified by preparative HPLC, performed using a DuPont Zorbax cyanopropyl column (25 cm x 9.4 mm i.d.), using hexane - propan-2-ol(9:1) as eluant, monitoring at 220 nm.

(2S)-N-Benzoyl-3-chlorovaline methyl ester, 2b, was prepared as described above for the chloride 2a : 55% yield; ^{1}H NMR as for 2a.

(2R)-[3-^{2}H]-N-Benzoylvaline methyl ester, 3a. (2R)-N-Benzoyl-3-chlorovaline methyl ester, 2a (0.81 g, 0.003 mole), and triphenyltin deuteride (8) (3.0 ml) in benzene (30 ml) were refluxed under nitrogen for 5 h. The mixture was concentrated and chromatographed on silica. Elution with ethyl acetate - dichloromethane (1:9) afforded (2R)-[3-^{2}H]-N-benzoylvaline methyl ester, 3a, which recrystallised from ethyl acetate - light petroleum (0.55 g, 78%): m.p. 108-109°; ^{1}H NMR (CCl_4) δ0.98 (6H, s), 3.70 (3H, s), 4.64 (1H, d, J = 8 Hz), 6.60 (1H, broad d, J = 8 Hz), and 7.1-7.9 (5H, m). Chiral integrity was established by GLC - none of the (2S)-isomer 3b was detected and the limits of detection were <0.5%.

(2S)-[3-^{2}H]-N-Benzoylvaline methyl ester, 3b, was prepared analogously to the (2R)-[3-^{2}H]-derivative 3a : 82% yield; m.p. 108-110°; ^{1}H NMR as for 3a; single isomer by GLC.

(2R)-[3-^{2}H]-Valine. A solution of (2R)-[3-^{2}H]-N-benzoylvaline methyl ester, 3a (0.4 g, 0.0017 mole), in 2N hydrochloric acid (50 ml) was heated under reflux for 3 h, then cooled, washed with chloroform (3 x 25 ml), and evaporated. The residue was dissolved in ethanol. Addition of pyridine induced precipitation of (2R)-[3-^{2}H]-valine which was isolated by filtration, then recrystallised from aqueous ethanol (0.16 g, 80%); $[\alpha]_D^{25}$= +27.9° (c = 1.5 in 5N HCl); ^{1}H NMR (D_2O) δ0.81 (3H, s), 0.86 (3H, s), and 3.44 (1H, s); ^{13}C NMR (broad-band ^{1}H-decoupled, D_2O) δ16.5 (s), 17.8 (s), 28.6 (t, J_{CD} = 20 Hz), 60.1 (s), and 174.0 (s). Residual protons at C-3 were not detected by ^{1}H NMR. This is consistent with a small signal in the ^{13}C NMR at δ29.0 from non-deuterated valine, indicating ⩽2% residual protons.

(2S)-[3-^{2}H]-Valine, was prepared as described for the (2R)-isomer : 77% yield; $[\alpha]_D^{25}$ = -28.1° (c = 1.5 in 5N HCl); ^{1}H NMR and ^{13}C NMR as for (2R)-[3-^{2}H]-valine.

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