Use of Carbohydrate Derivatives for Studies of Phosphorus Stereochemistry. Part I. Stereochemistry of 1,3,2-dioxaphosphorinan-2-ones and Synthesis of Optically Active Phosphine Oxides

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Pairs of 1,3,2-dioxaphosphorinan-2-ones, epimeric at phosphorus, have been prepared by treatment of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside and -galactopyranoside with phosphonic or phosphoric dihalides. The configuration at phosphorus in these derivatives has been assigned on the basis of n.m.r. and i.r. data and of comparison of the rates of formation and relative stabilities of the epimers. For the formation of the 1,3,2-dioxaphosphorinan-2-ones it is suggested that the kinetic preference for the thermodynamically less stable isomers depends on steric interactions in twist-ring transition intermediates, and that the subsequent equilibration depends on the relative stabilities of the chair conformers. The conversions of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*R*)- and (*S*)-4,6-methyl phosphonate into (*S*)- and (*R*)-ethylmethylphenylphosphine oxide, respectively, by sequential addition of phenylmagnesium bromide and ethylmagnesium bromide provide examples of the utility of carbohydrate 1,3,2-dioxaphosphorinan-2-ones for the stereospecific synthesis of optically active phosphine oxides.

THERE are many examples of the utility of carbohydrates for stereochemical studies, and the use of carbohydrates for the stereo-selective synthesis of optically active non-carbohydrate compounds has been well documented.[1] However, the use of carbohydrates for stereochemical studies of phosphorus chemistry has received little attention despite the fact that sugar phosphates are an important class of natural products. In this series, an attempt will be made to demonstrate that carbohydrates, in which the stereochemistry and nature of the functional groups may be conveniently modified, make excellent frameworks within which phosphorus stereochemistry may be studied and from which optically active non-carbohydrate phosphorus derivatives may be prepared.

Recently there has been considerable interest in establishing the relation between the stereochemistry at phosphorus and variously substituted carbon atoms in 1,3,2-dioxaphosphorinan-2-ones. Physical techniques such as n.m.r.[2] and i.r. spectroscopy,[3] *X*-ray crystallography,[4] and dipole moment measurements[5,6] have all been used in conformational and configurational studies of 1,3,2-dioxaphosphorinan-2-one rings. These studies show that the stable isomers of 1,3,2-dioxaphosphorinan-2-ones with electronegative *P*-substituents such as alkoxy-, aryloxy-, or halogeno-, adopt chair conformations in which the electronegative substituent is orientated axially. The situation is less clear for dioxaphosphorinan-2-ones carrying *P*-alkyl, -phenyl, or -arylalkyl substituents, and for these compounds stereochemical preference cannot be predicted, partly because of their conformational inhomogeneity.[6,7] Such difficulties, which are inherent in monocyclic systems, may be avoided, at least in part, by the use of bicyclic fused-ring systems, and in this paper some stereochemical studies of 1,3,2-dioxaphosphorinan-2-ones involved in *trans*-fused (glucose series) and *cis*-fused (galactose series) bicyclic systems are described. Of more importance, the defined absolute configuration of the carbohydrate portions of these molecules makes it possible to assign the absolute configuration at phosphorus. Further, chemical as well as physical procedures may be used to assist the configurational assignments.

Treatment of the diol (1) with methylphosphonic difluoride in the presence of triethylamine afforded the

[1] T. D. Inch, *Adv. Carbohydrate Chem. Biochem.*, 1972, **27**, 191.

[2] (*a*) R. S. Edmundson, *J.C.S. Perkin I*, 1972, 1660; (*b*) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc.* (*B*), 1971, 1454; (*c*) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1968, 3033; (*d*) E. Ye. Nifant'ev and A. A. Borisenko, *Tetrahedron Letters*, 1972, 309; (*e*) L. D. Hall and R. B. Malcolm, *Chem. and Ind.*, 1968, 92; (*f*) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1968, 2091; (*g*) R. S. Edmundson, *Tetrahedron Letters*, 1969, 1905; (*h*) J. R. Campbell and L. D. Hall, *Chem. and Ind.*, 1971, 1138; (*i*) J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, 1972, **94**, 8224; (*j*) W. G. Bentrude and H.-W. Tan, *J. Amer. Chem. Soc.*, 1973, **95**, 4666.

[3] J. P. Majoral and J. Navech, *Bull. Soc. chim. France*, 1971, 95, 1331, 2609.

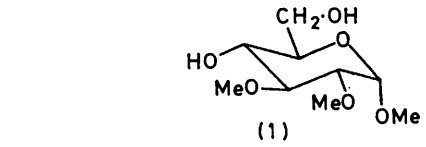
[4] (*a*) H. J. Geise, *Rec. Trav. chim.*, 1967, **86**, 362; (*b*) L. Silver and R. Rudman, *Acta Cryst.*, 1972, **B28**, 574; (*c*) R. C. G. Killean, J. L. Lawrence, and I. M. Magennis, *Acta Cryst.*, 1971, **B27**, 189; (*d*) M. Haque, C. N. Caughlan, J. H. Hargis, and W. G. Bentrude, *J. Chem. Soc.* (*A*), 1971, 1786; (*e*) T. A. Beineke, *Acta Cryst.*, 1969, **B25**, 413.

