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SYNTHESIS OF RACEMIC 3-METHYLPHOSPHONATE ANALOGUES OF *MYO*-INOSITOL 3,4-*BIS*- AND 1,3,4-*TRIS*PHOSPHATE

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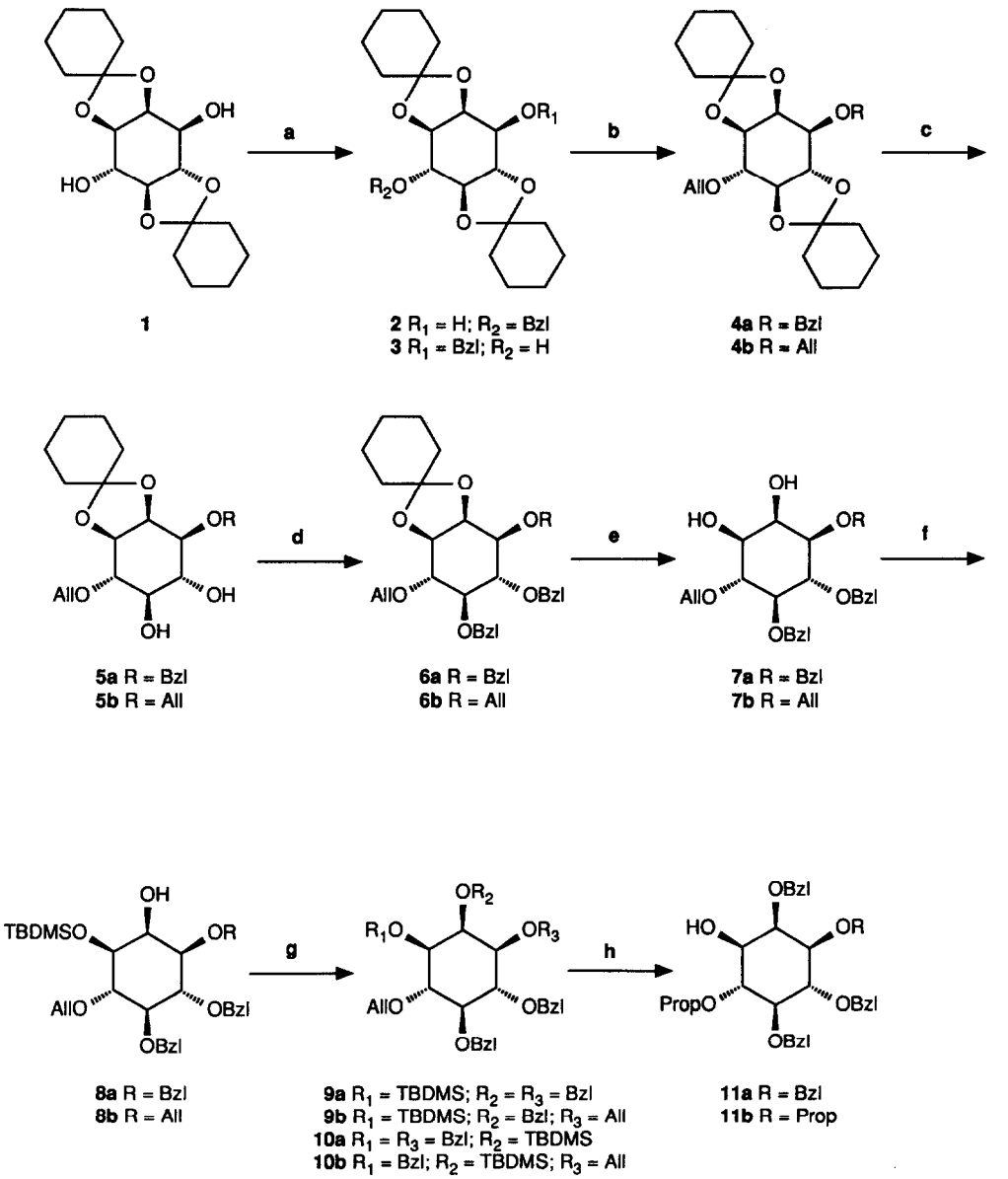
ABSTRACT: The partially benzyl protected *myo*-inositol derivatives **11a** and **11b**, the C-4 and C-1,4 hydroxyl function(s) of which are protected with temporary *trans*-prop-1-enyl protecting group(s), were readily converted into the respective title compounds **18a** and **18b** by sequential methylphosphonylation, mild cleavage of the *trans*-prop-1-enyl group(s), phosphorylation and removal of all permanent benzyl protecting groups.

It has been shown that agonist stimulation of several receptors results in the hydrolysis of phosphatidylinositol 4,5-*bis*phosphate (PtdIns[4,5]P_2) to give the second messengers diacylglycerol[1] and *myo*-inositol 1,4,5-*tris*phosphate (Ins[1,4,5]P_3)[2,3]. The intracellular second messenger Ins[1,4,5]P_3 mediates the release of calcium ions from intracellular stores, initiating several physiological responses. The major pathway for terminating the action of Ins[1,4,5]P_3 is dephosphorylation by a specific 5-phosphatase[4] to give Ins[1,4]P_2. The released Ins[1,4]P_2 is further metabolized *via* 1- and 4-phosphates to free *myo*-inositol, which is recycled to PtdIns[4,5]P_2. The alternate pathway for Ins[1,4,5]P_3 inactivation involves the phosphorylation by a 3-kinase[5] to give the putative second messenger Ins[1,3,4,5]P_4[6]. Subsequent hydrolysis of the 5-phosphate affords Ins[1,3,4]P_3[7], which is ultimately degraded to *myo*-inositol *via* Ins[1,3]P_2 and/or Ins[3,4]P_2.

The complexity of the signal transduction mechanism[8] has triggered a considerable interest[9,10] in the chemical synthesis of *myo*-inositol phosphates. However, in order to get a deeper insight into the biological pathways, the availability of *myo*-inositol phosphates having a modified phosphate at a specific position would be highly desirable. Up to now, the preparation of 5-modified Ins[1,4,5]P_3 analogues which act as long-lived Ca^{2+}-agonists, has been reported[11,12]. As part of an ongoing programme[13-15] directed towards the preparation of *myo*-inositol phosphates and analogues thereof, we here describe the synthesis of the racemic *myo*-inositol 3,4-*bis*- and 1,3,4-*tris*phosphate analogues **18a** and **18b**, the 3-phosphate of which is replaced by a methylphosphonate.

The synthetic route we adopted to attain our goal is based on the following heuristic sequence of events. The first one comprises the preparation (see Scheme 1) of the precursors **11a** and **11b** both of which have a free hydroxyl at C-3 required for the introduction of the methylphosphonate modification. In addition, mild cleavage of the temporary *trans*-prop-1-enyl group(s) at C-4 and C-1,4 in **11a** and **11b**, respectively, will engender the possibility to phosphorylate the free hydroxyl function(s). Finally, stepwise introduction of the methylphosphonate and phosphate esters can be accomplished (see Scheme 2) using the phosphonylating and phosphitylating reagents **12** and **13**, respectively.

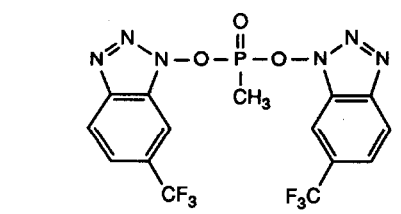
The route to the key precursors **11a** and **11b** commences, as outlined in Scheme 1, with the preparation of racemic 1,2;4,5-di-*O*-cyclohexylidene-*myo*-inositol (**1**).



Scheme 1: (a) BzlBr, BaO, $Ba(OH)_2.8H_2O$, DMF; (b) AllBr, NaH, DMF; (c) $HOCH_2CH_2OH$ (1 eq), pTsOH (cat), CH_2Cl_2; (d) BzlBr, NaH, DMF; (e) AcOH/H_2O (4/1, v/v), 95°C; (f) *tert*-butyldimethylsilyl chloride, pyridine, 50°C; (g) BzlBr, NaH, DMF; (h) Ir(COD)[$PMePh_2$]$_2PF_6$ (H_2), $ClCH_2CH_2Cl$; 0.5 M tetrabutylammonium fluoride, dioxane.

