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/Pd-C), gave the substituted pyrrolidine 14 and 22, which were converted into their corresponding N-Cbz derivatives 16 and 24 in conventional manner. Mild acid 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, not only in the modern organic chemistry. The synthesis of prolines and their derivatives is an active area of modern organic chemistry. The present paper describes a convenient route to (R)-proline 1 and (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, became available during studies on chiral pyrrolidine derivatives. Early syntheses of prolines 1 and 2 produced racemic mixtures which required resolution. Various asymmetric syntheses, including asymmetric transformations, have been reported, 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 from fermentation. Recent interest 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 an 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. 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 and asymmetric intramolecular aldolizations and asymmetric induction in conjugated additions, self-condensation of unsaturated aldehydes, Robinson annelation reactions, and in the synthesis of some alkaloids.

Results and discussion

Treatment of the toluene-p-sulfonate ester 10 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 dibutylaluminum 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)-trichlylamine 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)-prolinol 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, was rapid and proceeded smoothly to give the protected (R)-prolinol derivative 7, which on catalytic hydrogenolysis 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 azide 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 displacement reactions has been reviewed. Compound 19 yielded the crystalline pyrrolidine-2-one derivative 20 on reductive (Pd/C, H2) cyclization (vide supra).

Reaction of ester 19 with DIBAL in toluene at −78 °C, followed by reductive (Pd/C, H2) 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 aqueous methanolic sodium metaperiodate yielded the aldehyde 4, reduction of which with sodium borohydride in methanol gave the (S)-prolinol 3, via diol 25. 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 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, [α]D = −76.5° is marginally higher than the most recently cited value, [α]D = −63.7°, and both are much greater than those cited earlier for compound 4, derived from reduction of esters of (S)-proline 2. It had been implied 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 K2Cr2O7 in 0.05 m H2SO4 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. 1H NMR spectra were recorded with a Bruker AC 100 (100 MHz) or Bruker AC 300 (300 MHz) spectrometer on solutions in CDCl3 (internal Me4Si) or D2O or as indicated. 1J-Values are given in Hz. 13C 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 CDCl3 (internal Me4Si) or D2O (external 1,4-dioxane at δ2 = 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-O-isopropylidene-3-threo-hexanone [(4R,5S)-methyl 4-azido-5,6-(isopropylidenedioxy)hexanone] 11**

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, [α]D +14.4; δH(CDCI₃) 4.09 (m, 2 H, H-5, H-6), 3.82 (dd, J 6 and 8, 1 H, H-6), 3.70 (s, 3 H, OCH₃), 3.28 (m, 1 H, H-4), 2.50 (m, 2 H, H₂-2), 1.78 (m, 2 H, H₂-3) and 1.48 and 1.37 (2 s, each 3 H, CMe₂); δC(CDCI₃) 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); vmax( neat)/cm⁻¹ 2980, 2710 and 1730.

**Scheme 3 Reagents and conditions:** i, LiN₃, DMF, 20 °C; ii, DIBAL, −78 °C; iii, Pd–C (10%), H₂; iv, TsCl, KOH; v, PhCH₂OCOCI, NaHCO₃; vi, 80% HOAc–water; vii, NaIO₄; viii, NaBH₄; ix, NaClO₂; 2-methylbut-2-ene to the same temperature, treated with sodium sulfite 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; δ(CDCI₃) 9.81 (s, 1 H, CHO), 4.10 (m, 2 H, H-5, H-6), 3.82 (dd, J 6 and 8 and 1 H, H-6), 3.27 (m, 1 H, H-4), 2.68 (m, 2 H, H₂-2), 1.84–1.70 (m, 2 H, H₂-3) and 1.47 and 1.38 (2 s, each 3 H, CMe₂); δ(CDCI₃) 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); vmax( neat)/cm⁻¹ 2880, 2710, 2100 and 1710.

