Membrane-permeant analogues of the putative second messenger *myo*-inositol 3,4,5,6-tetrakisphosphate [1]

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For future investigations of the binding properties of D-*myo*-inositol 3,4,5,6- and 1,4,5,6-tetrakisphosphate [D-Ins(3,4,5,6)P_4 and D-Ins(1,4,5,6)P_4, respectively] to their putative target proteins, a set of analogues with modifications of the 1(3)- and/or 2-hydroxy group has been prepared. The reaction sequences started from D-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol or its D-1,4,5,6-enantiomer, respectively and allowed the introduction of groups with degenerative hydrogen-bonding potential like methoxy or chloride, replacing the hydroxy groups. Additionally, the corresponding DL-*scyllo*-inositol precursor 24 was prepared by a stereochemically optimized reduction of the 2-inosose derivative 23. Classical protection/deprotection chemistry and subsequent phosphorylation employing a common phosphite approach yielded the tetrakisphosphate analogues 1a–e, 3. These derivatives were converted to the uncharged, bioactivatable acetoxymethyl esters 2a–e, 4. To avoid cyclization of phosphates during acetoxymethyl alkylation and to increase lipophilicity of the potentially membrane-permeant InsP_4 derivatives hydroxy groups of the monosubstituted tetrakisphosphates were covered by intracellularly hydrolysable butyrates.

Introduction

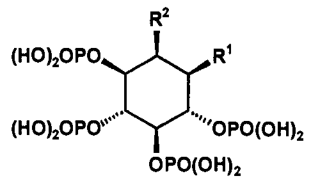
To increase the membrane-permeability of organic anions bioactivatable esters are frequently used to mask the negative charge.[2–4] These are supposed to be stable outside cells, allow diffusion across the plasma membrane, and should be subject to intracellular enzymic hydrolysis inside the cell, thus generating the parent molecule. Most widely used are acyloxymethyl esters, originally developed for carboxylic acids like penicillin [5] and later introduced to polycarboxylic acids, especially to transform ethylene glycol bis-(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA)-based fluorescent dyes like Fura-2 and Fluo-3 into their membrane-permeant derivatives.[6] This method was extended to organic phosphates,[7] mainly to increase the effectiveness of potential therapeutic drugs such as antiviral nucleotides [8–10] or phosphonoformate (foscarnet).[11] Acetoxymethyl esters were successfully applied to the phosphate-containing intracellular second messengers cAMP [12,13] and cGMP.[14] It was demonstrated in several biological assays that, *e.g.*, the acetoxymethyl ester of Bt_2cAMP was 2–3 orders of magnitude more potent than Bt_2cAMP itself, when applied extracellularly.[12] Synthetically more challenging appeared to be the introduction of multiple acyloxymethyl esters to molecules carrying several phosphates, like oligonucleotides [15] or *myo*-inositol polyphosphates.[16] Recently, the octakis(acetoxymethyl) ester of DL-1,2-di-*O*-butyryl-*myo*-inositol 3,4,5,6-tetrakisphosphate [Bt_2Ins(3,4,5,6)P_4, *rac*-2c] was prepared and it was demonstrated that the compound was able to penetrate the plasma membrane of T_{84} cells and result in an elevation of intracellular Ins(3,4,5,6)P_4 levels.[16] It could be shown that the use of this membrane-permeant, bioactivatable derivative of Ins(3,4,5,6)P_4 was capable of uncoupling the chloride secretion from the Ca^{2+} signal, without altering the Ca^{2+} signal itself. Hence, Ins(3,4,5,6)P_4 was considered to have intracellular messenger function. In order to identify the putative binding proteins of Ins(3,4,5,6)P_4, most likely to be the next step in the signalling cascade, it would be most desirable to synthesize a specific radio- or photo-labelled derivative of Ins(3,4,5,6)P_4 in the future. To help answer the question where such a label should be linked to Ins(3,4,5,6)P_4, we here report the syntheses of several analogues of Ins(3,4,5,6)P_4 **1a–e**, **3** modified on the 1- or 2-hydroxy position or both. Modifications were selected to be degenerative in respect to the hydrogen-bonding potential of the respective hydroxy group(s). All Ins(3,4,5,6)P_4 derivatives were converted to their potentially membrane-permeant acetoxymethyl esters **2a–e**, **4** in order to allow *in vivo* assaying of the compounds with T_{84} cells in the future.

Results and discussion

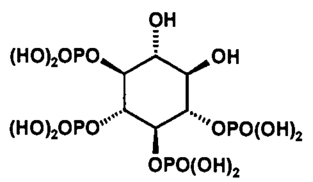
Racemic 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol *rac*-**5** was prepared by a modified procedure, originally described by Angyal and Tate.[17] In brief, DL-1,2-*O*-cyclohexylidene-*myo*-inositol was benzylated with an excess of benzyl chloride and KOH, using 18-crown-6 as a phase-transfer catalyst. The ketal of the resulting DL-3,4,5,6-tetra-*O*-benzyl-1,2-*O*-cyclohexylidene-*myo*-inositol was removed by treatment with trifluoroacetic acid (TFA) in acetonitrile and water (2:10:1) at room temperature for 2 h to give *rac*-**5**. The separation of the enantiomers was achieved by forming the 1(3)-monocamphanates of *rac*-**5** and subsequent crystallization of the resulting diastereomers. Hydrolysis of the esters gave enantiomerically pure 1 D-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol **5** and 1 D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol *ent*-**5** as described before.[16] Experimental and analytical data of the diastereomeric esters as well as of enantiomers **5** and *ent*-**5** are included in the Experimental section below.

Monomethylated *myo*-inositol 3,4,5,6-tetrakisphosphate derivatives 1a and 1b (Schemes 1 and 3)

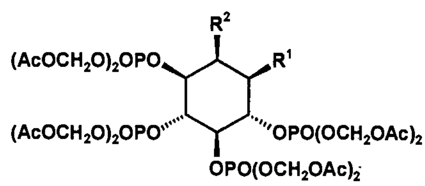
To methylate the 1-hydroxy group of the enantiomerically pure diol **5** regioselectively the dibutylstannylene derivative was



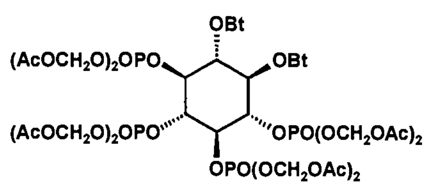
1a, *ent*-1a	$R^1 = OCH_3$, $R^2 = OH$
rac-1b	$R^1 = OH$, $R^2 = OCH_3$
1c, *ent*-1c	$R^1 = R^2 = OH$
1d, *ent*-1d	$R^1 = R^2 = OCH_3$
rac-1e	$R^1 = R^2 = Cl$



rac-3



2a, *ent*-2a	$R^1 = OCH_3$, $R^2 = OBt$
rac-2b	$R^1 = OBt$, $R^2 = OCH_3$
2c, *ent*-2c	$R^1 = R^2 = OBt$
2d, *ent*-2d	$R^1 = R^2 = OCH_3$
rac-2e	$R^1 = R^2 = Cl$



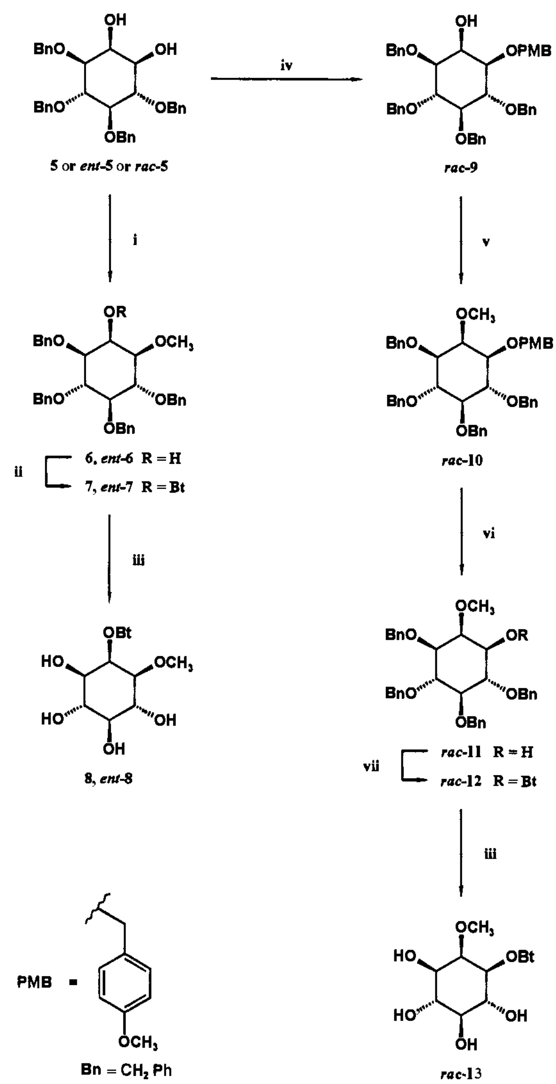
rac-4

Bt = COC_3H_7

Structures of D-*myo*-Ins(3,4,5,6)P_4 **1c** and analogues, including *scyllo*-Ins(3,4,5,6)P_4 **3**† and the octakis(acetoxymethyl) esters **2a–e** and **4**. The corresponding enantiomeric D-Ins(1,4,5,6)P_4-derivatives are not depicted.

prepared using dibutyltin oxide. Water produced by the reaction was trapped by molecular sieves (3 Å) in a Soxhlet apparatus. Regioselective alkylation with methyl iodide afforded compound **6** which was purified on silica gel.[18] Butyrylation of compound **6** with butyric anhydride in pyridine gave the fully protected compound **7**. Subsequent debenzylation by catalytic hydrogenolysis [H_2, Pd/C (10%)] afforded the 1-*O*-methyl-2-*O*-butyryl derivative **8**. Phosphorylation was accomplished using dibenzyl *N*,*N*-diethylphosphoramidite,[19] followed by oxidation with peracetic acid to give the fully

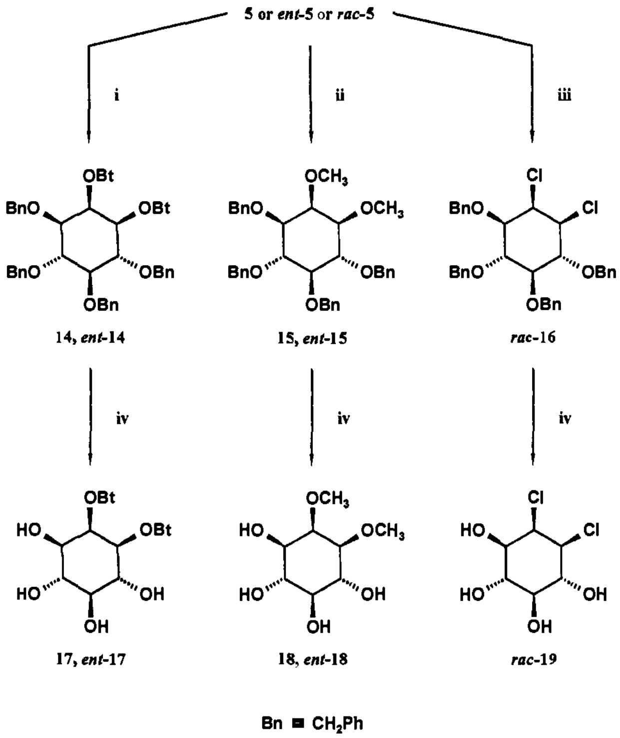
† Note that the nomenclature used in this paper for the *scyllo*-inositol tetrakisphosphates is designed to show the structural similarity to D-*myo*-Ins(3,4,5,6)P_4. The alternative name for compound **3** is as follows: D-*scyllo*-inositol 1,2,3,4-tetrakisphosphate. To avoid confusion, unphosphorylated precursors for **3** have been named in the same fashion.



Scheme 1 *Reagents and conditions:* i, (a) Bu_2SnO, MeOH, Soxhlet/molecular sieves 3 Å, reflux, 20 h, (b) MeI, DMF, 50 °C, 2 days (72%); ii, Bt_2O, pyridine, 50 °C, 2 days (95%); iii, H_2, Pd/C (10%), AcOH, 4 h (98–99%); iv, (a) Bu_2SnO, MeOH, Soxhlet/molecular sieves 3 Å, reflux, 20 h, (b) PMBCl, 50 °C, 2.5 h (76%); v, MeI, KOH powder, DMSO, 2.5 h (82%); vi, DDQ, CH_2Cl_2–water (19:1), 0.5 h (60%); vii, Bt_2O, DMAP, pyridine, 1.5 h (97%)

protected tetrakisphosphate derivative **20a**. Deblocking by catalytic hydrogenolysis yielded D-1-*O*-methyl-2-*O*-butyryl-Ins(3,4,5,6)P_4 **21a** as the free acid. The butyrate could be removed by treatment with 0.1 mol dm^{-3} KOH to afford D-1-*O*-methyl Ins(3,4,5,6)P_4 **1a**. Alternatively, acid **21a** was alkylated with acetoxymethyl bromide (bromomethyl acetate) in the presence of diisopropylethylamine (DIEA) to give the uncharged octakis(acetoxymethyl) ester **2a**. In an identical reaction sequence starting from enantiomerically pure D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol *ent*-**5** the corresponding L-enantiomer D-3-*O*-methyl-Ins(1,4,5,6)P_4 *ent*-**1a** and its octakis-(acetoxymethyl) ester derivative *ent*-**2a** were prepared.

