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THE SYNTHESIS OF SOME METHYL 6-DEOXY-2-*O*-*p*-TOLYLSULPHONYL-D-*xylo*-HEXOFURANOSID-5-ULOSE DERIVATIVES AND THEIR REACTIONS WITH BASES

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ABSTRACT

Methyl 6-deoxy-2,3-di-*O*-*p*-tolylsulphonyl-β-D-*xylo*-hexofuranosid-5-ulose (**8**) was prepared from 6-deoxy-1,2:3,5-di-*O*-methylene-α-D-*xylo*-hex-5-enofuranose (**5**). On treatment with bases, compound **8** readily loses *p*-toluenesulphonic acid to give a furan derivative (**9**); with 1,5-diazabicyclo[5.4.0]undec-5-ene, it also afforded a compound which gave a mass spectrum consistent with its being 3-methoxy-6-oxo-2-oxabicyclo[2.2.1]heptan-7-ol (**10**). The analogue (**13**) of compound **8** having a methyl group in place of the ester function at C-3 did not react when treated with the heterocyclic base.

INTRODUCTION

The polyfunctionality and chirality of carbohydrates makes them attractive and, frequently, readily available starting-materials for the synthesis of enantiomerically pure, non-carbohydrate substances; although this is being exploited increasingly[1], the number of reported applications is not large. We now report attempts to synthesise functionalised cyclopentanes from carbohydrates. These studies were initiated in particular because of current intense interest in prostanoid derivatives[2], but also because many other chiral and physiologically active five-membered carbocyclic compounds occur in Nature[3].

Enantiomerically pure prostaglandin analogues based on tetrahydrofurans have been made from carbohydrate precursors by two groups of workers. Hanessian and his co-workers[4] commenced with 1,4-anhydro-D-glucitol and proceeded by way of the branched-chain compound **1**, while Lourens and Koekemoer[5] adopted a similar approach involving desulphuration of the 1-thioglycoside **2**. To our knowledge, the only synthesis of an unmodified prostanoid which utilises a carbohydrate starting-material was reported recently by Stork and Raucher[6] who ingeniously transmitted

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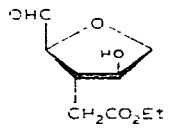
the chirality from 2,3-*O*-isopropylidene-L-erythrose into a functionalised cyclopentane, altering the tetrose appreciably prior to carbocyclic ring-closure*. It was our objective to test the possibility of bonding together 1,5-related carbon atoms of carbohydrate derivatives to give enantiomerically pure, carbocyclic compounds. Although such bonding of 1,5-disposed atoms of acyclic compounds represents a step in the biosynthesis of prostaglandins[7], the best known synthetic routes use alternative means of obtaining the required cyclopentanes.



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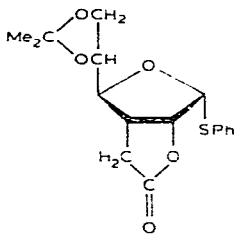

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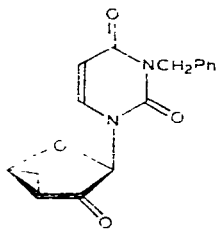
We are not aware of any previous report of the formal synthesis of five-membered carbocyclic systems from carbohydrates, although such compounds have been recognised as degradation products formed in the mass spectrometer[8] and by acid-catalysed degradation[9]. By comparison, several inositols and their derivatives have been synthesised from carbohydrates that contain a potential carbanionic centre, and a centre, five carbon atoms removed, which is susceptible to intramolecular attack by the nucleophilic carbon[10]. The literature appears to contain one reference to the synthesis from carbohydrate compounds of a cyclopropane derivative (**3**) formed by an intramolecular ring-closure[11], and one to a cyclobutane (**4**) obtained by a photochemical procedure[12].



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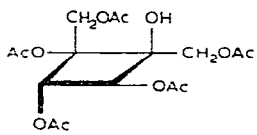

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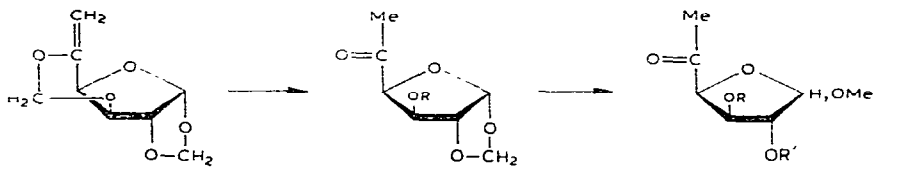
RESULTS AND DISCUSSION

With the objective of obtaining a carbanion generated from the methyl group of a 1-deoxyhexulose and using it to displace a sulphonyloxy group from C-5,

*See also: G. STORK AND T. TAKAHASHI, *J. Am. Chem. Soc.*, 99 (1977) 1275–1276.

