# The Synthesis of (*R*)- and (*S*)-Spirobi-1,4-dioxane and Related Spirobicycles from D-Fructose†

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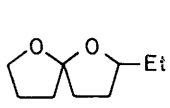
Stereospecific syntheses of (*R*)- and (*S*)-spirobi-1,4-dioxane [(**19**) and (**23**) respectively] have been achieved starting from 1,2-*O*-ethylene-β-D-fructopyranose (**6**) and 2-(β-D-fructopyranosyloxy)ethanol (**24**) respectively, which are both readily available from 2′-chloroethyl β-D-fructopyranoside. In the former case the triol grouping was cleaved by sodium periodate, and the dialdehyde (**7**) reduced with sodium borohydride to give the diol (**8**), which was ring closed to give the (*S*)-isomer. In the latter case the triol grouping of compound (**24**) was also cleaved by periodate to give 1,4,7,10-tetraoxaspiro-[5.5]undecane-3,11-diol which existed as a mixture of 3,11-epimers (**26**). Sequential acetylation, treatment with hydrogen bromide–acetic acid, and reduction with lithium aluminium hydride afforded the (*R*)-isomer. Conversion of the diol (**8**) into the dimesylate, followed by selective displacement with thioacetate, afforded the monomesylate (**18**) which on reaction with base afforded (R)-1,7,10-trioxa-4-thiaspiro[5.5]undecane (**22**). The aza-analogue (**20**) has been made by a related sequence of reactions.

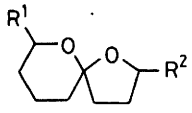


Spiroacetals are relatively widespread in Nature, occurring in some polyether antibiotics[1] and in the potent anti-parasitic agents the evermectins[2] and milbemycins.[3] Recently Francke and his co-workers[4] reported the isolation of a relatively simple spiroacetal, 2-ethyl-1,6-dioxaspiro[4.4]nonane (**1**), from the beetle *Pityogenes chalcographus*, a pest of Norway spruce, in which it functions as the principal aggregation pheromone. Two other simple spiroacetals, 7-methyl- and 2-methyl-1,6-dioxaspiro[4.5]decane, (**2**) and (**3**) respectively, which serve as repellents or aggression inhibitors, were isolated from workers of the common wasp, *Paravespula vulgaris*.[5] Another particularly interesting compound is 1,7-dioxaspiro[5.5]undecane (2,2′-spirobitetrahydropyran) (**4**) which functions as the sex pheromone of the olive fruit fly[6] where it occurs together with its 2-hydroxy and 5-hydroxy derivatives in the rectal gland of the female insect.[7] The spiroacetal (**4**) has been synthesized as the racemate and has been used with success for the control of the olive fruit fly.[8] No stereochemical information is available for the natural spiroacetal (**4**), but it may well occur as a single enantiomer, since studies with other bridged-ring acetal pheromones such as *exo*-brevicomin and frontalin strongly suggested that chirality was important in pheromone perception,[9] so that in each of these cases only one enantiomer was biologically active. Recently, the two enantiomers of compound (**4**) have been synthesized by routes[10] in which either a chiral keto triol or keto tetraol was allowed to cyclize spontaneously to give a separable mixture of the two diastereoisomers differing only in the configuration at the spiro ring junction. Subsequent removal of the remaining hydroxy groups in each diastereoisomer afforded (*R*)- and (*S*)-1,7-dioxaspiro[5.5]undecane.

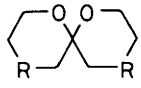
No other syntheses of spiroacetals exerted any control of the stereochemistry at the junction other than that fortuitously endowed by the operation of a powerful anomeric effect which ensured that the oxygens of the acetal group occupied axial positions relative to the other six-membered ring.[11] Indeed, as far as we are aware, there has been no enantiomerically specific synthesis of a spirobicycle in which the optical activity of the compound is due solely to the spiro ring junction. The development of such chiral syntheses of these simple spirobicycles in which the stereochemistry of the spiro ring junction is unambiguously defined is essential.



(**1**)



(**2**) $R^1$ = Me, $R^2$ = H
(**3**) $R^1$ = H, $R^2$ = Me



(**4**) R = $CH_2$
(**5**) R = O

With a fixed stereochemistry at the ring junction, the readily available spiroanhydride, 1,2-*O*-ethylene-β-D-fructopyranose (**6**), was a promising starting material for the synthesis of simple spiroacetals, such as spirobi-1,4-dioxane (**5**) which is a dioxa analogue of the olive fruit fly pheromone (**4**). The preparation of the fructose derivatives (**6**) is described in the preceding paper[12] and the glycoside is readily available *via* alkaline treatment of 2-chloroethyl β-D-fructopyranoside.

The first stage in the synthesis of the spiroacetal (**19**) was the cleavage of the pyranoside ring of compound (**6**) with periodate followed by reduction of the resulting dialdehyde (**7**) with sodium borohydride to give (*S*)-2-(2′-hydroxyethoxy)-2-hydroxymethyl-1,4-dioxane (**8**) in 74% overall yield as an oil. The $^1$H n.m.r. spectra of the syrupy di-*O*-acetyl derivative (**9**) and the crystalline di-*O*-mesyl derivative (**10**) were in total accord with the structures (Table 1) and the mass spectrum of the parent diol (**8**) showed very prominent ions, resulting from the cleavage of the exocyclic substituents, at *m*/*z* 147 ($M - CH_2OH$) and 117 ($M - CH_2CH_2OH$) which was a common and predictable fragmentation in this and all the other derivatives of this type.

