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

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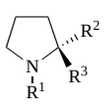
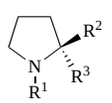
Carbohydrate-based enantiospecific syntheses of (*R*)-proline 1 and (*S*)-proline 2 from the previously reported D-*erythro*-hexonate ester 9 are described. Azide-substitution reactions on appropriately activated intermediates derived from ester 9, followed by reductive cyclization (H_2/Pd–C), gave the 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-glucono-1,5-lactone *via* the hexonate ester **9**,[3] became available during studies on chiral pyrrolidine derivatives. Early syntheses of prolines **1** and **2** produced racemic mixtures which required resolution.[4] Various asymmetric syntheses, including asymmetric transformations, have been reported,[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 hydrolysates or by fermentation.[15] Recent interest[16,17] 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 prolinols **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 reductions[18–24] asymmetric intramolecular aldolizations[25] and asymmetric induction in conjugated additions,[26] self-condensation of α,β-unsaturated aldehydes,[27] Robinson annelation reactions,[28] and in the synthesis of some alkaloids.[29,30]





1 $R^1 = R^3 = H$ $R^2 = CO_2H$ **2** $R^1 = R^3 = H$, $R^2 = CO_2H$
3 R^1 = Cbz, R^2 = CHO, $R^3 = H$ **4** R^1 = Cbz, R^2 = CHO, $R^3 = H$
5 R^1 = Cbz, $R^2 = CH_2OH$, $R^3 = H$ **6** R^1 = Cbz, $R^2 = CH_2OH$, $R^3 = H$
7 R^1 = Cbz, $R^2 = CO_2H$, $R^3 = H$ **8** R^1 = Cbz, $R^2 = CO_2H$, $R^3 = H$
where Cbz = $PhCH_2OCO$

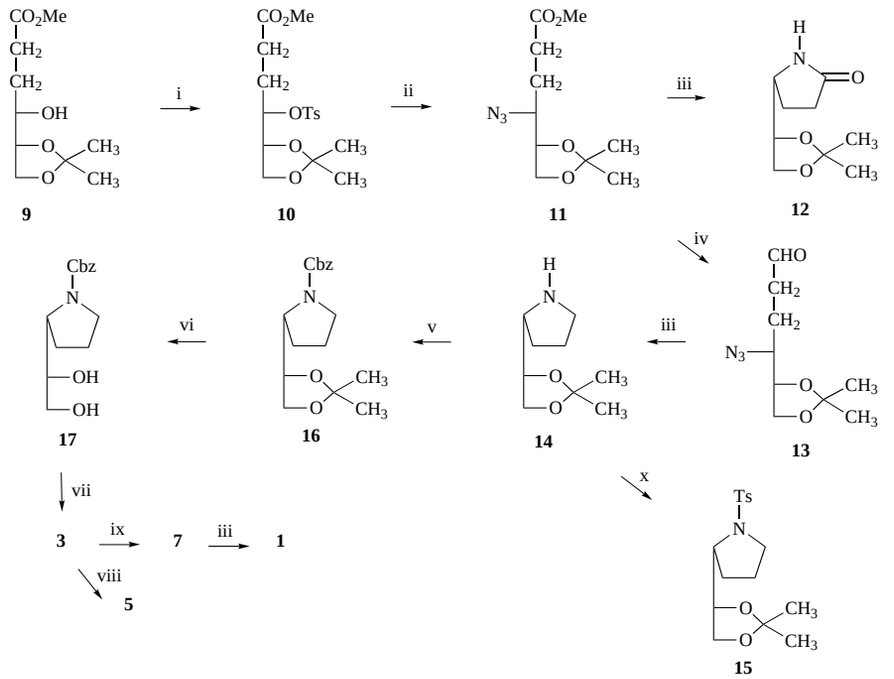
Results and discussion

Treatment of the toluene-*p*-sulfonate ester **10**[3] of compound **9** with sodium azide in *N*,*N*-dimethylformamide (DMF) gave the corresponding D-*threo*-azide **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 diisobutylaluminium 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*-sulfonyl chloride (TsCl)–triethylamine gave the crystalline *N*-toluene-*p*-sulfonate **15**. Treatment of compound **14** in aq. ethanol with benzyl chloroformate in the presence of sodium hydrogen carbonate in the usual manner gave the corresponding *N*-benzyloxycarbonyl (*N*-Cbz) derivative **16**. Hydrolysis (80% aq. acetic acid) of compound **16** gave the diol **17**, which on oxidation with aq. sodium metaperiodate in methanol gave the protected (*R*)-prolinal derivative **3**. Reduction of aldehyde **3** with sodium borohydride in methanol produced the corresponding (*R*)-prolinol derivative **5**.