Thus reaction of *myo*-inositol with 1,1-diethoxycyclohexane in the presence of a catalytic amount of acid at elevated temperature afforded a mixture of three di-*O*-cyclohexylidene derivatives, from which the desired compound **1**[13,16] readily crystallized. Subsequent acid catalyzed treatment of the mother liquid afforded, after work-up and crystallization, another quantity of **1**. Repetition of the latter ketal exchange process ultimately resulted in the isolation of **1** in a total yield of 75%. Regioselective benzylation of **1** according to Vacca *et al.*[17] gave, after silica gel column chromatography, the mono-benzylated *myo*-inositol derivatives **2** and **3** in 16 and 48% yield, respectively. On the other hand, selective benzylation[18] of compound **1** in the presence of barium oxide - barium hydroxide afforded almost exclusively the 3-*O*-benzyl derivative **3** in 70% yield. Subsequent allylation of the mono-benzyl derivative **3** with allyl bromide and sodium hydride yielded the crystalline *myo*-inositol derivative **4a**. The diallyl derivative **4b** was obtained after exhaustive allylation of starting compound **1**. Stepwise transformation of the mono- and di-allyl *myo*-inositol derivatives **4a** and **4b** into the key compounds **11a** and **11b** could be executed in an analogous way. Thus, selective removal of the *trans*-cyclohexylidene function in **4a,b** to give crystalline **5a,b** could be realized by *trans*-ketalization with ethylene glycol in the presence of a catalytic amount of acid. Benzylation of **5a,b**, followed by acidic hydrolysis of the *cis*-cyclohexylidene function in **6a,b** afforded the 2,3-diols **7a** and **7b** in 94 and 90% yield, respectively. Regioselective silylation[19] of the respective diols **7a,b** with *tert*-butyldimethylsilyl chloride in pyridine at elevated temperature gave exclusively the mono-substituted derivatives **8a,b** in excellent yields. Benzylation of **8a,b** afforded the positional isomers **9a,b** and **10a,b** in a ratio of 4:1. After silica gel column chromatography, the desired *myo*-inositol derivatives **9a,b** could be isolated in high yield. Isomerization[20] of the allyl-group(s) in **9a,b** into the isomeric *trans*-prop-1-enyl group(s) with 1,5-cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate[21], and subsequent removal of the *tert*-butyldimethylsilyl group with fluoride ion, afforded the crystalline *trans*-prop-1-enyl derivatives **11a** and **11b** in 86 and 83% yield, respectively.

The stepwise introduction of the methylphosphonate and phosphate functions is illustrated in Scheme 2. In the first step, the individual alcohols **11a,b** were reacted with a slight excess of the bifunctional phosphonylating agent *bis*[1-(6-trifluoromethyl)benzotriazolyl]methylphosphonate (**12**)[22] for 15 min at 20°C to give the corresponding putative [1-(6-trifluoromethyl)benzotriazolyl]methylphosphonate intermediates. *In situ* treatment of the latter intermediates with benzyl alcohol in the presence of *N*-methylimidazole gave, after 1 h at 20°C, the corresponding methylphosphonate diesters **14a,b**. Mild acidic hydrolysis of the *trans*-prop-1-enyl group(s) in **14a,b** resulted in the isolation of the alcohols **15a,b**. The identity of compound **15a** was firmly established by converting it *via* hydrogenolysis into the fully-deprotected methylphosphonate derivative **16**. ^{1}H- and ^{31}P-NMR data of **16** (see Table) were in excellent agreement with the proposed structure. Introduction of the phosphate functions was now effected by 1*H*-tetrazole-mediated phosphitylation of compounds **15a,b** with *N,N*-diisopropyl dibenzyl phosphoramidite[15,23] (**13**) and subsequent oxidation of the intermediate phosphite-triesters with *tert*-butyl hydroperoxide[24] to give, after purification by column-chromatography, the fully protected Ins[3,4]P_2 and Ins[1,3,4]P_3 analogues **17a** and **17b**, respectively.



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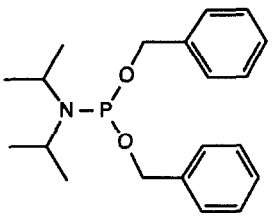

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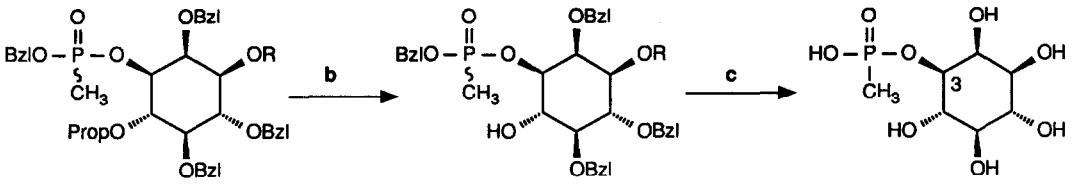
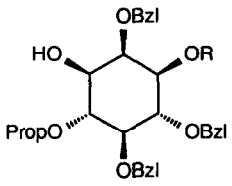


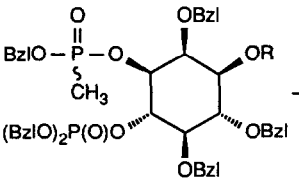
14a R = Bzl
14b R = Prop

15a R = Bzl
15b R = H

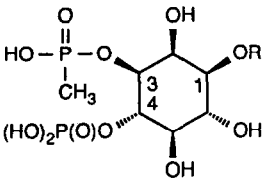
16



11a R = Bzl
11b R = Prop



17a R = Bzl
17b R = P(O)(OBzl)$_2$



18a R = H
18b R = P(O)(OH)$_2$

Scheme 2: (a) **12**, dioxane; BzlOH, *N*-methylimidazole; (b) 0.1 N HCl in CH_2Cl_2/MeOH (1/1, v/v); (c) H_2-Pd(C), MeOH/H_2O (4/1, v/v); (d) **13**, 1*H*-tetrazole, CH_3CN/CH_2Cl_2 (1/1, v/v); *tert*-butyl hydroperoxide; (e) H_2-Pd(C), MeOH/H_2O (4/1, v/v).

Finally, removal of all benzyl protecting groups was accomplished by hydrogenolysis over palladium on charcoal to afford the 3-methylphosphonate analogues **18a** and **18b** without the occurrence of phosphonate or phosphate migration to adjacent positions, as evidenced from the NMR data presented in the Table. In addition, the structures of the analogues **18a,b** could be further corroborated by selective phosphorus decoupling experiments of the ^{1}H-NMR spectra.

Table ^1H- and ^{31}P-NMR data[a] of compounds **16** and **18a,b**.

Chemical shifts[b]

	H-1	H-2	H-3	H-4	H-5	H-6	CH_3	P-1	P-3	P-4
16	3.56	4.19	3.99	3.73	3.33	3.65	1.40		29.12	
18a	3.58	4.17	4.19	4.31	3.49	3.70	1.44		30.44	0.78
18b	4.04	4.37	4.24	4.35	3.56	3.83	1.46	0.25	30.69	0.81

Coupling constants[c]

	H1-H2	H2-H3	H3-H4	H4-H5	H5-H6	H6-H1	CH_3-P	H1-P1	H3-P3	H4-P4
16	2.7	2.8	9.9	9.4	9.1	9.9	16.8		9.1	
18a	2.7	2.8	9.6	9.0	9.3	9.9	17.1		9.7	8.5
18b	2.8	2.7	9.7	9.0	9.5	9.8	17.1	8.6	9.7	8.7

a) Samples of **16** and **18a,b** are 20 mM in D_2O and adjusted to pH = 2.0 (T = 300 K). b) ^1H-shifts (δ) are given in ppm relative to tetramethylsilane, but referenced to D_2O at δ 4.80. ^{31}P-shifts (δ) are given in ppm relative to the external standard H_3PO_4. c) Coupling constants are in Hertz by first-order analysis.

The results presented in this paper clearly indicate that a judicious choice of protecting groups and phosphorylating reagents may give access to *myo*-inositol phosphate analogues having a methylphosphonate and natural phosphate functions at specific positions.