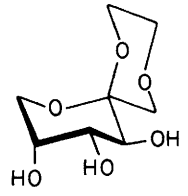
Initially, attempts to cyclize the dimesylate (**10**) with various bases, in anticipation that one or other of the sulphonate groups would suffer O–S fission followed by displacement of the remaining sulphonate group by the liberated alkoxide ion (*cf.*

† Preliminary communication: ref. 15; in the determination of configurational prefixes for these spiro derivatives, they are treated as having central chirality, rather than axial chirality, as proposed by Cahn, Ingold, and Prelog, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 397.

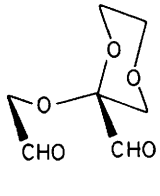
**Table 1.** $^1$H N.m.r. parameters (δ, *J*/Hz) of 2,2-disubstituted dioxanes

| Compound | (9)[a] | (10)[b] | (12)[b] | (13)[c] | (15)[c] | (16)[b] | (17)[b] | (18)[c] |
|---|---|---|---|---|---|---|---|---|
| 1′-$H_{a,b}$ | 3.51(m) | 3.85(m) | | 3.70(m) | 3.75(m) | | 3.75(m) | 3.64(t) |
| 2′-$H_{a,b}$ | ** | 4.45(m) | 3.5—3.8 | 4.05(m) | 4.10(m) | | 3.47(m) | 3.13(m) |
| 1″-$H_a$ | 4.18(d) | 4.23(d) | 4.20(d) | 3.88(d) | 4.16(d) | 4.22(d) | 4.23(d) | 4.21(d) |
| 1″-$H_b$ | 3.87(d) | 4.06(d) | 3.96(d) | 3.74(d) | 3.88(d) | 3.95(d) | 4.09(d) | 4.09(d) |
| 3-$H_{eq}$ | 3.86(d) | 3.83(d) | 3.81(d) | 3.71(d) | 3.71(d) | 3.86(d) | 3.82(d) | 3.81(d) |
| 3-$H_{ax}$ | 3.39(d) | 3.58(d) | 3.55(d) | 3.43(d) | 3.50(d) | 3.57(d) | 3.59(d) | 3.58(d) |
| 5-$H_{ax}$ | 3.23(td) | 3.65(td) | | 3.54(td) | 3.66(td) | 3.71(td) | 3.65(td) | 3.62(td) |
| 5-$H_{eq}$ | 3.31(m) | 3.60(m) | | 3.45(m) | 3.50(m) | | 3.58(m) | 3.64(m) |
| 6-$H_{ax}$ | 3.76(td) | 4.02(td) | 4.13(td) | 3.92(td) | 3.96(td) | 4.09(td) | 4.04(td) | 4.05(td) |
| 6-$H_{eq}$ | 3.02(br.d) | 3.78(m) | | ~3.70(m) | 3.80(m) | | 3.75(m) | 3.78(m) |
| $J_{1'_a,1'_b}$ | 12.1 | 11.4 | 12.2 | 11.0 | 12.4 | 12.3 | 11.3 | 11.2 |
| $J_{3_{ax},3_{eq}}$ | 11.8 | 11.9 | 11.8 | 11.9 | ~11.0 | 12.6 | 11.9 | ~12.0 |
| $J_{5_{ax},5_{eq}}$ | 11.2 | 13.3 | | ~11.0 | ~11.5 | 11.2 | 11.0 | ~12.0 |
| $J_{5_{ax},6_{ax}}$ | 11.0 | 11.0 | 11.1 | ~11.0 | 11.0 | 11.7 | 11.0 | ~11.5 |
| $J_{5_{ax},6_{eq}}$ | 3.0 | 3.0 | | ~2.0 | 2.5 | ~2.5 | ~2.5 | ~3.0 |
| $J_{5_{eq},6_{ax}}$ | 3.7 | 3.0 | 3.4 | ~3.0 | ~3.0 | 3.2 | ~3.0 | 3.2 |
| $J_{6_{ax},6_{eq}}$ | 11.0 | 11.0 | 11.1 | 11.1 | ~11.0 | 11.0 | 11.7 | 11.0 |

** 2′-$H_a$ δ 4.17 (ddd); 2′-$H_b$ δ *ca.* 4.08 (qt); $J_{2'_a,2'_b}$ 12.0, $J_{2'_a,2'_b}$ 5.3, $J_{2'_a,1'_b}$ 4.0 Hz. [a] At 250 MHz in [$^2H_6$]benzene. [b] 200 MHz in $CDCl_3$. [c] 250 MHz in $CDCl_3$.



(6)



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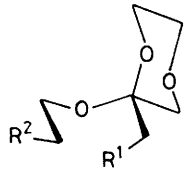
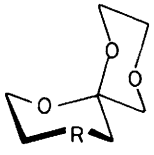
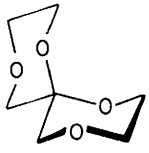


(8) $R^1 = R^2 = OH$
(9) $R^1 = R^2 = OAc$
(10) $R^1 = R^2 = OSO_2Me$
(11) $R^1 = OH, R^2 = OEt$
(12) $R^1 = OAc, R^2 = OEt$
(13) $R^1 = R^2 = OMes$
(14) $R^1 = OH, R^2 = OMes$
(15) $R^1 = OAc, R^2 = OMes$
(16) $R^1 = OAc, R^2 = Br$
(17) $R^1 = OSO_2Me, R^2 = N_3$
(18) $R^1 = OSO_2Me, R^2 = SAc$



(19) R = O
(20) R = NAc
(21) R = NH
(22) R = S



(23)

Mes = 2,4,6-$Me_3C_6H_2SO_2$–

the formation of some 2,3-anhydropyranosides from the alkaline treatment of 2,3-disulphonates[13]), yielded complex mixtures. However, the use of ethanolic potassium hydroxide gave mainly one product, (**11**), which was isolated as an oil in 69% yield, and had resulted from initial $S_N2$ displacement at the 2′-position* by $EtO^-$ and by hydrolysis of the 1″-sulphonate* group.

