Application of Pd^{II}-catalysed oxidative cyclisation of hydroxy(vinyl)furan: synthesis of (5*R*)-diastereomer of (+)-goniofufurone

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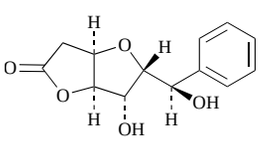
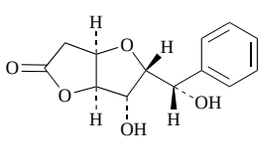
A convenient synthesis of the (5*R*)-diastereomer of (+)-goniofufurone 5 from D-mannose has been completed. A key step is the intramolecular $PdCl_2$-catalysed oxidative cyclisation of hydroxy(vinyl)furan 6 to lactol 16.

Introduction

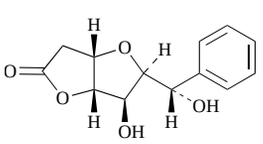
A novel styryl-lactone goniofufurone has been isolated[1,2] from ethanolic extracts of the stem bark of *Goniothalamus giganteus Hook. f.*, Thomas (Annonaceae) and shown to exhibit cytotoxic activity in tests with several human tumour cell lines.[3–6] The constitution and relative configuration was assigned to the natural goniofufurone (+)-**1** as D-*glycero*-D-*ido*, independently by Shing and Tsui[7] and Jager and Gracza[8] from the synthesis of both enantiomers. Thus, (+)-**1**, *epi*-goniofufurone (+)-**2** and their enantiomers (−)-**1** and (−)-**2** have been synthesised.[8–10] Enantiospecific synthesis of compounds **3** (3*S*,4*R*) and **4**



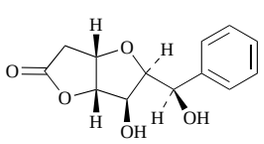
(+)-**1**



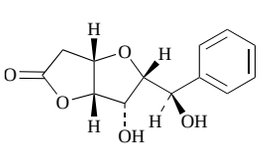
(+)-**2**



(−)-**1**



(−)-**2**



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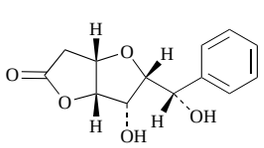

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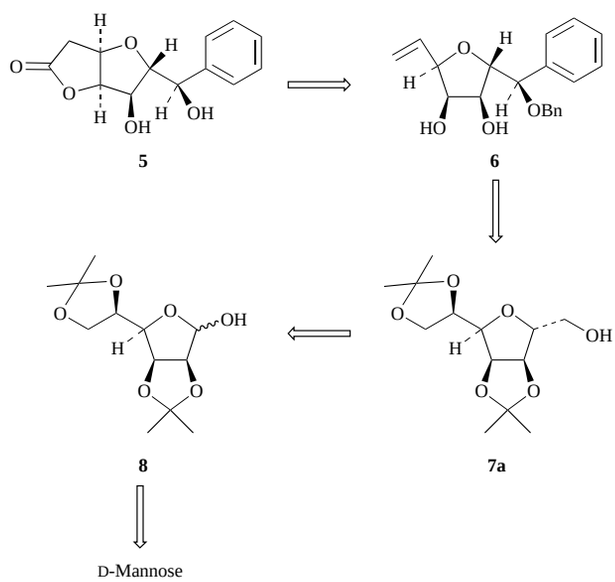
(3*S*,4*R*,7*S*) which are diastereomers of compounds (+)-**1**, (+)-**2** has also been achieved.[11] Owing to their potential as anti-tumour agents several other related styryl-lactones have also been consequently isolated, characterised and their analogues synthesised.[12]