The methylation of the 2-position of *rac*-**5** required a slightly more elaborate synthetic pathway: The dibutylstannylene derivative from diol *rac*-**5** was regioselectively alkylated to the known 1-*O*-*p*-methoxybenzyl (PMB) ether *rac*-**9** (ref. 20). Subsequent methylation[21] of the 2-position with methyl iodide in dimethyl sulfoxide (DMSO) under strongly basic conditions (powdered KOH) afforded the fully protected derivative *rac*-**10**. Selective deprotection[22] of the *p*-methoxybenzyl group using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in methylene dichloride–water (19:1) gave compound *rac*-**11**, which was butyrylated to the DL-1-*O*-butyryl-2-*O*-methyl derivative *rac*-**12**. The benzyl groups were removed by catalytic hydrogenolysis

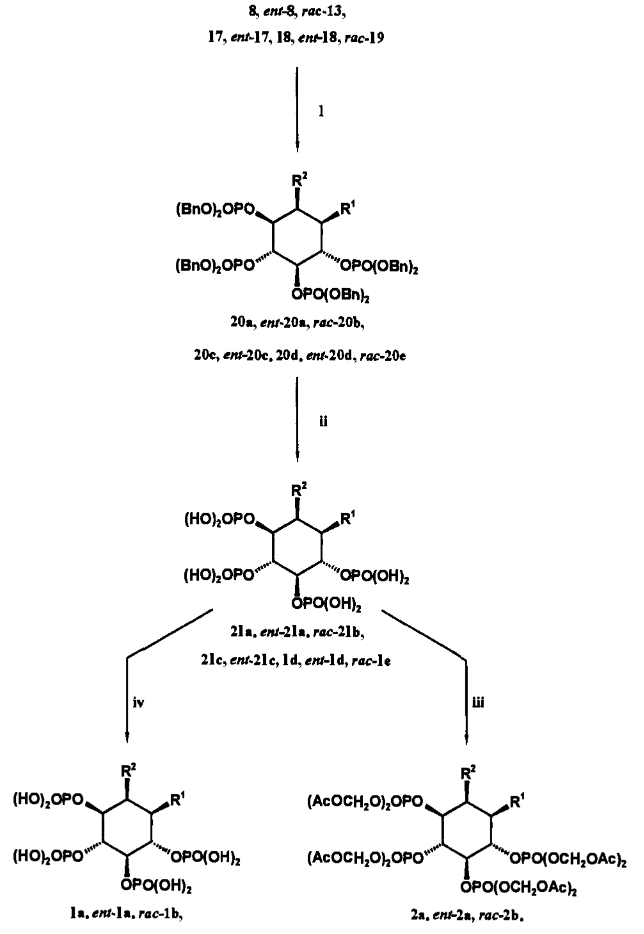


Scheme 2 *Reagents and conditions:* i, Bt_2O, DMAP, pyridine, 1.5 h (99%); ii, MeI, KOH powder, DMSO, 2.5 h (90%); iii, dry CCl_4, Ph_3P, reflux, 12 h (62%); iv, H_2, Pd/C (10%), AcOH, 4 h (99%)

to form the tetraol *rac*-**13**. Phosphorylation to the fully protected tetrakisphosphate *rac*-**20b** proceeded as described above. Hydrogenolysis afforded compound *rac*-**21b**, which was treated with KOH, followed by ion-exchange chromatography (Dowex 50 WX 8) to give DL-2-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakisphosphate *rac*-**1b** as the free acid. Compound *rac*-**21b** was alkylated with acetoxymethyl bromide, as described above, to give the octakis(acetoxymethyl) ester *rac*-**2b**.

1,2-Bismodified *myo*-inositol 3,4,5,6-tetrakisphosphate derivatives 1c–1e (Schemes 2 and 3)

The hydroxy groups of the diol **5** were bismodified simultaneously in three different ways (Scheme 2). Esterification of diol **5** or *ent*-**5** with butyric anhydride and 4-(dimethylamino)-pyridine (DMAP) in dry pyridine gave the 1,2-di-*O*-butyryl derivative **14** and the 2,3-di-*O*-butyryl derivative *ent*-**14**, respectively. The reaction of diol **5** or *ent*-**5** with methyl iodide and KOH in DMSO afforded the 1,2- and 2,3-di-*O*-methyl derivative **15** and *ent*-**15**, respectively. Finally, *rac*-**5** could be chlorinated under reflux in dry carbon tetrachloride and triphenylphosphine.[23] The substitution of each hydroxy group proceeded under inversion, therefore the *myo*-configuration was maintained. Purification by preparative high-performance liquid chromatography (HPLC) (RP-18, 10 μm; 90% MeOH) gave the dichloro-dideoxy-*myo*-inositol derivative *rac*-**16** in 62% yield. Subsequent catalytic hydrogenolysis [H_2, Pd/C (10%)] of tetrakis benzyl ethers **14**, *ent*-**14**, **15**, *ent*-**15**, and *rac*-**16** afforded the debenzylated derivatives **17**, *ent*-**17**, **18**, *ent*-**18** and *rac*-**19**, respectively, in quantitative yield (Scheme 2). The tetraols **17**, *ent*-**17**, **18**, *ent*-**18** and *rac*-**19** were each phosphitylated as described above. Subsequent oxidation with peracetic acid (32% v/w) afforded the fully protected tetrakisphosphates **20c**, *ent*-**20c**, **20d**, *ent*-**20d** and *rac*-**20e**, respectively (Scheme 3). Deblocking by catalytic hydrogenolysis formed the 1,2-di-*O*-butyryl derivatives **21c** and *ent*-**21c** and the deprotected Ins(3,4,5,6)P_4 derivatives **1d**, *ent*-**1d** and *rac*-**1e**. To cleave the butyric acid ester groups, compounds **21c** and *ent*-**21c** were treated with 0.1 mol dm^{-3} KOH (pH 12.8) for 20 h. Purification by ion-exchange chromatography (Dowex 50 WX 8) gave the free acids of *myo*-inositol 3,4,5,6-tetrakisphosphate **1c** and *ent*-**1c**, respectively. Alternatively, the derivatives **21c**, *ent*-**21c**, **1d**, *ent*-**1d** and *rac*-**1e** were alkylated with acetoxymethyl bromide in DIEA to form the octakis(acetoxymethyl) esters **2c**, *ent*-**2c**, **2d**, *ent*-**2d** and *rac*-**2e**, respectively.



1a	$R^1 = OCH_3, R^2 = OH$	**2a, 20a, 21a**	$R^1 = OCH_3, R^2 = OBt$
1b	$R^1 = OH, R^2 = OCH_3$	**2b, 20b, 21b**	$R^1 = OBt, R^2 = OCH_3$
1c	$R^1 = R^2 = OH$	**2c, 20c, 21c**	$R^1 = R^2 = OBt$
1d	$R^1 = R^2 = OCH_3$	**2d, 20d**	$R^1 = R^2 = OCH_3$
1e	$R^1 = R^2 = Cl$	**2e, 20e**	$R^1 = R^2 = Cl$

Scheme 3 *Reagents and conditions:* i, (a) $(BnO)_2PNEt_2$, 1*H*-tetrazole, CH_3CN, 3 days or $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_3CN, 1.5 h–3 days (b) CH_3CO_2OH, CH_3CN, −40 °C, 0.5–1 h (37–69%); ii, H_2, Pd/C (10%), AcOH, 4 h (98–99%); iii, $CH_3CO_2CH_2Br$, DIEA, CH_3CN, 2 days (30–90%); iv, (a) 0.1 mol dm^{-3} KOH, pH 12.8, 18 h, (b) Dowex 50 WX 8 (73–92%)

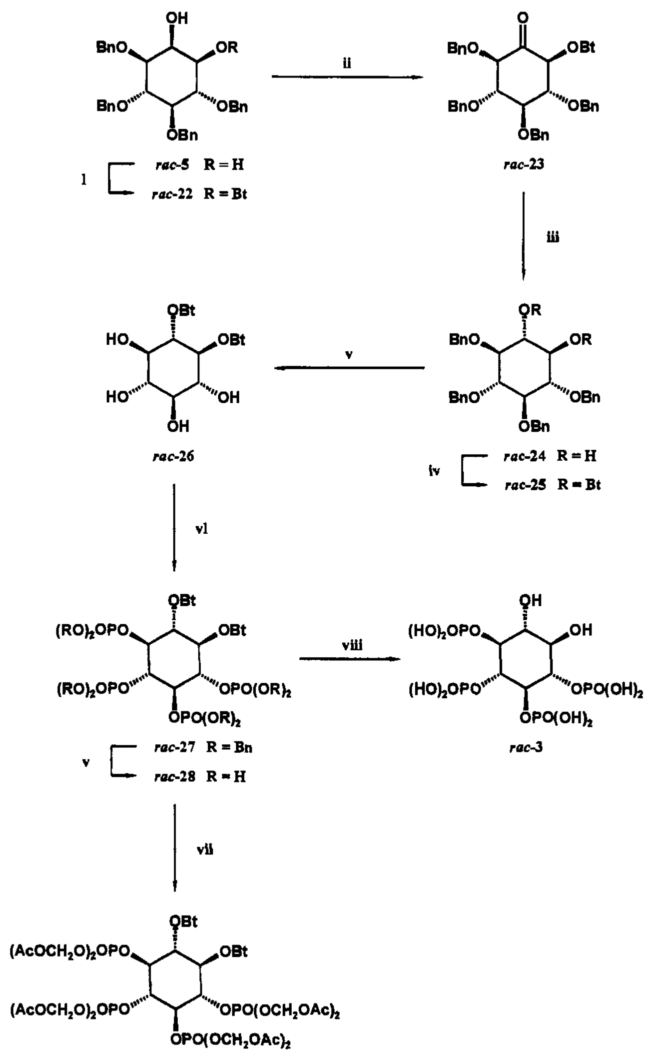
DL-*scyllo*-Inositol 3,4,5,6-tetrakisphosphate *rac*-3 (Scheme 4)

Regioselective butyrylation of the 1-OH of diol *rac*-**5** gave the monobutyrate *rac*-**22**. Subsequent Swern oxidation (DMSO–acetic anhydride) yielded the corresponding 2-inosose *rac*-**23**. The ketone was then to be reduced to the equatorial alcohol group to form the *scyllo*-configuration. Classic approaches with sodium borohydride in MeOH–tetrahydrofuran (THF),[24] ethanol[25] or acetonitrile (Table 1) are known to yield predominantly axial hydroxy groups. We therefore optimized the reaction by switching to propan-2-ol as the solvent, temperatures around 50 °C, and only a small excess of $NaBH_4$ (1.2 mol equiv.) (Table 1). The stereospecifity shifted to 3:1 in favour of the desired *scyllo*-inositol derivative *rac*-**24**. The butyrate was lost completely by this procedure. The *scyllo*- and *myo*-isomers could be conveniently separated by preparative HPLC (RP-18, 10 μm; 82% MeOH). The diol *rac*-**24** was esterified with butyric anhydride in pyridine to afford the

Table 1 Reduction of DL-3,4,5,6-tetra-*O*-benzyl-1-*O*-butyryl-*myo*/*scyllo*-inosose *rac*-**23**: *scyllo*/*myo* ratio of the products *rac*-**24**/*rac*-**5** under various conditions

Entry	$NaBH_4$ (mol equiv.)	Solvent	Temp. (T/°C)	*scyllo*/*myo* Ratio[a]
1	4	CH_3CN	0	1:10
2	4	CH_3CN	50	1:16
3	4	Pr^iOH	0	1.6:1
4	1.2	Pr^iOH	0	2:1
5	4	Pr^iOH	50	2.5:1
6	1.2	Pr^iOH	50	3:1

[a] As determined by HPLC (RP18, 85% MeOH).



Scheme 4 *Reagents and conditions:* i, Bt_2O, pyridine, 1 day (78%); ii, DMSO, Ac_2O, 15 h (81%); iii, $NaBH_4$, Pr^iOH, 50 °C, 0.5 h (73%); iv, Bt_2O, pyridine, 2 days (72%); v, H_2, Pd/C (10%), AcOH, 4 h (99%); vi, (a) $(BnO)_2PNPr^i_2$, 1*H*-tetrazole, CH_3CN, 20 h, (b) CH_3CO_2OH, CH_3CN, −40 °C, 0.5 h (68%); vii, $CH_3CO_2CH_2Br$, DIEA, CH_3CN, 2 days (48%); viii, (a) 0.1 mol dm^{-3} KOH, pH 12.8, 3 days, (b) Dowex 50 WX 8 (99%)

dibutyrate *rac*-**25** and subsequently the benzyl groups were removed by catalytic hydrogenolysis to give tetraol *rac*-**26** in 90% yield from *rac*-**24**. Phosphitylation with dibenzyl *N*,*N*-diisopropylphosphoramidite and subsequent oxidation afforded the fully protected *scyllo*-inositol tetrakisphosphate derivative *rac*-**27**. Hydrogenolysis gave *rac*-1,2-di-*O*-butyryl-*scyllo*-inositol 3,4,5,6-tetrakisphosphate *rac*-**28**, which could be deprotected to *scyllo*-inositol 3,4,5,6-tetrakisphosphate *rac*-**3** by treatment with 0.1 mol dm^{-3} KOH (pH 12.8). Compound *rac*-**3** was converted to the free acid by ion-exchange chromatography on Dowex 50 WX 8. Tetrakisphosphate *rac*-**28** was alkylated with acetoxymethyl bromide in DIEA to give the uncharged octakis(acetoxymethyl) ester *rac*-**4**.

For successful extracellular application the compounds not only have to pass the plasma membrane, but also multiple enzymic hydrolysis steps are required to cleave the acetoxymethyl esters and the butyrates inside the cell. Several studies have shown that the enzymic cleavage of bis(acetoxybenzyl) esters and bis(aryloxymethyl) esters of different phosphates and phosphonates was fast for the phosphate triesters and phosphonate diesters, respectively, but slower for the second ester when a negative charge was formed.[3,26,27] The problem could be avoided by use of a cyclic 4-acyloxy-1,3,2-dioxaphosphorinane which relied on β-elimination for the final deprotection step.[4] In living cells mass analysis by HPLC of some of the membrane-permeant tetrakisphosphates described here revealed that the hydrolysis of all acetoxymethyl (AM) esters was complete after less than 30 min (Guse and Schultz, unpublished results).

The potential of extracellular doses of compound **2c** to uncouple the Cl^--secretion of T_{84} cells from the intracellular Ca^{2+} signal has been published.[16] Similar experiments with the new and supposedly membrane-permeant Ins(3,4,5,6)P_4- and Ins(1,4,5,6)P_4-derivatives presented here are in progress.

