# Bicyclic Analogues of D-*myo*-Inositol 1,4,5-Trisphosphate Related to Adenophostin A: Synthesis and Biological Activity

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The high affinity of adenophostin A for 1D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)$P_3$] receptors may be related to an alteration in the position of its 2′-phosphate group relative to the corresponding 1-phosphate group in Ins(1,4,5)$P_3$. To investigate this possibility, two bicyclic trisphosphates **9** and **10**, designed to explore the effect of relocating the 1-phosphate group of Ins(1,4,5)$P_3$ using a novel fused-ring system, were synthesized from *myo*-inositol. Biological evaluation of **9** and **10** at the Ins(1,4,5)$P_3$ receptors of hepatocytes showed that both were recognized by hepatic Ins(1,4,5)$P_3$ receptors and both stimulated release of $Ca^{2+}$ from intracellular stores, but they had lower affinity than Ins(1,4,5)$P_3$. This finding may be explained by considering the three-dimensional structures of **9** and **10** in light of recent studies on the conformation of adenophostin A.

## Introduction

Many extracellular stimuli activate the hydrolysis of a phospholipid component of the plasma membrane, phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)$P_2$], to generate 1D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)$P_3$, **1**, Figure 1].[1] Ins(1,4,5)$P_3$ acts as a second messenger in most cells, where it binds to intracellular Ins(1,4,5)$P_3$ receptors [$IP_3R$] to cause the opening of an intrinsic $Ca^{2+}$ channel through which $Ca^{2+}$ leaks from the lumen of the endoplasmic reticulum to the cytosol. Each of the four subunits of each $IP_3R$ binds Ins(1,4,5)$P_3$ at a site formed by two distinct domains. The site includes several positively charged Arg and Lys residues which interact with the three phosphate groups of Ins(1,4,5)$P_3$.[2] Structure−activity studies[3] have shown that all high-affinity agonists of $IP_3R$ contain groups equivalent to the vicinal 4*R*,5*R*-*trans*-diequatorial bisphosphate and adjacent 6-hydroxyl group of Ins(1,4,5)$P_3$, together with an appropriately positioned nonvicinal phosphate group. Some variation in the positioning of this third phosphate group is tolerated, so that Ins(2,4,5)$P_3$ (**2**), for example, is also recognized by $IP_3$Rs, although typically with some 25-fold lower affinity than Ins(1,4,5)$P_3$.[4]

In 1993, two new ligands of Ins(1,4,5)$P_3$ receptors, adenophostins A and B (**3** and **4**, Figure 1) were isolated from culture broths of *Penicillium brevicompactum* and found to be up to 100 times more potent than Ins(1,4,5)$P_3$ itself.[5] In the adenophostins, the 3″,4″-bisphosphate and 2″-hydroxyl group of the glucopyranosyl ring are thought to mimic the inositol 4,5-bisphosphate and adjacent hydroxyl group of Ins(1,4,5)$P_3$. Intriguingly, the third phosphate group (analogous to the 1-phosphate of Ins(1,4,5)$P_3$) is located on a separate (ribofuranosyl) ring. Removal of the adenine from **3** to give **5** reduces affinity to about that of Ins(1,4,5)$P_3$,[6]

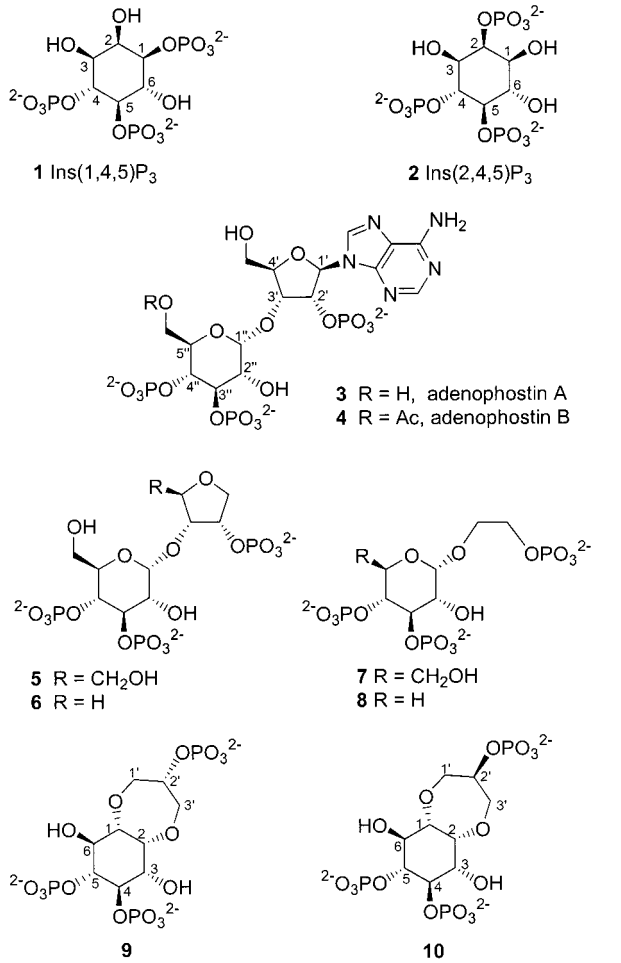


**Figure 1.** Structures of 1D-*myo*-inositol 1,4,5-trisphosphate (**1**), 1D-*myo*-inositol 2,4,5-trisphosphate (**2**), adenophostins A (**3**) and B (**4**), adenophostin analogues (**5**−**8**), and epimeric bicyclic Ins(1,4,5)$P_3$ analogues (**9** and **10**).

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although further simplification by removal of the 4′-hydroxymethyl group (**6**) has little further effect.[6,7] However, opening of the five-membered ring, with a consequent increase in the conformational mobility of the nonvicinal phosphate, causes a greater reduction in affinity. Thus, analogue **7**[8,9] and its xylose-based equivalent **8**[10] were found to be 10 or more times weaker than Ins(1,4,5)$P_3$.

It has been suggested[5,8] that, at the binding site of the $IP_3R$, the nonvicinal phosphate group in the adenophostins may be held further away from the vicinal pair than is the corresponding 1-phosphate of Ins(1,4,5)$P_3$, and that this modification may underlie the greater affinity of the adenophostins for the $IP_3R$. With this explanation, the adenosine motif of **3** and **4** functions simply to present the 2′-phosphate in a position that modifies its interaction with one or more residues at the receptor binding site. An alternative explanation for the enhanced potency of the adenophostins is that the adenine itself interacts with a region of the Ins(1,4,5)$P_3$ receptor close to the Ins(1,4,5)$P_3$-binding site.[11,12] The two alternative explanations for adenophostin activity (modified positioning of a phosphate group versus a specific interaction of the adenine with the receptor) are not necessarily mutually exclusive, and an interplay between the two may be involved.

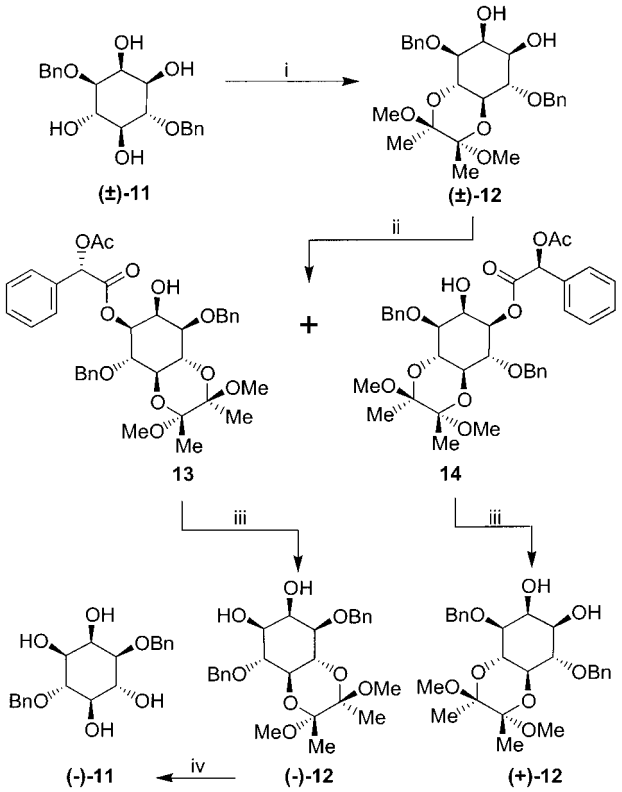
We sought to explore the consequences for biological activity of relocating the 1-phosphate group of Ins(1,4,5)$P_3$ to a region of space further away from the inositol ring by synthesising bicyclic analogues of Ins(1,4,5)$P_3$. Here we describe the synthesis and biological evaluation of the first two such analogues **9** and **10**. These epimeric molecules, based on *myo*-inositol fused to a seven-membered (1,4-dioxepane) ring, place their nonvicinal phosphate groups in regions of space more distant from the inositol ring than are normally accessible to the 1-phosphate group of Ins(1,4,5)$P_3$. They retain the three-atom (O−C−C) linkage between the six-membered ring and the nonvicinal phosphate characteristic of the adenophostins and analogues **5**−**8**, but they lack the conformational freedom allowed by the presence of the glycosidic linkage in these carbohydrate-based compounds. A preliminary report of the synthesis of **9** and **10** has appeared.[13]

## Results and Discussion

The synthetic route to **9** and **10** begins with the known DL-1,4-di-*O*-benzyl-*myo*-inositol [(±)-**11**, Scheme 1], readily accessible on a 20 g scale without chromatography from *myo*-inositol.[14] This tetrol contains two pairs of vicinal hydroxyl groups, one cis and one trans, and it was found that the trans pair could be protected selectively by using the butane diacetal (BDA) protecting group. Thus, acid-catalyzed reaction of (±)-**11** with tetramethoxybutane[15] in refluxing methanol, in the presence of trimethyl orthoformate, gave the crystalline racemic diacetal (±)-**12**. It was later found that identical results could be achieved more cheaply and conveniently using a modified procedure[16] in which tetramethoxybutane is replaced with commercially available butanedione.

