Epoxidation using Triphenylphosphine–Diethyl Azodicarboxylate: Synthesis of Methyl 3,4-Anhydro-α- and -β-D-tagatofuranosides

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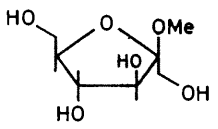
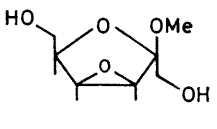
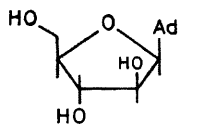
Summary Facile syntheses of the title compounds have been achieved by the one-step reaction of methyl α- or β-D-fructofuranoside with triphenylphosphine and diethyl azodicarboxylate in dimethylformamide, no blocking groups were necessary

As part of our studies on the mechanism of invertase,[1] methyl β-D-fructofuranoside (**1**) derivatives modified at C-3 and/or C-4 were required. The most ready access to such compounds would be *via* the unknown 3,4-epoxides (oxiranes). For our purposes the *tagato*-epoxide (**2**) was the most desirable, as the predictable[2] opening at C-4 would yield products with the fructose stereochemistry.

Recently, Mengel and Bartke[3] have described the use of the triphenylphosphine (TPP)–diethyl azodicarboxylate (DEAD) system[4] for the synthesis of nucleoside 2′,3′-epoxides. Thus, the *arabino*-nucleoside (**3**) on treatment with TPP–DEAD in dioxan at 70 °C for 50 min gave a high yield of the epoxy-nucleoside (**4**). Most noteworthy was that the 5′-CH_2OH group did not need protection during the epoxidation. The epoxide (**4**) is presumably formed stereospecifically *via* formation of the 3′-oxyphosphonium intermediate ($ROP\overset{+}{P}Ph_3$) on the less hindered α-face.


(1)


(2)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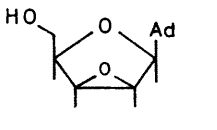
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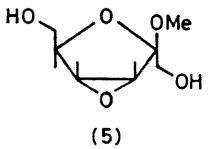
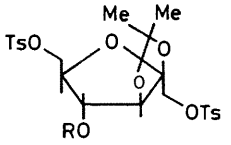

(5)

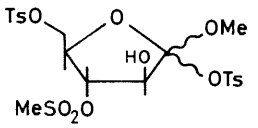
The stereochemistry of (**1**) bears a striking resemblance to that of (**3**), though it does have an extra hydroxymethyl group (on the α-face). Treatment of (**1**) with TPP–DEAD under the conditions used by Mengel[3] yielded a 3,4-epoxide (X) in good yield, most clearly demonstrated by the marked upfield shift (≃20 p.p.m.) of signals due to C-3 and C-4 in the ^{13}C n.m.r. spectrum, relative to their position in (**1**).

Since the epoxidation takes place by a nucleophilic displacement it was reasoned that it might be facilitated by a solvent such as dimethylformamide (DMF). Indeed the latter led to epoxidation in high yield at room temperature with no detectable side products. Reaction of methyl α-D-fructofuranoside with TPP–DEAD in DMF also gave a 3,4-epoxide (Y) in high yield.

Conclusive differentiation between the two possible structures for (X), *i.e.* (**2**) or (**5**) was not possible by ^1H n.m.r. spectroscopy, so an *X*-ray structural determination was carried out on the crystalline 1,6-di-*O*-toluenesulphonyl derivative of (X): this demonstrated conclusively that epoxide (X) had the *tagato*-configuration (**2**).[5]

Independent proof of the structures of (X) and (Y) was obtained by their synthesis by an unambiguous route. **2,3**-*O*-Isopropylidene-1,6-di-*O*-toluenesulphonyl-β-D-fructofuranose (**6**) (readily prepared from D-fructose)[6] was converted into its 4-*O*-methanesulphonyl derivative (**7**), followed by treatment with methanolic sulphuric acid, to give a mixture of anomers of methyl 4-*O*-methanesulphonyl-1,6-di-*O*-toluenesulphonyl-D-fructofuranoside (**8**). Very mild treatment of this mixture with methanolic sodium methoxide yielded a mixture of epoxides which was separated by chromatography and shown to be identical with the 1,6-di-*O*-toluenesulphonyl derivatives of (X) and (Y). Both epoxides must therefore have the *tagato*-configuration.


(6) R = H
(7) R = $MeSO_2$


(8) (α,β-mixture)

Ts = *p*-$MeC_6H_4SO_2$

Thus, methyl β-D-fructofuranoside (**1**) on treatment with TPP (2·5 equiv.)–DEAD (2·5 equiv.) in DMF at 0 °C and then at room temperature over 2 h gave methyl 3,4-anhydro-β-D-tagatofuranoside (**2**)† in 80% yield (after chromatography), a syrup, $[\alpha]_D^{25}$ −28·2° (*c* 1, MeOH); ^{13}C n.m.r. [$(CD_3)_2CO$] δ 105·8 (C-2), 78·1 (C-5), 65·6, 61·4 (C-1, C-6), 55·1, 57·3 (C-3, C-4), and 52·1 (OCH_3) p.p.m. characterised as its 1,6-di-*O*-toluenesulphonyl derivative, m.p. 110·5—111 °C, $[\alpha]_D^{25}$ −13·8° (*c* 1, $CHCl_3$).

Methyl 3,4-anhydro-α-D tagatofuranoside, a syrup, had $[\alpha]_D^{25}$ +49·6° (*c* 1, MeOH); ^{13}C n.m.r. [$(CD_3)_2CO$] 106·3 (C-2), 78·8 (C-5), 61·4, 59·7 (C-1, C-6), 57·8, 55·9 (C-3, C-4), and 49·1 (OCH_3), p.p.m., characterised as its 1,6-di-*O*-tosyl derivative, a syrup, $[\alpha]_D^{25}$ + 10·8° (*c* 1, $CHCl_3$).

Compound (**2**) and its α-anomer represent the first synthetically useful epoxy-derivatives in the ketohexose series.[7] Consideration of the wide use of epoxide intermediates in synthesis in the aldohexose series[2] suggests that these new epoxides have considerable potential synthetic utility.

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† All new compounds had satisfactory elemental analyses.

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[2] N. R. Williams, *Adv. Carbohydr. Chem.*, 1970, **25**, 109.
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[4] O. Mitsunobu, M. Wada, and T. Sano, *J. Am. Chem. Soc.*, 1972, **94**, 679.
[5] R. D. Guthrie, I. D. Jenkins, B. W. Skelton, A. H. White, and R. Yamasaki, *J. Chem. Soc., Perkin Trans.* 1, submitted for publication.
[6] W. T. J. Morgan and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 1023.
[7] 2,3-Anhydro-β-D-fructofuranose has been reported (M. Sarel-Imber and J. Leibowitz, *J. Org. Chem.*, 1959, **24**, 1897) but it is of little synthetic utility.