[5] M. Kainosho and T. Shimozawa, *Tetrahedron Letters*, 1969, 865.

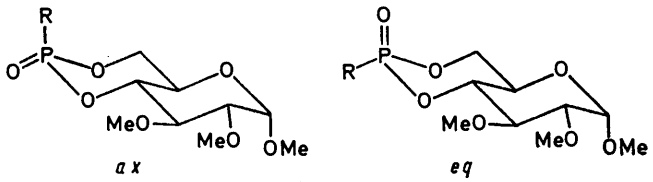
[6] C. Bodkin and P. Simpson, *Chem. Comm.*, 1969, 829.

[7] (*a*) W. G. Bentrude and J. H. Hargis, *Chem. Comm.*, 1969, 1113; (*b*) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1970, 752; (*c*) A. R. Katritzky, M. R. Nesbitt, J. Michalski, Z. Tulimowski, and A. Zwierzak, *J. Chem. Soc.* (*B*), 1970, 140.

crystalline (*R*)- and (*S*)-4,6-methylphosphonates (2*ax*) * and (2*eq*) * which were separated by chromatography over silica. Similarly, the ethyl phosphates (3*ax*) and (3*eq*) were prepared from (1) and ethyl phosphorodichloridate. The phosphonates (5*ax*) and (5*eq*) and the phosphates (6*ax*) and (6*eq*) were prepared from methyl 2,3-di-*O*-methyl-α-D-galactopyranoside (4) by

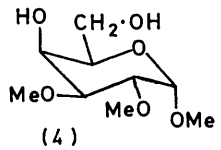


(1)

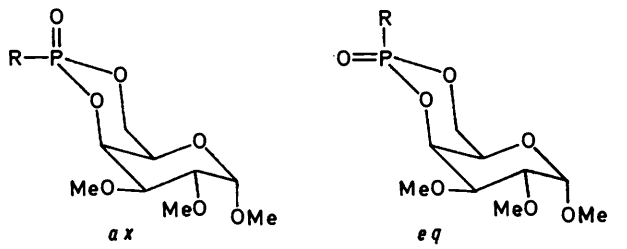


ax *eq*

(2) R = Me
(3) R = OEt



(4)



ax *eq*

(5) R = Me
(6) R = OEt

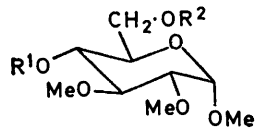
similar procedures. Tentative configurational assignments for these compounds were based on an observation that in 1,3,2-dioxaphosphorinan-2-ones the P=O i.r. stretching band is at higher frequency and the ^{31}P n.m.r. chemical shift is at higher field when the P=O group is equatorial rather than axial.[2j,3] The relevant data are shown in the Table. An increasing number of investigations has justified the use of such spectroscopic data for configurational assignments [8] of 1,3,2-dioxaphosphorinan-2-ones, particularly where the compounds are conformationally homogeneous and have chair conformations. The evidence that the compounds in the Table exist essentially in chair conformations and other n.m.r. data which support the assigned configurations are discussed later in this paper.

Support for the foregoing structural assignments was obtained from a comparison of the relative rates of formation of (2*ax*) and (2*eq*) and of (3*ax*) and (3*eq*). It was observed during repeat preparations of (2*ax*) and (2*eq*) that the relative proportions of these compounds varied with reaction conditions. Early processing of the reaction mixture, *i.e.* after 2—4 h, afforded (2*ax*) and (2*eq*) in ratios of *ca.* 5 : 1 whereas storage of the reaction mixture for 2 days before processing resulted in the isolation of the isomers in approximately equal amounts. This implication that (2*ax*) was the kinetically preferred product whereas (2*eq*) was the thermodynamically more stable product, was supported by t.l.c. indications and was substantiated in the following way.

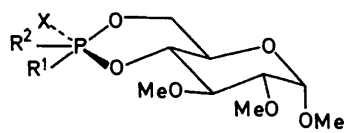
Spectroscopic data for 1,3,2-dioxaphosphorinan-2-ones

Compound	$\nu_{P=O}$/cm^{-1}	δ(^{31}P) †
(2*ax*)	1254 (KBr)	−25·5
	1270 ($CDCl_3$)	
(2*eq*)	1235 (KBr)	−31·5
	1238 ($CDCl_3$)	
(3*ax*)	1294 ($CDCl_3$)	+7·5
	1300 (CCl_4)	
(3*eq*)	1265 ($CHCl_3$)	+4·4
	1268 (CCl_4)	
(5*ax*)	1270 ($CDCl_3$)	
	1258 (KBr)	−22·7
(5*eq*)	1233 ($CDCl_3$)	−30·5
	1240 (KBr)	
(6*ax*)	1297 (film)	+8·5
(6*eq*)	1267 (film)	+6

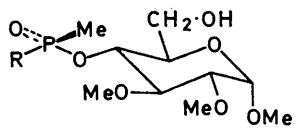
† In p.p.m. (low field negative) from 85% H_3PO_4.



