Application of the Bifunctional Phosphonylating Agent Bis[6-(trifluoromethyl)benzotriazol-1-yl] Methylphosphonate Towards the Preparation of Isosteric D-*myo*-Inositol Phospholipid and Phosphate Analogues

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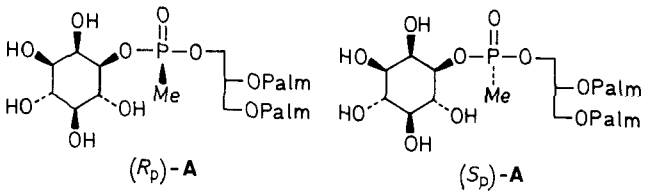
The individual diastereoisomeric methylphosphonate analogues of phosphatidyl-D-*myo*-inositol **A** (R_p and S_p) and D-*myo*-inositol 1-*(sodium methylphosphonate) were prepared using the bifunctional* phosphonylating agent bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate.

It is well established that receptor mediated activation of the enzyme phospholipase C is responsible for the cleavage of phosphatidylinositol [4,5]bisphosphate (PtdIns[4,5]P_2) into the second messengers *myo*-inositol 1,4,5-trisphosphate[1] and diacylglycerol.[2] The PtdIns[4,5]P_2 supply is maintained by sequential phosphorylation of the more abundant phosphatidylinositol by specific 4- and 5-kinases.[3]

After the pioneering work by Shvets and others,[4,5] several methods[6-12] towards the synthesis of inositol phospholipids and analogues thereof were published. For example, the individual diastereoisomeric phosphorothioate analogues of PtdIns[10-12] have been employed to determine the stereochemical course of the cleavage reaction by PtdIns-specific phospholipase C.

As part of an ongoing programme[7] directed towards the preparation of inositol phospholipids and phosphate analogues thereof, we now report a general method for the synthesis of the diastereoisomeric and uncharged methylphosphonate analogues **A** (R_p and S_p), which may act as potential phospholipase C inhibitors.



The target methylphosphonate analogues **A** could be obtained by the following three consecutive operations: (a) synthesis of a suitably protected D-*myo*-inositol derivative; (b) methylphosphonate diester bond formation and finally removal of the benzyl protecting groups.

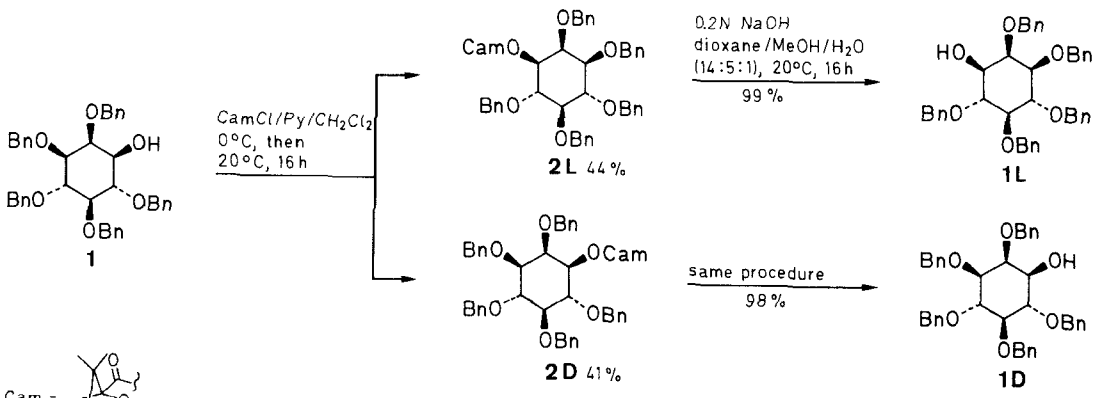
Firstly, optical resolution of 2,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (**1**), prepared in six steps from *myo*-inositol,[13] was accomplished (Scheme 1) by converting **1** into the corresponding diastereoisomeric camphanates **2**.[14] The individual diastereoisomers (**2L** and **2D**) were then separated by silica gel column chromatography.

Subsequent hydrolysis of the camphanates from the individual diastereomers (**2L** and **2D**) furnished the enantiomers **1L** and **1D**, respectively.