The mass spectrum of compound (**11**) showed prominent fragments derived from the loss of either $CH_2OH$ or $OCH_2CH_2OEt$ and the $^1$H n.m.r. spectrum of the derived *O*-acetyl derivative (**12**) indicated the presence of an *O*-acetyl group and an *O*-ethyl group. It was therefore apparent that in order to fix the second dioxane ring for the synthesis of the spiro compound (**19**) the diol (**8**) would need to be selectively sulphonylated. Accordingly, diol (**8**) was treated with a small excess of mesitylenesulphonyl chloride which gave the monosulphonate (**14**) as the major product in 60% yield together with 29% of the disulphonate (**13**); the mixture was readily separable by column chromatography. Although the position of the sulphonate group did not matter in the synthesis at hand, it was almost certainly at the 2′-position since it is well known the 2-(hydroxymethyl) group, which is of the neopentyl type, is much less reactive towards substitution with relatively bulky reagents such as mesitylenesulphonyl chloride. In agreement with this the mass spectrum of compound (**14**) showed a prominent fragment arising from the loss of $MesOCH_2CH_2O$, and comparison of the $^1$H n.m.r. spectra of the acetyl derivative (**15**) of the monosulphonate and the disulphonate (**13**) showed that the 1″-$H_a$ and 1″-$H_b$ resonances were about 0.27 and 0.15 p.p.m. to lower field in the former, which was consistent with the presence of the more deshielding acetoxy group at this position.

As an alternative to the introduction of one sulphonate group, the diol (**8**) was selectively brominated with triphenylphosphine–carbon tetrabromide in pyridine,[14] since it is known that $S_N2$ displacements at C-1″ are very much less favoured than at C-2′ because of steric constraints. As predicted, displacement only took place at the 2′-position to give the bromo alcohol which was isolated as its *O*-acetyl derivative (**16**) in rather poor yield (12%). The structure of the product was indicated by the prominent fragments in the mass spectrum arising from loss of the elements $CH_2OAc$ and $BrCH_2CH_2O$.

Treatment of either compound (**14**) or compound (**16**) with boiling methanolic sodium methoxide resulted in a smooth cyclization to give required (*R*)-spirobi-1,4-dioxane (**19**) in *ca.* 90—95% yield as a highly crystalline solid. Owing to its

* Carbon atoms in the longer chain are given primed numbers and that in the shorter chain is numbered as 1″.

**Table 2.** $^1$H N.m.r. parameters (δ, *J*/Hz) for spirobicycles

| Compound | (19)[a] | (20)[b] | (22)[a,c] | (29)[d] |
|---|---|---|---|---|
| 2-$H_{ax}$ | 4.07(td) | 4.46(td) | 4.11(td) | 4.05(dd) |
| 2-$H_{eq}$ | 3.58(m) | | 3.79(m) | 3.99(dd) |
| 3-$H_{ax}$ | 3.66(td) | | 3.75(td) | 6.16(dd) |
| 3-$H_{eq}$ | 3.76(m) | | 3.95(m) | |
| 5-$H_{ax}$ | 3.30(d) | 3.04(d) | 3.37(d) | 3.96(d) |
| 5-$H_{eq}$ | 3.60(d) | 3.47(d) | 4.07(td) | 3.85(d) |
| 8-$H_{ax}$ | 4.07(td) | | 4.05(td) | 4.34(td) |
| 8-$H_{eq}$ | 3.58(m) | | 3.65(m) | 3.72(m) |
| 9-$H_{ax}$ | 3.66(td) | 2.83(td) | 2.92(ddd) | 4.22(td) |
| 9-$H_{eq}$ | 3.76(m) | | 2.31(ddd) | 3.66(m) |
| 11-$H_{ax}$ | 3.30(d) | 2.57(d) | 2.71(d) | |
| 11-$H_{eq}$ | 3.60(d) | 3.41(d) | 2.35(dd) | 6.08(s) |
| $J_{2_{ax},2_{eq}}$ | 11.5 | ~13.5 | 11.8 | 11.5 |
| $J_{2_{ax},3_{ax}}$ | 11.5 | ~13.5 | 11.8 | 7.5 |
| $J_{2_{ax},3_{eq}}$ | 3.0 | ~1.5 | 2.1 | |
| $J_{2_{eq},3_{eq}}$ | ~1 | | 1 | |
| $J_{2_{eq},3_{ax}}$ | 3.0 | | 3.0 | 5.0 |
| $J_{3_{ax},3_{eq}}$ | 11.5 | | 11.5 | |
| $J_{5_{ax},5_{eq}}$ | 11.8 | 13.3 | 11.6 | 12.5 |
| $J_{8_{ax},8_{eq}}$ | 11.5 | | 11.5 | 11.5 |
| $J_{8_{ax},9_{ax}}$ | 11.5 | 12.7 | 11.8 | 11.5 |
| $J_{8_{ax},9_{eq}}$ | 3.0 | | 4.3 | 2.5 |
| $J_{8_{eq},9_{ax}}$ | 3.0 | 3.4 | 3.5 | |
| $J_{8_{eq},9_{eq}}$ | ~1 | | ~2 | ~1 |
| $J_{9_{ax},9_{eq}}$ | 11.5 | 13.0 | 13.5 | 11.5 |
| $J_{11_{ax},11_{eq}}$ | 11.8 | 13.5 | 13.3 | |

