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Total asymmetric synthesis of 6-deoxy-5-*C*-methyl-D-*ribo*-hexose: structure in aqueous solution*

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ABSTRACT

(1*R*,2*R*,4*R*)-2-*exo*-Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1*S*)-camphanate [**1**, Diels–Alder adduct of furan to 1-cyanovinyl (1*S*)-camphanate, a "naked sugar"] was transformed with high stereoselectivity into (1*S*,4*S*,5*R*,6*R*,7*R*)-6-*exo*,7-*exo*-(isopropylidenedioxy)-4-*exo*-methyl-2,8-dioxabicyclo[3.2.1]octan-3-one [(−)-**4**] and (1*S*,5*R*,6*R*,7*R*)-6-*exo*,7-*exo*-(isopropylidenedioxy)-4,4-dimethyl-2,8-dioxabicyclo[3.2.1] octan-3-one [(−)-**5**]. Reaction of (−)-**5** with Me_3SiCH_2Li gave 5,7-dideoxy-5,5-dimethyl-2,3-*O*-isopropylidene-D-*ribo*-heptofuranos-6-ulose [(+)-**8**, which was then converted into 6-deoxy-5-*C*-methyl-D-*ribo*-hexose (10 steps from furan, 59% overall yield) and derivatives. N.m.r. studies established that branching of 6-deoxy-D-allose by a methyl group at C-5 favours the furanose versus the pyranose form of the carbohydrate in aqueous solution.

INTRODUCTION

Except for noviose[2] (6-deoxy-5-*C*-methyl-4-*O*-methyl-L-*lyxo*-hexose), the aldose moiety of noviosylcoumarin antibiotics, branched-chain carbohydrates with the tertiary carbon atom at position 5 are rare natural compounds. Walton *et al.*[3] reported the conversion of D-ribose into methyl 6-deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-D-*ribo*-hexofuranoside (5 steps, 12% overall yield), and Nutt and Walton[4] prepared 5′,5′-di-*C*-methyladenosine *via* methyl 2,3,5-tri-*O*-benzoyl-6-deoxy-5-*C*-methyl-β-D-*ribo*-hexofuranoside. To our knowledge, the unprotected branched sugar has not been described. We now report a total synthesis of 6-deoxy-5-*C*-methyl-D-*ribo*-hexose and show that, in aqueous solution, the furanose form is preferred.

RESULTS AND DISCUSSION

Double hydroxylation of the optically pure Diels–Alder adduct **1** of furan and 1-cyanovinyl (1*S*)-camphanate (a "naked sugar"[5]), followed by diol protection as the isopropylidene derivative and saponification of the camphanate, was reported[6] to yield the ketone (+)-**2** and (1*S*)-camphanic acid (recovery of the chiral auxiliary). Baeyer–Villiger oxidation of (+)-**2** with 3-chloroperoxybenzoic acid ($NaHCO_3$, CH_2Cl_2, 20°)

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* Enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives as synthetic intermediates, Part XVI. For Part XV, see ref. 1.

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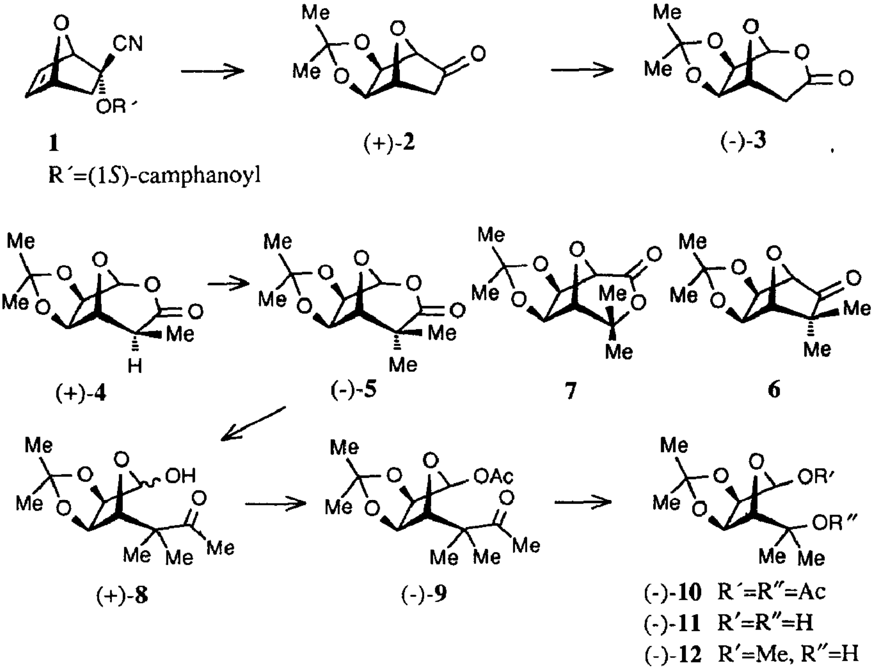
afforded 98% of the corresponding lactone (−)-**3**. Deprotonation of (−)-**3** with $(Me_3Si)_2NLi$ in tetrahydrofuran followed by quenching with methyl iodide gave the *exo*-monomethylated derivative (−)-**4** (98%) with high stereoselectivity. The *exo* configuration of the methyl group was indicated[7,8] by the absence of coupling between H-4 and H-5.

Deprotonation of (−)-**4** with $(Me_3Si)_2NLi$ in tetrahydrofuran at −65° followed by quenching with methyl iodide gave 96% of the dimethylated lactone (−)-**5**. Direct double α-methylation of the ketone (+)-**2** with potassium hydride and methyl iodide afforded 74% of **6**, whereas oxidation with 3-chloroperoxybenzoic acid afforded 74% of (−)-**5**. Only traces of the regioisomeric lactone **7** were formed under these conditions. The high regioselectivity of the Baeyer–Villiger oxidation **6**→**5** can be attributed[9] to the enhanced migratory aptitude of the C-1–C-2 bond due to the interaction with the electron pair on O-7. Although shorter than the method that involves isolation of (−)-**4**, the route **2**→**6**→**5** gave a lower overall yield (55%) than the route **2**→**3**→**4**→**5** (92%).



