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The preparation of phosphorylated intermediates for the synthesis of racemic and chiral *myo*-inositol 1,4,5-trisphosphate and its phosphorothioate analogues *,**

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ABSTRACT

Reaction of racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol 3-[di-(2,2,2-trichloroethyl) phosphate] with bis(2,2,2-trichloroethyl) phosphorochloridate gave a mixture of the 3,5- and 3,6-bisphosphate derivatives which were difficult to separate and could not be phosphorylated further. The bisphosphates were synthesised by the phosphorylation of the 5- and 6-*O*-(*cis*-prop-1-enyl) derivatives of racemic 1,2,4-tri-*O*-benzyl-*myo*-inositol [prepared from 1,2,4-tri-*O*-benzyl-3,5- and -3,6-di-*O*-(*cis*-prop-1-enyl)-*myo*-inositol, respectively] and subsequent acidic hydrolysis. 1D-2,3,6-Tri-*O*-benzyl-1,4-di-*O*-(*cis*-prop-1-enyl)-*myo*-inositol was converted into crystalline 1D-2,3,6-tri-*O*-benzyl-*myo*-inositol 1,4-bis(dibenzyl phosphate), and thence into the crystalline 1,4,5-tris(dibenzyl phosphate) which was also obtained, using dibenzyloxy(diisopropylamino)phosphine, from 1D-2,3,6-tri-*O*-benzyl-*myo*-inositol. The latter compound was converted, using bis(2-cyanoethoxy)(diisopropylamino)phosphine, into the crystalline 1,4,5-tris[di-(2-cyanoethyl)phosphate] which was also obtained from the 4,5-bis[di-(2-cyanoethyl)phosphate]. Both the tris[di-(2-cyanoethyl)phosphate] and the tris(dibenzyl phosphate) are intermediates suitable for the synthesis of 1,4,5-IP_3.

INTRODUCTION

In the preceding communication[1], the preparation of intermediates suitable for phosphorylation to give the second messenger 1D-*myo*-inositol 1,4,5-trisphosphate

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** Dedicated to Professor Stephen Angyal.

[1] Visiting scientist from the Instituto de Quimica Organica General, C.S.I.C., Madrid, Spain.

(1,4,5-IP_3) was described. We now report the phosphorylation of some of these intermediates to give protected derivatives of racemic and chiral *myo*-inositol 1,4,5-trisphosphate as well as phosphorylated intermediates suitable for the synthesis of the 1- or 5-phosphorothioate analogues of 1,4,5-IP_3.

RESULTS AND DISCUSSION

Our first studies of phosphorylation for the preparation of protected racemic *myo*-inositol 1,4,5-trisphosphate derivatives were carried out using bis(2,2,2-trichloroethyl) phosphorochloridate[6] (**1**). The racemic alcohol[1,7,8] **2** was treated with **1** in pyridine to give the crystalline phosphate derivative **3** which, on acidic hydrolysis, gave the crystalline diol **4**. Phosphorylation of **4** with **1** in pyridine gave a mixture of the bisphosphate derivatives **6** and **8** but these were not converted further into **5** presumably because of steric hindrance. Prolonged reaction times in pyridine led to lower yields of **6** and **8** due to the formation of the cyclic phosphate derivative **10**, which was hydrolysed on work-up to give the presumed polar phosphate diester derivatives **11**. The stability of **6** and **8** was improved by conducting the phosphorylation in dichloromethane that contained only sufficient pyridine to remove the hydrogen chloride formed, but even under these conditions, further phosphorylation of **6** and **8** with **1** could not be effected.

Trituration of the mixture of **6** and **8** (which were not separated by TLC) with light petroleum gave crystalline **6**, the structure of which has been established by ^{1}H NMR studies[3]. The mixture of **6** and **8** was analysed by conversion into the mixture of acetates **7** and **9** (which separated in TLC) from which crystalline **7** was obtained.

Compound **6** was phosphitylated[3] by the reagent **12**, the product was converted[3] into the phosphite derivative **13**, and thence into the phosphate derivative **14** and the phosphorothioate derivative **15**. Both **14** and **15** were completely deprotected[3] by the action of sodium in liquid ammonia to give racemic *myo*-inositol 1,4,5-trisphosphate and its 5-phosphorothioate analogue.

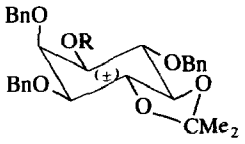
The mixture of **6** and **8** was treated with phosphorus oxychloride in pyridine, and subsequent addition of methanol gave a mixture of bisphosphate derivatives **16** which was resolved by chromatography. The more-polar isomer was crystalline, but its structure was not defined.

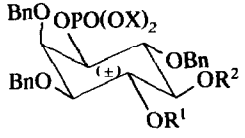
Likewise, phosphorylation of racemic 1,2,3,4-tetra-*O*-benzyl-*myo*-inositol[7] (**19**) with **1** gave a mixture of alcohols **17** which was treated with phosphorus oxychloride and methanol to give the mixture of bisphosphate derivatives **18**, chromatography of which gave the crystalline less-polar isomer **18**; the more-polar isomer had NMR spectra similar to those of **16** above, but the relative positions of the two phosphate groups were not assigned.

Because of the difficulty encountered in resolving the mixture of **6** and **8**, a more definitive route for the preparation of the individual compounds was investigated which would also be compatible with other methods of phosphorylation. For

$Cl-PO(OCH_2CCl_3)_2 \equiv Cl-PO(OX)_2$

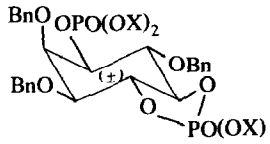
1





*2 R = H
3 R = $PO(OX)_2$

4 $R^1 = R^2 = H$
5 $R^1 = R^2 = PO(OX)_2$
6 $R^1 = PO(OX)_2$, $R^2 = H$
7 $R^1 = PO(OX)_2$, $R^2 = Ac$
8 $R^1 = H$, $R^2 = PO(OX)_2$
9 $R^1 = Ac$, $R^2 = PO(OX)_2$



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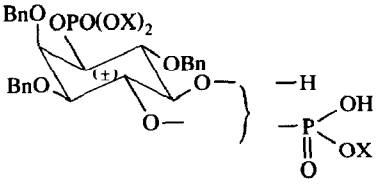

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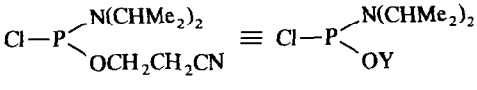

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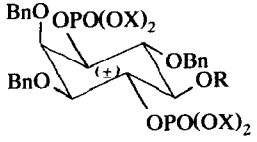
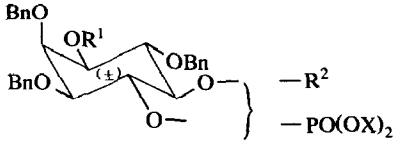
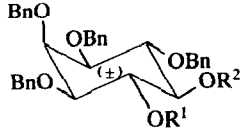


13 $R = P(OY)_2$
14 $R = PO(OY)_2$
15 $R = PS(OY)_2$

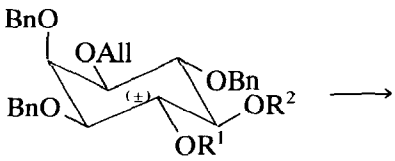


16 $R^1 = PO(OX)_2$, $R^2 = PO(OMe)_2$
17 $R^1 = Bn$, $R^2 = H$
18 $R^1 = Bn$, $R^2 = PO(OMe)_2$

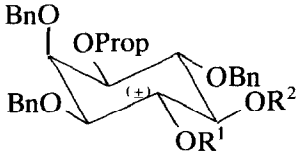


19 $R^1 = R^2 = H$
20 $R^1 = All$, $R^2 = H$
21 $R^1 = H$, $R^2 = All$
22 $R^1 = Prop$, $R^2 = H$
23 $R^1 = H$, $R^2 = Prop$

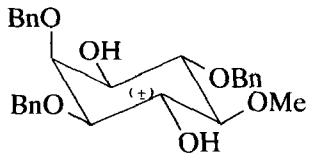
* In the formulae, racemic inositol derivatives are indicated with (±) in the ring; chiral inositol derivatives, represented in their correct absolute configurations, are shown with thickened lines in the ring, and *meso*-compounds are shown with neither of these modifications. $X = CH_2CCl_3$, $Y = CH_2CH_2CN$, $Bn = CH_2Ph$, $pMB = CH_2Ph(pOMe)$, $All = CH_2CH{=}CH_2$, $Prop = CH{=}CHMe$.