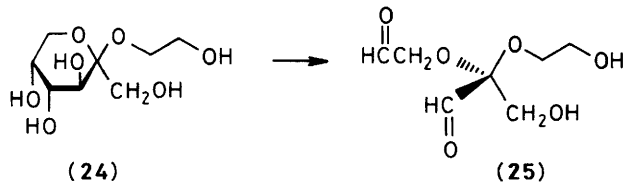
[a] In $CDCl_3$ at 400 MHz. [b] $CDCl_3$ at 200 MHz. [c] $J_{11_{eq},9_{eq}}$ 1.5 Hz at 200 MHz. [d] In $CDCl_3$ at 250 MHz.

symmetrical nature the product gave a relatively simple $^1$H n.m.r. spectrum which at 400 MHz was completely amenable to first-order analysis (the 250 MHz spectrum is shown in our preliminary communication[15]) and showed only six separate multiplets (Table 2), which indicated that the diacetal existed in the symmetrical conformation in which the two acetal oxygens were axial with respect to the six-membered rings such that the anomeric effect was most favourable. Deslongchamps and his co-workers[11] have shown that this conformation is the most favoured by 2.8 kcal mol$^{-1}$ in the spirobicycle (**4**) and we would expect the value for compound (**19**) to be similar so that, effectively, the other possible conformations are excluded. The $^{13}$C n.m.r. spectrum was similarly simple with only four resonances.

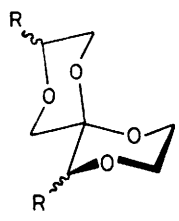
Although the dimesylate (**10**) was unsuitable for the synthesis of compound (**19**) it could be used for the preparation of analogues in which one of the oxygen atoms was replaced by a nitrogen or sulphur, by exploiting the difference in reactivity of the two sulphonyloxy groups towards nucleophilic displacement. Thus reaction of compound (**10**) with sodium azide in *N*,*N*-dimethylformamide (DMF) afforded the 2′-azide (**17**) in 88% yield and, under the conditions used, no other product could be detected. As for other products the structure of compound (**17**) was indicated by its mass spectrum which showed major fragments due to the loss of either $CH_2OMs$ or $N_3CH_2CH_2O$. The azide was reduced by catalytic hydrogenation and the amine which was initially formed was not isolated but cyclized immediately on being boiled with sodium acetate in ethanol to give morpholine-2-spiro-2′-(1,4-dioxane) (**21**) which was isolated as its crystalline *N*-acetyl derivative (**20**) after reaction with acetic anhydride. The $^1$H n.m.r. spectrum of the acetamide (**20**) indicated the presence of two rotamers due to lack of free rotation about the N–Ac bond and the $^{13}$C n.m.r. spectrum showed the same effect with those carbons flanking the nitrogen split into two lines separated by *ca.* 5 p.p.m.

The dimesylate (**10**) was also treated with potassium thioacetate in DMF to give the highly crystalline 2′-thioacetate (**18**), in 54% yield, which cyclized smoothly with base to give the crystalline 4-thia-1,7,10-trioxaspiro[5.5]undecane (**22**) in 68% yield. The $^1$H n.m.r. spectrum was largely first order and the assignments were made on the basis of a comparison of the spectrum with that of the tetraoxa isostere (**19**). The less deshielding sulphur at position 4 resulted in large upfield shifts for 3-$H_{ax}$, 3-$H_{eq}$, 5-$H_{ax}$, and 5-$H_{eq}$ and the fact that 2-$H_{ax}$ and 8-$H_{ax}$ appeared to lowest field as triplets of doublets indicated that compound (**22**) adopted the indicated conformation in which the two acetal oxygens were axial with respect to the two rings so as to maximize the benefit of the anomeric effect. The optical rotation of compound (**22**) was anomalous since it was positive (+0.9°) compared with the negative values obtained for compound (**19**) and (**20**) (−70° and −60° respectively). However, measurement of the circular dichroism of compound (**22**) indicated positive c.d. maxima at 230—240 nm ($n\rightarrow\sigma^*$ of –S–) and at *ca.* 210 nm ($\sigma\rightarrow\sigma^*$ of –S–), whereas the spirobidioxane (**19**) had c.d. maxima below 200 nm. The positive contributions to $[\alpha]_D$ by the Cotton effects at 240 and 210 nm were difficult to calculate with any precision but would have been greater than +44°, indicating that the observed rotation was not unreasonable.*

Having achieved an enantiospecific synthesis of the (*R*)-isomer of the spirobidioxane (**5**), our next target was the synthesis of the (*S*)-isomer (**23**) from the same starting material. It can be seen that the (*R*)-isomer is derived from cyclization between C-1 and C-2′ and between C-3 and C-5 whereas if this could be reversed such that C-3 and C-2′ were linked and C-5 and C-1 coupled, then the (*S*)-isomer would arise. Accordingly,



(**24**) (**25**)



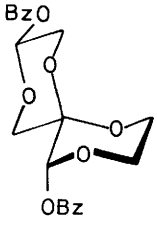
(**26**) R = OH
(**27**) R = OAc
(**28**) R = Br

2-(β-D-fructopyranosyloxy)ethanol (**24**)[12] was treated with sodium metaperiodate to give the dialdehyde (**25**). It is well known that such dialdehydes do not exist as such if they are able to form a stable hemiacetal with either a suitably placed hydroxy group or a hydrated aldehyde.[16] Consequently, compound (**25**) would be expected to cyclize to the spirodiacetal (**26**), which could exist as a mixture of four diastereoisomers differing in the configuration of the two hydroxy groups. Indeed, the 'dialdehyde' was obtained as a mixture of isomers from which one crystallized, but its configuration could not be

