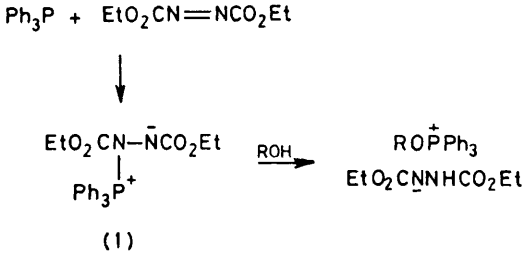
Epoxidations with Triphenylphosphine and Diethyl Azodicarboxylate. Part 1. Synthesis of Methyl 3,4-Anhydro-D-tagatofuranosides †

By **R. D. Guthrie,* Ian D. Jenkins, and Ryohei Yamasaki,** School of Science, Griffith University, Nathan, Brisbane, Queensland, 4111, Australia
Brian W. Skelton and **Allan H. White,** Department of Physical and Inorganic Chemistry, University of Western Australia, Nedlands, Perth, Western Australia, 6009, Australia

Treatment of methyl β-D-fructofuranoside (6) with triphenylphosphine and diethyl azodicarboxylate in dimethylformamide gives a high yield of methyl 3,4-anhydro-β-D-tagatofuranoside (5); no blocking of the hydroxy-groups at C-1 and C-6 is necessary. The structure of the product was confirmed by an *X*-ray structural study of its 1,6-bis-*O*-(*p*-tolylsulphonyl) derivative and by an unambiguous synthesis. A similar reaction of methyl α-D-fructofuranoside yielded the 3,4-anhydro-α-D-tagatofuranoside. The reaction mechanism is discussed.

EPOXIDES (oxirans) have found wide use as synthetic intermediates in organic synthesis, especially in carbohydrate chemistry.[1] Many methods of preparation have been devised, the most common in polyhydroxy-systems being from a vicinal *trans*-hydroxy-sulphonyloxy-grouping, the synthesis of which requires suitable blocking-group strategies.

In 1976, Mitsunobu *et al.*[2] reported that treatment of *trans*-cyclohexane-1,2-diol in ether with the betaine (1) derived from triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) (Scheme 1) gave cyclohexene

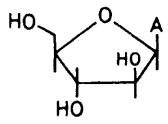


(1)

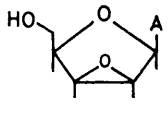
SCHEME 1

oxide in good yield. This was essentially a modification of the much used replacement (with inversion) of a hydroxy-group by an external nucleophile mediated by the TPP–DEAD system. The reaction was used by Loibner and Zbiral,[3] who reported that treatment of the diaxial cholestane-2β,3α-diol with the TPP–DEAD reagent gave a mixture of the two possible epoxides (2α,3α and 2β,3β). In a *trans*-vicinal diol, one hydroxy-group is converted into the oxotriphenylphosphonium ion and this excellent leaving group is displaced by the other hydroxy-group.

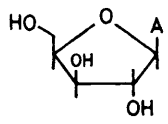
A useful extension of the reaction was the synthesis of a variety of oxygen heterocycles from α,ω-diols,[4] but more important was its use in nucleoside chemistry by Mengel and Bartke.[5] The *arabino*-nucleoside (2) when treated with the TPP–DEAD reagent in dioxan gave the *lyxo*-epoxide (3) in high yield: no blocking of the C-5′ hydroxy-group was required, nor was any coincident formation of a 2′,5′-anhydro-derivative or of a cyclonucleoside reported. The *xylo*-nucleoside (4) also gave the same epoxide (3) in good yield. We were particularly interested in Mengel and Bartke's results, as the ketose epoxide (5) was one of the target molecules in our search [6] for possible inhibitors of invertase (β-D-fructofuranosidase: EC.3.2.1.26).



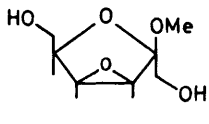
(2)



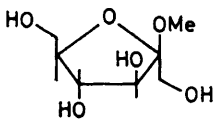
(3)



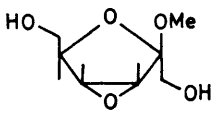
(4)



(5) R = H
(8) R = Ts
(9) R = Ac



(6)



(7)

A = adenine Ts = *p*-tolylsulphonyl

Methyl β-D-fructofuranoside (6) has a clear stereochemical resemblance to the *arabino*-nucleoside (2), so it was of interest to see if it would yield the required epoxide (5). Our target molecule (5) was of interest not only in its own right, but also because, by analogy with the 2,3-anhydro-pentofuranosides,[1] it should be opened at C-4 by nucleophiles to yield derivatives with the *fructo*-configuration. It would also provide a route to other ketose derivatives such as the epimines, olefins, *etc.*

Methyl β-D-fructofuranoside (6), when treated with TPP–DEAD in refluxing dioxan, yielded a 3,4-epoxide (X) and minor products. The oxiran structure was clearly demonstrated by its ^{13}C n.m.r. spectrum. It was

† Preliminary communication: R. D. Guthrie, I. D. Jenkins, and R. Yamasaki, *J. Chem. Soc., Chem. Commun.*, 1980, 784.

reasoned that, because of the nature of the displacement, a solvent such as *NN*-dimethylformamide (DMF) might be better than tetrahydrofuran (THF).[7]* At 95 °C both methyl α- and β-D-fructofuranosides reacted in DMF to give (Y) and (X), respectively, in about 30% yield. The low yields were apparently due to the formation of 1,2-diethoxycarbonylhydrazino-derivatives of the oxirans, as indicated by ^{1}H and ^{13}C n.m.r. (*cf.* ref. 8). Initial reaction of either methyl α- or β-fructofuranoside at 0 °C and then at room temperature for 1—2 h in DMF gave only one product, by t.l.c., in both cases; a high yield of the epoxides (X) or (Y) could be obtained after chromatography.