An optical resolution step was now used to isolate the required enantiomer of diol **12**. Following a report of the optical resolution of (±)-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol by regioselective esterification of the equatorial

**Scheme 1**[a]

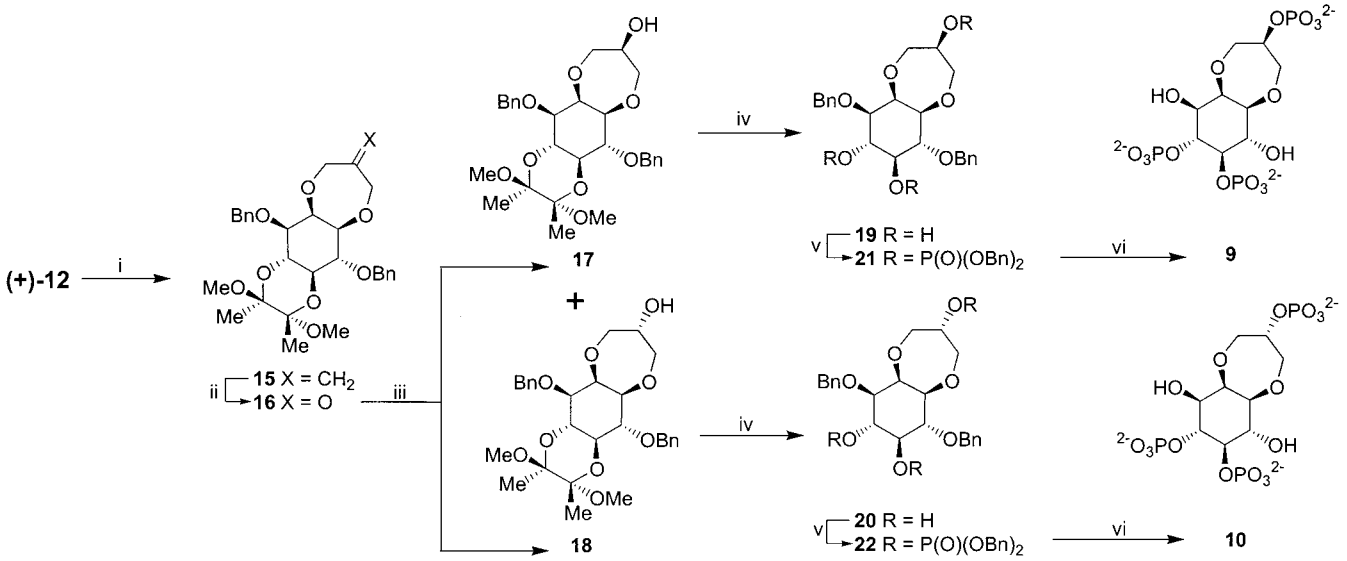



[a] Reagents and conditions: (i) butanedione, MeOH, $CH(OMe)_3$, (±)-10-camphorsulfonic acid, reflux, 80%; (ii) (*S*)-(+)-acetylmandelic acid, DCC, DMAP, $CH_2Cl_2$, −20 °C to room temperature, 34% (**13**), 36% (**14**); (iii) NaOH, MeOH, reflux, 95%; (iv) $CH_2Cl_2$/$CF_3COOH$/$H_2O$ 25:24:1, 98%. Compounds (±)-**11** and (±)-**12** are racemic

OH-group with (*S*)-(+)-acetylmandelic acid,[17] we have found that this method generally works well for *myo*-inositols with this pattern of protection, giving diastereoisomeric esters that are easily separated by flash chromatography.[18] An additional advantage of acetylmandelic acid as a resolving agent is that both enantiomers are commercially available at similar cost and in high optical purity. The resolution can initially be carried out on a small scale, and once the absolute configurations of the products are determined, the appropriate enantiomer of acetylmandelic acid can be chosen so as to optimize isolation of the required product on scale-up.

Applying this method to (±)-**11**, it was found that regioselective esterification of (±)-**11** with (*S*)-(+)-acetylmandelic acid gave diastereoisomeric acetylmandelate esters which were readily separated by flash chromatography followed by crystallization. The less polar ester was particularly easy to isolate and was highly crystalline, while the more polar ester required more careful chromatography and gave waxy, less satisfactory crystals. Saponification of **13** and **14** gave the enantiomeric diols (−)-**12** and (+)-**12**, respectively. To determine the absolute configurations, (−)-**12** was converted into the di-*O*-benzyl ether (−)-**11** by treatment with TFA. The tetrol (−)-**11** had an optical rotation in agreement with that reported for the known 1D-1,4-di-*O*-benzyl-*myo*-inositol,[18b] identifying the more polar ester as **13** and the more crystalline, less polar ester as the required **14**. Accordingly, (*S*)-(+)-acetylmandelic acid was used as resolving agent in the full-scale route.

**Scheme 2**[a]




[a] Reagents and conditions: (i) NaH, 3-chloro-2-chloromethyl-1-propene, DMF, 84%; (ii) $RuCl_3$, $NaIO_4$, EtOAc/$CH_3CN$/$H_2O$, 82%; (iii) $NaBH_4$, MeOH, 0 °C to room temperature, 21% (**17**), 67% (**18**); (iv) $CH_2Cl_2$/$CF_3COOH$/$H_2O$ 25:24:1, 83−84%; (v) (a) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, $CH_2Cl_2$; (b) *m*-CPBA, −78 °C to room temperature, 82−90%; (vi) $H_2$, 50 psi, Pd−C, MeOH, 89−90%.

Reaction of (+)-**12** with sodium hydride and 3-chloro-2-chloromethyl-1-propene in DMF (Scheme 2) gave the alkene **15** in 84% yield. Flash dihydroxylation[19] of the alkene employing $RuCl_3$/$NaIO_4$ gave an inseparable 3:1 mixture of epimeric diols within 4 min. Prolongation of the reaction time to 1.5 h gave the ketone **16**, which was isolated as a crystalline solid. Sodium borohydride was chosen to reduce ketone **16**, in the hope that both epimeric alcohols **17** and **18** might be obtained. This proved to be the case, and the reaction gave two alcohols in a ratio of approximately 1:3. These alcohols were separated by flash chromatography and isolated as crystalline solids. A single-crystal X-ray study of the more polar alcohol (major product) identified it as **18**, and thus the minor product was the epimer, **17**. The X-ray structure of **18** (Figure 2a) shows the relative configuration at the C-2′ position, and the 1,4-dioxepane ring is seen to take on a slightly twisted chair conformation. The supramolecular structure is consolidated by intermolecular hydrogen bonding, as shown in Figure 2b.

The BDA protecting groups were removed from **17** and **18** by treatment of each with TFA, giving the two triols **19** and **20**. Phosphitylation of **19** and of **20** using bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine activated by 1*H*-tetrazole, followed by in situ oxidation of phosphites with *m*-CPBA, gave the trisphosphate triesters **21** and **22**. While **22** was an oil, **21** was a crystalline solid. Finally, deprotection of each epimer by hydrogenolysis over Pd−C and purification of the products by ion-exchange chromatography on Q-Sepharose Fast Flow resin gave the pure epimeric trisphosphates **9** and **10** as their triethylammonium salts, which were quantified by a modification of the Briggs total phosphate assay.[20]

In equilibrium competition binding experiments using [$^3$H]-Ins(1,4,5)$P_3$ and membranes prepared from rat liver, adenophostin A, Ins(1,4,5)$P_3$, and each of analogues **9** and **10** completely displaced the specific [$^3$H]-Ins(1,4,5)$P_3$ binding in a concentration-dependent manner (Figure 3a). The affinity of adenophostin A for hepatic Ins(1,4,5)$P_3$ receptors was 8-fold greater than that of Ins(1,4,5)$P_3$, in line with previous results.[11] However, analogues **9** and **10** had affinities 21- and 14-fold lower than Ins(1,4,5)$P_3$, respectively (Table 1). These results were reflected in functional studies of $^{45}Ca^{2+}$ release (Figure 3b). Maximal concentrations of Ins(1,4,5)$P_3$ adenophostin A and analogues **9** and **10** each released the same fraction (50−60%) of the intracellular stores, but whereas adenophostin A was about 10-fold more potent than Ins(1,4,5)$P_3$, analogues **9** and **10** were about 18- and 14-fold less potent, respectively (Table 2). The rank order of potency of the ligands [adenophostin > Ins(1,4,5)$P_3$ > **10** > **9**] was therefore the same as that found with radioligand binding. In summary, both bicyclic analogues had lower affinity for hepatic $IP_3$Rs than Ins(1,4,5)$P_3$, and they appeared closer to Ins(2,4,5)$P_3$ in activity.

**Table 1.** Binding of Ins(1,4,5)$P_3$ (**1**), Adenophostin A (**3**), and the Bicyclic Analogues **9** and **10** to Hepatic Ins(1,4,5)$P_3$ Receptors

| | $K_d$ (nM)[a] | ratio[b] to Ins(1,4,5)$P_3$ | $h$[a] | $n$ |
|---|---|---|---|---|
| Ins(1,4,5)$P_3$ (**1**) | 4.56 ± 0.48 | 1 | 1.16 ± 0.19 | 4 |
| adenophostin A (**3**) | 0.55 ± 0.12 | 8.3 ± 2.0 | 1.17 ± 0.11 | 3 |
| **9** | 98 ± 28 | −21 ± 6 | 1.01 ± 0.07 | 5 |
| **10** | 62 ± 4 | −14 ± 2 | 1.12 ± 0.08 | 3 |

[a] $K_d$s and Hill coefficients ($h$) were determined using equilibrium competition binding with [$^3$H]-Ins(1,4,5)$P_3$. Results are shown as means ± SEM for $n$ independent experiments. [b] Ratios greater than 1 denote ligands with greater affinity than Ins(1,4,5)$P_3$, and ratios less than −1 denote ligands with lesser affinity than Ins(1,4,5)$P_3$.

