

**Note**

**Synthesis of (1*R*,5*R*)-2,6-dioxabicyclo[3.3.0]octan-3-one from D-glucose**

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Compounds of the type **1** (where *m* and *n* are variously 1 and 2) are related to part-structures of several natural products<sup>1</sup>, and substituted tetrahydrofurans and tetrahydropyrans are valuable synthons for polyether antibiotics<sup>2</sup>. Although there are several routes to these molecules, carbohydrate-based precursors have rarely been utilised<sup>2,3</sup>. We now report an enantiospecific synthesis of 2,6-dioxabicyclo[3.3.0]octan-3-one (**2**) starting from D-glucose; ( $\pm$ )-**2** has been prepared<sup>4</sup> by palladium-catalysed intramolecular oxycarbonylation of 4-pentene-1,3-diol.

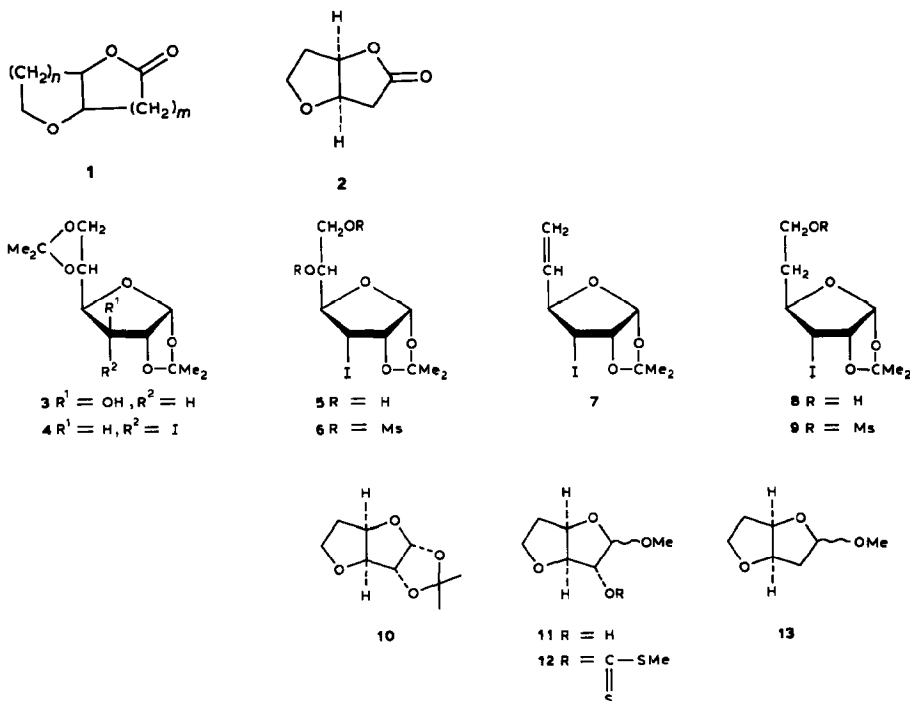


TABLE I

N.M.R. DATA<sup>a</sup>

Compound	H-1	H-2	H-3	H-4	H-5,5'	H-6,6'	Me <sub>2</sub> C	OMe <sup>d</sup>	Ms	SMe
<b>6</b>	5.81(d)	4.5	3.93(dd)	4.5(m)	5.09(m) <sup>c</sup>	4.5(m)	1.34(s) 1.53(s)	—	3.06(s) 3.12(s)	—
<b>7</b>	5.84(d)	4.62(t)	3.56(dd)	4.50(dd)	5.81(o)	5.1-5.6(m)	1.37(s) 1.56(s)	—	—	—
<b>8</b>	5.84(d)	4.62(d)	3.64(dd)	4.2(m)	1.9-2.5(m)	3.84(t)	1.38(s) 1.54(s)	—	—	—
<b>9</b>	5.81(d)	4.59(t)	3.56(dd)	4.0(m)	1.7-2.5(m)	4.40(t)	1.35(s) 1.53(s)	—	3.04(s)	—
<b>10</b>	5.84(d)	4.59(d)	4.37(d)	4.93(m)	2.0(m)	3.87(m)	1.27(s) 1.50(s)	—	—	—
<b>11</b>	—	—	—	—	2.0(m)	—	—	3.38(s) 3.50(s)	—	—
<b>12</b>	—	—	—	—	2.0(m)	3.9(m)	—	3.37(s)	—	2.57(s)
<b>13</b>	4.95(m)	2.0(m) <sup>b</sup>	4.3-4.9(m)	—	2.0(m)	4.0(m)	—	3.34(s)	—	—

