Chiral Syntheses of (*R*)-Spirobi-1,4-dioxan and Related Compounds from D-Fructose

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Syntheses of (*R*)-1,4,7,10-tetraoxaspiro[5.5]undecane (spirobi-1,4-dioxan), (*R*)-1,4,7-trioxa-10-thiaspiro[5.5]-undecane, and (*R*)-1,4,7-trioxa-10-azaspiro[5.5]undecane from 2′-chloroethyl β-D-fructopyranoside are reported, in which the chirality of the spiro-ring junction is defined by the configuration of the anomeric carbon atom of the glycoside.

Several relatively complex natural products (*e.g.* diosgenin) contain an acetal carbon atom at a spiro-ring-junction but there have been recent reports[1,2] of the isolation of several comparatively simple alkyl-1,7-dioxaspiro[5.5]undecanes, alkyl-1,7-dioxaspiro[4.5]decanes, and alkyl-1,6-dioxaspiro-[4.4]nonanes as insect pheromones. One particularly interesting compound is 1,7-dioxaspiro[5.5]undecane (2,2′-spirobitetrahydropyran) (**1**) which functions as a sex pheromone of the olive fruit fly.[2] Although no stereochemical information is available for (**1**) it may occur as a single enantiomer and therefore the development of a chiral synthesis of this and related compounds is desirable since none of the synthetic studies thus far has succeeded in controlling the stereochemistry at the spiro-carbon atom.[3] In this communication we describe chiral syntheses of some related spiro-compounds from D-fructose.

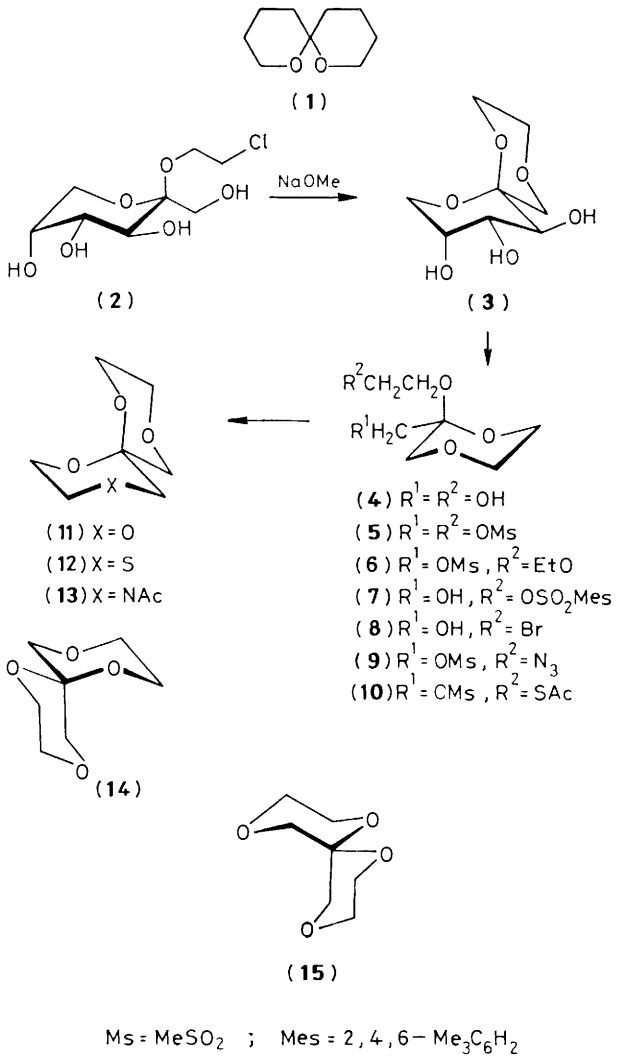
Reaction of D-fructose with 2-chloroethanol in the presence of an acid catalyst afforded an 80—90% yield of the highly crystalline 2′-chloroethyl β-D-fructopyranoside (**2**)† (m.p. 145—147 °C, $[\alpha]_D$ −148°, water). When the glycoside was treated with base, internal cyclisation occurred to give the crystalline 1,2′-spiroanhydride (**3**) (m.p. 131.5—132.5 °C, $[\alpha]_D$ −143°, methanol) in quantitative yield. The anhydride (**3**) consumed 3 equiv. of sodium metaperiodate to give a dialdehyde which was immediately reduced with boro-hydride to give the liquid diol (**4**) in 80—85% overall yield from (**3**). Initial attempts to cyclise the diol (**4**) to spirobi-1,4-dioxan (**11**) by conversion into the dimesyl ester (**5**) and ring closure with potassium hydroxide in ethanol were unsuccessful and led to (2*R*)-2-mesyloxymethyl-2-(2′-ethoxy-

† The glycoside (**2**) could also be prepared from sucrose in *ca.* 60% yield. It was first prepared by Miss. P. L. Cheong and will be the subject of a forthcoming paper. All compounds described in this paper had a satisfactory elemental analysis and spectroscopic data in accord with the structure proposed.

ethoxy)-1,4-dioxan (**6**) as the only product. Consequently, we introduced a leaving group at one position only, leaving the other hydroxy-group free, by selective mesitylene-sulphonylation which gave the monoester (**7**) in 60% yield. Alternatively, reaction of the diol (**4**) with carbon tetrabromide and triphenylphosphine[4] gave the 2-bromoethoxy-derivative (**8**) in 15—20% yield. When either (**7**) or (**8**) was treated with sodium methoxide a smooth cyclisation took place to give (*R*)-spirobi-1,4-dioxan (1,4,7,10-tetraoxaspiro[5.5]undecane) (**11**) in 91% yield as a crystalline solid (m.p. 84—85 °C, $[\alpha]_D$ −68.9°, chloroform).