EXPERIMENTAL

General methods and materials

Acetonitrile, dichloromethane, pyridine and triethylamine were dried by heating with CaH_2 (10 g per litre), under reflux, for 16 h and then distilled. Pyridine was redistilled from *p*-toluenesulfonyl chloride (60 g per litre) and KOH (25 g per litre). *N,N*-dimethylformamide was stirred with CaH_2 (10 g per litre) for 16 h and then distilled under reduced pressure. Dioxane and 1,2-dichloroethane were distilled from $LiAlH_4$ (5 g per litre). Ether and toluene were distilled from P_2O_5. Methanol and ethanol were dried by refluxing with the corresponding magnesium alkoxides and then distilled. Methanol was stored over molecular sieves 3Å. Acetontrile, dichloromethane, pyridine, *N,N*-dimethylformamide, 1,2-dichloroethane and ethanol were stored over molecular sieves 4Å. Dioxane was stored over molecular sieves 5Å. Ether and toluene were stored over sodium wire. Triethylamine was stored over CaH_2. Methylphosphonic dichloride (Janssen, Belgium), benzyl alcohol and *N*-methylimidazole were distilled before use. 1*H*-Tetrazole was purchased from Janssen (Belgium). *Myo*-inositol was purchased from Pfanstiehl Laboratories Inc. (USA). *Tert*-butyl hydroperoxide (80% solution in di-*tert*-butyl peroxide) was purchased from Merck-Schuchardt (Germany). Palladium on activated charcoal (10%) was purchased from Fluka (Switzerland). Sephadex C-25 was purchased from Pharmacia (Sweden).

1-Hydroxy-6-trifluoromethylbenzotriazole[25] was dried *in vacuo* over P_2O_5 for 70 h at 50°C.

Triethylammonium bicarbonate buffer (TEAB, 2 M): a mixture of triethylamine (825 mL) and water (2175 mL) was

saturated with carbon dioxide gas at 0°C until pH 7.0.

Schleicher & Schüll (Germany) DC Fertigfolien F 1500 LS 254 were used for TLC analysis. The following eluents were used: A, hexane/Et_2O, 50/50, v/v; B, hexane/EtOAc, 50/50, v/v; C, EtOAc; D, CH_2Cl_2/acetone, 97/3, v/v; E, CH_2Cl_2/MeOH, 95/5, v/v. Compounds were detected under UV light and by spraying with a solution of $KMnO_4$ (10 g) in 2% aqueous Na_2CO_3 or a solution of ammonium molybdate (25 g) and ceric ammonium sulfate (10 g) in 10% aqueous H_2SO_4, followed by heating at 100°C. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh, ASTM). Melting points are uncorrected.

^{1}H-NMR spectra were recorded on a Bruker WM-300 spectrometer, equipped with an ASPECT-2000 computer operating in the Fourier transform mode at 300 MHz. ^{13}C- and ^{31}P-NMR spectra were recorded on a Jeol JNM-FX 200 spectrometer on line with a JEC 980B computer at 50.1 and 80.7 MHz, respectively. ^{1}H- and ^{13}C-chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as internal standard and ^{31}P-chemical shifts in ppm (δ) to 85% H_3PO_4 as external standard.

1,1-diethoxycyclohexane

To a solution of cyclohexanone (51.74 mL, 0.50 mol) and triethyl orthoformate (83.05 mL, 0.50 mol) in dry EtOH (100 mL) was added *p*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol). The exothermic reaction was stirred for 3 h at 20°C, neutralized with NaOMe and concentrated *in vacuo*. Distillation (94°C/4.67 kPa) of the crude product afforded 1,1-diethoxycyclohexane (77.41 g, 90% yield), as a colourless liquid.

^{13}C{^{1}H}-NMR ($CDCl_3$): δ 15.51 (2 x CH_3, ethyl), 22.95, 25.67 and 33.79 (5 x CH_2, cyclohexylidene), 54.69 (2 x CH_2, ethyl), 99.96 (Cq, cyclohexylidene).

^{1}H-NMR ($CDCl_3$): δ 1.17 (t, 6H, 2 x CH_3, ethyl, J = 7.0 Hz), 1.32-1.66 (m, 10H, 5 x CH_2, cyclohexylidene), 3.46 (q, 4H, 2 x CH_2, ethyl, J = 7.0 Hz).

1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (1)

A mixture of *myo*-inositol (27.00 g, 150.00 mmol), 1,1-diethoxycyclohexane (67.50 g, 392.44 mmol) and *p*-toluenesulfonic acid monohydrate (0.50 g, 2.63 mmol) in DMF (375 mL) was stirred at 95°C for 2 h. The reaction mixture was cooled, diluted with CH_2Cl_2 and washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Crystallization from acetone/hexane afforded compound **1** (12.75 g, 25% yield). After concentration of the mother liquor the resulting syrup was dissolved in DMF (300 mL) and *p*-toluenesulfonic acid monohydrate (0.40 g, 2.11 mmol) was added and stirred for 2 h at 95°C. Work-up and crystallization as described above afforded another portion of **1** (9.25 g, 18% yield). Repetition of this procedure afforded 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**1**) in a total yield of 75%. R_f 0.12 (system D), R_f 0.49 (system E). Mp 179.5-180.5°C; lit.[16] mp 172-174°C.

^{13}C{^{1}H}-NMR ($CDCl_3$): δ 23.42, 23.80, 24.70, 34.84, 36.21 and 37.55 (10 x CH_2, cyclohexylidene), 69.67, 74.84, 77.12, 77.38, 77.82 and 81.26 (C-1, C-2, C-3, C-4, C-5 and C-6), 110.58 and 112.97 (2 x Cq, cyclohexylidene).

^{1}H-NMR ($CDCl_3$): δ 1.35-1.76 (m, 20H, 10 x CH_2, cyclohexylidene), 2.54 (d, 1H, 3-OH (exchangeable)), 2.83 (d, 1H, 6-OH (exchangeable)), 3.31 (dd, 1H, H-5, $J_{5,6}$ = 10.5 Hz), 3.82 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.88 (ddd, 1H, H-6, $J_{6,1}$ = 6.5 Hz, $J_{6,OH}$ = 3.0 Hz), 4.02 (ddd, 1H, H-3, $J_{3,4}$ = 10.0 Hz, $J_{3,OH}$ = 9.0 Hz), 4.07 (dd, 1H, H-1, $J_{1,2}$ = 5.0 Hz), 4.48 (dd, 1H, H-2, $J_{2,3}$ = 4.5 Hz).

6-*O*-benzyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (2) and **3-*O*-benzyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (3)**

To a suspension of compound **1** (6.80 g, 20.00 mmol), barium oxide (6.14 g, 40.00 mmol) and barium hydroxide octahydrate (0.79 g, 2.50 mmol) in DMF (100 mL) was added dropwise benzyl bromide (2.65 mL, 22.28 mmol) at 20°C. The reaction mixture was stirred for 72 h at 20°C. After addition of MeOH, the reaction mixture was neutralized with AcOH/H_2O (1/1, v/v) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O (3x), 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (125 g, elution: CH_2Cl_2/acetone, 100/0 to 97.5/2.5, v/v) of the crude product afforded compound **2** (0.34 g, 4% yield). R_f 0.17 (system A), R_f 0.36 (system D). Mp 132-133°C (from Et_2O/hexane); lit.[26] mp 135-136°C.

^{13}C{^{1}H}-NMR ($CDCl_3$): δ 23.45, 23.65, 23.91, 24.79, 24.88, 35.01, 36.21, 36.44 and 37.35 (10 x CH_2, cyclohexylidene), 71.74 (OCH_2, Bzl), 69.70, 77.15, 77.53, 78.11, 80.15 and 80.53 (C-1, C-2, C-3, C-4, C-5 and C-6), 110.35 and 112.77 (2 x Cq, cyclohexylidene), 127.37-128.10 (5 x CH, aromatic), 138.06 (Cq, Bzl).

