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AN ENANTIOSPECIFIC SYNTHESIS OF (*R*)-1,4,7-TRIOXASPIRO[5.5]UNDECANE FROM D-FRUCTOSE*

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ABSTRACT

Periodate oxidation of 1,2-*O*-ethylene-β-D-fructopyranose and ring closure of the resulting dialdehyde with nitromethane afforded a mixture of four 4-deoxy-1,2-*O*-ethylene-4-nitrohex-2-uloses having the α-L-*xylo*, β-D-*arabino*, α-L-*lyxo*, and β-D-*ribo* configurations, together with two heptuloses which arose from products of the incomplete oxidation of the starting material. When nitromethane was in excess of the base used for the cyclisation reaction, the α-L-*xylo*-hexulose was the major product, but this could be isomerised substantially to the β-D-*ribo* isomer when treated with excess sodium methoxide. Acetylation of the α-L-*xylo*-hexulopyranose, followed by reductive elimination of the acetoxy groups, afforded an approximately 1:1 mixture of (6*R*,10*R*)- and (6*R*,10*S*)-10-nitro-1,4,7-trioxaspiro[5.5]undecane. Acid-catalysed epimerisation of the (6*R*,10*S*) isomer afforded the (6*S*,10*S*) isomer. Oxidation of either the (6*R*,10*R*) or the (6*R*,10*S*) isomer with permanganate at pH 7 afforded the 10-one. This was reduced with sodium borohydride to give mainly (6*R*,10*S*)-1,4,7-trioxaspiro[5.5]undecan-10-ol, from which the OH group was removed to give enantiomerically pure (*R*)-1,4,7-trioxaspiro-[5.5]undecane.

INTRODUCTION

The spiroacetal linkage occurs widely in Nature and is present in several polyether antibiotics[1] and in two groups of potent antiparasitic agents, the avermectins[2] and the milbemycins[3]. Recently a number of simple spiroacetals have been reported as components of insect pheromones. For example, 2-ethyl-1,6-dioxaspiro[4.4]-

*This paper celebrates the centenary of the birth of, and is dedicated to the memory of Professor Hermann O. L. Fischer.

†A. C. R. was privileged to have been involved as Prof. Fischer's last co-worker (Berkeley, 1959–60) on the cyclisation of dialdehydes with nitroalkanes, a field which Fischer discovered and developed. Without the experience and inspiration gained from this contact with Hermann Fischer, the present work, and much past work, would not have been possible.

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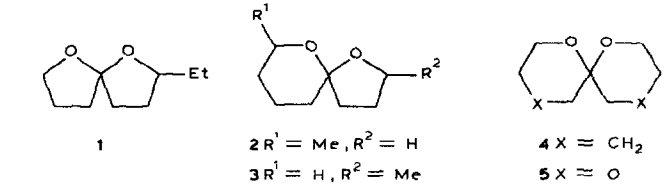
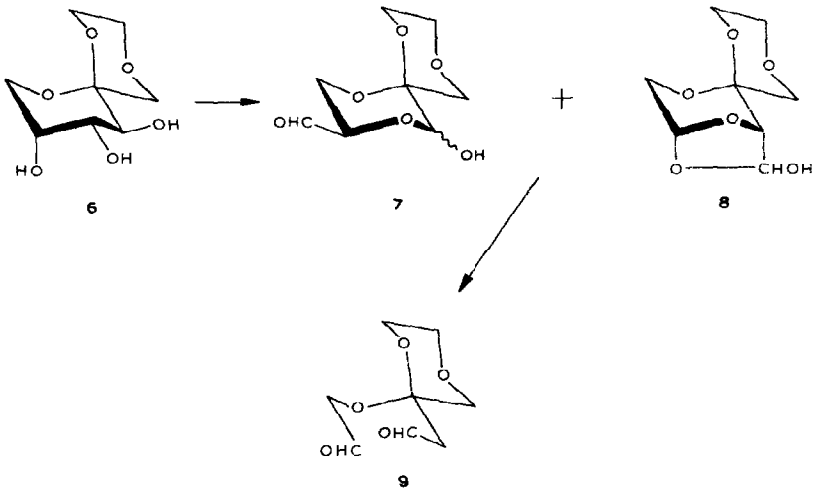


1 2 R^1 = Me, R^2 = H 3 R^1 = H, R^2 = Me 4 X = CH_2 5 X = O



6 7 8 9

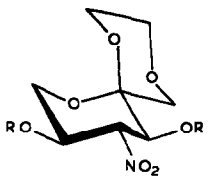
nonane (**1**) functions as the principal aggregation pheromone of the beetle *Pityogenies chalcographus*, a pest of the Norway spruce[4]. Two other simple spiroacetals, 7-methyl- and 2-methyl-1,6-dioxaspiro[4.5]decane, **2** and **3**, serve as repellents or aggression inhibitors of the common wasp *Paravespula vulgaris*[5]. A particularly interesting compound is 1,7-dioxaspiro[5.5]undecane (**4**), which functions as the main sex pheromone of the olive fruit fly[6], in which it occurs together with its 3- and 4-hydroxy derivatives in the rectal gland of the female insect[7]. The chirality of this compound is due solely to the spiro ring junction, and therefore the enantiospecific synthesis of each of its antipodes or the resolution of racemic **4** poses special problems. No information concerning the chirality of the naturally occurring enantiomer is available, although the racemic compound has been used for the control of the pest in olive-growing areas[8]. The published syntheses of the (*R*) and (*S*) enantiomers of **4** have relied upon the spontaneous cyclisation of either a chiral ketotriol or ketotetrol to give a separable mixture of diastereoisomers differing in configuration at the spiro ring junction[9,10]. Subsequent removal of the hydroxy groups from each diastereomer then afforded the pure enantiomers of **4**.

Recently we have utilised derivatives of fructose as chiral precursors of simple spiroacetals, in which the chirality of the anomeric carbon-2 defines that of the acetal carbon in the target spiroacetal. Thus, starting from 1,2-*O*-ethylene-β-D-fructose (**6**), which is readily available from 2-chloroethyl β-D-fructopyranoside[11], we were able to synthesise (*R*)-1,4,7,10-tetraoxaspiro[5.5]undecane (spirobi-1,4-dioxane) (**5**), and its enantiomer was prepared from 2-hydroxyethyl β-D-fructopyranoside[12]. We have now extended these studies to the enantiospecific synthesis of other spiroacetals and in this paper describe the synthesis of (*R*)-1,4,7-trioxaspiro[5.5]undecane (**32**) and several of its derivatives.