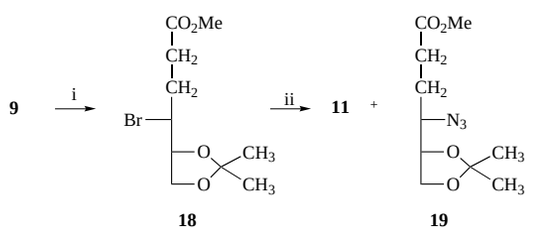
Oxidation of aldehyde **3** with sodium chlorite, in the presence of 2-methylbut-2-ene as a chlorine scavenger,[31] was rapid and proceeded smoothly to give the protected (*R*)-proline derivative **7**, which on catalytic hydrogenolysis[32] provided pure (*R*)-proline **1** (Scheme 1).

Treatment of the bromoester **18**[3] 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 azide[33] in DMF at room temp. for 7 days. Lithium azide is much more



Scheme 1 *Reagents and conditions:* i, TsCl, pyridine; ii, NaN_3, DMF; iii, Pd–C (10%), H_2; iv, DIBAL, −78 °C; v, $PhCH_2OCOCl$, $NaHCO_3$; vi, 80% HOAc–water; vii, $NaIO_4$; viii, $NaBH_4$; ix, $NaClO_2$, 2-methylbut-2-ene; x, TsCl, Et_3N



Scheme 2 *Reagents and conditions:* i, Ph_3P, CBr_4; ii, NaN_3, DMF, 100 °C

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 displacement 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 °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*-sulfonate **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 with aq. 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*-benzyloxycarbonyl derivative **6**, has been described[30] 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**, $[\alpha]_D$ −76.5† is marginally higher than the most recently cited[30] value, $[\alpha]_D$ −63.7, 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[36] 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.

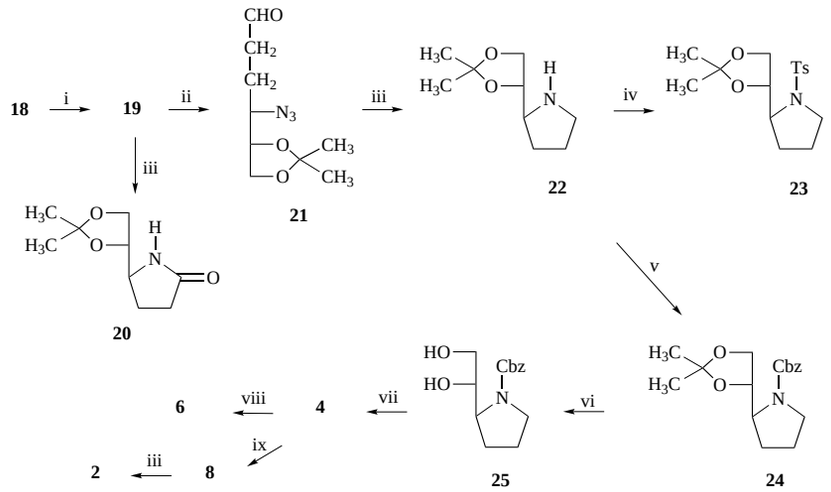
Further oxidation of aldehyde **4** with sodium chlorite in the same manner as described for its enantiomer **3** (*vide supra*) yielded the known, commercially available *N*-Cbz-(*S*)-proline **8**, which on catalytic hydrogenation (palladized charcoal, 10%) yielded (*S*)-proline **2**.

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 $K_2Cr_2O_7$ in 0.05 M H_2SO_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_4Si) or D_2O or as indicated. *J*-Values are given in Hz. ^{13}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_4Si) or D_2O (external 1,4-dioxane at δ_C 67.8). Mass spectra were recorded using a double-focusing VG 7070E

† $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.