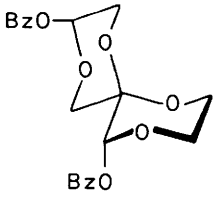
* We are grateful to Professor Hiroshi Meguro of Tohoku University, Sendai, Japan for these measurements and calculations.

established, and in all subsequent reactions the mixture was used. Acetylation of the diol (**26**) afforded a diacetyl derivative (**27**) which was apparently pure by t.l.c. but which was shown to be a mixture of at least three isomers by n.m.r. spectrometry. When the diol (**26**) was benzoylated, t.l.c. indicated that two isomers were formed which were then separated by column chromatography. The more mobile component was isolated as a crystalline solid in 40% yield and shown to be the (3-*R*,6-*S*,11*R*)-isomer (**29**) in which the 3-benzoyloxy group is equatorial and the other axial. The structure was indicated by the $^1$H n.m.r. spectrum in which the two protons adjacent to the benzoyloxy groups were well deshielded at below δ 6. The configuration at C-11 was indicated by the large downfield shift of 9-H [*ca.* 0.65 p.p.m. compared with that in (**19**)] which indicated that the 11-benzoyloxy group was axial. The 3-H resonance appeared as a double doublet (*J* 5.0 and 7.5 Hz) and indicated that 3-H was axial. The remaining spectrum was in agreement with the configuration proposed (Table 2).

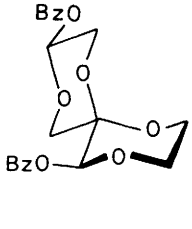
The other benzoate fraction, although apparently pure by t.l.c., was shown to be a 1:2 mixture of the diaxial isomer (**30**) and the diequatorial isomer (**31**) but they could not be separated. The $^1$H n.m.r. spectrum of the mixture, whilst complex, showed four resonances below δ 5.9 due to 3-H and 11-H of each isomer. Those attributable to the diaxial isomer (**30**) appeared as a doublet at δ 6.20 ($J_{3,2_{ax}}$ 1.8, $J_{3,2_{eq}}$ 0 Hz, 3-H) and a doublet at 6.03 ($J_{11,9_{eq}}$ 1.8 Hz, 11-H) and those attributable to the diequatorial isomer (**31**) resonated at δ 6.28 as a double doublet ($J_{3,4_{ax}}$ 8.4, $J_{3,4_{eq}}$ 4.9 Hz, 3-H) and at 5.92 (11-H) as a singlet. The configuration at C-11 in the latter was assigned on the basis that its higher field position in comparison with the 11-H resonances in (**29**) and (**30**) indicated that it was axial.




(**29**)




(**30**)




(**31**)

Bz = PhCO–

The displacement of the acetoxy groups of the diacetate (**27**) was accomplished by brief treatment with hydrogen bromide in acetic acid to give the dibromide (**28**) which was immediately reduced with lithium aluminium hydride to give crystalline (*S*)-spirobidioxane (**23**) in an overall yield of 32% from (**27**). It was indistinguishable from the (*R*)-isomer except for the sign of the optical rotation.

## Experimental

For general procedures see the previous paper.[12]

(R)-2-(2′-*Hydroxyethoxy*)-2-*hydroxymethyl*-1,4-*dioxane* (**8**).—1,2-*O*-ethylene-β-D-fructopyranose[12] (**6**) (10 g, 48.54 mmol) was added portionwise to a solution of sodium metaperiodate (20.8 g, 97.2 mmol) in water (150 ml) and the reaction mixture was stored at −5 °C for 18 h after which time the inorganic material was filtered off and the filtrate was neutralized by the cautious addition of sodium hydrogen carbonate (4 g, 48 mmol). The solution was then concentrated to dryness to give a solid residue which was extracted with two portions of ethanol (150 and 100 ml respectively). The combined extracts were then cooled in ice–water and treated portionwise with sodium borohydride (3 g). After 8 h at room temperature the reaction mixture was then neutralized with Amberlite IR-120($H^+$) resin and evaporated to dryness. Flash chromatography [ethyl acetate–ethanol (10:1) as eluant] afforded *the diol* (**8**) as a pale yellow-coloured oil (6.4 g, 74%), $[\alpha]_D$ −74° (Found: C, 47.2; H, 8.0. $C_7H_{14}O_5$ requires C, 47.2; H, 7.9%); *m/z* 147 (*M* − $CH_2OH$, 30%), 117 (*M* − $OCH_2CH_2OH$, 28), and 103 (*M* − $CH_2O$ − $C_2H_4$ − OH, 42).

Acetylation of the diol (**8**) afforded the liquid *diacetate* (**9**) in 92% yield, $[\alpha]_D$ −54° (Found: C, 50.6; H, 7.0. $C_{11}H_{18}O_7$ requires C, 50.4; H, 6.9%); $\delta_C$ 95.27 (C-2), 70.56 (C-1″), 66.18 (C-2′), 64.08, 63.25, 60.96, and 59.89 p.p.m.

(R)-2-(2′-*Mesyloxyethoxy*)-2-*mesyloxymethyl*-1,4-*dioxane* (**10**).—Mesyl chloride (15 ml, 194 mmol) was added dropwise to an ice-cold solution of the diol (**8**) (10 g, 56.2 mmol) in pyridine (80 ml). The reaction mixture was stored at 0 °C for 4 h after which t.l.c. [ethyl acetate–light petroleum (1:10)] indicated that the reaction was complete and that a single faster moving component had been formed. The reaction mixture was poured into ice–water and the product was extracted with chloroform in the usual way to give the *dimesylate* (**10**) (13.1 g, 70%) as a crystalline solid, m.p. 74—75 °C (from ethanol–chloroform); $[\alpha]_D$ −31° (Found: C, 32.15; H, 5.2. $C_9H_{18}O_9S_2$ requires C, 32.35; H, 5.4%); *m/z* 238 (*M* − $CH_3SO_3H$, 0.7%), 225 (*M* − $CH_2OSO_2CH_3$, 0.1), and 167 (19).