Experimental

Materials and methods

Mps were determined using a Gallenkamp Melting Point Apparatus and are uncorrected. ^1H and ^{31}P NMR spectra were recorded on a Bruker AM 360 spectrometer. Chemical shifts were measured in ppm relative to tetramethylsilane for ^1H NMR spectra and external 85% H_3PO_4 for ^{31}P NMR spectra. *J*-Values are given in Hz. Mass spectra were recorded using a Finnigan Mat 8222 mass spectrometer with fast atom bombardment (FAB) ionization. High-resolution masses were determined relative to known compounds with a mass not differing more than 10%. Optical rotations were measured on a Perkin-Elmer 1231 polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. pH-Values were determined with a pH meter E516 and a glass electrode from Metrohm Herisau. HPLC was performed on a LDC/Milton Roy Consta Metric III pump with a LDC/Milton Roy UV Monitor D (254 nm) or a Knauer refractive index detector. The analytical column was a Merck Hibar steel tube (250 mm x 4 mm) filled with RP 18 material (Merck LiChrosorb; 10 μm). Preparative HPLC was performed using a Shimadzu LC 8A pump with a preparative LDC UV III Monitor (254 nm) and a Merck Prepbar steel column (250 mm x 50 mm) filled with RP 18 material (Merck, LiChrospher 100; 10 μm). The eluents were methanol–water mixtures; compositions are given in % methanol (MeOH). Preparative column chromatography was performed on silica gel from ICN (63–200 mesh, 60 Å). Elemental analysis were performed by Mikroanalytisches Labor Beller, Göttingen, FRG. Filtration of the palladium/carbon catalyst was performed with a Sartorius filtration apparatus SM 162 01 using filters from regenerated cellulose (Sartorius, SM 116 04).

All reagents were obtained in the highest purity available. Where necessary, solvents were dried and/or distilled before use. Acetonitrile was distilled from phosphorus(V) oxide and stored over molecular sieves 3 Å. Methanol and *N*,*N*-dimethylformamide (DMF) were stored over molecular sieves 3 Å for at least 2 weeks. Pyridine and toluene were stored over molecular sieves 4 Å. DIEA was dried over sodium wire. Acetoxymethyl bromide[28] and dibenzyl *N*,*N*-diethylphosphoramidite[19] were prepared according to known procedures. $NaBH_4$ was obtained from Fluka. Palladium (10%) on carbon was from Acros Chemie. (1*S*)-(−)-Camphanoyl chloride, dibenzyl *N*,*N*-diisopropylphosphoramidite and tetrazole were from Aldrich. Acetic anhydride, butyric anhydride, DIEA and DMSO were from Merck. All other reagents were from Riedel-de Haën. Light petroleum refers to the fraction boiling in the range 55–65 °C, and phosphate buffer had the following composition:

Determination of purity by analytical HPLC

All products were checked for homogeneity on analytical reversed-phase HPLC, except for the free acids of the tetrakisphosphates. The octakis(acetoxymethyl) esters **2a–e**, **4** could be detected by a refractive index detector and were found to elute from the reversed-phase HPLC column with 50% MeOH, except for compounds **2c** and **4** which were eluted with 60% MeOH. The retention times were in the range 8–20 min and the purity exceeded 99% as determined by this method.

General procedure of phosphorylation

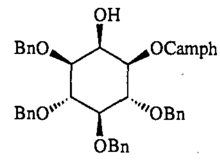
The selectively protected inositol derivative was dissolved in dry acetonitrile (2–10 cm^3) under argon before dry tetrazole and freshly prepared dibenzyl *N*,*N*-diethylphosphoramidite or dibenzyl *N*,*N*-diisopropylphosphoramidite were added. After stirring of the mixture at room temperature for 1.5 h–3 days, HPLC analysis showed no further reaction. The reaction mixture was cooled to −40 °C and peracetic acid (32% v/w; 1 mol equiv. for each mol equiv. of phosphoramidite) was added under vigorous stirring. The mixture was allowed to warm to room temperature. The solvents were removed under reduced pressure, the residual oil was dissolved in *tert*-butyl methyl ether, and the solution was washed twice with aq. sodium sulfite (10% v/w), and once with aq. sodium hydrogen carbonate (5% v/w) and water successively. The organic layer was dried over Na_2SO_4, filtered, and the ether was evaporated off. The crude residue was purified by preparative HPLC with the solvent specified to give the fully protected inositol tetrakisphosphate derivative.

General procedure of deprotection of benzyl groups by hydrogenolysis

A solution of the tetrabenzylinositol or the fully protected inositol tetrakisphosphate, respectively, in acetic acid (2–10 cm^3) was vigorously stirred with palladium on carbon (10%; 0.1 mol palladium for each mol of benzyl groups) under hydrogen in a self-build hydrogenation apparatus for 4 h. The catalyst was removed by ultrafiltration and the filtrate was freeze dried to give the respective product as a powder.

General procedure for the introduction of acetoxymethyl esters

In a silylated 50 cm^3 round-bottom flask the thoroughly dried inositol tetrakisphosphate derivate (free acid) was suspended in dry acetonitrile (0.5–1.0 cm^3) under argon. After dry DIEA (16–25 mol equiv.) and acetoxymethyl bromide (21–26 mol equiv.) had been added, the solution was stirred at room temperature for 2 days. All volatile components were evaporated off under reduced pressure and the product was isolated by one to three extractions with dry toluene. Evaporation of the toluene gave the inositol tetrakisphosphate octakis(acetoxymethyl) ester as a syrup.



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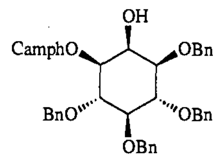

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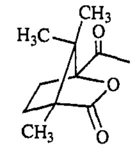

Preparation of enantiomerically pure D-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol 5 and D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol *ent*-5

(−)-Camphanoyl chloride (25 g, 113 mmol) was added to a solution of DL-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol *rac*-**5** (60 g, 111 mmol) in dry pyridine (40 cm^3). The reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the oily residue was dissolved in boiling methanol (200 cm^3) to crystallize the diastereomeric mixture, D-3,4,5,6-tetra-*O*-benzyl-1-*O*-camphanoyl-*myo*-inositol **29** and D-1,4,5,6-tetra-*O*-benzyl-3-*O*-camphanoyl-*myo*-inositol **30**, as needles. The crystals were extracted with boiling ethyl acetate–light petroleum (1 : 2) to precipitate pure isomer **30** from the extract. The filtrate was evaporated under reduced pressure and the residue was crystallized twice from ethyl acetate–light petroleum (3 : 1) to give pure isomer **29**.

Isomer **29**, mp 165–167 °C (lit.,[29] 169–170 °C) (Found: C, 73.4; H, 6.9. Calc. for $C_{44}H_{48}O_9$: C, 73.3; H, 6.7%); $[\alpha]_D^{24}$ +15.0 (*c* 1.7, $CHCl_3$) {lit.,[29] $[\alpha]_D$ +14.9 (*c* 1.3, $CHCl_3$)}; δ_H($CDCl_3$; 360 MHz) 7.35–7.20 (20 H, m, 4 × CH_2Ph), 4.95–4.65 (6 H, m, 3 × CH_2Ph), 4.72 (2 H, s, CH_2Ph), 4.70 (1 H, dd, *J* 9.2 and 2.8, H-1), 4.32 (1 H, dd, *J* 2.8 and 2.8, H-2), 4.13 (1 H, dd, *J* 9.8 and 9.2, H-6), 3.95 (1 H, dd, *J* 9.8 and 9.8, H-4), 3.58 (1 H, dd, *J* 9.8 and 2.8, H-3), 3.55 (1 H, dd, *J* 9.8 and 9.8, H-5), 2.39 (1 H, s, OH), 2.30 (1 H, m, camph), 1.92 (2 H, m, camph), 1.68 (1 H, m, camph), 1.11 (3 H, s, Me), 1.09 (3 H, s, Me) and 0.89 (3 H, s, Me); *m/z* (FAB^+) 721 (M + H^+, < 1%) and 91 (Bn^+, 100); (FAB^-) 719 (M − H^+, 43%), 629 (M − Bn^+, 2) and 197 ($camphO^-$, 100).

Isomer **30**, mp 176–178 °C (lit.,[29] 176–177 °C) (Found: C, 73.2; H, 6.9%); $[\alpha]_D^{24}$ −21.1 (*c* 1.6, $CHCl_3$) {lit.,[29] $[\alpha]_D^{24}$ −21.3 (*c* 5.1, $CHCl_3$)}; δ_H($CDCl_3$; 360 MHz) 7.33–7.20 (20 H, m, 4 × CH_2Ph), 4.95–4.65 (6 H, m, 3 × CH_2Ph), 4.73 (2 H, s, CH_2Ph), 4.71 (1 H, dd, *J* 9.2 and 2.8, H-1), 4.29 (1 H, dd, *J* 2.8, H-2), 4.15 (1 H, dd, *J* 9.8 and 9.2, H-6), 3.98 (1 H, dd, *J* 9.8, H-4), 3.55 (1 H, dd, *J* 9.8, H-5), 3.52 (1 H, dd, *J* 9.8 and 2.8, H-3), 2.39 (1 H, m, camph), 2.37 (1 H, s, OH), 1.89 (2 H, m, camph), 1.67 (1 H, m, camph), 1.10 (3 H, s, Me), 1.01 (3 H, s, Me) and 0.99 (3 H, s, Me); *m/z* (FAB^+) 721 (M + H^+, 1%) and 91 (Bn^+, 100); (FAB^-) 719 (M − H^+, 44%), 629 (M − Bn^+, 3) and 197 ($camphO^-$, 100).

To generate the enantiomerically pure compounds **5** and *ent*-**5** each ester was dissolved in methanol (100 cm^3), 1 mol dm^{-3} KOH (pH ~ 13; 10 cm^3) was added, and the solution was stirred at 50 °C for 1 day. The reaction mixture was evaporated under reduced pressure and the product was extracted with *tert*-butyl methyl ether. The organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated. Crystallization from methanol gave the pure enantiomers **5** (17.36 g, 29%) and *ent*-**5** (18.88 g, 31%), each as a solid.

Enantiomer **5**, mp 143.5–145 °C (lit.,[29] 142.5 °C) (Found: C, 75.4; H, 6.85. Calc. for $C_{34}H_{36}O_6$: C, 75.5; H, 6.7%); $[\alpha]_D^{24}$ +20.0 (*c* 2.5, $CHCl_3$) {lit.,[29] $[\alpha]_D$ +25.0 (*c* 1.3, $CHCl_3$)}; δ_H($CDCl_3$; 360 MHz) 7.35–7.23 (20 H, m, 4 × CH_2Ph), 4.96–4.72 (8 H, m, 4 × CH_2Ph), 4.21 (1 H, dd, *J* 2.8, H-2), 3.97 (1 H, dd, *J* 10.1, H-4), 3.82 (1 H, dd, *J* 10.1, H-6), 3.52–3.45 (3 H, m, H-1, -3 and -5), 2.48 (1 H, s, OH-2) and 2.42 (1 H, d, *J* 4.0, OH-1); m/z (FAB$^+$) 541 (M + H$^+$, 10%) and 91 (Bn$^+$, 100); (FAB$^-$) 539 (M − H$^+$, 100%) and 449 (M − Bn$^+$, 5).

Enantiomer *ent*-**5**, mp 143–145 °C (lit.,[29] 143 °C) (Found: C, 75.6; H, 6.8%); $[\alpha]_D^{24}$ −19.2 (*c* 2.5, $CHCl_3$) {lit.,[29] $[\alpha]_D$ −25.1 (*c* 1.3, $CHCl_3$)}. Spectral data were in accord with those of enantiomer **5**.

D-3,4,5,6-Tetra-*O*-benzyl-1,2-di-*O*-butyryl-*myo*-inositol 14
A solution of dry diol **5** (860 mg, 1.59 mmol), butyric anhydride (919 mm^3, 886 mg, 5.6 mmol) and DMAP (19.5 mg, 160 µmol) in dry pyridine (5 cm^3) was stirred at room temperature. After 1 h the reaction was complete as could be detected by HPLC (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 10.50 min). Evaporation of the reaction mixture gave a crude oil. Residual pyridine was removed by evaporation three times with octane. The residue was dissolved in *tert*-butyl methyl ether and was washed with 0.5 mol dm^{-3} phosphate buffer (25 cm^3 × 2) and brine (25 cm^3 × 1). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the mixture gave pure title compound **14** (1.07 g, 99%) as an oil, $[\alpha]_D^{24}$ +3.2 (*c* 0.4, $CHCl_3$); δ_H($CDCl_3$; 360 MHz) 7.30–7.20 (20 H, m, 4 × CH_2Ph), 5.77 (1 H, dd, all *J* 3.0, H-2), 4.91–4.60 (8 H, m, 4 × CH_2Ph), 4.50 (1 H, dd, *J* 9.7 and 3.0, H-1), 3.91 (1 H, dd, all *J* 9.7, H-4), 3.89 (1 H, dd, all *J* 9.7, H-6), 3.61 (1 H, dd, *J* 9.7 and 3.0, H-3), 3.58 (1 H, dd, all *J* 9.7, H-5), 2.39 (2 H, m, α-H_2), 2.18 (2 H, m, α-H_2), 1.68 (2 H, q, *J* 7.5, β-H_2), 1.62 (2 H, q, *J* 7.3, β-H_2), 0.99 (3 H, t, *J* 7.5, γ-H_3) and 0.93 (3 H, t, *J* 7.3, γ-H_3); m/z (FAB$^+$) 681 (M + H$^+$, < 1%), 573 (M − BnO$^-$, 1) and 91 (Bn$^+$, 100); (FAB$^-$) 679 (M − H$^+$, 1%), 609 (M − Bt$^+$, 1), 589 (M − Bn$^+$, 1) and 87 (BtO$^-$, 100%).

D-1,4,5,6-Tetra-*O*-benzyl-2,3-di-*O*-butyryl-*myo*-inositol *ent*-14
Diol *ent*-**5** was butyrylated as described above for the other enantiomer to give compound *ent*-**14**, $[\alpha]_D^{24}$ −3.8 (*c* 1.0, $CHCl_3$). Mass spectra and NMR data were identical with those obtained for compound **14**.

D-1,2-Di-*O*-butyryl-*myo*-inositol 17
Compound **14** (1.08 g, 1.58 mmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give tetraol **17** (505 mg, 99%) as a solid after freeze drying, mp 141–142 °C (Found: C, 51.7; H, 7.7. Calc. for $C_{14}H_{24}O_8$: C, 52.5; H, 7.55%); $[\alpha]_D^{24}$ +30.5 (*c* 0.6, MeOH); δ_H(D_2O; 360 MHz) 5.35 (1 H, dd, all *J* 2.7, H-2), 4.67 (1 H, dd, *J* 9.0 and 2.7, H-1), 3.96 (1 H, dd, all *J* 9.0, H-6), 3.90 (1 H, dd, *J* 9.5 and 2.7, H-3), 3.43 (1 H, dd, all *J* 9.5 and 9.0, H-4), 3.15 (1 H, dd, all *J* 9.0, H-5), 2.39 (2 H, m, α-H_2), 2.18 (2 H, m, α-H_2), 1.68 (2 H, q, *J* 7.5, β-H_2), 1.62 (2 H, q, *J* 7.3, β-H_2), 0.9 (3 H, t, *J* 7.5, γ-H_3) and 0.93 (3 H, t, *J* 7.3, γ-H_3); m/z (FAB$^+$) 321 (M + H$^+$, 39%), 233 (M − BtO$^-$, 19) and 71 (Bt$^+$, 100); (FAB$^-$) 319 (M − H$^+$, 21%), 249 (M − Bt$^+$, 5) and 87 (BtO$^-$, 100).