TABLE 1

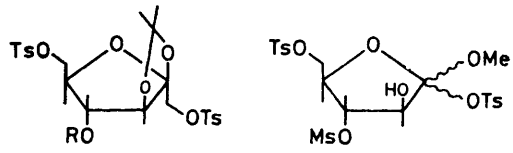
^{13}C N.m.r. data [$(CD_3)_2CO$] [a]

	C-1	C-2	C-3	C-4	C-5	C-6	OMe
(6)	62.0	105.0	79.4	77.4	83.6	64.3	49.5
α-Anomer of (6)	60.4	108.7	82.0	78.3	84.1	62.3	48.9
(5) [also (X)]	61.4	105.8	57.3 [b]	55.1 [b]	78.1	65.6	52.1
α-Anomer of (5) [also (Y)]	60.0	106.3	57.8 [b]	56.0 [b]	78.8	61.4	49.1
(8)	68.9	104.0	56.7 [b]	54.5 [b]	75.2	71.1	52.4
α-Anomer of (8)	65.5	104.5	57.6 [b]	55.9 [b]	76.2	69.0	49.7
(9)	63.1	104.6	57.0 [b]	54.9 [b]	75.4	66.3	52.4
α-Anomer of (9)	60.2	104.6	58.0 [b]	56.0 [b]	75.9	62.9	49.6

[a] Sugar carbons and methoxy-groups only. [b] Assignments may be interchanged.

The ^{1}H n.m.r. spectrum of (X) did not permit a confident differentiation between the possible *tagato*- (5) and *psico*- (7) configurations. Fortunately the 1,6-bis-*O*-(toluene-*p*-sulphonate) (8) was crystalline and an *X*-ray crystal structure determination was carried out (see below). This showed clearly that (X) was methyl 3,4-anydro-β-D-tagatofuranoside (5).

The ^{1}H n.m.r. spectrum of (Y) was equally useless for a configurational determination and none of the derivatives prepared was crystalline. A synthetic route was then attempted that would yield both the anomers of methyl 3,4-anydro-1,6-bis-*O*-(*p*-tolylsulphonyl)-D-tagatofuranoside. 2,3-*O*-Isopropylidene-1,6-bis-*O*-(*p*-tolylsulphonyl)-β-D-fructofuranose (10), described by Morgan and Reichstein,[9] was converted into its 4-*O*-methylsulphonyl derivative (11), which, when treated under methanolysis conditions, gave a mixture of the anomers of methyl 4-*O*-methylsulphonyl-1,6-bis-*O*-(*p*-tolylsulphonyl)-*p*-D-fructofuranoside (12).† This mixture when treated with methanolic sodium methoxide under mild conditions gave, after separation, the previously prepared β-anomer (8) and also a compound identical in all respects with the bis-*O*-(*p*-tolylsulphonyl) derivative of (Y). Thus (Y) is methyl 3,4-anhydro-α-D-tagatofuranoside.

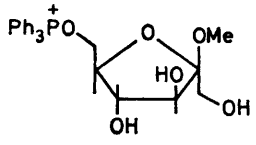


(10) R = H
(11) R = Ms
(12)

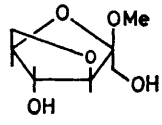
Ms = methylsulphonyl

Thus, a facile synthesis of methyl 3,4-anhydro-α- and -β-D-tagatofuranosides is readily available in one step, *with no blocking groups*, from the reaction of TPP–DEAD with the appropriate methyl D-fructofuranoside in DMF. These ketoside epoxides should have considerable potential in the chemistry of the ketoses. In preliminary experiments we have shown that the β-epoxide (5) opens at C-4 with nucleophiles to yield products with the *fructo*-configuration.

The generally accepted mechanism of formation of the oxyphosphonium intermediates is shown in Scheme 1. That blocking groups are not necessary in these syntheses is worthy of comment. The work of Grynkiewicz[10] on methyl α-D-glucopyranoside and of Mitsunobu *et al.*[7,11] on nucleoside phosphorylation has demonstrated clearly that, as expected, primary phosphonium salts are formed preferentially over secondary ones. In the case of methyl D-fructofuranosides it is known that the primary C(1)-OH suffers substantial steric hindrance, but the C(6)-O$\overset{+}{P}Ph_3$ (13) salt should be formed readily and might have been expected to lead to the 3,6-anhydro-fructofuranoside derivative (14). Such a bicyclic ring system is known in the anhydro-derivatives of sucrose (*i.e.* a 3′,6′-anhydro-sucrose).[12]



(13)



(14)

Mengel and Bartke[5] have demonstrated that the reaction of adenosine with TPP–DEAD in dioxan gives a 2′,3′-phosphorane ‡ which we would envisage as being formed by the initial formation of a C(5′)-phosphonium salt, (15), a shift to form a 3′,5′-phosphorane (16), and then further migration *via* a transient 3′-phosphonium salt (17) to form the 2′,3′-cyclic phosphorane (18).

Mengel and Bartke's results[5] with the *arabino*-nucleoside (2) and our results with the fructofuranosides suggest that the initially formed primary phosphonium salt could be in equilibrium with a secondary phosphonium salt *via* a six-membered cyclic phosphorane [*cf.* (15) ⟶ (17)] and that displacement of the secondary phosphonium salt by an adjacent secondary hydroxy-group to give the oxiran is faster than displacement of the primary phosphonium salt to give the larger anhydro-ring.

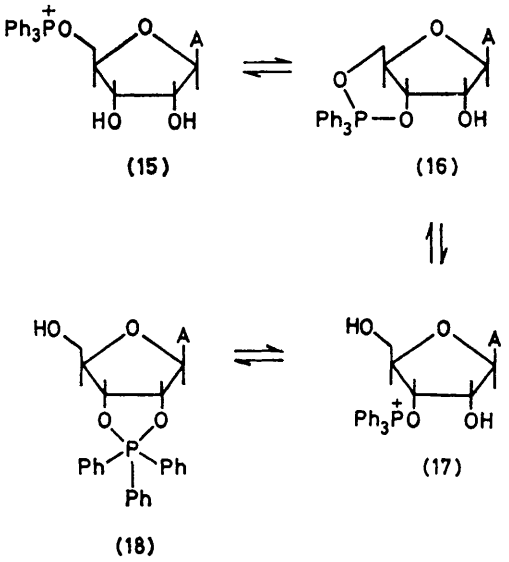
However, formation[5] of the oxiran from the *xylo*-

* It has been shown that phosphorylations mediated by the TPP–DEAD reagent are more efficient in hexamethylphosphoric triamide than in boiling dioxan (ref. 7).