24 $R^1 = R^2 = H$
25 $R^1 = All$, $R^2 = H$
26 $R^1 = H$, $R^2 = All$



27 $R^1 = Prop$, $R^2 = H$
28 $R^1 = H$, $R^2 = Prop$
29 $R^1 = Prop$, $R^2 = Me$
30 $R^1 = Prop$, $R^2 = All$
31 $R^1 = All$, $R^2 = Prop$



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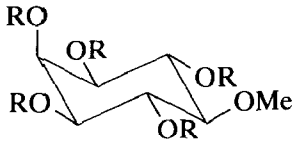
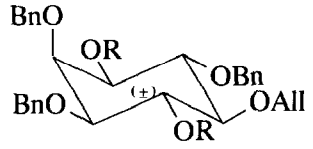
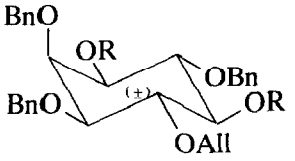


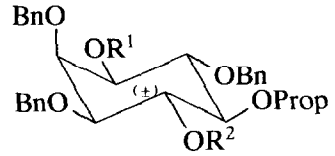
33 R = H
34 R = Ac



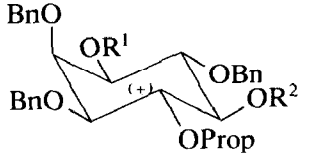
35 R = H
36 R = Ac



37 R = H
38 R = Ac

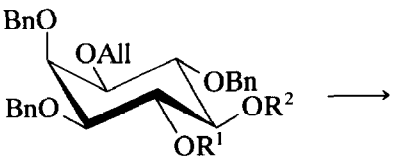


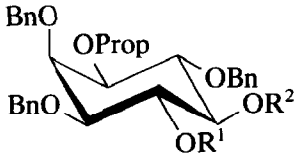
39 $R^1 = R^2 = H$
40 $R^1 = R^2 = Ac$
41 $R^1 = R^2 = PO(OX)_2$
42 $R^1 = PO(OX)_2$, $R^2 = H$
43 $R^1 = H$, $R^2 = PO(OX)_2$



44 $R^1 = R^2 = H$
45 $R^1 = R^2 = Ac$
46 $R^1 = R^2 = PO(OX)_2$
47 $R^1 = PO(OX)_2$, $R^2 = H$

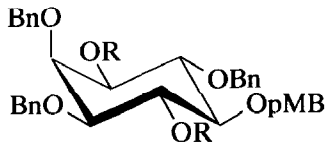
this purpose, a procedure was used that had been developed[7] for the separation of the mono-allyl ethers **20** and **21**, which were not separated by TLC. Isomerisation with potassium *tert*-butoxide in methyl sulphoxide[9] gave[7] the *cis*-prop-1-enyl ethers

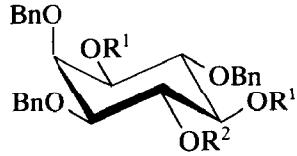




48 $R^1 = R^2 = H$
49 $R^1 = All$, $R^2 = H$
50 $R^1 = H$, $R^2 = All$

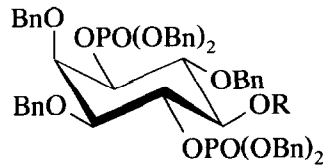
51 $R^1 = Prop$, $R^2 = H$
52 $R^1 = Prop$, $R^2 = Ac$
53 $R^1 = H$, $R^2 = Prop$
54 $R^1 = Ac$, $R^2 = Prop$
55 $R^1 = Prop$, $R^2 = pMB$
56 $R^1 = All$, $R^2 = Prop$





57 R = H
58 R = Ac
59 $R = P(OBn)_2$
60 $R = PO(OBn)_2$

61 $R^1 = H$, $R^2 = All$
62 $R^1 = Ac$, $R^2 = All$
63 $R^1 = pMB$, $R^2 = All$
64 $R^1 = pMB$, $R^2 = Prop$
65 $R^1 = pMB$, $R^2 = H$
66 $R^1 = pMB$, $R^2 = Ac$



67 R = H
68 $R = P(OBn)_2$
69 $R = PO(OBn)_2$
70 $R = PS(OBn)_2$

$(RO)_2P\ N(CHMe_2)_2$

71 R = Bn
72 $R = CH_2CH_2CN = Y$

22 and **23** which were readily separated by column chromatography. Therefore, the racemic diol[10] **24** was converted, by tin-mediated allylation, into the mixture of diallyl ethers **25** and **26** that (like **20** and **21**) were not separated by TLC. Isomerisation of the *O*-allyl groups in **25** and **26** gave the crystalline bis(*cis*-prop-1-enyl) ethers **27** and **28** which (like **22** and **23**) were separated readily by column chromatography.

The structure of the less-polar compound (TLC) was established as **27** by methylation to give **29**; subsequent acidic hydrolysis (to remove the *O*-prop-1-enyl

groups) gave **32** which, on hydrogenolysis, gave sequoyitol **33**, characterised as the known[7] penta-acetate **34**.

Allylation of **27** and **28** gave the allyl ethers **30** and **31**, respectively, acidic hydrolysis of which (to remove the *O-cis*-prop-1-enyl groups) gave the *O*-allyl derivatives **35** and **37** that gave the crystalline diacetates **36** and **38**, respectively. Isomerisation of the *O*-allyl groups in **35** and **37** with potassium *tert*-butoxide in methyl sulphoxide gave the *cis*-prop-1-enyl ethers **39** and **44**, respectively, which gave the crystalline diacetates **40** and **45**, respectively.

Phosphorylation of **39** with **1** gave the crystalline bisphosphate derivative **41**. The crystalline monophosphate derivatives **42** and **43** were isolated and characterised as intermediates in this reaction. Similarly, phosphorylation of **44** with **1** gave the crystalline bisphosphate derivative **46**; the crystalline monophosphate derivative **47** was isolated and characterised as an intermediate. Acidic hydrolysis of the *O-cis*-prop-1-enyl groups in **41** and **46** gave **6** and **8**, respectively.

The chiral analogues **51** and **53** of **27** and **28**, respectively, were prepared in the same way from 1D-1-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol[1] (**48**) via the mixture of diallyl ethers **49** and **50**. Allylation of **53** gave **56**, acidic hydrolysis of which (to remove the *O*-prop-1-enyl groups) gave the diol **61**, characterised as the bis(*p*-methoxybenzyl) ether **63**. Isomerisation of the allyl group of **63** gave the *cis*-prop-1-enyl ether **64**, acidic hydrolysis of which gave the alcohol **65** and thence the acetate **66**, both identical with the materials prepared previously[1].

p-Methoxybenzylation of **51** gave **55**, acidic hydrolysis of which (to remove the *O*-prop-1-enyl groups) gave the crystalline diol **57**. Phosphitylation[11,12] of **57** with the reagent[11] **71** gave the bisphosphite derivative **59**, which was oxidised[11] without isolation to give the crystalline bisphosphate derivative **60**. The *O-p*-methoxybenzyl group was removed from **60** by oxidation with dichlorodicyanobenzoquinone[13] or cerium(IV) ammonium nitrate[14] to give the crystalline alcohol **67**. The racemic analogue of **67** has been prepared[15] from the racemate of **60** by acidic hydrolysis of the *O-p*-methoxybenzyl group. In contrast to the analogous bis[di-(2,2,2-trichloroethyl)phosphate] derivative (**6**), the bis(dibenzyl phosphate) derivative **67** was degraded only slightly in solution in pyridine at 20° after 20 h.

Phosphitylation of **67** with **71** gave the phosphite derivative **68**, which was oxidised to the crystalline trisphosphate derivative **69** identical with the material (described below) obtained by phosphorylation of 1D-2,3,6-tri-*O*-benzyl-*myo*-inositol (**73**) with **71**. Oxidation of **68** with sulphur in pyridine should give the phosphorothioate **70**.

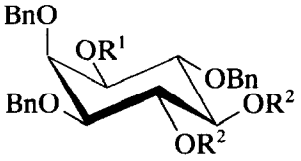
Phosphitylation[11] of 1D-2,3,6-tri-*O*-benzyl-1-*O-p*-methoxybenzyl-*myo*-inositol[1] (**74**) with the reagent **72** gave the bisphosphite derivative **75**, which was oxidised, without isolation, by 3-chloroperoxybenzoic acid to give the crystalline bisphosphate derivative **76**. The *p*-methoxybenzyl group was removed from **76** by oxidation with dichlorodicyanobenzoquinone[13] to give the syrupy alcohol **77**. Phosphitylation of **77** with **72** then gave the phosphite derivative **78**, which was oxidised to give the crystalline trisphosphate derivative **79** identical with the product prepared by

phosphitylation of 1L-1,2,4-tri-*O*-benzyl-*myo*-inositol[12] (**73**) with **72** and subsequent oxidation. Likewise, the enantiomer **83** (of **79**) was prepared from 1D-1,2,4-tri-*O*-benzyl-*myo*-inositol[10] (**81**). The phosphite **78** is a suitable intermediate for the preparation of the 1-phosphorothioate analogue of 1D-*myo*-inositol 1,4,5-trisphosphate, the racemate of which has been prepared[16].

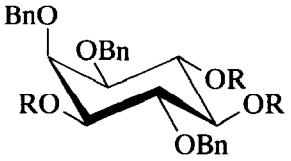
Phosphitylation of the racemic alcohol[1] **2** with **72** and subsequent oxidation of the phosphite derivative **85** gave the syrupy phosphate derivative **86** which, on acidic hydrolysis, gave the crystalline diol **87**. Further phosphorylation of **87** with **72** gave the syrupy racemic trisphosphate derivative **89** (cf. ref. 17) having NMR spectra identical with those of the chiral derivatives **79** and **83**.

Phosphitylation of 1L-1,2,4-tri-*O*-benzyl-*myo*-inositol[12] (**73**) with **71** gave the trisphosphite and subsequent oxidation gave the crystalline trisphosphate derivative **69**, the enantiomer of **84** described previously[12].