RESULTS AND DISCUSSION

In principle the synthesis of the 1,4,7-trioxaspiro[5.5]undecane (**32**) merely involves the reductive removal of the three hydroxyl groups from the "anhydroglycoside" 1,2-*O*-ethylene-β-D-fructopyranose (**6**). However, various stepwise procedures to remove these hydroxyl groups by halogenation/reduction and elimination failed to give the required product, probably because of the sensitivity of the acetal group, which epimerises relatively easily, leading to a racemic final product. We therefore studied an alternative procedure which involved the oxidation of 1,2-*O*-ethylene-β-D-fructopyranose with a glycol-cleaving reagent and cyclisation of the product with nitromethane, followed by stepwise removal of the substituents.

When the glycoside **6** was oxidised with sodium metaperiodate for 18 h, and the resulting dialdehyde[12] then reacted with an excess of nitromethane in the



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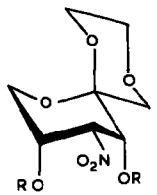
11 R = Ac



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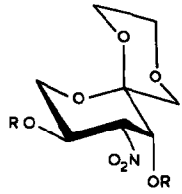

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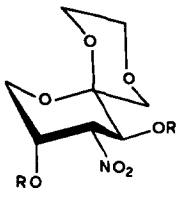

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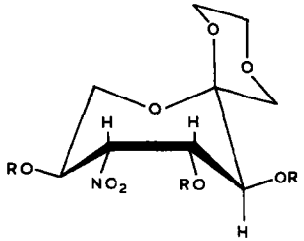

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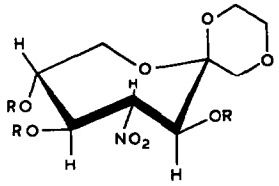


20 R = H
21 R = Ac

TABLE I

FIRST-ORDER N.M.R. PARAMETERS OF 1,4,7-TRIOXASPIRO[5.5]UNDECANES

Assignments[a]	*Values for individual compounds*										
	11[b]	**13**[c]	**15**[c]	**17**[c]	**22**[b]	**25**[d]	**24**[c]	**27**[b]	**29**[e]	**31**[e,f]	**32**[g]
Chemical shifts (δ)											
H-2ax	3.99dt		3.48dt	3.45dt	3.98dt	3.91dt		3.99dt	3.75dt	3.93dt	3.92dt
H-2eq	3.65dd		2.88dd	2.92dd	3.50dd	3.44ddd		3.51dd	3.01dd	3.06dd	3.07ddd
H-3ax	3.65dt		3.11dt	3.21m	3.68dt	3.62dt		3.67dt	3.29dt	3.30dt	3.35dt
H-3eq	3.78dd		3.26bd	3.21m	3.79dd	3.73ddd		3.79dd	3.37ddd	3.36	3.42dd
H-5ax	3.40d	3.52d	3.26d	3.45d	3.46d	3.41d	3.38d	3.41d	3.10d	3.04d	3.16d
H-5eq	3.66d	3.76d	3.64d	3.85d	3.71d	3.60d	3.71d	3.83d	3.57d	3.48d	3.66d
H-8ax	3.55d		3.16t[h]	3.14dd	3.79ddd	4.09dt		4.03ddd[g]	3.53dt	3.99dt	3.65ddd
H-8eq	4.08dd	3.85dd	4.01dd[h]	3.59dd	3.95ddd	3.78ddt		4.15ddd[g]	3.5m	3.36m	3.55ddt
H-9ax	5.43dt		5.98td[h]		2.09dq	2.00dddd		2.64ddd[g]	1.44qd	1.45tdd	1.36qt
H-9eq		5.44m		5.87dt[h]	2.31ddq	2.52ddq		2.39dq[g]	1.72m	1.38ddd	1.16m
H-10ax	5.05t	4.06t[h]	4.90dd[h]	4.83dd[h]	4.87tt		4.80ddd		5.33tt		1.83qt
H-10eq						4.52ddt				4.87m	1.29m
H-11ax	5.27d			5.87d[h]	1.77t	1.83dd	5.31d	2.31dd[g]	1.01t	0.99dd	0.98dt
H-11eq		5.73dd	5.75d[h]		2.27ddd	2.68dt		2.40dd[g]	1.90ddd	1.81ddd	1.32
Coupling constants (Hz)											
$J_{2ax,3eq}$	12		11.3	10.7	11.6	11.2		11.5	11.0	10.5	11.5
$J_{2ax,3ax}$	12		11.3	10.7	11.6	11.2		11.5	11.0	11.1	11.5

$J_{2ax,3eq}$	3		3.1	4.3	3.0	3.2		3.0	3.0	2.5	3
$J_{2eq,3ax}$			2.5	3.2	2.8	2.7		2.8	2.5	4.0	3
$J_{2eq,3eq}$								<0.5	<0.5	<0.5	0.5
$J_{3ax,3eq}$	12		11	11.0	11.6	11.2		11.5	11.5	12.7	11.5
$J_{5ax,5eq}$	12	11.7	11.7	12.0	11.6	11.5	11.8	11.7	11.4	11.4	11.5
$J_{8ax,8eq}$	11	13.3	10.8	13.2	11.7	12.1		11.5[i]	11.0	11.0	11.0
$J_{8ax,9ax}$	10.5		10.8	11	12.5	12.6		12.0[i]	11.0	11.0	13.0
$J_{8ax,9eq}$					2.3	2.5		3.4[i]	2.6	4.0	2.5
$J_{8eq,9ax}$	6	1.6	6.2	1.4	5.4	5.5		7.9[i]	4.5	4.8	4.0
$J_{8eq,9eq}$				1.6	2	1.0		1.4[i]	2.0	2.0	
$J_{9ax,9eq}$					12.5	15.0		14.8[i]	12	14	13.0
$J_{9ax,10ax}$	10.5		10.8		12.5		12.3		11.5		12.5
$J_{9ax,10eq}$						4.4				3.5	4.0
$J_{9eq,10ax}$		3.6		3.6	4.4		4.9		5		4.0
$J_{9eq,10eq}$						2.3				3.5	
$J_{9eq,11eq}$		1.0			2	2.2		1.9[i]	1.9	1.5	
$J_{10eq,10ax}$									5		4
$J_{10ax,11ax}$	10.5			10.8	12.1		10.4		11.5		13.5
$J_{10ax,11eq}$		3.6	3.4		4.4				5		4
$J_{10eq,11ax}$						5.5				3.5	4.5
$J_{10eq,11eq}$						2.3				3.5	
$J_{11ax,11eq}$					12.3	14.5		14.5[b]	11.5	14.7	13