D-2,3-Di-*O*-butyryl-*myo*-inositol *ent*-17
A similar reaction and work-up of the fully protected compound *ent*-**14** afforded tetraol *ent*-**17**, $[\alpha]_D^{24}$ −29.4 (*c* 1.1, MeOH). Spectral data were in accord with those of enantiomer **17**.

D-1,2-Di-*O*-butyryl-*myo*-inositol 3,4,5,6-tetrakis(dibenzyl phosphate) 20c
A solution of tetraol **17** (440 mg, 1.37 mmol) and tetrazole (1.27 g, 18.2 mmol) in acetonitrile (5 cm^3) was treated with dibenzyl *N,N*-diethylphosphoramidite (5.79 g, 18.2 mmol) for 3 days, oxidized with peracetic acid, and worked up as described in the general procedures. Purification by preparative HPLC (92% MeOH; 40 cm^3 min^{-1}; t_R = 35.25 min) gave compound **20c** (786 mg, 42%) as an oil, $[\alpha]_D^{24}$ −4.7 (*c* 0.6, $CHCl_3$) [Found: m/z, 1269.347 (M − Bn$^+$). Calc. for $C_{63}H_{69}O_{20}P_4$: m/z, 1269.333]; δ_H($CDCl_3$, 360 MHz) 7.30–7.12 (40 H, m, 8 × CH_2Ph), 5.83 (1 H, dd, all *J* 2.6, H-2), 5.10–4.80 (19 H, m, 8 × CH_2Ph, H-1, -4 and -6), 4.50 (1 H, ddd, all *J* 9.9, H-5), 4.41 (1 H, ddd, *J* 2.6, 9.9 and 9.9, H-3), 2.31 (2 H, m, α-H_2), 2.01 (2 H, m, α-H_2), 1.63 (2 H, m, β-H_2), 1.44 (2 H, m, β-H_2), 0.95 (3 H, t, γ-H_3) and 0.79 (3 H, t, γ-H_3); δ_P($CDCl_3$; 145.8 MHz; ^{1}H decoupled) −0.51 (1 P, s), −0.67 (1 P, s), −1.39 (1 P, s) and −1.45 (1 P, s); m/z (FAB$^+$) 1361 (M + H$^+$, < 1%) and 91 (Bn$^+$, 100); (FAB$^-$) 1269 (M − Bn$^+$, 8%) and 277 [$OPO(OBn)_2^-$, 100].

D-2,3-Di-*O*-butyryl-*myo*-inositol 1,4,5,6-tetrakis(dibenzyl phosphate) *ent*-20c
Tetraol *ent*-**17** was phosphitylated and oxidized as described above for compound **20c** to give the fully protected phosphate *ent*-**20c**, $[\alpha]_D^{24}$ +4.6 (*c* 5.2, $CHCl_3$). Spectral data were identical with those of enantiomer **20c**.

D-1,2-Di-*O*-butyryl-*myo*-inositol 3,4,5,6-tetrakisphosphate 21c
Compound **20c** (548 mg, 403 µmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give title compound **21c** (254 mg, 98%) as a solid after freeze drying, mp 138–139 °C; $[\alpha]_D^{24}$ +38.6 (*c* 0.4, water, free acid) [Found: m/z, 639.0079 (M − H$^+$). Calc. for $C_{14}H_{27}O_{20}P_4$: m/z, 639.0046]; δ_H($CDCl_3$; 360 MHz) 5.68 (1 H, dd, all *J* 2.8, H-2), 5.13 (1 H, dd, *J* 10.0 and 2.8, H-1), 4.55 (1 H, ddd, *J* 10.0 and 9.5, H-6), 4.43 (1 H, ddd, *J* 9.0, 9.0 and 2.8, H-3), 4.40 (1 H, ddd, *J* 9.5, 9.0 and 9.0, H-4), 4.35 (1 H, ddd, all *J* 9.5, H-5), 2.48 (2 H, m, α-H_2), 2.32 (2 H, m, α-H_2), 1.65 (2 H, q, *J* 7.7, β-H_2), 1.54 (2 H, q, *J* 7.5, β-H_2), 0.93 (3 H, t, *J* 7.7, γ-H_3) and 0.85 (3 H, t, *J* 7.5, γ-H_3); δ_P($CDCl_3$; 145.8 MHz; ^{1}H decoupled) 1.38 (1 P, s), 1.31 (1 P, s), 0.82 (1 P, s) and −0.05 (1 P, s); m/z (FAB$^+$) 641 [M + H$^+$, 17%) and 71 (Bt$^+$, 100); (FAB$^-$) 639 (M − H$^+$, 100%), 569 (M − Bt$^+$, 8) and 559 [M − $PO(OH)_2^+$, 9].

D-2,3-Di-*O*-butyryl-*myo*-inositol 1,4,5,6-tetrakisphosphate *ent*-21c
The fully protected phosphate *ent*-**20c** was hydrogenated as described above for the other enantiomer to give compound *ent*-**21c**, $[\alpha]_D^{24}$ −40.3 (*c* 0.5, water, free acid). Spectral data were in accord with those obtained for enantiomer **21c**.

D-*myo*-Inositol 3,4,5,6-tetrakisphosphate 1c
Compound **21c** (230 mg, 359 µmol) was treated with 0.1 mol dm^{-3} KOH (43 cm^3) to adjust the pH to 12.8. The solution was stirred at room temperature for 2 days. The reaction mixture was directly poured onto an ion-exchange column (Dowex 50 WX 8, H$^+$) for purification. Lyophilization gave the title compound **1c** (165 mg, 92%) as a solid, mp 197–199 °C (lit.,[30] 200 °C); $[\alpha]_D^{24}$ −2.9 (*c* 0.3, water, pH 1.6); $[\alpha]_D^{24}$ −5.6 [*c* 0.2, water, pH 7 (NaOH)] {lit.,[30] $[\alpha]_D^{24}$ −10.5 [*c* 2.15, water, pH 9.5 (cyclohexylamine)]} [Found: m/z, 498.9138 (M − H$^+$). Calc. for $C_6H_{15}O_{18}P_4$: m/z, 498.9209]; δ_H(D_2O; 360 MHz; free acid) (lit.,[28] pH 10.7) 4.48 (1 H, ddd, all *J* 9.7, H-4), 4.36 (1 H, ddd, all *J* 9.5, H-6), 4.2 (3 H, m, H-2, -3 and -5) and 3.72 (1 H, dd, *J* 9.7 and 2.7, H-1); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 0.82 (1 P, s), 0.55 (2 P, br s) and −0.11 (1 P, s); m/z (FAB$^+$) 501 (M + H$^+$, 100%) and 403 [M − $OPO(OH)_2^-$, 6]; (FAB$^-$) 499 (M − H$^+$, 100%) and 419 [M − $PO(OH)_2^+$, 9].

D-*myo*-Inositol 1,4,5,6-tetrakisphosphate *ent*-1c
A similar reaction and work-up of compound *ent*-**21c** afforded the tetrakisphosphate *ent*-**1c**, $[\alpha]_D^{24}$ +8.0 [*c* 1.1, water, pH 7 (NaOH)]. Spectral data were identical with those of enantiomer **1c**.

D-1,2-Di-*O*-butyryl-*myo*-inositol 3,4,5,6-tetrakisphosphate octakis(acetoxymethyl ester) 2c
DIEA (170 mm^3, 129 mg, 1 mmol) and acetoxymethyl bromide (100 mm^3, 158 mg, 100 µmol) were added to a suspension of tetrakisphosphate **21c** (32 mg, 50 µmol) in dry

acetonitrile as described in the general procedures. Extraction with toluene afforded title compound **2c** (50 mg, 82%) as a syrup, $[\alpha]_D^{24}$ + 1.9 (*c* 1.9, toluene) [Found: *m/z*, 1143.141 (M − CH_2OAc^+). Calc. for $C_{35}H_{55}O_{34}P_4$: *m/z*, 1143.153]; δ_H([$^2H_8$]-toluene; 360 MHz) 6.01 (1 H, dd, all *J* 2.8, H-2), 5.59–5.60 (16 H, m, 8 × CH_2OAc), 5.75 (1 H, dd, *J* 9.5 and 2.8, H-1), 5.07 (1 H, ddd, all *J* 9.5, H-4), 4.97 (1 H, ddd, all *J* 9.5, H-6), 4.81 (1 H, ddd, *J* 9.5, 9.5 and 2.8, H-3), 4.79 (1 H, ddd, all *J* 9.5, H-5), 2.44 (2 H, m, α-H_2), 2.17 (2 H, m, α-H_2), 1.90–1.76 (24 H, 8 s, 8 × OAc), 1.70 (2 H, m, β-H_2), 1.60 (2 H, m, β-H_2), 0.95 (3 H, t, γ-H_3) and 0.88 (3 H, t, γ-H_3); δ_P([$^2H_8$]toluene; 145.8 MHz; ^{1}H decoupled) −3.56 (1 P, s), −3.82 (1 P, s), −4.40 (1 P, s) and −4.72 (1 P, s); *m/z* (FAB$^+$) 1217 (M + H$^+$, 13%), 1145 (M − CH_2OAc^+ + 2 H$^+$, 54) and 1073 (M − 2 CH_2OAc^+ + 3 H$^+$, 100); (FAB$^-$) 1143 (M − CH_2OAc^+, 24%) and 241 [OPO-$(OCH_2OAc)_2^-$, 100].

D-2,3-Di-*O*-butyryl-*myo*-inositol 1,4,5,6-tetrakisphosphate octakis(acetoxymethyl ester) *ent*-2c

Compound *ent*-**21c** was alkylated by the same method described above to give the acetoxymethyl ester *ent*-**2c**, $[\alpha]_D^{24}$ −1.8 (*c* 1.5, toluene). Mass spectra and NMR data were identical with those obtained for enantiomer **2c**.

D-3,4,5,6-Tetra-*O*-benzyl-1,2-di-*O*-methyl-*myo*-inositol 15

Methyl iodide (125 mm^3, 282 mg, 2 mmol) was added to a stirred solution of diol **5** (270 mg, 0.5 mmol) and KOH powder (224 mg, 4 mmol) in DMSO (1 cm^3) at room temperature. After 2.5 h, HPLC analysis (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 6.05 min) showed the reaction to be complete. The solvents were removed under reduced pressure. The residue was dissolved in *tert*-butyl methyl ether and was washed (twice) with 0.5 mol dm^{-3} phosphate buffer (10 cm^3), aq. sodium dithionite (10 cm^3) and water (10 cm^3) successively. The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the mixture gave pure **15** (225 mg, 90%) as a solid, mp 98 °C (Found: C, 76.1; H, 7.1. Calc. for $C_{36}H_{40}O_6$: C, 76.0; H, 7.1%); $[\alpha]_D^{24}$ +6.5 (*c* 0.9, $CHCl_3$); δ_H($CDCl_3$; 360 MHz) 7.40–7.23 (20 H, m, 4 × CH_2Ph), 4.92–4.71 (8 H, m, 4 × CH_2Ph), 3.98 (1 H, dd, all *J* 9.8, H-4), 3.90 (1 H, dd, all *J* 9.8, H-6), 3.83 (1 H, dd, all *J* 2.5, H-2), 3.67 (3 H, s, OMe-2), 3.51 (3 H, s, OMe-1), 3.44 (1 H, dd, all *J* 9.8, H-5), 3.37 (1 H, dd, *J* 9.8 and 2.5, H-3) and 3.09 (1 H, dd, *J* 9.8 and 2.5, H-1); *m/z* (FAB$^+$) 569 (M + H$^+$, 4%) and 91 (Bn$^+$, 100).

D-1,4,5,6-Tetra-*O*-benzyl-2,3-di-*O*-methyl-*myo*-inositol *ent*-15

Compound *ent*-**5** was methylated by the procedure described above to give *ent*-**15**, $[\alpha]_D^{21}$ −6.96 (*c* 1.0, $CHCl_3$). Mass spectra and NMR data were identical with those obtained for enantiomer **15**.

D-1,2-Di-*O*-methyl-*myo*-inositol 18

Compound **15** (240 mg, 422 μmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give tetraol **18** (87 mg, 99%) as a solid after freeze drying, mp 154 °C (Found: C, 46.1; H, 7.8. Calc. for $C_8H_{16}O_6$: C, 46.15; H, 7.75%); $[\alpha]_D^{22}$ +14.9 (*c* 0.4, MeOH); δ_H(CD_3OD; 360 MHz) 3.80 (1 H, dd, all *J* 2.5, H-2), 3.61 (1 H, dd, all *J* 10.0, H-4), 3.56 (3 H, s, OMe-2), 3.53 (1 H, dd, all *J* 10.0, H-6), 3.47 (3 H, s, OMe-1), 3.33 (1 H, dd, *J* 10.0 and 2.5, H-3), 3.12 (1 H, dd, all *J* 10.0, H-5) and 3.02 (1 H, dd, *J* 10.0 and 2.5, H-1); *m/z* (FAB$^+$) 209 (M + H$^+$, 100); (FAB$^-$) 207 (M − H$^+$, 100).

D-2,3-Di-*O*-methyl-*myo*-inositol *ent*-18

Debenzylation of compound *ent*-**15** was carried out by the method described above to give *ent*-**18**, $[\alpha]_D^{21}$ −17.38 (*c* 1.2, MeOH). Mass spectra and NMR data were identical with those obtained for enantiomer **18**.