The simplest interpretation of these results is that the 2′-phosphate groups in **9** and in **10** are unable to interact effectively with the appropriate region of the Ins(1,4,5)$P_3$ receptor as a result of their three-dimensional location and orientation at the receptor binding site. This location will be influenced by the conformation of the dioxepane rings in **9** and **10**. In general, seven-membered rings are flexible systems for which there exist complex conformational equilibria between several

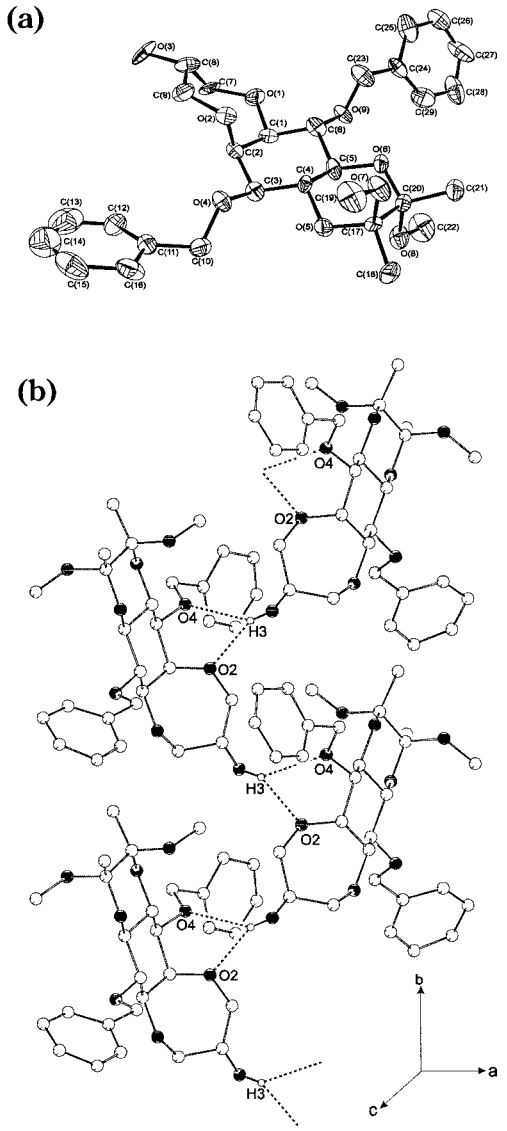



**Figure 2.** (a) ORTEX[31] plot of **18**. Ellipsoids are represented at the 30% probability level. (b) Hydrogen-bonding interactions in the supramolecular structure of **18**.

conformations of similar energies,[21] although in the bicyclic structures **9** and **10**, the fusion of the 1,4-dioxepane ring with *myo*-inositol greatly restricts the number of possible conformations. Measurement of vicinal coupling constants in the $^1$H NMR spectrum of the marginally more potent analogue **10**, taken in $D_2O$ buffered to physiological pH, confirmed that the conformation of the *myo*-inositol ring was close to a chair. A $^1$H NMR-NOESY spectrum of **10** showed NOEs between H-2 of the *myo*-inositol ring and one proton in each pair of methylene protons at C-1′ and C-3′. This supports the existence in solution of conformations of type **10a** (Figure 4a) in which the dioxepane ring adopts a twist-chair conformation similar to that seen in the X-ray structure of intermediate **18**. The measured vicinal coupling constants between H-2′ and the methylene protons on C-1′ and C-3′ in the dioxepane ring were not wholly consistent with theoretical values calculated[22] for **10a** alone, however, which suggested that other conformations may be present in equilibrium with **10a**, leading to an averaging of measured *J* values in the NMR spectrum. Molecular mechanics simulations

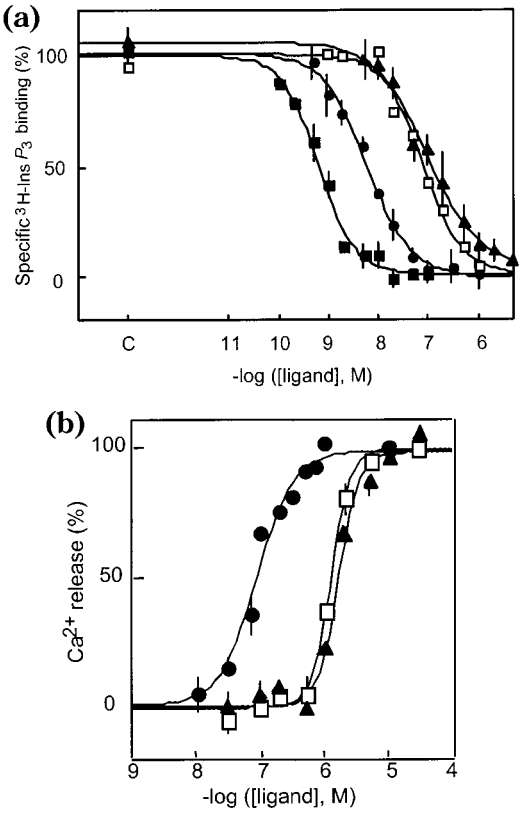



**Figure 3.** Effects of **9** and **10** on equilibrium competition binding of $^3$H-Ins(1,4,5)P$_3$ to liver membranes (a) and $^{45}Ca^{2+}$ release from the intracellular stores of permeabilized hepatocytes (b). (a) Specific $^3$H-Ins(1,4,5)P$_3$ binding (%) is shown in the presence of the indicated concentrations of adenophostin A (filled squares), Ins(1,4,5)P$_3$ (filled circles), **9** (filled triangles), and **10** (open squares). (b) The amounts of $^{45}Ca^{2+}$ released [% of the Ins(1,4,5)P$_3$-sensitive stores] by Ins(1,4,5)P$_3$, **9**, and **10** are shown [the symbols are the same as used in panel a]. For both panels, results are means ± SEM of three to five independent determinations.

**Table 2.** Effects of Ins(1,4,5)P$_3$ (**1**), Adenophostin A (**3**), and the Bicyclic Analogues **9** and **10** on $Ca^{2+}$ Release from the Intracellular Stores of Permeabilized Hepatocytes

| | $EC_{50}$ (nM)[a] | ratio[b] to Ins(1,4,5)P$_3$ | $h$[a] | maximal response (%)[a] |
|---|---|---|---|---|
| Ins(1,4,5)P$_3$ (**1**) | 90 ± 7 | 1 | 1.48 ± 0.21 | 59 ± 2 |
| adenophostin A (**3**) | 9.2 ± 1.7 | 9.8 ± 2.0 | 2.99 ± 0.32 | 49 ± 3 |
| **9** | 1650 ± 90 | −18 ± 2 | 2.61 ± 0.57 | 59 ± 1 |
| **10** | 1230 ± 50 | −14 ± 1 | 2.9 ± 0.55 | 59 ± 1 |

[a] Concentration causing half the maximal effect ($EC_{50}$), Hill coefficient ($h$), and the fraction of the total $Ca^{2+}$ stores released by a maximal concentration of each agonist are shown (means ± SEM) for $Ca^{2+}$ mobilization evoked by each of the ligands for three independent experiments. [b] Ratios greater than 1 denote ligands with greater potency than Ins(1,4,5)P$_3$ and ratios less than −1 denote ligands with lesser potency than Ins(1,4,5)P$_3$.

of **10** (see Experimental Section) supported this interpretation; conformations of type **10a** were predicted to be the most stable, but variants with different puckers of the dioexepane ring (Figure 4b) were also identified with only slightly higher (1 to 2 kcal/mol) calculated energies. Unfortunately, severe overlapping of signals in the $^1$H NMR spectrum of **9** precluded detailed analysis, but molecular modeling (not shown) as for **10** suggested that the 2′-phosphate group in **9** would be constrained to a similar region of space as in **10** as a result of the interplay between 2′-phosphate orientation

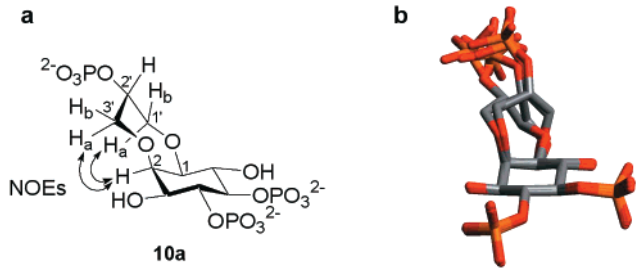



**Figure 4.** (a) NOESY spectrum of **10** in $D_2O$ at pH 7.2 shows NOEs between H-2 and two methylene protons in the 1,4-dioxepane ring, indicating the presence of conformations of type **10a**. (b) Superimposed low-energy conformations of **10** as determined by molecular mechanics calculations (see Experimental Section). For clarity, hydrogen atoms are not shown.

and dioxepane ring-pucker. This finding would account for the similar potencies of the two epimers.

While this work was in progress, a detailed conformational study of adenophostin A using a combination of NMR and molecular mechanics calculations was reported.[12] The authors proposed an active conformation of adenophostin A in which the 2′-phosphate group is held by the adenosine in a position close to the glucopyranosyl ring in a slightly more extended position than that of the 1-phosphate group in Ins(1,4,5)$P_3$. Independent evidence for this type of conformation of adenophostin A in solution has recently emerged from a combined NMR and potentiometric study by some of us,[23] which showed that, in solution, the protonation state of the 2′-phosphate group in adenophostin A influences the chemical shift of H-1″, presumably via an influence on the local electric field. There also appears to be some pH-dependent interaction between the 2′- and 3″-phosphates of adenophostin A, analogous to that between the 1- and 4-phosphates of Ins(1,4,5)$P_3$. (Indeed this study also found that, at physiological pH, the ionization states of the three phosphate groups in adenophostin A are remarkably similar to the corresponding phosphates in Ins(1,4,5)$P_3$, suggesting that differences in phosphate ionization are unlikely to account for the greater potency of adenophostin A).[23] Thus, molecular mechanics simulations (in vacuo) and studies of adenophostin A in solution favor conformations for adenophostin A in which the 2′-phosphate is held close to the glucopyranosyl ring. If this proximity is retained in the receptor-bound conformation of adenophostin A, the much lower potency of **9** and **10** would be a result of their 2′-phosphate groups being constrained to an overextended position in either possible orientation of these molecules at the $IP_3R$ binding site (Figure 5).

During the preparation of this manuscript, a report was published on the synthesis and evaluation of two glucose-based bicyclic analogues ("spirophostins" **23** and **24**, Figure 6a) designed as conformationally restricted analogues of adenophostin A.[24] These molecules constrain the nonvicinal phosphate group to a significantly different region of space than in **9** and **10**. However, the spirophostins also bind to Ins(1,4,5)$P_3$ receptors with affinities lower than Ins(1,4,5)$P_3$ (28-fold and 17-fold, respectively, in bovine adrenal cortex membranes) similar to those of **9** and **10** (21-fold and 14-fold lower than Ins(1,4,5)$P_3$, respectively, in hepatocytes).

