Enantiospecific syntheses of (R)- and (S)-proline and some derivatives from D-glucono-1,5-lactone

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Abstract: Carbohydrate-based enantiospecific syntheses of (R)-proline 1 and (S)-proline 2 from the previously reported D-erythro-hexonate ester 9 are described. Azide-substitution reactions on appropriately activated intermediates derived from ester 9, followed by reductive cyclization (H2/Pd–C), gave the substituted pyrrolidines 14 and 22, which were converted into their corresponding N-Cbz derivatives 16 and 24 in conventional manner. Mild acidic hydrolysis of these, followed by oxidation (sodium metaperiodate), gave the protected prolinals 3 and 4, which on further oxidation (sodium chlorite), followed by catalytic hydrogenolysis, gave the prolines 1 and 2. The N-Cbz-prolinol derivatives 5 and 6 are also reported.

Introduction

The stereospecific syntheses of enantiomerically pure compounds, especially those of natural origin, is an active area of modern organic chemistry. The synthesis of prolines and their derivatives seems currently of interest, inter alia, in this respect.1,2 A simple route to (R)-proline 1, (S)-proline 2 and the related protected aldehydes 3, 4 and alcohols 5, 6, from D-glucuronic acid via the hexonate ester 9, became available during studies on chiral pyrrolidine derivatives. Early syntheses of prolines 1 and 2 produced racemic mixtures which required resolution.3 Various asymmetric syntheses, including asymmetric transformations, have been reported,1,2,4,5,14 but with greater emphasis on the naturally occurring S-isomer 2. Compound 2 is responsible for conformational constraint in certain proteins and is obtained currently almost exclusively from protein hydrolyses or by fermentation.15 Recent interest16,17 has also centred on syntheses designed for the introduction of specific isotopic labelling into the products. The new route described here is noteworthy in its flexibility. Both enantiomers 1 and 2 and their related protected derivatives 3–6 are available, by choice, from one inexpensive source using simple reactions. Compound 3 has not been described previously and its enantiomer 4 is not obtained readily. The prolinals 5 and 6 are usually prepared by metal hydride reduction of suitably protected esters of prolines 1 and 2.18 Compounds 1 and 2 and derivatives thereof, including the alcohols 5 and 6, are useful chiral catalyst components or auxiliaries for inter alia, enantioselective catalytic reductions19–22 asymmetric intramolecular alidonizations23 and asymmetric induction in conjugated additions,24 self-condensation of α,β-unsaturated aldehydes,25 Robinson annelation reactions,26 and in the synthesis of some alkaloids.19–21

Results and discussion

Treatment of the tolune-p-sulfonate ester 10 with sodium azide in N,N-dimethylformamide (DMF) gave the corresponding d-threo-azole 11 as a syrup (91%) which was characterized by catalytic (palladized charcoal, 10%) reductive cyclic amination to give the crystalline pyrrolidine-2-one derivative 12. Reduction of compound 11 in toluene with disbutylaluminium hydride (DIBAL) at −78°C yielded the pure, but unstable aldehyde 13. Attempts to form a stable crystalline phenylhydrazone, or semicarbazone, of compound 13 were unsuccessful. Catalytic hydrogenation of compound 13 over palladized charcoal (10%) proceeded with concomitant ring closure to produce the substituted pyrrolidine 14, which on treatment with toluene-p-sulfon chloride (TsCl)–triethylamine gave the crystalline N-toluenesulfonate derivative 15. Treatment of compound 14 inaq. ethanol with benzyl chloroformate in the presence of sodium hydrogen carbonate in the usual manner gave the corresponding N-benzoyloxycarbonyl (N-Cbz) derivative 16. Hydrolysis (80%aq. acetic acid) of compound 16 gave the diol 17, which on oxidation withaq. sodium metaperiodate in methanol gave the protected (R)-proline derivative 3. Reduction of aldehyde 3 with sodium borohydride in methanol produced the corresponding (R)-proline derivative 5.