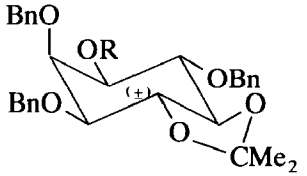
The protected trisphosphate derivatives **79** and **69** are suitable intermediates for the synthesis of 1D-*myo*-inositol 1,4,5-trisphosphate.



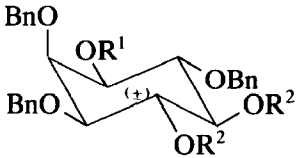
73 $R^1 = R^2 = H$
74 R^1 = pMB, $R^2 = H$
75 R^1 = pMB, $R^2 = P(OY)_2$
76 R^1 = pMB, $R^2 = PO(OY)_2$
77 $R^1 = H$, $R^2 = PO(OY)_2$
78 $R^1 = P(OY)_2$, $R^2 = PO(OY)_2$
79 $R^1 = R^2 = PO(OY)_2$
80 $R^1 = R^1 = P(OY)_2$



81 R = H
82 $R = P(OY)_2$
83 $R = PO(OY)_2$
84 $R = PO(OBn)_2$



85 $R = P(OY)_2$
86 $R = PO(OY)_2$



87 $R^1 = PO(OY)_2$, $R^2 = H$
88 $R^1 = PO(OY)_2$, $R^2 = P(OY)_2$
89 $R = R^2 = PO(OY)_2$

EXPERIMENTAL

General.—The general methods were as described[11,12].

(±)-2,3,6-Tri-O-*benzyl-4,5*-O-*isopropylidene*-myo-*inositol 1-[di-(2,2,2-trichloro-*

ethyl)phosphate] (**3**).—Bis(2,2,2-trichloroethyl) phosphorochloridate[6] (**1**, Aldrich; 1 g, 2.64 mmol) was added to a solution of the *O*-isopropylidene derivative[1,7,8] **2** (1.03 g, 2.1 mmol) in dry pyridine (10 mL). After 12 h at 20°, TLC (ether–light petroleum, 1:1) showed complete conversion of **2** (R_F 0.5) into the product (R_F 0.55). Water (0.5 mL) was added, and the solution was kept at 20° for 1 h, then diluted with water (30 mL) and extracted with ether. The extract was washed successively with ice-cold M HCl, satd aq KCl, and satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. Column chromatography (ether–light petroleum, 1:1) of the residue gave **3** (1.6 g, 90%), mp 114–115° (from light petroleum). NMR data: ^{1}H, δ 1.48 (s, 6 H, CMe_2), 3.37 (t, 1 H, *J* 9.5 Hz), 3.63 (dd, 1 H, *J* 1.9 and 10.4 Hz), 4.00–5.04 (m, 3 CH_2Ph, 2 CH_2CCl_3, and 4 ring protons with major peaks at δ 4.38, 4.45, 4.51, 4.67, 4.71, 4.77, 4.84, 4.88, and 4.92), 7.30–7.33 (m, 15 H, 3 Ph); ^{31}P, δ −5.18 (Found: C, 48.77; H, 4.65; Cl, 24.92; P, 3.29. $C_{34}H_{37}Cl_6O_9P$ calcd: C, 49.00; H, 4.48; Cl, 25.53; P, 3.72%).

*(±)-2,3,6-Tri-*O*-benzyl-*myo*-inositol 1-[di-(2,2,2-trichloroethyl) phosphate]* (**4**).—A solution of **3** (1 g) in acetone–MeOH–M HCl (5:6:1, 50 mL) was kept at 20° for 1 h when TLC (ether–light petroleum, 2:1) showed complete conversion of **3** (R_F 0.85) into the product (R_F 0.2). Anhyd NaOAc (500 mg) was added, the solution was concentrated, water (10 mL) and ether (50 mL) were added, and the ether layer was separated, dried ($MgSO_4$), and concentrated to give **4** (950 mg, 100%), mp 141–143° (from EtOAc–light petroleum, 1:3). NMR data: ^{1}H, δ 2.55 (s, 2 H, 2 OH), 3.26 (dd, 1 H, *J* 1.8 and 9.8 Hz), 3.48 (t, 1 H, *J* 8.9 Hz), 3.88–4.13 (m, 2 H), 4.26–5.01 (m, 3 CH_2Ph, 2 CH_2CCl_3, and 2 ring protons, with major peaks at δ 4.40, 4.41, 4.48, 4.54, 4.60, 4.82, 4.86, and 4.89), 7.32 (s, 15 H, 3 Ph); ^{31}P, δ −5.18 (Found: C, 47.01; H, 4.29; Cl, 26.12; P, 3.77. $C_{31}H_{33}Cl_6O_9P$ calcd: C, 46.93; H, 4.19; Cl, 26.82; P, 3.91%).

*Preparation of the mixture of (±)-2,3,6-tri-*O*-benzyl-*myo*-inositol 1,4-* (**6**) *and 1,5-bis[di-(2,2,2-trichloroethyl) phosphate]* (**8**), *the acetates* (**7** and **9**), *and the mixture of (±)-2,3,6-tri-*O*-benzyl-*myo*-inositol 1,4-bis[di-(2,2,2-trichloroethyl) phosphate] 5-(dimethyl phosphate) and 1,5-bis[di-(2,2,2-trichloroethyl) phosphate] 4-(dimethyl phosphate)* (**16**).—Dry pyridine (0.2 mL, 2.5 mmol) was added to a solution of **4** (500 mg, 0.63 mmol) and **1** (500 mg, 1.32 mmol) in dry CH_2Cl_2 (15 mL). The solution was kept at 20° for 6 h when TLC (ether–light petroleum, 3:1) showed the conversion of **4** (R_F 0.4) into a major product(s) (R_F 0.7) together with a minor product (R_F 0). Water (0.2 mL) was added, and the solution was stirred for 30 min, then washed successively with M HCl and satd aq KCl, dried (Na_2SO_4), and concentrated. Column chromatography (ether–light petroleum, 1:2) of the residue, as rapidly as possible on a short column in order to avoid cyclisation, removed a non-charring by-product. Further elution with ether–light petroleum (3:1) gave a mixture (500 mg, 70%) of **6** and **8**. NMR data: ^{1}H, δ 3.48 (dd, 1 H, *J* 1.8 and 9.8 Hz), 3.74 (t, 1 H, *J* 8.5 Hz), 4.03 (t, 1 H, *J* 9.2 Hz), 4.24–5.05 (m, 17 H, 3 CH_2Ph, 4 CH_2CCl_3, and 3 ring protons, with major peaks at δ 4.38, 4.39, 4.41, 4.45, 4.47, 4.52, 4.58, 4.63, 4.83, 4.87, and 4.93), 7.32 (s, 15 H, 3 Ph); ^{31}P, δ −5.25, −3.97.

The above mixture (335 mg) was treated with acetic anhydride–pyridine at 20° for 12 h when TLC (ether–light petroleum, 3:1) showed the conversion of **6** and **8** (R_F 0.7) into two major products **7** and **9** (R_F 0.9 and 0.8) together with a product (R_F 0) assumed to be the phosphate diester derivatives **11** produced via the cyclic phosphate derivative **10**. Column chromatography (ether–light petroleum, 3:1) of the mixture gave a mixture (246 mg, 71%) of **7** and **9**. Further elution with ethyl acetate–MeOH (4:1) gave the polar product (100 mg), presumed to be **11**, R_F 0. ^{31}P NMR data: δ −5.11, −4.17. This compound was not further investigated.

Phosphorus oxychloride (980 mg, 6.39 mmol) was added to a solution of the mixture (500 mg, 0.44 mmol) of **6** and **8** in dry CH_2Cl_2 (25 mL) and pyridine (2.4 mL, 29.7 mmol), and the solution was kept at 20° for 24 h. Dry MeOH (5 mL, 120 mmol) was added to the cooled solution which was then kept at 20° for 4 h. Water (40 mL) and ether (50 mL) were added, and the organic layer was separated, washed with satd aq KCl, M HCl, and satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. TLC ($CHCl_3$–MeOH, 30:1) showed the conversion of **6** and **8** (R_F 0.8) into two products (R_F 0.65 and 0.7). Column chromatography (as above) of the mixture gave **16** (500 mg, 91%). Crystallisation from light petroleum–EtOAc (20:1) gave the product, R_F 0.65 (100 mg), mp 145–148°. NMR data: ^1H, δ 3.49, 3.62, 3.75, 3.88 (4 s, 6 H, 2 OMe), 3.51 (dd, 1 H, H-3), 4.11–5.05 (m, 19 H, 3 CH_2Ph, 4 CH_2CCl_3, and 5 ring protons), 7.34 (s, 15 H, 3 Ph); ^{31}P, δ −5.32, −4.85, 0.94 (Found: C, 35.93; H, 3.35. $C_{37}H_{41}Cl_{12}O_{15}P_3$ calcd: C, 35.72; H, 3.32%). This compound was not characterised further.