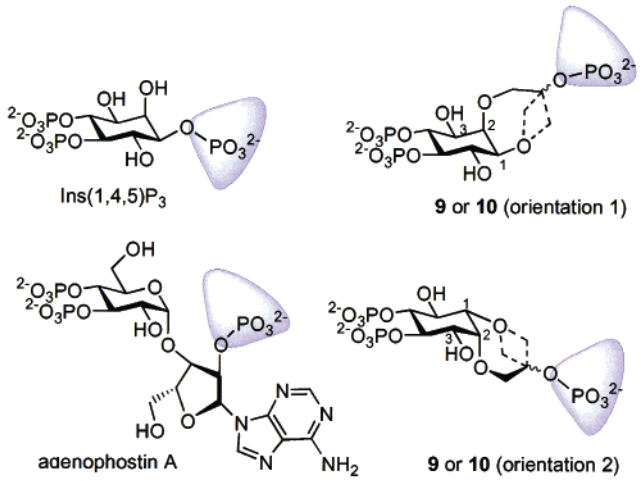



**Figure 5.** Comparison of Ins(1,4,5)$P_3$, adenophostin A and bicyclic analogues. The shaded cones indicate regions of space accessible to the nonvicinal phosphate group in each molecule. Adenophostin A is shown in the conformation proposed by a recent study.[12] Analogues **9** and **10** are represented by a single structure, shown in two binding orientations; dashed lines indicate alternative dioxepane ring conformations.

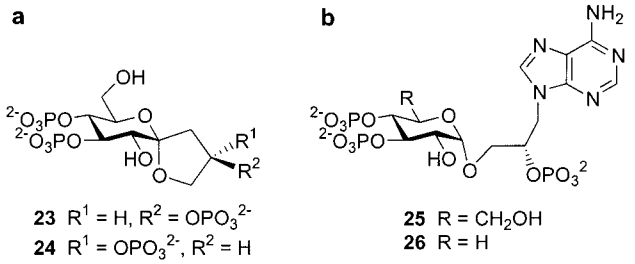



**Figure 6.** (a) Recently reported[24] glucose-based bicyclic analogues, spirophostins **23** and **24**. (b) Acyclophostin[25] (**25**) and its xylose-based equivalent **26**.[26]

These results do not necessarily imply that the goal of constructing potent Ins(1,4,5)$P_3$ analogues by conformational restriction alone is unattainable, although it is conceivable that adenophostin-like activity requires exquisite precision in the location and orientation of the 2′-phosphate group at the receptor binding site. It has been suggested, for example, that in the adenophostins the adenine may finely tune this positioning by a subtle effect on ribose conformation,[12] hence the merely Ins(1,4,5)$P_3$-like activity of analogues such as **5** and **6**. However, if the adenine itself is directly responsible for the novel properties of the adenophostins, then conformationally restricted analogues lacking the adenine (or similar structure) may never exceed Ins(1,4,5)$P_3$ in potency. In support of a specific role for the adenine, two recent reports[25,26] have shown that its introduction into analogues **7** and **8**, to give **25** ("acyclophostin") and **26**, respectively (Figure 6b), can increase affinity for the $IP_3R$ to Ins(1,4,5)$P_3$-like levels, demonstrating that the adenine can enhance binding to the $IP_3R$, even in combination with a flexible linkage to the nonvicinal phosphate. The accumulating evidence therefore favors the existence of a binding pocket for adenine, or for similar aromatic/hydrophobic structures, close to the Ins(1,4,5)$P_3$ binding site. We are currently exploring this possibility by investigating the effects of base-modified analogues of adenophostin A, prepared by total synthesis from D-xylose and D-glucose.[27]

## Experimental Section

Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60F$_{254}$) with detection by UV light or with phosphomolybdic acid in methanol followed by heating. Flash chromatography was performed on silica gel (particle size 40−63 $\mu$m). NMR spectra were recorded with a JEOL EX-270 or 400 spectrometer. Chemical shifts are reported in parts per million ($\delta$), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). $^1$H NMR and $^{13}$C NMR shifts are measured in ppm relative to internal tetramethylsilane (TMS). In the case of $^1$H NMR spectra taken in $D_2O$, acetone ($\delta$ 2.225 relative to TMS) was used as an internal reference. $^{31}$P NMR shifts were measured in ppm relative to external 85% phosphoric acid and are positive when downfield from this reference. Coupling constants ($J$) are given in Hz. FAB mass spectra were recorded at the University of Bath using *m*-nitrobenzyl alcohol as the matrix. Melting points (uncorrected) were determined using a Reichert−Jung hot stage microscope apparatus. Ion-exchange chromatography was performed on an LKB-Pharmacia medium-pressure ion exchange chromatograph using Q-Sepharose Fast Flow and gradients of triethylammonium bicarbonate (TEAB) as eluent. Quantitative analysis of phosphate was performed using a modification of the Briggs phosphate assay.[20] Adenophostin A was synthesized as previously reported.[28]

**X-ray Crystallography.** A crystal of **18** having approximate dimensions 0.5 × 0.4 × 0.15 mm was used for data collection. Crystal data: $C_{29}H_{38}O_9$, $M = 530.59$, orthorhombic, $a = 10.163(3)$ Å, $b = 10.216(2)$ Å, $c = 26.818(8)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $U = 2784.4(13)$ Å$^3$, space group $P2_12_12_1$, $Z = 4$, $D_c = 1.266$ g cm$^{-3}$, $\mu$(Mo-$K\alpha$) = 0.093 mm$^{-1}$, $F(000) = 1136$. Crystallographic measurements were made at 293(2) K on a CAD4 automatic four-circle diffractometer in the range $2.13 < \theta < 22.93°$. Data (2255 reflections) were corrected for Lorentz and polarization but not for absorption. Early searches for diffraction spots indicated that the sample chosen for this determination (largest in batch) was not a strong diffractor, possibly due to the smaller than desirable thickness of the crystal. In an effort to counteract this, the scan parameters for data collection were adjusted to increase the reliability of the weaker data and thus maximize structural solution ability using direct methods. In practice, the whole molecule was evident in the first electron density map produced. Anisotropic refinement of all atoms proceeded without any correlation problems, although isotropic restraints were placed on carbons 1, 11, 14, and 20. The absolute configuration of the molecule could not be determined reliably from a refined Flack parameter. This is probably due, in part, to the high proportion of weak data present, reflected in an $R(\sigma)$ value of 0.2796. In the final least squares cycles, all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions where relevant. Examination of the gross structure revealed the presence of a hydrogen bonding feature along *b*. Typically, the hydroxyl proton (H3) has possible contacts to O2 and O4 of the molecule generated via the $-x, -1/2 + y, 1/2 - z$ operation. The H3···O4 distance is tenuous, but as the hydrogens are included at calculated positions, this contact is also illustrated on the packing diagram (Figure 2b) [O3···O4, 3.23(1) Å; O3···O2, 2.81(1) Å; H3···O4, 2.5(1) Å; H3···O2, 2.1-(1) Å; O3−H3−O4, 144(9)°; O3−H3−O2, 147(9)°]. The solution of the structure (SHELX-90)[29] and refinement (SHELXL-97)[30] converged to a conventional [i.e., based on 805 $F^2$ data with $F_o > 4\sigma(F_o)$] $R1 = 0.0824$ and $wR2 = 0.1589$. Goodness of fit = 0.785. The maximum and minimum residual densities were 0.257 and −0.221 e Å$^{-3}$, respectively. The asymmetric unit (shown in Figure 2a), along with the labeling scheme used, was produced using ORTEX.[31]

**Molecular Modeling.** Modeling was carried out using the Sybyl software package (v6.3, Tripos Associates) on a Silicon Graphics workstation. The TRIPOS force field was used. Charges were calculated using a semiempirical method (AM1) for structures of **9** or **10** with fully-ionized phosphate groups, and the resulting charged structures were energy-minimized using the TRIPOS force field and a distance-dependent dielectric function of $\epsilon = r$, terminating at a gradient of 0.05 kcal mol$^{-1}$ Å$^{-1}$. Different conformations of the 1,4-dioxepane ring in each structure were generated by 100 cycles of heating to 1000 K for 2000 fs followed by exponential cooling to 0 K over 10000 fs. During these cycles of simulated annealing, the 4,5-diequatorial bisphosphate conformation was retained by constraining this region of the molecule as an aggregate. Each cooled structure was then re-minimized as before. The protocol was repeated three times, using different starting conformations of the dioxepane ring, to ensure that all stable conformations were located. Low-energy conformations identified in this way were further investigated by systematically varying the H2′-C2′-O2′-P2′ torsion in 10° steps, and re-minimizing after each step.

**[$^3$H]-Ins(1,4,5)P$_3$ Binding to Hepatic Membranes.** Rat liver membranes were prepared from a liver perfused in situ with cold saline, which was then excised and homogenized in cold buffered sucrose (250 mM sucrose, 5 mM Hepes, 1 mM EGTA, pH 7.4) using a Dounce homgenizer with 10 strokes of a loose-fitting plunger and three with a tight plunger, before filtration through gauze. After centrifugation (2500*g*, 10 min), the pellet was resuspended and centrifuged (35000*g*, 30 min) through a Percoll gradient (11.8%, Pharmacia). The membranes were harvested, washed twice (48000*g*, 10 min) in hypotonic medium (1 mM EGTA, 5 mM Hepes, pH 7.4), and then resuspended in binding medium (50 mM Tris, 1 mM EDTA, pH 8.3 at 4 °C) as previously described.[11] For binding experiments, membranes (0.1 mg protein/tube) in binding medium (500 $\mu$L) were incubated with [$^3$H]-Ins(1,4,5)P$_3$ (1.3−1.8 nM) and appropriate concentrations of competing ligand for 5 min at 4 °C, before separation of bound from free ligand by centrifugation (20000*g*, 5 min). After aspiration of the supernatant, the pellets were resuspended in Ecoscint A liquid scintillation cocktail (National Diagnostics, Atlanta, GA). Equilibrium competition binding curves were fitted to logistic equations using Kaleidagraph (Synergy Software), and the IC$_{50}$ values were then used to calculate equilibrium dissociation constants ($K_d$).

**$^{45}$Ca$^{2+}$ Release from Permeabilized Rat Hepatocytes.** The methods were similar to those reported previously.[11] Briefly, permeabilized hepatocytes were loaded to steady state (5 min at 37 °C) with $^{45}$Ca$^{2+}$ in a cytosol-like medium (CLM: 140 mM KCl, 20 mM NaCl, 2 mM $MgCl_2$, 1 mM EGTA, 300 $\mu$M $CaCl_2$, 20 mM Pipes, pH 7.0) containing ATP (1.5 mM), creatine phosphate (5 mM), creatine phosphokinase (5 units/mL), and FCCP (10 $\mu$M). After 5 min, thapsigargin (1.25 $\mu$M) was added to the cells to inhibit further Ca$^{2+}$ uptake, 30 s later the cells were added to appropriate concentrations of the agonists, and after a further 60 s the Ca$^{2+}$ contents of the stores were determined by rapid filtration. Concentration−response relationships were fitted to a four-parameter logistic equation using Kaleidegraph software (Synergy Software, PA) from which the maximal response, half-maximally effective agonist concentration (EC$_{50}$), and Hill slope ($h$) were determined. All results are expressed as means ± SEM. Ins(1,4,5)P$_3$ was from American Radiolabeled Chemicals.

