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Note

Synthesis of 1-[6,7-anhydro-4-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D(and -L)-*threo*-α-D-*manno*-octopyranosyl]thymines, precursors to higher-carbon sugar nucleosides

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Higher-carbon sugars are found as constituents of such nucleoside antibiotics as mildiomycin[1], amipurimycin[2], and hikizimycin[3]. Much work has been devoted to the synthesis of higher-carbon sugars[4], but little attention has been paid to the synthesis of the corresponding nucleosides. Terminal glycidyl nucleosides should provide an approach to this synthesis since epoxides can undergo regio- and stereoselective opening reactions. We now report the synthesis of the diastereomeric epoxides derived from 1-[(*E*)-6,7-dideoxy-α-D-*manno*-oct-6-enopyranosyl]thymine (**7**), which are precursors of functionalized higher-carbon sugar nucleosides.

The starting material was 1-(2,3-*O*-isopropylidene-α-D-mannopyranosyl)-thymine[5] (**1**), an alternative preparation of which involved Vorbruggen condensation of α-D-mannopyranose penta-acetate with bis(trimethylsilyl)thymine. Deacetylation and acetonation with 2,2-dimethoxypropane then gave **1**.

Treatment of **1** with trityl chloride in dry pyridine gave the 6-*O*-trityl derivative **2**, HO-4 of which was *tert*-butyldimethylsilylated[6] to give **3**. Selective cleavage of the trityl ether group in **3** with formic acid in ether[7] gave **4**. Attempts to oxidise HO-6 in **4** with chromium(VI) reagents gave intractable mixtures of products. However, the Swern reagent[8] gave satisfactory results and afforded the aldehyde **5**, which was unstable and was reacted[9] *in situ* with ethoxycarbonylmethylenetriphenylphosphorane to give the unsaturated ester **6**. Only one isomer was formed in this reaction. The ^{1}H-n.m.r. spectrum of **6** contained signals (2 dd) at 6.00 and 6.90 p.p.m. assigned to H-7 and H-6, respectively. From the large coupling constants (15.7 Hz), the *E* geometry was deduced for this double bond.

Selective reduction of the ester group in **6**, using di-isobutylaluminium hydride in ether, gave the allylic alcohol **7**. Epoxidation[10] of **7** in the presence of di-isopropyl D-tartrate at −20° gave the epoxide **8**, and ^{1}H-n.m.r. spectroscopy indicated that <4% of the other diastereoisomer was formed. Epoxidation of **7** in the presence of di-isopropyl L-tartrate gave **9** with no detectable trace of **8**. Configu-

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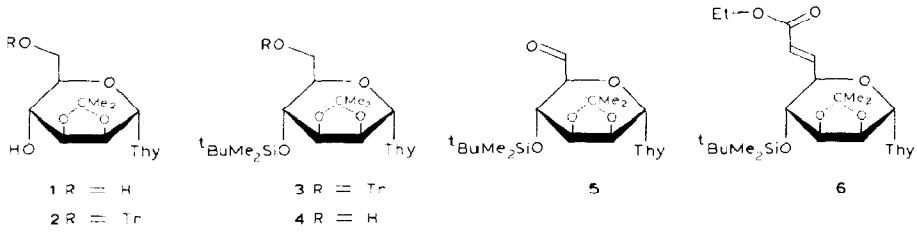
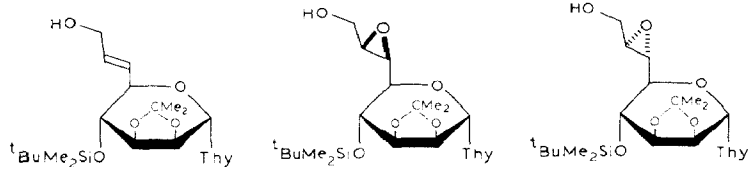
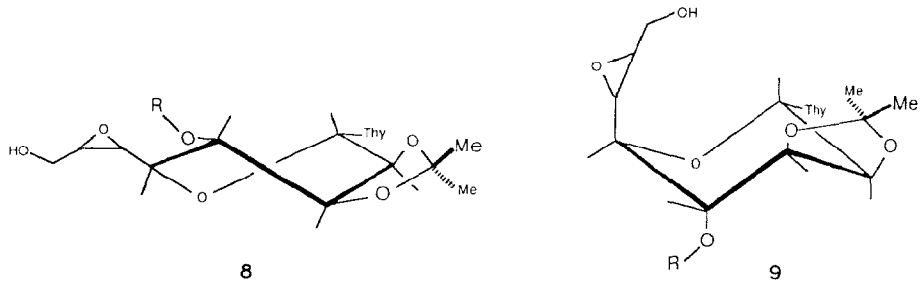




rations were assigned to **8** and **9** on the basis of the Sharpless model[11], since the reactions were reagent-controlled.