(-)-**10** R′=R″=Ac
(-)-**11** R′=R″=H
(-)-**12** R′=Me, R″=H

Attempts to generate the methylketone (+)-**8** addition of methyl lithium to the lactone (−)-**5** all failed. However, treatment of (−)-**5** with 2.5 equiv. of Me_3SiCH_2Li in pentane or tetrahydrofuran[10] followed by aqueous NH_4Cl work-up afforded 98% of the α,β-D-*ribo*-heptofuranos-6-ulose derivative (+)-**8**, which was transformed into the corresponding β-furanosyl acetate (−)-**9** (97%) by treatment with acetic anhydride–pyridine. Compound (−)-**9** could be obtained (87%) from (−)-**5** by a "one-pot" procedure (*cf.* 95% for the two-step procedure). Baeyer–Villiger oxidation of (−)-**9** with peroxytrifluoroacetic acid afforded 95% of the 6-deoxy-5-*C*-methyl-β-D-*ribo*-hexofuranose derivative (−)-**10**. Methanolysis of (−)-**10** gave (−)-**11** (98%), treatment of which with methanol, 2,2-dimethoxypropane, and *p*-toluenesulfonic acid gave the known[3] derivative (−)-**12**. Hydrolysis (M H_2SO_4, 80°, 2.5 h) of (−)-**12** gave the unprotected sugar as an 89:11 mixture (94%) of the furanose and pyranose forms **13α,β** and **14α,β**, respectively. The ^1H- (Table I) and ^{13}C-n.m.r. (Table II) signals of **13α**, **13β**, **14α**, and **14β** were assigned with the help of double-irradiation experiments and the $^{13}C/^1H$-correlated 2D spectrum (Fig. 1). The signal for H-1 at 4.75 p.p.m. ($J_{1,2}$ 7.8 Hz) is typical of β-D-allopyranose and its derivatives[11] with the $^4C_1$ conformation[15] (*trans*-diaxial protons), and that at 4.72 p.p.m. ($J_{1,2}$ 1.0 Hz) was attributed to the α-pyranose form **14α** for which a W-type coupling ($J_{2,4}$ 1.0 Hz) is possible only in the $^1C_4$ conformation, as for D-allose and 6-deoxy-4-*O*-methyl-D-allose[11]. As expected, the chemical shifts for the H-1 resonances are slightly larger for the furanoses **13α** and **13β** than for the corresponding pyranoses **14α** and **14β**. Distinction between the signals of **13α** and **13β** is based on the $^{13}C/^1H$-correlated 2D spectrum and the comparison of the ^{13}C chemical shifts with those reported for the α-furanose and β-furanose forms, respectively, of D-allose[12].

Integration of the various signals (Table I and II) established the proportions of **13α**, **13β**, **14α**, and **14β**. In contrast to 6-deoxy-5-*C*-methyl-D-*xylo*-hexose[16], which exists (at 40°) essentially as an 8:92 mixture of the α- and β-pyranose forms, and to D-allose[11] for which a 3:5.5:15.5:76 mixture of the corresponding α-furanose, β-furanose, α-pyranose, and β-pyranose forms is observed in aqueous solution at 24°, 6-deoxy-5-*C*-methyl-D-*ribo*-hexose prefers the furanose form. This observation can be interpreted in terms of a greater release of strain (*gauche* effects) between the hydroxyl groups and the methyl groups in both of the furanose forms **13α** and **13β** than in the pyranose forms **14α** and **14β**. For 6-deoxy-5-*C*-methyl-D-*xylo*-hexose, *gauche* interactions of HO-3 and the Me_2C-5-OH moiety (absent from **13α** and **13β**) are probably responsible for the relative instability of the corresponding α- and β-furanose forms.

Since (1*S*,2*S*,4*S*)-2-*exo*-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1*R*)-camphanate [the diastereometer of **1** derived from (1*R*)-camphanic acid][5] is as readily available as **1**, the above approach is also applicable to the total, asymmetric synthesis of 6-deoxy-5-*C*-methyl-L-*ribo*-hexose.

EXPERIMENTAL

For general remarks, see ref. 17.

*(1*S*,4*S*,5*R*,6*R*,7*R*)-6*-exo*,7*-exo*-(Isopropylidenedioxy)-4*-exo*-methyl-2,8-dioxabicyclo[3.2.1]octan-3-one* [(−)-**4**]. — A solution of (−)-**3**[6a] (5 g, 25 mmol) in anhydrous tetrahydrofuran (50 mL) at −40° was added with stirring to a solution of $(Me_3Si)_2NLi$ in the same solvent [prepared by addition of 15.6 mL of 1.6M BuLi in hexane (Fluka) to a solution of hexamethyldisilazane (6.2 mL) in anhydrous tetrahydrofuran (100 mL) at 0°] at −65°. The mixture was stirred at this temperature for 30 min, MeI (30 mL, 480 mmol) was added, and the temperature was allowed to rise to −20° during 20 min [the

TABLE I

^{1}H-N.m.r. data (250 MHz, δ in p.p.m., J in Hz, external Me_4Si) of 6-deoxy-5-*C*-methyl-α,β-D-*ribo*-hexose in D_2O

Compound	*Percentage*[a]										
	20°	*60°*	*H-1*	*H-2*	*H-3*	*H-4*	*Me$_2$*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{2,4}$
Furanose											
13α	36.5 ±0.3	36.7 ±0.2	5.08 (5.34)[b]	3.74	3.87	3.63	0.98, 0.96	4.1 (4.0)[b]	6.1	4.0	
13β	52.0 ±0.1	49.5 ±0.1	4.94 (5.22)	3.63	4.00	3.48	0.99, 0.98	2.2 (2.5)	4.9	6.3	
Pyranose											
14α	4.1 ±0.1	5.8 ±0.4	4.72 (5.13)	3.58	3.78	3.28	1.04, 0.95	1.0 (4.0)	3.1	3.0	1.0
14β	7.4 ±0.2	8.0 ±0.3	4.75 (4.87)	3.15 (3.39)	3.88 (4.15)	3.22 (3.62)	1.08, 0.95	7.8 (8.25)	3.4	3.4	

[a] Determined after storage of the solutions for 1 day (no further change); average of 10–12 independent integrations. [b] Figures in brackets for D-allose; see also refs. 10 and 13.

TABLE II

^{13}C-N.m.r. data [62.9 MHz, 20°, internal MeOH (49.6 p.p.m.), 125 mg/mL, δ in p.p.m., J in Hz] for 6-deoxy-5-*C*-methyl-α,β-D-*ribo*-hexose in D_2O

Compound	*Percentage*[a]	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*Me$_2$*
13α	35.7 ±0.5	96.8 (172)[b] *96.8*[c]	71.9 (149) *72.4*	70.2 (152) ?	90.5 (144) *84.3*	71.7 *70.2*	25.9 (125) 24.7 (125)
13β	53.2 ±0.5	100.8 (173) *101.6*	76.2 (153) *76.1*	70.6 (150) *73.3*	88.8 (147) *83.0*	71.5 *71.7*	26.2 (125) 24.3 (125)
14α	3.4 ±0.5	90.7 (168) *93.7*	72.0 (149) *67.9*	66.6 (140) *72.0*	74.5 (150) *66.9*	77.0[d] *67.7*	26.0 (125) 22.2 (125)
14β	7.6 ±0.5	90.8 (160) *94.3*	71.9 (149) *72.2*	71.2 (147) *72.0*	73.9 (144) *67.7*	77.9[d] *74.4*	29.1 (125) 20.8 (125)

[a] Determined after storage of the solution for 1 week at 20°; the C-1 signals were integrated as in ref. 14. [b] $^1J_{C,H}$ values in brackets. [c] Italics indicate data for D-allose[12,14]. [d] These assignments are not definitive.