**(2′*RS*,3′*RS*)-DL-1,4-Di-*O*-benzyl-5,6-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(±)-12].** To a suspension of DL-1,4-di-*O*-benzyl-*myo*-inositol[14] [(±)-**11,** 15.5 g, 43.0 mmol] in MeOH (200 mL) and trimethyl orthoformate (20 mL) were added camphorsulfonic acid (500 mg, 2.15 mmol) and butanedione (4.0 mL, 46 mmol). The mixture was heated at reflux under $N_2$ for 18 h. The resulting pink solution was allowed to cool, and $Et_3N$ (1 mL) was added. The solution was stirred at room temperature for a further 5 min, and the solvents were removed by evaporation under reduced pressure to give a foam. The foam was taken up in the minimum volume of $CH_2Cl_2$, loaded onto a short column of silica gel, and eluted with EtOAc/hexane (1:1) to give the racemic diol (±)-**12** (16.3 g, 34.3 mmol, 80% yield) as a white crystalline solid: mp 141−143 °C (from EtOAc/hexane); $^1$H NMR (270 MHz, $CDCl_3$) 1.36 (3 H, s, $CH_3$), 1.37 (3 H, s, $CH_3$), 2.62 (2 H, br s, $D_2O$ exch. OH-2 and OH-3), 3.30 (3 H, s, $OCH_3$), 3.33 (3 H, s, $OCH_3$), 3.43 (1 H, dd, $J$ =

9.9, 2.7, H-3), 3.48 (1 H, dd, $J$ = 9.2, 2.7, H-1), 3.64 (1 H, dd, $J$ = 9.9, 9.7, H-5), 3.83 (1 H, t-like dd, $J$ = 9.5, 9.5, H-4 or H-6), 4.15 (1 H, t-like dd, $J$ = 2.9, 2.9, H-2), 4.16 (1 H, t-like dd, $J$ = 9.9, 9.9, H-4 or H-6), 4.70, 4.85 (2 H, $AB_q$, $J_{AB}$ = 11.9, OC$H_2$Ph), 4.71, 5.03 (2 H, $AB_q$, $J_{AB}$ = 11.2, OC$H_2$Ph), 7.24−7.38 (10 H, m, 2 × Ph); $^{13}$C NMR ($CDCl_3$, 68 MHz) $\delta$ 17.74 (2 × $CH_3$), 47.87 (2 × $OCH_3$), 69.54, 70.40, 71.54, 71.81 (C-2, C-3, C-5, and C-6), 76.63, 78.26 (C-1 and C-4), 73.21, 75.30 (O$CH_2$-Ph), 99.22 (2 × $C_q$ BDA), 127.53, 127.68, 127.86, 128.31, 128.38 (Ph), 138.25, 138.64 (2 × C-1 of Ph); MS $m/z$ (+ve ion FAB) 497 [$(M + Na)^+$, 80%], 443 [$(M - OCH_3)^+$, 60%], 91 [$(C_7H_7)^+$, 100%]; MS $m/z$ (-ve ion FAB) 947 [$(2\ M - H)^-$, 20%], 627 [$(M + NBA)^-$, 80%], 473 [$(M - H)^-$, 100%]. Anal. ($C_{26}H_{34}O_8$) C, H.

**(2′*R*,3′*R*)-1D-3-*O*-[(*S*)-(+)-*O*-Acetylmandelyl]-1,4-di-*O*-benzyl-5,6-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol (13) and (2′*S*,3′*S*)-1D-1-*O*-[(*S*)-(+)-*O*-Acetylmandelyl]-3,6-di-*O*-benzyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol (14).** To a stirred solution of (±)-**12** (11.0 g, 23.2 mmol), DCC (5.00 g, 24.2 mmol), and DMAP (50 mg) in dry $CH_2Cl_2$ (100 mL) at −20 °C was added a solution of (*S*)-(+)-acetylmandelic acid (5.00 g, 25.7 mmol) in dry $CH_2Cl_2$ (50 mL) dropwise over 1 h. The cooling bath was removed, and stirring was continued for 1 h, after which the suspension was filtered through Celite to remove dicyclohexylurea. The filtrate was concentrated by evaporation under reduced pressure, and the residue was fractionated by flash chromatography ($CHCl_3$/acetone 30:1, then 10:1) on silica gel. The first fraction was obtained as a white solid (7.22 g), and crystallization from EtOAc/hexane gave pure **14** (5.39 g, 8.28 mmol, 36%, 72% of this diastereoisomer). Further elution gave a second fraction as an oil (6.63 g) slightly contaminated with **14**. Crystallization from EtOAc/hexane at −20 °C gave pure **13** as waxy crystals (5.18 g, 7.96 mmol, 34%, 68% of this diastereoisomer).

Data for **13**: mp 75−78 °C; $R_f$ 0.24 ($CHCl_3$/acetone 30:1); $[\alpha]_D^{26} = -9.5$ ($c$ = 2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.31 (3 H, s, $CH_3$), 1.34 (3 H, s, $CH_3$), 2.18 [3 H, s, $CH_3C(O)$], 2.67 (1 H, br s, $D_2O$ exch, OH-2), 3.15 (3 H, s, $OCH_3$), 3.31 (3 H, s, $OCH_3$), 3.54 (1 H, dd, $J$ = 10.3, 2.4, H-1), 3.62 (1 H, t-like dd, $J$ = 10.3, 9.8, H-5), 3.99 (1 H, t-like dd $J$ = 9.8, 9.8, H-4), 4.07 (1 H, d, $J$ = 11.2, $OCH_2Ar$), 4.16 (1 H, t-like dd, $J$ = 10.3, 9.8, H-6), 4.36 (1 H, br s, $D_2O$ exch gives t-like dd, $J$ = 2.4, 2.4, H-2), 4.55 (1 H, d, $J$ = 11.2, OC$H_2$Ph), 4.69, 4.82 (2 H, $AB_q$, $J$ = 11.7, OC$H_2$Ph), 5.99 [1 H, s, $O_2CCH$(OAc)Ph], 6.94−6.96 (2 H, m, Ph), 7.18−7.37 (11 H, m, Ph), 7.48−7.50 (2 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 17.67, 17.76 (2 × $CH_3$), 20.67 [$CH_3C(O)$], 47.82, 47.97 (2 × $CH_3O$), 68.80, 69.13, 71.03 (C-2, C-5 and C-6), 73.39 (O$CH_2$Ph), 74.87 (O$CH_2$Ph), 74.82, 75.10 75.55, 76.52 [C-1, C-3, C-6 and $O_2CCH$(OAc)Ph], 99.34 (2 × $C_q$ of BDA), 127.21, 127.47, 127.69, 127.80, 127.96, 128.38, 128.84, 129.42 (15 × CH of Ph), 133.12 (C-1 of acetylmandelate Ph), 138.06, 138.50 (2 × C-1 of Ph), 168.45 (s, C=O), 170.61 (s, C=O); MS $m/z$ (+ve ion FAB); 673 [$(M + Na)^+$, 50%], 619 [$(M - CH_3O)^+$, 70%], 91 [$(C_7H_7)^+$, 100%]; MS $m/z$ (−ve ion FAB); 803 [$(M + NBA)^-$, 70%], 649 [$(M - H)^-$, 100%]. Anal. ($C_{36}H_{42}O_{11}$) C, H.

Data for **14**: mp 132.5−134.5 °C; $R_f$ 0.36 ($CHCl_3$/acetone 30:1); $[\alpha]_D^{26} = +72$ ($c$ = 2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 1.34 (3 H, s, $CH_3$), 1.35 (3 H, s, $CH_3$), 2.19 [4 H, s, $D_2O$ exch. gives 3 H, s, $CH_3C(O)$ and OH-2], 3.25 (3 H, s, $OCH_3$), 3.30 (3 H, s, $OCH_3$), 3.49 (1 H, dd, $J$ = 10.1, 2.7, H-3), 3.66 (1 H, t-like dd, $J$ = 10.1, 9.8, H-5), 4.03 (1 H, t-like dd, $J$ = 9.8, 9.8, H-4 or H-6), 4.12−4.17 [2 H, m, H-2 and (H-4 or H-6)], 4.63−4.70 (2 H, m, 2 × 0.5 AB systems of OC$H_2$Ph), 4.78 (1 H, dd, $J$ = 10.1, 2.7, H-1), 4.78−4.87 (2 H, m, 2 × 0.5 AB systems of OC$H_2$-Ph), 5.95 [1 H, s, $O_2CCH$(OAc)Ph], 7.24−7.32 (13 H, m, Ph), 7.43−7.45 (2 H, m, Ph); $^{13}$C NMR ($CDCl_3$, 100 MHz) 17.72, 17.76 (2 × $CH_3$), 20.68 [$CH_3C(O)$], 47.88, 47.92 (2 × $CH_3O$), 68.65, 69.07, 71.20 (C-2, C-4, and C-5), 73.41 (O$CH_2$Ph), 74.78, 74.85, 75.43, 76.32 [C-1, C-3, C-6, and $O_2CCH$(OAc)Ph], 75.16 (O$CH_2$Ph), 99.34 (2 × BDA $C_q$), 127.39, 127.47, 127.61, 127.74, 127.94, 128.18, 128.35, 128.77, 129.22 (15 × CH of Ph), 133.37 (s, C-1 of acetylmandelate Ph), 138.11, 138.61 (2 × C-1 Ph), 168.09 (C=O), 170.79 (C=O); MS $m/z$ (+ve ion FAB); 673 [$(M + Na)^+$, 20%], 619 [$(M - CH_3O)^+$, 90%], 91 [$(C_7H_7)^+$, 100%]; MS $m/z$ (−ve ion FAB); 803 [$(M + NBA)^-$, 80%], 649 [$(M - H)^-$, 100%]. Anal. ($C_{36}H_{42}O_{11}$) C, H.

