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Note

A synthesis of 2,3-dideoxy-4,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-enono-1,5-lactone

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Some higher-carbon sugars have important biochemical roles[1] and others have interesting pharmacological properties (*e.g.*, lincosamine[2], hikosamine[3], Kdo[4], sialic acids, *etc.*).

The sialic acids belong to a group of sugars which can be derived formally from L-hexoses. The synthesis of α,β-unsaturated δ-lactones where the lactone carbon atom is L is one possible approach to this type of compound. Lactones of this type are also found in natural products (asperline[5], olguine[6], phomopsolides A and B[7], and cryptocaryolactone[8]) that are biologically active.

The synthesis of 2,3-dideoxy-4,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-enono-1,5-lactone (**7**) involves selective 3-*O*-*tert*-butyldimethylsilylation of 5,6-*O*-isopropylidene-D-glucose diethyl dithioacetal[9] (**1**) to give **2**, which reacted with 2,2-dimethoxypropane (catalysed by toluene-*p*-sulphonic acid) to give the 2,4:5,6-di-*O*-isopropylidene derivative **3** after column chromatography. The ^{13}C-n.m.r. spectrum of **3** contained signals at δ 109.2 and 99.2, corresponding[10] to the acetal carbon atoms of the 5,6- and 2,4-*O*-isopropylidene groups, respectively. Desilylation of **3** with tetrabutylammonium fluoride[11] yielded **4**.

The aldehyde function at C-1 was liberated by treatment of **4** with methyl iodide and calcium carbonate[12] in aqueous acetonitrile to give **5**, condensation of which with methoxycarbonylmethylenetriphenylphosphorane in methanol at 0° afforded the α,β-unsaturated ester **6** (*Z* isomer only, 76%; ^{1}H-n.m.r. data: $J_{2,3}$ 11.7 Hz). As shown[13] previously, the presence of the β-hydroxyaldehyde structure in **5** markedly enhanced the formation of the *Z* isomer **6**, which was also favoured by using methanol as solvent. The ester **6** was converted into the lactone **7** by heating in toluene in the presence of powdered molecular sieves (4A).

Since the transformation of a derivative of 2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone into a C_7 analogue of *N*-acetylneuraminic acid has been achieved[14], **7** may be useful for the preparation of sialic acids and glycosides thereof, using the methodology outlined[14]. The synthesis of **7** described above is an improvement on

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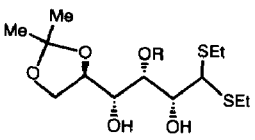

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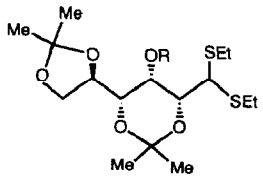
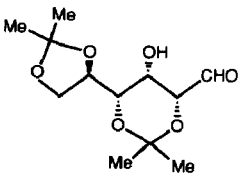
2 R = ^{t}BuMe$_2$Si



3 R = ^{t}BuMe$_2$Si
4 R = H



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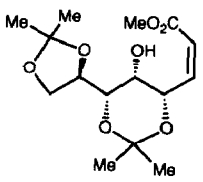

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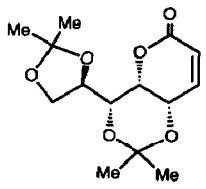

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previous methodology[15], and the presence of 1,3-dioxane and 1,3-dioxolane isopropylidene moieties should allow a selective stepwise deprotection of the hydroxyl groups. Compound **1** was prepared on a 10-g scale.

EXPERIMENTAL

General methods. — The ^{1}H- and ^{13}C n.m.r. spectra (internal Me_4Si) were recorded with a Varian 390, Varian XL 300, or Bruker AM200 spectrometer. Melting points were obtained with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 141 polarimeter and microanalyses were obtained using a Heraeus CHN-O-RAPID element analyser. T.l.c. was performed on Kieselgel 60 F_{254} (Merck) and flash column chromatography on Kieselgel 60 (230–400 mesh).

3-O-tert-Butyldimethylsilyl-2,4:5,6-di-O-isopropylidene-D-glucose diethyl dithioacetal (**3**). — To a solution of **1**[9] (13.71 g, 42.05 mmol) and imidazole (4.33 g, 63.67 mmol) in dry and freshly distilled *N,N*-dimethylformamide (150 mL) was added *tert*-butyldimethylsilyl chloride (9.62 g, 63.82 mmol). The reaction was monitored by t.l.c. in order to detect the appearance of a second silylated product. Silylation was then interrupted by the addition of water (150 mL) and hexane, and the hexane layer was dried (Na_2SO_4) and concentrated *in vacuo* to give **2** that was used directly in the next step. Extraction of the aqueous phase with ether yielded unreacted **1** (1.37 g, 10%).