The bidioxan (**11**) is capable of existing in three different chair–chair conformations, which differ from one another in that the acetal oxygens of each ring may be either axial or equatorial with respect to the other ring. Thus (**11**) is the axial–axial conformer and (**15**) is the equatorial–equatorial form and consequently in each case both of the rings are equivalent. In the case of (**14**) one oxygen is axial whilst the other is equatorial and the two rings are therefore not equivalent. Although the ^{1}H n.m.r. spectrum of the bidioxan was not entirely first-order (Figure 1) it is clear that the compound must be symmetrical since only six resonances can be located. The lowest field resonance at 4.1 p.p.m. was clearly due to an axial hydrogen (*J ca.* 12, 10, and 3 Hz) which had been deshielded by a 1,3-diaxial interaction with another oxygen atom. This clearly indicates that, in chloroform, the axial–axial conformer (**11**) is the favoured form in which the anomeric effect would be most favourable.[5]

The dimethanesulphonate (**5**) was then utilised for the synthesis of thia- and aza-analogues of (**11**). When (**5**) was allowed to react with sodium azide in *N*,*N*-dimethylformamide the 2-azidoethoxy-derivative (**9**) was formed, which upon sequential reduction and base-induced cyclisation afforded morpholine-2-spiro-1,4-dioxan which was isolated as the *N*-acetyl derivative (**13**) (m.p. 112—113.5 °C, $[\alpha]_D$ −59.9°, chloroform), the ^{1}H n.m.r. spectrum of which



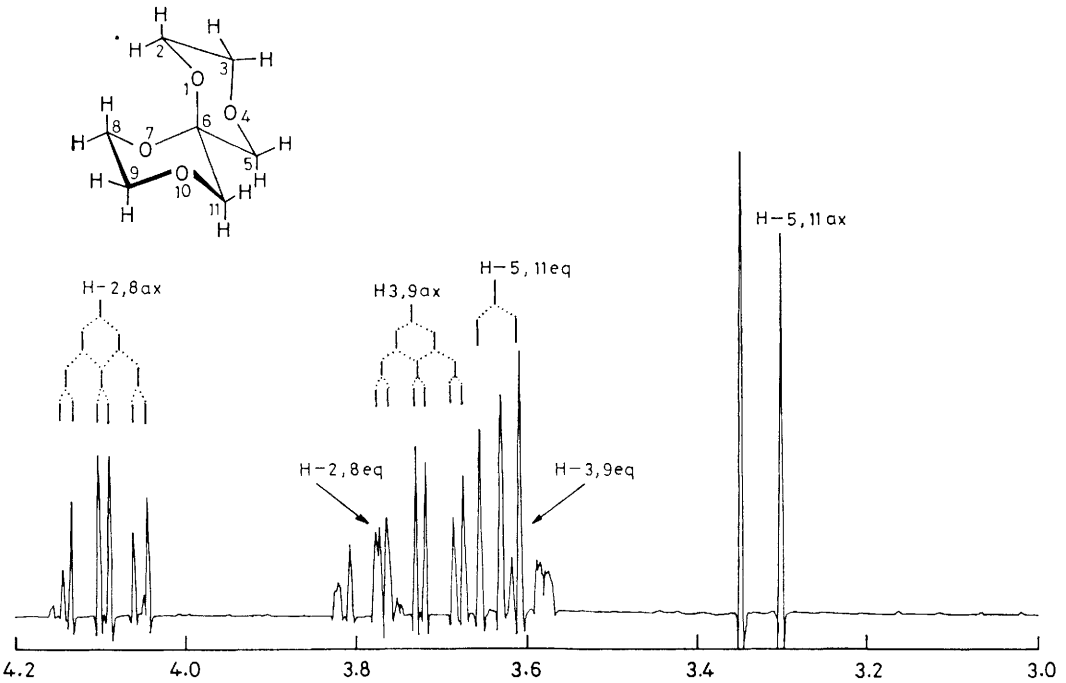


Figure 1. 250 MHz ^{1}H n.m.r. spectrum of 1,4,7,10-tetraoxaspiro[5.5]undecane (**11**) in deuteriochloroform run in the resolution-enhanced mode.

indicated that it existed as a mixture of rotamers about the *N*-acetyl bond. Similarly, the thia-analogue (**12**) was prepared from the dimethanesulphonate (**5**) by reaction with potassium thioacetate to give (**10**) followed by treatment with sodium methoxide which gave the crystalline (**12**) (m.p. 121—123 °C, $[\alpha]_D$ +0.5°, $[\alpha]_{365}$ +24.8°, chloroform).

As far as we are aware these syntheses are the first definitive chiral syntheses of simple spiro-compounds in which the chiralty is due solely to the spiro-ring-junction. It is clear that compounds (**2**) and (**3**) may be employed as precursors of a wide variety of chiral spiro-fused heterocycles including (**1**).

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