<sup>a</sup>Obtained with a Varian FT80A spectrometer on solutions in CDCl<sub>3</sub> (internal Me<sub>4</sub>Si). <sup>b</sup>Deoxy function at C-2. <sup>c</sup>Chemical shift for H-5. <sup>d</sup>Chemical shifts for  $\alpha$  and  $\beta$  anomers.

1,2:5,6-Di-*O*-isopropylidene- $\alpha$ -D-glucofuranose (**3**) was converted into the 3-deoxy-3-iodo-D-*allo* derivative **4** by treatment with triphenylphosphine, iodine, and imidazole<sup>5</sup>. The 5,6-*O*-isopropylidene group was removed from **4** with methanolic 0.8% sulfuric acid, to afford **5**. Treatment of the dimesylate (**6**) of **5** with sodium iodide in refluxing butanone gave 93% of the 5,6-ene **7**, the <sup>1</sup>H-n.m.r. spectrum of which accorded with the assigned structure (see Table I).

The reaction of **7** with borane in tetrahydrofuran at 0° followed by hydrogen peroxide in aqueous sodium acetate gave 73% of the alcohol **8**. The <sup>1</sup>H-n.m.r. spectrum of **8** contains signals for H-6,6' at  $\delta$  3.84 (t, *J* 6 Hz) and for H-5,5' at  $\delta$  1.9–2.5 (m). Further confirmation of the structure of **8** was obtained by its conversion into the 6-mesylate **9**. Comparison of the <sup>1</sup>H-n.m.r. spectra of **9** and **8** revealed the expected downfield shift of 0.56 p.p.m. of the signal for H-6,6' in the former.

Treatment of **8** with methanolic sodium methoxide for 8 h gave 3,6-anhydro-5-deoxy-1,2-*O*-isopropylidene-D-*xylo*-hexofuranose (**10**) in almost quantitative yield. Treatment of **10** with Amberlite IR-120 (H<sup>+</sup>) resin in refluxing methanol afforded the methyl  $\alpha,\beta$ -glycoside **11**, the <sup>1</sup>H-n.m.r. spectrum of which was not amenable to first-order analysis. Conversion of **11** into the xanthate derivative **12** was effected<sup>6</sup> by successive treatment with sodium hydride, carbon disulfide, and methyl iodide. The <sup>1</sup>H-n.m.r. spectrum of **12** was complex, although a singlet due to *S*-methyl was observed at  $\delta$  2.57. Treatment of **12** under reflux with tributyltin hydride gave the 2,5-dideoxy derivative **13**. The conversion of **13** into (1*R*,5*R*)-2,6-dioxabicyclo[3.3.0]octan-3-one (**2**, 70%) was then effected<sup>7</sup> using 3-chloroperoxybenzoic acid and boron trifluoride etherate in dichloromethane.

The structure of **2** was supported by its <sup>1</sup>H-n.m.r. spectrum, in which resonances (dt) at  $\delta$  5.09 and 4.68 were attributed to H-1 and H-5, respectively. The couplings ( $J_{1,5} = J_{1,8\alpha} = 4$ ,  $J_{1,8\beta} = 2$  Hz) for H-1 were similar to those for H-5. The signal for H-7,7' ( $\delta$  3.9) was a doublet of doublets (weak peaks were also observed around these signals), whereas those for H-4,4' and H-8,8' were multiplets at  $\delta$  2.65 and 1.8–2.5, respectively. In addition, the mass spectrum contained a peak for the molecular ion at *m/z* 128.