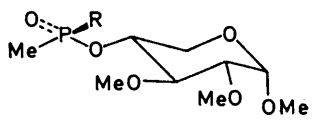
(7) R^1 = CH_2Ph, R^2 = H
(8) R^1 = CH_2Ph, R^2 = MeP(O)F
(9) R^1 = H, R^2 = MeP(O)F



(10) R^1 = =O, R^2 = Me, X = F
(11) R^1 = Me, R^2 = =O, X = F
(12) R^2 = =O, R^1 = OEt, X = Cl



(13) R = Ph
(17) R = Et



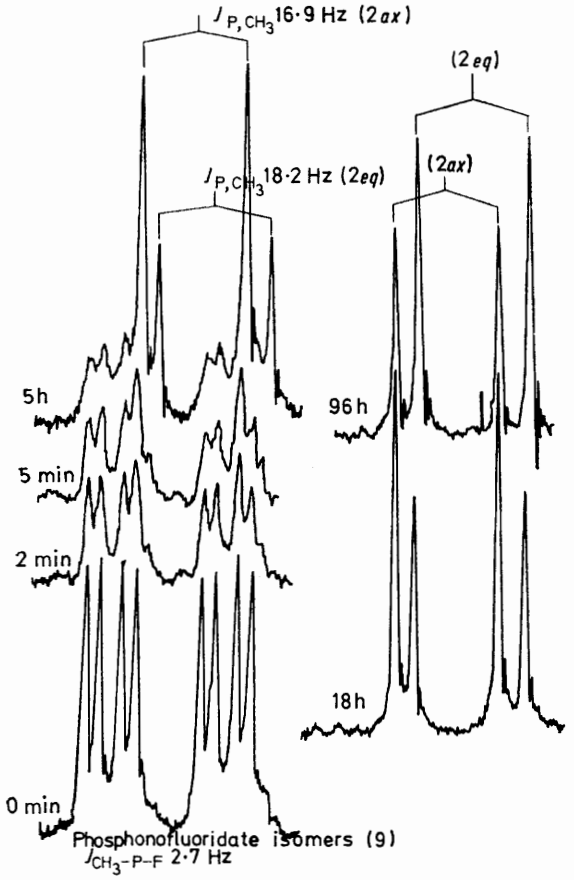
(15) R = Ph
(18) R = Et

Methyl 4-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranoside (7), prepared by sequential tritylation, benzylation, and detritylation of (1), afforded the methylphosohono-

* For isomeric 1,3,2-dioxaphosphorinan-2-ones the isomers with axial and equatorial substituents at phosphorus are denoted by *ax* and *eq*, respectively.

[8] D. B. Cooper, J. M. Harrison, T. D. Inch, and G. Lewis, following paper.

fluoridate (8) on treatment with methylphosphonic difluoride. Catalytic hydrogenolysis of (8) over palladium–charcoal in ethyl acetate gave the alcohol (9) as a chromatographically indistinguishable mixture of isomers (epimeric at phosphorus). The ^{1}H n.m.r. spectrum of (9) in $CDCl_3$ (Figure) showed a pair of quartets for the PMe groups with J_{PMe} 19 and J_{FMe} 2·7 Hz. Following addition of triethylamine to the solution the formation of (2*ax*) and (2*eq*) was monitored by ^{1}H n.m.r. (Figure; 2 min—96 h). At first the



Changes in P–Me signal with time following addition of triethylamine to (9) in CDCl

PMe doublet at δ 1·63 (J_{PMe} 16·9 Hz), characteristic of (2*ax*), preponderated but at equilibrium (2*eq*) (δ 1·60; J_{PMe} 18·2 Hz) was clearly the thermodynamically more stable product. The isomeric fluoridates disappeared from the reaction mixture at essentially the same rate (Figure) thus showing that the rate of racemisation was greater than the rate of dioxaphosphorinan-2-one formation. These results are most easily rationalised on the assumption that the transition intermediate leading to the formation of (2*ax*) is in the twist-ring conformation (10), in which the *P*-methyl group occupies a sterically unhindered pseudoequatorial orientation. The transition intermediate (11) which leads to (2*eq*) has the *P*-methyl group in the unfavoured pseudoaxial orientation. If it is further postulated that once a 1,3,2-dioxaphosphorinan-2-one is formed the conformational preference is for a chair rather than a twist-ring or boat form (and n.m.r. evidence is consistent with this) it is a logical consequence that equilibration of (2*ax*), in which 2,4-diaxial interactions are a destabilising influence, with (2*eq*) should occur. For the formation of (2*ax*) and (2*eq*) by direct treatment of (1) with methylphosphonic difluoride (or methylphosphonic dichloride), similar stereochemical considerations almost certainly apply and the initial preferential formation of (2*ax*) is consistent with the twist-ring hypothesis irrespective of whether phosphonylation occurs first at the C-4 or the C-6 hydroxy-group.