Results and discussion

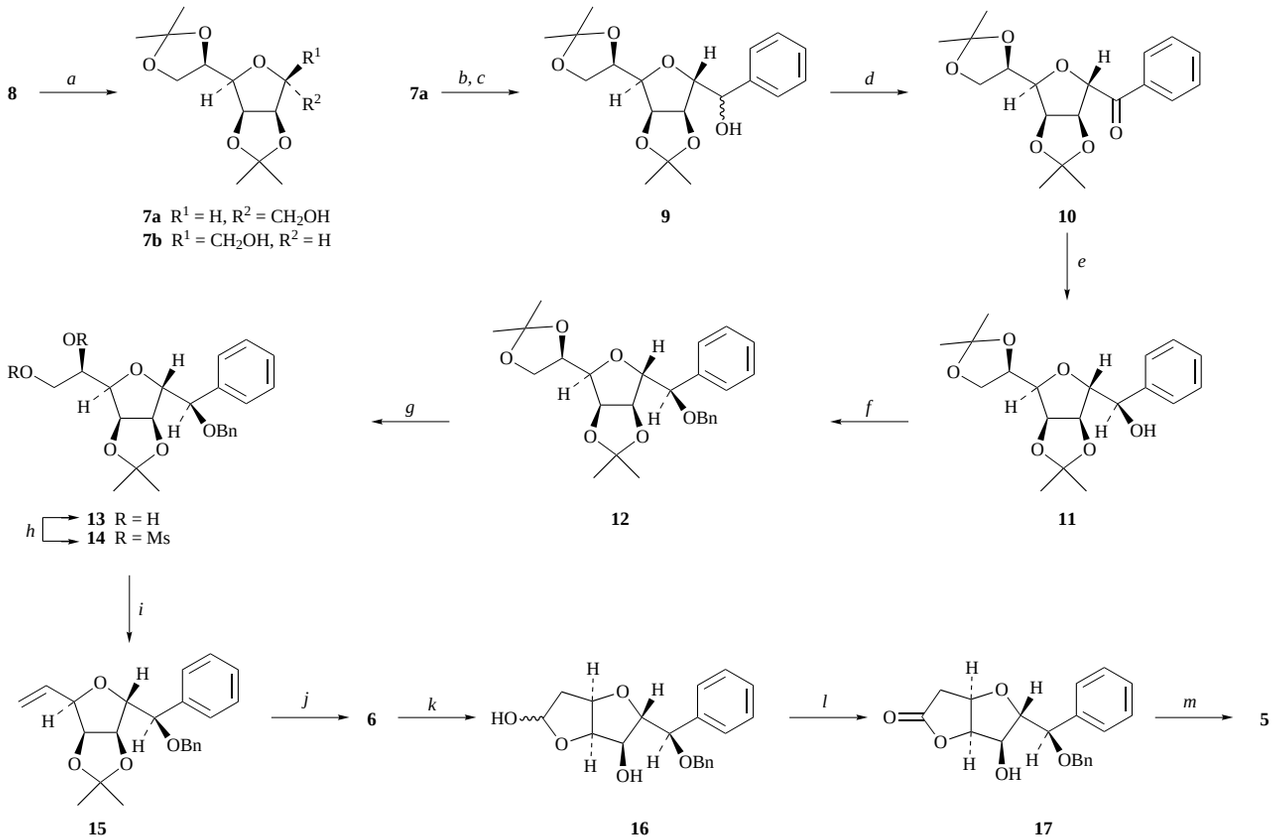
Herein we report a convenient synthesis of yet another 5*R* diastereomer (compound **5**) of natural goniofufurone (+)-**1**. From retrosynthetic analysis (Scheme 1) compound **5** could be visualised as arising from hydroxy(vinyl)furan derivative **6** by means of the $PdCl_2$-mediated oxidative cyclisation protocol previously developed by us as a key step.[13] Compound **6** in turn



5 **6** **8** **7a** D-Mannose

Scheme 1

could be realised from the *C*-glycoside **7a** by involving oxidation of the primary alcohol followed by Grignard addition to obtain the desired C-7 stereocentre of target molecule **5**. The vinyl group could be derived from the regioselective transformation of the primary acetonide by established methods. Compound **7a** is obtainable from diacetone-D-mannose **8**, involving C–C bond formation at C-1 to generate the required C-6 stereocentre of compound **5**.[14] C-2,3,4 stereocentres of D-mannose as such can be retained during these transformations to synthesise compound **5**. The crystalline diacetone-D-mannose **8** was obtained from D-mannose in 85% yield[15] (Scheme 2). Lactol **8** was treated with trimethylsulfoxonium iodide[16] (TMSOI) and potassium *tert*-butoxide in dry dimethyl sulfoxide (DMSO) at room temp for 1 h to obtain a diastereomeric mixture of *C*-glycosides **7a**,**7b** in the ratio 4:1 (by 1H NMR spectroscopy) as a thick syrup in 79% yield. Fractional crystallisation of mixture **7a**,**7b** (dichloromethane–hexane, 1:4) at 30 °C gave the required diastereomer **7a** as a crystalline compound (53%), mp 83–84 °C; $[\alpha]_D$ -12.6×10^{-1} deg cm^2 g^{-1} (*c* 1.0, $CHCl_3$) [lit.,[14] −10 (*c* 1.0, $CDCl_3$)]. Use of sodium hydride instead of KOBu^t resulted in the isolation of mixture **7a**,**7b** in the ratio 2.3:1.[14] Compound **7a** was unambiguously characterised from ^{1}H NMR spectroscopy (400 MHz) and X-ray crystallography (Fig. 1) due to some minor differences observed while comparing the