[a]For convenience, the numbering of the atoms follows that of the 1,4,7-trioxaspiro[5.5]undecanes and so may differ from the numbering used in the text, where nomenclature applicable to hexoses is used for some compounds. [b]In $CDCl_3$ at 400 MHz. [c]In C_6D_6 at 200 MHz. [d]In $CDCl_3$ at 250 MHz. [e]In C_6D_6 at 250 MHz. [f]H-2ax and H-8ax interchangeable. [g]In C_6D_6 at 400 MHz. [h]Assignment verified by spin decoupling. [i]Assignment verified by computer iteration. [j]For **32** and **25** $J_{8eq,10eq}$ 0.7; for **27** $J_{9ax,11ax}$ 0.7.

presence of sodium methoxide, the mixture of products formed had one major and three minor components as indicated by t.l.c. and h.p.l.c. This mixture was acetylated by acetic anhydride, with boron trifluoride etherate as catalyst, to give 3,5-di-*O*-acetyl-4-deoxy-1,2-*O*-ethylene-4-nitro-α-L-*xylo*-hex-2-ulopyranose (**11**) as a crystalline solid in 30% overall yield from **6**.

The structure of **11** was apparent from its ^{1}H-n.m.r. spectrum, in which the large vicinal coupling constants ($J_{3,4}$ 10.5, $J_{4,5}$ 10.4 and $J_{5,6ax}$ 10.3 Hz) indicated that all three substituents on the pyranose ring were equatorial. This limited the structure to two possibilities; either the α-L-*xylo*- or the β-D-*xylo*-hexulopyranose. The former structure was clearly favoured because of the existence of the spiro-bicycle in the $^2C_5$ conformation, in which each of the acetal oxygens is in an axial relationship to the other ring. This double anomeric effect has been shown to be energetically favoured to the extent of about 2.8 kcal.mol^{-1} in related compounds[13], and it usually dictates the conformation in which these compounds exist. *O*-Deacetylation of **11** with methanolic hydrogen chloride afforded the diol **10**, which was identical to a product obtained from the chromatographic fractionation of the nitropyranose mixture prior to acetylation. If the isomer had been the β-D-*xylo*-hexulopyranose, acid-catalysed epimerisation at C-2 would have been expected to give the thermodynamically more favourable α-D-*xylo*-hexulopyranose. The fact that no such epimerisation took place indicated that the isomer was the α-L-*xylo*-hexulopyranose **11**.

The other 4-nitropyranoses resulting from the cyclisation were best obtained from the reaction mixture by flash chromatography prior to acetylation. The first fraction eluted from the column was a mixture of the α-L-*lyxo* isomer **14** and the α-L-*xylo* isomer **10**, from which **14** crystallised in about 9% yield. The L-*xylo* isomer, identical to that obtained above by *O*-deacetylation of **11**, was obtained crystalline in low yield only after extensive further chromatographic fractionation. The final fraction was a mixture of **10, 14**, and a third, major component which crystallised quite readily and turned out to be the β-D-*arabino* isomer **16** (8% overall yield). The structures of these isomers were established by the ^{1}H-n.m.r. vicinal coupling constants $J_{3,4}$, $J_{4,5}$ and $J_{5,6ax}$ of the derived diacetyl derivatives (Table I). None of these hexulopyranoses were epimerised at C-2 when treated with acid, suggesting that the $^2C_5$ conformation, with its very favourable anomeric effect, was adopted in all cases.

An h.p.l.c. study of the proportions of the isomers present under a variety of conditions confirmed that the α-L-*xylo*-isomer **10** was the major component (>60%) at equilibrium (24 h) when nitromethane (2–5 equiv.) was in excess with respect to sodium methoxide (0.2–1.0 equiv.). However, when equimolar amounts of nitromethane, sodium methoxide, and the dialdehyde were reacted together, the β-D-*ribo* isomer (**12**), a minor component which could not be isolated from the above reaction mixture, became the predominant isomer (about 50%) within 24 h. This isomer was conveniently accessible by treating the mixture of nitropyranoses **10, 14**, and **16**, obtained in the conventional way, with an excess of sodium methoxide in methanol, whereupon **12** could be isolated crystalline by flash

chromatography in about 12% yield. The small vicinal coupling constants ($J_{3,4}$ 3.6, $J_{4,5}$ 3.6), and the long-range coupling ($J_{3,5}$ 1.0 Hz) found for **13** revealed it as the *ribo*-isomer.

The isolation of the four isomers **10, 14, 12, 16** from the cyclisation reaction was predictable from the work of Baer and his co-workers[14]. When these reactions are conducted with a deficiency of base, only products having an equatorial nitro group acetal group demands that the pyranose ring exist in the $^2C_5$ conformation, only the observed isomers would be expected. Baer *et al.*[14] have also shown that the equilibrium ratios of isomers depend upon whether the nitropyranoside exists as the *aci*-nitro salt or as the nitro derivative. In this former case, the sp^2 hybridisation of the ring-carbon atom and the planar nature of the *aci*-nitro group destabilises those isomers having equatorial hydroxyl groups flanking the *aci*-nitro group. Hence, in the presence of an excess of base, those isomers having axial hydroxy groups are more prominent, *e.g.* the *ribo* isomer just mentioned. However when the amount of nitromethane exceeds the amount of base present, the product composition is determined by the relative thermodynamic stabilities of the 4-nitropyranoses, and hence the all-equatorial isomer **10** is formed preferentially. Lichtenthaler and Yahya have studied[15] the condensation of the dialdehyde from benzyl β-D-fructopyranoside with nitromethane and similarly obtained the β-L-*xylo* pyranoside as the major product, together with a minor product formulated originally as the α-D-*lyxo*-pyranoside, but later found to be the β-L-*lyxo*-pyranoside (personal communication).

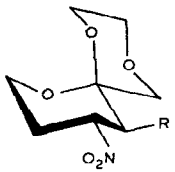
In addition to the above four isomers, two slower-moving trace components were always present in the reaction mixtures but were not at first isolated in pure condition. However, when the periodate oxidation of **6** was carried out for a shorter period, the nitromethane cyclisation afforded larger amounts of these isomers, which were separated with difficulty and obtained crystalline in about 1% yield each. The ^{1}H-n.m.r. spectra of the acetylated products indicated that they were tri-*O*-acetyl derivatives, and therefore heptuloses which had arisen because of the incomplete oxidation of **6**. Incomplete oxidation would result if the dialdehydes formed by cleavage of either the 3,4-bond or the 4,5-bond of **6** would cyclise to the thermodynamically very stable spirobicycles **7** and **8**, respectively, which would resist further oxidation because of slow reversion to the dialdehydes.