Scheme 3 *Reagents and conditions:* i, LiN_3, DMF, 20 °C; ii, DIBAL, −78 °C; iii, Pd–C (10%), H_2; iv, TsCl, KOH; v, $PhCH_2OCOCl$, $NaHCO_3$; vi, 80% HOAc–water; vii, $NaIO_4$; viii, $NaBH_4$; ix, $NaClO_2$, 2-methylbut-2-ene

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-*O*-isopropylidene-D-*threo*-hexonate [(4*R*,5*S*)-methyl 4-azido-5,6-(isopropylidenedioxy)-hexanoate] 11

A stirred mixture of compound **10**[3] (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 ($MgSO_4$), 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, $[\alpha]_D$ +14.4; $\delta_H(CDCl_3)$ 4.09 (m, 2 H, H-5, H^a-6), 3.82 (dd, *J* 8 and 6, 1 H, H^b-6), 3.70 (s, 3 H, OCH_3), 3.28 (m, 1 H, H-4), 2.50 (m, 2 H, H_2-2), 1.78 (m, 2 H, H_2-3) and 1.48 and 1.37 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 173.08, 78.49, 66.37, 62.73, 51.78, 30.32, 26.34, 25.9 and 25.17; *m/z* 228 ($M^+ - 15$, 11%), 216 (3.7), 130 (11.7), 101 (81), 87 (13), 59 (21) and 43 (100); ν_{max}(neat)/cm^{-1} 2980, 2110 and 1730.

(5*R*,4′*S*)-5-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)pyrrolidin-2-one 12

A solution of compound **11** (0.604 g, 2.49 mmol) in methanol (20 ml) was treated with palladized 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; $[\alpha]_D$ −54 (Found: C, 58.27; H, 8.11; N, 7.45. $C_9H_{15}NO_3$ requires C, 58.36; H, 8.16; N, 7.56%); δ_H(100 MHz; $CDCl_3$) 6.48 (br s, 1 H, NH), 4.03–3.67 (m, 4 H, H-4′, -5 and H_2-5′), 2.3–1.95 (m, 4 H, H_2-3 and -4) and 1.42 and 1.33 (2 s, each 3 H, CMe_2); ν_{max}(KBr)/cm^{-1} 3260, 1690 and 1650.

(4*R*,5*S*)-4-Azido-5,6-(isopropylidenedioxy)hexanal 13

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 decahydrate (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 ($NaSO_4$), 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, $[\alpha]_D$ +10.4; $\delta_H(CDCl_3)$ 9.81 (s, 1 H, CHO), 4.10 (m, 2 H, H-5, H^a-6), 3.82 (dd, *J* 6 and 8, 1 H, H^b-6), 3.27 (m, 1 H, H-4), 2.68 (m, 2 H, H_2-2), 1.84–1.70 (m, 2 H, H_2-3) and 1.47 and 1.38 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 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); ν_{max}(neat)/cm^{-1} 2880, 2710, 2100 and 1710.

(2*R*,4′*S*)-2-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)pyrrolidine 14

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 pyrrolidine **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%), $[\alpha]_D$ +9 (Found: C, 62.84; H, 10.41; N, 7.96. $C_9H_{17}NO_2$ requires C, 63.12; H, 10.01; N, 8.18%); $\delta_H(CDCl_3)$ 3.99 (m, 2 H, H_2-5), 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, 3 H) and 1.42 and 1.36 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 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); ν_{max}(film)/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; $[\alpha]_D$ −86 (Found: C, 58.67; H, 6.83; N, 4.31; S, 9.78. $C_{16}H_{23}NO_4S$ requires C, 59.05; H, 7.12; N, 4.30; S, 9.85%); $\delta_H(CDCl_3)$ 7.72 and 7.32 (2 d, each *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^a-5′), 3.98 (dd, *J* 8.5 and 6.3, 1 H, H^b-5′), 3.72 (m, 1 H, H-2), 3.41 (m, 1 H, H^a-5), 3.18 (m, 1 H, H^b-5), 2.43 (s, 3 H, C_6H_4Me), 1.90

‡ 1 bar = 10^5 Pa.