Scheme 2 *Reagents and conditions*: *a*, TMSOI, KoBu^t, DMSO, room temp, 1 h; *b*, Oxalyl dichloride, DMSO, TEA, CH_2Cl_2, −78 °C, 45 min; *c*, PhMgBr, THF, 0 °C, 3 h; *d*, PDC, CH_2Cl_2, reflux, 3 h; *e*, $NaBH_4$, MeOH, −10 °C, 30 min; *f*, BnBr, NaH, DMF, 0 °C; 1 h; *g*, 60% aq. AcOH, room temp, 8 h; *h*, MsCl, TEA, CH_2Cl_2, 0 °C, 30 min; *i*, NaI, butan-2-one, reflux, 8 h; *j*, 5% aq. H_2SO_4, 1,4-dioxane, reflux, 2 h; *k*, $PdCl_2$(cat), CuCl, O_2, aq. DMF (1 : 4), room temp, 4 h; *l*, PDC, CH_2Cl_2, reflux, 1 h; *m*, Pd–$BaSO_4$, H_2, MeOH, 6 h

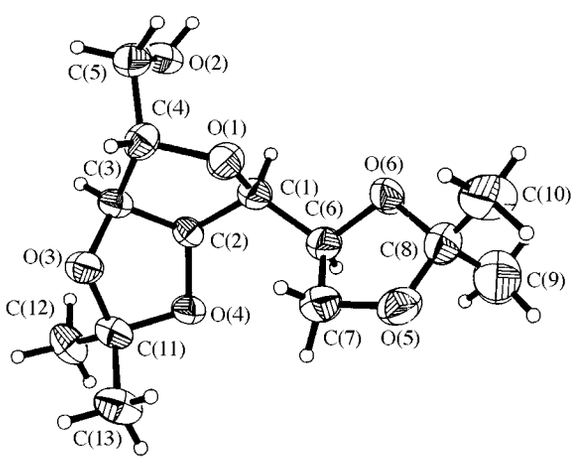


Fig. 1 An ORTEP drawing of compound **7a** with thermal ellipsoids (50% probability) and crystallographic numbering scheme

^{1}H NMR spectrum with that reported for **7a**.[14] Swern oxidation of primary alcohol **7a** resulted in the formation of the corresponding aldehyde, which was immediately allowed to react in dry tetrahydrofuran (THF) with phenylmagnesium bromide at 0 °C for 3 h to obtain a diastereomeric mixture of compound **9**† as a syrup in 77% yield. Mixture **9** was characterised from the appearance of benzylic alcohol protons at $\delta \sim 4.7$ (1 H) and the aromatic protons (5 H) between δ 7.3–7.5. Oxidation of secondary alcohol **9** with pyridinium dichromate (PDC) in CH_2Cl_2 at reflux temperature for 3 h gave ketone **10** as a syrup, $[a]_D$ +47.4 (*c* 1.2, $CHCl_3$), in 79% yield. Formation of ketone **10** was evident from the appearance of a carbonyl absorption in the IR (neat) spectrum at 1655 cm^{-1}. The ^{1}H NMR spectrum of compound **10** indicated the absence of a benzylic alcohol proton and the appearance of a downfield singlet of δ 5.27 for the 2-H proton which is now α to the carbonyl group. Stereoselective reduction[12] of ketone **10** with sodium borohydride in methanol at −10 °C for 30 min gave the required diastereomer **11** as a thick syrup, $[a]_D$ +14.28 (*c* 1.4, $CHCl_3$), in 80% yield. Alcohol **11** was protected as its benzyl ether **12** by reaction with $C_6H_5CH_2Br$–NaH-dimethylformamide (DMF) at 0 °C for 1 h; ether **12** was obtained as a crystalline solid, mp 118–119 °C; $[a]_D$ +83.2 (*c* 1.0, $CHCl_3$), in 86% yield. Regioselective hydrolysis of the terminal isopropylidene group of compound **12** proceeded smoothly in aq. 60% acetic acid for 8 h at room temp to give the diol **13** as a syrup, $[a]_D$ +62.5 (*c* 1.2, $CHCl_3$), in 85% yield. Reaction of diol **13** with methanesulfonyl chloride (MsCl)–triethylamine (TEA) in CH_2Cl_2 at 0 °C for 30 min gave the dimesyl derivative **14** as a thick syrup in 84% yield. Reductive elimination[17] of diester **14** with sodium iodide in butan-2-one at reflux temperature for 8 h gave the vinylfuran derivative **15** as a syrup, $[a]_D$ +49.9 (*c* 1.4, $CHCl_3$), in 81% yield. Olefin **15** was characterised from the ^{1}H NMR spectrum from the appearance of vinylic protons (3 H) at δ 5.25 (1 H), δ 5.3 (1 H) and δ 5.8–6.0 (1 H). The isopropylidene group of compound **15** was deprotected by refluxing for 2 h in 1,4-dioxane containing aq. 5% H_2SO_4 to obtain the diol **6** as a syrup, $[a]_D$ +44.8 (*c* 0.5, $CHCl_3$), in 86% yield. Diol **6** was subjected to intramolecular oxidative cyclisation[13] in water–DMF (1 : 4) containing $PdCl_2$ (0.2 mol equiv.), CuCl (1 mol equiv.) while oxygen was continuously bubbled through the solution for 4 h at room temperature to obtain, after work-up, a diastereomeric mixture of α/β lactols **16** in the ratio 1 : 2 (by ^{1}H NMR spectroscopy) as a thick syrup in 81% yield. Lactol **16** was carefully oxidised with PDC (1.0