*Treatment of the Dimesylate* (**10**) *with Base*.—The dimesylate (**10**) (2 g) was dissolved in 1M-ethanolic potassium hydroxide (30 ml) and the solution was heated under reflux for 16 h, after which t.l.c. [ethyl acetate–light petroleum (3:1)] indicated a single slower moving product. The reaction mixture was then cooled and neutralized with Amberlite IR-120($H^+$) resin and then evaporated to dryness. The pale yellow oil was then purified by column chromatography [ethyl acetate–light petroleum (1:1) as eluant] to give (R)-2-(2′-*ethoxyethoxy*)-2-*hydroxymethyl*-1,4-*dioxane* (**11**) as an oil (0.85 g, 69%), $[\alpha]_D$ −77° (Found: C, 52.5; H, 9.0. $C_9H_{18}O_5$ requires C, 52.45; H, 8.75%); *m/z* 175 (*M* − $CH_2OH$, 26%), 117 (*M* − $OCH_2$-$CH_2OEt$, 20), 87 (16.7), and 73 (64.6).

Acetylation of the alcohol (**11**), afforded the *monoacetate* (**12**) in 95% yield as a syrup, $[\alpha]_D$ −61° (Found: C, 53.95; H, 8.45. $C_{11}H_{20}O_6$ requires C, 53.25; H, 8.05%).

*Selective Mesitylenesulphonylation of the Diol* (**8**).—A solution of mesitylenesulphonyl chloride (8 g, 36.45 mmol) in pyridine (40 ml) was added to an ice-cold solution of the diol (**8**) (5 g, 28.1 mmol) in pyridine (110 ml). The reaction mixture was kept at 0—5 °C for 4 days, when t.l.c. [ethyl acetate–light petroleum (3:1)] indicated the presence of a major component and a faster moving minor component. The reaction mixture was then poured into ice–water and the products were extracted into chloroform in the usual way. The combined extracts were then washed successively with dil. hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). The resulting syrup was then fractionated by column chromatography [ethyl acetate–light petroleum (4:3) as eluant] to give initially the *disulphonate* (**13**) (4.5 g, 29%), m.p. 85—87 °C (decomp.) (from ethanol–chloroform), $[\alpha]_D$ −23° (Found: C, 55.25; H, 6.55. $C_{25}H_{34}O_9S_2$ requires C, 55.35; H, 6.25%); *m/z* 542 ($M^+$, 1.6%), 343 (*M* − OMes; 9), 329 (*M* − $CH_2OMes$, 4.8), 299 (*M* − $OCH_2CH_2OMes$, 0.1), and 227 (57).

Further elution of the column with ethyl acetate–light petroleum (1:1) yielded the slower moving (S)-2-*hydroxymethyl*-2-(2′-*mesitylenesulphonyloxyethoxy*)-1,4-*dioxane* (**14**) as a crystalline solid (6.1 g, 60%), m.p. 76—77.5 °C (from ether–

methanol); $[\alpha]_D$ −37° (Found: C, 53.3; H, 6.65. $C_{16}H_{24}O_7S$ requires C, 53.35; H, 6.65%); *m/z* 227 (10.1%), 160 (*M* − MesOH, 0.4), and 116 (*M* − $OCH_2CH_2OMes$, 3.2).

Acetylation of compound (**14**) afforded the *acetyl derivative* (**15**), m.p. 75—76.5 °C (from ethanol); $[\alpha]_D$ −35° (Found: C, 53.5; H, 6.8. $C_{18}H_{26}O_8S$ requires C, 53.75; H, 6.45%).

(R)-2-*Acetoxymethyl*-2-(2′-*bromoethoxy*)-1,4-*dioxane* (**16**).—To an ice-cold solution of the diol (**8**) (5 g, 28.1 mmol) in pyridine (50 ml) was added triphenylphosphine (8.8 g, 33.6 mmol) followed by carbon tetrabromide (4.8 g, 14.46 mmol). The reaction mixture was then heated at 70 °C for 90 min, when t.l.c. [ethyl acetate–ethanol (10:1)] indicated the formation of a faster moving product. The reaction mixture was then diluted with methanol (50 ml) and evaporated to dryness. The dark brown residue was dissolved in pyridine (40 ml) and acetic anhydride (5 ml) was added. After being kept 4 h at room temperature the reaction mixture was poured into ice–water and the product was extracted with chloroform in the usual way. The resulting crude product from work-up was fractionated by column chromatography [ethyl acetate–light petroleum (1:4) as eluant] which gave the syrupy *monobromide* (**16**) (0.32 g, 12%), $[\alpha]_D$ −78° (Found: C, 38.65; H, 5.6. $C_9H_{15}BrO_5$ requires C, 38.15; H, 5.3%); *m/z* 211 and 209 (*M* − $CH_2OAc$, 34.7 and 37.2% respectively), and 159 (*M* − $OCH_2CH_2Br$, 15.8).