(m, 2 H), 1.55 (m, 1 H), 1.43 and 1.39 (2 s, each 3 H, CMe_2) and 1.35 (m, 1 H); $\delta_C(CDCl_3)$ 143.57, 134.61, 129.73, 127.59, 109.40, 77.41, 67.56, 62.05, 49.17, 29.95, 26.52, 25.15, 24.06 and 21.52.

(2*R*,4′*S*)-*N*-Benzyloxycarbonyl-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)pyrrolidine 16

Treatment of a stirred solution of free amine **14** (336 mg, 1.97 mmol) in 50% aq. ethanol (25 ml), containing sodium hydrogen 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%), $[a]_D$ +59; $\delta_H(CDCl_3)$ 7.33 (m, 5 H, Ph), 5.13 (q_{AB}, *J* 15.6 and 12.4, 2 H, PhCH_2), 4.41 (m, 1 H), 4.13 (m, 1 H), 3.9 (m, 1 H), 3.84 (m, 1 H), 3.61 (m, 1 H), 3.36 (m, 1 H), 2.00–1.78 (m, 4 H, H_2-3 and -4) and 1.37 and 1.33 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 155.52, 136.64, 128.33, 127.83, 127.74, 108.77, 77.48, 66.80, 65.81, 57.75, 47.39, 27.66, 26.08, 25.19 and 23.89; *m*/*z* 290 ($M^+ - 15$, 1.95%), 160 (40.21), 91 (100) and 43 (18.21); ν_{max}(film)/cm^{-1} 3030, 2960, 2880, 1820 and 1680.

Methyl 4-azido-2,3,4-trideoxy-5,6-*O*-isopropylidene-D-*erythro*-hexonate [(4*S*,5*S*)-methyl 4-azido-5,6-(isopropylidenedioxy)-hexanoate] 19

A stirred solution of compound **18**[3] (2.85 g, 10.2 mmol) in dry DMF (24 ml) was treated with lithium azide[33] (2.45 g, 50 mmol) and then was set aside at room temp. for 7 days. The mixture was treated with a mixture of diethyl ether (100 ml) and water (100 ml). The separated aqueous layer was extracted with a further portion of diethyl ether (100 ml) and the combined ether layers were washed successively with saturated aq. sodium chloride and water, dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (hexane–ethyl acetate, 3:1) of the resultant residue gave pure (GLC) compound **19** (1.58 g, 65%) as an oil, $[a]_D$ −45; $\delta_H(CDCl_3)$ 4.07 (m, 2 H, H-5, H^a-6), 3.89 (dd, *J* 8 and 6, 1 H, H^b-6), 3.70 (s, 3 H, OCH_3), 3.59 (m, 1 H, H-4), 2.50 (m, 2 H, H_2-2), 1.96 (m, 1 H, H^a-3), 1.60 (m, 1 H, H^b-3) and 1.47 and 1.36 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 173.06, 109.79, 77.73, 65.80, 62.72, 51.74, 30.44, 26.17, 26.05 and 25.09; *m*/*z* 228 ($M^+ - 15$, 10%), 216 (3.7), 130 (3.2), 101 (57), 98 (22), 83 (16.5), 59 (20) and 43 (100); ν_{max}(film)/cm^{-1} 2980, 2110, 1730, 1240 and 1060.

(5*S*,4′*S*)-5-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)pyrrolidin-2-one 20

Reductive cyclization of compound **19** (0.458 g, 1.89 mmol) in the manner described above for compound **11** gave the *lactam* **20** (0.206 g, 59%), mp 125–126 °C (from diisopropyl ether–dichloromethane); $[a]_D$ +28.2 (Found: C, 58.40; H, 7.91; N, 7.53. $C_9H_{15}NO_3$ requires C, 58.36; H, 8.16; N, 7.56%); δ_H(100 MHz; $CDCl_3$) 6.60 (br s, 1 H, NH), 4.06–3.77 (m, 4 H, H-4′, -5 and H_2-5′), 2.45–1.75 (m, 4 H, H_2-3 and -4) and 1.43 and 1.35 (2 s, each 3 H, CMe_2); ν_{max}(film)/cm^{-1} 3430, 1690 and 1650.