The ^{1}H-n.m.r. spectra of the acetylated heptuloses both showed four resonances below δ 5, due to *H*COAc and *H*CNO$_2$ groups, so $J_{3,4}$, $J_{4,5}$, $J_{5,6}$, $J_{6,7ax}$, and $J_{6,7eq}$ could be measured. The methine resonance adjacent to the NO$_2$ group was assigned on the basis of its chemical shift, since in most other compounds of the series this signal occurred in the range δ 4.83–5.05 (Table I). In the more mobile isomer the *H*CNO$_2$ resonance appeared at δ 5.04, and the asymmetry of the nearby H-3 doublet (δ 5.22) clearly indicated that the two protons were not mutually coupled. Hence, it was concluded that this compound was a 5-nitrohept-2-ulo-septanose. The assignment of configuration to the septanose from the observed vicinial coupling constants ($J_{3,4}$ 6.8, $J_{4,5}$ 2.5, $J_{5,6}$ 10.1, $J_{6,7ax}$ 9.0 and $J_{6,7eq}$ 6.1 Hz) was

difficult because of the flexibility of the seven-membered ring. However bearing in mind the fact that the spiro ring junction would need to be arranged to maximise the favourable anomeric effect, and the nitro group would need to exist in an equatorial or pseudo-equatorial position, and also that at least one of the hydroxyl groups flanking it would be held equatorial or pseudo-equatorial, it is speculated that this isomer is the *α*-L-*galacto*-heptuloside **18**.

The less mobile isomer was a 4-nitroheptulose since the splitting in the H-3 doublet ($J_{3,4}$ 8.4 Hz) was matched only by an equal splitting in the $HCNO_2$ methine resonance. The observed vicinal coupling constants ($J_{3,4}$ 8.4, $J_{4,5}$ 10.5, $J_{5,6}$ 3.3, $J_{6.7ax}$ 3.3 and $J_{6.7eq}$ 1.0 Hz) suggested that the compound may be the *β*-D-*ido*-heptuloside **20**.

Our next task was the removal of the hydroxy substituents from the nitropyranoses. We first tried the method described by Baer and his co-workers[16], involving the reduction of the derived *O*-mesyl derivatives with sodium borohydride, a reaction which proceeds *via* the nitroalkenes. However, in our case we found preparation of the mesylate esters capricious, and so investigated the analogous reaction of the readily available *O*-acetyl derivatives **11, 13, 15**, and **17**. The result was that the reductive removal of the acetoxy groups from **11** was accomplished with ease by reaction with sodium borohydride in pyridine. The exothermic reaction resulted in the formation of 10-nitro-1,4,7-trioxaspiro[5.5]undecane as the *aci*-nitro salt, from which the borane–pyridine complex was removed by extraction with ether. On acidification by Amberlite IR-120 (H^+) resin two compounds were



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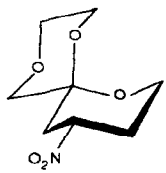
23 R = OH
24 R = OAc



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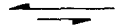

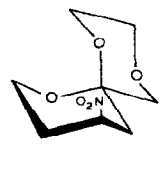

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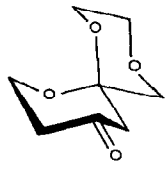

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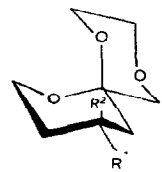

28 R^1 = OH, R^2 = H
29 R^1 = OAc, R^2 = H
30 R^1 = H, R^2 = OH
31 R^1 = H, R^2 = OAc
32 R^1 = R^2 = H

TABLE II

^{13}C-N.M.R. PARAMETERS IN $CDCl_3$

Assignments[a]	*Chemical shifts for individual compounds*						
	11	**22**	**25**	**27**	**29**	**31**	**32**
C-2	60.32[b]	59.72	59.62	59.99	59.47	59.67	60.72[b]
C-3	65.33	65.91	65.76	65.53	66.00	65.92	66.13
C-5	68.04	72.00	71.42	71.49	72.29	72.01	72.87
C-6	94.39	94.08	92.38	97.11	95.01	92.92	92.90
C-8	58.65[b]	58.50	56.11	59.50	58.99	55.89	59.49[b]
C-9	68.17	30.08	25.79	41.13	31.34	29.15	25.07
C-10	85.43	77.80	75.41	204.01	66.93	65.92	17.73
C-11	69.21	35.49	33.39	48.01	36.90	34.00	30.93

[a]See footnote *a*, Table I. [b]Interchangeable.

formed which were readily separated by flash chromatography to give crystalline (6*R*,10*R*)-10-nitro-1,4,7-trioxaspiro[5.5]undecane (**22**) and the (6*R*,10*S*) diastereomer **25** in isolated yields of 45 and 37%, respectively.

The structures of the two isomers were readily established by their ^{1}H-n.m.r. spectra, particularly since the resonance due to H-10 was clearly observed at low field in both cases (δ 4.87 and 4.52, respectively). In the spectrum of **25**, the signal for H-10 appeared as a complex multiplet as a result of four small couplings, indicating that the proton was equatorial and therefore the nitro substituent was held in an axial position. In the case of **22** the signal for H-10 appeared as a wide triple triplet reflecting two large diaxial couplings (12.5 and 12.1 Hz) and two small axial–equatorial couplings (4.4 each); therefore the compound was assigned as the equatorial isomer. When the same reaction was repeated on the mixture of nitrodiacetates, the same two isomers were obtained, but in a diminished combined yield of 40%. When the reaction was carried out in a mixture of dichloromethane and ethanol, the same two compounds were again obtained, together with several others of which **23** could be isolated with difficulty in 3% yield. For n.m.r. purposes **23** was converted into its *O*-acetyl derivative **24**, which showed a signal for one acetyl group and two low field resonances, at δ 5.31 (H-11, doublet, $J_{10,11}$ 10.4 Hz) and 4.80 (H-10). This indicated that **23** was a 11-hydroxy compound in which both the nitro and hydroxyl groups were equatorial.

The ratio of **22** and **25** varied with the nature of the acid used in the acidification process. The use of ion-exchange resin afforded the highest proportion of the axial isomer **25**, which must have arisen by kinetic protonation of the *aci*-nitro salt from the least hindered side. However, when **25** was treated with mild base (sodium acetate, basic alumina, etc.) it underwent epimerisation to the thermodynamically favoured equatorial isomer **22**.

When the (6*R*,10*S*) isomer (**25**) was heated under reflux in methanolic

hydrogen chloride it underwent substantial epimerisation at the acetal carbon, forming a 10:1 mixture of (6*S*,10*S*) isomer **26** and the starting material. The (6*S*) epimer was obtained crystalline in 60% yield and was identical in all respects to the (6*R*,10*R*) isomer except for the sign of the optical rotation.