Oxidation of aldehyde 3 with sodium chlorite, in the presence of 2-methylbut-2-ene as a chlorine scavenger,19 was rapid and proceeded smoothly to give the protected (R)-proline derivative 7, which on catalytic hydrogenolysis13 provided pure (R)-proline 1 (Scheme 1).

Treatment of the bromoester 18 with sodium azide in DMF did not proceed satisfactorily. Analysis (TLC and GLC) of the reaction mixture produced after 18 h indicated the presence of not only the expected azido derivative 19 but also its diastereomer 11 (vide supra), in the ratio 3:2, indicating that epimerization was occurring during the course of the substitution reaction. This was probably due to nucleophilic attack of bromide ions, produced during the initial phase of the displacement reaction, on remaining compound 18, with subsequent and concurrent replacement of both by azide ions (Scheme 2).

The required compound 19 was obtained successfully by treatment of bromide 18 with a solution of lithium azide25 in DMF at room temp. for 7 days. Lithium azide is much more...
soluble (~1 g/10 ml) than sodium azide in this solvent, thereby enabling the reaction to be conducted at ambient temperature. Lithium bromide produced during the reaction is also much less effective as a source of nucleophilic bromide ions under these conditions. The beneficial use of lithium azide in some nucleophilic displacements reactions has been reviewed.\(^{34}\) Compound 19 yielded the crystalline pyrrolidine-2-one derivative 20 on reductive (Pd/C, H\(_2\)) cyclization (vide supra).

Reaction of ester 19 with DIBAL in toluene at \(-78^\circ\mathrm{C}\), followed by reductive (Pd/C, H\(_2\)) cyclization of the resultant unstable aldehyde 21 gave the expected pyrrolidine derivative 22 as a syrup, which was characterized as the crystalline N-toluene-p-sulphonate 23. Compound 22 was also converted into the corresponding N-Cbz derivative 24 in the usual manner. Mild acidic hydrolysis of compound 24 gave the free diol 25, which on treatment withaq. methanolic sodium metaperiodate yielded the aldehyde 4, reduction of which with sodium borohydride in methanol gave the (S)-prolinol derivative 6 (Scheme 3).

A synthesis of the aldehyde 4 from commercially available (S)-prolinol, via Swern-type oxidation of the N-benzyloxy-carbonyl derivative 6, has been described\(^{38}\) relatively recently. The observed optical rotations for these two derivatives were in good overall agreement with the values reported here, and also with the numerical values for their enantiomeric counterparts, compound 3 and 5. The current value for compound 4, [\(\alpha\)]\(\text{D}\) \(-76.5^\circ\) is marginally higher than the most recently cited\(^{38}\) value, [\(\alpha\)]\(\text{D}\) \(-63.7^\circ\), and both are much greater than those cited earlier\(^{35,36}\) for compound 4, derived from reduction of esters of (S)-proline 2. It had been implied\(^{46}\) that amino aldehydes derived from chiral amino acids could be difficult to obtain with high optical purity. Compound 3 has not been described hitherto. The two enantiomeric aldehydes 3 and 4 described here probably have very high optical purities in view of their mode of synthesis. These two compounds could be stored (0°C) for appreciable periods of time (2–3 months) without any obvious deterioration or racemization.

Further oxidation of aldehyde 4 with sodium chlorite in the same manner as described for its enantiomer 3 (vide supra) yielded the known, commercially available N-Cbz-(S)-proline 8, which on catalytic hydrogenation (palladized charcoal, 10%) yielded (S)-proline 2.

The syntheses described illustrate the useful application of the ester 9 as a chiral synthon. Further studies on the use of the aldehydes 4 and 5 as sources of novel chiral ligands is currently in progress.