(4*S*,5*S*)-4-Azido-5,6-(isopropylidenedioxy)hexanal 21

A solution of compound **19** (1.26 g, 5.19 mmol) was treated with DIBAL (6.23 ml) and processed as described above. Column chromatography (light petroleum–ethyl acetate, 3:1) of the resulting material gave the aldehyde **21** (0.85 g, 77%), $[a]_D$ +46, as an oil; $\delta_H(CDCl_3)$ 9.81 (s, 1 H, CHO), 4.08 (m, 2 H, H-5, H^a-6), 3.91 (dd, 1 H, *J* 8 and 5, H^b-6), 3.55 (quintet, *J* 5, 1 H, H-4), 2.65 (m, 2 H, H_2-2), 1.97 (m, 1 H, H^a-3), 1.60 (m, 1 H, H^b-3) and 1.47 and 1.36 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 200.76, 109.85, 77.69, 65.86, 62.70, 40.29, 26.19, 25.07 and 23.24; *m*/*z* 186 ($M^+ + 1 - 28$, 0.45%), 101 (44.49), 82 (16.35), 55 (11.06) and 43 (100); ν_{max}/cm^{-1} 2980, 2890, 2720, 2120 and 1700.

(2*S*,4′*S*)-2-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)pyrrolidine 22

A solution of compound **21** (0.64 g, 3.0 mmol) in methanol (20 ml) was hydrogenated (1 atm) in the presence of palladized charcoal (10%; 60 mg) for 6 h and was then processed as described above. Distillation *in vacuo* (Kügelrohr, 80 °C/0.5 mbar) of the material gave pure compound **22** (0.322 g, 62.5%), $[a]_D$ +16 (Found: C, 63.4; H, 9.86; N, 8.01. $C_9H_{17}NO_2$ requires C, 63.12; H, 10.01; N, 8.18%); $\delta_H(CDCl_3)$ 4.04 (m, 2 H, H_2-5′), 3.76 (dd, *J* 8 and 6, 1 H, H-4′), 3.15 (m, 1 H, H-2), 2.92 (m, 2 H, H_2-5), 1.96 (br s, 1 H, NH), 1.95–1.54 (m, 4 H, H_2-3 and -4) and 1.42 and 1.35 (2 s, each 3 H, CMe_2); $\delta_C(CDCl_3)$ 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); ν_{max}(neat)/cm^{-1} 3340, 2920 and 1690.

Treatment of a portion (100 mg) of compound **22** in the manner described above for compound **14** gave the N-*toluene*-p-*sulfonate* **23** (109 mg, 57%), mp 71.5–72.5 °C (from light petroleum); $[a]_D$ +95.3 (Found: C, 59.23; H, 7.04; N, 4.33; S, 9.90. $C_{16}H_{23}NO_4NS$ requires C, 59.05; H, 7.12; N, 4.30; S, 9.85%); $\delta_H(CDCl_3)$ 7.73 and 7.32 (2 d, *J* 8.5 and 6.3, each 1 H, ArH), 4.54 (dt, *J* 6.6 and 4.0, 1 H, H-4′), 4.10 (dd, *J* 9 and 6.8, 1 H, H^a-5′), 3.98 (dd, *J* 9 and 6.4, 1 H, H^b-5′), 3.82 (quintet, *J* 4.2, H-2), 3.35 (m, 2 H, H_2-5), 2.43 (s, 3 H, C_6H_4Me), 1.89–1.60 (m, 3 H), 1.42 and 1.35 (2 s, each 3 H, CMe_2) and 1.33 (m, 1 H); $\delta_C(CDCl_3)$ 143.66, 134.10, 129.71, 127.70, 109.26, 77.51, 65.61, 50.24, 27.29, 26.17, 24.99, 24.44 and 21.53.