† The diastereomeric mixture **9** was separated by flash chromatography to obtain compounds **9** (*threo*) and **11** (*erythro*) isomers. In the ^{1}H NMR spectrum of **9** (*threo*), H-7 appeared at δ 4.91 (t, $J_{6,7} = J_{7,OH} = 3.42$).

mol equiv.) in CH_2Cl_2 at reflux for 1 h to obtain the lactone **17** as a crystalline solid, mp 144–145 °C; $[a]_D$ +133.3 (*c* 1.1, $CHCl_3$), in 76% yield. Lactone **17** was characterised from the appearance of a five-membered lactone absorption at 1784 cm^{-1} in the IR(KBr) spectrum and also from the ^1H NMR (400 MHz) spectrum by the appearance of the 2-H axial proton at δ 2.68 (dd, J_{gem} = 18.8, $J_{2,3}$ = 1.9), the 2-H equatorial proton at δ 2.74 (dd, $J_{2',3}$ = 6.0) and the 4-H shifted downfield, due to the formation of a lactone, at δ 4.92 (dd, $J_{3,4}$ = 5.0, $J_{4,5}$ = 5.11). Finally the O-benzyl protecting group of compound **17** was deprotected by catalytic hydrogenolysis with 10% Pd–$BaSO_4$ in methanol under hydrogen for 6 h at room temp to give the 5*R*-diastereomer of goniofufurone, compound **5** as a crystalline solid in 82% yield, mp 136–138 °C, $[a]_D$ −32.4 (*c* 1.0, $CHCl_3$).

Experimental

^1H NMR spectra were measured with a Varian Gemini (200 and 400 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J*-Values are given in Hz. ^{13}C NMR spectra were taken with a Varian Gemini (50 MHz) spectrometer with $CDCl_3$ as internal standard (δ_C 77.0) for solutions in deuteriochloroform. Optical rotations were measured with a JASCO DIP-370 instrument, and $[a]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a Perkin-Elmer 1310 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C *in vacuo*.

3,6-Anhydro-1,2 : 4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-heptitol 7a

A mixture of TMSOI (6.3 g, 28.8 mmol) and potassium *tert*-butoxide (2.8 g, 23.0 mmol) in dry DMSO (20 cm^3) was stirred for 30 min at 10 °C. A solution of 2,3 : 5,6-di-*O*-isopropylidene-D-mannofuranose **8** (5.0 g, 18.2 mmol) in DMSO (10 cm^3) was added to the above reaction mixture and the combined solution was brought to room temp and stirred for 30 min. When the reaction was complete, the mixture was quenched with saturated aq. ammonium chloride (75 cm^3) and extracted into diethyl ether (2 × 100 cm^3); the combined organic phases were washed with water (2 × 50 cm^3), dried (Na_2SO_4), and concentrated under reduced pressure to obtain a syrupy residue, which was filtered on a bed of silica gel [SiO_2, 60–120 mesh; hexane–ethyl acetate (1 : 1)] to obtain a diastereomeric mixture of compounds **7a**,**7b** (4.21 g, 79%) from which the *title compound* **7a** (2.85 g, 53.4%) was separated by fractional crystallisation (dichloromethane–hexane; 1 : 4) as needles, mp 83–84 °C (Found: C, 56.84; H, 7.95. $C_{13}H_{22}O_6$ requires C, 56.92; H, 8.08%); $[a]_D$ −12.6 (*c* 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3600 (OH); δ_H(400 MHz; $CDCl_3$) 1.35, 1.38, 1.45 and 1.51 (12 H, 4 s, 4 × CH_3), 3.61 (1 H, dd, $J_{7,7'}$ 11.4, $J_{6,7}$ = $J_{6,7'}$ = 5.47, 7-H), 3.64 (1 H, dd, 7-H′), 3.97 (1 H, dd, $J_{2,3}$ 7.29, $J_{3,4}$ 3.9, 3-H), 4.08 (1 H, dd, $J_{1,1'}$ 9.6, $J_{1,2}$ 7.29, 1-H), 4.09 (1 H, dd, $J_{1',2}$ 7.26, 1-H′), 4.17 (1 H, dt, $J_{5,6}$ 1.3, 6-H), 4.39 (1 H, ddd, 2-H), 4.67 (1 H, dd, $J_{4,5}$ 6.0, 5-H) and 4.79 (1 H, dd, 4-H); δ_C(50 MHz; $CDCl_3$) 24.35, 24.85, 25.89 and 26.56 (4 × CH_3), 62.0, 66.40, 73.60, 80.93, 81.32, 82.42 and 84.78 (C-1 to -7) and 108.97 and 112.72 (2 × CMe_2).