**Experimental**

Optical rotations were determined with a Perkin-Elmer model 241 automatic polarimeter on 1% solutions in chloroform at 25°C, unless indicated otherwise. TLC on pre-coated plates of silica gel (Merck) was performed with light petroleum-ethyl acetate (1:1). Detection was affected by spraying with 0.1 m K\(_2\)Cr\(_2\)O\(_7\) in 0.05 m H\(_2\)SO\(_4\) and heating at 140°C. Column chromatography and flash-column chromatography were performed on silica gel 60 and 60 H with the solvent mixtures indicated. GLC was performed with a Hewlett-Packard 5890 gas chromatograph; a fused-silica capillary column (25 m) coated with HP-1 cross-linked methyl silicone gumphase operating at 100–150°C (\(t = 0\) min, 100°C isothermal; \(t = 5\) min, 5°C min\(^{-1}\)) and nitrogen as the carrier gas at 2 ml min\(^{-1}\) was used. 1\(H\) NMR spectra were recorded with a Bruker AC 100 (100 MHz) or Bruker AC 300 (300 MHz) spectrometer on solutions in CDCl\(_3\) (internal Me\(_2\)Si) or D\(_2\)O or as indicated. J-Values are given in Hz. 1\(^3\)C NMR spectra were recorded with Bruker AC 100, AC 300 or AM 400 spectrometers operating at 25, 75 and 100.6 MHz respectively on solutions in CDCl\(_3\) (internal Me\(_2\)Si) or D\(_2\)O (external 1,4-dioxane at \(\delta\)_\(d\) 67.8). Mass spectra were recorded using a double-focusing VG 7070E.
spectrometer or a Varian Saturn 2 GC-MS ion-trap system. IR spectra were determined on a Perkin-Elmer 298 spectrometer as indicated. DIBAL was purchased as a 1 M solution in hexane. Light petroleum is the fraction distilled between 60–80 °C.

Methyl 4-azido-2,3,4-trideoxy-5,6-(isopropylidenedioxy)-hexan-1-olate

A stirred mixture of compound 10 (2.4 g, 6.45 mmol) and sodium azide (1.28 g, 19.7 mmol) in DMF (50 ml) was heated for 12 h at 100 °C, cooled and then treated with ice-water (200 ml). The mixture was extracted with diethyl ether (2 × 150 ml) and the combined extracts were washed successively with saturated aq. sodium chloride (2 × 20 ml) and water (2 × 20 ml), dried (MgSO₄), and concentrated in vacuo. Column chromatography (ethyl acetate–light petroleum, 3:1) of the residue yielded compound 11 (1.43 g, 91%) as a pure TLC and GLC syrup, 2980, 2110, 2020, 1730. Light petroleum is the fraction distilled between 60–80 °C.

Scheme 3: Reagents and conditions: i, L,N₃, DMF, 20 °C; ii, DIBAL, –78 °C; iii, Pd–C (10%), H₂; iv, TsCl, KOH; v, PhCH₂OCOCl, NaHCO₃; vi, 80% HOAc–water; vii, NaIO₄; viii, NaBH₄; ix, NaClO₂, 2-methylbut-2-ene

(5R,4S)-5-(2′,2′-Dimethyl-1′,3′-dioxolano-4′)-ylpyrrolidin-2-one

A solution of compound 11 (0.604 g, 2.49 mmol) in methanol (20 ml) was treated with palladium charcoal (10%; 60 mg) and was then hydrogenated (1 atm) at room temp. The inorganic material was removed by filtration and washed with methanol (20 ml), and the combined filtrate and washings were concentrated in vacuo to give an oil which crystallized on storage (48 h). Recrystallization (diisopropyl ether–dichloromethane) gave pure lactam 12 (0.23 g, 63%), mp 102–104 °C; [α]D = 54 (Found: C, 58.27; H, 8.11; N, 7.45. C₅H₈N₃O requires C, 58.36; H, 8.16; N, 7.56%). δH (100 MHz; CDCl₃) 6.48 (br s, 1 H, NH), 4.03–3.67 (m, 4 H, H-4′, -5 and H-5′), 2.3–1.95 (m, 4 H, H-3′ and -4′) and 1.42 and 1.33 (2 s, each 3 H, CMe₂); νmax(KBr) cm⁻¹ 3260, 1690 and 1650.