^{1}H-NMR ($CDCl_3$): δ 1.34-1.73 (m, 20H, 10 x CH_2, cyclohexylidene), 2.40 (d, 1H, 3-OH (exchangeable)), 3.36 (dd,

1H, H-5, $J_{5,6}$ = 10.5 Hz), 3.65 (dd, 1H, H-6, $J_{6,1}$ = 6.0 Hz), 3.78 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.97 (ddd, 1H, H-3, $J_{3,4}$ = 10.0 Hz, $J_{3,OH}$ = 9.5 Hz), 4.18 (dd, 1H, H-1, $J_{1,2}$ = 5.0 Hz), 4.45 (dd, 1H, H-2, $J_{2,3}$ = 4.5 Hz), 4.86 (s, 2H, OCH_2, Bzl), 7.26-7.44 (m, 5H, H aromatic).
and compound **3** (6.04 g, 70% yield). R_f 0.18 (system A), R_f 0.30 (system D). Mp 109-110°C (from Et_2O/hexane).
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 23.30, 23.48, 23.65, 24.67, 34.81, 35.98, 36.27 and 37.46 (10 x CH_2, cyclohexylidene), 71.28 (OCH_2, Bzl), 74.37, 74.52, 75.77, 76.39, 78.14 and 81.06 (C-1, C-2, C-3, C-4, C-5 and C-6), 110.26 and 112.51 (2 x Cq, cyclohexylidene), 127.40-128.01 (5 x CH, aromatic), 137.79 (Cq, Bzl).
^1H-NMR ($CDCl_3$): δ 1.29-1.78 (m, 20H, 10 x CH_2, cyclohexylidene), 2.52 (d, 1H, 6-OH (exchangeable)), 3.26 (dd, 1H, H-5, $J_{5,6}$ = 10.0 Hz), 3.78 (dd, 1H, H-3, $J_{3,4}$ = 10.0 Hz), 3.88 (ddd, 1H, H-6, $J_{6,1}$ = 7.0 Hz, $J_{6,OH}$ = 3.0 Hz), 3.94 (dd, 1H, H-1, $J_{1,2}$ = 4.5 Hz), 4.04 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 4.36 (dd, 1H, H-2, $J_{2,3}$ = 4.0 Hz), 4.87 (AB, 2H, OCH_2, Bzl), 7.25-7.45 (m, 5H, H aromatic).

6-*O*-allyl-3-*O*-benzyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (4a)
To a solution of compound **3** (4.54 g, 10.56 mmol) and NaH (0.32 g, 13.33 mmol) in dry DMF (50 mL) was added dropwise allyl bromide (0.98 mL, 11.58 mmol) at 0°C. The reaction mixture was stirred for 2 h at 20°C. Excess NaH was destroyed with MeOH and the reaction mixture concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Crystallization from EtOH/H_2O afforded homogeneous **4a** (4.81 g, 97% yield). R_f 0.71 (system D). Mp 89.5-90.5°C.
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 23.45, 23.74, 24.88, 24.94, 35.13, 36.27, 36.36 and 37.49 (10 x CH_2, cyclohexylidene), 71.07 and 71.48 (2 x OCH_2, All and Bzl), 74.37, 76.12, 76.56, 78.26, 80.15 and 80.65 (C-1, C-2, C-3, C-4, C-5 and C-6), 110.32 and 112.51 (2 x Cq, cyclohexylidene), 117.06 (=CH_2, All), 127.60-128.22 (5 x CH, aromatic), 134.76 (-CH=, All), 137.94 (Cq, Bzl).
^1H-NMR ($CDCl_3$): δ 1.29-1.83 (m, 20H, 10 x CH_2, cyclohexylidene), 3.28 (dd, 1H, H-5, $J_{5,6}$ = 10.5 Hz), 3.64 (dd, 1H, H-6, $J_{6,1}$ = 6.5 Hz), 3.74 (dd, 1H, H-3, $J_{3,4}$ = 10.0 Hz), 4.00 (dd, 1H, H-1, $J_{1,2}$ = 5.0 Hz), 4.03 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 4.28-4.31 (m, 2H, OCH_2, All), 4.34 (dd, 1H, H-2, $J_{2,3}$ = 4.0 Hz), 4.87 (AB, 2H, OCH_2, Bzl), 5.15-5.36 (m, 2H, =CH_2, All), 5.89-6.02 (m, 1H, -CH=, All), 7.26-7.42 (m, 5H, H aromatic).

3,6-di-*O*-allyl-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol (4b)
To a solution of compound **1** (4.76 g, 14.00 mmol) and NaH (0.84 g, 35.00 mmol) in dry DMF (70 mL) was added dropwise allyl bromide (2.61 mL, 30.85 mmol) at 0°C. The reaction mixture was stirred for 2 h at 20°C. Excess NaH was destroyed with MeOH and the reaction mixture concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Crystallization from EtOH/H_2O afforded homogeneous **4b** (5.53 g, 94% yield). R_f 0.56 (system D). Mp 63-64.5°C.
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 23.42, 23.68, 23.77, 24.91, 35.13, 36.30 and 37.44 (10 x CH_2, cyclohexylidene), 70.78 and 71.07 (2 x OCH_2, All), 74.66, 75.86, 76.42, 78.26, 80.18 and 80.65 (C-1, C-2, C-3, C-4, C-5 and C-6), 110.29 and 112.45 (2 x Cq, cyclohexylidene), 117.03 and 117.68 (2 x =CH_2, All), 134.64 and 134.73 (2 x -CH=, All).
^1H-NMR ($CDCl_3$): δ 1.26-1.80 (m, 20H, 10 x CH_2, cyclohexylidene), 3.32 (dd, 1H, H-5, $J_{5,6}$ = 10.5 Hz), 3.64 (dd, 1H, H-6, $J_{6,1}$ = 6.5 Hz), 3.78 (dd, 1H, H-3, $J_{3,4}$ = 10.0 Hz), 3.97 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 4.07 (dd, 1H, H-1, $J_{1,2}$ = 5.0 Hz), 4.23-4.37 (m, 4H, 2 x OCH_2, All), 4.46 (dd, 1H, H-2, $J_{2,3}$ = 4.0 Hz), 5.17-5.37 (m, 4H, 2 x =CH_2, All), 5.91-6.04 (m, 2H, 2 x -CH=, All).

6-*O*-allyl-3-*O*-benzyl-1,2-*O*-cyclohexylidene-*myo*-inositol (5a)
A solution of compound **4a** (4.42 g, 9.40 mmol) in 0.1 M ethylene glycol in CH_2Cl_2 (94 mL, 9.40 mmol) in the presence of *p*-toluenesulfonic acid monohydrate (75 mg, 0.39 mmol) was stirred for 2 h at 20°C. After neutralization with Et_3N the reaction mixture was washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (40 g, elution: CH_2Cl_2/MeOH, 100/0 to 95/5, v/v) of the crude product afforded pure **5a** (2.93 g, 80% yield). R_f 0.46 (system E). Mp 125.5-126.5°C (from CH_2Cl_2/hexane).
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 23.56, 23.83, 24.88, 35.07 and 37.64 (5 x CH_2, cyclohexylidene), 71.36, 72.74, 73.38, 77.12, 78.72 and 81.79 (C-1, C-2, C-3, C-4, C-5 and C-6), 72.33 (2 x OCH_2, All and Bzl), 110.35 (Cq, cyclohexylidene), 117.24 (=CH_2, All), 127.84-128.36 (5 x CH, aromatic), 134.87 (-CH=, All), 137.88 (Cq, Bzl).
^1H-NMR ($CDCl_3$): δ 1.22-1.81 (m, 10H, 5 x CH_2, cyclohexylidene), 2.70 (s (br), 2H, 4-OH and 5-OH,

(exchangeable)), 3.34 (dd (br), 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.46 (dd, 1H, H-6, $J_{6,1}$ = 7.0 Hz), 3.52 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.95 (dd (br), 1H, H-4, $J_{4,5}$ = 9.5 Hz), 4.01 (dd, 1H, H-1, $J_{1,2}$ = 5.0 Hz), 4.16-4.23 (m, 1H, OCH_2, All), 4.31 (dd, 1H, H-2, $J_{2,3}$ = 4.0 Hz), 4.38-4.45 (m, 1H, OCH_2, All), 4.77 (AB, 2H, OCH_2, Bzl), 5.16-5.34 (m, 2H, $=CH_2$, All), 5.88-6.03 (m, 1H, -CH=, All), 7.30-7.44 (m, 5H, H aromatic).

3,6-di-*O*-allyl-1,2-*O*-cyclohexylidene-*myo*-inositol (5b)

A solution of compound **4b** (5.25 g, 12.50 mmol) in 0.1 M ethylene glycol in CH_2Cl_2 (125 mL, 12.50 mmol) in the presence of *p*-toluenesulfonic acid monohydrate (95 mg, 0.50 mmol) was stirred for 2 h at 20°C. After neutralization with Et_3N the reaction mixture was washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (40 g, elution: CH_2Cl_2/MeOH, 100/0 to 95/5, v/v) of the crude product afforded pure **5b** (3.02 g, 71% yield). R_f 0.35 (system E). Mp 126.5-127°C (from CH_2Cl_2/hexane).