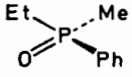
The twist-ring intermediate hypothesis also accounts for the observation that when (1) and ethyl phosphorodichloridate in ether were treated with triethylamine the isomer with the equatorial *P*-ethoxy-group (3*eq*) preponderated initially but rearranged in the reaction mixture to give a preponderance of the more stable isomer (3*ax*). The more rapid formation of (3*eq*) is consistent with the well recognised axial preference of electronegative substituents [2,4] in 1,3,2-dioxaphosphorinan-2-ones (analogous to the 'anomeric effect' in carbohydrate chemistry) only if a non-chair conformation such as (12) is invoked, and the subsequent conversion of (3*eq*) into (3*ax*) is also consistent with this stereochemical preference in the stable chair conformation finally adopted.

Since the foregoing arguments satisfactorily account for the observed differences in the rates of formations and stabilities of the pairs of isomers (2*ax*) and (2*eq*), and (3*ax*) and (3*eq*), and since there appears to be no adequate explanation for these differences if the configurational assignments of (2*ax*) and (2*eq*) and of (3*ax*) and (3*eq*) are reversed, the foregoing results provide a strong justification for the validity of the initial configurational assignments. These results additionally provide interesting information about the conformational preference of transition intermediates in ring-forming processes.

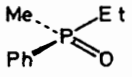
The indications from t.l.c. and n.m.r. studies were that the phosphonate (5*ax*) was formed more rapidly than the thermodynamically more stable (5*eq*) and that the phosphate (6*eq*) was formed more rapidly than the more stable (6*ax*). Thus the stereochemical requirements for the rate of formation and stability of 1,3,2-dioxaphosphorinanes are independent of whether the dioxaphosphorinan is part of a *trans*- or a *cis*-fused bicyclic system.

The optical purity of the cyclic phosphorus derivatives (2), (3), (5), and (6) makes them potentially suitable substrates for the synthesis of non-carbohydrate optically active phosphorus derivatives. The conversions of (2*ax*) and (2*eq*) into the (*S*)- and (*R*)-ethylmethylphenylphosphine oxides, respectively, are examples of such syntheses. The cyclic phosphonate (2*ax*) was converted into the (*S*)-4-methylphenylphosphonate (13) by heating under reflux for 1 h with

phenylmagnesium bromide in benzene–ether. Compound (13) underwent further reaction when treated under reflux with ethylmagnesium bromide for 2 days to afford (−)-(*S*)-ethylmethylphenylphosphine oxide (14), $[\alpha]_D$ −23° (MeOH).[9] Similarly (2*eq*) was converted *via* (15) into (+)-(*R*)-ethylmethylphenylphosphine oxide (16).



(14)



(16)

The foregoing procedure is analogous to that used by Mislow and his co-workers,[9-11] who prepared optically active phosphine oxides by treating diastereoisomeric menthyl alkylaryl- (or alkylalkyl-) phosphinates, which were separated by fractional crystallisation, with Grignard or organolithium reagents. Use of carbohydrate derivatives has the same limitation as use of menthol derivatives in that the ease of displacement of the carbohydrate unit from the phosphinate depends on the nature of the groups attached to phosphorus. Thus although (13) and (15) were converted into (14) and (16), respectively, by treatment with ethylmagnesium bromide, the formation of (14) and (16) by treatment of (17) and (18), respectively, with phenylmagnesium bromide was not found possible. However, syntheses of optically active phosphine oxide from carbohydrate cyclic phosphorus esters has the advantage that the starting substrates may be separated chromatographically (and that the proportions of isomers may be controlled to some extent by choice of reaction conditions) and that in principle, at least, enantiomeric phosphine oxides may be obtained from the same cyclic precursor by reversing the order of addition of Grignard or organolithium reagents.

The ease of ring opening also depends on the nature of the carbohydrate derivative. Thus whereas ring opening of the *trans*-fused 1,3,2-dioxaphosphorinan-2-ones with Grignard reagents occurred under mild conditions, in the *cis*-fused galactose series the 1,3,2-dioxaphosphorinan-2-ones were essentially inert to attack by Grignard reagents even under forcing conditions (*i.e.* up to 96 h under reflux in benzene).