#### EXPERIMENTAL

*3-Deoxy-3-iodo-1,2-O-isopropylidene-5,6-di-O-mesyl- $\alpha$ -D-allofuranose* (**6**). — A solution of **4** (ref. 5) (20 g, 54 mmol) in methanol (100 mL) and aqueous 0.8% sulfuric acid (30 mL) was stored at room temperature for 18 h, then neutralised (BaCO<sub>3</sub>), and filtered, and the insoluble material was washed with methanol. The combined filtrate and washings were concentrated and co-distilled with benzene, to afford the diol **5**. To a solution of **5** in pyridine (50 mL) was added methanesulfonyl chloride (16 mL) at 0°. After stirring for 3 h at room temperature, the usual work-up gave a product which was crystallised from ethyl acetate–light petroleum, to afford **6** (20 g, 76%), m.p. 146°,  $[\alpha]_D +69^\circ$  (*c* 0.7, chloroform).

*Anal.* Calc. for  $C_{11}H_{19}O_9S_2$ : C, 27.1; H, 3.9; S, 13.2. Found: C, 27.1; H, 3.7; S, 13.1.

**3,5,6-Trideoxy-3-iodo-1,2-O-isopropylidene-D-ribo-hex-5-enofuranose (7).** — A solution of **6** (8 g, 16.4 mmol) in ethyl methyl ketone (100 mL) and sodium iodide (8 g) was heated under reflux for 12 h and then concentrated, and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed successively with aqueous sodium thiosulfate, aqueous sodium carbonate, and water, dried, and concentrated. Column chromatography (silica gel; ethyl acetate–light petroleum, 1:4) of the residue afforded **7** (4.5 g, 93%), m.p. 85°,  $[\alpha]_D^{25} +69^\circ$  (c 0.7, chloroform).

*Anal.* Calc. for  $C_9H_{13}O_3$ : C, 36.5; H, 4.4. Found: C, 36.1; H, 4.4.

**3,5-Dideoxy-3-iodo-1,2-O-isopropylidene- $\alpha$ -D-ribo-hexofuranose (8).** — To a solution of **7** (9 g, 30.4 mmol) in tetrahydrofuran (50 mL) at 0° under nitrogen was added M diborane in tetrahydrofuran (18 mL). The mixture was stored for 1.5 h at 0°, and methanol was then added followed by 3M sodium acetate (18 mL) and aqueous 30% hydrogen peroxide (18 mL). After 2 h at room temperature, the solution was concentrated, the residue was extracted with ethyl acetate, and the extract was dried and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:4) of the residue gave **8** (7 g, 73%),  $[\alpha]_D^{25} +77^\circ$  (c 0.8, chloroform).

*Anal.* Calc. for  $C_9H_{15}O_4$ : C, 34.4; H, 4.8. Found: C, 34.1; H, 4.2.

**3,6-Anhydro-5-deoxy-1,2-O-isopropylidene- $\alpha$ -D-xylo-hexofuranose (10).** — A solution of **8** (5 g, 3.18 mmol) in methanolic M sodium methoxide (50 mL) was heated under reflux for 8 h, then neutralised with Amberlite IR-120 ( $H^+$ ) resin, filtered, and concentrated. Short-column chromatography (ethyl acetate) of the residue afforded **10** (2.96 g, 100%),  $[\alpha]_D^{25} +17^\circ$  (c 1, chloroform).

*Anal.* Calc. for  $C_9H_{14}O_4$ : C, 58.1; H, 7.5. Found: C, 57.7; H, 7.1.

**Methyl 3,6-anhydro-5-deoxy- $\alpha,\beta$ -D-xylo-hexofuranoside (11).** — A mixture of **10** (2.0 g, 10.7 mmol), Amberlite IR-120 ( $H^+$ ) resin (5 g), and dry methanol (20 mL) was heated under reflux for 3 h, then filtered, and concentrated, to afford **11** (1.5 g, 87%).

*Anal.* Calc. for  $C_7H_{12}O_4$ : C, 52.5; H, 7.5. Found: C, 52.4; H, 7.5.

**Methyl 3,6-anhydro-2,5-dideoxy- $\alpha,\beta$ -D-xylo-hexofuranoside (13).** — To a solution of **11** (1.5 g, 9.3 mmol) in dry tetrahydrofuran (15 mL) under nitrogen was added sodium hydride (0.9 g, 50% dispersion in oil). After 2 h, dry carbon disulfide (1 mL) was introduced followed, after 20 min, by methyl iodide (1 mL). The solution was stirred overnight and then concentrated. Column chromatography (ethyl acetate–light petroleum, 1:4) of the residue gave the xanthate derivative **12** (1.63 g, 70%).