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 23.48, 23.80, 24.88, 35.16 and 37.58 (5 x CH_2, cyclohexylidene), 71.34, 72.82, 73.26, 76.88, 78.78 and 81.82 (C-1, C-2, C-3, C-4, C-5 and C-6), 72.30 (2 x OCH_2, All), 110.46 (Cq, cyclohexylidene), 117.27 and 117.82 (2 x $=CH_2$, All), 134.67 and 134.82 (2 x -CH=, All).

^1H-NMR ($CDCl_3$): δ 1.27-1.83 (m, 10H, 5 x CH_2, cyclohexylidene), 2.85 (d, 1H, 4-OH, (exchangeable)), 2.86 (d, 1H, 5-OH, (exchangeable)), 3.36 (ddd, 1H, H-5, $J_{5,6}$ = 9.5 Hz, $J_{5,OH}$ = 2.0 Hz), 3.47 (dd, 1H, H-6, $J_{6,1}$ = 7.0 Hz), 3.49 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.90 (ddd, 1H, H-4, $J_{4,5}$ = 9.5 Hz, $J_{4,OH}$ = 2.0 Hz), 4.07 (dd, 1H, H-1, $J_{1,2}$ = 5.0 Hz), 4.17-4.30 (m, 3H, 2 x OCH_2, All), 4.39-4.46 (m, 1H, 2 x OCH_2, All), 4.44 (dd, 1H, H-2, $J_{2,3}$ = 4.0 Hz), 5.17-5.36 (m, 4H, 2 x $=CH_2$, All), 5.89-6.05 (m, 2H, 2 x -CH=, All).

4-*O*-allyl-1,5,6-tri-*O*-benzyl-*myo*-inositol (7a)

To a solution of compound **5a** (2.77 g, 7.10 mmol) and NaH (0.43 g, 17.92 mmol) in dry DMF (35 mL) was added dropwise benzyl bromide (1.86 mL, 15.64 mmol) at 0°C. The reaction mixture was stirred for 2 h at 20°C. Excess NaH was destroyed with MeOH and the reaction mixture concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude **6a** was stirred in a mixture of AcOH and H_2O (35 mL, 4/1, v/v) for 2 h at 95°C. The reaction mixture was cooled and concentrated *in vacuo* and coevaporated with toluene (3 x 50 mL). The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (30 g, elution: CH_2Cl_2/MeOH, 100/0 to 95/5, v/v) of the crude product afforded pure **7a** (3.27 g, 94% yield). R_f 0.16 (system D), R_f 0.59 (system E). Mp 98-99°C (from Et_2O/hexane); lit.[27] mp 99-101°C.

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 69.35 and 71.71 (C-2 and C-3), 72.62, 74.34, 75.72 and 75.89 (4 x OCH_2, All and Bzl), 79.89, 81.06, 81.53 and 83.25 (C-1, C-4, C-5 and C-6) 117.03 ($=CH_2$, All), 127.60-128.51 (15 x CH, aromatic), 135.17 (-CH=, All), 137.85, 138.58 and 138.73 (3 x Cq, Bzl).

^1H-NMR ($CDCl_3$): δ 2.53 (s (br), 1H, 2-OH, (exchangeable)), 2.54 (d, 1H, 3-OH, (exchangeable)), 3.42 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.44 (ddd, 1H, H-3, $J_{3,4}$ = 9.5 Hz, $J_{3,OH}$ = 5.0 Hz), 3.45 (dd, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 3.71 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.93 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.22 (dd (br), 1H, H-2, $J_{2,3}$ = 3.0 Hz), 4.22-4.29 (m, 1H, OCH_2, All), 4.38-4.46 (m, 1H, OCH_2, All), 4.67-4.92 (m, 6H, 3 x OCH_2, Bzl), 5.15-5.31 (m, 2H, $=CH_2$, All), 5.88-6.02 (m, 1H, -CH=, All), 7.25-7.36 (m, 15H, H aromatic).

1,4-di-*O*-allyl-5,6-di-*O*-benzyl-*myo*-inositol (7b)

To a solution of compound **5b** (2.68 g, 7.88 mmol) and NaH (0.47 g, 19.58 mmol) in dry DMF (40 mL) was added dropwise benzyl bromide (2.06 mL, 17.32 mmol) at 0°C. The reaction mixture was stirred for 2 h at 20°C. Excess NaH was destroyed with MeOH and the reaction mixture concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude **6b** was stirred in a mixture of AcOH and H_2O (40 mL, 4/1, v/v) for 2 h at 95°C. The reaction mixture was cooled and concentrated *in vacuo* and coevaporated with toluene (3 x 50 mL). The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (40 g, elution: CH_2Cl_2/MeOH, 100/0 to 95/5, v/v) of the crude product afforded pure **7b** (3.12 g, 90% yield). R_f 0.11 (system D), R_f 0.48 (system E). Mp 76.5-78°C (from CH_2Cl_2/hexane); lit.[28] mp 78-80°C.

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 69.29 and 71.45 (C-2 and C-3), 71.54, 74.14, 75.45 and 75.69 (4 x OCH_2, All and Bzl), 79.48, 80.83, 81.26 and 82.96 (C-1, C-4, C-5 and C-6), 116.83 and 117.38 (2 x $=CH_2$, All), 127.37-128.13 (10 x CH,

aromatic), 134.41 and 134.93 (2 x -CH=, All), 138.38 and 138.47 (2 x Cq, Bzl).
^{1}H-NMR ($CDCl_3$): δ 2.75 (d, 1H, 2-OH, (exchangeable)), 2.77 (d, 1H, 3-OH, (exchangeable)), 3.36 (dd, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 3.40 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.47 (ddd, 1H, H-3, $J_{3,4}$ = 9.5 Hz, $J_{3,OH}$ = 5.0 Hz), 3.70 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.88 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.16-4.29 (m, 3H, 2 x OCH_2, All), 4.20 (ddd, 1H, H-2, $J_{2,3}$ = 3.0 Hz, $J_{2,OH}$ = 1.0 Hz), 4.38-4.45 (m, 1H, 2 x OCH_2, All), 4.77-4.89 (m, 4H, 2 x OCH_2, Bzl), 5.15-5.33 (m, 4H, 2 x $=CH_2$, All), 5.86-6.02 (m, 2H, 2 x -CH=, All), 7.25-7.34 (m, 10H, H aromatic).

4-*O*-allyl-1,5,6-tri-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (8a)
A mixture of compound **7a** (2.45 g, 5.00 mmol) and *tert*-butyldimethylsilyl chloride (1.85 g, 12.29 mmol) in pyridine (25 mL) was stirred for 16 h at 50°C. The reaction mixture was cooled, concentrated *in vacuo*, taken up in CH_2Cl_2 and washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (35 g, elution: hexane/Et_2O, 100/0 to 50/50, v/v) of the crude product afforded pure **8a** (2.54 g, 84% yield). R_f 0.44 (system A). Mp 62.5-63.5°C (from pentane).
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -4.93 and -4.55 (2 x $Si(CH_3)_2$, TBDMS), 17.99 ($\underline{C}(CH_3)_3$, TBDMS), 25.78 (3 x $C(\underline{C}H_3)_3$, TBDMS), 70.93 and 73.32 (C-2 and C-3), 72.82, 74.46 and 75.80 (4 x OCH_2, All and Bzl), 79.39, 81.06 and 83.25 (C-1, C-4, C-5 and C-6), 116.30 ($=CH_2$, All), 127.46-128.33 (15 x CH, aromatic), 135.14 (-CH=, All), 138.06, 138.67 and 138.82 (3 x Cq, Bzl).
^{1}H-NMR ($CDCl_3$): δ 0.06 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.10 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.90 (s, 9H, $C(CH_3)_3$, TBDMS), 2.43 (s (br), 1H, 2-OH, (exchangeable)), 3.36 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.37 (dd, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 3.45 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.62 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.90 (dd (br), 1H, H-2, $J_{2,3}$ = 3.0 Hz), 3.97 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.21-4.34 (m, 2H, OCH_2, All), 4.68-4.94 (m, 6H, 3 x OCH_2, Bzl), 5.10-5.26 (m, 2H, $=CH_2$, All), 5.87-6.00 (m, 1H, -CH=, All), 7.27-7.39 (m, 15H, H aromatic).