**(2′*S*,3′*S*)-1D-3,6-Di-*O*-benzyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(+)-12].** A solution of **14** (5.69 g, 8.74 mmol) in MeOH (150 mL) containing NaOH pellets (2.0 g, 50 mmol) was heated at reflux for 1 h. The solution was allowed to cool and then neutralized by addition of solid $CO_2$. The solvents were removed by evaporation under reduced pressure, and the residue was partitioned between $CH_2Cl_2$ and water (100 mL of each). The organic layer was separated, washed with water (2 × 100 mL), and dried ($MgSO_4$). Evaporation under reduced pressure gave the diol as a white hygroscopic foam (3.94 g, 8.30 mmol, 95%); waxy crystals of monohydrate (with difficulty) from $Et_2O$/hexane at −20 °C: $[\alpha]_D^{24} = +69$ ($c$ = 1, $CHCl_3$); spectroscopic data were identical to those obtained for (±)-**12**. Anal. ($C_{26}H_{34}O_8 \cdot H_2O$) C, H.

**(2′*R*,3′*R*)-1D-1,4-Di-*O*-benzyl-5,6-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-*myo*-inositol [(−)-12].** Saponification of **13** (5.0 g, 7.68 mmol) as described for **14** gave (−)-**12** as a white hygroscopic foam (3.46 g, 7.29 mmol, 95%); waxy crystals of monohydrate (with difficulty) from $Et_2O$/hexane at −20 °C: $[\alpha]_D^{26} = -68$ ($c$ = 1, $CHCl_3$); spectroscopic data were identical to those obtained for (+)-**12**. Anal. ($C_{26}H_{34}O_8 \cdot H_2O$) C, H.

**1D-1,4-Di-*O*-benzyl-*myo*-inositol [(−)-11].** To a solution of [(−)-**12**] (420 mg, 0.885 mmol) in $CH_2Cl_2$ (5 mL) was added 95% aqueous TFA (5 mL). The mixture was stirred at room temperature for 30 min and then concentrated by evaporation under reduced pressure to give (−)-**11** as a white solid (312 mg, 0.866 mmol, 98%); crystals from EtOH: mp 172−173 °C, Lit.[18b] mp 172−173 °C; $[\alpha]_D^{20} = -14$ ($c$ = 1, MeOH), Lit.[18b] $[\alpha]_D^{20} = -16$ ($c$ = 1, MeOH); NMR data were identical to those previously reported.[18b]

**(2′*S*,3′*S*)-1D-3,6-Di-*O*-benzyl-4,5-(2′,3′-dimethoxybutane-2′,3′-diyl)-1,2-*O*-[(2″-methylene)propane-1″,3″-diyl]-*myo*-inositol (15).** To a solution of (+)-**12** (3.94 g, 8.30 mmol) in dry DMF (40 mL) was added NaH (1.30 g of a 60% dispersion in oil, 32.5 mmol). The mixture was stirred at room temperature for 30 min, and then 3-chloro-2-chloromethyl-1-propene (2.0 mL, 2.16 g, 17.3 mmol) was added. After 1 h, TLC (ether) showed that all the starting material ($R_f$ 0.36) had been consumed, with conversion into a major product at $R_f$ 0.66. Excess NaH was destroyed by cautious addition of MeOH, and the solvents were removed by evaporation under reduced pressure. The residue was partitioned between $CH_2Cl_2$ and water (100 mL of each). The organic layer was washed with water (2 × 100 mL), dried ($MgSO_4$), and evaporated to give an oil. Purification by flash chromatography (EtOAc/hexane 1:4) gave the alkene **15** as a colorless oil, later solidifying to a brittle glass, which could not be recrystallized (3.67 g, 6.97 mmol, 84%): $[\alpha]_D^{20} = +24$ ($c$ = 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 1.36 (3 H, s, $CH_3$), 1.38 (3 H, s, $CH_3$), 3.29 (3 H, s, $OCH_3$), 3.34 (3 H, s, $OCH_3$), 3.43 (1 H, dd, $J$ = 10.1, 3.1, H-1 or H-3), 3.59 (1 H, dd, $J$ = 10.1, 2.1, H-1 or H-3), 3.66 (1 H, t-like dd, $J$ = 9.5, 9.5, H-5), 3.85 (1 H, t-like dd, $J$ = 3.1, 2.1, H-2); 3.99 (1 H, br d, $J$ = 13.4, H-1″a or H-3″a), 4.09−4.17 (3 H, m, H-4, H-6 and H-3″a or H-1″a), 4.18 (1 H, br d, $J$ = 13.4, H-1″b or H-3″b), 4.47 (1 H, br d, $J$ = 14.3, H-3″b or H-1″b), 4.69, 4.82 (2 H, $AB_q$, $J_{AB}$ = 12.4, OC$H_2$Ph), 4.78 (1 H, 0.5 of $AB_q$, $J_{AB}$ = 11.6, OC$H_2$Ph), 4.96−4.99 (2 H, m, C=C$Ha$Hb and OC$H_2$Ph), 5.06 (1 H, br s, C=CHa$Hb$), 7.24−7.42 (10 H, m, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) 17.81 (2 × $CH_3$), 47.88, 48.10 (2 × $OCH_3$), 66.53 (C-1″ or C-3″), 69.17, 72.46 (2 × inositol ring CH), 73.15, 73.57, 74.69 [2 × O$CH_2$Ph and (C-1″ or C-3″)], 73.26, 75.88, 77.63, 80.39 (4 × inositol ring CH), 99.25, 99.41 (2 × $C_q$ of BDA), 113.97 (=$CH_2$), 127.58, 127.93, 128.25, 128.31 (10 × CH of Ph), 138.63, 138.93 (2 × C-1 of Ph), 146.96 (C-2″); MS $m/z$ (+ve ion FAB) 495 [$(M - CH_3O)^+$, 70%], 266(90), 91 [$(C_7H_7)^+$, 100%]. Anal. ($C_{30}H_{38}O_8$) C, H.

**(2′*S*,3′*S*)-1D-3,6-Di-*O*-benzyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1,2-*O*-[(2″-oxo)propane-1″,3″-diyl]-*myo*-inositol (16).** To a vigorously stirred solution of alkene **15** (3.67 g, 6.97 mmol) in EtOAc (20 mL) and $CH_3CN$ (20 mL) was added $NaIO_4$ (7.00 g, 32.7 mmol) followed by a solution of $RuCl_3 \cdot 3H_2O$ (40 mg in 20 mL of distilled water). The suspen-

sion was stirred at room temperature for 1.5 h, after which time TLC (EtOAc/hexane 1:2) showed complete conversion of the alkene ($R_f$ 0.40) into a slightly more polar product ($R_f$ 0.34). Water (200 mL) and $Et_2O$ (200 mL) were then added. The organic layer was separated and washed with water (200 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (100 mL). The organic layer, which was now almost colorless, was dried ($MgSO_4$) and concentrated in vacuo to give the crude ketone **16** as a foam (3.02 g, 5.71 mmol, 82%) which was used in the next step without further purification. For analytical purposes, a small portion of this was purified by flash chromatography (EtOAc/hexane 1:2) to give **16** as a white crystalline solid: mp 128−129 °C (from EtOAc/hexane); $[\alpha]_D^{24} = -9$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.37 (3 H, s, $CH_3$), 1.40 (3 H, s, $CH_3$), 3.31 (3 H, s, $OCH_3$), 3.34 (3 H, s, $OCH_3$), 3.49 (1 H, dd, $J = 10.5$, 3.1, H-1 or H-3), 3.74 (1 H, t-like dd, $J = 9.8$, 9.4, H-5), 3.78 (1 H, dd, $J = 9.8$, 2.7, H-1or H-3), 3.85 (1 H, d, $J = 16.2$, H-1″a or H-3″a), 3.86 (1 H, t-like dd, $J = 3.1$, 2.7, H-2), 3.99 (1 H, d, $J = 17.4$, H-3″a or H-1″a), 4.08 (1 H, t-like dd, $J = 10.2$, 10.2, H-4 or H-6), 4.16 (1 H, d, $J = 16.2$, H-1″b or H-3″b), 4.17 (1 H, t-like dd, $J = 9.8$, 9.4, H-4 or H-6), 4.38 (1 H, d, $J = 17.4$, H-3″b or H-1″b), 4.67, 4.88 (2 H, $AB_q$, $J_{AB} = 12.5$, $OCH_2Ph$), 4.74, 5.04 (2 H, $AB_q$, $J_{AB} = 11.7$, $OCH_2Ph$), 7.27−7.38 (10 H, m, Ph); $^{13}$C NMR (68 MHz, $CDCl_3$) 17.78 (2 × $CH_3$), 47.97, 48.12 (2 × $OCH_3$), 68.76 (inositol ring CH), 70.27 (C-1″ or C-3″), 71.88, 72.40 (2 × inositol ring CH), 73.56, 74.67 ($OCH_2Ph$), 75.43 (inositol ring CH), 78.19 (C-1″ or C-3″), 78.35, 84.30 (2 × inositol ring CH), 99.27, 99.45 (2 × $C_q$ of BDA), 127.65, 127.83, 127.88, 128.01 (10 × CH of Ph), 138.34, 138.37 (2 × C-1 of Ph), 210.52 (C-2″); MS *m*/*z* (+ve ion FAB); 551[(M + Na)$^+$, 20%], 527(20), 497 [(M − $CH_3O$)$^+$, 75%], 266(40), 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 681 [(M + NBA)$^-$, 100%], 527 [(M − H)$^-$, 40%]. Anal. ($C_{29}H_{36}O_9$) C; H.

**(2′*S*,3′*S*,2″*R*)-1D-3,6-Di-*O*-benzyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1,2-*O*-[(2″-hydroxy)propane-1″,3″-diyl]-*myo*-inositol (17) and (2′*S*,3′*S*,2″*S*)-1D-3,6-Di-*O*-benzyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1,2-*O*-[(2″-hydroxy)propane-1″,3″-diyl]-*myo*-inositol (18).** To a stirred solution of ketone **16** (2.38 g, 4.50 mmol) in methanol (100 mL) at 0 °C was added $NaBH_4$ (800 mg, 21.1 mmol). The solution was stirred at 0 °C for a further 5 min and then allowed to warm to room temperature. TLC ($CHCl_3$/acetone 10:1) showed total conversion of the ketone ($R_f$ 0.48) into a major product at $R_f$ 0.12 and a minor product at $R_f$ 0.20. Water (10 mL) was added, and stirring was continued for a further 1 h. The solvents were removed by evaporation under reduced pressure to give a solid residue which was partitioned between $CH_2Cl_2$ and water (100 mL of each). The organic layer was removed, dried ($MgSO_4$), and evaporated under reduced pressure to give a white foam which was fractionated by flash chromatography ($CHCl_3$/acetone 10:1) to give first the alcohol **17** (495 mg, 0.933 mmol, 21%). Second to elute was the epimeric alcohol **18** (1.60 g, 3.02 mmol, 67%).