The conformations of **8** and **9** were assigned on the basis of the 300-MHz ^{1}H-n.m.r. spectra ($CDCl_3$). The signals were assigned using homodecoupling techniques, and the coupling constants were computed in the simplified Karplus equation[12] to give the corresponding dihedral angles. The results reported in Table I show that **9** adopts the $^1C_4$ conformation, and **8** the skew $^4S_0$ form (Scheme 1). The present study should help to predict the outcome of opening reactions of these epoxides, which are being studied further.



Scheme 1. Conformations of compounds **8** and **9**.

TABLE I

COUPLING CONSTANTS AND DIHEDRAL ANGLES FOR **8** AND **9**

Compound	$J_{1,2}$ ($\phi_{1,2}$)	$J_{2,3}$ ($\phi_{2,3}$)	$J_{3,4}$ ($\phi_{3,4}$)	$J_{4,5}$ ($\phi_{4,5}$)
8	7.3 (152.9°)	6.7 (24.6°)	6.2 (145.2°)	9 (171.1°)
9	7.6 (155.2°)	6.8 (23.7°)	4.2 (42.7°)	6.8 (23.7°)

EXPERIMENTAL

General. — Optical rotations were measured with a Roussel Quick polarimeter, u.v. spectra with a Varian M 635 spectrophotometer, i.r. spectra with a Perkin–Elmer 137 instrument, and ^{1}H-n.m.r. spectra ($CDCl_3$, internal Me_4Si) with a Bruker MSL 300 spectrometer. Reactions were monitored by t.l.c. on silica gel (Merck, 5735), with detection by u.v. light (254 nm) or by charring with sulphuric acid. Flash column chromatography was carried out on Chromagel 60 Å (S.D.S., 200.17) at 10 p.s.i. Solvents for chromatography were *A*, ethyl aceate; and ethyl acetate–hexane; *B*, 70:30; *C*, 50:50; *D*, 30:70; *E*, 60:40.

*1-(2,3-*O*-Isopropylidene-α-*D*-mannopyranosyl)thymine* (**1**). — A solution of 1-α-D-mannopyranosylthymine[5] (0.289 g, 1 mmol), 2,2-dimethoxypropane (2 mL, 16 mmol), and *p*-toluenesulfonic acid (0.039 g, 0.2 mmol) in dry acetone (2 mL) was stirred for 30 min at room temperature. Water (4 mL) was added and stirring was continued for 16 h. The solution was then neutralised with aqueous sodium hydrogencarbonate and concentrated. Column chromatography (ethyl acetate) of the residue gave **1** and crystallisation from aqueous acetone gave material (0.25 g, 76%) having m.p. 196°, $[\alpha]_D$ +52.5° (*c* 0.1, methanol); R_F 0.2 (solvent *A*); λ_{max} 264 nm (ε 9600).

Anal. Calc. for $C_{14}H_{20}N_2O_7 \cdot H_2O$: C, 48.55; H, 6.35; N, 8.09. Found: C, 48.41; H, 6.27; N, 8.24.

*1-(2,3-*O*-Isopropylidene-6-*O*-trityl-α-*D*-mannopyranosyl)thymine* (**2**). — To a solution of **1** (0.328 g, 1 mmol) in pyridine (5 mL) was added trityl chloride (0.306 g, 1 mmol). The mixture was stirred for 2 h at 80°, then concentrated. Column chromatography (dichloromethane, then ethyl acetate) of the residue gave **2** (0.445 g, 78%), m.p. 136–138° (from methanol), $[\alpha]_D$ +22.5° (*c* 1, chloroform); R_F 0.5 (solvent *B*); λ_{max} 264 nm (ε 10,000).

Anal. Calc. for $C_{33}H_{34}N_2O_2 \cdot H_2O$: C, 67.35; H, 6.12; N, 4.76. Found: C, 67.30; H, 5.99; N, 4.70.