1,4-di-*O*-allyl-5,6-di-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (8b)
A mixture of compound **7b** (2.20 g, 5.00 mmol) and *tert*-butyldimethylsilyl chloride (1.85 g, 12.29 mmol) in pyridine (25 mL) was stirred for 16 h at 50°C. The reaction mixture was cooled, concentrated *in vacuo*, taken up in CH_2Cl_2 and washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (35 g, elution: hexane/Et_2O, 100/0 to 50/50, v/v) of the crude product afforded pure **8b** (2.52 g, 91% yield). R_f 0.48 (system A). Mp 59-60.5°C (from pentane).
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -4.93 and -4.58 (2 x $Si(CH_3)_2$, TBDMS), 17.96 ($\underline{C}(CH_3)_3$, TBDMS), 25.75 (3 x $C(\underline{C}H_3)_3$, TBDMS), 70.98 and 73.26 (C-2 and C-3), 71.95, 74.46 and 75.77 (4 x OCH_2, All and Bzl), 79.25, 81.00 and 83.16 (C-1, C-4, C-5 and C-6), 116.30 and 117.30 (2 x $=CH_2$, All), 127.43-128.22 (10 x CH, aromatic), 134.76 and 135.08 (2 x -CH=, All), 138.61 and 138.73 (2 x Cq, Bzl).
^{1}H-NMR ($CDCl_3$): δ 0.13 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.14 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.93 (s, 9H, $C(CH_3)_3$, TBDMS), 2.46 (s (br), 1H, 2-OH, (exchangeable)), 3.31 (dd, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 3.36 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.51 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.63 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.93 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.01 (dd (br), 1H, H-2, $J_{2,3}$ = 3.0 Hz), 4.19-4.36 (m, 4H, 2 x OCH_2, All), 4.78-4.91 (m, 4H, 2 x OCH_2, Bzl), 5.11-5.63 (m, 4H, 2 x $=CH_2$, All), 5.88-6.04 (m, 2H, 2 x -CH=, All), 7.28-7.34 (m, 10H, H aromatic).

4-*O*-allyl-1,2,5,6-tetra-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (9a) and 4-*O*-allyl-1,3,5,6-tetra-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (10a)
To a solution of compound **8a** (2.02 g, 3.34 mmol) and benzyl bromide (0.45 mL, 3.78 mmol) in DMF (15 mL) was added NaH (0.10 g, 4.17 mmol). The reaction mixture was stirred for 2 h at 20°C. Excess NaH was destroyed with MeOH and the reaction mixture concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (30 g, elution: hexane/Et_2O, 100/0 to 80/20, v/v) of the crude product afforded pure compound **9a** (1.72 g, 74% yield), as an oil. R_f 0.55 (system A).
$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -4.64 (2 x $Si(CH_3)_2$, TBDMS), 18.05 ($\underline{C}(CH_3)_3$, TBDMS), 25.90 (3 x $C(\underline{C}H_3)_3$, TBDMS), 72.80, 74.43, 74.90, 75.74 and 75.89 (5 x OCH_2, All and Bzl), 73.93 (C-2), 79.42, 80.53, 81.38, 81.73 and 83.89 (C-1, C-3, C-4, C-5 and C-6), 116.16 ($=CH_2$, All), 127.17-128.28 (20 x CH, aromatic), 135.40 (-CH=, All), 138.40, 138.79, 138.93 and 139.25 (4 x Cq, Bzl).
^{1}H-NMR ($CDCl_3$): δ 0.04 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.10 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.91 (s, 9H, $C(CH_3)_3$, TBDMS), 3.37 (dd, 1H, H-1, $J_{1,2}$ = 2.5 Hz), 3.38 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.45 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.74 (dd, 1H, H-2, $J_{2,3}$ = 2.5 Hz), 3.77 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 4.01 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.29-4.31 (m, 2H, OCH_2,

All), 4.60-4.92 (m, 8H, 4 x OCH_2, Bzl), 5.10-5.28 (m, 2H, $=CH_2$, All), 5.88-6.03 (m, 1H, -CH=, All), 7.24-7.34 (m, 20H, H aromatic).

and compound **10a** (0.42 g, 18% yield), as an oil. R_f 0.50 (system A).

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -4.73 (2 x $Si(CH_3)_2$, TBDMS), 18.49 ($\underline{C}(CH_3)_3$, TBDMS), 25.84 (3 x $C(\underline{C}H_3)_3$, TBDMS), 69.53 (C-2), 72.65, 72.77, 74.37, 75.63 and 76.04 (5 x OCH_2, All and Bzl), 80.53, 80.71, 80.97, 81.32 and 83.54 (C-1, C-3, C-4, C-5 and C-6), 116.54 ($=CH_2$, All), 127.37-128.13 (20 x CH, aromatic), 135.34 (-CH=, All), 138.23, 138.32 and 138.76 (4 x Cq, Bzl).

^1H-NMR ($CDCl_3$): δ 0.04 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.05 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.88 (s, 9H, $C(CH_3)_3$, TBDMS), 3.20 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.26 (dd, 1H, H-1, $J_{1,2}$ = 2.0 Hz), 3.40 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.84 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.93 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.21 (dd, 1H, H-2, $J_{2,3}$ = 2.0 Hz), 4.27-4.41 (m, 2H, OCH_2, All), 4.61-4.90 (m, 8H, 4 x OCH_2, Bzl), 5.13-5.30 (m, 2H, $=CH_2$, All), 5.92-6.05 (m, 1H, -CH=, All), 7.26-7.36 (m, 20H, H aromatic).

1,4-di-*O*-allyl-2,5,6-tri-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (9b) and **1,4-di-*O*-allyl-3,5,6-tri-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-*myo*-inositol (10b)**

To a solution of compound **8b** (1.98 g, 3.57 mmol) and benzyl bromide (0.47 mL, 3.95 mmol) in DMF (17.5 mL) was added NaH (0.11 g, 4.58 mmol). The reaction mixture was stirred for 2 h at 20°C. Excess NaH was destroyed with MeOH and the reaction mixture concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with H_2O, 1 M $NaHCO_3$ and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (30 g, elution: hexane/Et_2O, 100/0 to 50/50, v/v) of the crude product afforded pure compound **9b** (1.86 g, 81% yield), as an oil. R_f 0.67 (system A).

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -4.67 (2 x $Si(CH_3)_2$, TBDMS), 18.02 ($\underline{C}(CH_3)_3$, TBDMS), 25.87 (3 x $C(\underline{C}H_3)_3$, TBDMS), 71.54, 74.37, 74.81, 75.63 and 75.77 (5 x OCH_2, All and Bzl), 73.82 (C-2), 79.19, 80.39, 81.32, 81.64 and 83.80 (C-1, C-3, C-4, C-5 and C-6), 116.01 and 116.51 (2 x $=CH_2$, All), 127.11-128.16 (15 x CH, aromatic), 134.96 and 135.37 (2 x -CH=, All), 138.79, 138.93 and 139.17 (3 x Cq, Bzl).

^1H-NMR ($CDCl_3$): δ 0.11 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.12 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.93 (s, 9H, $C(CH_3)_3$, TBDMS), 3.29 (dd, 1H, H-1, $J_{1,2}$ = 2.5 Hz), 3.37 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.50 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.76 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.84 (dd, 1H, H-2, $J_{2,3}$ = 2.5 Hz), 3.96 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.07-4.20 (m, 2H, 2 x OCH_2, All), 4.29-4.31 (m, 2H, 2 x OCH_2, All), 4.75-4.95 (m, 6H, 3 x OCH_2, Bzl), 5.10-5.36 (m, 4H, 2 x $=CH_2$, All), 5.86-6.02 (m, 2H, 2 x -CH=, All), 7.22-7.45 (m, 15H, H aromatic).

and compound **10b** (0.39 g, 17% yield), as an oil. R_f 0.61 (system A).

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ -4.87 and -4.64 (2 x $Si(CH_3)_2$, TBDMS), 18.52 ($\underline{C}(CH_3)_3$, TBDMS), 25.87 (3 x $C(\underline{C}H_3)_3$, TBDMS), 69.50 (C-2), 71.66, 72.77, 74.43, 75.72 and 76.07 (5 x OCH_2, All and Bzl), 80.53, 80.62, 81.00, 81.32 and 83.51 (C-1, C-3, C-4, C-5 and C-6), 116.54 and 116.62 (2 x $=CH_2$, All), 127.37-128.25 (15 x CH, aromatic), 134.87 and 135.40 (2 x -CH=, All), 138.47, 138.82 and 138.88 (3 x Cq, Bzl).