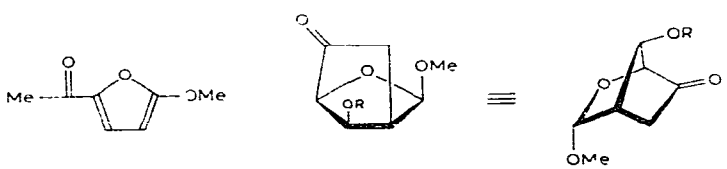
compound **8** was prepared as indicated in Scheme 1 (**5**→**6**→**7**→**8**). Partial hydrolysis of the 5-enofuranose **5** gave the ketone **6**; both **5** and **6** were smoothly methanolysed in the presence of acidic resin to a mixture of furanosides **7**, from which a crystalline ditosylate ($[\alpha]_D$ −41.5°) was obtained in 51% yield. N.m.r. spectroscopy indicated that this was a 30:70 mixture of α and β anomers; after four recrystallisations, it yielded the pure major component ($[\alpha]_D$ −99°), which was assigned the β structure (**8**) on account of its levorotatory character relative to the anomer, and its being derived from the β-furanoside which would be preponderant in an equilibrium mixture[13]. As the H-1 resonances cannot be used reliably for anomeric assignments[14], these parameters did not provide confirmation.



5 **6** R = H; **15** R = Ts; **16** R = Me **7** R = R′ = H; **8** R = R′ = Ts, β anomer; **13** R = Me, R′ = Ts

Scheme 1

When compound **8** was heated in acetonitrile with potassium carbonate, it underwent loss[15] of two molecules of *p*-toluenesulphonic acid to give the crystalline furan **9**. Likewise, treatment of **8** in dry benzene at 40° with 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) gave the furan as main product; when this reaction was carried out at 5°, as well as the furan (65% isolated), a further product (34% isolated) was obtained which gave a mass spectrum consistent with its being the 6-oxo-2-oxa-bicyclo [2.2.1]heptan-7-ol **10** formed by attack of the C-6 carbanion at C-2 and base-

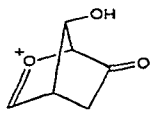


9 **10** R = H; **11** R = Ac

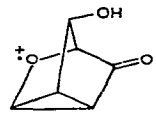
catalysed cleavage of the sulphonic ester at C-3. Such cleavages of sulphonates are known and follow nucleophilic attack at sulphur[16], but the intermediacy of a 2,3-epoxide is suggested below.

The molecular ion (*m/e* 158) and ions formed by six fragmentation paths were observed in the mass spectrum of compound **10**, and these, especially the second, third, and fourth, provide strong evidence for the assigned structure:

1. Loss of methoxyl and methanol (standard for methyl glycosides)



m/e 127



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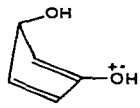
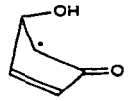
2 Loss of methyl formate (O-2, C-3) (retrodiene cleavage[17])



m/e 98



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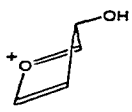
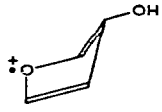
3. Loss of ketene (C-5, C-6) (retrodiene cleavage)



m/e 85



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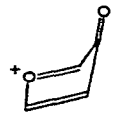

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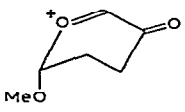
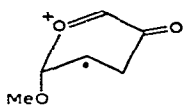
4. Loss of CHO, HCHO, and CH_2OH[18]



m/e 129



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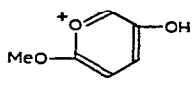

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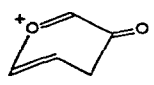