(7*R*/*S*)-3,6-Anhydro-1,2 : 4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol 9

Dry dichloromethane (25 cm^3) containing DMSO (1.5 g, 14.2 mmol) was added to a solution of oxalyl dichloride (1.65 g, 13.1 mmol) in dry dichloromethane (10 cm^3) at −78 °C and the resulting solution was stirred for 15 min. A solution of the alcohol **7a** (3.0 g, 10.9 mmol) in dry dichloromethane (5 cm^3) was added to the above reaction mixture and the whole was stirred for 45 min, followed by the addition of TEA (3.3 g, 32.7 mmol). The reaction mixture was brought gradually to room temp and diluted with dichloromethane (50 cm^3). The organic layer was washed with brine (2 × 25 cm^3), dried (Na_2SO_4), filtered, and evaporated to obtain the aldehyde as a yellow oil, and this was immediately treated with a solution of phenylmagnesium bromide (9.2 cm^3, 14.3 mmol; 1.5 mmol dm^{-3}) in dry THF (20 cm^3) under nitrogen for 20 min. (Phenylmagnesium bromide was freshly prepared from bromobenzene and magnesium in THF.) The reaction mixture was then stirred for a further 3 h at 0 °C, quenched with saturated aq. ammonium chloride (25 cm^3), and was filtered through Celite. The filtrate so obtained was concentrated to afford a syrupy residue and this was extracted into diethyl ether (2 × 75 cm^3). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to obtain an inseparable diastereomeric mixture of the *title compound* **9** (2.58 g, 77%) as a yellow syrup (Found: C, 65.07; H, 7.42. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%); δ_H(200 MHz; $CDCl_3$) 1.25, 1.3, 1.32, 1.41, 1.42 and 1.45 (12 H, 6 s, 4 × CH_3), 3.95–4.2 (4 H, m, 1-H_2, 3- and 6-H), 4.25–4.4 (1 H, m, 2-H), 4.7–5.0 (3 H, m, 4-, 5- and 7-H) and 7.3–7.5 (5 H, m, ArH).

2,5-Anhydro-3,4 : 6,7-di-*O*-isopropylidene-1-*C*-phenyl-D-*glycero*-D-*talo*-heptose 10

PDC (5.37 g, 14.2 mmol) was added in one portion to a stirred solution of the diastereomeric mixture **9** (2.5 g, 7.1 mmol) in dry dichloromethane (50 cm^3) containing powdered 4 Å molecular seives (0.3 g) at room temp. The reaction mixture was refluxed at 50 °C for 3 h. Progress of the reaction was monitored by TLC; when the reaction was complete, Celite (1.0 g) and diethyl ether (50 cm^3) were added to the reaction mixture and the slurry was stirred at room temp for another 15 min, then was filtered through a bed of silica gel, and the solvent was evaporated off to obtain a crude residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (4 : 1)] to obtain the *title compound* **10** (1.98 g, 79%) as an oil (Found: C, 65.41; H, 6.88. $C_{19}H_{24}O_6$ requires C, 65.50; H, 6.94%); $[a]_D$ +47.4 (*c* 1.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1600 (C=O); δ_H(200 MHz; $CDCl_3$) 1.38, 1.4 and 2 × 1.42 (12 H, 3 s, 4 × CH_3), 3.85 (1 H, dd, $J_{5,6}$ 7.4, $J_{4,5}$ 4.5, 5-H), 3.9–4.15 (2 H, m, 7-H_2), 4.3–4.45 (1 H, m, 6-H), 4.78 (1 H, dd, $J_{3,4}$ 5.3, 4-H), 5.27 (1 H, s, 2-H), 7.4–7.7 (3 H, m, ArH) and 8.01 (2 H, d, ArH); δ_C(50 MHz; $CDCl_3$) 24.68, 25.13, 26.11 and 26.69 (4 × *C*H_3), 66.89, 73.04, 80.83, 2 × 82.68 and 85.21 (C-2/-7), 109.18 and 113.01 (2 × *C*Me_2), 128.63–134.13 (aromatic) and 196.20 (C=O).

(7*R*)-3,6-Anhydro-1,2 : 4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol 11

To a stirred solution of the ketone **10** (1.90 g, 5.45 mmol) in methanol (20 cm^3) at −10 °C was added sodium borohydride (0.41 g, 10.9 mmol). The reaction mixture was quenched after 30 min with a few drops of acetic acid and was then gradually brought to room temp. Methanol was removed under reduced pressure and the resulting residue was extracted with diethyl ether (2 × 75 cm^3). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to obtain a residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (3 : 1)] to obtain the *title compound* **11** (1.5 g, 80%) as a syrup (Found: C, 65.01; H, 7.39. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%); $[a]_D$ +14.3 (*c* 1.4, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 1.29, 1.39 and 2 × 1.47 (12 H, 3 s, 4 × CH_3), 4.04 (1 H, dd, $J_{2,3}$ 7.45, $J_{3,4}$ 3.7, 3-H), 4.06–4.13 (2 H, m, 1-H_2), 4.15 (1 H, dd, $J_{5,6}$ 1.3, $J_{6,7}$ 8.3, 6-H), 4.41 (1 H, ddd, $J_{1,2}$ 7.27, $J_{1',2}$ 7.25, 2-H), 4.56 (1 H, d, 7-H), 4.66 (1 H, dd, $J_{4,5}$ 6.0, 5-H), 4.83 (1 H, dd, 4-H) and 7.3–7.5 (5 H, m, ArH).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-1,2 : 4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol 12