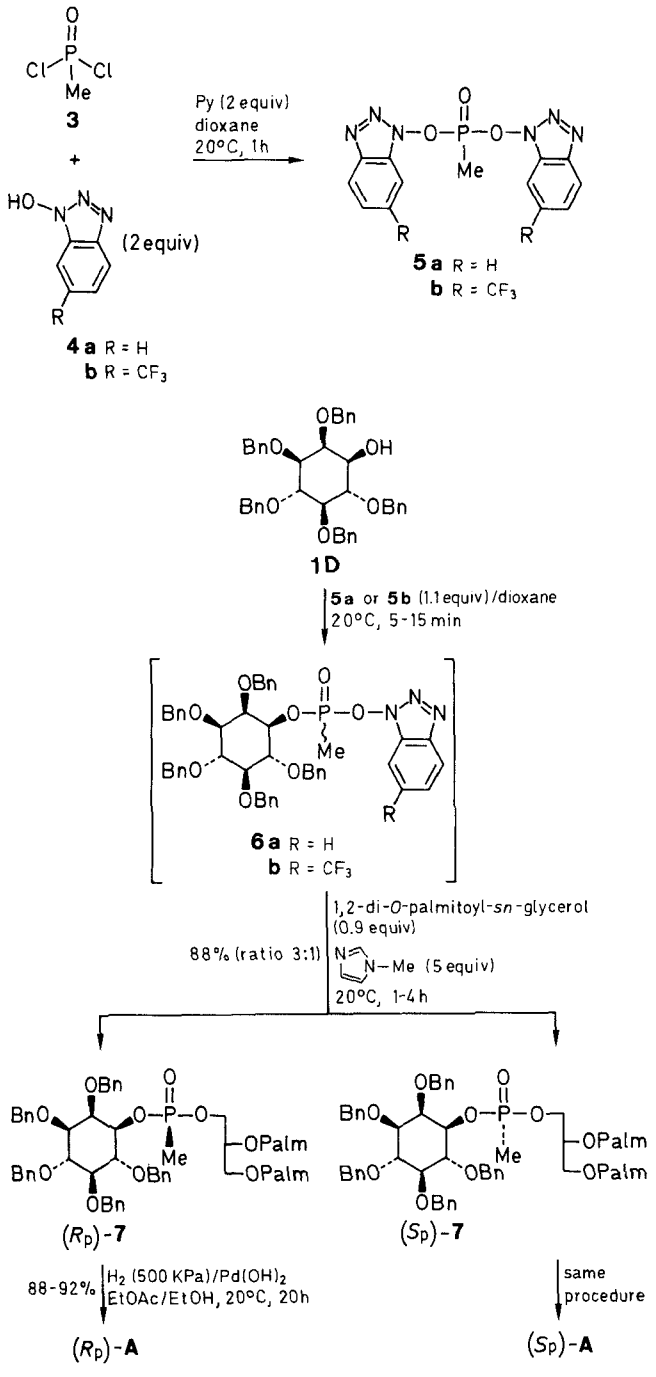
Based on the observed negative value of the specific rotation[15-18] of one enantiomer (i.e. **1D**), we concluded[19] that the lower running camphanate **2D** must be derived from 2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol.

Secondly, the introduction of the methylphosphonate diester bond between the *myo*-inositol derivative **1D** and 1,2-di-*O*-palmitoyl-*sn*-glycerol was realized by the two-step one-pot phosphonylation procedure shown in Scheme 2.

Alcohol **1D** was reacted with a slight excess of the bifunctional phosphonylating agent **5a**, prepared[20] in situ from methylphosphonic dichloride (**3**) and 1-hydroxybenzotriazole (**4a**), to give, after 15 min, the putative (benzotriazol-1-yl) methylphosphonate **6a**. Intermediate **6a** was treated with 1,2-di-*O*-palmitoyl-*sn*-glycerol[21] in the presence of *N*-methylimidazole to afford, after 4 h at 20 °C, the diastereoisomeric methylphosphonate diesters **7**. Since the second phosphonylation step proceeded rather sluggishly, we expected[22] that replacement of the benzotriazolyl by 6-(trifluoromethyl)benzotriazolyl groups would result in a more reactive phosphonylating