(4R,5S)-4-Azido-5,6-(isopropylidenedioxy)hexan-1-olate

A solution of DIBAL (7.1 ml) was added dropwise to a stirred, cooled (−78 °C) solution of compound 11 (1.44 g, 5.9 mmol) in light petroleum–toluene (25 ml; 1:1) maintained under nitrogen. The mixture was stirred for a further 1 h at the same temperature, treated with sodium sulfate dehydrate (1.5 g), diluted with dichloromethane (25 ml) and stirred at room temp. for 1 h. The mixture was then treated with anhydrous sodium sulfate, and filtered, the inorganic material was washed with dichloromethane, and the combined filtrate and washings were washed with water (2 × 20 ml), dried (NaSO₄), and concentrated in vacuo. Column chromatography (light petroleum–ethyl acetate, 1:1) of the resultant material gave aldehyde 13 (1.04 g, 82%) as an oil, [α]D = 10.4; δH(CDCl₃) 9.61 (s, 1 H, CHO), 3.90 (m, 2 H, H-5, H-6′), 3.82 (dd, 2 J 6 and 8, 1 H, H-6′), 3.72 (m, 2 H, H-2′), 1.84–1.70 (m, 2 H, H-3′) and 1.47 and 1.38 (2 s, each 3 H, CMe₂); δH(CDCl₃) 200.73, 110.12, 78.53, 66.33, 62.71, 40.22, 26.32, 25.13 and 23.01; m/z 186 (M⁺ + 1 – 28, 2.8%), 101 (100), 82 (44), (55 (12) and 43 (97); νmax(neat) cm⁻¹ 2880, 2710, 2100 and 1710.

A solution of compound 13 (0.442 g, 2.07 mmol) in methanol (25 ml) was treated with palladized charcoal (10%; 45 mg) and was then hydrogenated (1 atm) at room temp. for 7 h. The inorganic material was removed by filtration and washed with methanol (10 ml). The combined filtrate and washings were concentrated in vacuo at <25 °C to give the pyrrolidin-14 (0.34 g, 96%). A portion of the product (172 mg) was distilled in vacuo (Kügelrohr, 80 °C/0.25 mbar) to give pure compound 14 (130 mg, 76%); [α]D = +9 (Found: C, 62.84; H, 10.41; N, 7.96. C₇H₈N₂O requires C, 63.12; H, 10.01; N, 8.18%). δH(CDCl₃) 3.99 (m, 2 H, H-5), 3.64 (m, 1 H, H-4′), 3.09–2.89 (m, 3 H), 2.10 (br s, 1 H, NH), 1.85–1.67 (m, 6 H, CMe₂) and 1.42 and 1.36 (2 s, each 3 H, CMe₂); δH(CDCl₃) 109.13, 79.40, 67.11, 60.95, 46.30, 27.43, 26.77, 25.37 and 25.24; m/z 172 (M⁺ + 1, 8.4%). 156 (3,3), 70 (100) and 43 (31); νmax(films) cm⁻¹ 3330, 2940, 2850 and 1690.

A portion of the above material (98.4 mg, 0.575 mmol) in methanol (2 ml) containing trimethylamine (0.163 ml, 1.17 mmol) was treated with TsCl (134 mg, 0.702 mmol), set aside at room temp. for 4 h, and processed in the usual manner. Recrystallization (light petroleum) of the resultant crude crystalline material (151 mg) gave the N-toluene-p-sulfonate 15 (125 mg, 67%); mp 95–97 °C; [α]D = –86 (Found: C, 58.67; H, 6.83; N, 4.31; S, 9.78. C₂₅H₂₈N₂O₂S requires C, 59.05; H, 7.12; N, 4.30; S, 9.85%). δH(CDCl₃) 7.72 and 7.32 (2 d, each 2 J 8.2, each 2 H, ArH), 4.21 (q, J 6.3, 1 H, H-4′), 4.13 (dd, J 8.5 and 6.3, 1 H, H-5′), 3.98 (dd, J 8.5 and 6.3, 1 H, H-5′), 3.72 (m, 1 H, H-2′), 3.41 (m, 1 H, H-5′), 3.18 (m, 1 H, H-5′), 2.43 (s, 3 H, C₆H₅Me), 1.90

† 1 bar = 10⁵ Pa.
(2R,4'S)-N-Benzoylcarbonyl-2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)pyrrolidin-16