D-1,2-Di-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakis(dibenzyl phosphate) 20d

A solution of compound **18** (81 mg, 165 μmol) and tetrazole (427 mg, 6.1 mmol) in acetonitrile (2 cm^3) was treated with dibenzyl *N*,*N*-diethylphosphoramidite (1.94 mg, 6.1 mmol) for 3 days, oxidized with peracetic acid, and worked up as described in the general procedures. Purification by preparative HPLC (90% MeOH; 30 cm^3 min^{-1}; t_R = 34.15 min) gave title compound **20d** (206 mg, 43%) as an oil, $[\alpha]_D^{21}$ −6.5 (*c* 0.5, $CHCl_3$); δ_H($CDCl_3$; 360 MHz) 7.34–7.12 (40 H, m, 8 × CH_2Ph), 5.10–4.91 (16 H, m, 8 × CH_2Ph), 4.97 (1 H, ddd, all *J* 9.5, H-4), 4.80 (1 H, ddd, all *J* 9.5, H-6), 4.50 (1 H, ddd, all *J* 9.5, H-5), 4.21 (1 H, dd, all *J* 2.5, H-2), 4.17 (1 H, ddd, *J* 9.5, 7.2 and 2.5, H-3), 3.52 (3 H, s, OMe-2), 3.26 (3 H, s, OMe-1) and 3.18 (1 H, dd, *J* 9.5 and 2.5, H-1); δ_P($CDCl_3$; 145.8 MHz; ^{1}H decoupled) −0.79 (1 P, s), −0.89 (1 P, s), −1.67 (1 P, s) and −1.78 (1 P, s); *m/z* (FAB$^+$) 1249 (M + H$^+$, 1%) and 91 (Bn$^-$, 100); (FAB$^-$) 1157 (M − Bn$^+$, 12%) and 277 [$(BnO)_2PO^-$, 100].

D-2,3-Di-*O*-methyl-*myo*-inositol 1,4,5,6-tetrakis(dibenzyl phosphate) *ent*-20d

Compound *ent*-**18** was phosphorylated as described above to give compound *ent*-**20d**, $[\alpha]_D^{21}$ +5.23 (*c* 0.7, $CHCl_3$). Mass spectra and NMR data were identical with those obtained for enantiomer **20d**.

D-1,2-Di-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakisphosphate 1d

Compound **20d** (191 mg, 153 μmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give compound **1d** (80 mg, 99%) as a solid after freeze drying, $[\alpha]_D^{21}$ +6.0 (*c* 0.3, water, free acid) [Found: *m/z*, 526.9561 (M − H$^+$). Calc. for $C_8H_{19}O_{18}P_4$: *m/z*, 526.9522]; δ_H(D_2O; 360 MHz; free acid) 4.45 (1 H, ddd, all *J* 9.5, H-4), 4.34 (1 H, ddd, all *J* 9.5, H-6), 4.27–4.13 (3 H, m, H-2, -3 and -5), 3.58 (3 H, s, OMe-2), 3.46 (3 H, s, OMe-1) and 3.45 (1 H, dd, *J* 9.5 and 2.8, H-1); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 1.2 (1 P, s), 0.5 (1 P, s) and 0.1 (2 P, s); *m/z* (FAB$^+$) 529 (M + H$^+$, 100%) and 431 [M − $OPO(OH)_2^-$, 4)]; (FAB$^-$) 527 (M − H$^+$, 100%) and 447 [M − $PO(OH)_2^+$, 6].

D-2,3-Di-*O*-methyl-*myo*-inositol 1,4,5,6-tetrakisphosphate *ent*-1d

In a similar reaction compound *ent*-**20d** was hydrogenated to give the tetrakisphosphate *ent*-**1d**, $[\alpha]_D^{21}$ −4.5 (*c* 0.4, water). Mass spectra and NMR data were identical with those obtained for enantiomer **1d**.

D-1,2-Di-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakisphosphate octakis(acetoxymethyl ester) 2d

DIEA (136 mm^3, 103 mg, 800 μmol) and acetoxymethyl bromide (116 mm^3, 183 mg, 1.2 mmol) was added to a suspension of tetrakisphosphate **1d** (26 mg, 50 μmol) in acetonitrile (1 cm^3) as described in the general procedures. Extraction with toluene afforded compound **2d** (17 mg, 30%) as a syrup, $[\alpha]_D^{21}$ +0.5 (*c* 0.6, toluene) [Found: *m/z*, 1031.095 (M − CH_2OAc^+). Calc. for $C_{29}H_{47}O_{32}P_4$: *m/z*, 1031.100]; δ_H([$^2H_8$]toluene; 360 MHz) 5.92–5.60 (16 H, m, 8 × CH_2OAc), 4.99 (1 H, ddd, all *J* 9.5, H-4), 4.85 (1 H, ddd, all *J* 9.5, H-6), 4.59 (1 H, ddd, all *J* 9.5, H-5), 4.39 (1 H, ddd, *J* 9.5, 7.5 and 2.5, H-3), 4.19 (1 H, dd, all *J* 2.5, H-2), 3.48 (3 H, s, OMe-2), 3.21 (3 H, s, OMe-1), 2.85 (1 H, dd, *J* 9.5 and 2.5, H-1) and 1.82–1.73 (24 H, 8 s, 8 × OAc); δ_P([$^2H_8$]toluene; 145.8 MHz; ^{1}H decoupled) −3.48 (1 P, s), −3.84 (1 P, s), −4.07 (1 P, s) −5.30 (1 P, s); *m/z* (FAB$^+$) 1105 (M + H$^+$, 76%), 1033 (M − CH_2OAc^+ + 2 H$^+$, 88) and 961 (M − 2 CH_2OAc^+ + 3 H$^+$, 100); (FAB$^-$) 1031 (M − CH_2OAc^+, 41%) and 241 [$OPO(OCH_2OAc)_2^-$, 100].

D-2,3-Di-*O*-methyl-*myo*-inositol 1,4,5,6-tetrakisphosphate octakis(acetoxymethyl ester) *ent*-2d

Compound *ent*-**1d** was alkylated by the same method described above to give the acetoxymethyl ester *ent*-**2d**, $[\alpha]_D^{21}$ −0.7 (*c* 1.0, toluene). Mass spectra and NMR data were identical with those obtained for enantiomer **2d**.

DL-3,4,5,6-Tetra-*O*-benzyl-1,2-dichloro-1,2-dideoxy-*myo*-inositol *rac*-16

Compound *rac*-**5** (900 mg, 1.67 mmol) and triphenylphosphine were heated to reflux in CCl_4 (20 cm^3). After 3 days HPLC analysis (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 7.35 min) showed no further reaction. The mixture was cooled to room temperature and CCl_4 was evaporated off. The residue was dissolved in CH_2Cl_2, and the solution was washed with water, dried over $MgSO_4$, and filtered. After evaporation of the organic layer the crude product was purified by preparative HPLC (90% MeOH; 30 cm^3 min^{-1}; t_R = 52.00 min) to give dichloride *rac*-**16** (598 mg, 62%) as a solid, mp 94 °C (Found: C, 70.6; H, 5.9; Cl, 12.3. Calc. for $C_{34}H_{34}Cl_2O_4$: C, 70.7; H, 5.9; Cl, 12.3%); δ_H($CDCl_3$; 360 MHz) 7.45–7.32 (20 H, m, 4 × CH_2*Ph*), 5.02–4.86 (6 H, m, 3 × *C*H_2Ph), 4.74 (2 H, dd, *C*H_2Ph), 4.57 (1 H, dd, all *J* 3.0, H-2), 4.13 (1 H, dd, all *J* 9.5, H-4), 4.07 (1 H, dd, *J* 9.5 and 3.0, H-1), 4.03 (1 H, dd, all *J* 9.5, H-6), 3.66 (1 H, dd, *J* 9.5 and 3.0, H-3) and 3.55 (1 H, dd, all *J* 9.5, H-5); *m/z* (FAB^+) 576 (M + H^+, 2%) and 91 (Bn^+, 100); (FAB^-) 611 (M + Cl^-, 100%) and 485 (M − Bn^+, 17).

DL-1,2-Dichloro-1,2-dideoxy-*myo*-inositol *rac*-19

Compound *rac*-**16** (0.52 g, 0.91 mmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give *rac*-**19** (195 mg, 99%) as a solid after freeze drying, mp 193 °C (Found: C, 34.0; H, 5.6. Calc. for $C_6H_{10}Cl_2O_4$: C, 33.2; H, 4.6%); δ_H(D_2O; 360 MHz) 4.61 (1 H, dd, all *J* 3.0, H-2), 4.19 (1 H, dd, *J* 10.5 and 3.0, H-1), 3.82–3.70 (3 H, m, H-3, -4 and -6) and 3.30 (1 H, dd, all *J* 9.2, H-5); *m/z* (FAB^-) 251 (M + Cl^-, 100%) and 215 (M − H^+, 77).

DL-1,2-Dichloro-1,2-dideoxy-*myo*-inositol 3,4,5,6-tetrakis-(dibenzyl phosphate) *rac*-20e

A solution of *rac*-**19** (0.1 g, 0.46 mmol) and tetrazole (0.9 g, 12.8 mmol) in acetonitrile (7 cm^3) was treated with dibenzyl *N,N*-diethylphosphoramidite (4.1 g, 12 mmol) for 2 days, oxidized with peracetic acid and worked up as described in the general procedures. Purification by preparative HPLC (90% MeOH; 30 cm^3 min^{-1}; t_R = 43.40 min) gave compound *rac*-**20e** (399 mg, 69%) as an oil [Found: *m/z*, 1165.180 (M − Bn^+). Calc. for $C_{55}H_{55}Cl_2O_{16}P_4$: *m/z*, 1165.182]; δ_H($CDCl_3$; 360 MHz) 7.36–7.13 (40 H, m, 8 × CH_2*Ph*), 5.10–4.90 (18 H, m, 8 × *C*H_2Ph, H-4 and -6), 4.82 (1 H, dd, all *J* 3.0, H-2), 4.51 (1 H, ddd, *J* 11.5, 8.8 and 2.5, H-5), 4.38 (1 H, ddd, *J* 10.0, 3.0 and 2.5, H-3) and 4.09 (1 H, dd, *J* 10.0 and 3.0, H-1); δ_P($CDCl_3$; 145.8 MHz; ^{1}H decoupled) 0.96 (1 P, s), −1.15 (1 P, s), −1.70 (1 P, s) and −1.79 (1 P, s); *m/z* (FAB^+) 1257 (M + H^+, < 1%) and 91 (Bn^+, 100); (FAB^-) 1255 (M − H^+, 1%), 1165 (M − Bn^+, 7) and 277 [$OPO(OBn)_2^-$, 100].

DL-1,2-Dichloro-1,2-dideoxy-*myo*-inositol 3,4,5,6-tetrakis-phosphate *rac*-1e

Compound *rac*-**20e** (0.32 g, 0.25 mmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give compound *rac*-**1e** (133 mg, 99%) as a solid after freeze drying [Found: *m/z*, 534.8554 (M − H^+). Calc. for $C_6H_{13}Cl_2O_{16}P_4$: *m/z*, 534.8531]; δ_H(D_2O; 360 MHz; free acid) 4.81 (1 H, dd, all *J* 3.0, H-2), 4.60 (2 H, 2 ddd, all *J* 9.5, H-4 and -6), 4.46 (1 H, dd, *J* 9.5 and 3.0, H-1), 4.44 (1 H, ddd, *J* 9.5, 9.5 and 3.0, H-3) and 4.31 (1 H, ddd, all *J* 9.5, H-5); δ_P(D_2O; 145.8 MHz; ^{1}H decoupled) 1.15 (1 P, s), 0.47 (1 P, s), −0.27 (1 P, s) and −0.46 (1 P, s); *m/z* (FAB^+) 537 (M + H^+, 100%); (FAB^-) 535 (M − H^+, 100%) and 455 [M − $PO(OH)_2^+$, 11].

DL-1,2-Dichloro-1,2-dideoxy-*myo*-inositol 3,4,5,6-tetrakis-phosphate octakis(acetoxymethyl ester) *rac*-2e

DIEA (0.17 cm^3, 129 mg, 1 mmol) and acetoxymethyl bromide (100 mm^3, 158 mg, 1 mmol) were added to a suspension of *rac*-**1e** (21 mg, 40 µmol) in acetonitrile (0.5 cm^3) as described in the general procedures. Extraction with toluene afforded compound *rac*-**2e** (31 mg, 70%) as a syrup, δ_H([$^2H_8$]toluene; 360 MHz) 5.96–5.61 (16 H, m, 8 × *C*H_2OAc), 5.14 (1 H, ddd, *J* 9.0, 9.0 and 3.0, H-3), 5.05 (2 H, 2 ddd, all *J* 9.0, H-4 and -6), 4.98 (1 H, dd, all *J* 3.0, H-2), 4.88 (1 H, ddd, all *J* 9.0, H-5), 4.43 (1 H, dd, *J* 9.0 and 3.0, H-1) and 1.85–1.73 (24 H, 8 s, 8 × OAc); δ_P([$^2H_8$]toluene; 145.8 MHz; ^{1}H decoupled) −3.67 (1 P, s), −3.78 (1 P, s), −4.08 (1 P, s) and −5.16 (1 P, s); *m/z* (FAB^+) 1113 (M + H^+, 16%), 1041 (M − CH_2OAc^+ + 2 H^+, 60) and 969 (M − 2 CH_2OAc^+ + 3 H^+, 100); (FAB^-) 1039 (M − CH_2OAc^+, 32%) and 241 [$OPO(OCH_2OAc)_2^-$, 100].

D-3,4,5,6-Tetra-*O*-benzyl-1-*O*-methyl-*myo*-inositol 6

Compound **5** (1.1 g, 2 mmol) and dibutyltin oxide (498 mg, 2 mmol) were heated to reflux in dry methanol (50 cm^3) in a Soxhlet apparatus filled with activated molecular sieves (3 Å) for 20 h. The reaction mixture was cooled to room temperature and the methanol was evaporated off under reduced pressure to give a syrup. The syrup was dissolved in dry DMF (20 cm^3) under argon, methyl iodide (0.5 cm^3, 1.135 g, 8 mmol) was added, and the solution was stirred at 50 °C. After 2 days, HPLC analysis (85% MeOH; 1.5 cm^3 min^{-1}; t_R = 8.24 min) showed no further reaction. Excess of methyl iodide and DMF were removed under reduced pressure. The crude product was extracted with *tert*-butyl methyl ether (50 cm^3) and washed successively with aq. sodium dithionite (25% w/v; 10 cm^3, ×2) and water (10 cm^3, ×2). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was chromatographed on silica gel [ethyl acetate–light petroleum (1:2)] to give the title compound **6** (773 mg, 72%) as a solid, mp 119–120 °C (from MeOH) (lit.,[31] **6**, 110–112 °C) (Found: C, 75.9; H, 7.0. Calc. for $C_{35}H_{38}O_6$: C, 75.8; H, 6.9%); $[\alpha]_D^{20}$ +2.6 (*c* 1.0, $CHCl_3$); δ_H($CDCl_3$; 360 MHz) 7.42–7.27 (20 H, m, 4 × CH_2*Ph*), 4.91–4.71 (8 H, m, 4 × *C*H_2Ph), 4.30 (1 H, dd, all *J* 3, H-2), 3.98 (1 H, dd, all *J* 9.5, H-4), 3.98 (1 H, dd, all *J* 9.5, H-6), 3.52 (3 H, s, OMe), 3.45 (1 H, dd, all *J* 9.5, H-5), 3.42 (1 H, dd, *J* 9.5 and 3.0, H-3), 3.14 (1 H, dd, *J* 9.5 and 3.0, H-1) and 2.46 (1 H, s, OH); *m/z* (FAB^+) 555 (M + H^+, 1%) and 91 (Bn^+, 100); (FAB^-) 553 (M − H^+, 100%) and 463 (M − Bn^+, 40).