Scheme 1

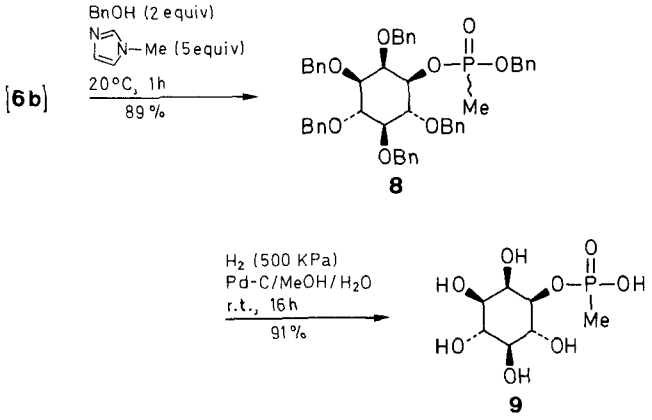


Scheme 2

agent. Indeed, when alcohol **1D** was treated with a small excess of the new bifunctional phosphonylating agent **5b**, prepared in a similar fashion as described for **5a**, intermediate **6b** was formed after 5 min at 20 °C. Subsequent addition of 1,2-di-*O*-palmitoyl-*sn*-glycerol and *N*-methylimidazole afforded, within 1 h at 20 °C, the diastereoisomeric methylphosphonate diesters **7** (R_p and S_p) in high yield. In this respect it is noteworthy that the individual diastereoisomers **7** were readily separated by silica gel column chromatography. The assignment of the absolute configuration at the phosphorus center is presently under investigation.

Finally, in order to prohibit migration of the methylphosphonate diester function to adjacent positions, it was obligatory to execute the hydrogenolysis of the benzyl groups from the individual diastereoisomers **7** (R_p and S_p) under neutral conditions. Attempts to remove the benzyl groups in the presence of palladium on charcoal failed. However, the individual diastereoisomers of **7** were deprotected, without the occurrence of unwanted sideproducts by hydrogenolysis, in the presence of palladium hydroxide, to furnish the homogeneous D-*myo*-inositol methylphosphonolipids **A**.

The successful preparation of the isosteric analogues of PtdIns **A**, urged us to find out whether the phosphonylating agent **5b** could also be applied to the synthesis of *myo*-inositol phosphate analogues. To this end (Scheme **3**), benzyl alcohol was added to the intermediate active ester **6b** in the presence of *N*-methylimidazole to give, after 1 h at 20 °C, the fully protected *myo*-inositol methylphosphonate **8** as a diastereoisomeric mixture (ratio 1 : 3). Benzyl protecting groups could in this particular case be removed by hydrogenolysis over palladium on charcoal to yield the *myo*-inositol 1-phosphate analogue **9**, which may act as a potential *myo*-inositol monophosphatase inhibitor.



Scheme 3

In conclusion, the results presented in this paper clearly demonstrate that a new class of *myo*-inositol phospholipid and phosphate analogues is readily accessible using the effective bifunctional phosphonylating agent bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate (**5b**). Furthermore, we believe that reagent **5b** promises to be very convenient for the future synthesis of methylphosphonate mono- and diesters of other naturally occurring phosphate esters.

CH_2Cl_2 and pyridine 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). CH_2Cl_2 and pyridine were stored over molecular sieves 4 Å. Dioxane was distilled from $LiAlH_4$ (5 g per litre) and stored over molecular sieves 5 Å. Methylphosphonic dichloride (Janssen, Belgium), benzyl alcohol and *N*-methylimidazole were distilled before use. (−)-Camphanic chloride and Pd−C (10%) were purchased from Fluka (Switzerland). $Pd(OH)_2$−C moist was purchased from Janssen (Belgium). Sephadex C-25 was purchased from Pharmacia (Sweden). 1-Hydroxy-6-trifluoromethylbenzotriazole[23] was dried *in vacuo* over P_2O_5 for 70 h at 50 °C. 2,3,4,5,6-penta-*O*-benzyl-*myo*-inositol[13] and 1,2-di-*O*-palmitoyl-*sn*-glycerol[21] were prepared according to literature procedures. Triethylammonium bicarbonate buffer (TEAB, 2 M): a mixture of freshly