In order to remove the nitro substituent, reduction by tributylstannane[17] was attempted, but the reaction did not proceed satisfactorily and therefore indirect methods were studied. Oxidative removal of the nitro group by alkaline permanganate was attempted, but the intermediate ketone **27** rapidly underwent further oxidation. However, when the *aci*-nitro form of **22/25** was preformed with sodium methoxide in methanol and then added to aqueous potassium permanganate buffered at pH ~7, oxidation took place with great ease to give the highly crystalline, enantiomerically pure 1,4,7-trioxaspiro[5.5]undecan-10-one (**27**) in 75% yield. Previous methodology[18] for the oxidation of aliphatic nitro groups has involved moderately alkaline media, which are unsuitable for enolisable ketones, and therefore unsatisfactory for larger-scale reactions. The present modification may overcome these drawbacks. In the present case the buffering of the oxidation mixture was also important because of the susceptibility of the ketone to racemisation at both acid and alkaline pH values. For example, at pH 9 and at room temperature **27** had a half life of only 20 min as determined by polarimetry. Hence attempts to reduce the ketone by Wolff–Kishner procedures *via* the *N*-tosylhydrazone resulted in racemic material. Conversion of **27** to the enol triflate by reaction with trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine also resulted in racemisation, so that **32** formed by subsequent hydrogenation was racemic.

Reduction of the ketone **27** with sodium borohydride was rapid and gave rise to a 7:3 mixture (g.l.c.) of two compounds, **30** and **28**, which could be separated by conventional flash chromatography only after *O*-acetylation. The two *O*-acetyl derivatives **31** and **29** were isolated in overall yields of 51% and 25% respectively, and characterised by their ^{1}H-n.m.r. spectra, in which the structure of the H-10 resonance was quite diagnostic of whether the OH group was axial or equatorial (Table I). Predictably, the borohydride preferentially attacked by an equatorial approach to give the axial isomer as the major product. The corresponding alcohols (**30** and **28**, respectively) were prepared by *O*-deacetylation with sodium methoxide.

For the removal of the remaining hydroxyl group, we employed an adaptation of the procedure used by Redlich and Francke[10] in their synthesis of 1,7-dioxaspiro[5.5]undecane. The axial alcohol (**30**) was converted into the triflate, which underwent a facile elimination reaction in the presence of basic alumina to give a mixture of two alkenes (g.l.c.–m.s.). These were not separated or characterised, but immediately hydrogenated to give the required 1,4,7-trioxaspiro[5.5]undecane (**32**) as a colourless oil in 56% yield. The specific rotation (−95.2°) of freshly prepared **32** indicated that it was optically pure, since this value agrees very well with the value that can be calculated from the optical rotations of both diasteroisomers of

the 10-nitro-, 10-acetoxy- and 10-hydroxy derivatives of **32**. In these calculations (*cf.* Hudson's rules of rotation[19]) it was assumed that the contributions of the two chiral centres were additive, which is not unreasonable given that the conformation is the same in all the compounds. The resulting values were −97°, −101.5°, and −96°, respectively. When the same elimination–reduction procedure was applied to the equatorial isomer **28**, the elimination stage was much slower, allowing partial racemisation to occur. The spiroacetal also underwent a slow racemisation during storage, even at −18°.

EXPERIMENTAL

General methods. — Unless otherwise stated optical rotations were determined at a concentration of ~1% in chloroform at 18–20° in 1 dm tubes on a Perkin Elmer 141 automatic polarimeter. ^{1}H-N.m.r. spectra were recorded on a Bruker WH-400 (400 MHz), a Bruker WM-250 (250 MHz), or a Nicolet NT-200 (200 MHz) spectrometer, and ^{13}C spectra were recorded on either a Bruker WP-60 or WM-250 instrument. In all cases tetramethylsilane was used as internal standard. Mass spectra were determined on a Kratos MS-25 spectrometer by electron impact at 70 eV. Melting points were measured on a Kofler hot stage and are uncorrected. Reactions were monitored by t.l.c. on silica gel ready coated on aluminium sheet (Merck 5554) and spots visualised by spraying with 5% conc. sulphuric acid in ethanol. Flash chromatography was performed on silica gel G (Merck 9385) at a pressure of 70–140 kPa. When a separation was completed the column was washed with either acetone or methanol and used again after equilibration with the eluting solvent. Normally the same silica was used 5 to 10 times before being discarded.

1,2-O-Ethylene-β-D-fructopyranoside (**6**). — Potassium hydroxide (34.8 g, 0.62 mol) was boiled in ethanol (400 mL) for about 1 h with stirring. The solution was cooled and 2-chloroethyl β-D-fructopyranoside[11] (100 g, 0.41 mol) was added. The reaction mixture was heated for 15 min under reflux and cooled, and the precipitated inorganic material filtered off. The filtrate was neutralised with Amberlite IR-120 (H^+) resin and then evaporated to dryness. The residual brown syrup was dissolved in water (400 mL) and the solution deionised with a mixture of Amberlite IR-120 (H^+) and Amberlite IRA-400 (HO^-) resins. Evaporation to dryness afforded a colourless syrup, which readily crystallised. Recrystallisation from a mixture of propan-1-ol (100 mL) and ethanol (50 mL) gave the spiroglycoside **6** (60 g, 70%), m.p. 130–132°, identical to an authentic specimen[11] having m.p. 131.5–132.5°.

Sodium metaperiodate oxidation and subsequent nitromethane cyclisation reactions of **6**. — (*a*). To a cooled (ice-water), stirred aqueous solution (150 mL) of sodium metaperiodate (32.7 g, 0.15 mol) was added **6** (15 g, 0.073 mol). The reaction mixture was kept for 18 h at 5°, after which no starting material was present (t.l.c., 5:1 chloroform–methanol). The precipitated inorganic salts were filtered off, and sodium hydrogencarbonate (6.1 g, 0.073 mol) was added. When carbon dioxide

evolution had ceased, propan-1-ol (150 mL) was added and the reaction mixture was again filtered and evaporated to dryness. The residue was extracted with propan-1-ol (75 mL), the extract was filtered, and the filtrate was finally evaporated to give clear syrupy dialdehyde **9**.