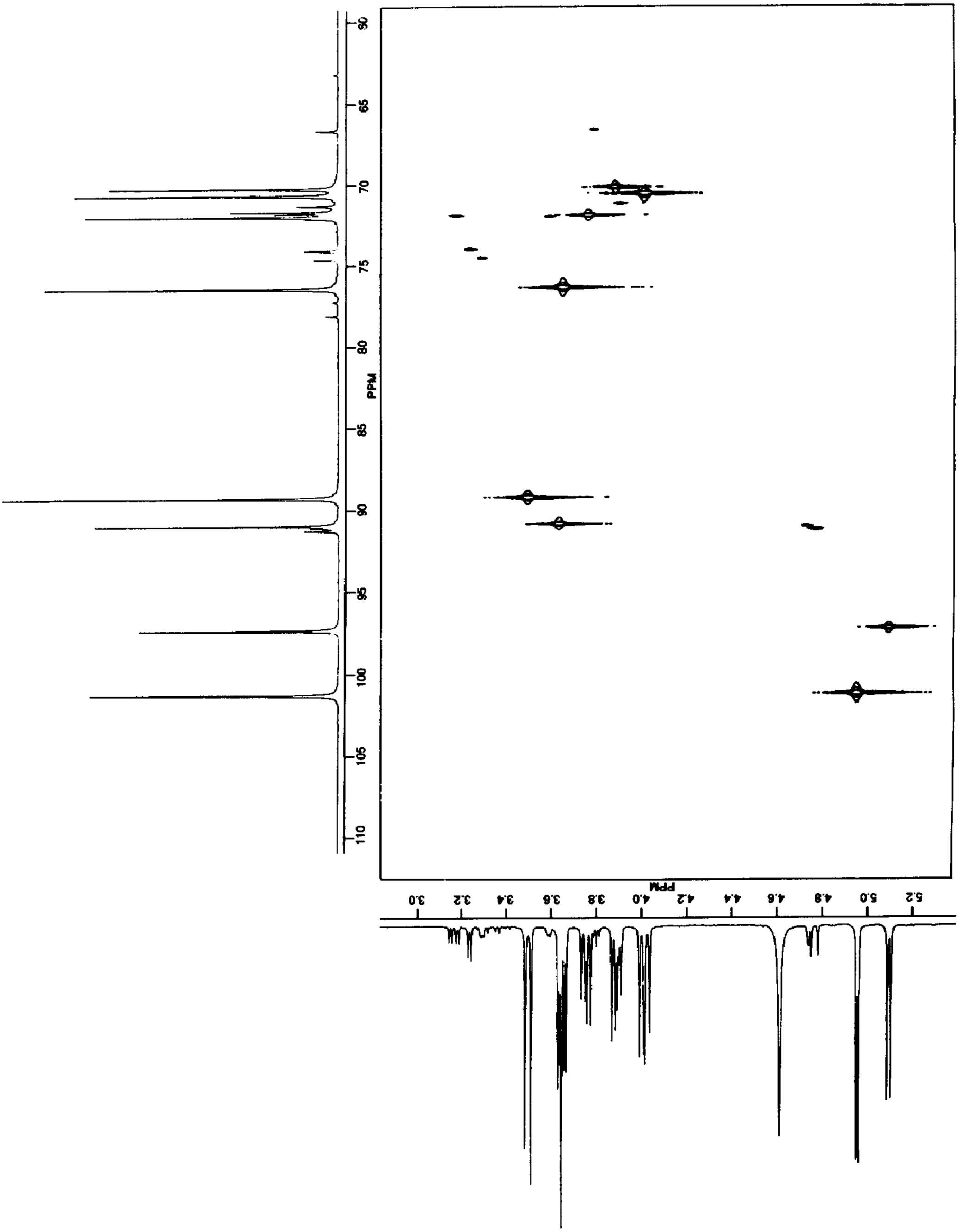
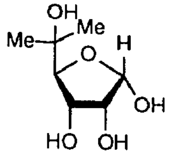
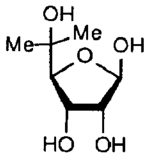


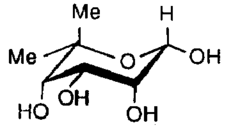
Fig. 1. ^{13}C/^{1}H-correlated 2D-spectrum of **13α,β** + **14α,β** (400 MHz, D$_2$O, 125 mg/mL, 25°, program: XHCORRDC.AUR, Bruker). The 1D-spectra were measured under the usual conditions.



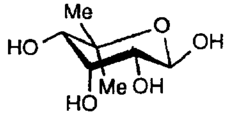
13α



13β



14α ($^1C_4$)



14β ($^4C_1$)

end of the reaction was determined by t.l.c.on silica gel with CH_2Cl_2–Et_2O (3:1) and detection with vanillin]. The mixture was poured into a vigorously stirred mixture of CH_2Cl_2 (100 mL) and saturated aqueous NH_4Cl at 0°. The organic layer was collected and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. The white solid was recrystallised from AcOEt–light petroleum (1:3) to yield (−)-**4** (5.24 g, 98%), m.p.133.5–134°, $[\alpha]_{589}^{25}$ −35°, $[\alpha]_{578}^{25}$ −38°, $[\alpha]_{546}^{25}$ −43.5°, $[\alpha]_{436}^{25}$ −80.5°, $[\alpha]_{365}^{25}$ −140° (*c* 0.635, chloroform); λ_{max} (iso-octane) 218 nm (ε 73), λ_{max} (95% EtOH) 218 nm (ε 75);ν_{max}^{KBr} 2980, 2935, 1735, 1380, 1365, 1190, 985, 860, 835, and 720 cm^{-1}. N.m.r. data ($CDCl_3$): ^1H (250 MHz), δ 5.70 (d, 1 H, $J_{1,5}$ 1 Hz, H-1), 4.79, 4.63 (2 d, 2 H,$J_{6,7}$ 5.8 Hz, H-6,7), 4.28 (d,1 H, $J_{1,5}$ 1 Hz, H-5), 2.55 (q,1 H, $J_{4,Me}$ 7.8 Hz, H-4), 1.46 (d, 3 H, $J_{Me,4}$ 7.8 Hz, Me-4), 1.45, 1.30 (2 s, each 3 H, CMe_2); ^{13}C (90.55 MHz), δ 168.5 (s, C-3), 113.4 (s), 103.2 (d, $^1J_{C,H}$ 184 Hz, C-1), 84.2 (d, $^1J_{C,H}$ 157 Hz), 83.6 (d, $^1J_{C,H}$ 161 Hz), 81.6 (d, $^1J_{C,H}$ 157 Hz) C-5,6,7), 40.7 (d, $^1J_{C,H}$ 130 Hz, C-4), 25.9 24.9 (2 q, $^1J_{C,H}$ 127 Hz), 17.9 (q, $^1J_{C,H}$ 130 Hz, Me). Mass spectrum (70 eV): *m/z* 214 (3%, M^{+}), 199 (53,), 185 (6), 141 (8), 112 (39), 100 (57), 85 (99), 83 (93), 71 (74), 59 (100), 55 (57).