(R)-1,4,7,10-*Tetraoxaspiro*[5.5]*undecane* (*Spirobi*-1,4-*dioxane*) (**19**).—The monosulphonate (**14**) (7 g) was dissolved in 1M-methanolic sodium methoxide (35 ml) and the solution was heated under reflux for 10 min. The reaction mixture was then cooled and neutralized with Amberlite IR-120($H^+$) resin and then evaporated to dryness. The solid residue was then extracted with two portions of chloroform (100 ml and 50 ml) and, after being dried ($MgSO_4$), the combined extracts were evaporated to dryness to give the highly crystalline *spirobicycle* (**19**) (2.85 g, 92%), m.p. 84—85 °C (from hexane); $[\alpha]_D$ −70° (Found: C, 52.45; H, 7.5. $C_7H_{12}O_4$ requires C, 52.5; H, 7.5%); *m/z* 160 ($M^+$, 34.6), 130 (*M* − $CH_2O$, 6.3), 103 ($HOCH_2$-$CH_2OCH_2CO^+$, 7.4), 102 (*M* − $CH_2O$ − $C_2H_4$, 67.7), 99 (*M* − $OCH_2CH_2OH$, 28.3), and 85 ($CH_2$=$CHOCH_2CO^+$, 0.2); $\delta_C$ 90.64 (C-6), 69.25 (C-5 and -11), 66.13 (C-3 and -9), and 59.94 p.p.m. (C-2 and -8).

The same product could be obtained in a similar yield when the monobromide (**16**) was treated in the same way.

(S)-2-(2′-*Azidoethoxy*)-2-*mesyloxymethyl*-1,4-*dioxane* (**17**).—The dimesylate (**10**) (5 g) was heated at 100 °C with sodium azide (5 g) in DMF (75 ml) for 4 h, when t.l.c. [ethyl acetate–light petroleum (5:1)] indicated that a single faster moving product had been formed. The reaction mixture was cooled and processed by dilution with water and extraction with ether. The resulting syrup was purified by column chromatography on a short column [ethyl acetate–light petroleum (1:1) as eluant] to give the 2′-*azide* (**17**) (3.7 g, 88%) as a syrup, $[\alpha]_D$ −4° (Found: C, 34.55; H, 5.05; N, 14.45. $C_8H_{15}N_3O_6S$ requires C, 34.15; H, 5.35; N, 14.95%); *m/z* 195 (*M* − $OCH_2CH_2N_3$, 1.6%) and 172 (*M* − $CH_2OSO_2CH_3$, 29.9).

(R)-10-*Acetyl*-1,4,7-*trioxa*-10-*azaspiro*[5.5]*undecane* (**20**).—The 2′-azide (**17**) (2 g) was hydrogenated in methanol (50 ml) over palladium–charcoal (0.2 g) at 45 p.s.i. for 16 h. The reaction mixture then contained a single slower moving product as indicated by t.l.c. [ethyl acetate–ethanol (3:1)]. The reaction mixture was filtered through a pad of HiFlo Supercell and evaporated to dryness. The resulting syrup was then dissolved in ethanol containing sodium acetate (3 g) and the mixture was heated under reflux for 16 h, when t.l.c. [ethyl acetate–ethanol (3:1)] indicated that starting product had been transformed into a major product together with several minor components. After the reaction mixture had been evaporated to dryness, the product was extracted into chloroform (2 × 100 ml). When the dried ($MgSO_4$) combined extracts were evaporated to dryness a yellow oil was obtained which was dissolved in methanol and treated with acetic anhydride (3 ml). The reaction mixture was then left at room temperature for 6 h, when t.l.c. [chloroform–acetone (10:1)] indicated that the reaction was complete. The mixture was then evaporated to dryness to give a product which was purified by column chromatography [chloroform–methanol (50:1) as eluant] to give the *spirobicycle* (**20**) as a crystalline solid (1.0 g, 70%), m.p. 112—113.5 °C (from ethyl acetate—methanol); $[\alpha]_D$ −60° (Found: C, 53.9; H, 7.5; N, 6.95. $C_9H_{15}NO_4$ requires C, 53.75; H, 7.5; N, 7.0%); *m/z* 201 ($M^+$, 0.36%), 171 (*M* − $CH_2O$, 0.1), 158 (*M* − Ac, 0.15), 143 (*M* − $CH_2O$ − $C_2H_4$, 0.8), 128 (9.3), and 99 (75); $\delta_C$ 91.81 and 91.03 (C-6), 69.88 (C-5), 65.98 (C-3), 59.89 and 59.70 (C-8), 59.48 (C-2), 50.78 and 45.61 (C-11), and 45.13 and 41.18 p.p.m. (C-9).

(R)-2-(2′-*Acetylthioethoxy*)-2-*mesyloxymethyl*-1,4-*dioxane* (**18**).—A stirred solution of the dimesylate (**10**) (4.5 g) and potassium thioacetate (4.5 g) in DMF (70 ml) was heated at 70 °C for 2 h, when t.l.c. [ethyl acetate–light petroleum (3:1)] indicated that the reaction was complete and that a major faster moving product had been formed along with several minor components. The reaction mixture was cooled and poured into water, and the product was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to dryness to give a crude product which was purified by column chromatography [ethyl acetate–light petroleum (1:1) as eluant] to give the highly crystalline 2′-*thioacetate* (**18**) as long needles (2.3 g, 54%) from ethanol, m.p. 74—75 °C; $[\alpha]_D$ −32° (Found: C, 35.8; H, 5.75. $C_9H_{18}O_7S_2$ requires C, 35.8; H, 5.95%). The product was very unstable and in spite of precautions over storage always decomposed within a few days and consequently was only prepared as required.