A solution of **2** in 2,2-dimethoxypropane (50 mL) containing a catalytic amount of toluene-*p*-sulphonic acid was stirred for 24 h at 4°. Solid K_2CO_3 was added, and the mixture was stirred for 10 min, then filtered, and concentrated *in vacuo*. Column chromatography (24:1 hexane–ethyl acetate) of the residue gave **3** (13.94 g, 69% from **1**), isolated as an oil, $[\alpha]_D$ +29° (*c* 1.4, $CHCl_3$). N.m.r. data ($CDCl_3$): ^{1}H, δ 4.2–3.4 (m, 7 H, H-1/6), 2.7 (q, 2 H, *J* 7 Hz, CH_2S), 2.6 (q, 2 H, *J* 7 Hz, CH_2S), 1.4 (s, 9 H, 3 Me), 1.3 (s,

3 H, Me), 1.2 (2 t, 6 H, *J* 7 Hz, 2 SCH_2CH_3), 0.9 (s, 9 H, 'Bu), 0.2 (2 s, 6 H, 2 SiMe); ^{13}C, δ 109.2, 99.2, 76.2, 75.9, 72.6, 68.0, 64.2, 51.3, 29.4, 26.9, 26.3, 25.4, 25.1, 23.1, 19.2, 14.4, 0.0, −3.6, −4.2.

Anal. Calc. for $C_{22}H_{44}O_5S_2Si$: C, 54.96; H, 9.22. Found: C, 55.01; H, 9.23.

2,4:5,6-Di-O-isopropylidene-D-glucose diethyl dithioacetal (**4**). — To a solution of **3** (8.0 g, 16.66 mmol) in tetrahydrofuran (300 mL) was added tetrabutylammonium fluoride trihydrate (5.92 g, 23 mmol). The solution was stirred for 24 h at room temperature, then diluted with ether, and washed with water. The organic phase was separated, dried, and concentrated *in vacuo*. Column chromatography (8:2 hexane–ethyl acetate) of the residue gave **4** (5.61 g, 92%), isolated as an oil, $[\alpha]_D$ −8.9° (*c* 1.5, $CHCl_3$). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.3–3.6 (m, 7 H, H-1/6), 2.7 (bq, 4 H, *J* 6 Hz, 2 CH_2S), 2.3–2.11 (1 H, OH), 1.4 (s, 9 H, 3 Me), 1.3 (s, 3 H, Me), 1.2 (t, 6 H, *J* 6 Hz, 2 SCH_2CH_3).

Anal. Calc. for $C_{16}H_{30}O_5S_2$: C, 52.43; H, 8.25. Found: C, 52.41; H, 8.29.

Methyl (Z)-2,3-dideoxy-4,6:7,8-di-O-isopropylidene-D-gluco-oct-2-enonate (**6**). — To a solution of **4** (3.70 g, 100 mmol) in 5:2 acetonitrile–water (42 mL) were added $CaCO_3$ (1.5 g) and MeI (4.0 mL). The mixture was stirred in a closed vessel for 72 h, then filtered, and concentrated *in vacuo*. The oily residue (**5**) decomposed on storage and was used immediately in the following step. ^{1}H-N.m.r. data ($CDCl_3$): δ 9.5 (s, 1 H, H-1), 4.1–3.5 (m, 6 H, H-2/6), 2.3 (1 H, OH), 1.6–1.1 (m, 12 H, 4 Me). Mass spectrum (70 eV): *m/z* 245 [$M^+ - 15$] (4%), 187 (7), 101 (42), 85 (13), 59 (62), 43 (100).

A solution of **5** (1.30 g, 5.0 mmol) and methoxycarbonylmethylenetriphenylphosphorane (2.20 g, 6.6 mmol) in methanol (50 mL) at 0° was stirred for 2 h, then concentrated. Column chromatography (7:3 hexane–ethyl acetate) of the residue gave **6** (1.20 g, 76%), m.p. 70–71° (from hexane–ether), $[\alpha]_D$ +103° (*c* 0.24, $CHCl_3$). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.32 (dd, 1 H, $J_{2,3}$ 11.7, $J_{3,4}$ 7.0 Hz, H-3), 5.92 (dd, 1 H, $J_{2,4}$ 1.4 Hz, H-2), 5.52 (bd, 1 H, *J* 7.0 Hz, H-4), 4.30–4.04 (m, 2 H), 3.90–3.75 (m, 3 H), 3.73 (s, 3 H, COOMe), 2.39 (d, 1 H, *J* 11.0 Hz, OH), 1.53 (s, 3 H, Me), 1.44 (s, 6 H, 2 Me), 1.35 (s, 3 H, Me). Mass spectrum (70 eV): *m/z* 301 [$M^+ - 15$] (6%), 151 (8), 143 (24), 115 (12), 98 (63), 85 (14), 83 (23), 69 (21), 59 (45), 43 (100).