Anal. Calc. for $C_{10}H_{14}O_5$ (214.22): C, 56.06; H, 6.59. Found: C, 56.13; H, 6.50.

*(1*RS*,4*RS*,5*SR*,6*SR*,7*SR*)-6-*exo*,7*exo*-(isopropylidenedioxy)-4-*exo*-methyl-2,8-dioxabicyclo[3.2.1]octan-3-one* [(±)-**4**]. — Prepared from (±)-**3**[6,18], as described above, (±)-**4** had m.p. 118–119°.

*(1*S*,5*R*,6*R*,7*R*)-6-*exo*,7-*exo*-(Isopropylidenedioxy)-4,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-one* [(−)-**5**]. — A solution of (−)-**4** (30 g, 140 mmol) in anhydrous tetrahydrofuran (300 mL) at −40° was added to a stirred solution of $(Me_3Si)_2NLi$ [prepared from 35 mL of $(Me_3Si)_2NH$ in 600 mL of tetrahydrofuran and 100 mL of 1.6M BuLi in hexane] at −65°. The mixture was stirred at −60° for 30 min, MeI (180 mL, 2.8 mol) was added, and the temperature was allowed to rise to −20° during 30 min. The mixture was monitored and worked-up essentially as described for (−)-**4**, and the product was recrystallised from AcOEt–light petroleum (1:1) to yield (−)-**6** (30.6 g, 96%), m.p. 119.5–120°, $[\alpha]_{589}^{25}$ −14°, $[\alpha]_{578}^{25}$ −15°, $[\alpha]_{546}^{25}$ −17°, $[\alpha]_{436}^{25}$ −35°, $[\alpha]_{365}^{25}$ −67° (*c* 0.645, chloroform); λ_{max} (iso-octane) 284 (ε 26), 230 nm (ε 246), λ_{max} (95% EtOH) 284 (ε 25), 229 nm (sh. ε 232); ν_{max}^{KBr} 2995, 2980, 2950, 1750, 1375, 1210, 1155, 1090, 995, 865, 835, and 740 cm^{-1}. N.m.r. data ($CDCl_3$): ^1H (250 MHz), δ 5.65 (d, 1 H, $J_{1,5}$ 0.5 Hz, H-1), 4.85, 4.76 (2 d, 2 H, $J_{6,7}$ 5.5 Hz, H-6,7), 4.12 (d, 1 H, $J_{1,5}$ 0.5 Hz, H-5), 1.47 (s, 6 H, 2 Me); 1.32, 1.27 (2 s, each 3 H, CMe_2); ^{13}C (90.55 MHz), δ 172.1 (s, C-3), 113.3 (s), 103.5 (d, $^1J_{C,H}$ 184 Hz, C-1), 87.8 (d, $^1J_{C,H}$ 159 Hz), 83.5 (d, $^1J_{C,H}$ 162 Hz), 78.1 (d, $^1J_{C,H}$ 158 Hz, C-5,6,7), 43.7 (s, C-4), 27.5, 26.0, 25.0, 20.4 (4 q, $^1J_{C,H}$ 127–130 Hz, 4 Me). Mass spectrum (70 eV): *m/z*

228 (4%, $M^{+\cdot}$), 213 (31), 126 (20), 111 (12), 100 (51), 97 (42), 85 (100), 69 (26), 55 (29), 45 (10).

Anal. Calc. for $C_{11}H_{16}O_5$ (228.10): C, 57.92; H, 7.07. Found: C, 52.72; H, 7.08.

*(1*RS,5SR,6SR,7SR*)-6-*exo,7-exo*-(Isopropylidenedioxy)-4,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-one* [(±)-**5**], — Prepared by the above procedure from (±)-**4**, (±)-**5** had m.p. 141–141.5°.

*(1*RS,4RS,5RS,6RS*)-5-*exo,6-exo*-(Isopropylidenedioxy)-3,3-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one* (**6**). – A 20% suspension of KH (1.5 g) in oil was washed with anhydrous pentane (freshly distilled from Na) (25 mL, 5 times). The resulting white powder was dried under Ar, anhydrous tetrahydrofuran (25 mL) was added, the mixture was cooled to 0°, MeI (3.4 mL, 54 mmol) was added, and the temperature was allowed to rise to 18°. A solution of (±)-**2**[18] (1 g, 5.4 mmol) in anhydrous tetrahydrofuran (25 mL) was added dropwise with vigorous stirring during ~15 min. MeOH (10 mL) was added, the mixture was poured into ice–water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated. The yellowish solid was recrystallised from Et_2O–light petroleum (1:2) and then purified by flash-column chromatography on silica gel (40 g) with AcOEt–light petroleum (1:3) to give **6** (850 mg, 74%), m.p. 104.5–105°; λ_{max} (iso-octane) 315 nm (ε 31), λ_{max} (95% EtOH) 313 nm (ε 30); ν_{max}^{KBr} 2980, 2940, 2880, 1760, 1375, 1210, 1080, 1065, 1005, 860, 835, 780, and 730 cm^{-1}. N.m.r. data ($CDCl_3$): ^1H (250 MHz), δ 4.68, 4.38 (2 d, 2 H, $J_{5,6}$ 5.5 Hz, H-5,6), 4.25 (s, 2 H, H-1,4), 1.44, 1.25, 1.18, 0.92 (4 s, each 3 H, 4Me); ^{13}C (90.55 MHz), δ 214.6 (s, C-2), 113.4 (s), 87.8 (d, $^1J_{C,H}$ 162 Hz), 85.0 (d, $^1J_{C,H}$ 169 Hz), 79.0 (d, $^1J_{C,H}$ 157 Hz), 78.8 (d, $^1J_{C,H}$ 159) (C-1,4,5,6), 45.3 (s, C-3), 25.8, 25.1 (2 q, $^1J_{C,H}$ 127 Hz), 23.2, 18.5 (2 q, $^1J_{C,H}$ 130 Hz). Mass spectrum (70 eV): *m/z* 212 (11%, $M^{+\cdot}$), 197 (52), 183 (13), 155 (3), 127 (12), 109 (50), 97 (86), 85 (100), 69 (61), 59 (48), 55 (66).