† In an effort to increase yields the 1,6-bis-*O*-(trimethylphenyl)sulphonyl analogue of (10) was prepared; however the yield proved to be no better.

‡ *Note added in proof*: This structural assignment has been disputed: Mitsunobu *et al.* (*Bull. Chem. Soc. Jpn.*, 1980, **53**, 3670) claim a 3′,5′-phosphorane structure.

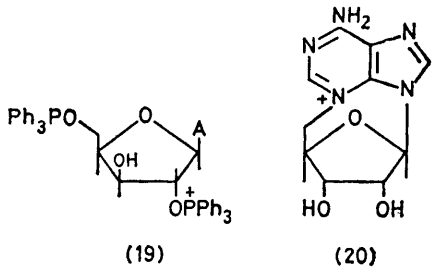
nucleoside (4) could not occur by such a process and the only possible pathway would appear to be *via* a 2′,5′-bisphosphonium salt (19), from which oxiran formation occurred in preference to either oxetan or cyclonucleoside formation. In view of this, a 3,5-bisphosphonium salt could be a possible intermediate for formation of the oxiran from (6) [similarly from (2)].



SCHEME 2

The German workers'[5] results with adenosine should be compared with those of Mitsunobu *et al.*[7] who treated adenosine with TPP–DEAD in hexamethylphosphoric triamide or DMF in the presence of dibenzyl hydrogen-phosphate and obtained the N^3,5′-cycloadenosine salt (20) in high yield. Presumably dibenzyl hydrogen-phosphate is not sufficiently nucleophilic to compete with displacement of the C(5′)-phosphonium salt (15) by the purine N^3.

The reaction of the 4-*O*-methylsulphonyl-1,6-bis-*O*-(*p*-tolylsulphonyl) compound (12) with alkali described



above is of interest here because in this compound there is the potential for both 3,6-anhydro- and 3,4-oxiran formation, but only the latter was formed.

During the later stages of our work, two papers have appeared on the use of the TPP–DEAD reagent system (though not in DMF) for the formation of epoxides in aldopyranosyl systems.[13]

STRUCTURAL COMMENTARY

The unit cell contents comprise discrete molecules of (8) [see (21) and Figures], a single molecule comprising the asymmetric unit. This study appears to be the first structural determination of a furanoid epoxide.

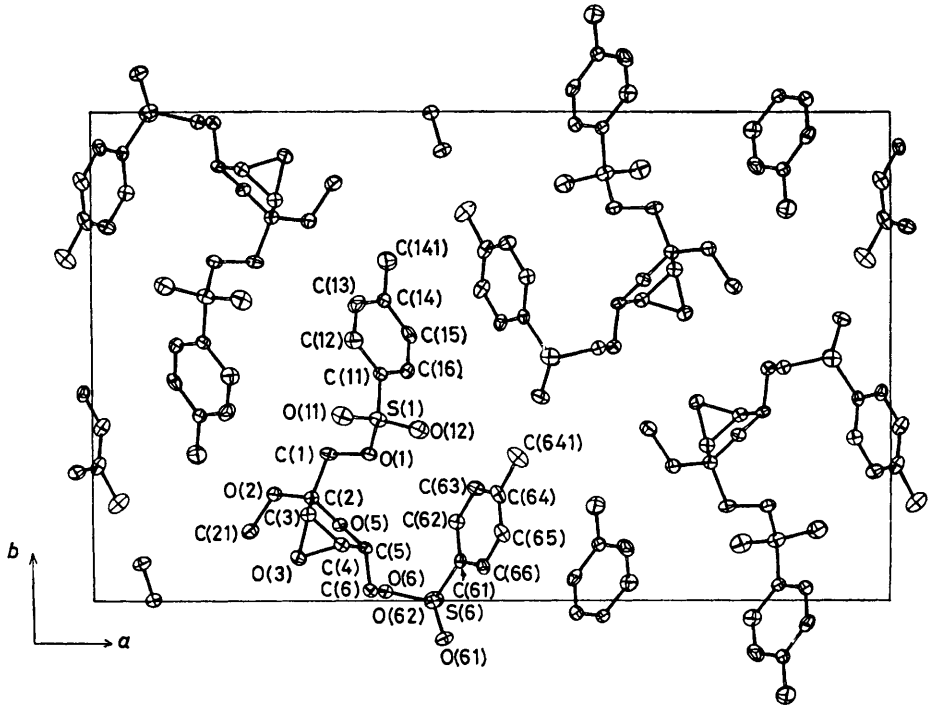
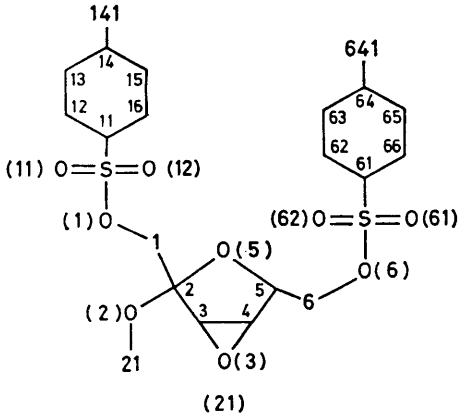


FIGURE 1 Unit cell contents for (8) projected down *c*, showing carbon atom numbering and 20% thermal ellipsoids for the non-hydrogen atoms

Within the furanose ring, C(2)—C(5) define a reasonable plane; atom deviations are given in Table 2. The furan ring is in the ^{O}E-conformation with the ring oxygen only slightly out-of-the-plane of the C(2)—C(5) ring, but, perhaps surprisingly, on the *same* side of the sugar ring as the epoxide oxygen (the β-face). This is probably to



(21)

minimise the interaction with O(1) which is situated over the furanose ring, producing a close contact of 2.819(6) Å between O(1) and O(5). Other close contacts are found between O(3) and H(6B) and H(21B) [2.69(7) and 2.59(9) Å, respectively] (see Experimental section); although

TABLE 2

Least squares planes for compound (21) [a]