To an ice-cold solution of the above dialdehyde in ethanol (90 mL) was added nitromethane (20 mL, 0.37 mol) and M methanolic sodium methoxide (73 mL). The yellow reaction mixture was kept for 18 h at 20°, when t.l.c. (5:1 chloroform–methanol) indicated the formation of one major and several minor products. The reaction mixture was neutralised with Amberlite IR-120 (H^+) resin, and evaporated to dryness in the presence of silica gel. The silica gel was then placed on top of a short column of dry silica gel and the column was eluted with ether (1 L). Subsequent removal of the solvent afforded a clear yellow syrup, which was immediately acetylated by a mixture of acetic anhydride (50 mL) and boron trifluoride etherate (~1 mL). The reaction was complete after about 2 h, as judged by t.l.c. (5:1 ether–light petroleum). Sodium hydrogencarbonate was then added and the mixture was filtered and evaporated to dryness, the last traces of acetic anhydride being removed by co-evaporation with toluene. Addition of ethanol resulted in the crystallisation of 3,5-di-*O*-acetyl-4-deoxy-1,2-*O*-ethylene-4-nitro-α-L-*xylo*-hex-2-ulopyranose (**11**), which was recrystallised from ethanol to give fine needles (6.8 g, 30%), m.p. 150–166° (dec.), $[\alpha]_D$ −72°.

Anal. Calc. for $C_{12}H_{17}NO_9$: C, 45.1; H, 5.4; N, 4.4. Found: C, 44.8; H, 5.4; N, 4.4.

(*b*). The dialdehyde **9** (10 g, 0.049 mol, obtained as described above) was dissolved in ethanol (60 mL) and reacted with nitromethane (3.9 mL, 0.073 mol) in the presence of M methanolic sodium methoxide (15 mL). The reaction mixture was initially cooled (ice-bath) for about 10 min before being kept for 12 h at 5°. Workup as described in (*a*) afforded a colourless syrup (9 g). A portion (3 g) of the syrup was then subjected to flash chromatography (ether). First eluted was an oily mixture which was discarded because its i.r. spectrum showed no NO_2-stretch absorption. The following fractions contained small amounts of almost pure **14**, which crystallized readily, but most of the **14** was obtained as a syrup (1.5 g) contaminated with isomer **10**. Seeding of this syrup gave 4-deoxy-1,2-*O*-ethylene-4-nitro-α-L-*lyxo*-hex-2-ulopyranose (**14**) (330 mg, 9%), which when recrystallized from ethanol had m.p. 170–185° (dec.), $[\alpha]_D$ −31° (*c* 0.60, methanol); m.s.: *m/z* 236 (0.3, $M^+ + 1$), 218 (0.4, $M^+ - H_2O$), 205 (0.1, $M^+ - CH_2O$), 189 ($M^+ - NO_2$), 188 (1.4), 178 (3.1, $M^+ - CH_2O{-}C_2H_3$), and 103 (100).

Anal. Calc. for $C_8H_{13}NO_7$: C, 40.9; H, 5.6; N, 6.0. Found: C, 40.8; H, 5.6; N, 5.8.

A small amount was acetylated (acetic anhydride–boron trifluoride etherate) to give a crystalline solid (**15**) for n.m.r. analysis.

4-Deoxy-1,2-*O*-ethylene-4-nitro-α-L-*xylo*-hex-2-ulopyranose (**10**) failed to crystallize from the syrup, but it could be obtained crystalline in low yield by repeatedly chromatographing the residue. The compound had m.p. 155–170°

(dec.), $[\alpha]_D$ −77.5° (methanol), identical with the values determined for the free nitro sugar obtained by methanolysis of **11**.

Anal. Calc. for $C_8H_{13}NO_7$: C, 40.9; H, 5.6; N, 6.0. Found: C, 40.6; H, 5.5; N, 5.6.

The next fraction (0.5 g) contained some **10** and **14**, but 4-deoxy-1,2-*O*-ethylene-4-nitro-β-D-*arabino*-hex-2-ulopyranose (**16**) was the major component, crystallising readily from ether (300 mg, 8%). Recrystallisation from ethanol afforded short needles, m.p. 183° (dec.), $[\alpha]_D$ −174° (*c* 0.5, methanol).

Anal. Calc. for $C_8H_{13}NO_7$: C, 40.9; H, 5.6; N, 6.0. Found: C, 40.8; H, 5.5; N, 5.7.

A small amount was acetylated (acetic anhydride–boron trifluoride etherate) to give a crystalline solid (**17**) for n.m.r. analysis.

(*c*). The periodate oxidation was performed as in (*a*) above, using 15 g (0.073 mol) of **6**, but the reaction mixture was processed after only 40 min. The hemialdal product was then cyclised with nitromethane (12 mL, 0.2 mol) in the presence of M methanolic sodium methoxide (4 mL), and this reaction mixture kept for 24 h at 5°. The solvent was evaporated, and following removal of inorganic material by filtration through silica gel as described above, a colourless syrup (15 g) was obtained. A portion (3 g) of this residue was then chromatographed (7:5 petroleum ether–acetone). Early fractions containing **10, 14, 12**, and **16** were followed by the 1,2-*O*-ethylene-heptulose **18** (contamined with traces of **10, 14**, and **16**). Compound **18** crystallised from ether (50 mg, 1%), m.p. 170° (dec.), $[\alpha]_D$ −42° (*c* 0.15, methanol).

Anal. Calc. for $C_9H_{15}NO_8$: C, 40.8; H, 5.7; N, 5.3. Found: C, 40.5; H, 5.7; N, 5.2.

A small amount was acetylated (acetic anhydride–boron trifluoride etherate), giving **19**, ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 5.82 (m, 1 H, $J_{6,7a}$ 6.1, $J_{6,7b}$ 9.0, $J_{5,6}$ 10.1 Hz, H-6), 5.80 (dd, 1 H, $J_{4,5}$ 2.5, $J_{3,4}$ 6.8 Hz, H-4), 5.22 (d, 1 H, $J_{3,4}$ 6.8 Hz, H-3), 5.04 (dd, 1 H, H-5), 4.10–3.40 (10 H, OCH_2), 2.19, 2.12, and 2.04 (3 s, CH_3CO).

The slowest moving product was initially eluted together with lesser amounts of **18**, with which it cocrystallised. However, when this fraction was chromatographed again, the 1,2-*O*-ethylene-heptulose **20** was obtained as an amorphous solid (60 mg, 1%), m.p. 121° (dec.), $[\alpha]_D$ −87° (*c* 0.5, methanol).

Anal. Calc. for $C_9H_{15}NO_8$: C, 40.9; H, 5.7; N, 5.3. Found: C, 40.7; H, 5.7; N, 5.6.