*1-(4-*O*-tert-Butyldimethylsilyl-2,3-*O*-isopropylidene-6-*O*-trityl-α-*D*-mannopyranosyl)thymine* (**3**). — To a solution of **2** (0.57 g, 1 mmol) in dry *N,N*-dimethylformamide (6 mL) were added successively imidazole (0.095 g, 1.4 mmol) and *tert*-butyldimethylsilyl chloride (0.226 g, 1.5 mmol). The mixture was stirred for 6 h at room temperature, then concentrated under reduced pressure. A solution of the residue in ethyl acetate was washed with water, dried (Na_2SO_4), and concentrated, and the residue was crystallised from ethanol to give **3** (0.56 g, 82%), m.p. 189–190°, $[\alpha]_D$ +39° (*c* 0.1, chloroform); R_F 0.66 (solvent *B*); λ_{max} 265 nm (ε 10,300). ^{1}H-N.m.r. data* ($CDCl_3$): δ 7.54–7.35 (m, 15 H, trityl), 5.9 (d, 1 H, $J_{1',2'}$ 6.9 Hz, H-1'), 4.57 (t, 1 H, $J_{2',3'}$ 6.8 Hz, H-2'), 4.4 (t, 1 H, $J_{3',4'}$ 5.9 Hz, H-4'), 4.06 (m, 2 H, H-3',5'), 3.48 (dd, 1 H, $J_{5',6'}$ 3, J_{gem} 10.1 Hz, H-6'), 3.39 (dd, 1 H, $J_{5',6'}$ 6, J_{gem} 9.9 Hz, H-6').

Anal. Calc. for $C_{39}H_{48}N_2O_7Si$: C, 68.42; H, 7.01; N, 4.09. Found: C, 68.52; H, 7.00; N, 4.15.

*Primed numbers refer to the sugar moieties.

*1-(4-*O*-tert-Butyldimethylsilyl-2,3-*O*-isopropylidene-α-*D*-mannopyranosyl)-thymine* (**4**). — To a solution of **3** (0.684 g, 1 mmol) in ether (15 mL) was added formic acid (10 mL). The solution was stirred for 7 min, then concentrated. Column chromatography (solvent *C*) of the residue and crystallisation from ethyl acetate–hexane gave **4** (0.465 g, 81%), m.p. 221–222°, $[\alpha]_D$ +57.5° (*c* 0.1, chloroform); R_F 0.3 (solvent *D*); λ_{max} 264 nm (ε 9800). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.66 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1'), 4.38–4.28 (m, 2 H, H-2',3'), 4.07 (m, 1 H, H-5'), 3.61 (m, 3 H, H-4',6'a,6'b).

Anal. Calc. for $C_{20}H_{34}N_2O_7Si$: C, 54.30; H, 7.69; N, 6.33. Found: C, 54.17; H, 7.62; N, 6.31.

*1-(Ethyl 4-*O*-tert-butyldimethylsilyl-6,7-dideoxy-2,3-*O*-isopropylidene-α-*D*-manno-oct-6-enopyranosyluronate)thymine* (**6**). — To a solution of oxalyl chloride (0.116 mL, 1.36 mmol) in dry dichloromethane (10 mL) under nitrogen at −70° was added methyl sulfoxide (0.185 mL, 0.26 mmol). After 15 min, a solution of **4** (0.314 g, 1 mmol) in dichloromethane (6 mL) was added and, after 20 min, triethylamine (0.64 mL, 4.7 mmol). The mixture was stored for 20 min and a solution of ethoxycarbonylmethylenetriphenylphosphorane (1 g, 2.8 mmol) in dichloromethane (6 mL) was added. After 20 min, the mixture was allowed to attain room temperature, diluted with dichloromethane, washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (solvent *E*) and crystallisation from ethyl acetate–hexane gave **6** (0.35 g, 71%), m.p. 86–88°, $[\alpha]_D$ +19° (*c* 0.1, chloroform); R_F 0.42 (solvent *A*); λ_{max} 265 (ε 9300). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.89 (dd, 1 H, $J_{6',7'}$ 15.8, $J_{5',6'}$ 4.5 Hz, H-6'), 5.99 (dd, 1 H, $J_{6',7'}$ 15.7, $J_{5',7'}$ 1.6 Hz, H-7'), 5.64 (d, 1 H, $J_{1',2'}$ 6.7 Hz, H-1'), 4.4–4.31 (m, 2 H, H-2',3'), 4.27 (ddd, 1 H, $J_{4',5'}$ 9, $J_{5',6'}$ 4.6, $J_{5',7'}$ 1.7 Hz, H-5'), 4.1 (m, 2 H, J_{gem} 14.3 Hz, $-CH_2$), 3.76 (dd, 1 H, $J_{3',4'}$ 6.2, $J_{4',5'}$ 9 Hz, H-4').

Anal. Calc. for $C_{24}H_{38}N_2O_7Si$: C, 56.47; H, 7.45; N, 5.49. Found: C, 56.46; H, 7.49; N, 5.49.