	Sugar ring [b]	Phenyl ring 1	Phenyl ring 6
10^4p	6 284	7 027	8 255
10^4q	7 111	3 550	−1 617
10^4r	3 153	6 167	−5 408
δ	6.865	9.720	9.871
σ	0.007	0.006	0.010
δ C(1)	1.35	0.00	−0.01
δ O(1)	2.37	−1.22	
δ C(2)	0.00	0.00	−0.01
δ O(2)	−0.89		
δ C(3)	−0.01	0.00	0.01
δ O(3)	−1.20		
δ C(4)	0.01	0.00	−0.01
δ C(5)	0.00	0.00	0.00
δ O(5)	−0.27		
δ C(6)	−1.06	0.00	0.01
δ O(6)	−1.20		−1.60
δ C(41)		0.01	−0.07
δ S		0.04	−0.14
δ O(1, 61)		−0.17	−0.01
δ O(1, 62)		1.13	0.66

[a] Least-squares planes through the three ring-systems are given in the form $pX + qY + rZ = s$, the orthogonal R.H. Å frame being defined by $X = ax$, $Y = by$, $Z = cz$. Defining atom-deviations for each plane are italicized; atom deviations, δ, and σ (defining atoms) are in Å. [b] Dihedral angle to epoxide ring 73.6°.

free rotation should be possible in an isolated molecule, consideration of the environments of C(2) and C(5) (Figure 2) suggests that, in spite of the presence of these possible repulsions, this disposition may represent the minimum energy arrangement for these substituents. The epoxide-ring geometry is normal; within the five-membered ring, the angle at the oxygen O(5) is greater [110.6(5)°] than

TABLE 3

Atomic co-ordinates of (21)

Atom	x	y	z
O(1)	0.346 1(2)	0.304 1(3)	0.180 7(9)
C(1)	0.295 5(3)	0.304 8(5)	0.061 2(14)
H(1A)	0.275(3)	0.345(4)	0.139(12)
H(1B)	0.298(2)	0.326(4)	−0.103(13)
C(2)	0.274 0(3)	0.214 3(4)	0.062 8(11)
O(2)	0.227 6(2)	0.221 9(3)	−0.067 3(8)
C(21)	0.196 7(4)	0.145 0(6)	−0.097 6(18)
H(21A)	0.221(3)	0.096(5)	−0.136(15)
H(21B)	0.179(3)	0.135(6)	0.049(16)
H(21C)	0.170(3)	0.168(5)	0.199(16)
C(3)	0.269 9(3)	0.179 4(4)	0.305 9(12)
H(3)	0.259(2)	0.215(4)	0.431(11)
O(3)	0.257 1(2)	0.089 9(3)	0.312 3(8)
C(4)	0.311 4(3)	0.116 9(5)	0.333 7(12)
H(4)	0.331(2)	0.115(4)	0.485(12)
C(5)	0.340 5(3)	0.110 6(4)	0.110 8(12)
H(5)	0.371(2)	0.143(4)	0.121(13)
O(5)	0.309 4(2)	0.158 0(3)	−0.053 9(8)
C(6)	0.346 6(3)	0.021 7(5)	0.023 1(13)
H(6A)	0.367(2)	−0.006(4)	0.127(11)
H(6B)	0.315(3)	−0.001(4)	0.013(13)
O(6)	0.365 8(2)	0.019 9(3)	−0.213 6(7)
O(1)-*p*-tolylsulphonyl			
S(1)	0.357 14(8)	0.375 22(12)	0.366 40(35)
O(11)	0.312 9(2)	0.382 4(4)	0.518 8(9)
O(12)	0.408 2(2)	0.353 7(3)	0.452 9(11)
C(11)	0.360 5(3)	0.467 7(4)	0.197 4(12)
C(12)	0.327 7(3)	0.536 5(5)	0.249 3(15)
H(12)	0.305(3)	0.524(5)	0.402(14)
C(13)	0.331 8(3)	0.609 3(5)	0.117 8(17)
H(13)	0.308(3)	0.655(5)	0.153(14)
C(14)	0.365 7(3)	0.616 8(5)	−0.063 3(14)
C(141)	0.369 8(3)	0.696 8(6)	−0.207 1(18)
H(141A)	0.336(—)	0.708(—)	−0.274(—)
H(141B)	0.378(—)	0.744(—)	−0.106(—)
H(141C)	0.394(—)	0.703(—)	−0.334(—)
C(15)	0.396 8(3)	0.547 7(5)	−0.112 9(15)
H(15)	0.420(3)	0.549(5)	−0.227(13)
C(16)	0.394 5(3)	0.474 0(5)	−0.013 9(15)
H(16)	0.416(3)	0.424(4)	−0.018(13)
O(6)-*p*-tolylsulphonyl			
S(6)	0.425 09(7)	−0.002 22(12)	−0.266 11(31)
O(61)	0.439 0(2)	−0.078 7(3)	−0.151 6(9)
O(62)	0.426 8(2)	0.002 5(3)	−0.512 0(8)
C(61)	0.459 7(2)	0.083 4(4)	−0.145 5(12)
C(62)	0.455 3(3)	0.164 0(5)	−0.240 5(14)
H(62)	0.436(3)	0.167(4)	−0.391(12)
C(63)	0.479 8(3)	0.233 0(5)	−0.138 3(14)
H(63)	0.472(3)	0.287(4)	−0.204(13)
C(64)	0.507 3(3)	0.220 4(5)	0.065 2(13)
C(641)	0.532 2(4)	0.297 2(6)	0.187 4(17)
H(641A)	0.555(—)	0.326(—)	0.091(—)
H(641B)	0.504(—)	0.337(—)	0.233(—)
H(641C)	0.551(—)	0.290(—)	0.335(—)
C(65)	0.512 2(3)	0.140 0(6)	0.157 8(14)
H(65)	0.530(3)	0.141(5)	0.288(13)
C(66)	0.488 8(3)	0.071 1(5)	0.055 8(14)
H(66)	0.492(2)	0.013(4)	0.110(12)

the angles at the epoxide junction [107.3(6) and 108.1(6)°], and at C(2) and C(5) [105.0(5) and 105.4(5)]. At C(2) and C(5), the angles C(3)–C(2)–O(2) [118.1(6)°] and C(4)–C(5)–C(6) [114.1(6)°] are larger than the remainder and perhaps are indicative of the presence of some repulsive interaction between the substituent atoms and O(3). Within the *p*-tolylsulphonyl groups, we find an angular distortion of the geometry about the sulphur atom, the angle between the non-bonded sulphonyl oxygen atoms being greater than the remainder, in accordance with the expectations of electron-pair repulsion theory. A