It is of interest that the attack of Grignard reagents on (2*ax*) and (2*eq*) resulted in preponderant cleavage of the P–O(6) bond. That the products obtained were 4-phosphonates was apparent from a characteristic n.m.r. signal for H-4 ($J_{3,4} = J_{P,4} = 10$ Hz); it was also shown that (17) and (18) differed chromatographically and spectroscopically from the mixture of 6-ethylmethylphosphinyl isomers obtained by catalytic hydrogenolysis of methyl 4-*O*-benzyl-2,3-di-*O*-methyl-6-[(*RS*)-ethylmethylphosphinoyl]-α-D-glucopyranoside. Traces of a minor product with spectroscopic properties consistent with a 6-methylphosphinoyl derivative were isolated from the reaction of (2*eq*) with phenylmagnesium bromide, but although there was some chromatographic evidence for the formation of minor products in the other Grignard reactions no products were isolated in sufficient amount for tentative identification.

N.m.r. Studies.—Provided that it is demonstrated that both isomers (epimeric at phosphorus) of any 1,3,2-dioxaphosphorinan-2-one exist essentially in the same chair conformation and not as an equilibrium mixture of their forms[7] or as flexible ring forms,[2a] it is reasonable to conclude on the basis of available evidence[3,8] that the isomers for which the i.r. phosphoryl stretching frequencies are at higher wavelength and for which the ^{31}P n.m.r. chemical shifts are at higher field are those in which the 2-substituents are orientated axially. Evidence that the pairs of isomers of (2), (3), (5), and (6) had chair conformations was obtained from the phosphorus resonances in these compounds. For the methylphosphonates each resonance appeared as a poorly resolved 1 : 4 : 6 : 4 : 1 quintet, consistent with $J_{P,CH_3} = J_{P,H\text{-}6eq} = 16$—22 Hz, with each peak broadened by further coupling with H-4 and H-6*ax* ($J_{P,H\text{-}4} = J_{P,H\text{-}6ax} = 2$—3 Hz) and to a lesser extent with H-5. For ethyl phosphates the phosphorus resonances appeared as 1 : 2 : 1 : 1 : 2 : 1 sextets with $J_{P,H\text{-}6eq}$ 20—25, J_{P,CH_3} 8·5 Hz, with each peak further broadened by coupling with H-4 and H-6*ax* ($J_{P,H\text{-}4} = J_{P,H\text{-}6ax} = 2$—3 Hz). Some corroboration of these coupling constants was obtained from the ^1H n.m.r. spectra, particularly of (5*eq*) for which a reasonably detailed first-order analysis was possible. These values are all consistent with the chair conformations depicted for it has been shown clearly that only in chair conformations are large (*ca.* 20 Hz), vicinal, *trans* P–O–C–H and small (2—4 Hz), *gauche*, vicinal P–O–C–H couplings observed.[12]

Certain proton chemical shift data are also consistent with the assigned configurations and conformations. Thus in the galactopyranoside series H-4 and H-6*ax* signals are at lower field in the isomers (5*eq*) and (6*eq*) than in (5*ax*) and (6*ax*), respectively, which is to be expected for protons in a 2,4 (or 2,6)-diaxial relationship with a P=O group.[7a] Unfortunately it was not possible to extract, by first-order analysis, similar data for the compounds in the glucopyranoside series.

It is possible to compare the limited data available from the n.m.r. spectra of the 4-phosphinates (13), (15), (17), and (18) in a way which provides some indication of the stereochemistry at phosphorus in (13) and (15). The distinctive feature of the spectra of the four 4-phosphinates is that whereas the methoxy-resonances of (13), (17), and (18) are at similar field, one of the methoxy-groups of (15) (δ 3·07) is appreciably shielded and its

[9] O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4842.
[10] O. Korpiun and K. Mislow, *J. Amer. Chem. Soc.*, 1967, **89**, 4784.
[11] R. A. Lewis and K. Mislow, *J. Amer. Chem. Soc.*, 1969, **91**, 7009.
[12] L. D. Hall and R. B. Malcolm, *Canad. J. Chem.*, 1972, **50**, 2092, 2102.

resonance lies outside this range. The conformation depicted for (15) in which the aromatic group lies above the 3-*O*-methyl group is one conformation which could provide this effect. The value of $J_{P,H-4}$ (9—10 Hz) which was observed for all four 4-phosphinates is consistent with the P–O–C–H torsion angle which approaches zero [13] in this conformation. However, conformations of (13) are also possible in which the 3-*O*-methyl group is strongly shielded and in which $J_{P-O-C-H}$ is 9—10 Hz, so that the n.m.r. result is far from unequivocal. Also the possibility exists that the methoxy-group that is shielded is not that in the 3-position. The distinctive shift of a methoxy-resonance in a compound of known configuration has however provided a useful correlative guide to the configuration of other methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 4-phenylphosphinates.[14]

EXPERIMENTAL

T.l.c. was performed by upward irrigation (with multiple irrigation where necessary) on microscope slides coated with Merck silica gel G, and column chromatography was performed with Merck silica gel of particle size 0·05—0·2 mm in the same solvent as used for t.l.c.