*(±)-1,2,3,4-Tetra-*O*-benzyl-*myo*-inositol 5- or 6-[di-(2,2,2-trichloroethyl) phosphate] 6- or 5-(dimethyl phosphate)* (**18**).—Racemic 1,2,3,4-tetra-*O*-benzyl-*myo*-inositol[7] (**19**) was treated with **1**, and the products were isolated, as described for the mixture of **6** and **8**, to give the mixture of monophosphate derivatives **17**. TLC (ether) showed the conversion of **19** (R_F 0.7) into **17** (R_F 0.9). The mixture **17** was treated with phosphorus oxychloride in pyridine followed by MeOH, and the products were isolated as described for the preparation of **16**. TLC (ether) showed two products **18** (R_F 0.4 and 0.5) which were separated by column chromatography. The less polar isomer (R_F 0.5) had mp 130–131° (from EtOAc–light petroleum, 1:10). NMR data: ^1H, δ 3.33–3.54 (m, 2 H, H-1,3), 3.62, 3.69, 3.75, 3.86 (4 s, 6 H, 2 OMe), 3.83–5.18 (m, 16 H, 4 CH_2Ph, 2 CH_2CCl_3, and 4 ring protons), 7.25–7.71 (m, 20 H, 4 Ph); ^{31}P, δ −4.85, 0.13 (Found: C, 47.83; H, 4.40; Cl, 21.32; P, 7.00. $C_{40}H_{44}Cl_6O_{12}P_2$ calcd: C, 48.46; H, 4.47; Cl, 21.46; P, 6.25%).

The more polar isomer had R_F 0.4. NMR data: ^1H, δ 3.34 (d, 2 H, J 10.9 Hz, H-1,3), 3.45, 3.58, 3.72, 3.85 (4 s, 6 H, 2 OMe), 3.93–4.15 (m, 2 H, H-2,4), 4.37–5.17 (m, 14 H, 4 CH_2Ph, 2 CH_2CCl_3, and 2 ring protons), 7.25–7.32 (m, 20 H, 4 Ph); ^{31}P, δ −5.05, 0.74 (cf. the NMR data for **16**). The two isomers of **18** were not investigated further.

*(±)-2,3,6-Tri-*O*-benzyl-1,4-* (**27**) *and 1,5-di-*O*-(*cis*-prop-1-enyl)-*myo*-inositol* (**28**).—A mixture of the racemic diol[10] **24** (3.75 g, 7.6 mmol), dibutyltin oxide (2.25 g, 9 mmol) tetrabutylammonium bromide (2.44 g, 7.6 mmol), acetonitrile (150 mL), and

allyl bromide (25 mL) was heated under reflux, with molecular sieve 3A (2.5 g) in a Soxhlet apparatus, for 30 h when TLC (ether–light petroleum, 2:1) showed the complete conversion of **24** (R_F 0.2) into a product (R_F 0.8). The solvents were evaporated and the residue was distributed between ether (100 mL) and water (100 mL). The ether layer was separated, stirred with satd aq $NaHCO_3$ (100 mL) for 2 h, filtered through Celite, dried (K_2CO_3), and concentrated. Column chromatography (ether–light petroleum, 2:1) of the residue gave a mixture (3.8 g, 94%) of the alcohols **25** and **26**. A solution of this mixture (3.8 g, 7.16 mmol) in dry Me_2SO (30 mL) containing potassium *tert*-butoxide (3.5 g, 28.6 mmol) was kept at 50° for 3 h when TLC (ether–light petroleum, 1:1) showed the conversion of **25** and **26** (R_F 0.5) into two products (R_F 0.55 and 0.7). Semi-satd aq KCl (30 mL) was added to the cooled solution and the precipitated products were extracted with ether. The extract was dried (K_2CO_3), a few drops of triethylamine were added, and the extract was concentrated. Column chromatography (ether–light petroleum, 1:2) of the residue gave, initially, **27** (1.7 g, 44%), R_F 0.7, mp 126–128° (from light petroleum containing a little triethylamine). NMR data: ^1H, δ 1.60, 1.67 (2 dd, 6 H, J 1.2 and 4.9 Hz, 2 =CH*Me*), 2.44 (d, 1 H, J 2.4 Hz, OH), 3.33 (dd, 1 H, J 1.8 and 9.7 Hz, H-1 or H-3), 3.45–3.64 (m, 2 H, H-1 or H-3 and H-5), 3.85–4.14 (m, 3 H, H-2,4,6), 4.20–4.46 (m, 2 H, 2 =C*H*Me), 4.58, 4.79 (2 ABq, 4 H, 2 CH_2Ph), 4.84 (s, 2 H, CH_2Ph), 6.06, 6.24 (2 dd, 2 H, J 1.8 and 6.1 Hz, 2 OCH=), 7.31 (s, 15 H, 3 Ph) (Found: C, 74.35; H, 7.42. $C_{33}H_{38}O_6$ calcd: C, 74.69; H, 7.22%).

Further elution with the same solvent gave a small mixed fraction and then **28** (1.6 g, 42%), R_F 0.55, mp 104–106° (solvent as for **27**). NMR data: ^1H, δ 1.63, 1.71 (2 dd, 6 H, J 1.2 and 6.1 Hz, 2 =CH*Me*), 2.52 (d, 1 H, J 1.8 Hz, OH), 3.22 (dd, 1 H, J 2.4 and 9.8 Hz, H-3), 3.35–3.60 (m, 2 H), 3.92–4.55 (m, 5 H, 2 =C*H*Me and 3 ring protons), 4.56, 4.69 (2 s, 4 H, 2 CH_2Ph), 4.84 (ABq, 2 H, CH_2Ph), 5.98, 6.20 (2 dd, 2 H, 2 OCH=), 7.23–7.38 (m, 15 H, 3 Ph) (Found: C, 74.66; H, 7.47%).

Compound **27** was treated with MeI and NaH in DMF, and the product was isolated in the usual way to give the 5-*O*-methyl derivative **29**, R_F 0.9 (ether–light petroleum, 1:2). A solution of **29** in acetone–M HCl (9:1) was heated under reflux for 20 min, and the diol **32** (R_F 0, as above) was isolated in the usual way. A solution of **32** in EtOH was hydrogenolysed over Pd/C for 24 h, then filtered. Insoluble material was washed with water, and the filtrate and washings were combined and concentrated to give **33**, which was acetylated with acetic acid anhydride–pyridine to give 1,2,3,4,6-penta-*O*-acetyl-5-*O*-methyl-*myo*-inositol (**34**), mp and mixture mp 201–203° (from EtOH), identical with the material described previously[7]. NMR data: ^1H, δ 1.99 (6 H), 2.08 (6 H), 2.19 (3 H), (3 s, 15 H, 5 Ac), 3.41 (t, 1 H, J 9.8 Hz, H-5), 3.45 (s, 3 H, OMe), 5.00 (dd, 2 H, J 3.1 and 10.4 Hz, H-1, 3) 5.35–5.57 (m, 3 H, H-2, 4, 6).

*(±)-5-*O*-Allyl-1,2,4-tri-*O*-benzyl*-myo-*inositol* (**35**).—Racemic **27** (R_F 0.65) was treated with allyl bromide and NaH in DMF and the product was isolated in the usual way to give the allyl ether **30** as an oil, R_F 0.75 (TLC ether–light petroleum, 1:2). A solution of **30** in acetone–M HCl (9:1) was heated under reflux for 20 min

when TLC (as above) showed the complete conversion of **30** into **35** (R_F 0). An excess of $NaHCO_3$ was added and the solvents were evaporated. Extraction of the residue with CH_2Cl_2 gave **35**, mp 56–58° (from light petroleum–EtOAc) (Found: C, 73.67; H, 6.83. $C_{30}H_{34}O_6$ calcd: C, 73.44; H, 6.99%).

The 1,4-diacetate (**36**) of **35** had mp 106–107° (from light petroleum–EtOAc, 10:1). NMR data: ^1H, δ 1.90, 2.04 (2 s, 6 H, 2 Ac), 3.34 (t, 1 H, J 9.7 Hz, H-5), 3.41 (dd, 1 H, H-1), 3.96–5.28 (m, 13 H, 3 CH_2Ph, OCH_2CH=, =CH_2, and 3 ring protons), 5.59 (t, 1 H, J 9.8 Hz, H-6), 5.59–5.89 (m, 1 H, CH=), 7.30 (s, 15 H, 3 Ph) (Found: C, 71.28; H, 6.77. $C_{34}H_{38}O_8$ calcd: C, 71.06; H, 6.67%).

*(±)-1,2,4-Tri-*O*-benzyl-5-*O*-(*cis*-prop-1-enyl)-*myo*-inositol* (**39**).—A solution of **35** (2 g, 4.1 mmol) and potassium *tert*-butoxide (1.5 g, 12.3 mmol) in dry Me_2SO (25 mL) was kept at 50° for 4 h. TLC (ether–light petroleum, 1:1) showed no difference in mobility of the product from that of **35** (R_F 0.3). Therefore, the product from a small portion of the solution (obtained as described below) was treated with acetone–M HCl (9:1) at reflux for 15 min. TLC (as above) then showed a new product (R_F 0), indicating that the isomerisation of the allyl group to the prop-1-enyl group was complete. The solution was diluted with semi-satd aq KCl and the precipitate was extracted with ether. The extract was washed with satd aq KCl, dried (K_2CO_3), and concentrated in the presence of a few drops of triethylamine to give **39**, mp 85–86° (from 1:3 ether–light petroleum, containing a little triethylamine) (Found: C, 73.60; H, 7.01. $C_{30}H_{34}O_6$ calcd: C, 73.44; H, 6.99%).