A small amount was acetylated (acetic anhydride–boron trifluoride etherate), giving **21**, ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 5.62 (dd, 1 H, $J_{5,6}$ 3.3, $J_{4,5}$ 10.5 Hz, H-5), 5.57 (d, 1 H, $J_{3,4}$ 8.3 Hz, H-3), 5.41 (td, $J_{6,7a}$ ~1, $J_{6,7b}$ ~3 Hz, H-6), 5.10 (dd, 1 H, H-4), 4.20–3.55 (10 H, OCH_2), 1.97, 2.11, and 2.18 (3 s, CH_3CO).

*4-Deoxy-1,2-*O*-ethylene-4-nitro-α-*L*-xylo-hex-2-ulopyranose* (**10**). — The diacetate **11** (0.70 g) was dissolved in acetone (1 mL) and added to a solution of M methanolic hydrogen chloride (20 mL). The mixture was heated for 2 h under reflux, when t.l.c. (ether) indicated that a single slower-moving product had been

formed. The reaction mixture was evaporated to dryness, and the residue was subjected to several additions and evaporations, first of methanol and then ethyl acetate. The resulting crystalline solid was decolourised with charcoal in ethanol and recrystallised from ethyl acetate to give **10** (0.45 g, 87%), m.p. 155–170° (dec.), $[\alpha]_D$ −77.5° (*c* 0.7, methanol).

Anal. Calc. for $C_8H_{13}NO_7$: C, 40.8; H, 5.6; N, 6.0. Found: C, 40.4; H, 5.4; N, 5.7.

*4-Deoxy-1,2-O-ethylene-4-nitro-β-*D-ribo-*hex-2-ulopyranose* (**12**). — A portion (3 g) of the nitro-diol mixture from (*b*) above was dissolved in M methanolic sodium methoxide (15 mL, 1.2 equiv.) and kept for 14 h at room temperature. After neutralisation of the solution with Amberlite IR-120 (H^+) resin, the faster-moving nitro sugar **12** was readily separated by flash chromatography (20:1 chloroform-methanol), yield 350 mg (10%), m.p. 100–133° (dec.), $[\alpha]_D$ −104° (*c* 0.55, methanol).

Anal. Calc. for $C_8H_{13}NO_7$: C, 40.9; H, 5.6; N, 6.0. Found: C, 40.8; H, 5.6; N, 6.0.

A small amount was acetylated (acetic anhydride–boron trifluoride etherate) to give a syrup (**13**) for n.m.r. analysis.

(6R,10R)-10-Nitro-1,4,7-trioxaspiro[5.5]undecane (**22**) *and its (6R,10S) isomer* (**25**). — To a cooled (ice-water), gently stirred solution of **11** (4.2 g, 0.013 mol) in pyridine (30 mL) was added sodium borohydride (3.8 g, 0.10 mol). An exothermic reaction took place with vigorous evolution of hydrogen. The mixture was stirred for 3 h with occasional additions of tetrahydrofuran to maintain the fluidity of the gelatinous solution. T.l.c. (5:1, ether–light petroleum) indicated the absence of starting material and the formation of three products. One, which did not respond to charring reagents but was visualised by u.v. light, was shown to be the pyridine–borane complex. The reaction mixture was evaporated to dryness and toluene was evaporated from the residue to give a solid powder, from which the pyridine–borane complex was extracted with dry ether in a Soxhlet apparatus. The residue was then dissolved in methanol (100 mL) and boiled for 30 min in order to decompose the excess of borohydride. Sufficient Amberlite IR-120 (H^+) resin was then added to adjust the pH to about 7. The solvent was evaporated, and the residue partitioned between chloroform (100 mL) and water (50 mL). The chloroform phase was dried ($MgSO_4$) and evaporated to a syrupy residue, which was chromatographed (5:1, ether–light petroleum).

The faster-moving component (6*R*,10*R*)-10-nitro-1,4,7-trioxaspiro[5.5]-undecane (**22**; 1.2 g, 45%), had m.p. 60–61° (from hexane), $[\alpha]_D$ −90°; m.s.: *m/z* 203 (0.1, M^+), 173 (2, $M^+ - CH_2O$), 157 (10, $M^+ - NO_2$), 146 (14, 173 − C_2H_3), 127 (16, 157 − CH_2O), 99 (62, 127 − C_2H_4), and 55 (100).

Anal. Calc. for $C_8H_{13}NO_5$: C, 47.3; H, 6.4; N, 6.9. Found: C, 47.3; H, 6.5; N, 6.5.

The slower-moving compound (6*R*,10*S*)-10-nitro-1,4,7-trioxaspiro[5.5]-undecane (**25**; 1.0 g, 37%), had m.p. 100–102°, $[\alpha]_D$ −104°; m.s.: *m/z* 173 (2, M^+

– CH_2O), 157 (11, $M^+ - NO_2$), 146 (14, 173 – C_2H_3), 127 (16, 173 – NO_2), 99 (62, 127 – C_2H_4), and 55 (100).

Anal. Calc. for $C_8H_{13}NO_5$: C, 47.3; H, 6.4; N, 6.9. Found: C, 47.2; H, 6.4; N, 6.4.

(11S,10R,6R)-11-Hydroxy-10-nitro-1,4,7-trioxaspiro[5.5]undecane (**23**). — To a solution of **11** (6.3 g, 0.02 mol) in dichloromethane (125 mL) and ethanol (25 mL) was added sodium borohydride (6.1 g, 0.16 mol). The suspension was stirred and kept for 5 h at reflux, when in addition to the major products **22** and **25**, several minor products had also formed. Acetic acid (~35 mL) was carefully added to decompose the excess of borohydride, and the reaction mixture was evaporated to dryness. The residue was partitioned between chloroform and water, the chloroform extract was evaporated to dryness, and the residue was chromatographed (5:1 ether–light petroleum) to give pure **22** (1.0 g, 25%), whilst **25** was obtained as an inseparable mixture (0.90 g) with a slightly slower-moving component **23**. (11*S*,10*R*,6*R*)-11-Hydroxy-10-nitro-1,4,7-trioxaspiro[5.5]undecane (**23**) crystallised on the addition of ether, yield 135 mg (3%), m.p. 145–156° (dec.), $[\alpha]_D$ −99° (*c* 0.6, methanol); m.s.: *m/z* 219 (<0.1, M^+), 173 (1.0, $M^+ - NO_2$), 162 (1.3, $M^+ - CH_2O - C_2H_3$), 115 (4.3, $M^+ - NO_2 - CH_2O - C_2H_4$), 103 (26.9), and 28 (100).

Anal. Calc. for $C_8H_{13}NO_6$: C, 43.8; H, 6.0; N, 6.4. Found: C, 43.9; H, 5.9; N, 6.3.