To a slurry of hexane-washed sodium hydride (0.15 g, 6.42 mmol) in dry DMF (5 cm^3) was added a solution of compound **11** (1.5 g, 4.28 mmol) in DMF (5 cm^3) at 0 °C. To this suspension was added dropwise benzyl bromide (0.87 g, 5.1 mmol) and the mixture was stirred for 1 h at room temp. When reaction

was complete, excess of sodium hydride was quenched by addition of methanol (1.0 cm^3), and the reaction mixture was poured into ice-cold water (50 cm^3) and extracted with diethyl ether (2 × 50 cm^3). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to obtain a residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (4:1)] to yield the *title compound* **12** (1.66 g, 86%) as a crystalline solid, mp 118–119 °C (Found: C, 70.82; H, 7.27. $C_{26}H_{32}O_6$ requires C, 70.89; H, 7.32%); $[\alpha]_D$ +83.2 (*c* 1.0, $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 1.28, 1.32, 1.38 and 1.43 (12 H, 4 s, 4 × CH_3), 3.9–4.3 (6 H, m, 1-H_2, 2-, 3- and 6-H, and C_6H_5CHH), 4.39 (1 H, d, $J_{4,5}$ 5.9, 5-H), 4.55 (1 H, d, J_{gem} 12.0, C_6H_5CHH), 4.7–4.75 (2 H, m, 4- and 7-H) and 7.25–7.48 (10 H, m, ArH); δ_C(50 MHz; $CDCl_3$) 24.80, 25.31, 26.20 and 26.92 (4 × CH_3), 67.05, 70.65, 73.72, 81.46, 82.06, 83.10 and 83.62 (C-1 to -6 and OCH_2Ph), 87.47 (C-7), 109.09 and 112.43 (2 × CMe_2) and 127.46–137.89 (aromatic).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-4,5-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol 13

A mixture of compound **12** (1.3 g, 2.95 mmol) and 60% aq. acetic acid (25 cm^3) was stirred at room temp for 8 h. Reaction was monitored by TLC and, when complete, acetic acid was removed by azeotropic distillation with toluene *in vacuo* to obtain a crude, syrupy residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (2:1)] to yield the *title compound* **13** (1.0 g, 85%) as a syrup (Found: C, 69.92; H, 6.99. $C_{23}H_{28}O_6$ requires C, 69.98; H, 7.05%); $[\alpha]_D$ +62.5 (*c* 1.2, $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 1.34 and 1.47 (6 H, 2 s, 2 × CH_3), 3.65–3.90 (3 H, m, 1-H_2 and 2-H), 4.02–4.25 (3 H, m, 3- and 6-H and C_6H_5CHH), 4.4 (1 H, d, $J_{4,5}$ 5.9, 5-H), 4.55 (1 H, d, J_{gem} 12.0, C_6H_5CHH), 4.7–4.8 (2 H, d, 4- and 7-H) and 7.2–7.5 (10 H, m, ArH).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-4,5-*O*-isopropylidene-1,2-bis-*O*-(methylsulfonyl)-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol 14

To a stirred solution of the diol **13** (0.9 g, 2.25 mmol) in dichloromethane (20 cm^3) at 0 °C were added TEA (0.68 g, 6.7 mmol) and MsCl (0.61 g, 5.4 mmol) and the mixture was stirred for 30 min and brought to room temp. The reaction mixture was diluted with chilled water (20 cm^3) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 × 25 cm^3) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to obtain the *title compound* **14** (1.05 g, 84%) as a syrup (Found: C, 53.85; H, 5.69; S, 11.47. $C_{25}H_{32}O_{10}S_2$ requires C, 53.93; H, 5.79, S, 11.52%); δ_H(200 MHz; $CDCl_3$) 1.30 and 1.45 (6 H, 2 s, 2 × CH_3), 2.98 and 3.05 (6 H, 2 s, 2 × SCH_3), 4.09–4.2 (2 H, m, 6-H and C_6H_5CHH), 4.39–4.45 (4 H, m, 1-H_2, 3- and 5-H), 4.55 (1 H, d, J_{gem} 12.0, C_6H_5CHH), 4.75–4.90 (3 H, m, 2-, 4- and 7-H) and 7.2–7.48 (10 H, m, ArH).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-1,2-dideoxy-4,5-*O*-isopropylidene-7-*C*-phenyl-D-*altro*-hept-1-enitol 15