The diacetate (**40**) of **39** had mp 110–112° (from light petroleum containing a little pyridine). NMR data: ^1H, δ 1.56 (dd, 3 H, J 1.8 and 6.7 Hz, =CH*Me*), 1.92, 2.01 (2 s, 6 H, 2 Ac), 3.43 (dd, 1 H, J 2.5 and 10.4 Hz, H-1), 3.54 (t, 1 H, J 9.15 Hz, H-5), 3.98–4.95 (m, 9 H, 3 CH_2Ph and H-2,3,4), 5.65 (t, 1 H, J 10.1 Hz, H-6), 6.03 (dd, 1 H, J 1.8 and 6.1 Hz, OCH=), 7.28, 7.30 (2 s, 15 H, 3 Ph) (Found: C, 70.91; H, 6.71. $C_{34}H_{38}O_8$ calcd: C, 71.06; H, 6.67%).

*(±)-2,3,6-Tri-*O*-benzyl-5-*O*-(*cis*-prop-1-enyl)-*myo*-inositol 1,4-bis[di-(2,2,2-trichloroethyl) phosphate]* (**41**), *1-[di-(2,2,2-trichloroethyl) phosphate]* (**42**), *and 4-[di-(2,2,2-trichloroethyl) phosphate]* (**43**).—A solution of **39** (840 mg, 1.71 mmol) and **1** (1.5 g, 3.96 mmol) in dry pyridine (20 mL) was kept at 20° for 24 h. TLC (ether–light petroleum, 3:1) during this time showed the conversion of **39** (R_F 0.6) through products (R_F 0.4, 0.65, and 0.75) into a single product (R_F 0.65). Water (1 mL) was added, and the solution was kept at 20° for 1 h, then diluted with water (50 mL). The precipitate was extracted with CH_2Cl_2, the extract was washed with ice-cold M HCl and satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. Column chromatography (ether–light petroleum, 2:1) of the residue gave **41** (1.87 g, 93%), mp 158–159° (from CH_2Cl_2–light petroleum). NMR data: ^1H, δ 1.64 (dd, 3 H, J 1.5 and 7.0 Hz, =CH*Me*), 3.50 (dd, 1 H, J 1.8 and 9.8 Hz, H-3), 3.66 (t, 1 H, J 9.1 Hz, H-5), 3.99–5.18 (m, 18 H, 3 CH_2Ph, 4 CH_2CCl_3, and 4 ring protons), 6.17 (dd, 1 H, J 1.8 and 6.1 Hz, OCH=), 7.25–7.34 (m, 15 H, 3 Ph); ^{31}P, δ −5.32, −4.64 (Found: C, 39.02; H, 3.25; P, 5.04. $C_{38}H_{40}Cl_{12}O_{12}P_2$ calcd: C, 38.81; H, 3.43; P, 5.27%).

Column chromatography (as above) of the partially phosphorylated compounds (R_F 0.4 and 0.75) described above gave **42**, R_F 0.75 mp 109–110° (from light petroleum). NMR data: ^{1}H, δ 1.61 (dd, 3 H, J 1.5 and 7.0 Hz, =CH*Me*), 2.48 (d, 1 H, J 1.8 Hz, OH), 3.29 (dd, 1 H, J 2.2 and 9.5 Hz, H-3), 3.49 (t, 1 H, J 8.8 Hz, H-5), 3.96–4.95 (m, 15 H, 3 C*H*$_2$Ph, 2 CH$_2$CCl$_3$, =C*H*Me, and 4 ring protons), 6.22 (dd, 1 H, J 1.5 and 6.5 Hz, OCH=), 7.32–7.37 (m, 15 H, 3 Ph); ^{31}P, δ −5.45 (Found: C, 48.44; H, 4.48; P, 3.40. $C_{34}H_{37}Cl_6O_9P$ calcd: C, 49.00; H, 4.48; P, 3.72%). Acidic hydrolysis of **42** gave **4**.

Further elution gave **43**, R_F 0.4, mp 131–133° (from ether–light petroleum, 1:2). NMR data: ^{1}H, δ 1.67 (dd, 3 H, J 1.2 and 6.7 Hz, =CH*Me*), 2.18 (d, 1 H, J 5.5 Hz, OH), 3.39–3.91 (m, 4 H), 4.05 (t, 1 H, J 2.2 Hz, H-2), 4.27–5.15 (m, 14 H, 3 C*H*$_2$Ph, 2 CH$_2$CCl$_3$, =C*H*Me, and 1 ring proton), 7.33–7.49 (m, 15 H, 3 Ph); ^{31}P, δ −4.64 (Found: C, 48.40; H, 4.48; P, 3.50%).

*(±)-1,5-Di-*O*-acetyl-4-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol* (**38**).—The alcohol **28** was treated with allyl bromide and NaH in DMF, and the syrupy product was isolated in the usual way. TLC (ether–light petroleum, 1:2) showed the conversion of **28** (R_F 0.2) into the allyl ether **31** (R_F 0.5) which was hydrolysed, as described for the preparation of **35**, and the syrupy product **37** was acetylated to give **38**, mp 92–94° (from EtOAc–light petroleum). NMR data: ^{1}H, δ 1.92, 1.98 (2 s, 6 H, 2 Ac), 3.52 (dd, 1 H, J 1.8 and 9.8 Hz, H-3), 3.76–4.30 (m, 5 H, H-2,4,6 and OC*H*$_2$CH=), 4.54–4.79 (m, 7 H, 3 C*H*$_2$Ph and H-1), 4.93–5.28 (m, 3 H, =CH$_2$ and H-5), 5.65–6.02 (m, 1 H, CH=), 7.28, 7.33 (2 s, 15 H, 3 Ph) (Found: C, 71.27; H, 6.79. $C_{34}H_{38}O_8$ calcd: C, 71.06; H, 6.67%).

*(±)-1,5-Di-*O*-acetyl-2,3,6-tri-*O*-benzyl-4-*O*-(*cis*-prop-1-enyl)-*myo*-inositol* (**45**).—The diol **37** (regenerated from **38**) was treated with potassium *tert*-butoxide in Me$_2$SO and the product was isolated, as described for the preparation of **39**. TLC (ether–light petroleum, 1:1) showed the conversion of **37** (R_F 0.4) into **44** (R_F 0.5), which was isolated as a syrup and acetylated to give **45**, mp 108–110° (from light petroleum containing a little pyridine). NMR data: ^{1}H, δ 1.55 (dd, 3 H, J 1.2 and 6.7 Hz, =CH*Me*), 1.91, 1.95 (2 s, 6 H, 2 Ac), 3.55 (dd, 1 H, J 2.1 and 9.5 Hz, H-3), 3.92–4.92 (m, 13 H, 3 C*H*$_2$Ph, =CH*Me*, and 4 ring protons), 5.16 (t, 1 H, J 9.8 Hz, H-5), 6.08 (dd, 1 H, J 1.8 and 6.1 Hz, CH=), 7.28, 7.32 (2 s, 15 H, 3 Ph) (Found: C, 71.30; H, 6.82. $C_{34}H_{38}O_8$ calcd: C, 71.06; H, 6.67%).

*(±)-2,3,6-Tri-*O*-benzyl-4-*O*-(*cis*-prop-1-enyl)-*myo*-inositol 1,5-bis[di-(2,2,2-trichloroethyl) phosphate]* (**46**) *and 1-[di-(2,2,2-trichloroethyl) phosphate]* (**47**).—The diol **44** (regenerated from **45**) was phosphorylated, as described above for **39**, and TLC showed similar behaviour for the phosphorylated products. The bisphosphate **46**, isolated as described for **41**, had mp 148–149° (from light petroleum–EtOAc). NMR data: ^{1}H, δ 1.66 (dd, 3 H, J 1.6 and 7.0 Hz, =CH*Me*), 3.42 (dd, 1 H, J 1.8 and 9.8 Hz, H-3), 4.11–5.12 (m, 19 H, 3 C*H*$_2$Ph, 4 CH$_2$CCl$_3$, and 5 ring protons), 6.18 (dd, 1 H, J 1.8 and 6.1 Hz, OCH=), 7.23–7.44 (m, 15 H, 3 Ph); ^{31}P, δ −5.38, −4.04 (Found: C, 38.98; H, 3.55. $C_{38}H_{40}Cl_{12}O_{12}P_2$ calcd: C, 38.81; H, 3.43%).

The monophosphate **47** had mp 119–120° (from EtOAc–petroleum, 1:5 con-

taining a little pyridine). NMR data: ^{1}H, δ 1.62 (dd, 3 H, J 1.5 and 7.0 Hz, =CH*Me*), 2.48 (d, 1 H, J 1.8 Hz, OH), 3.38 (dd, 1 H, J 2.1 and 9.5 Hz, H-3), 3.62 (t, 1 H, J 8.9 Hz, H-5), 3.90–5.03 (m, 17 H, 3 CH_2Ph, 2 CH_2CCl_3, =C*H*Me, and 4 ring protons), 6.23 (dd, 1 H, J 1.5 and 6.4 Hz, OCH=), 7.31–7.41 m, 15 H, 3 Ph); ^{31}P, δ −5.38 (Found: C, 48.73; H, 4.53; P, 3.50. $C_{34}H_{37}Cl_6O_9P$ calcd: C, 49.00; H, 4.48; P, 3.72%). Acidic hydrolysis of **47** gave **4**.