distilled triethylamine (825 mL) and H_2O (2175 mL) was saturated with CO_2 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); B, hexane/EtOAc (50:50); C, CH_2Cl_2/Et_2O (99:1); D, CH_2Cl_2/MeOH (85:15). Compounds were detected under UV light and by spraying with a solution of $KMnO_4$ (10 g) in 2% aq Na_2CO_3 or a solution of $(NH_4)_2MoO_4$ (25 g) and ammonium cerium(IV) sulfate (10 g) in 10% aq. 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. Optical rotations were measured at 20 °C using a Perkin-Elmer 141 Polarimeter. ^{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. TMS as internal standard for the ^{1}H- and ^{13}C-NMR spectra and 85% H_3PO_4 as external standard for the ^{31}P-NMR spectra.

1-*O*-Camphanyl-2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol (2L) and 1-*O*-Camphanyl-2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol (2D):
To a cooled solution (0 °C) solution of 2,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (**1**; 3.15 g, 5.00 mmol) in pyridine (25 mL) is added (−)-camphanic chloride (1.35 g, 6.24 mmol). After stirring for 16 h at 20 °C, MeOH (1 mL) is added and the mixture is concentrated *in vacuo*. The residue is taken up in CH_2Cl_2 (100 mL), washed with H_2O (25 mL), 1 M $NaHCO_3$ (25 mL) and H_2O (25 mL). The organic layer is dried ($MgSO_4$) and concentrated *in vacuo*. Medium-pressure silica gel column chromatography (220 g, elution: hexane/CH_2Cl_2, 10:90 to 0:100) of the crude product gives pure 1-*O*-camphanyl-2,3,4,5,6-penta-*O*-benzyl-L-*myo*-inositol **(2L)**; yield: 1.78 g (44%); R_f 0.24 (system A), R_f 0.21 (system C); mp 140.5–141 °C (*i*-Pr_2O/pentane); $[\alpha]_D^{20}$ +11.8° (*c* = 1, $CHCl_3$).

$C_{51}H_{54}O_9$	calc.	C 75.53	H 6.71
(811.0)	found	75.39	6.64

^{1}H-NMR ($CDCl_3$): δ = 0.90 (s, 3H, CH_3, camphanyl), 1.00 (s, 3H, CH_3, camphanyl), 1.08 (s, 3H, CH_3, camphanyl), 1.60–1.67 (m, 1H, CH_2, camphanyl), 1.76–1.90 (m, 2H, CH_2, camphanyl), 2.24–2.33 (m, 1H, CH_2, camphanyl), 3.57 (dd, 1H, $J_{3,4}$ = 10.0 Hz, H-3), 3.57 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 4.10 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 4.13 (dd, 1H, $J_{2,3}$ = 2.5 Hz, H-2), 4.17 (dd, 1H, $J_{6,1}$ = 10.5 Hz, H-6), 4.64–4.94 (m, 10H, 5 × OCH_2, benzyl), 4.98 (dd, 1H, $J_{1,2}$ = 2.5 Hz, H-1), 7.19–7.40 (m, 25 H_{arom}).

^{13}C{^{1}H}-NMR ($CDCl_3$): δ = 9.46 (CH_3, camphanyl), 16.38, 16.53 (2 × CH_3, camphanyl), 28.62, 30.52 (2 × CH_2, camphanyl), 53.96, 54.52 (2 × Cq, camphanyl), 72.77, 74.78, 74.99, 75.69 (5 × OCH_2, benzyl), 74.69, 75.74, 78.90, 80.65, 81.23, 83.19 (C-1, C-2, C-3, C-4, C-5, C-6), 90.58 (Cq, camphanyl), 127.02–128.19 (25 × CH, aromatic), 137.85, 138.09, 138.17, 138.38 (5 × Cq, benzyl), 167.05, 177.68 (2 × C=O).

And 1-*O*-camphanyl-2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol **(2D)**; yield: 1.66 g (41%); R_f 0.23 (system A), R_f 0.14 (system C); mp 156.5–157 °C (*i*-Pr_2O/pentane); $[\alpha]_D$ −18.9° (*c* = 1, $CHCl_3$).