Anal. Calc. for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.82; H, 7.69.

2,3-Dideoxy-4,6:7,8-di-O-isopropylidene-D-gluco-oct-2-enono-1,5-lactone (**7**). — A solution of **6** (730 mg, 2.31 mmol) in dry toluene (75 mL) containing powdered 4A molecular sieves (4.0 g) was kept for 20 h at 150–160°, then filtered, and concentrated *in vacuo*. Column chromatography (6:4 hexane–ethyl acetate) of the residue yielded **7** (490 mg, 83%), m.p. 133–134° (from hexane–ether), $[\alpha]_D$ +30° (*c* 0.1, $CHCl_3$). N.m.r. data ($CDCl_3$): ^{1}H, δ 6.87 (dd, 1 H, $J_{2,3}$ 9.6, $J_{3,4}$ 6.0 Hz, H-3), 6.25 (d, 1 H, H-2), 4.49 (ddd, 1 H, $J_{6,7}$ 8.3, $J_{7,8A}$ 6.3, $J_{7,8B}$ 4.3 Hz, H-7), 4.36 (dd, 1 H, $J_{4,5}$ 1.8 Hz, H-4), 4.28 (dd, 1 H, $J_{5,6}$ 1.8 Hz, H-5), 4.13 (dd, 1 H, $J_{8A,8B}$ 8.9 Hz, H-8A), 3.94 (dd, 1 H, H-8B), 3.80 (dd, 1 H, H-6); ^{13}C, δ 162.9, 140.4, 125.6, 109.5, 99.4, 72.4, 71.3, 69.5, 66.9, 60.2, 29.2, 26.9, 24.9, 19.0. Mass spectrum (70 eV): *m/z* 284 [M^+] (0.1%), 269 (14), 227 (16), 211 (26), 183 (5), 169 (6), 151 (9), 101 (63), 83 (20), 59 (18), 43 (100).

Anal. Calc. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.97; H, 7.25.

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REFERENCES

1 S. J. Danishefsky and M. P. DeNinno, *Angew. Chem. Int. Ed. Engl.*, 26 (1987) 15–23.
2 B. J. Magerlein, in D. Pearlman (Ed.), *Structure Activity Relationships Among the Semisynthetic Antibiotics*, Academic Press, New York, 1977, pp. 601–650.
3 M. Vuilhorgne, S. Ennifar, B. C. Das, J. M. Paschal, R. Nagarajan, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 42 (1977) 3289–3291.
4 F. M. Unger, *Adv. Carbohydr. Chem. Biochem.*, 38 (1981) 323–388.
5 A. D. Argoudelis and J. F. Zieserl, *Tetrahedron Lett.*, (1966) 1969–1973.
6 A. Alemany, C. Marquez, C. Pascual, S. Valverde, M. Martinez-Ripoll, J. Fayos, and A. Perales, *Tetrahedron Lett.*, (1979) 3579–3582.
7 J. F. Grove, *J. Chem. Soc., Perkin Trans. 1*, (1985) 865–869.
8 H. H. Meyer, *Liebigs Ann. Chem.*, (1984) 977–981.
9 T. B. Grindley, C. J. P. Cote, and C. Wickramage, *Carbohydr. Res.*, 140 (1985) 215–238.
10 J. G. Buchanan, A. R. Edgar, D. I. Rawson, P. Shahidi, and R. H. Wightman, *Carbohydr. Res.*, 100 (1982) 75–86.
11 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94 (1972) 6190–6191.
12 A. L. Markezich, W. E. Willy, B. E. McCarry, and W. S. Johnson, *J. Am. Chem. Soc.*, 93 (1973) 4415–4416.
13 S. Valverde, M. Martin-Lomas, B. Herradon, and S. Garcia-Ochoa, *Tetrahedron*, 43 (1987) 1895–1901.
14 S. Valverde and S. Garcia-Ochoa, *J. Carbohydr. Chem.*, 8 (1989) 553–563.
15 S. Valverde, S. Garcia-Ochoa, and M. Martin-Lomas, *Carbohydr. Res.*, 147 (1986) c1–c2.