Anal. Calc. for $C_{11}H_{16}O_4$ (212.10): C, 62.25; H, 7.60. Found: C, 61.99; H, 7.59.

*(1*RS,5SR,6SR,7RS*)-6-*exo,7-exo*-(Isopropylidenedioxy)-4,4-dimethyl-3,8-dioxabicyclo[3.2.1]octan-2-one* (**7**). — A mixture of **6** (594 mg, 2.8 mmol), $NaHCO_3$ (950 mg, 11.2 mmol), 3-chloroperoxybenzoic acid (55%, 1.8 g, 5.6 mmol), and $CHCl_3$ (60 mL) was stirred at 20° for 15 h. The reaction was monitored by t.l.c. as described above. After the addition of CH_2Cl_2 (40 mL), the solution was washed with H_2O (100 mL), then with saturated aqueous $NaHCO_3$ (50 mL). The aqueous phases were extracted with CH_2Cl_2 (50 mL). The organic extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. The residue was recrystallised from AcOEt–light petroleum (1:4) to yield (±)-**5** (472 mg, 74%). Column chromatography on silica gel LOBAR C (Lichroprep Si60, 40–63 μm, 1:3 AcOEt–light petroleum) of the material in the mother liquor gave **7** (6 mg, 1%). ^1H-N.m.r. data (360 MHz, $CDCl_3$): δ 5.01 and 4.80 (2 d, $J_{6,7}$ 6.0 Hz, H-6,7), 4.59 (s, H-1), 4.10 (s, H-5), 1.58, 1.52, 1.44, and 1.36 (4 s, 4 Me).

*5,7-Dideoxy-2,3-*O*-isopropylidene-5,5-dimethyl-α,β-*D-ribo*-heptofuranos-6-ulose* [(±)-**8**]. — A M solution of Me_3SiCH_2Li in pentane (55 mL, 55 mmol) was added slowly to a stirred solution of (−)-**5** (5 g, 21.9 mmol) in anhydrous tetrahydrofuran (250 mL) at −65° under Ar. The mixture was stirred at −65° for 5 min and the reaction was monitored by t.l.c. [CH_2Cl_2–Et_2O (3:1), detection with vanillin and 2,4-dinitrophenylhydrazine], MeOH (30 mL) was added dropwise, the temperature was adjusted to −40° for 20 min, and the reaction was monitored by t.l.c. (Et_2O-light petroleum, 2:1). The mixture was poured into saturated aqueous NH_4Cl at 0° (400 mL) and extracted with CH_2Cl_2 (3 × 250 mL), the extracts were combined and dried ($MgSO_4$), and the solvent was evaporated. The residue was distilled (Büchi, bulb-to-bulb) at 80–100°/0.15 Torr to yield (±)-**8** (5.26 g, 98%), as a colourless oily 1:1 α,β-mixture, $[\alpha]_{589}^{25}$ +0.2°, $[\alpha]_{578}^{25}$ +0.6°, $[\alpha]_{546}^{25}$ +0.8°, $[\alpha]_{436}^{25}$ +4.0°, $[\alpha]_{365}^{25}$ +21°, (*c* 0.645, chloroform); λ_{max} (iso-octane) 286 nm (ε 27), λ_{max} (95% EtOH) 286 nm (ε 32); ν_{max}^{Film} 3500, 3420, 2990, 2940, 1710, 1370, 1215, 1150, 1075, 870, 850, amd 805, cm^{-1}. α Anomer: n.m.r. data (C_6D_6): ^1H (250 MHz), δ 5.22 (dd, 1 H, $J_{1,2}$ 4.4, $J_{1,OH}$ 8.2 Hz, H-1), 4.44 (dd, 1 H, $J_{2,3}$ 7.2, $J_{3,4}$ 3.8 Hz, H-3), 4.18 (dd, 1 H, $J_{2,3}$ 7.2, $J_{1,2}$ 4.4 Hz, H-2), 4.08 (d, 1 H, $J_{3,4}$ 3.8 Hz, H-4), 3.99 (d, 1 H, $J_{1,OH}$ 8.2 Hz, OH), 1.78 (s, 3 H, MeCO), 1.26, 1.01, 0.93, 0.87 (4 s, each 3 H, 4 Me); ^{13}C (90.55 MHz, $CDCl_3$), δ 212.3 (s, C-6), 114.7 (s), 96.7 (d, $^1J_{C,H}$ 178 Hz, C-1), 87.4 (d, $^1J_{C,H}$ 148 Hz), 81.0 (d, $^1J_{C,H}$ 158 Hz), 80.1 (d, $^1J_{C,H}$ 160 Hz) (C-2,3,4), 49.9 (s, C-5), 26.4, 26.3, 24.7, 22.1, 20.7 (5 q, $^1J_{C,H}$ 125–130 Hz, 5 Me). β Anomer: n.m.r. data (C_6D_6): ^1H (250 MHz), δ 5.49 (dd, 1 H, $J_{1,2}$ 0.9, $J_{1,OH}$ 6.5 Hz, H-1), 4.55 (dd, 1 H, $J_{2,3}$ 6.3, $J_{3,4}$ 3.1 Hz, H-3), 4.49 (dd, 1 H, $J_{2,3}$ 6.3, $J_{1,2}$ 0.9 Hz, H-2), 4.12 (d, 1 H, $J_{3,4}$ 3.1 Hz, H-4), 3.78 (d, 1 H, $J_{1,OH}$ 6.5 Hz, OH), 1.76 (s, 3 H, MeCO), 1.39, 1.09, 0.95, 0.94 (4 s, each 3 H, 4 Me); ^{13}C (90.55 MHz, $CDCl_3$): δ 214.1 (s, C-6), 112.9 (s), 103.6 (d, $^1J_{C,H}$ 171 Hz, C-1), 92.7 (d, $^1J_{C,H}$ 149 Hz), 87.0 (d, $^1J_{C,H}$ 157 Hz), 80.6 (d, $^1J_{C,H}$ 158 Hz) (C-2,3,4), 50.5 (s, C-5), 26.9, 26.3, 25.1, 22.5, 20.7 (5 q, $^1J_{C,H}$ 126–130 Hz, 5 Me). Mass spectrum (c.i., NH_3): *m/z* 262 (74%), 244 (14, $M^{\overset{+}{\cdot}}$), 227 (100), 98 (14), 86 (19).

Anal. Calc. for $C_{12}H_{20}O_5$ (244.29): C, 59.00; H, 8.25. Found: C, 59.29; H, 8.36.