^1H-NMR ($CDCl_3$): δ 0.06 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.09 (s, 3H, $Si(CH_3)_2$, TBDMS), 0.89 (s, 9H, $C(CH_3)_3$, TBDMS), 3.14 (dd, 1H, H-1, $J_{1,2}$ = 2.0 Hz), 3.21 (dd, 1H, H-3, $J_{3,4}$ = 9.5 Hz), 3.38 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.83 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.86 (dd, 1H, H-6, $J_{6,1}$ = 9.5 Hz), 4.03-4.17 (m, 2H, 2 x OCH_2, All), 4.18 (dd, 1H, H-2, $J_{2,3}$ = 2.0 Hz), 4.26-4.41 (m, 2H, 2 x OCH_2, All), 4.67-4.87 (m, 6H, 3 x OCH_2, Bzl), 5.11-5.32 (m, 4H, 2 x $=CH_2$, All), 5.84-6.05 (m, 2H, 2 x -CH=, All), 7.27-7.36 (m, 15H, H aromatic).

1,2,5,6-tetra-*O*-benzyl-4-*O*-*trans*-prop-1-enyl-*myo*-inositol (11a)

To a solution of compound **9a** (1.40 g, 2.02 mmol) in 1,2-dichloroethane (15 mL) under an inert helium atmosphere was added 1,5-cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate[21] (25 mg) in 1,2-dichloroethane (0.5 mL). The catalyst was activated by passing over a stream of hydrogen for 2 min. The solution was degassed and left under a stream of helium for 4 h. After concentration of the reaction mixture, the residue was dissolved in dioxane (10 mL). 1 M tetrabutylammonium fluoride in dioxane (10 mL, 10.00 mmol) was added and the reaction mixture was stirred for 1 h at 20°C. The reaction mixture was diluted with CH_2Cl_2, washed with 1 M $NaHCO_3$ and a saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (15 g, elution: hexane/Et_2O, 100/0 to 50/50, v/v) of the crude product afforded pure **11a** (1.01 g, 86% yield). R_f 0.26 (system A), R_f 0.57 (system B), R_f 0.62 (system D). Mp 84.5-85.5°C (from pentane).

$C_{37}H_{40}O_6$	calc.	C	76.53	H	6.94
(580.7)	found		76.23		6.86

$^{13}C\{^1H\}$-NMR ($CDCl_3$): δ 12.12 (CH_3, Prop), 71.51, 76.94, 80.85, 81.41, 82.72 and 84.04 (C-1, C-2, C-3, C-4, C-5

and C-6), 72.97, 74.75, 75.54 and 75.86 (4 x OCH_2, Bzl), 99.98 (-CH=, Prop), 127.57-128.30 (20 x CH, aromatic), 138.12, 138.23, 138.50 and 138.67 (4 x Cq, Bzl), 148.42 (OCH=, Prop).
^{1}H-NMR ($CDCl_3$): δ 1.52 (dd, 3H, CH_3, Prop), 2.27 (d, 1H, 3-OH, (exchangeable)), 3.39 (dd, 1H, H-5, $J_{5,6}$ = 9.0 Hz), 3.45 (dd, 1H, H-1, $J_{1,2}$ = 2.5 Hz), 3.51 (ddd, 1H, H-3, $J_{3,4}$ = 9.5 Hz, $J_{3,OH}$ = 6.5 Hz), 3.88 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 4.02 (dd, 1H, H-6, $J_{6,1}$ = 10.0 Hz), 4.05 (dd, 1H, H-2, $J_{2,3}$ = 2.5 Hz), 4.70-4.89 (m, 8H, 4 x OCH_2, Bzl), 4.99 (dq, 1H, -CH=, Prop, $J_{2,3}$ = 6.5 Hz), 6.27 (dq, 1H, OCH=, Prop, $J_{1,2}$ = 12.0 Hz, $J_{1,3}$ = 1.5 Hz), 7.27-7.35 (m, 20H, H aromatic).

2,5,6-tetra-*O*-benzyl-1,4-di-*O*-*trans*-prop-1-enyl-*myo*-inositol (11b)
To a solution of compound **9b** (1.30 g, 2.02 mmol) in 1,2-dichloroethane (15 mL) under an inert helium atmosphere was added 1,5-cyclooctadiene-*bis*[methyldiphenylphosphine]iridium hexafluorophosphate[21] (25 mg) in 1,2-dichloroethane (0.5 mL). The catalyst was activated by passing over a stream of hydrogen for 2 min. The solution was degassed and left under a stream of helium for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in dioxane (10 mL). 1 M tetrabutylammonium fluoride in dioxane (10 mL, 10.00 mmol) was added and the reaction mixture was stirred for 1 h at 20°C. The reaction mixture was diluted with CH_2Cl_2, washed with 1 M $NaHCO_3$ and a saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (15 g, elution: hexane/Et_2O, 100/0 to 50/50, v/v) of the crude product afforded pure **11b** (0.89 g, 83% yield). R_f 0.31 (system A), R_f 0.61 (system B). R_f 0.64 (system D). Mp 62-63°C (from pentane).

$C_{33}H_{38}O_6$	calc.	C	74.69	H	7.22
(530.7)	found		74.81		7.29

^{13}C{^{1}H}-NMR ($CDCl_3$): δ 12.09 and 12.27 (2 x CH_3, Prop), 71.01, 77.44, 80.62, 81.82, 82.34 and 83.89 (C-1, C-2, C-3, C-4, C-5 and C-6), 74.90, 75.54 and 75.60 (3 x OCH_2, Bzl), 99.86 and 101.29 (2 x -CH=, Prop), 127.57-128.19 (15 x CH, aromatic), 138.12 and 138.38 (3 x Cq, Bzl), 146.20 and 148.39 (2 x OCH=, Prop).
^{1}H-NMR ($CDCl_3$): δ 1.51 (dd, 3H, CH_3, Prop), 1.56 (dd, 3H, CH_3, Prop), 2.25 (d, 1H, 3-OH, (exchangeable)), 3.39 (dd, 1H, H-5, $J_{5,6}$ = 9.5 Hz), 3.54 (ddd, 1H, H-3, $J_{3,4}$ = 9.5 Hz, $J_{3,OH}$ = 7.0 Hz), 3.64 (dd, 1H, H-1, $J_{1,2}$ = 2.5 Hz), 3.86 (dd, 1H, H-4, $J_{4,5}$ = 9.5 Hz), 3.97 (dd, 1H, H-6, $J_{6,1}$ = 10.0 Hz), 4.06 (dd, 1H, H-2, $J_{2,3}$ = 3.0 Hz), 4.61-4.84 (m, 6H, 3 x OCH_2, Bzl), 4.99 (dq, 1H, -CH=, Prop, $J_{2,3}$ = 7.0 Hz), 5.00 (dq, 1H, -CH=, Prop, $J_{2,3}$ = 7.0 Hz), 6.19 (dq, 1H, OCH=, Prop, $J_{1,2}$ = 12.0 Hz, $J_{1,3}$ = 1.5 Hz), 6.26 (dq, 1H, OCH=, Prop, $J_{1,2}$ = 12.0 Hz, $J_{1,3}$ = 1.5 Hz), 7.20-7.39 (m, 15H, H aromatic).

***Bis*(1-[6-trifluoromethyl]benzotriazolyl)methylphosphonate (12)**
A solution of methylphosphonic dichloride (1.33 g, 10.00 mmol) in anhydrous dioxane (10 mL) was added dropwise to stirred solution of dry 1-hydroxy-6-trifluoromethylbenzotriazole (4.06 g, 20.00 mmol) and pyridine (1.62 mL, 20 mmol) in anhydrous dioxane (40 mL) at 20°C. The solution was stirred for 1 h at 20°C and the salts were removed by filtration. The 0.2 M stock solution of **12** (^{31}P-NMR: δ 47.60) thus obtained could be stored for several weeks at -20°C.