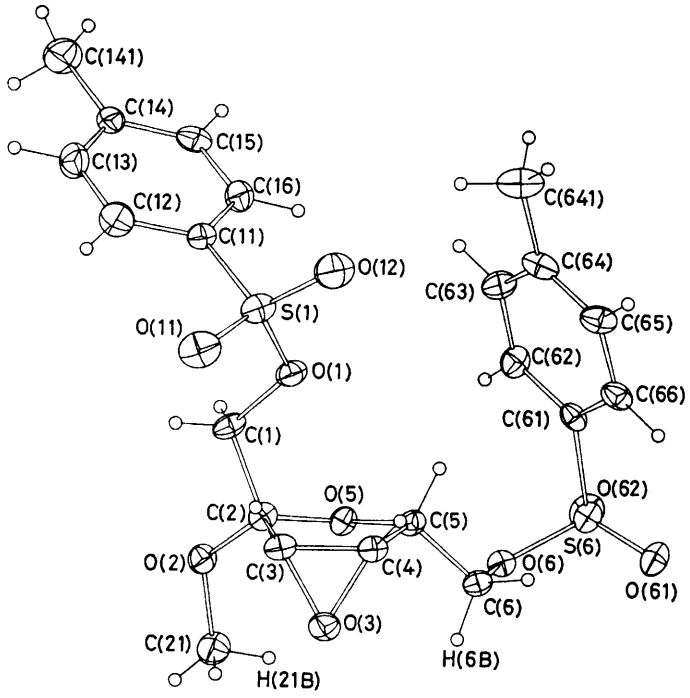


FIGURE 2 A single molecule. Hydrogen atoms are shown with arbitrary radii of 0.1 Å

curious and consistent disparity is found however, between O(n)–S(n)–O(n1 and n2) for the two groups, the angles being 109.6(3) and 109.6(3)°, and 103.4(3) and 102.2(3)°, respectively. For each of the two groups n = 1 and 6, we find O(n1) lies close to the plane of the associated phenyl ring and has a close contact [2.32(7) and 2.49(6) Å] to the nearby *ortho*-hydrogen atom; presumably this disposition of the sulphonyl group represents energy minimization relative to the phenyl ring.

TABLE 4

Molecular non-hydrogen geometry—sugar residue of compound (21)

Atoms	Distance (Å)	Atoms	Distance (Å)
C(1)–O(1)	1.46(1)	C(6)–O(6)	1.45(1)
C(1)–C(2)	1.52(1)	C(5)–C(6)	1.49(1)
C(2)–O(5)	1.43(1)	C(5)–O(5)	1.44(1)
C(2)–C(3)	1.51(1)	C(4)–C(5)	1.49(1)
C(3)–O(3)	1.44(1)	C(4)–O(3)	1.45(1)
C(3)–C(4)	1.45(1)		
C(2)–O(2)	1.40(1)		
O(2)–C(21)	1.45(1)		

Atoms	Angles (°)	Atoms	Angles (°)
S(1)–O(1)–C(1)	118.4(4)	S(6)–O(6)–C(6)	120.4(4)
O(1)–C(1)–C(2)	107.9(6)	O(6)–C(6)–C(5)	111.9(6)
C(1)–C(2)–C(3)	111.6(6)	C(4)–C(5)–C(6)	114.1(6)
C(1)–C(2)–O(5)	110.4(5)	C(6)–C(5)–O(5)	108.4(6)
C(3)–C(2)–O(5)	105.0(5)	C(4)–C(5)–O(5)	105.4(5)
C(2)–C(3)–C(4)	107.3(6)	C(3)–C(4)–C(5)	108.1(6)
C(2)–C(3)–O(3)	113.1(6)	C(5)–C(4)–O(3)	112.3(6)
O(3)–C(3)–C(4)	60.1(4)	O(3)–C(4)–C(3)	59.7(4)
C(3)–O(3)–C(4)	60.2(5)		
C(2)–O(5)–C(5)	110.6(5)		
C(2)–O(2)–C(21)	116.7(6)		
C(1)–C(2)–O(2)	102.7(5)		
C(3)–C(2)–O(2)	118.1(6)		
O(5)–C(2)–O(2)	109.1(5)		

TABLE 5

p-Tolylsulphonyl non-hydrogen geometries of compound (21)

Atoms	Distance (Å) [a]
S(n)–O(n)	1.571(5), 1.573(5)
S(n)–O(n1)	1.430(6), 1.414(5)
S(n)–O(n2)	1.429(6), 1.421(5)
S(n)–C(n1)	1.749(7), 1.749(7)
C(n1)–C(n2)	1.39(1), 1.38(1)
C(n1)–C(n6)	1.37(1), 1.39(1)
C(n2)–C(n3)	1.37(1), 1.38(1)
C(n3)–C(n4)	1.36(1), 1.38(1)
C(n4)–C(n5)	1.37(1), 1.37(1)
C(n4)–C(n41)	1.51(1), 1.53(1)
C(n5)–C(n6)	1.37(1), 1.37(1)

Atoms	Angles (°) [b]
O(n)–S(n)–O(n1)	109.6(3), 109.6(3)
O(n)–S(n)–O(n2)	103.4(3), 102.2(3)
O(n)–S(n)–C(n1)	102.5(3), 103.5(3)
O(n1)–S(n)–O(n2)	121.0(4), 120.2(3)
O(n1)–S(n)–C(n1)	108.4(3), 110.0(3)
O(n2)–S(n)–C(n1)	110.3(3), 109.9(3)
S(n)–C(n1)–C(n2)	119.5(6), 120.2(5)
S(n)–C(n1)–C(n6)	121.4(5), 119.5(5)
C(n2)–C(n1)–C(n6)	119.1(7), 120.1(7)
C(n1)–C(n2)–C(n3)	118.5(8), 120.7(7)
C(n2)–C(n3)–C(n4)	123.0(8), 118.5(7)
C(n3)–C(n4)–C(n5)	117.2(7), 120.6(7)
C(n3)–C(n4)–C(n41)	122.6(7), 119.1(7)
C(n5)–C(n4)–C(n41)	120.2(7), 120.3(7)
C(n4)–C(n5)–C(n6)	122.1(8), 121.2(7)
C(n5)–C(n6)–C(n1)	120.0(7), 118.8(7)