Treatment of a stirred solution of free amine 14 (336 mg, 1.97 mmol) in 50% aq. ethanol (25 ml), containing sodium hydroxide carbonate (336 mg), with benzyl chloroformate (0.45 ml, 3.2 mmol) followed by processing in the usual manner and column chromatography (hexane-ethyl acetate, 3:1) of the resulting material gave compound 16 (491 mg, 82%), \([\delta]_D^{23} +61\) (Found: C, 63.4; H, 9.86; N, 8.01. \(\text{C,H}_8\text{NO}_4\) requires C, 63.12; H, 10.01; N, 8.18%). \(\delta_2(CDCl_3) 4.04\) (m, 2 H, \(H_2^5\)), 3.76 (dd, \(J = 8\) and 6, 1 H, \(H_4^4\)), 3.15 (m, 1 H, \(H_2^2\)), 2.92 (m, 2 H, \(H_2^5\)), 1.96 (br s, 1 H, NH), 1.95–1.54 (m, 4 H, \(H_2^2\), -4 and -4) and 1.42 and 1.35 (2 x each 3 H, \(CMe_2\)); \(\delta_3(CDCI_3) 108.97, 78.86, 67.59, 60.53, 46.98, 28.19, 26.65, 25.71 and 25.26; \(m/z\) 172 (M' + 1, 3.25%), 156 (4.08), 96 (15.37), 70 (100) and 43 (32.51); \(\nu_{\text{max}}(\text{film}) cm^{-1} 3340, 2940, 2850 and 1690.

Treatment of a portion (100 mg) of compound 22 in the manner described above for compound 14 gave the \(N\)-toluenesulfonyl-22 (109 mg, 57%), mp 71.5–72.5°C (from light petroleum; \([\delta]_D^{23} +95.3\) (Found: C, 59.23; H, 7.04; N, 4.33; S, 9.90.). \(\text{C}_2\text{H}_5\text{NO}_3\text{S}\) requires C, 59.05; H, 7.12; N, 4.30; S, 9.85%). \(\delta_2(CDCl_3) 7.73\) and 7.32 (2 d, \(J = 8.5\) and 6.3, each 1 H, ArH), 4.54 (dt, \(J = 6.0\) and 4.1, 1 H, \(H_4^4\)), 4.10 (dd, \(J = 9.6\) and 6.1, 1 H, \(H_4^5\)), 3.98 (dd, \(J = 9.6\) and 6.1, 1 H, \(H_4^6\)), 3.82 (quintet, \(J = 4.2\), 2 H, 2.35 (m, 2 H, \(H_2^5\)), 2.43 (s, 3 H, \(\text{CH}_3\text{Me}\)), 1.89–1.60 (m, 3 H), 1.42 and 1.35 (2 x each 3 H, \(CMe_2\)) and 1.33 (m, 1 H); \(\delta_3(CDCl_3) 143.66, 134.10, 129.71, 127.70, 109.26, 77.51, 65.61, 50.24, 27.29, 26.17, 24.44 and 21.53.

(2R,4'S)-N-Benzoylcarbonyl-2-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)pyrrolidin-24

Treatment of a portion of compound 22 (260 mg, 1.52 mmol) with benzyl chloroformate (0.23 ml, 1.52 mmol) followed by processing in the usual manner, and column chromatography (hexane-ethyl acetate, 3:1) gave compound 24 (302 mg, 65%), \([\delta]_D^{23} -49\) (400 MHz; 61°C; \(\text{CDCI}_3) 7.52\) (m, 5 H, Ph), 5.13 (gab. \(J = 19.6\) and 12.5, 2 H, PhCH_2), 4.26 (m, 1 H, \(H_4^6\)), 3.99 (m, 1 H, \(H_4^3\)), 3.37 (m, 2 H, \(H_2^2\)), 2.02 (m, 2 H, \(H_2^3\)), 1.88 (m, 2 H), 1.40 and 1.31 (2 x each 3 H, \(CMe_2\)); \(\delta_6(1^C, \text{CDCI}_3) 155.29, 137.00, 128.50 and 127.91 (2x), 127.56, 109.10, 76.67, 67.69, 66.86, 55.44, 47.06, 26.36 (2x), 25.20 and 23.82; \(m/z\) 306 (M' + 1, 0.18%), 290 (1.5), 160 (35.34), 91 (100) and 43 (16.49); \(\nu_{\text{max}}(\text{film}) cm^{-1} 3430, 3200, 2900, 2800 and 1690.