^{1}H N.m.r. spectra were measured with a JEOL JNM-4-H-100 spectrometer at 100 MHz with deuteriochloroform as solvent and tetramethylsilane as internal standard. ^{31}P N.m.r. spectra were measured at 40 MHz and chemical shifts are quoted in p.p.m. from 85% H_3PO_4 (low field negative). Solvents were dried over $MgSO_4$ and light petroleum refers to the fraction of b.p. 60—80°.

Although only selected n.m.r. data are reported all compounds had n.m.r. spectra consistent with the assigned structures.

Optical rotations were measured for solutions in chloroform.

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (R)- *and* (*S*)-4,6-*Methylphosphonate* [(2*ax*) *and* (2*eq*)].—Methylphosphonic difluoride [15] (3·5 g) was added dropwise to a solution of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside [16] (1) (7·8 g) and triethylamine (3·5 g) in dichloromethane. The solution was stored at room temperature for 2 days then diluted with water, and the dichloromethane fraction was dried and concentrated. The two products [(2*ax*), R_F 0·27; (2*eq*), R_F 0·35] were separated by chromatography over silica in benzene–acetone–methanol (7 : 1 : 1). The (S)-*methylphosphonate* (2*eq*) (3·9 g, 41%) had m.p. 96—98° (from di-isopropyl ether), $[\alpha]_D$ +72° (*c* 2) (Found: C, 42·6; H, 6·7. $C_{10}H_{19}O_7P$ requires C, 42·6; H, 6·8%), δ_H 3·48, 3·55, and 3·59 (3 OMe) and 1·64 (PMe, J_{P,CH_3} 18·2 Hz). The (R)-*methylphosphonate* (2*ax*) (3·9 g, 41%) had m.p. 205° (from acetone–light petroleum), $[\alpha]_D$ +114° (*c* 2) (Found: C, 42·8; H, 6·7%), δ_H 3·47, 3·55, and 3·63 (3 OMe) and 1·68 (PMe, $J_{P\ OH_3}$ 16·9 Hz).

Methyl 4-O-*Benzyl*-2,3-*di*-O-*methyl*-α-D-*glucopyranoside* (7).—A solution of trityl chloride (5 g) in pyridine was added dropwise to a stirred solution of (1) (4 g) in pyridine. The solution was stored at room temperature for 2 h, poured into water, and extracted with chloroform, and the chloroform extract was dried and concentrated to afford methyl 2,3-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (6 g, 72%), m.p. 80—82° (from methanol). To a cooled solution of the trityl derivative (6 g) in dimethylformamide was added sodium hydride (5 g; 50% dispersion in oil), and after 30 min benzyl bromide (5 ml) was also added. The mixture was stored overnight at room temperature, the excess of sodium hydride was decomposed with methanol, the solution was diluted with chloroform and washed with water, and the chloroform extract was dried and concentrated to afford methyl 4-*O*-benzyl 2,3-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (6·8 g, 94%), m.p. 94—96° (from light petroleum). This product was stored at room temperature for 1 h in ether saturated with hydrogen chloride. The solution was then poured into water and extracted with chloroform. The extract was dried, concentrated, and chromatographed over silica in ether–light petroleum (2 : 1) to give the unchanged 7-*O*-trityl derivative and *methyl* 4-O-*benzyl*-2,3-*di*-O-*methyl*-α-D-*glucopyranoside* (7) (1·9 g, 50%), m.p. 94° (from light petroleum), $[\alpha]_D$ −43·7° (*c* 2) (Found: C, 61·5; H, 7·6. $C_{16}H_{24}O_6$ requires C, 61·5; H, 7·7%).

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (*RS*)-6-*Methylphosphonofluoridate* (9).—A solution of (7) (1·8 g), triethylamine (0·5 g), and methylphosphonic difluoride (0·6 g) in ether was stored at room temperature for 15 min, then diluted with water; the ether layer was then dried and concentrated. The residue (R_F 0·7) was purified by chromatography in benzene–acetone–methanol (7 : 3 : 1) to afford the methylphosphonofluoridate (8) (2 g, 90%) as a chromatographically homogeneous syrup. A solution of (8) (0·5 g) in ethyl acetate was hydrogenated over 10% palladium–charcoal at atmospheric pressure, filtered, and concentrated to yield chromatographically homogeneous (9) [t.l.c. in benzene–acetone–methanol (7 : 1 : 1), R_F 0·5], $[\alpha]_D$ +82° (*c*. 1·1).