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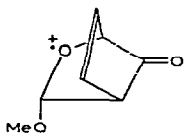
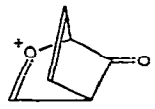
5. Loss of water



m/e 140



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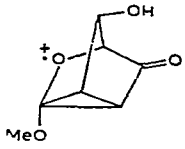
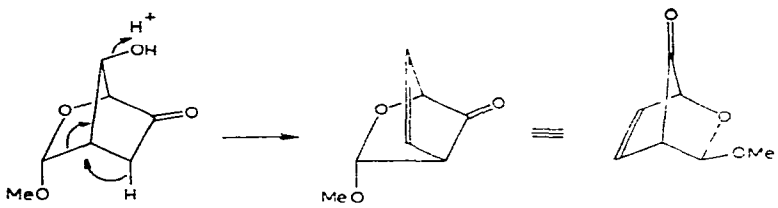
6. Loss of hydrogen



m/e 156

From the alcohol **10**, a monoacetate was obtained which did not show a molecular ion at *m/e* 200 but gave ions at 199 and 198 consequent upon loss of hydrogen. The molecular ion also gave fragments with *m/e* 140 (loss of methyl formate), 168 (loss of methanol), 127 (loss of methoxyl and ketene), and 128 (loss from the bridge position). No ion was observed for loss of water (*m/e* 182), but the ion at *m/e* 140 may have had a contribution from that derived by loss of acetic acid, and an intense ion with *m/e* 98 may then have been derived by loss of ketene. The spectrum is therefore consistent with the acetate's having structure **11**.

However, the n.m.r. spectrum obtained for compound **10** was not consistent with the assigned structure, showing resonances for eight protons two of which were vinylic. This phenomenon has not been fully investigated, but may result from a process, catalysed by acid in the deuterated chloroform used as solvent, which involved the elimination of water. The spectrum is in agreement with structure **12** formed as shown (Scheme 2).

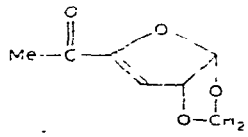


10 12

Scheme 2

In an effort to reduce formation of the furan **9**, the 3-*O*-methyl analogue (**13**) of the ditosylate **8** was investigated. Addition of methanol to the unsaturated aldehyde **14**, obtained by treatment of the tosylate **15** with DBU, was attempted following the procedure of Brown and Jones[19], but conditions that caused addition also caused degradation and this approach had to be abandoned. However, methylation of the alcohol **6** occurred readily in *N,N*-dimethylformamide at 4° with methyl iodide and silver oxide, and the crystalline methyl ether **16** was isolated in high yield. Under conditions in which **6** underwent methanolysis to give the glycosides **7**, **16** reacted only partially and gave mixed products. However, extension of the reaction time gave a mixture from which the syrupy methyl furanosides were obtained after column chromatography in 17% yield, and tosylation of the furanosides gave a crystalline ester, isolated in 26% yield, which is assigned the β configuration (**13**) on the basis of its optical rotation. Surprisingly, **13** was unaffected by DBU under conditions in which the ditosylate **8** gave the furan **9** and the product assigned structure **10**. Vicinally related disulphonates can give epoxides under basic conditions[20], and it is conceivable that the ditosylate **8** was converted into the corresponding 2,3-anhydro-D-*ribo*-product which was then attacked at C-2 by the carbanion generated at C-6. Such transannular openings of related epoxides are known[21]. In this event, the configuration at position 7

(alicyclic numbering) of compounds **10** and **11** would be the opposite of that represented.



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For the series here reported, it is concluded that elimination reactions compete too efficiently with intramolecular carbocyclic ring-closure to make these compounds suitable synthetic precursors of cyclopentanes, but that the evidence obtained relating to compound **10** establishes that functionalised cyclopentanes can be prepared from carbohydrate derivatives.

TABLE 1

N.M.R. PARAMLTERS[a]

Compound	*Chemical shifts* (δ)					*Others*
	H-1	*H-2*	*H-3*	*H-4*	*H-6*	
6	6.02	4.42	4.48	4.52	2.23	4.98 (CH_2) 3.24 (OH)
15	6.05	4.68	5.02	4.44	2.12	4.98 (CH_2) 2.45 (Me) 7.30,7.68 (Ar)
16	6.00	4.44	4.02	4.44	2.18	4.98 (CH_2) 3.31 (Me)
14	6.01	5.39	5.69	—	2.30	4.68,5.11 (CH_2)
8	———	4.90–5.03	——→	4.58	2.16	3.40 (OMe) 2.46 (CMe) 7.2–7.9 (Ar)
13	———	4.0–4.9	——→		2.18	2.40 (CMe) 3.20 (OMe) 3.26 (OMe) 7.2–7.7 (Ar)
9	—	—	7.15	5.30	2.30	3.90 (OCH_3)

[a]*Coupling constants:* Compounds **6**, **15**, and **16**: $J_{1,2}$ 4, $J_{2,3}$ 0, $J_{3,4}$ 4 Hz; **14**: $J_{1,2}$ 4, $J_{2,3}$ 2.5, $J_{\text{methylene}}$ 0 Hz; **8** and **13**: $J_{2,3}$ 0, $J_{3,4}$ 5 Hz; and **9**: $J_{3,4}$ 4 Hz.