*(±)-2,3,6-Tri-*O*-benzyl-*myo*-inositol 1,4-bis[di-(2,2,2-trichloroethyl) phosphate]* (**6**) *and the 5-acetate* (**7**).—(*a*) A solution of **41** (200 mg) in acetone (10 mL), MeOH (8 mL), and M HCl (2 mL) was heated under reflux for 30 min, when TLC (ether–light petroleum, 2:1) showed the complete conversion of **41** (R_F 0.7) into a product with R_F 0.5. Anhyd NaOAc (200 mg) and water (10 mL) were added, the organic solvents were evaporated, the precipitate was extracted with ether, and the extract was washed with satd aq $NaHCO_3$ and satd aq KCl, dried ($MgSO_4$), and concentrated. The residual syrup (185 mg) was dissolved in ether (2 mL), and light petroleum (6 mL) was added to give **6** (113 mg, 58%), mp 153–154°, with ^{1}H and ^{31}P NMR data as described above for the mixture of **6** and **8** (Found: C, 36.83; H, 3.31; Cl, 37.31; P, 4.93. $C_{35}H_{36}Cl_{12}O_{12}P_2$ calcd: C, 37.00; H, 3.19; Cl, 37.45; P, 5.45%).

The alcohol **6** was acetylated and the product **7** was isolated, as described above for the acetylation of the mixture of **6** and **8**. The acetate **7** co-chromatographed with the less-polar product (R_F 0.9) of the mixture of acetates (**7** and **9**). Crystallisation from EtOAc–light petroleum gave **7**, mp 197–198°. NMR data: ^{1}H, δ 2.07 (s, 3 H, Ac), 3.56 (dd, 1 H, J 1.9 and 9.3 Hz, H-3), 4.02–5.07 (m, 18 H, 3 CH_2Ph, 4 CH_2CCl_3, and 4 ring protons, with major peaks at δ 4.32, 4.39, 4.41, 4.43, 4.45, 4.47, 4.51, 4.55, 4.58, 4.60, 4.63, 4.73, and 4.88), 5.23 (t, 1 H, J 9.15 Hz, H-5), 7.29, 7.34 (2 s, 15 H, 3 Ph); ^{31}P, δ −5.38, −5.05 (Found: C, 37.92; H, 3.37; Cl, 37.59; P, 5.00. $C_{37}H_{38}Cl_{12}O_{13}P_2$ calcd: C, 37.72; H, 3.25; Cl, 36.11; P, 5.26%).

Crystallisation of the mixture of acetates **7** and **9** (prepared, as described above, from the mixture of alcohols **6** and **8**) from ether gave **7** identical with the material described above. TLC of the mother liquors showed that little **7** remained; the residue obtained on concentration was almost pure syrupy **9** (R_F 0.8) which had a ^{1}H NMR spectrum identical with that described below.

(*b*) Light petroleum (6 mL) was added to a solution of the mixture (160 mg) of alcohols **6** and **8** in ether (3 mL) and EtOAc (3 mL), and the solution was kept at 20° for 24 h to give **6** (30 mg), mp 152–154°. Acetylation of this gave a product, TLC of which (as described above for the mixture of acetates **7** and **9**) showed it to be almost pure **7** with a trace of **9**.

*(±)-2,3,6-Tri-*O*-benzyl-*myo*-inositol 1,5-bis[di-(2,2,2-trichloroethyl) phosphate]* (**8**) *and the 4-acetate* (**9**).—Compound **46** was hydrolysed and **8** was isolated as described above for the preparation of **6** from **41**. Compound **8** had mp 153–154° with ^{1}H and ^{31}P NMR data as described for the mixture of **6** and **8** (Found: C, 36.91; H, 3.22; P, 5.22. $C_{35}H_{36}Cl_{12}O_{12}P_2$ calcd: C, 37.00; H, 3.19; P, 5.45%).

Acetylation of **8** and isolation of the product, as described above for the

acetylation of the mixture of **6** and **8**, gave syrupy **9** which co-chromatographed with the more-polar product (R_F 0.8) in the mixture of **7** and **9**. NMR data: ^{1}H, δ 2.11 (s, 3 H, Ac), 3.45 (dd, 1 H, *J* 1.8 and 10.4 Hz, H-3), 4.22–5.05 (m, 18 H, 3 C*H*$_2$Ph, 4 CH$_2$CCl$_3$, and 4 ring protons), 5.69 (t, 1 H, *J* 9.8 Hz, H-4), 7.30–7.43 (m, 15 H, 3 Ph); ^{31}P, δ −5.25, −4.91 (Found: C, 37.85; H, 3.30; P, 5.10. $C_{37}H_{38}Cl_{12}O_{13}P_2$ calcd: C, 37.72; H, 3.25; P, 5.26%).

*1D-2,3,6-Tri-*O*-benzyl-1,4-di-*O*-(*cis*-prop-1-enyl)-*myo*-inositol* (**51**), *the 5-acetate* (**52**), *and 1D-4-*O*-acetyl-2,3,6-tri-*O*-benzyl-1,5-di-*O*-(*cis*-prop-1-enyl)-*myo*-inositol* (**54**).—1D-1-*O*-Allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol[1] (**48**) was converted via the mixed di-allyl ethers (**49** and **50**) into **51** and **53**, using the method described above for the preparation of racemic **27** and **28**. The initial separation of **51** and **53** was by crystallisation from light petroleum containing a little triethylamine, to remove most of the **51**, followed by column chromatography of the residue as described above for the racemates. The less-polar alcohol **51** had mp 143–144° (from light petroleum containing a little triethylamine), $[\alpha]_D^{25}$ +48° (*c* 1, $CHCl_3$), with a ^{1}H NMR spectrum identical to that described for the racemate **27** (Found: C, 75.05; H, 7.19. $C_{33}H_{38}O_6$ calcd: C, 74.69; H, 7.22%).

The 5-acetate (**52**) of **51** had mp 78–80° (from light petroleum containing a little pyridine), $[\alpha]_D^{25}$ +20° (*c* 1, $CHCl_3$). NMR data: ^{1}H, δ 1.55, 1.66 (2 dd, 6 H, *J* 1.83 and 6.72 Hz, 2 =CH*Me*), 1.91 (s, 3 H, Ac), 3.41 (dd, 1 H, *J* 2.44 and 9.76 Hz, H-1 or -3), 3.58 (dd, 1 H, *J* 1.83 and 9.76 Hz, H-1 or -3), 3.88–4.50 (m, 5 H, H-2,4,6 and 2 =C*H*Me), 4.58 (s, 2 H, C*H*$_2$Ph), 4.67 (ABq, 2 H, C*H*$_2$Ph), 4.84 (s, 2 H, C*H*$_2$Ph), 5.08 (t, 1 H, *J* 9.77 Hz, H-5), 6.01–6.08 (m, 2 H, 2 OCH=), 7.27–7.37 (m, 15 H, 3 Ph) (Found: C, 73.63; H, 7.10. $C_{35}H_{40}O_7$ calcd: C, 73.40; H, 7.04%).

The more polar compound **53** was obtained as a syrup, with a ^{1}H NMR spectrum identical to that described for the racemate **28**, which gave a crystalline acetate **54**, mp 114–116° (from light petroleum containing a little pyridine), $[\alpha]_D^{25}$ +20° (*c* 1, $CHCl_3$). NMR data: ^{1}H, δ 1.57 (dd, 3 H, *J* 1.83 and 6.72 Hz, =CH*Me*), 1.70 (dd, 3 H, *J* 1.23 and 6.71 Hz, =CH*Me*), 2.02 (s, 3 H, Ac), 3.23–3.57 (m, 3 H, H-1,3,5), 3.99–4.40 (m, 4 H, H-2,6 and 2 =C*H*Me), 4.47 (ABq, 2 H, C*H*$_2$Ph), 4.69, 4.86 (2 s, 4 H, 2 C*H*$_2$Ph), 5.65 (t, 1 H, *J* 9.98 Hz, H-4), 5.90–6.14 (m, 2 H, 2 OCH=), 7.28–7.38 (m, 15 H, 3 Ph) (Found: C, 73.51; H, 7.16. $C_{35}H_{40}O_7$ calcd: C, 73.40; H, 7.04%).

*1D-1,5-Di-*O*-acetyl-4-*O*-allyl-2,3,6-tri-*O*-benzyl-*myo*-inositol* (**62**).—Compound **53** was converted into the syrupy allyl ether **56** which was hydrolysed to give the syrupy diol **61**, as described above for the preparation of the racemate **37**. Acetylation of **61** gave **62**, mp 101–103° (from light petroleum), $[\alpha]_D^{25}$ −17.5° (*c* 1, $CHCl_3$), with ^{1}H NMR data identical to those described for the racemate **38** (Found: C, 71.40; H, 6.62. $C_{34}H_{38}O_8$ calcd: C, 71.06; H, 6.67%).