*5,7-Dideoxy-2,3-*O*-isopropylidene-5,5-dimethyl-α,β-*DL-ribo*-heptofuranos-6-ulose* [(±)-**8**]. — Obtained by the above procedure from (±)-**5**, (±)-**8** had m.p. 64–65° (from AcOEt–light petroleum, 1:5).

*5,7-Dideoxy-2,3-*O*-isopropylidene-5,5-dimethyl-β-*D-ribo*-heptofuranosyl-6-ulose acetate* [(−)-**9**]. — (*a*) A mixture of (+)-**8** (9.6 g, 39.3 mmol), Ac_2O (37 mL, 391 mmol), pyridine (31 mL, 384 mmol), and tetrahydrofuran (60 mL) was stirred at 20° for 1 h, then concentrated. Toluene (2 × 25 mL) was evaporated from the residue, which was then distilled at 120°/0.1 Torr to yield (−)-**9** (10.9 g, 97%), m.p. 83.5–84°, $[\alpha]_{589}^{25}$ −34°, $[\alpha]_{578}^{25}$ −36°, $[\alpha]_{546}^{25}$ −41°, $[\alpha]_{436}^{25}$ −64°, $[\alpha]_{365}^{25}$ −82° (*c* 1.015, chloroform); λ_{max} (iso-octane) 283 (ε 30), 222 nm (sh, ε 75), λ_{max} (95% EtOH) 283 nm (ε 34); ν_{max}^{KBr} 2985, 2940, 1745, 1700, 1370, 1235, 1215, 1105, 1080, 975, 965, 865, 850, and 800 cm^{-1}. N.m.r. data (C_6D_6): ^1H (250 MHz), δ 6.46 (s, 1 H, H-1), 4.63 (dd, 1 H, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 3.0 Hz, H-3), 4.44 (d, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 4.36 (d, 1 H, $J_{3,4}$ 3.0 Hz, H-4), 1.86 (s, 3 H, MeCO), 1.59 (s, 3 H, CH_3CO_2), 1.40, 1.13, 0.98, 0.96 (4 s, each 3 H, 4 Me); ^{13}C (90.55 MHz, $CDCl_3$), δ 211.5 (s, C-6), 169.3 (s), 113.4 (s), 101.8 (d, $^1J_{C,H}$ 179 Hz, C-1), 93.6 (d, $^1J_{C,H}$ 152 Hz), 85.4 (d, $^1J_{C,H}$ 159 Hz), 80.0 (d, $^1J_{C,H}$ 158 Hz) (C-2,3,4), 50.0 (s, C-5), 26.9, 26.7, 25.2, 21.6, 21.0, 20.4 (6 q, $^1J_{C,H}$ 126–130 Hz, 6 Me). Mass spectrum (c.i., NH_3): *m/z* 304 (100%), 260 (3), 244 (15), 227 (32), 77 (14).

Anal. Calc. for $C_{14}H_{22}O_6$ (286.33): C, 58.72; H, 7.74. Found: C, 58.65; H, 7.70.

(*b*) A M solution of Me_3SiCH_2Li in pentane (330 mL) was added slowly to a stirred solution of (−)-**5** (30 g, 131.4 mmol) in anhydrous tetrahydrofuran (1.5 L) at −65° under Ar. The mixture was stirred at −65° for 15 min and the reaction was monitored by t.l.c. (CH_2Cl_2–Et_2O, 3:1). MeOH (180 mL) was added slowly and the temperature allowed to rise to −40°. The mixture was stirred at −40° for 20 min and the reaction was monitored by t.l.c. (Et_2O–light petroleum, 2:1). The mixture was poured into saturated aqueous NH_4Cl (1 L) at 0°, the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL), the organic extracts were combined, and the solvent was evaporated. The residue was dissolved in tetrahydrofuran (180 mL), Ac_2O (115 mL) and pyridine (95 mL) were added, and the mixture was stirred at 20° for 1 h, then concentrated. Toluene (3 × 75 mL) was evaporated from the residue, which was then recrystallised from AcOEt–light petroleum (1:2) to yield (−)-**9** (28g, 87%).

*5,7-Dideoxy-2,3-*O*-isopropylidene-5,5-dimethyl-β-*DL-ribo-*heptofuranosylulose acetate* [(±)-**9**]. — Prepared by the above procedure from (±)-**8** or (±)-**5**, ±**9** had m.p. 76–76.5°.

*1,5-Di-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-β-*D-ribo*-hexofuranose* [(−)-**10**]. — Freshly prepared $(CF_3CO)_2O$ (4 mL, 28.8 mmol) was added to a stirred mixture of 90% H_2O_2 (0.55 mL, 22.5 mmol) and CH_2Cl_2 (5.45 mL) at 0°, and stirring was continued at 0° for 1 h. 2.25M CF_3CO_3H in CH_2Cl_2 (0.89 mL, 2.0 mmol) was mixed with CH_2Cl_2 (3 mL) and added dropwise to a stirred solution of (−)-**9** (200 mg, 0.7 mmol) in CH_2Cl_2 (3 mL) during 30 min (20° under Ar). After the end (~3 h) of the oxidation (t.l.c.; Et_2O–light petroleum, 2:1; vanillin), CH_2Cl_2 (10 mL) was added and the solution was washed with M $NaHCO_3$ (10 mL), then with half-saturated aqueous $NaHCO_3$ (10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (15 mL). The organic phases were combined, then dried ($MgSO_4$), and the solvent was evaporated to yield (−)-**10** (200 mg, 95%), m,p. 109–110° (from AcOEt–light petroleum, 1:3), $[\alpha]^{25}_{589}$ −93°, $[\alpha]^{25}_{578}$ −97°, $[\alpha]^{25}_{546}$ −110°, $[\alpha]^{25}_{436}$ −185°, $[\alpha]^{25}_{365}$ −285° (*c* 0.650, chloroform): λ_{max} (iso-octane) 214 nm (ε 170); λ_{max} (95% EtOH) 210 nm (ε 125); ν^{KBr}_{max} 2990, 2950, 1735, 1385, 1370, 1245, 1165, 1150, 1105, 1065, 1005, 975, and 865 cm^{-1}. N.m.r. data (C_6D_6): ^1H (250 MHz), δ 6.52 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.61 (dd, 1 H, $J_{2,3}$ 6.0, $J_{3,4}$ 1.9 Hz, H-3), 4.47 (dd, 1 H, $J_{1,2}$ 0.8, $J_{2,3}$ 6.0 Hz, H-2), 4.07 (d, 1 H, $J_{3,4}$ 1.9 Hz, H-4), 1.57 (s, 3 H, Ac), 1.47 (s, 6 H, Ac+Me), 1.36, 1.34, 1.13 (3 s, each 3 H, 3 Me); ^{13}C (62.9 MHz), δ 169.0, 168.5 (2 s, 2 CO), 113.1 (s), 102.8 (d, $^1J_{C,H}$ 180 Hz, C-1), 94.6 (d, $^1J_{C,H}$ 154 Hz), 86.3 (d, $^1J_{C,H}$ 160 Hz), 80.9 (d, $^1J_{C,H}$ 158 Hz) (C-2,3,4), 81.3 (s, C-5), 27.0, 25.4, 22.4, 21.9, 21.8, 20.5 (6 q, $^1J_{C,H}$ 126–129 Hz, 6 Me). Mass spectrum (c.i., NH_3): *m*/*z* 320 (82%, M + 18), 287 (15), 260 (10), 243 (100), 201 (30), 185 (24), 143 (42), 131 (40), 100 (54), 85 (47).