(6S,10S)-10-Nitro-1,4,7-trioxaspiro[5.5]undecane (**26**). — The axial (10*S*)-nitro derivative **25** (240 mg, 1.18 mmol) was heated under reflux in 0.2M methanolic hydrogen chloride for 4 h, generating a mixture of the starting material and a faster-moving major product in the ratio 1:10 as revealed by h.p.l.c. analysis. Some degradation was indicated by the presence of traces of two other components. The mixture was neutralised with sodium hydrogen-carbonate, filtered, and evaporated to dryness before being chromatographed to give (6*S*,10*S*)-10-nitro-1,4,7-trioxaspiro[5.5]undecane (**26**; 145 mg, 60%), m.p. 59.5–60°, $[\alpha]_D$ +89°; i.r. identical with that of **22**.

Anal. Calc. for $C_8H_{13}NO_5$: C, 47.3; H, 6.4; N, 6.9. Found: C, 47.6; H, 6.5; N, 7.6.

(6R)-1,4,7-trioxaspiro[5.5]undecan-10-one (**27**). — A solution of the mixture of the nitro compounds **22** and **25** (2.7 g, 0.013 mol) in M methanolic sodium methoxide (25 mL) was added to a stirred, cooled (ice-water) aqueous solution (100 mL) of potassium permanganate (3.1 g, 0.02 mol) and potassium dihydrogen-phosphate (10.2 g, 0.075 mol, pH ~6.5). A rapid oxidation took place, and after 5 min, the reaction mixture was worked up by filtration through Hyflo Supercell, and extraction of the aqueous filtrate with chloroform (100 mL, followed by three additional 50 mL portions). The combined extracts were dried ($MgSO_4$) and evaporated to dryness to give the highly crystalline ketone **27**, which was recrystallised from hexane (1.6 g, 75%), m.p. 78–80°, $[\alpha]_D$ −108° (*c* 0.5, methanol); m.s.: *m/z* 172 (5, M^+), 142 (11, $M^+ - CH_2O$), 115 (28, 142 – C_2H_3), and 55 (100).

Anal. Calc. for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.8; H, 7.1.

(6R,10R)-10-Acetoxy-1,4,7-trioxaspiro[5.5]undecane (**29**) *and its (6R,10S)-isomer* (**31**). — To cooled (ice-water) methanol (10 mL) was added sodium borohydride (0.36 g, 0.01 mol), followed immediately by the ketone **27** (1.0 g, 0.064 mol). Vigorous evolution of hydrogen took place, and within 3 min all the starting material had been converted into slower-moving components, not well resolved by t.l.c. The excess reducing agent was destroyed by the addition of acetic acid (~0.5 mL), and ether (30 mL) was then added to precipitate inorganic material, which was filtered off. Examination of the solution by g.l.c. and g.l.c.–m.s. indicated two components. The faster-moving **30** [m.s.: *m/z* 144 (13, $M^+ - CH_2O$), 127 (12, 144 − OH), 126 (13, 144 − H_2O), 117 (45, $M^+ - CH_2O - C_2H_4$), 99 (35), and 73 (100)] was the major product (71%). The slower-moving product **28** [m.s.: *m/z* 117 (47, $M^+ - CH_2O - C_2H_4$), 99 (24, 117 − H_2O), and 73 (100)] comprised 29% of the mixture.

The solution was concentrated to dryness, and the residue acetylated in the conventional way with pyridine (3 mL) and acetic anhydride (3 mL). T.l.c. (5:1.5 ethyl acetate–light petroleum) indicated the presence of two products, which were readily separated by column chromatography. The minor, faster-moving compound **29** was obtained as a syrup (310 mg, 25%), $[\alpha]_D$ −85°.

Anal. Calc. for $C_{10}H_{15}O_5$: C, 55.6; H, 7.5. Found: C, 55.1; H, 7.5.

The major slower-moving acetate **31** crystallised from hexane (695 mg, 51%), m.p. 112–117° (dec.), $[\alpha]_D$ −118°.

Found: C, 55.4; H, 7.4.

Both acetates were readily deacetylated to give their parent alcohols. The (10*R*)-isomer **29** afforded **28** as a syrup, $[\alpha]_D$ −94°.

Anal. Calc. for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 54.8; H, 7.9.

The (10*S*)-acetate **31** afforded **30** as a crystalline solid, m.p. 60–61° (hexane), $[\alpha]_D$ −98.2° (*c* 0.8, chloroform).

Found: C, 55.3; H, 8.0.

(6R)-1,4,7-Trioxaspiro[5.5]undecane (**32**). — The axial (10*S*)-alcohol **30** (125 mg, 0.72 mmol) was dissolved in dry dichloromethane (2 mL) and dry pyridine (0.28 mL, 3.5 mmol) in a two-neck, round-bottom flask fitted with a magnetic stirrer and flushed with dry nitrogen. The stirred solution was cooled to −20° (solid CO_2–methanol) and under an atmosphere of nitrogen, trifluoromethanesulphonic anhydride (429 mg, 1.53 mmol) was carefully added over 5 min. The reaction mixture was allowed to reach 0° and kept for 0.5 h at this temperature. By then almost all of the starting material had been converted into a mixture of two products, of which the slower-moving was the major component.

Dry ether (15 mL) was added to the solution and the precipitated pyridinium triflate filtered off. Following the addition of a spatula-tip of basic alumina, the filtrate was concentrated under reduced pressure. The alumina residue was extracted with ether (~20 mL), giving an almost colourless solution to which another portion of basic alumina (~4 g) was added. This ethereal solution was then stirred for 2 h, when t.l.c. showed that full conversion of the slower-moving product

into the faster-moving one had taken place. Examination of the solution by g.l.c. and g.l.c.–m.s. indicated one major product and trace amounts of another. The two compounds had almost identical mass spectra [*m/z* 156 (M^+), 126 ($M^+ - CH_2O$), and 99], and the values indicated that they were olefins. The alumina was filtered off and washed with ether, the colourless ethereal solution was concentrated to 3–4 mL, a drop of triethylamine was added, and the mixture was hydrogenated at 1 atm pressure over Pd-on-C for 1 h. This afforded a slightly faster-moving material which on chromatography finally gave the desired spiroacetal **32** as a colourless oil (64 mg, 56%), $[\alpha]_D$ −95.2° (*c* 1.2, *n*-hexane); m.s.: *m/z* 158 (10, M^+), 128 (51, $M^+ - CH_2O$), and 101 (100, $M^+ - C_3H_5O$).

Anal. Calc. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 61.0; H, 9.1.

When the equatorial (10*R*)-alcohol **29** (100 mg) was employed, the elimination of triflic acid was considerably slower (2 days). Thus after hydrogenation the product obtained had $[\alpha]_D$ −70°, indicating that some isomerisation had occurred.

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