**Scheme 3 Reagents and conditions:** i, LiN₃, DMF, 20 °C; ii, DIBAL, −78 °C; iii, Pd–C (10%), H₂; iv, TsCl, KOH; v, PhCH₂OCOCI, NaHCO₃; vi, 80% HOAc–water; vii, NaIO₄; viii, NaBH₄; ix, NaClO₂; 2-methylbut-2-ene
A solution of compound 19 (1.26 g, 5.19 mmol) was treated with Dibal-H (2.03 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%), [α]D +46, as an oil; δ(CDC13) 9.81 (s, 1 H, CHO), 4.08 (m, 2 H, H-5, H-6), 3.91 (dd, 1 H, J 8 and 5, H-4), 3.55 (quintet, J 5, 1 H, H-5), 2.65 (m, 2 H, H-2), 1.97 (m, 1 H, H-3), 1.60 (m, 1 H, H-4), 1.47 and 1.36 (2 each, 3 H, CMe2); δ(CDC13) 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); v(Ascending, cm-1) 2980, 2890, 2720, 2170 and 1240.

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

A solution of compound 19 (1.26 g, 5.19 mmol) was treated with Dibal-H (2.03 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%), [α]D +46, as an oil; δ(CDC13) 9.81 (s, 1 H, CHO), 4.08 (m, 2 H, H-5, H-6), 3.91 (dd, 1 H, J 8 and 5, H-4), 3.55 (quintet, J 5, 1 H, H-5), 2.65 (m, 2 H, H-2), 1.97 (m, 1 H, H-3), 1.60 (m, 1 H, H-4), 1.47 and 1.36 (2 each, 3 H, CMe2); δ(CDC13) 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); v(Ascending, cm-1) 2980, 2890, 2720, 2170 and 1240.

(2R,4′S)-N-Benzoylcarbonyl-2-(2′,2′-dimethyl-1′,3′-dioxolane-4′-yl)pyrrolidine 22

A solution of compound 19 (0.64 g, 3.0 mmol) in methanol (20 ml) was hydrogenated (1 atm) in the presence of palladium charcoal (10%; 60 mg) for 6 h and was then processed as described above. Distillation in vacuo (Kugelrohr, 80 °C/0.5 mbar) of the material gave pure compound 22 (0.32 g, 62.5%), [α]D +16 (Found: C, 63.4; H, 9.86; N, 8.01; CH3NO requires C, 63.2; H, 10.01; N, 8.18%); δ(CDC13) 4.04 (m, 2 H, H-5, H-6), 3.76 (dd, J 8 and 6, 1 H, H-4), 3.15 (m, 1 H, H-2), 2.92 (m, 2 H, H-5, H-6), 1.96 (br s, 1 H, NH), 1.95–1.54 (m, 4 H, H-3 and -4) and 1.42 and 1.35 (2 each, 3 H, CMe2); δ(CDC13) 108.97, 78.86, 67.59, 60.53, 49.68, 28.95, 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); v(Ascending, cm-1) 3340, 2920 and 1690.

A solution of 100 mg of compound 22 in the manner described above for compound 14 gave the N-toluenesulfonylamine 23 (109 mg, 57%), mp 71.5–72.5 °C (from light petroleum); [α]D +95.3 (Found: C, 59.23; H, 7.04; N, 4.33; S, 9.90; C14H18NO3S requires C, 59.05; H, 7.12; N, 4.30; S, 9.85%); δ(CDC13) 7.73 and 7.32 (2, 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 9.9 and 6.8, 1 H, H-5, H-6), 3.98 (dd, J 9.9 and 6.8, 1 H, H-5, H-6), 3.82 (quintet, J 4.2, H-2), 3.35 (m, 2 H, H-5, H-6), 2.43 (s, 3 H, CH3Me), 1.89–1.60 (m, 1 H, 3.1) and 1.42 and 1.35 (2 each, 3 H, CMe3) and 1.33 (m, 1 H); δ(CDC13) 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.

(2R,4′S)-N-Benzoylcarbonyl-2-(2′,2′-dimethyl-1′,3′-dioxolane-4′-yl)pyrrolidine 24

A solution of a stirred solution of free amine 21 (335 mg) with benzyl chloroformate (0.45 ml, 3.2 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 24 (18.0 mg, 57%), mp 112.5–113.5 °C (from ethyl acetate); [α]D +19.5 (Found: C, 63.2; H, 11.5; N, 8.2%; S, 7.6%; C10H17NO3S requires C, 63.1; H, 11.3; N, 8.7%; S, 7.7%).