(2R,1'S)-N-Benzoylcarbonyl-2-(1,2-dihydroxyethyl)pyrrolidine 17

A solution of compound 16 (491 mg) in 80% aq. acetic acid (10 ml) was set aside for 5 days and was then concentrated in vacuo. Water (5 ml) followed by toluene (3 x 10 ml) was distilled in vacuo from the residue to give diol 17 (403 mg, 95%) as an oil, \([\delta]_D^{23} +66\) (\(\text{CDCI}_3) 7.36\) (m, 5 H, Ph), 5.15 (s, 2 H, PhCH_2), 4.05 (m, 1 H, \(H_2^2\)), 3.60 (m, 1 H, 3.37 (M, 1 H) and 2.09–1.73 (m, 4 H, \(H_2^2\) and -4); \(\delta_{17} 157.90, 136.15, 128.14, 128.13, 128.07, 75.64, 67.45, 64.04, 59.99, 47.31, 28.48 and 24.12; \(m/z\) 266 (M' + 1, 0.16%), 204 (24.04), 160 (45.83), 114 (7.79), 91 (100), 70 (17.04), 65 (14.85), 43 (10.32), 41 (15.28), 39 (13.27), 31 (8.33) and 28 (19.73); \(\nu_{\text{max}}(\text{KBr}) cm^{-1} 3430, 3040, 2940, 2865 and 1665.

(2S,1'S)-N-Benzoylcarbonyl-2-(1,2-dihydroxyethyl)pyrrolidine 25

Treatment of compound 24 (302 mg) with 80% aq. acetic acid (15 ml) followed by processing in the above manner, yielded compound 25 (235 mg, 90%), \([\delta]_D^{23} -20\) (\(\text{CDCI}_3) 7.35\) (m, 5 H, Ph), 5.14 (gab. \(J = 12.7\) and 12.7, 2 H, 3.92 (1 H, m, \(H_2^2\)), 3.59 (br s, 1 H, \(H_2^2\)), 3.46 (m, 3 H, \(H_2^2\)), 2.09 (m, 1 H) and 1.91 (m, 3 H); \(\delta_{17}(\text{CDCl}_3) 158.8, 136.3, 128.51, 128.11, 127.81, 72.62, 67.41, 62.73, 59.32, 47.18, 27.62 and 23.31; \(m/z\) 266 (M' + 1, 0.16%), 204 (40.24), 160 (45.83), 114 (4.34), 91 (100), 70 (13.74), 65 (27.77), 43 (28.04), 41 (21.55), 39 (18.89), 31 (19.97) and 28 (13.94); \(\nu_{\text{max}}(\text{KBr}) cm^{-1} 3380, 3020, 2980 and 1660.


3354
A stirred solution of compound 17 (405 mg, 1.52 mmol) in a mixture of water (12 ml) and methanol (6 ml) was treated with sodium metaperiodate (325 mg, 1.52 mmol) and sodium hydrogen sulphite (0.5 g, 4.15 mmol) in water (6 ml), and then was set aside at room temperature for a further 1 h. The mixture was concentrated in vacuo, the residue was dissolved in water (10 ml), the pH was adjusted to 7–8 with dil.aq. sodium hydroxide, and the mixture was extracted with hexane (2 × 20 ml). The aqueous phase was then adjusted to pH 3 by addition of 10% aq. t-tartaric acid, extracted with diethyl ether (3 × 10 ml) and the combined extracts were dried (Na2SO4) and concentrated in vacuo to give compound 7 (131 mg, 88%), mp 74–75 °C; [α]D +69.7 (lit.37 mp 76–77 °C; [α]D +61.2 (AcOH)); δ(CDC13) 9.10 (br s, 1 H, CO2H), 7.34 (m, 5 H, Ph), 5.16 (m, 2 H, PhCHO2), 4.42 (m, 2 H, H-2), 3.52 (m, 2 H, H-5), 2.19 (m, 2 H, H-3) and 1.96 (m, 2 H, H-4); δ(CDC17) 178.01 + 175.59 (1 C), 156.15 + 154.34 (1 C), 136.46 + 136.17 (1 C), 128.51, 128.39, 128.17, 127.96, 127.89 + 127.67 (1 C), 67.64 + 67.10 (1 C), 59.37 + 58.56 (1 C), 46.90 + 46.71 (1 C), 30.49 + 29.04 (2 C) and 24.30 + 23.45 (1 C); m/z 249 (M+1 • 1.84%), 160 (13.82), 114 (32.49), 91 (100), 70 (12.45), 65 (12.40) and 39 (5.19); νmax(KBr)/cm−1 3080, 2980, 2935, 2860, 2510, 1650, 1417 and 1365.