(2*S*,4′*S*)-*N*-Benzyloxycarbonyl-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)pyrrolidine 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%), $[a]_D$ −39; δ_H(400 MHz; 61 °C; $CDCl_3$) 7.52 (m, 5 H, Ph), 5.13 (q_{AB}, *J* 19.6 and 12.5, 2 H, PhCH_2), 4.26 (m, 1 H), 3.99 (m, 1 H), 3.76 (m, 1 H), 3.49 (m, 2 H), 2.02 (m, 2 H), 1.85 (m, 2 H) and 1.40 and 1.31 (2 s, each 3 H, CMe_2); δ_C(61 °C; $CDCl_3$) 155.29, 137.00, 128.50 and 127.91 (2×), 127.56, 109.10, 76.67, 67.69, 66.86, 55.54, 47.06, 26.36 (2×), 25.20 and 23.82; *m*/*z* 306 ($M^+ + 1$, 0.18%), 290 (1.5), 160 (35.34), 91 (100) and 43 (16.49); ν_{max}(film)/cm^{-1} 3430, 3020, 2960, 2800 and 1690.

(2*R*,1′*S*)-*N*-Benzyloxycarbonyl-2-(1,2-dihydroxyethyl)pyrrolidine 17

A solution of compound **16** (491 mg) in 80% aq. acetic acid (10 ml) was set aside at room temperature for 5 days and was then concentrated *in vacuo*. Water (5 ml), followed by toluene (3 × 10 ml) was distilled *in vacuo* from the residue to give diol **17** (403 mg, 95%) as an oil, $[a]_D$ +66; $\delta_H(CDCl_3)$ 7.36 (m, 5 H, Ph), 5.15 (s, 2 H, PhCH_2), 4.05 (m, 1 H, H-2), 3.60 (m, 1 H), 3.37 (m, 1 H) and 2.09–1.73 (m, 4 H, H_2-3 and -4); δ_C 157.90, 136.15, 128.14, 128.14, 128.03, 127.80, 75.64, 67.45, 64.04, 59.99, 47.31, 28.48 and 24.12; *m*/*z* 266 ($M^+ + 1$, 0.16%), 204 (40.24), 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); ν_{max}(KBr)/cm^{-1} 3400, 3030, 2940, 2885 and 1665.

(2*S*,1′*S*)-*N*-Benzyloxycarbonyl-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%), $[a]_D$ −20; $\delta_H(CDCl_3)$ 7.35 (m, 5 H, Ph), 5.14 (q_{AB}, *J* 12.7 and 12.7, 2 H), 3.92 (1 H, m, H-2), 3.59 (br s, 1 H, H-4′), 3.46 (m, 3 H), 2.09 (m, 1 H) and 1.91 (m, 3 H); $\delta_C(CDCl_3)$ 158.8, 136.3, 128.51, 128.1, 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); ν_{max}(KBr)/cm^{-1} 3380, 3020, 2950, 2880 and 1660.

(2*R*)-*N*-(Benzyloxycarbonyl)pyrrolidine-2-carbaldehyde 3

A stirred solution of compound **17** (403 mg, 1.52 mmol) in a mixture of water (12 ml) and methanol (8 ml) was treated with sodium metaperiodate (325 mg, 1.52 mmol) and set aside in the dark for 2 h. The mixture was extracted with dichloromethane (2 × 20 ml) and the combined extracts were washed with water (20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue gave the aldehyde **3** (280 mg, 79%), $[\alpha]_D$ + 83; $\delta_H(CDCl_3)$ 9.59 (d, 0.5 H, *J* 1.6, CHO), 9.49 (d, *J* −2.3, 0.5 H, CHO), 7.32 (m, 5 H, Ph), 5.16 (m, 2 H, PhC*H*$_2$), 4.30 (m, 0.5 H, H-2), 4.20 (m, 0.5 H, H-2), 3.56 (m, 2 H, H_2-5), 2.05 (m, 2 H, H_2-3) and 1.92 (m, 2 H, H_2-4); $\delta_C(CDCl_3)$ 199.98, 155.23 + 154.37 (1 C), 136.35 + 136.12 (1 C), 128.85, 128.39, 127.99, 67.13, 65.15 + 64.76 (1 C), 47.12 + 46.59 (1 C), 27.67 + 26.47 (1 C) and 24.37 + 23.60 (1 C); *m*/*z* 204 (M^+ − 29, 3.15%), 160 (18.92), 91 (100) and 65 (12.60); ν_{max}(neat)/cm^{-1} 2978, 2880, 1735 and 1694.