EXPERIMENTAL

M.p.s were determined with a Tottoli apparatus and are uncorrected. I.r. spectra were obtained with a Perkin-Elmer 377 spectrophotometer. Optical rotations were

measured on a Perkin-Elmer 241 polarimeter at 25 °C. ^{1}H N.m.r. spectra were recorded with either a Varian EM-360 or a JEOL PX-100 spectrometer and ^{13}C n.m.r. spectra with a Brucker HX-90 spectrometer at 22.3 MHz (Table 1). Silica gel GF_{254} was used for t.l.c. and Merck Kieselgel 60 (70—230 mesh) was used for column chromatography. Flash chromatography was conducted as described in the literature.[14]

Acetylation was carried out with acetic anhydride in pyridine for 24 h at room temperature and *p*-tolylsulphonylation with *p*-tolylsulphonyl chloride in pyridine. Organic solutions were dried with magnesium sulphate (anhydrous) and evaporations were performed under reduced pressure at a bath temperature below 50 °C. DMF was dried over molecular sieves (4 Å) after distillation over phosphorus pentoxide under reduced pressure. Micro-analyses were performed by the Department of Chemistry, Queensland University, Australia.

Methyl Fructosides.—Glycosidation of D-fructose (10 g) was carried out using 2.9% methanolic sulphuric acid (v/v, 350 ml) at room temperature for 30 min. After neutralization with Amberlite IR-45 resin (CO_3^{2-}), the mixture was passed through a short column of the same resin, and the column was washed with methanol (1.5 l). The eluate and washings were combined and evaporated to give a syrup which was chromatographed on a column of Dowex-1(OH) using water at a flow rate of 120 ml h^{-1} to give methyl β-D-fructopyranoside (1.1 g, 10.2%), methyl β-D-fructofuranoside (6) (4.65 g, 43.1%), and methyl α-D-fructofuranoside (4.43 g, 41.1%).

Methyl 3,4-*Anhydro*-β-D-*tagatofuranoside* (5).—(a) To a chilled solution of methyl β-D-fructofuranoside (6) (4.65 g) and TPP (15.8 g, 2.5 mol equiv.) in dry DMF (50 ml), DEAD (9.9 ml, 2.5 mol equiv.). was added in drops, with stirring (10 min). After being warmed to room temperature and stirred for 2 h, the mixture was evaporated under reduced pressure to give a thick syrup which was purified by flash chromatography [5 × 15 cm, acetone–dichloromethane (1 : 2)] to give the β-epoxide (5) as a syrup (3.54 g, 84%), $[\alpha]_D$ −28.2° (*c* 1.0, methanol).

Acetylation of compound (5) followed by flash chromatography [acetone–hexane (1 : 3)] gave *methyl* 1,6-*bis*-O-(*acetyl*)-3,4-*anhydro*-β-D-*tagatofuranoside* (9) (89%) as an oil, $[\alpha]_D$ −34.2° (*c* 1.0, chloroform); ^{1}H n.m.r. ([$^2H_6$]-benzene) δ 1.73—1.78 (each 3 H, both s, OAc), 3.47 (3 H, s, OMe), 3.39 (1 H, d, $J_{3,4}$ 2.9 Hz, 3-H), 3.29 (1 H, dd, $J_{4,5}$ 1.1 Hz, 4-H), 3.97 (1 H, m, $J_{5,6'}$ 3.6, 2.0 Hz, 5-H), 4.36 (1 H, m, 6-H), 4.29 (1 H, m, 1-H), 4.25 (1 H, m, $J_{6,6'}$ 11.3 Hz, 6′-H), and 4.02 (1 H, m, $J_{1,1'}$ 11.6 Hz, 1′-H) (Found: C, 51.1; H, 6.4. $C_{11}H_{16}O_7$ requires C, 50.8; H, 6.2%).

(b) Methyl β-D-fructofuranoside (6) (50 mg) was treated with TPP (101 mg, 1.5 mol equiv.) and DEAD (48 μl, 1.5 mol equiv.) in dioxan (4 ml) for 16 h at 75 °C. T.l.c. showed the presence of *ca*. half of the starting material. The mixture was refluxed for 3 h after a further mol equiv. of each of the reagents had been added. The mixture was worked up (described above) to give compound (5) (27 mg, 59%).

(c) Compound (6) (4.5 g) was treated with TPP (12.4 g, 2 mol equiv.) and DEAD (9.3 ml, 2 mol equiv.) in dry DMF (40 ml) at 95 °C for 20 min, work-up as described above gave compound (5) (1.2 g, 29%).

Methyl 3,4-*Anhydro*-1,6-*bis*-O-(p-*tolylsulphonyl*)-β-D-*tagatofuranoside* (8).—Compound (5) (200 mg) was esterified for 1 h at 0 °C and for 24 h at room temperature. The mixture was treated with water and extracted with chloroform. Evaporation gave a crystalline residue, which was recrystallized from chloroform–hexane, to give *the product* (8) as needles (467 mg, 85%), m.p. 110.5—111 °C, $[\alpha]_D$ −13.8° (*c* 1.0, chloroform); ^{1}H n.m.r. ([$^2H_6$]benzene) δ 1.84 (each 3 H, both s, ArMe), 2.97 (1 H, dd, $J_{4,5}$ 0.9 Hz, 4-H), 3.13 (3 H, s, OMe), 3.18 (1 H, d, $J_{3,4}$ 3.0 Hz, 3-H), 3.77—4.09 (5 H, 1, 1′-, 5-, 6-, 6′-H), and 6.62—6.80 and 7.58—7.73 (8 H, ArH) (Found: C, 51.8; H, 5.0; S, 13.1. $C_{21}H_{24}O_9S_2$ requires C, 52.1; H, 5.0; S, 13.2%).