Compound **12** (1.63 g) was heated under reflux with tributyltin hydride in toluene (15 mL) containing  $\alpha,\alpha'$ -azobisisobutyronitrile (5 mg) for 8 h. After the usual work-up, column chromatography (ethyl acetate–light petroleum, gradient 1:10  $\rightarrow$  1:4) of the residue gave **13** (0.8 g, 85%).

*Anal.* Calc. for  $C_7H_{12}O_3$ : C, 58.3; H, 8.3. Found: C, 58.15; H, 8.0.

(1R,5R)-2,6-Dioxabicyclo[3.3.0]octan-3-one (**2**). — To a stirred solution of **13** (0.2 g, 1.38 mmol) in dry dichloromethane (3 mL) under nitrogen were added boron trifluoride etherate (0.01 mL) and 3-chloroperoxybenzoic acid (0.25 g, 1.73 mmol) successively at room temperature. After stirring for 2 h, the mixture was diluted with ether, washed successively with aqueous sodium thiosulphate, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. Column chromatography (ethyl acetate–light petroleum, 1:4) of the residue gave **2** (0.12 g, 70%),  $[\alpha]_D +62^\circ$  (c 0.9, chloroform);  $\nu_{\max}^{\text{liquid}}$  1770  $\text{cm}^{-1}$  (lactone).  $^1\text{H-N.m.r.}$  data ( $\text{CDCl}_3$ ):  $\delta$  1.8–2.5 (m, 2 H, H-8,8'), 2.68 (m, 2 H, H-4,4'), 3.93 (dd, 2 H, H-7,7'), 4.68 (dt, 1 H,  $J_{1,5}$  3.5 Hz, H-5), 5.09 (dt, 1 H, H-1). Mass spectrum:  $m/z$  128 ( $\text{M}^+$ ).

*Anal.* Calc. for  $C_6H_8O_3$ : C, 56.25; H, 6.25. Found: C, 56.1; H, 6.3.

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#### REFERENCES

- 1 M. J. AUKLAND, J. R. HANSON, P. B. HITHCOCK, AND A. H. RATCLIFFE, *J. Chem. Soc., Perkin Trans. 1*, (1985) 843–847; A. A. EBRAHIM EL-ZAYAT, N. R. FERRIGNI, T. G. MCCLOUD, A. T. MCKENZIE, S. R. BYRN, J. M. CASSADY, C. J. CHANG, AND J. L. MCLAUGHLIN, *Tetrahedron Lett.*, (1985) 955–956; D. SEEBACH, M. DUST, R. NAET, AND M. BANZIGER, *Angew. Chem., Int. Ed. Engl.*, 23 (1984) 530–531; P. AVATO, G. BIANCHI, AND F. SALAMINI, *Phytochemistry*, (1985) 1994–1997.
- 2 J. W. WESTLEY (Ed.), *Polyether Antibiotics*, Vol. 2, Dekker, New York, 1983, ch. 1; J. D. MORRISON (Ed.), *Asymmetric Synthesis*, Vol. 3, Academic Press, New York, 1984.
- 3 Y. ICHIKAWA, N. ISOBE, AND T. GOTA, *Tetrahedron Lett.*, (1984) 5049–5052; M. F. SEMMELHACK, C. BODUROW, AND M. BAUM, *ibid.*, (1984) 3171–3174; Y. TAMARU, H. HIGASHIMURA, K. NAKA, M. HOJO, AND Z. YOSHIDA, *Angew. Chem., Int. Ed. Engl.*, 24 (1985) 1045–1046.
- 4 Y. TAMARU, T. KOBAYASHI, S. KAWAMURA, A. OCHIAI, M. HOJO, AND Z. YOSHIDA, *Tetrahedron Lett.*, (1985) 3207–3210.
- 5 P. J. GAREGG AND B. SAMUELSON, *J. Chem. Soc., Perkin Trans. 1*, (1980) 2866–2869.
- 6 D. H. R. BARTON AND S. W. MCCOMBIE, *J. Chem. Soc., Perkin Trans. 1*, (1975) 1574–1585.
- 7 P. A. GRIECO, T. OGURI, AND Y. HOKOYAMA, *Tetrahedron Lett.*, (1978) 419–420.