(R)-1,7,10-*Trioxa*-4-*thiaspiro*[5.5]*undecane* (**22**).—The preceding thioacetate (**18**) (4 g) was heated under reflux in 1M-methanolic sodium methoxide for 30 min after which t.l.c. [ethyl acetate–light petroleum (3:1)] indicated that the reaction was complete and that the starting material had been converted into a single slower moving product. The reaction mixture was then cooled, neutralized with Amberlite IR-120($H^+$) resin, and then evaporated to dryness. The crude solid product was then purified by column chromatography [ethyl acetate–light petroleum (1:1)] to give the *spirobicycle* (**22**) (2.2 g, 68%), m.p. 122—123 °C (from hexane); $[\alpha]_D$ +0.9°, $[\alpha]_{365}$ +20° (Found: C, 47.85; H, 7.2. $C_7H_{12}O_3S$ requires C, 47.75; H, 6.8%); *m/z* 176 ($M^+$, 4%), 148 (*M* − $C_2H_4$, 8.4), 118 (*M* − $CH_2O$ − $C_2H_4$, 6.2), and 103 (11.6); $\delta_C$ 89.44 (C-6), 72.27 (C-11), 65.89 (C-9), 60.72 (C-8), 60.14 (C-2), 30.85 (C-5), and 25.68 p.p.m. (C-3).

*Periodate Oxidation of* 2′-*Hydroxyethyl* β-D-*Fructopyranoside* (**24**).—The hydroxyethyl glycoside[12] (**24**) (5 g, 22.32 mmol) was added in small portions to a stirred solution of sodium metaperiodate (9.6 g, 45 mmol) in water (80 ml). The reaction mixture was kept at 0—5 °C for 16 h after which time t.l.c. [methanol–chloroform (1:1)] indicated that the reaction was complete and that a major faster moving product had been formed. The inorganic material which had crystallized out was filtered off and the filtrate was neutralized by the careful addition of solid sodium hydrogen carbonate (1.9 g, 22.6 mmol). The resulting neutral solution was then evaporated to dryness and the white crystalline solid was extracted with ethanol (2 × 100 ml). The combined extracts were then concentrated to dryness to give a syrup which was purified by flash chromatography with chloroform–methanol (10:1) as solvent.

The major product (3RS,6S,11RS)-1,4,7,10-*tetraoxaspiro*[5.5]*undecane*-3,11-*diol* (**26**) was obtained as a syrupy mixture of anomers (3.6 g, 84%) which partially crystallized to give a single anomer, m.p. 69—71 °C, which could not be recrystallized, $[\alpha]_D$ +110° (*c* 1.2 in methanol) (Found: C, 43.45; H, 6.25. $C_7H_{12}O_6$ requires C, 43.75; H, 6.25%); *m/z* 175 (*M* − OH, 13%), 174 (*M* − $H_2O$, 2.7), 163 (*M* − $CH_2OH$, 3.2), 119 [$HOCH_2CH_2OCH(OH)CO^+$, 10.7], 101 [$CH_2$=$CHOCH(OH)CO^+$, 10.8], and 73 ($CH_2$=$CHOCHOH^+$, 100).

Acetylation of the above syrupy mixture of anomers afforded a product which was purified by column chromatography [ethyl acetate–light petroleum (1:2) as eluant] to give a syrup (91%), $[\alpha]_D$ +170°, which although apparently pure (t.l.c.; several solvents) was shown to be a *mixture of anomers* (**27**) by n.m.r. spectrometry (Found: C, 47.35; H, 5.6. $C_{11}H_{16}O_8$ requires C, 47.85; H, 5.8%); *m/z* 276 ($M^+$, 0.1%) 217 (*M* − OAc, 5.4).

Benzoylation of the syrupy mixture gave what appeared to be two products according to t.l.c. [ethyl acetate–light petroleum (1:2)] which were separated by column chromatography [ethyl acetate–light petroleum (1:16) as eluant]. The more mobile component was characterized as (3R,6S,11R)-1,4,7,10-*tetraoxaspiro*[5.5]*undecane*-3,11-*diyl dibenzoate* (**29**) (40%), m.p. 103—105 °C (from ethanol); $[\alpha]_D$ +120° (Found: C, 62.85; H, 5.1. $C_{21}H_{20}O_8$ requires C, 63.0; H, 5.0%).

The less mobile component was obtained in 45% yield and was apparently pure by t.l.c. but was found to be a 1:2 mixture of the (3S,6S,11R)- and (3R,6S,11S)-*isomer*, (**30**) and (**31**) respectively, $[\alpha]_D$ +110° (Found: C, 62.5; H, 4.75%).

(S)-1,4,7,10-*Tetraoxaspiro*[5.5]*undecane* (**23**).—To an ice-cold solution of the preceding diacetate mixture (**27**) (3.8 g) in methylene dichloride (50 ml) was added hydrogen bromide in acetic acid (45% v/v; 10 ml). The reaction mixture was kept at room temperature for 1 h and then diluted with methylene dichloride (500 ml). The solution was then successively washed well with water and aqueous sodium hydrogen carbonate, and dried ($MgSO_4$). The solution was then evaporated to dryness to give a pale yellow syrup (*ca.* 2 g). A solution of this syrup in dry ether (25 ml) was added dropwise to a solution of lithium aluminium hydride (2 g) in dry ether (25 ml). The reaction mixture was left at room temperature for 2 h and then decomposed by the cautious addition of water (2 ml) which was followed by 4M-sodium hydroxide (2 ml) and more water (6 ml). The inorganic material, which had separated out, was filtered off and the filtrate was evaporated to dryness. The crude product was purified by column chromatography [ethyl acetate–light petroleum (4:1) as eluant] to give the *spirobicycle* (**23**) (0.7 g, 32%), m.p. 84—85 °C (from hexane); $[\alpha]_D$ +70 °C (Found: C, 52.3; H, 7.45. $C_7H_{12}O_4$ requires C, 52.5; H, 7.5%). This product was indistinguishable from the (*R*)-isomer (**19**) (n.m.r., m.s., i.r.).

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