*1D-4-*O*-Allyl-2,3,6-tri-*O*-benzyl-1,5-di-*O*-p-methoxybenzyl-*myo*-inositol* (**63**).—The diol **61** (regenerated from the crystalline diacetate **62**) was treated with *p*-methoxybenzyl chloride and NaH in DMF and the product was isolated in the usual way to give **63**, mp 92–94° (from light petroleum), $[\alpha]_D^{25}$ +12° (*c* 1, $CHCl_3$).

NMR data: ^{1}H, δ 3.20–3.49 (m, 3 H, H-1,3,5), 3.79, 3.81 (2 s, 6 H, 2 OMe), 3.89–4.10 (m, 3 H, H-2,4,6), 4.32–4.38 (m, 2 H, OCH_2CH=), 4.54 (s, 2 H, CH_2Ph), 4.62 (ABq, 2 H, CH_2Ph), 4.77 (s, 2 H, CH_2Ph), 4.84–4.86 (m, 4 H, 2 CH_2Ph), 5.09–5.35 (m, 2 H, =CH_2), 5.79–6.20 (m, 1 H, CH=), 6.78–7.48 (m, 23 H, aromatic) (Found: C, 75.75; H, 6.79. $C_{46}H_{50}O_8$ calcd: C, 75.59; H, 6.90%).

*1D-2,3,6-Tri-*O*-benzyl-1,5-di-*O*-*p*-methoxybenzyl-4-*O*-(*cis*-prop-1-enyl)-*myo*-inositol* (**64**).—The allyl ether **63** was treated with potassium *tert*-butoxide in Me_2SO at 50° in the usual way. TLC (ether–light petroleum, 1:1) showed the conversion of **63** (R_F 0.8) into **64**, R_F 0.85, mp 104–106° (from light petroleum containing a little triethylamine), $[\alpha]_D^{25}$ −1.6° (*c* 1, $CHCl_3$). NMR data: ^{1}H, δ 1.65 (dd, 3 H, *J* 1.5 and 7.0 Hz, =CH*Me*), 3.23–3.52 (m, 3 H, H-1,3,5), 3.77, 3.80 (2 s, 6 H, 2 OMe), 3.84–4.43 (m, 4 H, =C*H*Me and H-2,4,6), 4.52 (s, 2 H, CH_2Ph), 4.60 (ABq, 2 H, CH_2Ph), 4.69 (s, 2 H, CH_2Ph), 4.82 (s, 4 H, 2 CH_2Ph), 6.22–6.31 (m, 1 H, OCH=), 6.76–7.32 (m, 23 H, aromatic) (Found: C, 75.36; H, 6.72. $C_{46}H_{50}O_8$ calcd: C, 75.59; H, 6.90%).

Hydrolysis of **64** in the usual way (see above) gave the alcohol **65**, which gave the 4-acetate **66**. Both were identical with the materials described[1].

*1D-2,3,6-Tri-*O*-benzyl-5-*O*-p-methoxybenzyl-*myo*-inositol (57).*—The alcohol **51** was treated with *p*-methoxybenzyl chloride and NaH in DMF and the product was isolated in the usual way. TLC (ether–light petroleum, 1:2) showed the conversion of **51** (R_F 0.5) into a product with R_F 0.6. Column chromatography (ether–light petroleum, 1:2) removed by-products and gave **55** as a syrup still contaminated (NMR data) with methyl *p*-methoxybenzyl ether. Crude **55** was treated with acetone–MeOH–M HCl (3:7:1) at 40° for 40 min, when TLC (ether–light petroleum, 2:1) showed conversion of **55** (R_F 0.9) into a product with R_F 0.3, together with some remaining by-product (R_F 0.9). Column chromatography (ether–light petroleum, 2:1) then gave **57** (89% from **51**), mp 100–102° (from ether–light petroleum), $[\alpha]_D^{25}$ +5.9° (*c* 1, CHCl). NMR data: ^{1}H, δ 2.27 (d, 1 H, *J* 6.1 Hz, OH), 2.52 (d, 1 H, *J* 2.5 Hz, OH), 3.21–3.68 (m, 3 H, H-1,3,5), 3.78 (s, 3 H, OMe), 3.88–4.25 (m, 3 H, H-2,4,6), 4.63–4.89 (m, 8 H, 4 CH_2Ph), 6.79–7.32 (m, 19 H, aromatic) (Found: C, 73.96; H, 6.69. $C_{35}H_{38}O_7$ calcd: C, 73.66; H, 6.71%).

The diacetate (**58**) of **57** had mp 115–117° (from ether–light petroleum), $[\alpha]_D^{25}$ −16° (*c* 1, $CHCl_3$). NMR data: ^{1}H, δ 1.91, 1.95 (2 s, 6 H, 2 Ac), 3.77 (s, 3 H, OMe), 4.02–4.23 (m, 2 H, H-2,6), 4.37–4.93 (m, 9 H, 4 CH_2Ph and H-1), 5.63 (t, 1 H, *J* 10.4 Hz, H-4), 6.77–7.29 (m, 19 H, aromatic) (Found: C, 71.52; H, 6.46. $C_{39}H_{42}O_9$ calcd: C, 71.54; H, 6.47%).

*1D-2,3,6-Tri-*O*-benzyl-5-*O*-p-methoxybenzyl-*myo*-inositol 1,4-bis(dibenzyl phosphate)* (**60**).—The diol **57** (100 mg) was treated with **71** and tetrazole in dry CH_2Cl_2 as described[11] for the preparation of related compounds. TLC (ether–light petroleum, 1:1) showed the conversion of **57** (R_F 0.1) into the bisphosphite **59** (R_F 0.7) which was oxidised[11] with 3-chloroperoxybenzoic acid to give **60**, R_F 0 [R_F 0.5 (ether)]. The product was isolated in the usual way[11] and column chromatography (ether) gave **60** (169 mg, 88%), mp 88–90° (from EtOAc–light petroleum), $[\alpha]_D^{25}$

+7.9° (*c* 1, $CHCl_3$). NMR data: ^1H, δ 3.34–3.58 (m, 2 H, H-3,5), 3.72 (s, 3 H, OMe), 3.94–4.32 (m, 3 H, H-1,2,6), 4.53–4.97 (m, 17 H, 8 CH_2Ph and H-4, with major peaks at δ 4.53, 4.71, 4.77, 4.80, 4.84, 4.86, 4.88, and 4.97), 6.65–7.24 (m, 39 H, aromatic); ^{31}P, δ −1.61, −1.41 (Found: C, 69.69; H, 5.96; P, 5.66. $C_{63}H_{64}O_{13}P_2$ calcd: C, 69.35; H, 5.91; P, 5.68%).

*1D-2,3,6-Tri-*O*-benzyl-*myo*-inositol 1,4-bis(dibenzyl phosphate)* (**67**).—(*a*) A solution of **60** (950 mg) in acetonitrile–water (9:1, 20 mL) was stirred at 20° and a solution of cerium(IV) ammonium nitrate (1.91 g) in acetonitrile–water (9:1, 10 mL) was added dropwise. The initial dark-yellow colour changed to light yellow as the oxidation proceeded. TLC ($CHCl_3$–MeOH, 20:1) showed the conversion of **60** (R_F 0.5) into a product with R_F 0.45 together with traces of more-polar products, presumably formed by oxidative debenzylation. When the reaction was complete, water (100 mL) was added, the acetonitrile was evaporated, and the precipitate was extracted with CH_2Cl_2. The extract was washed with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated, and the residue was crystallised from ether containing a little light petroleum to give **67** (590 mg). Column chromatography ($CHCl_3$–MeOH, 20:1) of the contents of the mother liquors and crystallisation gave more **67** (70 mg; total yield, 72%), mp 80–82°, $[\alpha]_D^{25}$ +7.9° (*c* 1, $CHCl_3$), which the ^1H NMR spectrum indicated to be an etherate. NMR data: ^1H, δ 1.21 (t, 6 H, *J* 6.7 Hz, 2 OCH_2Me), 1.74 (s, 1 H, OH), 3.31–4.33 (m, ring protons and 2 OCH_2Me, with peaks at δ 3.30, 3.35, 3.43, 3.51, 3.60, 3.66, 3.78, 3.87, 3.97, 4.07, 4.14, 4.26, and 4.33), 4.47–5.07 (m, 7 CH_2Ph and ring protons, with major peaks at δ 4.47, 4.67, 4.74, 4.77, 4.90, 4.98, 5.03, and 5.07), 7.22–7.38 (m, 35 H, 7 Ph); ^{31}P, δ −1.75, 0.34 (Found: C, 68.23; H, 5.89; P, 6.61. $C_{55}H_{56}O_{12}P_2 \cdot C_4H_{10}O$ calcd: C, 67.80; H, 6.37; P, 5.93%).

The 5-acetate of **67** was a syrup. NMR data: ^1H, δ 1.79 (s, 3 H, Ac), 3.45 (d, 1 H, *J* 9.8 Hz, H-3), 3.94–5.07 (m, 18 H, 7 CH_2Ph and 4 ring protons, with major peaks at δ 4.49, 4.62, 4.69, 4.75, 4.80, 4.87, 4.89, 4.95, and 4.98), 5.17 (t, 1 H, *J* 9.2 Hz, H-5), 7.23, 7.26 (2 s, 35 H, 7 Ph); ^{31}P, δ −1.82.