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (R)- *and* (S)-4,6-(*Ethyl Phosphate*) [(3*ax*) *and* (3*eq*)].—A solution of (1) (1 g), triethylamine (1 g), and ethyl phosphorodichloridate [17] (1 g) in dichloromethane was stored at room temperature. The reaction was monitored by t.l.c. (benzene–acetone–methane, 7 : 3 : 1). The preponderant product initially was (3*eq*) (R_F 0·5) but after 15—20 min, when no starting material remained, (3*ax*) (R_F 0·6) was the preponderant product. The solution was diluted with water and the dichloromethane extract was dried and concentrated. The residue was separated chromatographically over silica in benzene–acetone (7 : 3) to afford (i) the (R)-*phosphate* (3*ax*) (0·3 g, 22%), m.p. 115° (from di-isopropyl ether), $[\alpha]_D$ +114° (*c* 2) (Found: C, 42·2; H, 6·7. $C_{11}H_{21}O_8P$ requires C, 42·3; H, 6·8%); coupling constants from ^{31}P n.m.r. data: $J_{P,H-6eq}$ 20, J_{P,OCH_3} 8·5, $J_{P,H-4} = J_{P,H-6ax} = 2$—4 Hz); and (ii) the (*S*)-phosphate (3*eq*) (0·2 g, 15%), $[\alpha]_D$ +90°; coupling constants from ^{31}P n.m.r.: $J_{P,H-6eq}$ 25, J_{P-O-CH_3} 8·5, $J_{P,H-4} = J_{P,H-6ax} =$ 2 Hz. Isomer (3*eq*) was subsequently prepared more conveniently by treatment of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4,6-phosphorochloridate with ethanol alone or in the presence of triethylamine.[18]

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Methyl 2,3-*Di*-O-*methyl*-α-D-*galactopyranoside* (R)- *and* (S)-4,6-*Methylphosphonate* [(5*eq*) *and* (5*ax*)].—A solution of triethylamine (3·8 g) in dichloromethane (20 ml) was added dropwise to a stirred solution at room temperature of methyl 2,3-di-*O*-methyl-α-D-galactopyranoside [19] (3 g) and methylphosphonic dichloride (2·3 g) in dichloromethane (25 ml). The reaction was monitored by t.l.c. in light petroleum–acetone–methanol (7 : 3 : 1) [R_F values: (5*eq*), 0·3; (5*ax*), 0·2; galactopyranoside, 0·4]. After 25 h no starting material remained and the dichloromethane solution was washed with water, dried, and concentrated. The residue was chromatographed over silica in benzene–acetone–methanol (10 : 4 : 1) to afford (i) the (R)-4,6-*phosphonate* (5*eq*) (0·88 g, 23%), $[\alpha]_D$ +148° (*c* 2), δ_H 4·85 (H-1, $J_{1,2}$ 3 Hz), 5·06 (H-4, $J_{3,4} = J_{4,5} = J_{4,P}$ = 1—2 Hz), 4·22 (H-6*eq*, $J_{5,6eq}$ 2, $J_{6ax,6eq}$ 12·7, $J_{6eq,P}$ 19·8 Hz), 4·72 (H-6*ax* $J_{P,6ax}$ 3, $J_{6ax,5}$ 2—3 Hz), and 1·68 (PMe, J_{P,OH_3} 18 Hz); (ii) the (S)-4,6-*phosphonate* (5*ax*) (0·28 g, 8%), m.p. 230° (from acetone–di-isopropyl ether), $[\alpha]_D$ +179° (*c* 2) (Found: C, 42·5; H, 6·6. $C_{10}H_{19}O_7P$ requires C, 42·6; H, 6·8%) δ_H 4·9 (H-1), 4·92 (H-4, $J_{3,4} = J_{4,5} = J_{4,P}$ = 1—2 Hz), 4·15—4·6 (H-6*ax* and -6*eq*), and 1·60 (PMe, J_{P,OH_3} 16·5 Hz).

Methyl 2,3-*Di*-O-*methyl*-α-D-*galactopyranoside* (S)- *and* (R)-4,6-(*Ethyl Phosphate*) [(6*ax*) *and* (6*eq*)].—A solution of methyl 2,3-di-*O*-methyl-α-D-galactopyranoside (1·8 g), ethyl phosphorodichloridate (1·92 g), and triethylamine (2·52 g) in dichloromethane was stored at room temperature for 1 h. The reaction was monitored by t.l.c. in benzene–acetone–methanol (14 : 6 : 1) [R_F values: (6*ax*), 0·4; (6*eq*), 0·3]. The dichloromethane solution was washed with water, dried, and concentrated and the residue was chromatographed over silica in benzene–acetone (3 : 2) to afford (i) the (S)-4,6-*ethyl phosphate* (6*ax*) (0·55 g, 22%), $[\alpha]_D$ +134° (*c* 1·2), δ_H 4·88 (H-1), 4·92 (H-4), and 4·1—4·55 (H-6*ax* and -6*eq*); (ii) the (R)-4,6-*ethyl phosphate* (6*eq*) (0·79 g, 31%), $[\alpha]_D$ +159° (*c* 1·8), δ_H 4·95 (H-1), 5·08 (H-4), and 4·72 (H-6*ax* $J_{6ax,5} = J_{6ax,P}$ = 2—3, $J_{6ax,6eq}$ 12·3 Hz).