$C_{51}H_{54}O_9$	calc.	C 75.53	H 6.71
(811.0)	found	75.67	6.76

^{1}H-NMR ($CDCl_3$): δ = 0.83 (s, 3H, CH_3, camphanyl), 0.96 (s, 3H, CH_3, camphanyl), 1.07 (s, 3H, CH_3, camphanyl), 1.61–1.70 (m, 1H, CH_2, camphanyl), 1.80–1.95 (m, 2H, CH_2, camphanyl), 2.23–2.32 (m, 1H, CH_2, camphanyl), 3.57 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 3.57 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 4.11 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 4.17 (dd, 1H, $J_{6,1}$ = 10.0 Hz, H-6), 4.21 (dd, 1H, $J_{2,3}$ = 2.0 Hz, H-2), 4.64–4.87 (m, 10H, 5 × OCH_2, benzyl), 4.90 (dd, 1H, $J_{1,2}$ = 2.5 Hz, H-1), 7.25–7.39 (m, 25 H_{arom}).

^{13}C{^{1}H}-NMR ($CDCl_3$): δ = 9.52 (CH_3, camphanyl), 16.47 (2 × CH_3, camphanyl), 28.79, 30.81 (2 × CH_2, camphanyl), 53.93, 54.63 (2 × Cq, camphanyl), 72.94, 74.58, 75.74 (5 × OCH_2, benzyl), 75.13, 78.81, 80.85, 81.29, 83.42 (C-1, C-2, C-3, C-4, C-5, C-6), 90.69 (Cq, camphanyl), 127.08–128.30 (25 × CH, aromatic), 137.88, 138.17, 138.26, 138.50 (5 × Cq, benzyl), 167.29, 177.71 (2 × C=O).

2,3,4,5,6-Penta-*O*-benzyl-L-*myo*-inositol (1L) and 2,3,4,5,6-Penta-*O*-benzyl-D-*myo*-inositol (1D):
The camphanate **2L** or **2D** (1.62 g, 2.00 mmol) is dissolved in 0.2 N NaOH in a mixture of dioxane/MeOH/H_2O (25 mL, 14:5:1) and stirred for 16 h at 20 °C. The mixture is concentrated *in vacuo* and the residue is taken up in CH_2Cl_2 (100 mL), washed with H_2O (2 × 25 mL). The organic layer is dried ($MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography (15 g, elution: hexane/Et_2O 100:0 to 50:50) of the crude product yields the pure enantiomer **1L** or **1D**, respectively.

1L; yield: 1.25 g (99%); R_f 0.28 (system A); mp 61.5–62.5 °C (*i*-Pr_2O/hexane); $[\alpha]_D^{20}$ +9.2° (*c* = 1, $CHCl_3$) (Lit.[15] mp 55–58 °C; $[\alpha]_D^{20}$ +9.2° (*c* = 3.25, $CHCl_3$); Lit.[16] mp 59–60 °C; $[\alpha]_D^{20}$ +14.0° (*c* = 0.34, $CHCl_3$); Lit.[17] mp 58.8–60 °C; $[\alpha]_D^{20}$ +13.9° (*c* = 0.3, $CHCl_3$); Lit.[18] mp 64–65 °C; $[\alpha]_D^{20}$ +10.0° (*c* = 1, $CHCl_3$)).

$C_{41}H_{42}O_6$	calc.	C 78.07	H 6.71
(630.8)	found	77.95	6.64

^{1}H-NMR ($CDCl_3$): δ = 2.22 (d, 1H, 1-OH, exchangeable), 3.46 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 3.48 (ddd, 1H, $J_{1,2}$ = 2.5 Hz, $J_{1,OH}$ = 6.5 Hz, H-1), 3.48 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 3.81 (dd, 1H, $J_{6,1}$ = 9.5 Hz, H-6), 4.03 (dd, 1H, $J_{2,3}$ = 2.5 Hz, H-2), 4.06 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 4.69–5.01 (m, 10H, 5 × OCH_2, benzyl), 7.24–7.36 (m, 25 H_{arom}).