(2R,4′S)-N-Benzoylcarbonyl-2-(2′,2′-dimethyl-1′,3′-dioxolane-4′-yl)pyrrolidine 25

A solution of a stirred solution of free amine 21 (335 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) gave compound 25 (225 mg, 100%), mp 165–166 °C (from ethyl acetate); [α]D +19.6 (Found: C, 63.1; H, 11.0; N, 8.3%; S, 7.6%; C10H17NO3S requires C, 63.2; H, 11.3; N, 8.7%; S, 7.7%).
(2R)-N-(Benzyloxy carbonyl)pyrrolidine-2-carbaldheyde 3
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 set aside in the dark for 2 h. The mixture was extracted with dichloromethane (20 ml) and the combined extracts were washed with water (20 ml), dried (Na2SO4) and concentrated in vacuo. Column chromatography (light petroleum-ethyl acetate, 3:1) of the residue gave the aldehyde 3 (280 mg, 79%), δH (CDCl3) 9.59 (d, 0.5 H, J = 1.6 CH), 9.49 (d, J = 2.3, 0.5 H, CHO), 7.32 (5 H, Ph), 5.16 (2 H, PhCH2), 4.30 (m, 0.5 H, H-2), 2.40 (m, 0.5 H, H-2), 3.56 (2 H, H-2), 2.05 (2 H, H-3) and 1.92 (2 H, H-4); δC (CDCl3) 199.98, 155.23, 153.47 (1 C), 136.35 + 136.12 (1 C), 128.85, 128.39, 128.79, 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); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2978, 2880, 1735 and 1694.

(2S)-N-(Benzyloxy carbonyl)-2-hydroxymethyl)pyrrolidine [(R)-N-(benzyloxy carbonyl)prolinol] 5
A stirred solution of compound 25 (234 mg, 0.83 mmol) with sodium metaperiodate (189 mg, 0.83 mmol) as described above yielded the aldehyde 4 (165 mg, 80%), δH (CDCl3) 7.65 [lit.\(^{36}\) δH (MeOH)] -63.7 (MeOH); δC (CDCl3) 9.58 (d, J = 1.7, 0.5 H, CHO), 9.48 (d, 0.5 H, J = 2.3, 0.5 H, CHO), 7.32 (5 H, Ph), 5.16 (2 H, PhCH2), 4.46 (m, 1 H, H-2), 3.86 (m, 1 H, H-3), 3.08 + 2.97 (1 C, 2 H, H-2), 3.51 + 3.50 (2 H, H-2), 0.94 + 1.58 (4 H, 4 H, H-3 and -4); δC (CDCl3) 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); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2978, 2860, 1720 and 1690.

(2R)-N-(Benzyloxy carbonyl)pyrrolidine-2-carboxaldehyde 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 filtrate was concentrated in vacuo to give compound 8 (161 mg, 96%), mp 220 °C (from EtOH); δH (CDCl3) 8.0 (water) [lit.\(^{37}\) mp 76-77 °C; δH (CDCl3) 8.95 (br s, 1 H, CO2H), 7.33 (m, 5 H, ArH), 5.16 (2 H, PhCH2), 4.40 (m, 1 H, H-2), 3.52 (2 H, H-2), 2.20 (m, 2 H, H-3) and 1.96 (2 H, H-4); δC (CDCl3) 179.01 + 175.99 (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), 59.57 + 58.56 (1 C), 46.9 + 46.71 (1 C), 34.6 + 34.04 (1 C), 29.04 (1 C), 24.30 + 23.45 (1 C); m/z 249 (M+ 1%, 1.95%), 160 (13.82), 114 (32.49), 91 (100), 70 (12.45), 65 (12.40) and 39 (5.19); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 3080, 2980, 2935, 2860, 2510, 1650, 1417 and 1365.

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References