(2*S*)-*N*-(Benzyloxycarbonyl)pyrrolidine-2-carbaldehyde 4

Treatment of compound **25** (234 mg, 0.83 mmol) with sodium metaperiodate (189 mg, 0.83 mmol) as described above yielded aldehyde **4** (165 mg, 80%), $[\alpha]_D$ −76.5 {lit.,[30] $[\alpha]_D^{20}$ −63.7 (MeOH)}; $\delta_H(CDCl_3)$ 9.58 (d, *J* 1.7, 0.5 H, CHO), 9.48 (d, 0.5 H, *J* 2.3, CHO), 7.32 (m, 5 H, Ph), 5.16 (m, 2 H, PhC*H*$_2$), 4.28 (m, 0.5 H, H-2), 4.19 (m, 0.5 H, H-2), 3.55 (m, 2 H, H_2-5), 2.05 (m, 2 H, H_2-3) and 1.91 (m, 2 H, H_2-4); $\delta_C(CDCl_3)$ 199.88, 155.24 + 154.37 (1 C), 136.37, 128.40, 127.93, 67.14, 65.17 + 64.77 (1 C), 47.20 + 46.67 (1 C), 27.70 + 26.49 (1 C) and 24.39 + 23.62 (1 C); *m*/*z* 204 (M^+ − 29, 3.67%), 160 (19.80), 91 (100) and 65 (12.62); ν_{max}(neat)/cm^{-1} 2980, 2860, 1720 and 1690.

(2*R*)-*N*-Benzyloxycarbonyl-2-(hydroxymethyl)pyrrolidine [(*R*)-*N*-(benzyloxycarbonyl)prolinol] 5

A stirred solution of compound **3** (148 mg, 0.63 mmol) in methanol (10 ml) was treated portionwise with sodium borohydride (60 mg, 1.9 mmol), and then was stirred for a further 30 min when analysis (TLC) indicated complete reaction. The stirred mixture was treated cautiously with water (50 ml), extracted with dichloromethane (2 × 20 ml) and the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (hexane–ethyl acetate, 1:1) of the residue gave compound **5** (130 mg, 88%), $[\alpha]_D$ +40 as an oil; $\delta_H(CDCl_3)$ 7.34 (m, 5 H, Ph), 5.13 (q_{AB}, *J* 12.5 and 14.2, 2 H, PhC*H*$_2$), 4.46 (br s, 1 H, OH), 3.98 (m, 1 H, H-2), 3.63 (d, *J* 5.6, 2 H, H_2-1′), 3.51–3.38 (m, 2 H, H_2-5) and 2.04–1.58 (m, 4 H, H_2-3 and -4); δ_C 156.71, 136.34, 128.30, 127.84, 127.68, 66.97, 66.18, 60.35, 47.08, 28.26 and 23.78; *m*/*z* 235 (M^+, 0.55%), 204 (26.65), 160 (23.87), 91 (100), 65 (12.32) and 41 (9.42); ν_{max}(KBr)/cm^{-1} 2960, 2885 and 1690.

(2*S*)-*N*-Benzyloxycarbonyl-2-(hydroxymethyl)pyrrolidine [(*S*)-*N*-(benzyloxycarbonyl)prolinol] 6

Treatment of compound **4** (100 mg) in the above manner gave compound **6** (77 mg, 88%), $[\alpha]_D$ −41 (lit.,[30] $[\alpha]_D$ −41.4); $\delta_H(CDCl_3)$ 7.36 (m, 5 H, ArH), 5.14 (q_{AB}, *J* 12.5 and 13.9, 2 H, PhC*H*$_2$), 4.43 (br s, 1 H, OH), 3.99 (m, 1 H, H-2), 3.64 (d, 2 H, *J* 6.3, H_2-1′), 3.54 (m, 1 H), 3.39 (m, 1 H), 2.05–1.57 (m, 4 H, H_2-3 and -4); $\delta_C(CDCl_3)$ 156.94, 136.38, 128.39, 127.94, 127.78, 67.10, 66.63, 60.54, 47.19, 28.42 and 23.99; *m*/*z* 235 (M^+, 0.81%), 204 (36.59), 160 (32.53), 91 (100), 65 (18.65) and 41 (15.10); ν_{max}(KBr)/cm^{-1} 3030, 2960, 2880 and 1680.