To a solution of dimesyl compound **14** (1.0 g, 1.79 mmol) in butan-2-one (25 cm^3) was added sodium idodide (0.8 g, 5.4 mmol) and the reaction mixture was refluxed for 8 h. Progress of reaction was monitored by TLC; when the reaction was complete, solvent was removed under vacuum, saturated aq. sodium thiosulfate (20 cm^3) was added, and the mixture was extracted with diethyl ether (2 × 50 cm^3). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to obtain a syrupy residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (5:1)] to obtain the *title compound* **15** (0.54 g, 81%) as an oil (Found: C, 75.27; H, 7.09. $C_{23}H_{26}O_4$ requires C, 75.38; H, 7.15%); $[\alpha]_D$ +49.9 (*c* 1.4, $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 1.3 and 1.45 (6 H, 2 s, 2 × CH_3), 4.1–4.25 (2 H, m, 6-H and C_6H_5CHH), 4.39–4.48 (2 H, m, 3- and 5-H), 4.51–4.7 (3 H, m, 7-, 4-H and C_6H_5CHH), 5.25 (1 H, dd, $J_{6,7trans}$ 10.0, 1-H), 5.32 (1 H, dd, $J_{6,7cis}$ 16.5, 1-H′), 5.8–6.0 (1 H, m, 2-H) and 7.20–7.48 (10 H, m, ArH).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-1,2-dideoxy-7-*C*-phenyl-D-*altro*-hept-1-enitol 6

To a solution of compound **15** (0.5 g, 1.36 mmol) in 1,4-dioxane (10 cm^3) was added 5% aq. sulfuric acid (0.3 cm^3) and the reaction mixture was refluxed for 2 h. After completion of the reaction the solvent was removed under vacuum and the residue obtained was extracted into ethyl acetate (50 cm^3). The ethyl acetate phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to obtain the *title compound* **6** (0.38 g, 86%) as a syrup (Found: C, 73.55; H, 6.72. $C_{20}H_{22}O_4$ requires C, 73.60; H, 6.79%); $[\alpha]_D$ +44.8 (*c* 0.5, $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 3.95 (1 H, d, $J_{1,2}$ 3.5, 2-H), 4.09–4.22 (2 H, m, 3- and 4-H), 4.28–4.40 (2 H, m, 5-H and C_6H_5CHH), 4.52–4.67 (2 H, m, 1-H and C_6H_5CHH), 5.3 (1 H, dd, $J_{6,7trans}$ 10.0, 7-H), 5.35 (1 H, dd, $J_{6,7cis}$ 16.5, 7-H′), 5.82–6.02 (1 H, m, 6-H) and 7.22–7.50 (10 H, m, ArH).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-2-deoxy-7-*C*-phenyl-D-*altro*-1,4-heptanolactol 16

To a solution of diol **6** (0.35 g, 1.07 mmol) in aq. DMF [10 cm^3, DMF–water, 8:2] was added palladium(II) chloride (0.038 g, 0.2 mmol) and copper(I) chloride (0.1 g, 1.07 mmol). Oxygen was bubbled through the solution for 4 h at room temp. Progress of the reaction was monitored by TLC. When reaction was complete the reaction mixture was diluted with diethyl ether (75 cm^3), filtered through a bed of silica gel, and eluted with diethyl ether. The extract was washed successively with 2% aq. hydrochloric acid (25 cm^3) and finally with water (2 × 25 cm^3). The extract was dried (Na_2SO_4), and concentrated to obtain a residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (4:6)] to obtain a diastereomeric mixture of the *title compound* **16** (0.29 g, 81%) as a thick syrup (Found: C, 70.03; H, 6.39. $C_{20}H_{22}O_5$ requires C, 70.16; H, 6.48%); δ_H(200 MHz; $CDCl_3$) 1.4–1.8 (1 H, br s, OH), 1.9–2.3 (2 H, m, 2-H_2), 3.7–4.35 (4 H, m, 3-, 5-, 6-H and C_6H_5CHH), 4.4–5.0 (3 H, m, 4-, 7-H, C_6H_5CHH), 5.5 (0.65 H, br d, 1-H^{α}), 5.63 (0.35 H, t, 1-H^{β}) and 7.3–7.5 (10 H, m, ArH).