D-1,4,5,6-Tetra-*O*-benzyl-3-*O*-methyl-*myo*-inositol *ent*-6

A similar reaction and work-up of the diol *ent*-**5** gave compound *ent*-**6**, mp 115–116 °C (from MeOH) (lit.,[31] *ent*-**6**, 115–116 °C); $[\alpha]_D^{20}$ −2.6 (*c* 0.6, $CHCl_3$). Spectral data were identical with those obtained for enantiomer **6**.

D-3,4,5,6-Tetra-*O*-benzyl-2-*O*-butyryl-1-*O*-methyl-*myo*-inositol 7

A solution of alcohol **6** (472 mg, 850 µmol) in dry pyridine (5 cm^3) was treated with butyric anhydride (1 cm^3, 970 mg, 6.1 mmol) and stirred at 50 °C. When HPLC analysis (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 8.15 min) showed no more starting material (2 days), the reaction mixture was evaporated under reduced pressure to give a crude oil. To remove residual pyridine the oil was dissolved in octane and evaporated three times. The oil was purified on silica gel [ethyl acetate–light petroleum (1:1)] to give compound **7** (504 mg, 95%) as an oil, $[\alpha]_D^{20}$ −13.3 (*c* 1.0, $CHCl_3$) [Found: *m/z*, 625.3169 (M + H^+). Calc. for $C_{39}H_{45}O_7$: *m/z*, 625.3165]; δ_H($CDCl_3$; 360 MHz) 7.38–7.27 (20 H, m, 4 × CH_2*Ph*), 5.85 (1 H, dd, all *J* 3, H-2), 4.90–4.51 (8 H, m, 4 × *C*H_2Ph), 3.85 (1 H, dd, all *J* 9.5, H-4), 3.81 (1 H, dd, all *J* 9.5, H-6), 3.49 (1 H, dd, all *J* 9.5, H-5), 3.49 (1 H, dd, *J* 9.5 and 3.0, H-3), 3.46 (3 H, s, OMe), 3.22 (1 H, dd, *J* 9.5 and 3.0, H-1), 2.39 (2 H, t, *J* 7.5, α-H_2), 1.69 (2 H, m, β-H_2) and 0.97 (3 H, t, *J* 7.5, γ-H_3); *m/z* (FAB^+) 625 (M + H^+, 1%) and 91 (Bn^+, 100).

D-1,4,5,6-Tetra-*O*-benzyl-2-*O*-butyryl-3-*O*-methyl-*myo*-inositol *ent*-7
Compound *ent*-6 was butyrylated as described above for the other enantiomer to give compound *ent*-7, $[\alpha]_D^{20}$ +14.0 (*c* 0.5, $CHCl_3$). Spectral data were in accord with those of enantiomer **7**.

D-2-*O*-Butyryl-1-*O*-methyl-*myo*-inositol 8
Compound **7** (497 mg, 795 µmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give compound **8** (207 mg, 98%) as a solid after freeze drying, mp 158–159 °C (Found: C, 49.75; H, 7.7. Calc. for $C_{11}H_{20}O_7$: C, 50.0; H, 7.6%); $[\alpha]_D^{20}$ +16.4 (*c* 1.5, MeOH); δ_H(CD_3OD; 360 MHz) 5.60 (1 H, dd, all *J* 3.0, H-2), 3.54 (3 H, m, H-3, -4 and -6), 3.39 (3 H, s, OMe), 3.22 (1 H, dd, all *J* 9.5, H-5), 3.15 (1 H, dd, *J* 9.5 and 3.0, H-1), 2.35 (2 H, t, *J* 7.5, α-H_2), 1.65 (2 H, m, β-H_2) and 0.97 (3 H, t, *J* 7.5, γ-H_3); *m*/*z* (FAB^+) 265 ($M + H^+$, 100%) and 177 ($M - BtO^-$, 7); (FAB^-) 527 ($2M - H^+$, 4%), 263 ($M - H^+$, 1) and 87 (BtO^-, 100).

D-2-*O*-Butyryl-3-*O*-methyl-*myo*-inositol *ent*-8
Tetraol *ent*-**8** was prepared by hydrogenolysis of substrate *ent*-**7** as described above, mp 155 °C; $[\alpha]_D^{20}$ −17.0 (*c* 1.3, MeOH). Mass spectra and NMR data were identical with those obtained for enantiomer **8**.

D-2-*O*-Butyryl-1-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakis-(dibenzyl phosphate) 20a
A solution of compound **8** (79 mg, 300 µmol) and tetrazole (336 mg, 4.8 mmol) in acetonitrile (10 cm^3) was treated with dibenzyl *N*,*N*-diethylphosphoramidite (1.52 g, 4.8 mmol) for 3 days, oxidized with peracetic acid, and worked up as described in the general procedures. Purification by preparative HPLC (90% MeOH; 30 cm^3 min^{-1}; t_R = 48.50 min) gave compound **20a** (209 mg, 53%) as an oil, $[\alpha]_D^{20}$ −5.6 (*c* 0.5, $CHCl_3$) [Found: *m*/*z*, 1213.306 ($M - Bn^+$). Calc. for $C_{60}H_{65}O_{19}P_4$: *m*/*z*, 1213.307]; δ_H($CDCl_3$; 360 MHz) 7.37–7.06 (40 H, m, 8 × CH_2*Ph*), 5.93 (1 H, dd, all *J* 3.0, H-2), 5.10–4.87 (17 H, m, 8 × CH_2Ph and H-4), 4.68 (1 H, ddd, all *J* 9.5, H-6), 4.55 (1 H, ddd, all *J* 9.5, H-5), 4.36 (1 H, ddd, *J* 9.5, 8.0 and 3.0, H-3), 3.28 (1 H, dd, *J* 9.5 and 3.0, H-1), 3.20 (3 H, s, OMe), 2.31 (2 H, m, α-H_2), 1.62 (2 H, m, β-H_2) and 0.92 (3 H, t, *J* 7.5, γ-H_3); δ_P($CDCl_3$; 145.8 MHz; ^{1}H decoupled) −0.70 (1 P, s), −1.11 (1 P, s) and −1.68 (2 P, s); *m*/*z* (FAB^+) 1305 ($M + H^+$, 2%) and 91 (Bn^+, 100); (FAB^-) 1213 ($M - Bn^+$, 10%) and 277 [$OPO(OBn)_2^-$, 100].

D-2-*O*-Butyryl-3-*O*-methyl-*myo*-inositol 1,4,5,6-tetrakis-(dibenzyl phosphate) *ent*-20a
Tetraol *ent*-**8** was phosphitylated and oxidized as described above for compound **20c** to give the fully protected phosphate *ent*-**20a**, $[\alpha]_D^{20}$ +8.7 (*c* 1.0, $CHCl_3$). Spectral data were identical with those of enantiomer **20a**.

D-2-*O*-Butyryl-1-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakis-phosphate 21a
Compound **20a** (122 mg, 93 µmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give compound **21a** (54 mg, 99%) as a solid after freeze drying, $[\alpha]_D^{20}$ +4.3 [*c* 1.1, water, pH 1.6 (free acid)] [Found: *m*/*z*, 582.9839 ($M - H^+$). Calc. for $C_{11}H_{23}O_{19}P_4$: *m*/*z*, 582.9784]; δ_H(D_2O; 360 MHz; free acid) 5.83 (1 H, dd, all *J* 3.0, H-2), 4.55 (1 H, ddd, all *J* 9.5, H-4), 4.43 (1 H, ddd, all *J* 9.5, H-6), 4.37 (1 H, ddd, *J* 9.5, 9.5 and 3.0, H-3), 4.35 (1 H, ddd, all *J* 9.5, H-5), 3.64 (1 H, dd, *J* 9.5 and 3.0, H-1), 3.43 (3 H, s, OMe), 2.48 (2 H, m, α-H_2), 1.65 (2 H, m, β-H_2) and 0.93 (3 H, t, *J* 7.5, γ-H_3); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 1.4 (1 P, s), 0.9 (1 P, s) and 0.4 (2 P, s); *m*/*z* (FAB^+) 585 ($M + H^+$, 100%) and 487 [$M - OPO(OH)_2^-$, 3]; (FAB^-) 583 ($M - H^+$, 100%) and 513 ($M - Bt^+$, 1).

D-2-*O*-Butyryl-3-*O*-methyl-*myo*-inositol 1,4,5,6-tetrakis-phosphate *ent*-21a
A similar reaction with the fully protected substrate *ent*-**20a** afforded the free acid *ent*-**21a** after freeze drying, $[\alpha]_D^{20}$ +11.8 [*c* 1.1, water, pH 10 (KOH)]. Spectral data were in accord with those obtained for enantiomer **21a**.

D-1-*O*-Methyl-*myo*-inositol 3,4,5,6-tetrakisphosphate 1a
Compound **21a** (14 mg, 24 µmol) was treated with 0.1 mol dm^{-3} KOH (5.19 cm^3) to adjust the pH to 12.8. The solution was stirred at room temperature for 1 day. The reaction mixture was directly poured onto an ion-exchange column (Dowex 50 WX 8, H^+) for purification. Lyophilization gave the title compound **1a** (9 mg, 73%) as a solid, $[\alpha]_D^{20}$ +2.7 (*c* 0.5, water, free acid) [Found: *m*/*z*, 512.9330 ($M - H^+$). Calc. for $C_7H_{17}O_{18}P_4$: *m*/*z*, 512.9365]; δ_H(D_2O; 360 MHz; free acid) 4.51 (1 H, ddd, all *J* 9.5, H-4), 4.45 (1 H, dd, all *J* 2.8, H-2), 4.42 (1 H, ddd, all *J* 9.5, H-6), 4.27 (1 H, ddd, all *J* 9.5, H-5), 4.21 (1 H, ddd, *J* 9.5, 9.5 and 2.8, H-3), 3.43 (1 H, dd, *J* 9.5 and 2.8, H-1) and 3.42 (3 H, s, OMe); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 1.3 (1 P, s), 0.9 (1 P, s) and 0.4 (2 P, s); *m*/*z* (FAB^+) 515 ($M + H^+$, 100%) and 417 [$M - OPO(OH)_2^-$, 14]; (FAB^-) 513 ($M - H^+$, 100%) and 433 [$M - PO(OH)_2^+$, 12].

D-3-*O*-Methyl-*myo*-inositol 1,4,5,6-tetrakisphosphate *ent*-1a
The butyryl groups of substrate *ent*-**21a** were hydrolysed by the same method described above to give the tetrakisphosphate *ent*-**1a**, $[\alpha]_D^{20}$ −2.5 (*c* 0.6, water, free acid). Mass spectra and NMR data were identical with those of enantiomer **1a**.

D-2-*O*-Butyryl-1-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakis-phosphate octakis(acetoxymethyl ester) 2a
DIEA (136 mm^3, 103 mg, 800 µmol) and acetoxymethyl bromide (116 mm^3, 184 mg, 1.2 mmol) were added to a suspension of compound **21a** (28 mg, 48 µmol) in acetonitrile (1 cm^3) as described in the general procedures. Extraction with toluene afforded compound **2a** (50 mg, 90%) as a syrup, $[\alpha]_D^{20}$ −3.9 (*c* 0.9, toluene) [Found: *m*/*z*, 1087.126 ($M - CH_2OAc^+$). Calc. for $C_{32}H_{51}O_{33}P_4$: *m*/*z*, 1087.126]; δ_H([$^2H_8$]toluene; 360 MHz) 6.05 (1 H, dd, all *J* 3.0, H-2), 5.97–5.68 (16 H, m, 8 × CH_2OAc), 5.06 (1 H, ddd, all *J* 9.5, H-4), 4.88–4.27 (3 H, m, H-3, -5 and -6), 3.38 (3 H, s, OMe), 3.21 (1 H, m, H-1), 2.09 (2 H, m, α-H_2), 1.86–1.75 (24 H, 8 s, 8 × OAc), 1.55 (2 H, m, β-H_2) and 0.84 (3 H, t, *J* 7.5, γ-H_3); δ_P([$^2H_8$]toluene; 145.8 MHz; ^{1}H decoupled) −3.66 (1 P, s), −3.72 (1 P, s), −4.07 (1 P, s) and −4.80 (1 P, s); *m*/*z* (FAB^+) 1161 ($M + H^+$, 33%), 1089 ($M - CH_2OAc^+ + 2H^+$, 61) and 1017 ($M - 2CH_2OAc^+ + 3H^+$, 100); (FAB^-) 1087 ($M - CH_2OAc^+$, 21%) and 241 [$OPO(OCH_2OAc)_2^-$, 100].

D-2-*O*-Butyryl-3-*O*-methyl-*myo*-inositol 1,4,5,6-tetrakis-phosphate octakis(acetoxymethyl ester) *ent*-2a
Alkylation of the phosphate *ent*-**21a** as described above afforded the octakis(acetoxymethyl ester) *ent*-**2a**, $[\alpha]_D^{20}$ +4.2 (*c* 0.8, toluene). Spectral data were identical with those obtained for enantiomer **2a**.