Data for **17**: mp 126−127 °C (from hexane); $R_f$ 0.20 ($CHCl_3$/acetone 10:1); $[\alpha]_D^{25} = +33$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 1.356 (3 H, s, $CH_3$), 1.362 (3 H, s, $CH_3$), 2.72 (1 H, d, $J = 10.7$, OH-2″), 3.29 (3 H, s, $OCH_3$), 3.32 (3 H, s, $OCH_3$), 3.37 (1 H, dd, $J = 12.7$, 2.0, H-1″a or H-3″a), 3.45 (1 H, dd, $J = 10.1$, 3.4, H-1 or H-3), 3.57−3.64 [3 H, m, H-5, H-2″ and (H-1 or H-3)], 3.73 (1 H, t-like dd, $J = 9.8$, 9.8, H-4 or H-6), 3.78 (1 H, t-like dd, $J = 3.4$, 3.4, H-2), 3.81−3.89 [2 H, m, (H-1″a and H-1″b) or (H-3″a and H-3″b)], 4.07 (1 H, t-like dd, $J = 10.3$, H-4 or H-6), 4.07 (1 H, br d, $J = 12.7$, H-1″b or H-3″b) 4.68, 4.89 (2 H, $AB_q$, $J = 12.2$, $OCH_2Ph$), 4.83, 4.91 (2 H, $AB_q$, $J = 11.2$ Hz, $OCH_2Ar$), 7.25−7.42 (10 H, m, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) 17.76, 17.81 (2 × $CH_3$), 47.88, 48.08 (2 × $OCH_3$), 67.14 ($OCH_2$), 68.54, 70.39, 71.14 (3 × CH), 73.59, 75.26 (2 × $OCH_2$), 75.51 (CH), 78.09 ($OCH_2$), 78.47, 78.51, 79.44 (3 × CH), 99.21, 99.32 (2 × $C_q$ of BDA), 127.56, 127.63, 127.69, 128.13, 128.20, 128.36 (10 × CH of Ph), 138.82, 138.62 (2 × C-1 of Ph); MS *m*/*z* (+ve ion FAB); 553 [(M + Na)$^+$, 60%], 529(50), 499 [(M − $CH_3O$)$^+$, 20%], 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 683 [(M + NBA)$^-$, 100%]. Anal. ($C_{29}H_{38}O_9$) C, H.

Data for **18**: mp 165−167 °C (from EtOAc/hexane); $R_f$ 0.12 ($CHCl_3$/acetone 10:1); $[\alpha]_D^{25} = +29$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 1.36 (3 H, s, $CH_3$), 1.38 (3 H, s, $CH_3$), 2.58 (1 H, d, $J = 7.1$, OH-2″), 3.29 (3 H, s, $OCH_3$), 3.32 (3 H, s, $OCH_3$), 3.40 (1 H, dd, $J = 10.3$, 2.9, H-1 or H-3), 3.53 (1 H, dd, $J = 12.7$, 2.9, H-1″a or H-3″a), 3.59 (1 H, dd, $J = 12.7$, 5.9, H-3″a or H-1″a), 3.60−3.66 [2 H, m, H-5 and (H-1 or H-3)], 3.80 (1 H, br d, $J = 12.7$, H-3″b or H-1″b), 3.92−3.97 (1 H, br m, H-2″), 3.98−4.10 [4 H, m, H-2, H-4, H-6 and (H-1″b or H-3″b)], 4.69, 4.82 (2 H, $AB_q$, $J_{AB} = 12.2$, $CH_2Ph$), 4.78, 4.93 (2 H, $AB_q$, $J_{AB} = 11.7$, $CH_2Ph$), 7.24−7.42 (10 H, m, Ph); $^{13}$C NMR (68 MHz, $CDCl_3$) 17.80 (2 × $CH_3$), 47.89, 48.10 (2 × $OCH_3$), 64.79 ($OCH_2$), 68.76, 71.29, 71.89 (3 × CH), 73.24 ($OCH_2$), 73.95 (inositol ring CH), 74.88 ($OCH_2$), 75.74 (CH), 77.63, 80.05 (2 × CH), 99.27, 99.34 (2 × BDA $C_q$), 127.58, 127.63, 127.99, 128.25, 128.35 (10 × CH of Ph), 138.52, 138.89 (2 × C-1 of Ph); MS *m*/*z* (+ve ion FAB); 553 [(M + Na)$^+$, 40%], 529(20), 499 [(M − $CH_3O$)$^+$, 80%], 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 683 [(M + NBA)$^-$, 100%]. Anal. ($C_{29}H_{38}O_9$) C, H.

**(2′*S*)-1D-3,6-Di-*O*-benzyl-1,2-*O*-[(2′-hydroxy)propane-1′,3′-diyl]-*myo*-inositol (19).** To a solution of the alcohol **17** (530 mg, 1.00 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added 95% aqueous TFA (5 mL). The mixture was stirred at room temperature for 15 min. The solvents were removed by evaporation under reduced pressure, and the residue was purified by flash chromatography (EtOAc/hexane 5:1) to give the triol **19** as a hygroscopic white foam (346 mg, 0.83 mmol, 83%): $[\alpha]_D^{23} = -3$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 2.96 (1 H, d, $J = 10.7$, OH-2′), 3.07 (1 H, br s, OH-4 or OH-5), 3.16 (1 H, br s, OH-4 or OH-5), 3.23−3.27 (2 H, m, H-3 and (H-1′a or H-3′a)], 3.43 (1 H, t-like dd, $J = 9.3$, 8.8, H-5), 3.59−3.64 (2 H, m, H-2′ and H-6), 3.69 (1 H, dd, $J = 8.8$, 3.4, H-1), 3.77−3.81 [2 H, m, H-2 and (H-3′a or H-1′a)], 3.85−3.92 [2 H, m, H-4 and (H-3′b or H-1′b)], 4.04 (1 H, br d, $J = 12.7$, H-1′b or H-3′b), 4.62, 4.72 (2 H, $AB_q$, $J_{AB} = 11.7$, $CH_2Ar$), 4.78, 4.93 (2 H, $AB_q$, $J_{AB} = 11.2$, $CH_2Ar$), 7.25−7.39 (10 H, m, Ph); $^{13}$C NMR (68 MHz, $CDCl_3$) 67.56 (C-1′ or C-3′), 70.40, 71.15 (2 × CH), 72.93 ($OCH_2Ar$), 73.86 (CH), 74.96, ($OCH_2Ph$), 77.55 (d, CH), 77.60 (C-1′ or C-3′), 78.14, 78.74, 81.04 (3 × CH), 127.83, 128.02, 128.14, 128.25, 128.44, 128.62 (10 × CH of Ph), 137.82 138.40 (2 × C-1 of Ph); MS *m*/*z* (+ve ion FAB); 417 [(M + H)$^+$, 15%], 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 569 [(M + NBA)$^-$, 100%], 415 [(M − H)$^-$, 60%]. Anal. ($C_{23}H_{28}O_7 \cdot 0.5H_2O$) C, H.

**(2′*R*)-1D-3,6-Di-*O*-benzyl-1,2-*O*-[(2′-hydroxy)propane-1′,3′-diyl]-*myo*-inositol (20).** The BDA group was removed from **18** as described for the epimer **17**. Purification by flash chromatography (ethyl acetate) gave the triol **20** as a hygroscopic white foam in 84% yield: $[\alpha]_D^{23} = -7$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 2.52 (1 H, d, $J = 6.3$ Hz, $D_2O$ exch., OH-2′), 2.74 (1 H, br s, $D_2O$ exch., OH-4 or OH-5), 2.80 (1 H, br s, $D_2O$ exch., OH-4 or OH-5), 3.20 (1 H, dd, $J = 9.8$, 2.9, H-1 or H-3), 3.44 (1 H, dd, $J = 12.6$, 3.5, H-1′a or H-3′a) 3.45 (1 H, t-like dd, $J = 9.2$, 9.0, H-5), 3.66 (1 H, dd, $J = 12.7$, 6.4, H-3′a or H-1′a), 3.69 (1 H, dd, $J = 9.9$, 2.7, H-1or H-3), 3.82−3.89 (2 H, m, H-4 and H-6), 3.93 (1 H, br d, $J = 12.7$, H-3′b or H-1′b), 3.95−4.03 (1 H, m, C-2′-H), 4.08 (1 H, buried, H-2), 4.09 (1 H, dd, $J = 12.6$, 5.9, H-1′b or H-3′b), 4.63, 4.68 (2 H, $AB_q$, $J_{AB} = 11.7$, $CH_2Ph$), 4.79, 4.90 (2 H, $AB_q$, $J_{AB} = 11.2$, $CH_2$-Ph), 7.26−7.41 (10 H, m, Ph); $^{13}$C NMR (68 MHz, $CDCl_3$) 65.29 (C-1′ or C-3′), 70.90, 71.41 (2 × CH), 72.28 ($OCH_2Ph$), 74.41 (CH), 74.45, 76.37 (2 × $OCH_2$), 77.24, 77.41, 77.73, 78.10 (4 × CH), 127.75, 127.94, 128.07, 128.38, 128.57 (10 × CH of Ph), 137.61, 138.51 (2 × C-1 of Ph); MS *m*/*z* (+ve ion FAB); 838 [(2 M + H)$^+$, 60%], 439 [(M + Na)$^+$, 10%], 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 569 [(M + NBA)$^-$, 100%], 415[(M − H)$^-$, 50%]. Anal. ($C_{23}H_{28}O_7 \cdot 0.5H_2O$) C, H.