(S)-*Ethylmethylphenylphosphine Oxide* (14) *from* (2*ax*).—A solution of (2*ax*) (3 g) in benzene, to which phenylmagnesium bromide (1·5 mol. equiv.) in ether had been added, was boiled under reflux for 1 h; no starting material then remained. The mixture was poured into aqueous ammonium chloride and extracted with chloroform, and the extract was dried, concentrated, and purified by chromatography over silica in benzene–acetone–methanol (7 : 3 : 1) to afford methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4-methylphenylphosphinate (13) (1·8 g, 47%), $[\alpha]_D$ +38·7° (*c* 1·0), δ_H 1·83 (PMe), 4·42 (H-4, $J_{3,4} = J_{4,5} = J_{4,P}$ = 9—10 Hz), and 3·41, 3·56, and 3·66 (3 OMe). A solution of (13) (0·7 g) in benzene containing a ten-fold excess of ethylmagnesium bromide in ether was boiled under reflux for 48 h. The solution was poured into aqueous ammonium chloride and extracted with chloroform; the extract was dried and concentrated. The product (14) (81 mg), was separated with difficulty by chromatography over silica in benzene–acetone–methanol (7 : 3 : 1) and had $[\alpha]_D$ −23° (*c* 0·7) and i.r. and n.m.r. spectra indistinguishable from those of authentic ethylmethylphenylphosphine oxide.

(R)-*Ethylmethylphenylphosphine oxide* (16) *from* (2*eq*).—A solution of (2*eq*) (3 g) in benzene was treated with phenylmagnesium bromide and processed under similar conditions to those described for (2*ax*). Chromatography of the crude product over silica in benzene–acetone–methanol (7 : 3 : 1) afforded in order of elution (i) (2*eq*) (trace); (ii) methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*R*)-4-methylphenylphosphinate (15) (1·5 g, 40%), $[\alpha]_D$ +67° (*c* 0·8), δ_H 4·23 (H-4, $J_{3,4} = J_{4,5} = J_{P,4}$ = 9—10 Hz), 1·78 (PMe), and 3·07, 3·41, and 3·43 (3 OMe); (iii) a trace of material with n.m.r. and i.r. spectra consistent with a 6-methylphenylphosphinate. A solution of (15) (0·5 g) in benzene and ether containing a ten-fold excess of ethylmagnesium bromide was boiled under reflux for 48 h. T.l.c. in benzene–acetone–methanol (7 : 3 : 1) indicated the presence of some unchanged (15), (1), and (16). Conventional processing of the reaction mixture and chromatography over silica gave (*R*)-ethylmethylphenylphosphine oxide (16) (0·07 g), $[\alpha]_D$ +21° (*c* 0·5).

Reactions of Ethylmagnesium Bromide with Compounds (2*ax*) *and* (2*eq*).—(i) A solution of (2*ax*) (1 g) in dry benzene and ether containing ethylmagnesium bromide (2 mol. equiv.) was boiled under reflux for 30 min, then processed in the usual way to afford *methyl* 2,3-*di*-O-*methyl*-α-D-*glucopyranoside* (S)-4-*ethylmethylphosphinate* (17), (0·6 g, 53%), m.p. 150—152° (from di-isopropyl ether), $[\alpha]_D$ +118° (*c* 1) (Found: C, 46·1; H, 7·9. $C_{11}H_{25}O_7P$ requires C, 46·2; H, 8·1%), δ_H 1·19 (P·CH_2·CH_3, J_{P-C-OH_3} 19·1 Hz), 1·58 (PMe, $J_{P,Me}$ 13·8 Hz), and 4·23 (H-4, $J_{3,4} = J_{4,5} = J_{P,4}$ = 9—10 Hz).

(ii) A solution of (2*eq*) (3 g) in dry benzene and ether containing ethylmagnesium bromide (2 mol. equiv.) was boiled under reflux for 30 min. The solution was processed in the usual way to afford *methyl* 2,3-*di*-O-*methyl*-α-D-*glucopyranoside* (R)-4-*ethylmethylphosphinate* (18) (1·5 g, 44%), m.p. 131° (from di-isopropyl ether), $[\alpha]_D$ +124° (*c* 2) (Found: C, 46·5; H, 8·0%), δ_H 1·21 (P·CH_2·CH_3, J_{P-C-OH_3} 19·2 Hz), 1·50 (PMe, $J_{P,Me}$ 13·8 Hz), and 4·26 (H-4, $J_{3,4} = J_{4,5} = J_{P,4}$ = 9—10 Hz).

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