DL-3,4,5,6-Tetra-*O*-benzyl-1-*O*-(4-methoxybenzyl)-*myo*-inositol *rac*-9
Compound *rac*-**5** (1.1 g, 2 mmol) and dibutyltin oxide (498 mg, 2 mmol) were heated to reflux in dry methanol (80 cm^3) in a Soxhlet apparatus filled with activated molecular sieve (3 Å) for 20 h. The reaction mixture was cooled to room temperature and the methanol was evaporated off under reduced pressure to give a syrup. The intermediate product was dissolved in dry DMF (20 cm^3) under argon and *p*-methoxybenzyl chloride (1.621 cm^3, 2.496 g, 16 mmol) was added. After the solution had been stirred at 50 °C for 2.5 h, HPLC analysis (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 5.35 min) showed no further reaction. Excess of

p-methoxybenzyl chloride and DMF were removed in high vacuum. The crude product was chromatographed by preparative HPLC (90% MeOH; 40 cm^3 min^{-1}; t_R = 30.30 min) to give the title compound *rac*-**9** (1.0 g, 76%) as a solid, mp 128–129 °C (lit.,[20] 126–127 °C) (Found: C, 76.5; H, 6.9. Calc. for $C_{42}H_{44}O_7$: C, 76.3; H, 6.7%); δ_H($CDCl_3$; 360 MHz) 7.39–7.26 (22 H, m, 4 × CH_2*Ph* and PMB ArH), 6.87 (2 H, d, PMB ArH), 4.95–4.83 (6 H, m, 3 × CH_2Ph), 4.73 (2 H, s, CH_2Ph-3), 4.65 (2 H, s, CH_2 in PMB), 4.22 (1 H, dd, all *J* 2.8, H-2), 4.02 (1 H, dd, all *J* 9.5, H-4), 3.99 (1 H, dd, all *J* 9.5, H-6), 3.82 (3 H, s, OMe), 3.47 (1 H, dd, all *J* 9.5, H-5), 3.40 (1 H, dd, *J* 9.5 and 2.8, H-3) and 3.38 (1 H, dd, *J* 9.5 and 2.8, H-1); *m/z* (FAB^-) 659 (M – H^+, 100%), 569 (M – Bn^+, 42) and 539 (M – PMB^+, 37).

DL-3,4,5,6-Tetra-*O*-benzyl-1-*O*-(4-methoxybenzyl)-2-*O*-methyl-*myo*-inositol *rac*-10

A solution of alcohol *rac*-**9** (427 mg, 646 μmol) in DMSO (1 cm^3) was treated with KOH powder (150 mg, 2.7 mmol) and methyl iodide (81 mm^3, 185 mg, 1.3 mmol). After the reaction mixture had been stirred at room temperature for 2 h, no starting material could be detected by HPLC (95% MeOH; 1.5 cm^3 min^{-1}; t_R = 4.25 min). Excess of methyl iodide and DMSO were evaporated off under reduced pressure. The mixture was then dissolved in *tert*-butyl methyl ether and washed twice with 0.5 mol dm^{-3} phosphate buffer (10 cm^3), aq. sodium dithionite (10 cm^3) and water (10 cm^3) successively. The organic layer was dried over Na_2SO_4, filtered, and the ether was evaporated off to give an oil. The crude oil was purified by preparative HPLC (95% MeOH; 40 cm^3 min^{-1}; t_R = 26.05 min) to give the title compound *rac*-**10** (359 mg, 82%) as a solid, mp 79 °C (Found: C, 76.4; H, 6.9. Calc. for $C_{43}H_{46}O_7$: C, 76.5; H, 6.9%); δ_H($CDCl_3$; 360 MHz) 7.38–7.24 (22 H, m, 4 × CH_2*Ph* and PMB ArH), 6.87 (2 H, d, PMB ArH), 4.96–4.58 (10 H, m, 4 × CH_2Ph and CH_2 in PMB), 3.99 (1 H, dd, all *J* 9.5, H-4), 3.97 (1 H, dd, all *J* 9.5, H-6), 3.83 (3 H, s, OMe), 3.70 (1 H, dd, all *J* 2.5, H-2), 3.66 (3 H, s, OMe-2), 3.44 (1 H, dd, all *J* 9.5, H-5), 3.33 (1 H, dd, *J* 9.5 and 2.5, H-3) and 3.31 (1 H, dd, *J* 9.5 and 2.5, H-1); *m/z* (FAB^+) 675 (M + H^+, 3%) and 121 (PMB^+, 100); (FAB^-) 583 ([M – Bn^+]$^-$, 100%) and 553 (M – PMB^-, 22).

DL-3,4,5,6-Tetra-*O*-benzyl-2-*O*-methyl-*myo*-inositol *rac*-11

DDQ (147 mg, 648 μmol) was added to a solution of *rac*-**10** (291 mg, 432 μmol) in CH_2Cl_2 (4 cm^3) containing small amounts of water (5%). After the suspension had been stirred at room temperature for 30 min HPLC analysis (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 4.44 min) showed the reaction to be complete. The reaction mixture was evaporated under reduced pressure and purified by preparative HPLC (92% MeOH; 40 cm^3 min^{-1}; t_R = 20.05 min) to give *rac*-**11** (144 mg, 60%) as a solid, mp 121 °C (lit.,[32] *ent*-**11**, 135–137.5 °C) (Found: C, 75.5; H, 6.8. Calc. for $C_{35}H_{38}O_6$: C, 75.8; H, 6.9%); δ_H($CDCl_3$; 360 MHz) 7.38–7.26 (20 H, m, 4 × CH_2*Ph*), 4.96–4.72 (8 H, m, 4 × CH_2Ph), 3.97 (1 H, dd, all *J* 9.8, H-4), 3.79 (1 H, dd, all *J* 2.5, H-2), 3.76 (1 H, dd, all *J* 9.8, H-6), 3.67 (3 H, s, OMe), 3.47 (1 H, ddd, *J* 9.8, 5.5 and 2.5, H-1), 3.46 (1 H, dd, all *J* 9.8, H-5), 3.44 (1 H, dd, *J* 9.5 and 2.5, H-3) and 2.33 (1 H, d, *J* 5.5, OH); *m/z* (FAB^+) 555 (M + H^+, 2%) and 91 (Bn^+, 100); (FAB^-) 553 (M – H^+, 100%) and 463 (M – Bn^-, 42).

DL-3,4,5,6-Tetra-*O*-benzyl-1-*O*-butyryl-2-*O*-methyl-*myo*-inositol *rac*-12

A solution of dried alcohol *rac*-**11** (138 mg, 248 μmol), butyric anhydride (408 mm^3, 395 mg, 2.5 mmol) and DMAP (3 mg, 25 μmol) in pyridine (1.25 cm^3) was stirred at room temperature until no starting material could be detected (1.5 h) by HPLC (90% MeOH; 1.5 cm^3; t_R = 3.25 min). The solvents were evaporated off under high vacuum to give an oil. Residual pyridine was removed by evaporation three times with octane. The residue was dissolved in *tert*-butyl methyl ether and was washed twice with 0.5 mol dm^{-3} phosphate buffer (20 cm^3) and then with water (10 cm^3). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of the solvent gave pure *rac*-**12** (150 mg, 97%) as a solid, mp 76 °C (Found: C, 74.9; H, 7.2. Calc. for $C_{39}H_{44}O_7$: C, 75.0; H, 7.1%); δ_H($CDCl_3$; 360 MHz) 7.37–7.23 (20 H, m, 4 × CH_2*Ph*), 4.94–4.69 (8 H, m, 4 × CH_2Ph), 4.78 (1 H, dd, *J* 10.2 and 2.5, H-1), 3.99 (1 H, dd, *J* 10.2 and 9.5, H-6), 3.98 (1 H, dd, all *J* 9.5, H-4), 3.85 (1 H, dd, all *J* 2.5, H-2), 3.58 (3 H, s, OMe), 3.50 (1 H, dd, all *J* 9.5, H-5), 3.50 (1 H, dd, *J* 9.5 and 2.5, H-3), 2.27 (2 H, m, α-H_2), 1.64 (2 H, m, β-H_2) and 0.94 (3 H, t, *J* 7.5, γ-H_3); *m/z* (FAB^+) 625 (M + H^+, 1%) and 91 (Bn^+, 100).

DL-1-*O*-Butyryl-2-*O*-methyl-*myo*-inositol *rac*-13

Compound *rac*-**12** (140 mg, 225 μmol) was hydrogenated with palladium (10%) on carbon as described in the general procedures to give compound *rac*-**13** (59 mg, 99%) as a solid after freeze drying, mp 114–115 °C (Found: C, 49.8; H, 7.4. Calc. for $C_{11}H_{20}O_7$: C, 50.0; H, 7.6%); δ_H(CD_3OD; 360 MHz) 4.67 (1 H, dd, *J* 10.2 and 2.8, H-1), 3.73 (1 H, dd, *J* 10.2 and 9.2, H-6), 3.66 (1 H, dd, all *J* 2.8, H-2), 3.55 (1 H, dd, *J* 10.0 and 9.2, H-4), 3.51 (3 H, s, OMe), 3.43 (1 H, dd, *J* 10.0 and 2.8, H-3), 3.17 (1 H, dd, all *J* 9.2, H-5), 2.38 (2 H, m, α-H_2), 1.67 (2 H, m, β-H_2) and 0.97 (3 H, t, *J* 7.5, γ-H_3); *m/z* (FAB^+) 265 (M + H^+, 100%) and 177 (M – BtO^-, 14); (FAB^-) 263 (M – H^+, 15%) and 87 (BtO^-, 100).

DL-1-*O*-Butyryl-2-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakis-(dibenzyl phosphate) *rac*-20b

A solution of compound *rac*-**13** (49.2 mg, 186 μmol) and tetrazole (209 mg, 2.98 mmol) in acetonitrile (2 cm^3) was treated with dibenzyl *N*,*N*-diisopropylphosphoramidite (874 mm^3, 898 mg, 2.6 mmol) for 1.5 h, oxidized with peracetic acid, and worked up as described in the general procedures. Purification by preparative HPLC (90% MeOH; 40 cm^3 min^{-1}; t_R = 31.55 min) gave title compound *rac*-**20b** (160 mg, 66%) as an oil, δ_H($CDCl_3$; 360 MHz) 7.33–7.12 (40 H, m, 8 × CH_2*Ph*), 5.08–4.84 (19 H, m, 8 × CH_2Ph, H-1, -4 and -6), 4.43 (1 H, ddd, all *J* 9.5, H-5), 4.21 (1 H, ddd, all *J* 9.5, H-3), 4.07 (1 H, dd, all *J* 2.5, H-2), 3.46 (3 H, s, OMe), 2.12 (2 H, m, α-H_2), 1.48 (2 H, m, β-H_2) and 0.80 (3 H, t, *J* 7.5, γ-H_3); δ_P($CDCl_3$; 145.8 MHz; ^{1}H decoupled) –0.57 (1 P, s), –0.69 (1 P, s), –1.31 (1 P, s) and –1.73 (1 P, s); *m/z* (FAB^+) 1305 (M + H^+, 2%) and 91 (Bn^+, 100); (FAB^-) 1213 (M – Bn^+, 8%) and 277 [$(BnO)_2OPO^-$, 100].

DL-1-*O*-Butyryl-2-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakis-phosphate *rac*-21b

Compound *rac*-**20b** (91 mg, 70 μmol) was hydrogenated with palladium (10%) on carbon as described in the general procedures to give the phosphoric acid *rac*-**21b** (40 mg, 99%) as a solid after freeze drying [Found: *m/z*, 582.9755 (M – H^+). Calc. for $C_{11}H_{23}O_{19}P_4$: *m/z*, 582.9784]; δ_H(D_2O; 360 MHz) 5.08 (1 H, dd, *J* 10.4 and 2.5, H-1), 4.52 (1 H, ddd, all *J* 10.4, H-6), 4.48 (1 H, ddd, all *J* 10.4, H-4), 4.36–4.24 (2 H, m, H-3 and -5), 4.04 (1 H, dd, all *J* 2.5, H-2), 3.57 (3 H, s, OMe), 2.43 (2 H, m, α-H_2), 1.60 (2 H, m, β-H_2) and 0.88 (3 H, t, *J* 7.5, γ-H_3); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 1.15 (1 P, s), 0.63 (1 P, s) and 0.00 (2 P, s); *m/z* (FAB^+) 623 (M + K^+, 21%) and 585 (M + H^+, 100); (FAB^-) 583 (M – H^+, 100%) and 97 [$(HO)_2OPO^-$, 17].

DL-2-*O*-Methyl-*myo*-inositol 3,4,5,6-tetrakisphosphate *rac*-1b

Compound *rac*-**21b** (12 mg, 20 μmol) was treated with 0.1 mol dm^{-3} KOH (4.32 cm^3) to adjust the pH to 12.8. The solution was stirred for 2 days at room temperature. The reaction mixture was directly poured onto an ion-exchange column (Dowex 50 WX 8, H^+) for purification. Lyophilization gave the title compound *rac*-**1b** (8 mg, 78%) as a solid [Found: *m/z*, 512.9332 (M − H$^+$). Calc. for $C_7H_{17}O_{18}P_4$: *m/z*, 512.9365]; δ_H(D_2O; 360 MHz) 4.45 (1 H, ddd, all *J* 9.3, H-6), 4.30 (1 H, ddd, all *J* 9.3, H-4), 4.23 (1 H, ddd, *J* 9.3, 9.3 and 2.3, H-3), 4.19 (1 H, ddd, all *J* 9.3, H-5), 3.92 (1 H, dd, all *J* 2.3, H-2), 3.74 (1 H, dd, *J* 9.3 and 2.3, H-1) and 3.57 (3 H, s, OMe); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 1.02 (1 P, s), 0.64 (1 P, s), 0.55 (1 P, s) and −0.02 (1 P, s); *m/z* (FAB$^+$) 515 (M + H$^+$, 100%); (FAB$^-$) 513 (M − H$^+$, 100%) and 97 [$(HO)_2OPO^-$, 17].