**(2′*R*)-1D-3,6-Di-*O*-benzyl-4,5-bis-*O*-[di(benzyloxy)phosphoryl]-1,2-*O*-{2′-[di(benzyloxy)phosphoryloxy]propane-1′,3′-diyl}-*myo*-inositol (21).** To a solution of bis(benzyloxy)-diisopropylaminophosphine (870 mg, 2.52 mmol) in dry $CH_2Cl_2$ (5 mL) was added 1*H*-tetrazole (350 mg, 5.00 mmol). The mixture was stirred at room temperature for 20 min, and then

the triol **19** (175 mg, 0.420 mmol, previously dried in vacuo at 30 °C) was added. After 1 h at room temperature, the mixture was cooled to −78 °C, *m*-CPBA (60%, 760 mg, 2.64 mmol) was added, and the cooling bath was removed. The mixture was allowed to reach room temperature and then diluted with $CH_2Cl_2$ (50 mL). The clear solution was washed with 10% $Na_2SO_3$, saturated $NaHCO_3$, and brine (50 mL of each), dried ($MgSO_4$), and concentrated by evaporation under reduced pressure. Purification of the residue by flash chromatography ($CHCl_3$/acetone 3:1) afforded **21** (412 mg, 0.344 mmol, 82%) as a colorless oil which crystallized after a few days: mp 103−105 °C (from ethanol); $[\alpha]_D^{19} = -14$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz $CDCl_3$) 3.31 (1 H, br d, $J = 13.2$, H-1′a or H-3′a), 3.50 (1 H, dd, $J = 9.3$, 2.5 Hz, H-3), 3.61−3.66 [2 H, m, H-2 and (H-3′a or H-1′a], 3.73 (1 H, dd, $J = 9.2$, 2.9 Hz, H-1), 3.94−4.02 [2 H, m, C-6-H and (H-3′b or H-1′b)], 4.07 (1 H, br d, $J = 13.2$, H-1′b or H-3′b), 4.37−4.42 (1 H, m, H-2′), 4.46−4.53 (2 H, m, H-5 and 0.5 AB system of C$H_2$Ph), 4.65−4.72 (3 H, m, 1.5 AB systems of C$H_2$Ph), 4.80−5.06 (13 H, m, 6 × AB systems of C$H_2$Ph and H-4), 6.98−7.01 (2 H, m, Ph), 7.11−7.34 (38 H, m, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 66.72 (broadened by $J_{CP}$ coupling, C-1′ or C-3′), 69.72−69.53 (overlapping signals with $J_{CP}$ couplings, 6 × POC$H_2$Ph), 73.15, 74.07 (2 × OC$H_2$Ph), 74.43 ($J_{CP} = 3.7$, C-1′ or C-3′), 76.74 (CH), 76.85 ($J_{CP} = 5.5$, C-2′), 77.36 (CH), 77.63 (with poorly resolved $J_{CP}$ couplings, CH), 78.44, 78.77 (2 × CH), 78.91 ($J_{CP} = 7.4$, 5.5, CH), 127.12−128.66 (40 × CH of Ph), 135.50−136.15 (6 × C-1 of POC$H_2$*Ph* with $J_{CP}$ couplings), 137.86, 138.68 (2 × C-1 of Ph); $^{31}$P NMR (162 MHz, $^1$H-coupled, $CDCl_3$) −1.97 (1 P, apparent sextet, $J \sim 8$), −1.65 (1 P, apparent sextet, $J \sim 8$), −1.36 (1 P, apparent sextet, $J \sim 8$), MS *m*/*z* (+ve ion FAB); 1197 [$(M + H)^+$, 90%], 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 1349 [$(M + NBA)^-$, 70%], 1242(20), 1105(40), 277 [$(BnO)_2P(O)O^-$, 100%]. Anal. ($C_{65}H_{67}O_{16}P_3$) C, H.

**(2′*S*)-1D-3,6-Di-*O*-benzyl-4,5-bis-*O*-[di(benzyloxy)phosphoryl]-1,2-*O*-{2′-[di(benzyloxy)phosphoryloxy]propane-1′,3′-diyl}-*myo*-inositol (22).** Triol **20** (175 mg, 0.420 mmol) was phosphorylated using the procedure described for **19**. Purification by flash chromatography ($CHCl_3$/acetone 5:1) afforded **22** as a colorless oil (449 mg, 0.375 mmol, 89%): $[\alpha]_D^{20} = -23$ ($c = 1$, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 3.24 (1 H, dd, $J = 12.7$, 5.9, H-1′a or H-3′a), 3.42 (1 H, dd, $J = 9.8$, 2.4 H-3), 3.58 (1 H, dd, $J = 13.2$, 7.3, H-3′a or H-1′a), 3.69 (1 H, dd, $J = 9.3$, 2.9, H-1), 3.80−3.84 [2 H, m, H-2 and (H-3′b or H-1′b)], 3.93 (1 H, t-like dd, $J = 9.3$, 9.3 H-6), 4.11 (1 H, dd, $J = 12.7$, 6.1, H-1′b or H-3′b), 4.42−4.53 (3 H, m, H-2′, H-5 and 0.5 AB system of OC$H_2$Ph), 4.63 (1 H, d, $J = 12.2$, 0.5 AB system of OC$H_2$Ph), 4.69−5.08 (15 H, m, AB systems of OC$H_2$-Ph and C-4-H), 7.01−7.04 (2 H, m, Ph), 7.11−7.36 (38 H, m, Ph); $^{13}$C NMR (100 MHz, $CDCl_3$) 65.40 (C-1′ or C-3′), 69.13, 69.39, 69.55 (signals with $J_{CP}$ couplings, 3 × POC$H_2$Ph), 72.73, 73.61 (2 × OC$H_2$Ph), 73.85 ($^3J_{CP}$ 5.5, C-1′ or C-3′), 75.76 ($J_{CP} = 5.6$, C-2′), 76.41, 76.74, 77.25 (3 × CH), 77.38 (broadened by $J_{CP}$ couplings CH), 77.61 (CH), 79.08 ($J_{CP} = 5.5$, 5.5, CH), 127.34−128.75 (40 × CH of Ph), 135.57, 135.97, 136.11 (6 × C-1 of POC$H_2$*Ph*, with $J_{CP}$ couplings), 137.60, 138.42 (2 × C-1 of Ph); $^{31}$P NMR (162 MHz, $^1$H-decoupled, $CDCl_3$,) −1.65 (1 P), −1.79 (1 P), −2.01 (1 P) (overlapping sextets in $^1$H-coupled spectrum); MS *m*/*z* (+ve ion FAB); 1197 [$(M + H)^+$, 90%], 91 [$(C_7H_7)^+$, 100%]; MS *m*/*z* (−ve ion FAB); 1349 [$(M + NBA)^-$, 60%], 1242(30), 1105(50), 277 [$(BnO)_2P(O)O^-$, 100%]. Anal. ($C_{65}H_{67}O_{16}P_3$) C, H.

**(2′*R*)-1D-1,2-*O*-[(2′-Phosphoryloxy)propane-1′,3′-diyl]-*myo*-inositol 4,5-bisphosphate (9).** To a solution of **21** (160 mg, 134 $\mu$mol) in MeOH (40 mL) and water (10 mL) was added Pd−C (10%, 50% water, 400 mg). The mixture was shaken in a Parr hydrogenator under $H_2$ (50 psi) for 23 h. The catalyst was removed by filtration through a PTFE syringe filter, and 1.0 M triethylammonium bicarbonate buffer (TEAB, 1 mL) was added. The solvents were removed by evaporation under reduced pressure, and the residue was purified by ion-exchange chromatography on Q-Sepharose Fast Flow resin eluting with a gradient of TEAB (0 to 1 M). The product eluted between 0.60 and 0.70 M TEAB. The combined fractions were concentrated by evaporation in vacuo, and MeOH was added and evaporated repeatedly, eventually leaving the pure triethylammonium salt of **9** as a colorless glass (121 $\mu$mol, 90%): $[\alpha]_D^{21} = -28$ ($c = 1$, MeOH); $^1$H NMR (400 MHz, 50 mM phosphate buffer in $D_2O$, pD 7.2) 3.76 (1 H, dd, $J = 9.8$, 3.5, H-1 or H-3), 3.77 (1 H, dd, $J = 13.3$, 3.1, H-1′a or H-3′a), 3.82 (1 H, dd, $J = 9.4$, 3.1 H-1 or H-3), 3.90−4.00 (2 H, m, H-5 and H-6), 4.04−4.17 [5 H, m, H-2, H-4, ($H_2$-3′b or $H_2$-1′b) and (H-1′b or H-3′b)], 4.27−4.33 (1 H, m, $^3J_{HP}$ 9.8, H-2′); $^{31}$P NMR (162 MHz, $^1$H-coupled, $D_2O$) −0.29 (1 P, d, $^3J_{HP}$ 9.4, P-2′), 0.44 (2 P, br m, P-4 and P-5); MS *m*/*z* (+ve ion FAB) 102 [$Et_3NH^+$, 100%]; MS *m*/*z* (−ve ion FAB) 475 [$M^-$, 100%]. Accurate FAB$^-$ calcd for $C_9H_{18}O_{16}P_3^-$: 474.9808. Found: 474.9814.

**(2′*S*)-1D-1,2-*O*-[(2′-Phosphoryloxy)propane-1′,3′-diyl]-*myo*-inositol 4,5-bisphosphate (10).** Compound **22** (150 mg, 125 $\mu$mol) was deprotected as described for the epimer **22.** Purification by ion-exchange chromatography as before gave the triethylammonium salt of **10** as a colorless glass (111 $\mu$mol, 89%): $[\alpha]_D^{22} = -24$ ($c = 1.3$, MeOH); $^1$H NMR (400 MHz, 50 mM phosphate buffer in $D_2O$, pD 7.2) 3.53 (1 H, dd, $J = 12.5$, 6.2, H-3′a), 3.75 (1 H, dd, $J = 9.8$, 3.1 Hz, H-3), 3.81 (1 H, dd, $J = 9.8$, 2.7 H-1), 3.91 (1 H, dd, $J = 13.3$, 7.0, H-1′a), 3.92−4.05 (2 H, m, H-5 and H-6), 4.10 (1 H, dd, $J = 13.3$, 2.0, H-1′b), 4.14 (1 H, q-like ddd, $J \sim 9$, H-4), 4.19 (1 H, t-like dd, $J = 3.1$, 2.7, H-2), 4.31 (1 H, dd, $J = 12.5$, 6.6, H-3′b), 4.35−4.43 (1 H, m H-2′); $^{31}$P NMR (162 MHz, $^1$H-coupled, $D_2O$) −0.37 (1 P, d, $^3J_{HP}$ 9.5, P-2′), 0.47 (2 P, br m, P-4 and P-5); MS *m*/*z* (+ve ion FAB) 102 [$Et_3NH^+$, 100%]; MS *m*/*z* (−ve ion FAB, relative intensity); 950.5 (90), 474.9 [$M^-$, 100%]. Accurate FAB$^-$ calcd for $C_9H_{18}O_{16}P_3^-$: 474.9808. Found: 474.9823.

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**Supporting Information Available:** NOESY spectrum of **10** and X-ray structural data for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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