^{13}C{^{1}H}-NMR ($CDCl_3$): δ = 72.33 (C-1), 72.88, 74.66, 75.42, 75.66, 75.77 (5 × OCH_2, benzyl), 77.06 (C-2), 81.03, 81.82, 82.08, 83.54 (C-3, C-4, C-5, C-6), 127.52–128.48 (25 × CH, aromatic), 138.17, 138.58, 138.67 (5 × Cq, benzyl).

1D; yield: 1.24 g (98%); R_f 0.27 (system A); mp 62.5–63 °C (*i*-Pr_2O/hexane); $[\alpha]_D^{20}$ −9.0° (*c* = 1, $CHCl_3$) (Lit.[16] mp 59.2–60 °C; $[\alpha]_D^{20}$ −13.5° (*c* = 0.16, $CHCl_3$); Lit.[17] mp 59.1–60 °C; $[\alpha]_D^{20}$ −13.5° (*c* = 0.3, $CHCl_3$)).

$C_{41}H_{42}O_6$	calc.	C 78.07	H 6.71
(630.8)	found	77.96	6.78

^{1}H-NMR and ^{13}C{^{1}H}-NMR spectral data are identical to those of compound **1L**.

Bis[6-(trifluoromethyl)benzotriazol-1-yl] Methylphosphonate (5b); Typical Procedure:
A solution of methylphosphonic dichloride (**3**; 1.33 g, 10.00 mmol) in anhydrous dioxane (10 mL) is added dropwise to a stirred solution of dry 1-hydroxy-6-trifluoromethylbenzotriazole (**4b**; 4.06 g, 20.00 mmol) and pyridine (1.62 mL, 20.06 mmol) in anhydrous dioxane (40 mL) at 20 °C. The solution is stirred for 1 h at 20 °C and the salts are removed by filtration. The 0.2 M stock solution of bis[6-(trifluoromethyl)benzotriazo-1-yl] methylphosphonate **(5b)** thus obtained can be stored for several weeks at −20 °C.

^{31}P-NMR: δ = 47.60.

2,3,4,5,6-Penta-*O*-benzyl-D-*myo*-inositol 1-(1,2-Di-*O*-palmitoyl-*sn*-glycer-3-yl Methylphosphonate) (7, R_p and S_p); Typical Procedure:
A solution of bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate **(5b)** in dioxane (0.2 M, 3.05 mL, 0.61 mmol) is added to 2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol **(1D)** (347 mg, 0.55 mmol), which has been dried by repeated coevaporation with pyridine (2 × 10 mL). The reaction is stirred for 5 min at 20 °C. Subsequently 1,2-di-*O*-palmitoyl-*sn*-glycerol (284 mg, 0.50 mmol) and *N*-methylimidazole (219 µL, 2.75 mmol) are added and the mixture is stirred for another 1 h at 20 °C. After addition of 1 M TEAB (1 mL), the mixture is diluted with CH_2Cl_2 (50 mL) and washed successively with H_2O (10 mL), 1 M TEAB (10 mL) and H_2O (10 mL). The organic layer is dried ($MgSO_4$) and concentrated *in vacuo*. Medium-pressure silica gel column chromatography (220 g, elution: hexane/EtOAc, 100:0 to 50:50) of the crude product affords the pure diastereoisomers of **7** as oils.

Higher running isomer of **7**; yield: 133 mg (21%); R_f 0.09 (system A), R_f 0.49 (system B).

$C_{77}H_{111}O_{12}P$	calc.	C 73.42	H 8.88	P 2.46
(1259.7)	found	73.57	8.78	2.50

^{13}C-NMR ($CDCl_3$): δ = 11.61 ($J_{C,P}$ = 147.90 Hz, CH_3), 14.02 (2 × CH_3, palmitoyl), 22.60–34.11 (28 × CH_2, palmitoyl), 61.64 (C-1, glycerol), 63.80 ($J_{C,P}$ = 5.87 Hz, C-3, glycerol), 69.63 ($J_{C,P}$ = 7.33 Hz, C-2, glycerol), 72.88, 75.10, 75.36, 75.74, 75.89 (5 × OCH_2, benzyl), 76.14 ($J_{C,P}$ = 7.32 Hz, C-1), 77.15 (C-2), 79.96 ($J_{C,P}$ = 4.40 Hz, C-6), 80.65, 81.38, 83.31 (C-3, C-4, C-5), 127.40–128.22 (25 × CH_{arom}), 138.12, 138.47, 138.64 (5 × Cq, benzyl), 172.66, 172.95 (2 × C=O, palmitoyl).