EXPERIMENTAL

*6-Deoxy-1,2-O-methylene-α-*D-xylo-*hexofuranos-5-ulose* (**6**). — A solution of 6-deoxy-1,2:3,5-di-*O*-methylene-α-D-*xylo*-hex-5-enofuranose[22] (**5**, 2.5 g) in ethanol

(25 ml, 95%) was heated under reflux with Amberlite IR-120(H^+) resin (10 g), with vigorous stirring, for 1 h. Removal of the resin and solvent gave the crystalline ketone **6** (2.2 g, 95%) which, when recrystallised from ethanol, had m.p. 102–103°, $[\alpha]_D$ −107° (*c* 1, chloroform). See Table I for n.m.r. data.

Anal. Calc. for $C_7H_{10}O_5$: C, 48.3; H, 5.8. Found: C, 48.6; H, 6.1.

The 2,4-dinitrophenylhydrazone of **6**, obtained in 69% yield by use of 2,4-dinitrophenylhydrazine in the presence of orthophosphoric acid, had m.p. 212–214°, $[\alpha]_D$ −54° (*c* 0.8, ethanol).

Anal. Calc. for $C_{13}H_{14}N_4O_8$: C, 44.1; H, 4.0; N, 15.8. Found: C, 43.9; H, 4.1; N, 15.8.

*Methyl 6-deoxy-α,β-*D-xylo-*hexofuranosid-5-ulose* (**7**). — A solution of 6-deoxy-1,2:3,5-di-*O*-methylene-α-D-*xylo*-hex-5-enofuranose (**5**, 8 g) in methanol (50 ml) was treated with Amberlite IR-120(H^+) resin (25 g) for 20 h at 70°. Removal of the resin and solvent gave a syrup (6.5 g), which was fractionated on a column of silica gel with chloroform–ethanol (9:1). The first fraction to be eluted afforded **6** (2.5 g, 33%), and the second a mixture of the anomeric methyl furanosides **7** (1.2 g, 24% of converted diacetal), $[\alpha]_D$ −18° (*c* 1.4, chloroform). Methanolysis of compound **6** could be effected similarly.

*Methyl 6-deoxy-2,3-di-*O-p-*tolylsulphonyl-β-*D-xylo-*hexofuranosid-5-ulose* (**8**). — The methyl glycosides (**7**, 1.5 g) were sulphonylated with tosyl chloride (4.0 g, 2.5 mol. equiv.) in pyridine (7 ml) in the usual way. The crystalline product was recrystallised from ethanol to give a ditosylate (2.1 g, 47%), m.p. 124–125°, $[\alpha]_D$ −41.5° (*c* 2.7, chloroform). The n.m.r. spectrum indicated the presence of an αβ-mixture [δ 3.42 (MeO-1β, 70%) and 3.30 (MeO-1α, 30%)]. Four further crystallisations from ethanol gave the pure β anomer, m.p. 131°, $[\alpha]_D$ −99° (*c* 1, chloroform). See Table I for n.m.r. data.

Anal. Calc. for $C_{21}H_{24}O_9S_2$: C, 52.1; H, 5.0; S, 13.2. Found: C, 52.4; H, 5.3; S, 13.15.

*6-Deoxy-3-*O-*methyl-1,2-*O-*methylene-α-*D-xylo-*hexofuranos-5-ulose* (**16**). — The alcohol (**6**, 2 g) was dissolved in *N*,*N*-dimethylformamide (2 ml) at 4°, cold methyl iodide (20 ml) and silver oxide (3.5 g) were added, and the mixture was stirred for 18 h at the same temperature. Removal of the solids and solvent gave a syrup which crystallised from ethanol to give **16** (1.8 g, 83%), m.p. 89.5–90°, $[\alpha]_D$ −92° (*c* 0.4, chloroform). See Table I for n.m.r. data.

Anal. Calc. for $C_8H_{12}O_5$: C, 51.5; H, 6.4. Found: C, 51.5; H, 6.1.