Anal. Calc. for $C_{14}H_{22}O_7$ (302.33): C, 55.62; H, 7.33. Found: C, 55.79; H, 7.28.

*1,5-Di-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-β-*DL-ribo*-hexofuranose* [(±)-**10**]. — Prepared by the above procedure from (±)-**9**, (±)-**10** had m.p. 86–86.5°.

*6-Deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-β-*D-ribo*-hexofuranose* [(−)-**11**]. — A mixture of (−)-**10** (100 mg, 0.33 mmol), K_2CO_3 (23 mg, 0.16 mmol), and MeOH (4 mL) was stirred at 20° for 5 h, then filtered through silica gel (5 g), and the solvent was evaporated to yield (−)-**11** (72 mg, 98%), as a colourless oil, $[\alpha]^{25}_{589}$ −9.1°, $[\alpha]^{25}_{578}$ −9.5°,

$[\alpha]^{25}_{546}$ $-11°$, $[\alpha]^{25}_{436}$ $-17°$, $[\alpha]^{25}_{365}$ $-23°$, (*c* 1.455, chloroform); λ_{max} (iso-octane) 291 (ε 22), 283 (ε 25), 230 (ε 175), 206 nm (ε 525); λ_{max} (95% EtOH) 228 (sh, ε 130), 204 nm (ε 440); ν^{film}_{max} 3250 (br), 2990, 1380, 1250, 1205, 1170, 1075, 1060, 1030, 950, 870, 840, and 800 cm^{-1}. N.m.r. data (C_6D_6): ^{1}H (250 MHz), δ 5.49 (d, 1 H, $J_{1,OH}$ 6.4 Hz, H-1), 4.86 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 0.5 Hz, H-3), 4.82 (d, 1 H, $J_{1,OH}$ 6.4 Hz, OH), 4.53 (d, 1 H, $J_{2,3}$ 5.9 Hz, H-2), 4.05 (d, 1 H, $J_{3,4}$ 0.5 Hz, H-4), 3.60 (s, 1 H, OH), 1.41, 1.17, 1.10, 1.03 (4 s, each 3 H, 4 Me); ^{13}C (62.9, C_6D_6), 112.1 (s), 103.4 (d, $^1J_{C,H}$ 173 Hz, C-1), 94.9 (d, $^1J_{C,H}$ 148 Hz), 87.5 (d, $^1J_{C,H}$ 157 Hz), 81.3 (d, $^1J_{C,H}$ 157 Hz) (C-2,3,4), 70.7 (s, C-5), 27.1, 26.7, 25.6, 24.9 (4 q, $^1J_{C,H}$ 126 Hz, 4 Me). Mass spectrum (c.i., NH_3): *m/z* 236 (66%, M + 18), 218 (100, $M^{+\cdot}$), 201 (55), 117 (15), 101 (17), 85 (20).

Anal. Calc. for $C_{10}H_{18}O_5$ (218.25): C, 55.03; H, 8.31. Found: C, 55.16; H, 8.34.

*6-Deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-β-*DL-ribo-*hexofuranose* [(±)-**11**]. — Prepared by the above procedure from (±)-**10**, (±)-**11** had m.p. 74–75° (from AcOEt–light petroleum, 1:5).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-β-*D-ribo-*hexofuranoside* [(−)-**12**]. — A mixture of (−)-**11** (0.5 g, 2.3 mmol), 2,2-dimethoxypropane (4.2 mL), *p*-toluenesulfonic acid monohydrate (0.87 g, 4.6 mmol), and MeOH (10 mL) was stirred at 20° for 48 h, then neutralised with AcONa (470 mg, 5.8 mmol), filtered through Celite, and concentrated. Column chromatography (CH_2Cl_2–Et_2O, 3:1) of the residue on silica gel (10 g) gave a yellowish oil (480 mg, 90%) that was distilled at 90°/0.1 Torr to give (−)-**12**, m.p. 35.5–36.5°, $[\alpha]^{25}_{589}$ $-64°$, $[\alpha]^{25}_{578}$ $-66°$, $[\alpha]^{25}_{546}$ $-75°$, $[\alpha]^{25}_{436}$ $-123°$, $[\alpha]^{25}_{365}$ $-182.5°$ (*c* 3.750, chloroform); lit.[3] m.p. 35–36°, $[\alpha]^{25}_{589}$ $-63°$; λ_{max} (iso-octane) 236 (ε 83), 218 nm (ε 75); λ_{max} (95% EtOH) 243 (ε 85), 216 nm (ε 61); ν^{KBr}_{max} 3470 (br), 2980, 2940, 2840, 1375, 1210, 1090, 1030, 950, 865, and 835 cm^{-1}. N.m.r. data ($CDCl_3$): ^{1}H (250 MHz), δ 4.95 (s, H-1), 4.87, 4.55 (2 d, 2 H, $J_{2,3}$ 6.0 Hz, H-2,3), 4.09 (s, 1 H, H-4), 3.46 (s, 3 H, MeO), 3.44 (s, 1 H, OH), 1.46, 1.30 (2 s, each 3 H, 2 Me), 1.23 (s, 6 H, 2 Me); ^{13}C (62.9 MHz), δ 111.9 (s), 110.5 (d, $^1J_{C,H}$ 174 Hz, C-1), 95.1 (d, $^1J_{C,H}$ 149 Hz), 85.7 (d, $^1J_{C,H}$ 159 Hz), 80.8 (d, $^1J_{C,H}$ 156 Hz) (C-2,3,4), 70.1 (s, C-5), 55.9 (q, $^1J_{C,H}$ 143 Hz, MeO), 27.0, 26.4, 25.1, 24.7 (4 q, $^1J_{C,H}$ 126 Hz, 4 Me). Mass spectrum (c.i., NH_3): *m/z* 250 (100%, M + 18), 233 (10, M + 1), 218 (20), 201 (4), 115 (3), 101 (2).