***N,N*-diisopropyl dibenzyl phosphoramidite (13)**
To a cooled (-10°C) solution of *N,N*-diisopropyl dichlorophosphoramidite[29] (10.1 g, 50.00 mmol) in anhydrous Et_2O (150 mL) was added dropwise a solution of benzyl alcohol (10.35 mL, 100.15 mmol) and Et_3N (15.30 mL, 109.98 mmol) in anhydrous Et_2O (100 mL) over 1 h. The reaction mixture was stirred for 2 h at 20°C and the salts were filtered off. The ethereal phase was washed with 1 M $NaHCO_3$ and a saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (250 g, elution: hexane/Et_3N, 97.5/2.5 to 95/5, v/v) of the crude product afforded **13** (15.35 g, 89% yield), as an oil.
^{31}P-NMR (CH_3CN): δ 148.99.

1,2,5,6-tetra-*O*-benzyl-*myo*-inositol 3-(benzyl methylphosphonate) (15a)
A solution of compound **12** in dioxane (0.2 M, 7.00 mL, 1.40 mmol) was added to **11a** (0.73 g, 1.26 mmol), which had been dried by repeated coevaporation with pyridine. The reaction was stirred for 5 min at 20°C. Subsequently benzyl alcohol (0.26 mL, 2.52 mmol) and *N*-methylimidazole (0.50 mL, 6.28 mmol) were added and the reaction mixture was stirred for another 1 h at 20°C. After addition of 1 M TEAB the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 M TEAB and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. R_f 0.33 (system B), R_f 0.31 (system D). ^{31}P-NMR (CH_2Cl_2): δ 30.82 and 33.70 (ratio, 1/4).

To a solution of the crude **14a** in CH_2Cl_2 (7.5 mL) was added 0.2 N HCl in MeOH (7.5 mL) and the reaction mixture was stirred for 1 h at 20°C. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 M TEAB and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (12.5 g, elution: hexane/EtOAc, 100/0 to 50/50, v/v) of the crude product afforded pure **15a** (0.79 g, 89% yield), as an oil. R_f 0.50 (system C).

$C_{42}H_{45}O_8P$	calc.	C	71.17	H	6.40	P	4.37
(708.8)	found		70.97		6.32		4.30

^{31}P-NMR (CH_2Cl_2): δ 31.82 and 34.51 (ratio, 1/4).

2,5,6-tri-*O*-benzyl-*myo*-inositol 3-(benzyl methylphosphonate) (15b)

A solution of compound **12** in dioxane (0.2 M, 7.00 mL, 1.40 mmol) was added to **11b** (0.66 g, 1.25 mmol), which had been dried by repeated coevaporation with pyridine. The reaction was stirred for 5 min at 20°C. Subsequently benzyl alcohol (0.26 mL, 2.52 mmol) and *N*-methylimidazole (0.50 mL, 6.28 mmol) were added and the reaction mixture was stirred for another 1 h at 20°C. After addition of 1 M TEAB the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 M TEAB and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. R_f 0.36 (system B), R_f 0.31 (system D). ^{31}P-NMR (CH_2Cl_2): δ 30.92 and 33.82 (ratio, 1/4).

To a solution of the crude **14b** in CH_2Cl_2 (7.5 mL) was added 0.2 N HCl in MeOH (7.5 mL) and the reaction mixture was stirred for 1 h at 20°C. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 M TEAB and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (10 g, elution: hexane/EtOAc, 100/0 to 50/50, v/v) of the crude product afforded pure **15b** (0.68 g, 88% yield), as an oil. R_f 0.32 (system C).

$C_{35}H_{39}O_8P$	calc.	C	67.95	H	6.35	P	5.01
(618.7)	found		67.78		6.38		5.09

^{31}P-NMR (CH_2Cl_2): δ 32.40 and 34.63 (ratio, 1/4).

***myo*-Inositol 3-(methylphosphonate) (Na^+-form) (16)**

Compound **15a** (0.14 g, 0.20 mmol) was dissolved in a mixture of MeOH and H_2O (25 mL, 4/1, v/v) and hydrogenated over 10% palladium on charcoal (0.20 g) at 500 kPa for 16 h at 20 °C. The solution is filtered and concentrated *in vacuo* (30°C) to a small volume. After Sephadex C-25 (Na^+-form, 0.9 g, 2.1 mmol) cation-exchange and lyophilization, **16** (49 mg, 89% yield) was obtained, as a white solid (see Table).

$C_7H_{14}O_8PNa$	calc.	P	11.06
(280.2)	found		10.88

1,2,5,6-tetra-*O*-benzyl-*myo*-inositol 3-(benzyl methylphosphonate) 4-(dibenzylphosphate) (17a)

A mixture of compound **15a** (355 mg, 0.50 mmol) and amidite **13** (0.26 g, 0.75 mmol) was coevaporated with toluene (2 x 10 mL) and dissolved in CH_2Cl_2 (3 mL). Subsequently a solution of 1*H*-tetrazole (65 mg, 0.93 mmol) in CH_3CN (3 mL) was added and the reaction mixture was stirred for 15 min. ^{31}P-NMR showed the presence of four peaks (δ 32.06 and 33.57 (ratio, 1/4), 142.91 and 143.00 (ratio, 1/4)). The reaction mixture was cooled (0°C) and *tert*-butyl hydroperoxide (0.38 mL) was added and stirring was continued for 45 min at 0°C. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 M TEAB and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (7.5 g, elution: hexane/EtOAc, 100/0 to 50/50, v/v) of the crude product afforded homogeneous **17a** (432 mg, 89% yield), as an oil. R_f 0.51 (system C).

$C_{56}H_{58}O_{11}P_2$	calc.	C	69.41	H	6.03	P	6.39
(969.0)	found		69.27		6.12		6.21

^{31}P-NMR (CH_2Cl_2): δ -1.00, 33.82 and 34.03 (ratio, 4/1).

2,5,6-tri-*O*-benzyl-*myo*-inositol 3-(benzyl methylphosphonate) 1,4-*bis*(dibenzylphosphate) (17b)

A mixture of compound **15b** (0.31 g, 0.50 mmol) and amidite **13** (0.52 g, 1.51 mmol) was coevaporated with toluene (2 x 15 mL) and dissolved in CH_2Cl_2 (5 mL). Subsequently a solution of 1*H*-tetrazole (0.13 g, 1.86 mmol) in CH_3CN (5 mL) was added and the reaction mixture was stirred for 15 min. ^{31}P-NMR showed the presence of five peaks (δ 32.24 and 33.70 (ratio, 1/4), 141.22, 142.94 and 143.30 (ratio, 1/4)). The reaction mixture was cooled (0°C) and *tert*-butyl hydroperoxide (0.75 mL) was added and stirring was continued for 45 min at 0°C. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 M TEAB and H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (7.5 g, elution: hexane/EtOAc, 100/0 to 50/50, v/v) of the

crude product afforded homogeneous **17b** (525 mg, 92% yield), as an oil. R_f 0.42 (system C).

$C_{63}H_{65}O_{14}P_3$	calc.	C	66.43	H	5.75	P	8.16
(1139.1)	found		66.65		5.72		8.04

^{31}P-NMR (CH_2Cl_2): δ -1.06, -0.94, 33.91 and 34.06 (ratio, 4/1).

***myo*-Inositol 3-(methylphosphonate) 4-phosphate (Na^+-form) (18a)**

Compound **17a** (198 mg, 0.20 mmol) was dissolved in a mixture of MeOH and H_2O (25 mL, 4/1, v/v) and hydrogenated over 10% palladium on charcoal (0.20 g) at 500 kPa for 16 h at 20°C. The solution was filtered and concentrated *in vacuo* (30°C) to a small volume. After Sephadex C-25 (Na^+-form, 2.6 g, 6.0 mmol) cation-exchange and lyophilization **18a** (72 mg, 87% yield) was obtained, as a white solid (see Table).

$C_7H_{13}O_{11}P_2Na_3$	calc.	P	15.33
(404.1)	found		15.12

***myo*-Inositol 3-(methylphosphonate) 1,4-*bis*(phosphate) (Na^+-form) (18b)**

Compound **17b** (219 mg, 0.19 mmol) was dissolved in a mixture of MeOH and H_2O (25 mL, 4/1, v/v) and hydrogenated over 10% palladium on charcoal (0.20 g) at 500 kPa for 16 h at 20°C. The solution was filtered and concentrated *in vacuo* (30°C) to a small volume. After Sephadex C-25 (Na^+-form, 4.2 g, 9.7 mmol) cation-exchange and lyophilization **18b** (86 mg, 85% yield) was obtained, as a white solid (see Table).

$C_7H_{12}O_{14}P_4Na_5$	calc.	P	17.60
(528.0)	found		17.48

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