DL-1-*O*-Butyryl-2-*O*-methyl-*myo*-inositol 3,4,5,6-tetrakisphosphate octakis(acetoxymethyl ester) *rac*-2b

DIEA (122 mm^3, 93 mg, 720 μmol) and acetoxymethyl bromide (105 mm^3, 165 mg, 1.08 mmol) were added to a suspension of the phosphoric acid *rac*-**21b** (26 mg, 45 μmol) in dry acetonitrile (1 cm^3). The mixture was stirred at room temperature for 2 days and the volatile components were evaporated off in high vacuum. Extraction with toluene afforded compound *rac*-**2b** (36 mg, 69%) as a syrup, δ_H([$^2H_8$]toluene; 360 MHz), 5.94–5.56 (16 H, m, 8 × C*H*$_2$OAc), 5.23 (1 H, dd, *J* 9.8 and 2.7, H-1), 5.04 (1 H, ddd, all *J* 9.8, H-6), 4.98 (1 H, ddd, all *J* 9.8, H-4), 4.98 (1 H, ddd, all *J* 9.8, H-5), 4.68 (1 H, ddd, *J* 9.8, 9.8 and 2.7, H-3), 4.29 (1 H, dd, all *J* 2.7, H-2), 3.57 (3 H, s, OMe), 2.64–2.33 (2 H, m, α-H$_2$), 1.90–1.78 (24 H, 8 s, 8 × OAc), 1.72 (2 H, m, β-H$_2$) and 0.96 (3 H, t, *J* 7.5, γ-H$_3$); δ_P([$^2H_8$]toluene; 145.8 MHz; ^{1}H decoupled) −3.52 (1 P, s), −3.67 (1 P, s), −3.98 (1 P, s) and −4.84 (1 P, s); *m/z* (FAB$^+$) 1161 (M + H$^+$, 24%), 1089 (M − CH_2OAc^+ + 2 H$^+$, 75) and 1017 (M − 2 CH_2OAc^+ + 3 H$^+$, 100); (FAB$^-$) 1087 (M − CH_2OAc^+, 27%), 1015 (M − 2 CH_2OAc^+ + H$^+$, 5) and 241 [$OPO(OCH_2OAc)_2^-$, 100].

DL-3,4,5,6-Tetra-*O*-benzyl-1-*O*-butyryl-*myo*-inositol *rac*-22

A solution of dried diol *rac*-**5** (20 g, 37 mmol) and butyric anhydride (6 cm^3, 5.8 g, 36.8 mmol) in dry pyridine (50 cm^3) was stirred at room temperature for 1 day. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in boiling methanol to crystallize the crude product. Purification on silica gel [ethyl acetate–light petroleum (1 : 2)] gave the title compound *rac*-**22** (17.6 g, 78%) as a solid, mp 123 °C (Found: C, 74.8; H, 7.0. Calc. for $C_{38}H_{42}O_7$: C, 74.7; H, 6.9%); δ_H($CDCl_3$; 360 MHz) 7.36–7.23 (20 H, m, 4 × CH$_2$*Ph*), 4.92–4.68 (9 H, m, 4 × C*H*$_2$Ph, H-1), 4.29 (1 H, dd, all *J* 3.0, H-2), 4.08 (1 H, dd, all *J* 9.5, H-6), 3.96 (1 H, dd, all *J* 9.5, H-4), 3.57 (1 H, dd, *J* 9.5 and 3.0, H-3), 3.55 (1 H, dd, all *J* 9.5, H-5), 2.39–2.21 (2 H, m, α-H$_2$), 1.68–1.58 (2 H, m, β-H$_2$) and 0.94 (3 H, t, γ-H$_3$); *m/z* (FAB$^+$) 611 (M + H$^+$, 42%) and 91 (Bn$^+$, 100); (FAB$^-$) 609 (M − H$^+$, 44%), 539 (M − Bt$^+$, 100) and 519 (M − Bn$^+$, 77).

DL-3,4,5,6-Tetra-*O*-benzyl-1-*O*-butyryl-*myo*/*scyllo*-2-inosose *rac*-23

Acetic anhydride (3.5 cm^3, 3.8 g, 37 mmol) was added to a solution of dry alcohol *rac*-**22** (2.3 g, 3.8 mmol) in dry DMSO (30 cm^3, 33 g, 422 mmol). After the reaction mixture had been stirred at room temperature for 15 h, no more starting material could be detected by HPLC (90% MeOH; 1.5 cm^3 min^{-1}; t_R = 5.50 min). The volatile components were evaporated off under high vacuum and the resulting oil was poured on water (30 cm^3). The emulsion was applied to a reversed-phase chromatography column (RP-18, 25–40 μm) and washed with water to remove residual DMSO. The product was eluted with acetone (120 cm^3) to give ketone *rac*-**23** (1.9 g, 81%) as a solid, mp 98 °C (Found: C, 75.7; H, 6.5. Calc. for $C_{38}H_{41}O_7$: C, 75.8; H, 6.4); δ_H($CDCl_3$; 360 MHz) 7.40–7.23 (20 H, m, 4 × CH$_2$*Ph*), 5.32 (1 H, dd, *J* 10.5 and 1.5, H-1), 4.94–4.51 (8 H, m, 4 × C*H*$_2$Ph), 4.31 (1 H, dd, *J* 9.5 and 1.5, H-3), 3.98 (1 H, dd, all *J* 9.5, H-4), 3.67 (1 H, dd, *J* 10.5 and 9.5, H-6), 3.63 (1 H, dd, all *J* 9.5, H-5), 3.55 (1 H, dd, all *J* 9.5, H-5), 2.49–2.30 (2 H, m, α-H$_2$), 1.76–1.64 (2 H, m, β-H$_2$) and 1.00 (3 H, t, γ-H$_3$); *m/z* (FAB$^+$) 609 (M + H$^+$, 2%) and 91 (Bn$^+$, 100).

DL-3,4,5,6-Tetra-*O*-benzyl-*scyllo*-inositol (DL-1,2,3,4-tetra-*O*-benzyl-*scyllo*-inositol) *rac*-24

A solution of dried ketone *rac*-**23** (720 mg, 1.18 mmol) and $NaBH_4$ (50 mg, 1.35 mmol) in dry propan-2-ol was stirred at 50 °C. After 0.5 h, 0.5 mol dm^{-3} aq. $NaHSO_4$ (20 cm^3) was added. The solution was extracted with *tert*-butyl methyl ether and washed twice with 0.5 mol dm^{-3} phosphate buffer (20 cm^3) and then with water (20 cm^3). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by preparative HPLC (85% MeOH; 30 cm^3 min^{-1}; t_R = 36.00 min) gave title compound *rac*-**24** (466 mg, 73%) as a solid, mp 179 °C (Found: C, 75.5; H, 6.8. Calc. for $C_{34}H_{36}O_6$: C, 75.5; H, 6.7%); δ_H($CDCl_3$; 360 MHz) 7.37–7.27 (20 H, m, 4 × CH$_2$*Ph*), 4.89 (4 H, dd, 2 × C*H*$_2$Ph), 4.85 (4 H, dd, 2 × C*H*$_2$Ph), 3.59 (2 H, m, H-1 and -2), 3.52–3.39 (4 H, m, H-3, -4, -5 and -6), 2.50 (1 H, s, OH) and 2.49 (1 H, s, OH); *m/z* (FAB$^-$) 539 (M − H$^+$).

DL-3,4,5,6-Tetra-*O*-benzyl-1,2-di-*O*-butyryl-*scyllo*-inositol (DL-1,2,3,4-tetra-*O*-benzyl-5,6-di-*O*-butyryl-*scyllo*-inositol) *rac*-25

A solution of dry diol *rac*-**24** (0.27 g, 0.5 mmol) and butyric anhydride (0.49 cm^3, 475 mg, 3 mmol) in dry pyridine (5 cm^3) was stirred at room temperature for 2 days. Evaporation of the reaction mixture gave a crude oil. Residual pyridine was removed by evaporation three times with octane. The residue was dissolved in *tert*-butyl methyl ether and was washed twice with 0.5 mol dm^{-3} aq. $NaHSO_4$ (10 cm^3), 0.5 mol dm^{-3} phosphate buffer (10 cm^3) and water (10 cm^3) successively. The organic layer was dried over Na_2SO_4 and filtered. Crystallization from methanol gave pure compound *rac*-**25** (245 mg, 72%) as a solid, mp 106 °C (Found: C, 74.25; H, 7.2. Calc. for $C_{42}H_{48}O_8$: C, 74.1; H, 7.1%); δ_H($CDCl_3$; 360 MHz) 7.32–7.20 (20 H, m, 4 × CH$_2$*Ph*), 5.56–5.51 (2 H, m, H-1 and -2), 4.89–4.80 (6 H, m, 3 × C*H*$_2$Ph), 4.64 (2 H, d, C*H*$_2$Ph), 3.66–3.57 (4 H, m, H-3, -4, -5 and -6), 2.15–2.09 (4 H, m, 2 × α-H$_2$), 1.58–1.48 (4 H, m, 2 × β-H$_2$) and 0.88 (6 H, t, 2 × γ-H$_3$); *m/z* (FAB$^+$) 681 (M + H$^+$, 1%), 573 (M − BnO$^-$, 2) and 91 (Bn$^+$, 100).

DL-1,2-Di-*O*-butyryl-*scyllo*-inositol *rac*-26

Compound *rac*-**25** (0.23 g, 0.34 mmol) was hydrogenated with palladium (10%) on carbon as described in the general procedures to give tetraol *rac*-**26** (108 mg, 99%) as a solid after freeze drying, mp 126 °C; δ_H([$^2H_6$]acetone; 360 MHz) 5.12–5.06 (2 H, m, H-1 and -2), 3.58–3.47 (4 H, m, H-3, -4, -5 and -6), 2.28–2.18 (4 H, m, 2 × α-H$_2$), 1.61–1.48 (4 H, m, 2 × β-H$_2$) and 0.90 (6 H, t, 2 × γ-H$_3$); *m/z* (FAB$^+$) 321 (M + H$^+$, 34%), 233 (M − BnO$^-$, 23) and 71 (Bn$^+$, 100); (FAB$^-$) 319 (M − H$^+$, 19%), 249 (M − Bt$^+$, 2) and 87 (BtO$^-$, 100).

DL-1,2-Di-*O*-butyryl-*scyllo*-inositol 3,4,5,6-tetrakis(dibenzyl phosphate) *rac*-27

A solution of tetraol *rac*-**26** (23 mg, 72 μmol) and tetrazole (70 mg, 1 mmol) in acetonitrile (1 cm^3) was treated with dibenzyl *N*,*N*-diisopropylphosphoramidite (336 mm^3, 345 mg, 1 mmol) for 20 h, oxidized with peracetic acid, and worked up as described in the general procedures. Purification by preparative HPLC (92% MeOH; 40 cm^3 min^{-1}; t_R = 27.00 min) gave compound *rac*-**27** (67 mg, 68%) as an oil, δ_H($CDCl_3$; 360 MHz) 7.32–7.16 (40 H, m, 8 × CH$_2$*Ph*), 5.30–5.25 (2 H, m, H-1 and -2), 5.09–4.84 (16 H, m, 8 × C*H*$_2$Ph), 4.70–4.60 (4 H, m, H-3, -4, -5 and -6), 2.12–2.05 (4 H, m, 2 × α-H$_2$), 1.50–1.33 (4 H, m, 2 × β-H$_2$) and 0.79 (6 H, t, 2 × γ-H$_3$); δ_P(CD_3OD; 145.8 MHz; ^{1}H decoupled) −0.66 (2 P, s) and −1.18 (2 P, s); *m/z* (FAB$^+$) 1361 (M + H$^+$, 1%) and 91 (Bn$^+$, 100); (FAB$^-$) 1269 (M − Bn$^+$, 5%) and 277 [$OPO(OBn)_2^-$, 100].

DL-1,2-Di-*O*-butyryl-*scyllo*-inositol 3,4,5,6-tetrakisphosphate *rac*-28

Compound *rac*-**27** (40 mg, 0.03 mmol) was hydrogenated with palladium (10%) on carbon under hydrogen as described in the general procedures to give tetrakisphosphate *rac*-**28** (19 mg, 99%) as a solid after freeze drying [Found: *m/z*, 639.0108 (M − H^+). Calc. for $C_{14}H_{27}O_{20}P_4$: *m/z*, 639.0046]; δ_H(D_2O; 360 MHz; free acid) 5.27–5.19 (2 H, m, H-1 and -2), 4.40–4.29 (4 H, m, H-3, -4, -5 and -6), 2.43–2.28 (4 H, m, 2 × α-H_2), 1.59–1.50 (4 H, m, 2 × β-H_2) and 0.87 (6 H, t, 2 × γ-H_3); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 1.0 (2 P, s) and −0.1 (2 P, s); *m/z* (FAB^-) 639 (M − H^+, 100%), 569 (M − Bt^+, 8) and 559 [M − $PO(OH)_2^+$, 9]; *m/z* (FAB^-) 639 (M − H^+, 52%), 569 (M − Bt^+, 100) and 559 [M − $PO(OH)_2^+$, 5].

DL-*scyllo*-Inositol 3,4,5,6-tetrakisphosphate (DL-*scyllo*-inositol 1,2,3,4-tetrakisphosphate) *rac*-3

Compound *rac*-**28** (18 mg, 23 μmol) was treated with 0.1 mol dm^{-3} KOH (4.97 cm^3). The pH was adjusted to 12.8. The solution was stirred at room temperature for 3 days. The reaction mixture was directly poured onto an ion-exchange column (Dowex 50 WX 8, H^+) for purification. Lyophilization gave the title compound *rac*-**3** (11 mg, 99%) as a solid, δ_H(D_2O; 360 MHz; free acid) 4.12–4.03 (2 H, m, H-4 and -5), 3.98–3.90 (2 H, m, H-3 and -6) and 3.59–3.52 (2 H, m, H-1 and -2); δ_P(D_2O; 145.8 MHz; free acid; ^{1}H decoupled) 4.2 (2 P, s) and 2.3 (2 P, s).

DL-1,2-Di-*O*-butyryl-*scyllo*-inositol 3,4,5,6-tetrakisphosphate octakis(acetoxymethyl ester) *rac*-4

DIEA (119 mm^3, 90 mg, 700 μmol) and acetoxymethyl bromide (70 mm^3, 107 mg, 700 μmol) were added to a suspension of tetrakisphospate *rac*-**28** (17 mg, 17 μmol) in acetonitrile (1 cm^3) as described in the general procedures. Extraction with toluene afforded title compound *rac*-**4** (10 mg, 48%) as a syrup, δ_H([$^2H_8$]toluene; 360 MHz) 5.92–5.54 (18 H, m, 8 × CH_2OAc, H-1 and -2), 4.34–4.27 (4 H, m, H-3, -4, -5 and -6), 2.61–2.30 (4 H, m, 2 × α-H_2), 1.83–1.76 (24 H, 4 s, 8 × OAc), 1.73–1.67 (4 H, m, 2 × β-H_2) and 1.04 (6 H, t, 2 × γ-H_3); δ_P([$^2H_8$]toluene; 145.8 MHz; ^{1}H decoupled) −4.20 (2 P, s) and −4.25 (2 P, s); *m/z* (FAB^-) 1143 (M − CH_2OAc^+, 27%), 1071 (M − 2 CH_2OAc^+ + H^+, 90) and (M − 3 CH_2OAc^+ + 2 H^+, 100).

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