Methyl 3,4-*Anhydro*-α-D-*tagatofuranoside*.—(a) Methyl α-D-fructofuranoside (350 mg) was treated with TPP (1.2 g, 2.5 mol equiv.) and DEAD (884 μl, 2.5 mol equiv.) in dry DMF (4 ml) for 2 h at room temperature, as described for the β-anomer. The mixture was evaporated under reduced pressure to give a syrup which was purified by flash chromatography [2 × 15 cm, dichloromethane–acetone (2 : 1)] to give the α-*epoxide* as a syrup (264 mg, 83%), $[\alpha]_D$ +49.6° (*c* 1.0, methanol) characterised by acetylation (followed by flash chromatography) to give *methyl* 1,6-*bis*-O-(*acetyl*)-3,4-*anhydro*-α-D-*tagatofuranoside* as an oil (89%), $[\alpha]_D$ +47.8° (*c* 1.0, chloroform); ^{1}H n.m.r. ([$^2H_6$]benzene) δ 1.67, 1.69 (each 3 H, both s, OAc), 3.11 (3 H, s, OMe), 3.18 (1 H, dd, $J_{4,5}$ 0.75 Hz, 4-H), 3.53 (1 H, d, $J_{3,4}$ 2.5 Hz, 3-H), 3.82 (1 H, m, 5-H), and 3.90—4.51 (4 H, 1-, 1′, 6-, 6′-H) (Found: C, 50.9; H, 6.4. $C_{11}H_{16}O_7$ requires C, 50.8; H, 6.2%).

(b) Methyl α-D-fructofuranoside (2.33 g) was treated with TPP (6.3 g, 2 mol equiv.) and DEAD (4.0 ml, 2 mol equiv.) in dry DMF (27 ml) at 95 °C for 20 min. Flash chromatography gave a syrup which appeared to be a single product by t.l.c. [ethyl acetate–methanol (9 : 1)]. Acetylation followed by chromatography on silica gel [2 × 40 cm, acetone–hexane (1 : 4)] gave the bis-*O*-(acetyl)-epoxide (870 mg, 28%) and two other components A (310 mg), R_F 0.35 and B (532 mg), R_F 0.29 [acetone–hexane (1 : 2)].

^{13}C N.m.r. spectroscopy showed that both components A and B were epoxides, but with bis(ethoxycarbonyl)hydrazine groups, confirmed by ^{1}H n.m.r. [bis(ethoxycarbonyl)] and i.r. (NH). Although the compounds were not further investigated, the data obtained suggested that component A was the 6-(1,2-diethoxycarbonyl)hydrazino-derivative (bonded *via* N), and that component B was the 1,6-bis-hydrazino-derivative.

Methyl 3,4-*Anhydro*-1,6-*bis*-O-(p-*tolylsulphonyl*)-α-D-*tagatofuranoside*.—Esterification of methyl 3,4-anhydro-α-D-tagatofuranoside (200 mg) in a similar manner to that described for the β-anomer, followed by flash chromatography [2 × 15 cm, acetone–hexane (1 : 3)], gave the *product* as a syrup, $[\alpha]_D$ +10.8° (*c* 1.0, chloroform); ^{1}H n.m.r. (100 MHz, [$^2H_6$]benzene) δ 1.84, 1.87 (each 3 H, both s, ArMe), 2.97 (3 H, s, OMe_3), 2.92 (1 H, d, 4-H), 3.36 (1 H, d, $J_{3,4}$ 2.4 Hz, 3-H), 3.75 (1 H, m, 5-H), 3.81—4.12 (4 H, 1-, 1′-, 6-, 6′-H), and 6.63—6.73 and 7.62—7.72 (8 H, ArH) (Found: C, 52.1; H, 5.3; S, 12.9. $C_{21}H_{24}O_9S_2$ requires C, 52.1; H, 5.0; S, 13.2%).

2,3-O-*Isopropylidene*-5-O-*methylsulphonyl*-1,6-*bis*-O-(p-*tolylsulphonyl*)-β-D-*fructofuranose* (11).—Treatment of 1,2-*O*-isopropylidene-1,6-bis-*O*-(*p*-tolylsulphonyl)-β-D-fructofuranose (3.0 g) with methylsulphonyl chloride (1.2 ml) in dry pyridine (30 ml) at 0 °C for 1 h, and then overnight at room temperature, followed by chromatography on silica [2.5 × 40 cm, acetone–hexane (1 : 3)], afforded the 4-O-*mesylate* (11) (2.97 g, 86%), as a syrup, $[\alpha]_D$ +19.8° (*c* 1.0, chloroform); ^{1}H n.m.r. (60 MHz, $CDCl_3$) δ 1.27, 1.35 (each 3 H, both s, isopropylidene), 2.41 (6 H, s, ArMe), 3.10 (3 H,

s, OSO_2Me), 4.0—4.43 (5 H, 1-, 5-, 6-, 6′-H), 4.72 (1 H, s, 4-H), and 4.95 (1 H, (3 H), d, $J_{3,4}$ 2.5 Hz) (Found: C, 47.9; H, 5.3. $C_{24}H_{30}O_{12}S_3$ requires C, 47.5; H, 5.0%).

Methyl 4-O-*Methylsulphonyl*-1,6-*bis*-O-(p-*tolylsulphonyl*)-*fructofuranosides* (12), *and their Reactions with Alkali*.—A solution of compound (11) (1.7 g) in 1M methanolic sulphuric acid (25 ml) was refluxed for 12 h under a stream of dry nitrogen. The mixture was neutralized with concentrated ammonia and then diluted with chloroform (100 ml). The organic solution was washed with water and evaporated to give a syrup, (12).

The dried syrup (1.2 g) was treated with 1M sodium methoxide (2.9 ml) in dry methanol (20 ml) at room temperature for 10 min. The mixture was neutralized with IRA-20 resin (H^+ form), filtered, and evaporated to give a syrup which was chromatographed on silica [1.5 × 30 cm, acetone–hexane (1 : 3)] to give methyl 3,4-anhydro-1,6-bis-*O*-(*p*-tolylsulphonyl)-β-D-tagatofuranoside (8) (372 mg, 26%) and the α-anomer (314 mg, 22%), respectively. I.r. and ^1H n.m.r. spectra for both anomers were identical with those of authentic compounds.