Anal. Calc. for $C_{11}H_{20}O_5$ (232.28): C, 56.88; H, 8.68. Found: C, 56.95; H, 8.59.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*C*-methyl-β-*DL-ribo-*hexofuranoside* [(±)-**12**]. — Prepared by the above procedure from (±)-**11**, (±)- **12** had m.p. 37.5–38.5°.

*6-Deoxy-5-*C*-methyl-α,β-*D-ribo-*hexose* (**13**α,β + **14**α,β). — A solution of (−)-**11** (1g, 4.6 mmol) in 0.5M H_2SO_4 (20 mL) was heated to 80° for 150 min, then cooled to 20°, neutralised with $BaCO_3$ to pH 7–8, and filtered (Celite), and the solvent was evaporated. A solution of the residue in acetone was dried ($MgSO_4$) and then concentrated to yield the title mixture (770 mg, 94%), as a colourless oil, $[\alpha]^{25}_{589}$ $+25°$, $[\alpha]^{25}_{578}$ $+25°$, $[\alpha]^{25}_{546}$ $+27.5°$, $[\alpha]^{25}_{436}$ $+39°$, $[\alpha]^{25}_{365}$ $+53°$ (*c* 2.59, water). The ^{1}H- (250 MHz, D_2O) and ^{13}C-n.m.r. data (62.9) MHz, D_2O) are recorded in Tables I and II, respectively.

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REFERENCES

1 Y. Chen, D.-P. Neff, and P. Vogel, *Helv. Chim. Acta*, 74 (1991) 508–516.

2 J. Kiss and H. Spiegelberg, *Helv. Chim. Acta*, 47 (1964) 398–407; B. P. Vaterlaus, J. Kiss, and H. Spiegelberg, *ibid.*, 47 (1964) 381–390; A. Klemer and M. Waldmann, *Liebigs Ann. Chem.*, (1986) 221–225; O. Achmatowicz, G. Grynkiewicz, and B. Szechner, *Tetrahedron*, 32 (1976) 1051–1054; T. D. Brock, *Antibiotics*, 1 (1967) 651–665; J. Berger and A. D. Batcho, *J. Chromatogr.*, 15 (1978) 101–158; J. W. Hinman, E. L. Caron, and H. Höksema, *J. Am. Chem. Soc.*, 79 (1957) 3789–3800; L. Dolak, *J. Antibiot.*, 26 (1973) 121–125; F. Reusser and L. Dolak, *ibid.*, 39 (1986) 272–274; C. A. Claridge, R. P. Elander, and K. E. Price, *Drugs Pharm. Sci.*, 22 (1984) 413–425; H. Kawaguchi, T. Naito, and H. Tsukiura, *J. Antibiot., Ser. A*, 18 (1965) 11–25; J. Berger, A. J. Schocker, A. D. Batcho, B. Pecherer, O. Kella, J. Maricq, A. E. Karr, B. P. Vaterlaus, A. Furlenmeier, and H. Spiegelberg, *Antimicrob. Agents Chemother.*, (1965) 778–785; A. Arnone, G. Nasini, and B. Cavalleri, *J. Chem. Soc., Perkin Trans. 1*, (1987) 1353–1359; J. E. Hochlowski, S. J. Swanson, L. M. Ranfranz, D. N. Whittern, A. M. Buko, and J. B. McAlpine, *J. Antibiot.*, 40 (1987) 575–588.

3 E. Walton, J. O. Rodin, C. H. Stammer, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 80 (1958) 5168–5173.

4 R. F. Nutt and E. Walton, *J. Med. Chem.*, 11 (1968) 151–153.

5 A. Warm and P. Vogel, *J. Org. Chem.*, 51 (1986) 5348–5353; P. Vogel, Y. Auberson, M. Bimwala, E. De Guchteneere, E. Vieira, and J. Wagner, *ACS Symp. Ser.*, 386 (1989) 197–241, P. Vogel, D. Fattori, F. Gasparini, and C. Le Drian, *Synlett*, (1990) 173–185; P. Vogel, *Bull. Soc. Chim. Belg.*, 99 (1990) 395–439.

6 J. Wagner, E. Vieira, and P. Vogel, *Helv. Chim. Acta*, 71 (1988) 624–630; Y. Auberson and P. Vogel, *ibid.*, 72 (1989) 278–286.

7 D. Gagnaire and E. Payo-Subiza, *Bull. Soc. Chim. Fr.*, (1963) 2627–2631; K. C. Ramey and D. C. Lini, *J. Magn. Reson.*, 3 (1970) 94–102; W. L. Nelson and D. R. Allen, *J. Heterocycl. Chem.*, 9 (1972) 561–568; F. Kienzle, *Helv. Chim. Acta*, 58 (1975) 1180–1183; C. Mahaim and P. Vogel, *ibid.*, 65 (1982) 866–886; K. A. Black and P. Vogel, *J. Org. Chem.*, 51 (1986) 5341–5348.

8 J. Wagner and P. Vogel, *J. Chem. Soc., Chem. Commun.*, (1989) 1634–1635.

9 K. Röser, P.-A. Carrupt, P. Vogel, E. Honegger, and E. Heilbronner, *Helv. Chim. Acta*, 73 (1990) 1–12.

10 M. Demuth, *Helv. Chim. Acta*, 61 (1978) 3136–3138; D. E. Seitz and A. Zapata, *Tetrahedron Lett.*, 21 (1980) 3451–3454; J. W. Connolly and G. Uny, *Inorg. Chem.*, 2 (1963) 615–616.

11 S. J. Angyal and V. A. Pickles, *Aust. J. Chem.*, 25 (1972) 1695–1710; H. S. El Khadem and V. Nelson, *Carbohydr. Res.*, 98 (1981) 195–201.

12 K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–66; D. E. Dorman and J. D. Roberts, *J. Am. Chem. Soc.*, 92 (1970) 1355–1361; W. A. Szarek, D. M. Vyas, S. D. Gero, and G. Lukacs, *Can. J. Chem.*, 52 (1974) 3394–3400.

13 U. P. Singh and R. K. Brown, *Can. J. Chem.*, 49 (1971) 1179–1186.

14 D. Horton and Z. Walaszek, *Carbohydr. Res.*, 105 (1982) 145–153.

15 L. M. J. Kroon-Batenburg, P. van den Sluis, and J. A. Kanter, *Acta Crystallogr., Sect. C*, 40 (1984) 1863–1865.

16 S. J. Angyal, V. A. Pickles, and R. Ahluwahlia, *Carbohydr. Res.*, 1 (1966) 365–370.

17 F. Gasparini and P. Vogel, *J. Org. Chem.*, 55 (1990) 2451–2457.

18 R. R. Schmidt, C. Beitzke, and A. K. Forrest, *J. Chem. Soc., Chem. Commun.*, (1982) 909–910; E. Vieira and P. Vogel, *Helv. Chim. Acta*, 65 (1982) 1700–1706.