(2S)-N-(Benzyloxycarbonyl)proline 8

A solution of compound 7 (131 mg, 0.53 mmol) in methanol (10 ml) was treated with palladium on charcoal (10%; 13 mg) and the mixture was hydrogenated (1 atm) for 5 h. The insoluble material was removed by filtration, then washed with methanol, and the combined filtrates and washings were concentrated in vacuo to give compound 8 (161 mg, 96%), mp 220 °C (from EtOH); [α]D +61.1 (water); lit.38 mp 215–222 °C. [α]D +81.5; δ(CD2O) 3.91 (m, 1 H, H-2), 3.16 (m, 2 H, H-5) and 2.30–1.7 (m, 4 H, H-3 and -4); δ(CD2) 177.41, 63.95, 48.82, 31.76 and 26.51; νmax(KBr)/cm−1 3080, 2980, 2935, 2860, 2510, 1650, 1417 and 1365.

(2S)-N-(Benzyloxycarbonyl)proline Compound 8 (150 mg, 0.64 mmol) in the manner described above for compound 3 yielded the acid 8 (144 mg, 90.7%); mp 75 °C (from diethyl ether–hexane); [α]D −69.7 (lit.37 mp 76–77 °C; [α]D −61.7 (AcOH)); δ(CDC13) 8.95 (br s, 1 H, CO2H), 7.33 (m, 5 H, ArH), 5.16 (m, 2 H, PhCHO2), 4.40 (m, 1 H, H-2), 3.52 (m, 2 H, H-5), 2.20 (m, 2 H, H-3) and 1.96 (m, 2 H, H-4); δ(CD2O) 178.09 + 175.93 (1 C), 156.00 + 154.36 (1 C), 136.45 + 136.21 (1 C), 128.50, 128.38, 128.14, 127.94, 127.87 + 127.66 (1 C), 67.67 + 67.14 (1 C), 59.32 + 58.57 (1 C), 46.89 + 46.67 (1 C), 30.87 + 29.15 (1 C) and 24.27 + 23.43 (1 C); m/z 249 (M+1 • 2.67%), 160 (18.25), 114 (36.77), 91 (100), 70 (17.48), 65 (17.10) and 39 (12.37); νmax(KBr)/cm−1 3020, 2960, 2880 and 1730.

(2S)-N-Benzyloxy carbonyl-2-(hydroxymethyl)pyrrolidine [D]-N-(benzyloxy carbonyl)proline 9

A stirred solution of compound 8 (131 mg, 0.53 mmol) in the presence of palladized charcoal (10%; 13 mg) as described above for compound 7 gave title compound 9 (66 mg, 98%), mp 224 °C (from EtOH); [α]D −83.4 (water); lit.39 mp 227–229 °C; [α]D −83 (water); δ(CD2O) 3.89 (m, 1 H, H-2), 3.16 (m, 2 H, H-5) and 2.30–1.96 (m, 4 H, H-3 and -4); δ(CD2) 177.35, 63.97, 48.81, 31.72 and 26.58; νmax(KBr)/cm−1 3080, 2985, 2940, 2860, 2515, 2480, 1655, 1420 and 1362.

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