^{31}P-NMR (CH_2Cl_2): δ = 31.34.

Lower running isomer of **7**; yield: 421 mg (67%); R_f 0.05 (system A), R_f 0.44 (system B).

$C_{77}H_{111}O_{12}P$	calc.	C 73.42	H 8.88	P 2.46
(1259.7)	found	73.52	8.81	2.41

^{13}C-NMR ($CDCl_3$): δ = 11.07 ($J_{C,P}$ = 143.50 Hz, CH_3), 14.02 (2 × CH_3, palmitoyl), 22.60–34.05 (28 × CH_2, palmitoyl), 61.64 (C-1, glycerol), 62.75 ($J_{C,P}$ = 5.86 Hz, C-3, glycerol), 69.42 ($J_{C,P}$ = 7.33 Hz, C-2, glycerol), 72.91, 74.99, 75.34, 75.77, 75.86 (5 × OCH_2, benzyl), 76.27 ($J_{C,P}$ = 5.87 Hz, C-1), 77.58 (C-2), 80.02 ($J_{C,P}$ = 4.40 Hz, C-6), 80.68, 81.38, 83.34 (C-3, C-4, C-5), 127.28–128.19 (25 × CH_{arom}), 138.09, 138.35, 138.58, 138.73 (5 × Cq, benzyl), 172.57 and 172.95 (2 × C=O, palmitoyl).

^{31}P-NMR (CH_2Cl_2): δ = 33.36.

D-*myo*-Inositol 1-(1,2-Di-*O*-palmitoyl-*sn*-glycer-3-yl Methylphosphonate) (Higher and Lower Running Isomer of A):

The higher or lower running isomer of **7** (125 mg, 0.099 mmol) is dissolved in a mixture of EtOAc and MeOH (25 mL, 3:1 v/v) and hydrogenated over $Pd(OH)_2$–C (175 mg) at 500 kPa for 20 h at 20°C. The solution is filtered and concentrated *in vacuo* (30°C). Silica gel column chromatography (1.5 g, elution: CH_2Cl_2/MeOH, 75:25, v/v) of the crude product affords pure D-*myo*-inositol 1-(1,2-di-*O*-palmitoyl-*sn*-glycer-3-yl methylphosphonate) **(A)**, as a solid. Higher running isomer of **A**; yield: 71 mg (88%); R_f 0.32 (system D).

$C_{42}H_{81}O_{12}P$	calc.	C 62.35	H 10.09	P 3.83
(809.1)	found	62.44	9.96	3.77

^{1}H-NMR ($CDCl_3$/CD_3OD, 3:1) δ = 0.89 (t, 6H, J = 7.0 Hz, 2 × CH_3, palmitoyl), 1.21–1.34 (m, 48H, 24 × CH_2, palmitoyl), 1.57–1.62 (m, 4H, 2 × C(=O)CH_2CH_2, palmitoyl), 1.60 (d, 3H, $J_{H,P}$ = 18.0 Hz, P–CH_3), 2.32 (t, 2H, J = 8.0 Hz, C(=O)CH_2, palmitoyl), 2.35 (t, 2H, J = 7.5 Hz, C(=O)CH_2, palmitoyl), 3.23 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5 inositol), 3.41 (dd, 1H, $J_{3,4}$ = 10.0 Hz, H-3 inositol), 3.66 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4 inositol), 3.82 (dd, 1H, $J_{6,1}$ = 9.0 Hz, H-6 inositol), 4.13 (dd, 1H, $J_{2,3}$ = 2.5 Hz, H-2 inositol), 4.16 (m, 1H, $J_{1,2}$ = 2.5 Hz, H-1 inositol), 4.16 (dd, 1H, $J_{1a,1b}$ = 12.0 Hz, $J_{1a,2}$ = 6.5 Hz, H-1a glycerol), 4.22 (ddd, 1H, $J_{3a,3b}$ = 11.5 Hz, $J_{3a,P}$ = 7.5 Hz, H-3a glycerol), 4.28 (ddd, 1H, $J_{3b,P}$ = 7.0 Hz, H-3b glycerol), 4.37 (dd, 1H, $J_{1b,2}$ = 3.5 Hz, H-1b glycerol), 5.27 (m, 1H, $J_{2,3a}$ = 6.0 Hz, $J_{2,3b}$ = 4.5 Hz, H-2 glycerol).