*Methyl 6-deoxy-3-*O-*methyl-2-*O-p-*tolylsulphonyl-*D-xylo-*hexofuranosid-5-ulose* (**13**). — A solution of **16** (0.4 g) in methanol (10 ml) was heated under reflux for 32 h in the presence of Amberlite IR-120(H^+) resin (10 g) to give mixed products which were resolved on a column of silica gel. A fraction (0.06 g, 17%), $[\alpha]_D$ −16.2° (chloroform), was shown by n.m.r. spectroscopy to be a mixture of the corresponding methyl glycosides; from this, a crystalline tosylate was obtained in 26% yield after preparative t.l.c. Crystallised from ethanol, it had m.p. 111–112°, $[\alpha]_D$ −104° (*c* 1.5, chloroform). The n.m.r. data were consistent with its being the 2-tosylate, but

indicated that it was an ~1:2 mixture of α and β anomers. See Table I for n.m.r. data.

Anal. Calc. for $C_{15}H_{20}O_7S$: C, 52.3; H, 5.8; S, 9.3. Found: C, 52.4; H, 5.9; S, 9.2.

Treatment of the ditosylate **8** *and the monotosylate* **13** *with base.* — A solution of **8** (0.5 g) in dry benzene (5 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (0.15 g, 1.1 mol. equiv.) for 5 min at 40°. The excess of base was removed with Amberlite IR-120(H^+) resin (2 g); removal of the solvent left a syrup which was fractionated on a column of silica gel with light petroleum–ethyl acetate (3:2). The major product (65 mg, 45%) was crystallised from light petroleum (b.p. 60–66°)–ethyl acetate (2:1) to give 2-acetyl-5-methoxyfuran (**9**), m.p. 48–49°, $[\alpha]_D$ 0° (*c* 0.5, chloroform); λ_{max}^{EtOH} 300 nm (ε 19,500). See Table I for n.m.r. data.

Anal. Calc. for $C_7H_8O_3$: C, 60.0; H, 5.7. Found: C, 60.3; H, 5.4.

When the ditosylate **8** (0.4 g) was treated in dry benzene (5 ml) with the base (0.14 g) for 5 min at 5°, two products were formed and the starting material had reacted completely. Treatment as before, with fractionation of the products by preparative t.l.c., gave the furan **9** (75 mg, 65%) and a syrupy compound (45 mg, 34%), $[\alpha]_D$ +4° (*c* 1, chloroform); λ_{max} 296 nm (ε 21); ν_{max} 1657 cm^{-1}; δ ($CDCl_3$): 5.55 (t, 2 H, *J* 1.5 Hz), 3.50 (m, 1 H), 3.35 (m, OMe+H), and 1.93 (t, 1 H, *J* 1.5 Hz); which was identified by mass spectrometry (see Discussion) as 3-methoxy-6-oxo-2-oxabicyclo[2.2.1]heptan-7-ol (**10**).

The derived monoacetate (**11**) had $[\alpha]_D$ +25° (*c* 0.8, chloroform).

Anal. Calc. for $C_9H_{12}O_5$: C, 54.0; H, 6.0. Found: C, 54.0; H, 5.6.

When the monotosylate **13** (20 mg) was treated with the base (8 mg) in dry benzene for 10 min at 40°, the compound obtained after the usual processing was identified (t.l.c., i.r.) as starting material.

*6-Deoxy-1,2-*O*-methylene-3-*O*-*p*-tolylsulphonyl-α-*D*-xylo-hexofuranos-5-ulose* (**15**). — The hydroxyketone **6** (2 g) in dry pyridine (5 ml) was treated with tosyl chloride (2.2 g) in pyridine (10 ml) for 15 h at 5°. The mixture was poured onto ice, and the resulting solid was recrystallised from ethanol to give **15** (3.4 g, 90%), m.p. 120–121°, $[\alpha]_D$ −62° (*c* 2, chloroform). See Table I for n.m.r. data.

Anal. Calc. for $C_{14}H_{16}O_7S$: C, 51.2; H, 4.9; S, 9.8. Found: C, 50.9; H, 5.0; S, 9.9.

*3,6-Dideoxy-1,2-*O*-methylene-α-*D*-glycero-hex-3-enofuranos-5-ulose* (**14**). — The tosylate **15** (2 g) in dry benzene (15 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (1.0 g, 1.1 mol. equiv.). After 5 min at 40°, the excess of base was neutralised with acidic resin, and the solvent was removed to leave a residue which crystallised from ethanol to give **14** (0.8 g, 84%), m.p. 105°, $[\alpha]_D$ +23° (*c* 1, chloroform). See Table I for n.m.r. data.

Anal. Calc. for $C_7H_8O_4$: C, 53.85; H, 5.1. Found: C, 54.0; H, 5.2.

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