(*b*) Compound **60** was treated with dichlorodicyanobenzoquinone in CH_2Cl_2–H_2O and the products were isolated, as described[12] for related reactions to remove the *O-p*-methoxybenzyl group. The product, which contained more polar by-products than that of (*a*), was purified by column chromatography as in (*a*) to give **67**.

*1D-2,3,6-Tri-*O*-benzyl-*myo*-inositol 1,4,5-tris(dibenzyl phosphate)* (**69**).—(*a*) The chiral triol[12] **73** was treated with **71** and the intermediate trisphosphite was oxidised to **69**, as described[12] for the preparation of the enantiomer **84**. Compound **69** had mp 112–113° (from EtOAc–light petroleum, 1:10), $[\alpha]_D^{25}$ −3.5° (*c* 1, $CHCl_3$). NMR data: ^1H, δ 3.46 (d, 1 H, *J* 8.6 Hz, H-3), 3.98–5.03 (m, 23 H, 9 CH_2Ph and 5 ring protons, with major peaks at δ 4.18, 4.33, 4.48, 4.59, 4.64, 4.72, 4.77, 4.81, 4.90, 4.95, 4.99, and 5.03), 7.00–7.26 (m, 45 H, 9 Ph); ^{31}P (aq 4% H_3PO_4 as external standard), δ −2.01, −1.81, −1.61. The same values were obtained for the enantiomer[12] **84** on this occasion; lit.[12] for **84**, mp 113–115°, $[\alpha]_D^{25}$ +3.5° (*c* 1,

$CHCl_3$); ^{31}P NMR data (aq 85% H_3PO_4 as external standard): δ −1.95, −1.68, −1.55.

(*b*) The alcohol **67** was treated with **71**, the intermediate phosphite **68** was oxidised to **69** in the usual way, and the product was isolated and purified as in (*a*) to give **69**.

1D-2,3,6-Tri-O-benzyl-1-O-p-methoxybenzyl-myo-inositol 4,5-bis[di-(2-cyanoethyl) phosphate] (**76**).—1D-2,3,6-Tri-*O*-benzyl-1-*O*-*p*-methoxybenzyl-*myo*-inositol[1] (**74**, 500 mg) was treated with **72** and tetrazole in the usual way[11] to give the bisphosphite **75** which was oxidised[11] to give **76**. Column chromatography (CH_2Cl_2 followed by CH_2Cl_2–MeOH, 20:1) gave **76** (450 mg, 54%), mp 84–86° (from EtOH), $[\alpha]_D^{25}$ +4.4° (*c* 1, $CHCl_3$). NMR data: ^1H, δ 2.10–2.46 (m, 4 H, 2 CH_2CN), 2.62–2.75 (t, 4 H, 2 CH_2CN), 3.40 (d, 2 H, *J* 9.7 Hz, H-1,3), 3.79 (s, 3 H, OMe), 3.86–4.95 (m, 19 H, 4 CH_2Ph, 4 CH_2CH_2CN, and 3 ring protons), 5.03 (t, 1 H, *J* 11.6 Hz, H-4), 6.74–7.34 (m, 19 H, aromatic); ^{31}P, δ −3.50, −3.30 (Found: C, 60.27; H, 5.29; N, 6.06; P, 6.52. $C_{47}H_{52}N_4O_{13}P_2$ calcd: C, 59.87; H, 5.56; N, 5.94; P, 6.57%).

1D-2,3,6-Tri-O-benzyl-myo-inositol 4,5-bis[di-(2-cyanoethyl) phosphate] (**77**).—Compound **76** was treated with dichlorodicyanobenzoquinone and the product was isolated, as described[12] for related reactions to remove the *O*-*p*-methoxybenzyl group. TLC (CH_2Cl_2–MeOH, 20:1) showed the conversion of **76** (R_F 0.5) into a product with R_F 0.45. Column chromatography (CH_2Cl_2 followed by CH_2Cl_2–MeOH, 20:1) gave **77** (90%), isolated as a syrup, $[\alpha]_D^{25}$ +7.4° (*c* 1, $CHCl_3$). NMR data: ^1H, δ 2.21–2.39 (m, 4 H, 2 CH_2CN), 2.60–2.83 (m, 4 H, 2 CH_2CN), 3.40–4.47 (m, 14 H, 4 OCH_2CH_2CN and 6 ring protons), 4.63–5.02 (m, 6 H, 3 CH_2Ph, with major peaks at δ 4.63, 4.66, 4.78, 4.83, 4.87, and 4.90), 7.34 (s, 15 H, 3 Ph); ^{31}P, δ −3.43, −3.30 (Found: C, 57.56; H, 5.43; N, 7.17; P, 7.42. $C_{39}H_{44}N_4O_{12}P_2$ calcd: C, 56.93; H, 5.39; N, 6.81; P, 7.53%).

1D-2,3,6-Tri-O-benzyl-myo-inositol 1,4,5-tris[di-(2-cyanoethyl) phosphate] (**79**).—(*a*) The triol[12] **73** (R_F 0.5; $CHCl_3$–MeOH, 15:1) was treated with **72** and the intermediate trisphosphite **80** (R_F 0.7) was oxidised as described for related reactions[11], to give **79** (R_F 0.3). Column chromatography (EtOAc–MeOH, 8:1) of the crude product gave **79** (1.81 g, 72%), mp 105–107° (from EtOAc–light petroleum), $[\alpha]_D^{25}$ +4.0° (*c* 1, $CHCl_3$). NMR data: ^1H, δ 2.20–2.80 (m, 12 H, 6 CH_2CN, with major peaks at δ 2.27, 2.33, 2.49, 2.56, 2.62, 2.66, and 2.73), 3.62 (d, 1 H, *J* 9.1 Hz, H-3), 3.86–5.06 (m, 23 H, 3 CH_2Ph, 6 OCH_2CH_2CN, and 5 ring protons, with major peaks at δ 4.04, 4.10, 4.23, 4.31, 4.47, 4.63, 4.73, 4.88, and 4.93), 7.37 (s, 15 H, 3 Ph); ^{31}P, δ −3.36 (1 P), −3.16 (2 P) (Found: C, 53.57; H, 4.73; N, 8.41; P, 8.82. $C_{45}H_{51}N_6O_{15}P_3$ calcd: C, 53.57; H, 5.10; N, 8.33; P, 9.21%).

(*b*) The bisphosphate **77** (R_F 0.5 in CH_2Cl_2–MeOH, 20:1) was treated with **72** and the intermediate phosphite **78** (R_F 0.55) was oxidised to give the trisphosphate **79** (R_f 0.5). The product was isolated as described in (*a*).

1L-2,3,6-Tri-O-benzyl-myo-inositol 1,4,5-tris[di(2-cyanoethyl) phosphate] (**83**).—The triol[10] **81** was converted via the trisphosphite **82** into **83** and the product was

purified, as described above for the preparation of the enantiomer **79**. Compound **83** had mp 105–107°, $[\alpha]_D^{25}$ −3.7° (*c* 1, $CHCl_3$), and ^1H and ^{31}P NMR spectra identical to those of the enantiomer **79** (Found: C, 53.66; H, 4.97; N, 8.02; P, 8.74%).

*(±)-1,2,4-Tri-*O*-benzyl-*myo*-inositol 3-[di-(2-cyanoethyl) phosphate]* (**87**).—The racemic alcohol **2** (R_F 0.4; ether–light petroleum, 1:2) was treated with **72** to give the phosphite **85** (R_F 0.2 as above) which was oxidised, as described in related reactions[11], to give the phosphate **86** (R_F 0.8 in EtOAc). Column chromatography (ether–EtOAc, 1:1) gave pure **86** (88%), isolated as a syrup that was treated with acetone–MeOH–M HCl (5:6:1) at 20° for 2 h. TLC (ether–EtOAc, 1:1) then showed the complete conversion of **86** (R_F 0.7) into a product with R_F 0.4. An excess of NaOAc was added, the solvents were evaporated, and the product was extracted from the residue with CH_2Cl_2 to give **87**, mp 122–124° (from EtOAc–light petroleum). NMR data: ^1H, δ 2.32–2.53 (m, 4 H, 2 CH_2CN), 2.66 (s, 2 H, 2 OH), 3.31 (dd, 1 H, *J* 1.8 and 9.8 Hz, H-1), 3.53 (t, 1 H, *J* 7.8 Hz), 3.85–4.47 (m, 8 H, 2 CH_2CH_2CN and 4 ring protons), 4.60–5.09 (m, 6 H, 3 CH_2Ph, with major peaks at δ 4.60, 4.67, 4.74, 4.82, 4.88, and 4.96), 7.34–7.41 (m, 15 H, 3 Ph); ^{31}P, δ −3.23 (Found: C, 62.53; H, 5.90; N, 4.89; P, 4.95. $C_{33}H_{37}N_2O_9P$ calcd: C, 62.26; H, 5.86; N, 4.40; P, 4.87%).

The diol **87** was treated with **72** and the intermediate bisphosphite **88** was oxidised to give the racemic trisphosphate **89** which was purified as described for the chiral derivative **79**. The pure product **89** was obtained as a syrup (67%) with ^1H and ^{31}P NMR spectra identical with those of the chiral derivatives **79** and **83**.

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