(7*R*)-3,6-Anhydro-7-*O*-benzyl-2-deoxy-7-*C*-phenyl-D-*altro*-1,4-heptanolactone 17

To a stirred solution of the lactol **16** (0.25 g, 0.73 mmol) in dry dichloromethane (25 cm^3) containing powdered 4 Å molecular seives (0.05 g) was added PDC (0.28 g, 0.73 mmol) in one portion and the reaction mixture was refluxed for 1 h. After completion of the reaction, Celite (0.5 g) and diethyl ether (25 cm^3) were added to the reaction mixture and the whole was filtered through a bed of silica gel and eluted with diethyl ether. The ethereal solution was concentrated to obtain a residue, which was chromatographed [SiO_2, 60–120 mesh; hexane–ethyl acetate (1:1)] to obtain the *title compound* **17** (0.19 g, 76%) as a crystalline solid, mp 144–145 °C (Found: C, 70.48; H, 5.85. $C_{20}H_{20}O_5$ requires C, 70.57; H, 5.92%); $[\alpha]_D$ +133.0 (*c* 1.1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1784 (C=O); δ_H(400 MHz; $CDCl_3$) 2.03 (1 H, d, *J* 7.6, OH), 2.68 (1 H, dd, J_{gem} 18.8, $J_{2,3}$ 1.92, 2-H), 2.74 (1 H, dd, $J_{2',3}$ 6.01, 2-H′), 4.01 (1 H, dd, $J_{5,6}$ 6.49, $J_{6,7}$ 3.37, 6-H), 4.29 (1 H, d, J_{gem} 12.0, C_6H_5CHH), 4.35 (1 H, ddd, $J_{4,5}$ 5.11, 5-H), 4.52 (1 H, d, 7-H), 4.58 (1 H, d, C_6H_5CHH), 4.84 (1 H, ddd, $J_{3,4}$ 5.0, 3-H), 4.92 (1 H, dd, 4-H) and 7.25–7.42 (10 H, m, ArH); δ_C(50 MHz; $CDCl_3$) 36.8 (C-2), 70.9, 73.18, 77.64, 80.8, 82.9 and 85.6 (C-3 to -7 and OCH_2Ph), 127.5–137.6 (aromatic) and 175.2 (C=O).

(7*R*)-3,6-Anhydro-2-deoxy-7-*C*-phenyl-D-*altro*-1,4-heptanolactone 5

Compound **17** (0.1 g, 0.29 mmol) was dissolved in methanol (20 cm^3) to which 10% Pd–$BaSO_4$ (20 mg) was added and the mixture was stirred under hydrogen for 6 h. The catalyst was filtered off and the solvent was removed *in vacuo* to obtain the *title compound* **5** (0.06 g, 82%) as a crystalline solid, mp 136–138 °C (Found: C, 62.18; H, 5.61. $C_{13}H_{14}O_5$ requires C, 62.39; H,

5.64%); $[\alpha]_D$ −32.4 (*c* 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1752 (C=O); δ_H(400 MHz; $CDCl_3$) 2.08 (1 H, d, *J* 9.5, 5-OH), 2.42 (1 H, d, *J* 6.3, 7-OH), 2.72 (1 H, d, J_{gem} 17.8, 2-H), 2.82 (1 H, dd, $J_{2',3}$ 6.1, 2′-H), 3.98 (1 H, dd, $J_{5,6}$ 8.0, $J_{6,7}$ 3.37, 6-H), 4.39 (1 H, ddd, $J_{4,5}$ 4.61, 5-H), 4.82 (1 H, dd, 7-H), 4.9 (1 H, dd, $J_{3,4}$ 4.61, 3-H), 4.99 (1 H, t, $J_{3,4} = J_{4,5}$ 4.61, 4-H), 7.25–7.40 (5 H, m, ArH); δ_C(50 MHz, $CDCl_3$) 36.96 (C-2), 71.8, 72.69, 76.54 (merged), 83.12, 84.15 (C-3 to -7), 127.5–137.6 (aromatic), 175.6 (C=O).

X-Ray structure determination

Crystal data of compound 7a. $C_{13}H_{22}O_6$, needles, orthorhombic. Space group $P2_12_12_1$, $a = 5.392(1)$, $b = 10.757(2)$, $c = 24.716(4)$ Å, $V = 1433.6(4)$ Å^3, $Z = 4$, $D_c = 1.271$ g cm^{-3}, $T = 293$ K, crystal dimensions $0.12 \times 0.12 \times 0.17$ mm, 1185 reflections measured, $2\theta_{max} = 45°$, $0 \leqslant h \leqslant 5$, $0 \leqslant k \leqslant 11$, $0 \leqslant l \leqslant 26$, 1157 unique reflections, and 826 with $I \geqslant 3\sigma(I)$, $\mu = 0.10$ mm^{-1}. Final $R = 0.063$ (172 parameters and unit weights), maximum shift/error = 0.001, $\Delta\rho_{max} = 0.14$ e Å^{-3}, $\Delta\rho_{min} = -0.12$ e Å^{-3}. Mo-Kα radiation ($\lambda = 0.710$ 73 Å), graphite crystal monochromator, Siemens R3m/V four-circle diffractometer (ω–2θ scan technique). Data corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods (SHELXTL-Plus)[18] and non-H-atoms were anisotropically refined. H-Atoms were included at geometrically calculated positions and refined as riding atoms with fixed isotropic temperature factors ($U = 0.08$ Å^2). Fig. 1 was prepared using SHELXTL-Plus. All calculations were made on a MicroVax-3100 workstation. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instruction for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/154.

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