(2*R*)-*N*-(Benzyloxycarbonyl)proline 7

A stirred solution of the aldehyde **3** (140 mg) in a mixture of 2-methylpropan-2-ol (12.5 ml) and 2-methylbut-2-ene (3.0 ml) was treated dropwise over a period of 10 min with a solution of sodium chlorite (0.5 g, 5.33 mmol) and sodium dihydrogen phosphate (0.57 g, 4.15 mmol) in water (6 ml), and was then 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. L-tartaric acid, extracted with diethyl ether (3 × 10 ml) and the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give compound **7** (131 mg, 88%), mp 74–75 °C; $[\alpha]_D$ +69.7 {lit.,[37] mp 76–77 °C; $[\alpha]_D$ +61.2 (AcOH)}; $\delta_H(CDCl_3)$ 9.10 (br s, 1 H, CO_2H), 7.34 (m, 5 H, Ph), 5.16 (m, 2 H, PhC*H*$_2$), 4.42 (m, 1 H, H-2), 3.52 (m, 2 H, H_2-5), 2.19 (m, 2 H, H_2-3) and 1.96 (m, 2 H, H_2-4); $\delta_C(CDCl_3)$ 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), 30.98 + 29.04 (1 C) and 24.30 + 23.45 (1 C); *m*/*z* 249 (M^+, 1.84%), 160 (13.82), 114 (32.49), 91 (100), 70 (12.45), 65 (12.40) and 39 (5.19); ν_{max}(KBr)/cm^{-1} 3010, 2980, 2885 and 1750.

(*R*)-Proline 1

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 filtrate and washings were concentrated *in vacuo* to give compound **1** (61 mg, 96%), mp 220 °C (from EtOH); $[\alpha]_D$ +80 (water) {lit.,[38] mp 215–222 °C; $[\alpha]_D$ +81.5}; $\delta_H(D_2O)$ 3.91 (m, 1 H, H-2), 3.16 (m, 2 H, H_2-5) and 2.30–1.7 (m, 4 H, H_2-3 and -4); $\delta_C(D_2O)$ 177.41, 63.95, 48.82, 31.76 and 26.51; ν_{max}(KBr)/cm^{-1} 3080, 2980, 2935, 2860, 2510, 1650, 1417 and 1365.

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

Treatment of the aldehyde **4** (150 mg, 0.64 mmol) in the manner described above for compound **3** yielded the acid **8** (144 mg, 90.5%), mp 75 °C (from diethyl ether–hexane), $[\alpha]_D$ −69.7 {lit.,[37] mp 76–77 °C; $[\alpha]_D$ −61.7 (AcOH)}; $\delta_H(CDCl_3)$ 8.95 (br s, 1 H, CO_2H), 7.33 (m, 5 H, ArH), 5.16 (m, 2 H, PhC*H*$_2$), 4.40 (m, 1 H, H-2), 3.52 (m, 2 H, H_2-5), 2.20 (m, 2 H, H_2-3) and 1.96 (m, 2 H, H_2-4); $\delta_C(D_2O)$ 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), 67.57 + 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^+, 2.67%), 160 (18.25), 114 (36.77), 91 (100), 70 (17.48), 65 (17.10) and 39 (12.37); ν_{max}(KBr)/cm^{-1} 3020, 2960, 2880 and 1730.

(*S*)-Proline 2

Hydrogenolysis 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 **2** (66 mg, 98%), mp 224 °C (from EtOH); $[\alpha]_D$ −83.4 (water) {lit.,[13] mp 227–229 °C; $[\alpha]_D$ −83 (water)}; $\delta_H(D_2O)$ 3.89 (m, 1 H, H-2), 3.16 (m, 2 H, H_2-5) and 2.30–1.96 (m, 4 H, H_2-3 and -4); $\delta_C(D_2O)$ 177.35, 63.97, 48.81, 31.72 and 26.58; ν_{max}(KBr)/cm^{-1} 3080, 2985, 2940, 2860, 2515, 2480, 1655, 1420 and 1362.

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