*1-(4-*O*-tert-Butyldimethylsilyl-6,7-dideoxy-2,3-*O*-isopropylidene-α-*D*-manno-oct-6-enopyranosyl)thymine* (**7**). — To a solution of **6** (0.494 g, 1 mmol) in ether (10 mL) was added at 0° under nitrogen a solution of diisobutylaluminium hydride (2.1 mL, 2.1 mmol) in hexane. The mixture was stirred for 5 min, 2M hydrochloric acid (2 mL) was added slowly, and stirring was continued for 1 h. The ether layer was separated, washed with aqueous sodium hydrogensulfate and brine, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *C*) of the residue and crystallisation from ethyl acetate–hexane gave **7** (0.370 g, 79%), m.p. 156–157°, $[\alpha]_D$ +50.5° (*c* 0.1, chloroform); R_F 0.3 (solvent *C*); λ_{max} 265 nm (ε 9200). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.9 (dt, 1 H, $J_{6',7'}$ 15.7, $J_{7',8'}$ 4.7 Hz, H-7'), 5.76 (m, 2 H, H-1',6'), 4.29 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 6.5 Hz, H-2'), 4.22 (dd, 1 H, $J_{2',3'}$ 6.4, $J_{3',4'}$ 5.0 Hz, H-3'), 4.17 (dd, 1 H, $J_{4',5'}$ 6.1, $J_{5',6'}$ 6.8 Hz, H-5'), 4.08 (m, 2 H, H-8'), 3.86 (dd, 1 H, $J_{3',4'}$ 4.9, $J_{4',5'}$ 6.1 Hz, H-4').

Anal. Calc. for $C_{22}H_{36}N_2O_7Si$: C, 56.41; H, 7.69; N, 5.98. Found: C, 56.58; H, 7.70; N, 5.90.

*1-(6,7-Anhydro-4-*O*-tert-butyldimethylsilyl-2,3-*O*-isopropylidene-*D*-threo-α-*D*-manno-octopyranosyl)thymine* (**8**). — To a solution of **7** (0.468 g, 1 mmol) and di-isopropyl D-tartrate (0.304 g, 1 mmol) in dry dichloromethane (10 mL) at −25° under nitrogen was added titanium(IV) isopropoxide (0.33 mL, 1.1 mmol), and the mixture was stirred for 15 min. *tert*-Butyl hydroperoxide (0.4 mL, 3.2M in toluene) was then added and the mixture was stored at −25° for 48 h, then warmed to 0°. Aqueous 10% tartaric acid (4 mL) was added, stirring was continued for 30 min, dichloromethane (20 mL) was added, and the solution was washed three times with water, dried (Na_2SO_4), and concentrated. Column chromatography (solvent *D*) of the residue gave **8** as a semi-crystalline solid (0.387 g, 80%), m.p. 90–95°, $[\alpha]_D$ +57.5° (*c* 0.1, chloroform); R_F 0.38 (solvent *C*); λ_{max} 265 nm (ε 9100). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.67 (d, 1 H, $J_{1',2'}$ 7.5 Hz, H-1'), 4.4 (m, 2 H, H-2',3'), 4.06 (dd, 1 H, $J_{3',4'}$ 6.3, $J_{4',5'}$ 9 Hz, H-4'), 3.94 (m, 1 H, H-8'), 3.8 (dd, 1 H, $J_{4',5'}$ 9, $J_{5',6'}$ 2.9 Hz, H-5'), 3.67 (m, 1 H, H-8'), 3.15 (m, 2 H, H-6',7').

Anal. Calc. for $C_{22}H_{36}N_2O_8Si$: C, 54.54; H, 7.44; N, 5.76. Found: C, 54.52; H, 7.75; N, 5.34.

*1-(6,7-Anhydro-4-*O*-tert-butyldimethylsilyl-2,3-*O*-isopropylidene-*L*-threo-α-*D*-manno-octopyranosyl)thymine* (**9**). — Epoxidation of **7** in the presence of di-isopropyl L-tartrate as in the above procedure, for 36 h, gave **9** (0.416 g, 86%), m.p. 182–183° (from ethyl acetate–hexane), $[\alpha]_D$ +62.5° (*c* 0.1, chloroform); R_F 0.38 (solvent *C*); λ_{max} 265 nm (ε 9300). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.67 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.24 (m, 2 H, H-2',3'), 4.0 (dd, 1 H, $J_{3',4'}$ 4.6, $J_{4',5'}$ 6.5 Hz, H-4'), 3.74 (dd, 1 H, $J_{7',8'}$ 3.2, J_{gem} 12.8 Hz, H-8'), 3.67 (dd, 1 H, $J_{4',5'}$ 6.4, $J_{5',6'}$ 3.9 Hz, H-5'), 3.58 (dd, 1 H, $J_{7',8'}$ 4.1, J_{gem} 12.7 Hz, H-8'), 3.24 (dd, 1 H, $J_{5',6'}$ 3.8, $J_{6',7'}$ 2.2 Hz, H-6'), 3.15 (m, 1 H, H-7').

Anal. Calc. for $C_{22}H_{36}N_2O_8Si$: C, 54.54; H, 7.44; N, 5.76. Found: C, 54.83; H, 7.46; N, 5.71.

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