2,3-O-*Isopropylidene*-1,6-*bis*-O-(*trimethylphenyl*)*sulphonyl*-β-D-*fructofuranose*.*—This compound was prepared in a manner similar to that described for the bis-*O*-(*p*-tolylsulphonyl) analogue (10).[9] The *required product* had m.p. 170—171 °C (recrystallized from ethanol), $[\alpha]_D$ +22.5° (*c* 2.09, chloroform); ^1H n.m.r. (60 MHz, $CDCl_3$) δ 1.30 (6 H, s, CMe_2), 2.30 (6 H, s, *p*-ArMe), 2.62 (12 H, s, *o*-ArMe), 4.00—4.45 (7 H, m, 1-, 1′-, 4-, 5-, 6-, 6′-H and OH), 4.55 (1 H, s, 3-H), and 6.95 (4 H, s, ArH) (Found: C, 55.4, H, 6.15; S, 10.8. $C_{27}H_{36}O_{10}S_2$ requires C, 55.5; H, 6.2; S, 11.0%).

The product was characterized as its 4-O-*acetyl derivative*, m.p. 114—115.5 °C (from methanol), $[\alpha]_D$ +24.0° (*c* 1.0, dichloromethane) (Found: C, 55.15; H, 6.05; S, 10.5. $C_{29}H_{38}O_{11}S_2$ requires C, 55.6; H, 6.1; S, 10.2%) and as its 4-O-*methylsulphonyl derivative*, m.p. 111—112 °C (from methanol), $[\alpha]_D$ +22.0° (*c* 1.5, chloroform) (Found: C, 50.6; H, 5.95; S, 15.0. $C_{28}H_{38}O_{12}S_3$ requires C, 50.7; H, 5.8; S, 14.5%).

Crystal Data for Compound (8).—$C_{21}H_{24}O_9S_2$, M = 484.6, orthorhombic, space group $P2_12_12_1$ (D_2^4, No. 19), a = 25.36(2), b = 15.68(1), c = 5.770(4) Å, U = 2 294(3) Å^3, D_m = 1.40(1), D_c = 1.40 g cm^{-3}, Z = 4, $F(000)$ = 1 016. Monochromatic Mo-K_α radiation, λ = 0.710 69 Å, μ(Mo) = 2.8 cm^{-1}, specimen size: 0.3 × 0.3 × 0.4 mm, T = 295(1) K.

Structural Determination of Compound (8).—A unique data set was measured within the limit $2\theta_{max.} < 45°$ by a conventional 2θ/θ scan using a Syntex $P2_1$ four-circle diffractometer, yielding 2 364 independent reflections, 1 241 of which had $I > 3\sigma(I)$ and were considered ' observed ' and used in the least-squares refinement, without correction of absorption, after the solution by direct methods.

Refinement was basically by 9 × 9 block-diagonal least-squares, but with hydrogen atom parameters, where refined, included in the block of the parent carbon-atom. Positional co-ordinates of the hydrogen atom were refined for all cases except those of the tolyl methyl-groups; the latter were included as invariants at constrained tetrahedral estimates ' improved ' from those obtained from difference maps. U_H was set at 1.5 $\bar{U}_{ii}$ (parent C, methyl H); and 1.25 $\bar{U}_{ii}$ (parent C, others). Anisotropic thermal parameters were refined for the non-hydrogen atoms. Refinement converged at residuals R,R' S 0.042, 0.048, and 1.3, respectively. The chirality of the molecule is based on the fructose configuration; it was considered that in the present case the relatively poor quality of the data did not justify any serious attempt to establish the chirality independently from the relatively minor f'' terms of the atoms concerned. Neutral atom-scattering-factors were employed throughout;[15] C, O, S were corrected for anomalous dispersion (f', f'').[16] Computation was carried out using the X-RAY 76 program system [17] implemented on a Perkin-Elmer 8/32 computer by S. R. Hall. Non-hydrogen atom-numbering is pseudo-systematic [see (21)]; hydrogen atom-numbering follows that of the parent carbon, distinguished as A, B, C where needful. Results are given in the Figures and Tables. Tables of structure-factor amplitudes, thermal parameters, and hydrogen-atom geometries are available in Supplementary Publications No. SUP 23028 (14 pp.).†

We gratefully acknowledge support of the *X*-ray part of this work by a grant from the Australian Research Grants Committee.

[0/1848 *Received*, 2*nd December*, 1980]

* These preparations were carried out by J. J. Waters.

† See Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 1*, 1980, Index issue.

REFERENCES

[1] N. R. Williams, *Adv. Carbohydr. Chem.*, 1970, **25**, 109.
[2] O. Mitsunobu, J. Kimura, K. Ihzumi, and N. Yanagida, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 510.
[3] H. Loibner and E. Zbiral, *Helv. Chim. Acta*, 1977, **60**, 41.
[4] J. T. Carlock and M. P. Mack, *Tetrahedron Lett.*, 1978, 5153.
[5] R. Mengel and M. Bartke, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 679.
[6] R. D. Guthrie, I. D. Jenkins, P. J. Rogers, W. F. Sum, J. J. Watters, and R. Yamasaki, *Carbohydr. Res.*, 1979, **75**, C1.
[7] J. Kimura, Y. Fujisawa, T. Yoshizawa, K. Fukuda, and O. Mitsunobu, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1191.
[8] G. Grynkiewicz, J. Jurczak, and A. Zamojski, *Bull. Acad. Pol. Sci.*, 1976, **24**, 83; G. Grynkiewicz, *ibid*, 1978, **26**, 537.
[9] W. T. J. Morgan and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 1023.
[10] G. Grynkiewicz, *Pol. J. Chem.*, 1979, **53**, 2501.
[11] O. Mitsunobu, K. Kato, and J. Kimura, *J. Am. Chem. Soc.*, 1969, **91**, 6510.
[12] R. Khan, *Adv. Carbohydr. Chem.*, 1976, **33**, 235.
[13] H. H. Brandstetter and E. Zbiral, *Helv. Chim. Acta*, 1980, **63**, 327; E. Mark, E. Zbiral, and H. H. Brandstetter, *Monatsh. Chem.*, 1980, **111**, 289.
[14] W. C. Still, M. Khan and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
[15] D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, 1968, **24**, 321; R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.
[16] D. T. Cromer and D. Liberman, *J. Chem. Phys.*, 1970, **53**, 1891.
[17] ' The X-Ray System—Version of March, 1976,' Technical Report TR-446, Computer Science Center, University of Maryland, U.S.A.