^{31}P-NMR (CH_2Cl_2/MeOH, 3:1): δ = 33.00.

Lower running isomer of **A**; yield: 74 mg (92%); R_f 0.32 (system D).

$C_{42}H_{81}O_{12}P$	calc.	C 62.35	H 10.09	P 3.83
(809.1)	found	62.26	10.14	3.89

^{1}H-NMR ($CDCl_3$/CD_3OD, 3:1) δ = 0.88 (t, 6H, J = 7.0 Hz, 2 × CH_3, palmitoyl), 1.24–1.34 (m, 48H, 24 × CH_2, palmitoyl), 1.58–1.64 (m, 4H, 2 × C(=O)CH_2CH_2, palmitoyl), 1.65 (d, 3H, $J_{H,P}$ = 18.0 Hz, P–CH_3), 2.33 (t, 2H, J = 7.5 Hz, C(=O)CH_2, palmitoyl), 2.36 (t, 2H, J = 7.5 Hz, C(=O)CH_2, palmitoyl), 3.23 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5 inositol), 3.42 (dd, 1H, $J_{3,4}$ = 10.0 Hz, H-3 inositol), 3.66 (dd, 1H, $J_{4,5}$ = 9.5 Hz, H-4 inositol), 3.81 (dd, 1H, $J_{6,1}$ = 9.5 Hz, H-6 inositol)), 4.12 (dd, 1H, $J_{2,3}$ = 3.0 Hz, H-2 inositol), 4.14 (ddd, 1H, $J_{1,2}$ = 2.5 Hz, $J_{H,P}$ = 9.0 Hz), H-1 inositol), 4.11–4.24 (m, 2H, H-3a, H-3b glycerol), 4.18 (dd, 1H, $J_{1a,1b}$ = 12.0 Hz, $J_{1a,2}$ = 6.5 Hz, H-1a glycerol), 4.38 (dd, 1H, $J_{1b,2}$ = 3.5 Hz, H-1b glycerol), 5.27 (m, 1H, $J_{2,3a}$ = 6.0 Hz, $J_{2,3b}$ = 4.5 Hz, H-2 glycerol).

^{31}P-NMR (CH_2Cl_2/MeOH, 3:1): δ = 35.29.

2,3,4,5,6-Penta-*O*-benzyl-D-*myo*-inositol 1-(Benzyl Methylphosphonate) (8):

A solution of bis[6-(trifluoromethyl)benzotriazol-1-yl] methylphosphonate **(5b)** in dioxane (0.2 M, 2.75 mL, 0.55 mmol) is added to 2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol **(1D)** (315 mg, 0.50 mmol), which has been dried by repeated coevaporation with pyridine (2 × 10 mL). The reaction is stirred for 5 min at 20°C. Subsequently BnOH (105 µL, 1.02 mmol) and *N*-methylimidazole (0.20 mL, 2.51 mmol) are added and the mixture is stirred for another 1 h at 20°C. After addition of 1 M TEAB (1 mL), the mixture is diluted with CH_2Cl_2 (50 mL) and washed with H_2O (10 mL), 1 M TEAB (10 mL) and H_2O (10 mL). The organic layer is dried ($MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography (10 g, elution: hexane/EtOAc, 100:0 to 50:50) of the crude product affords pure 2,3,4,5,6-penta-*O*-benzyl-D-*myo*-inositol 1-(benzyl methylphosphonate) **(8)** as an oil; yield: 357 mg (89%); R_f 0.05/0.03 (1:3) (system A), R_f = 0.31/0.26 (1:3) (system B).

$C_{49}H_{51}O_8P$	calc.	C 73.67	H 6.43	P 3.88
(798.9)	found	73.79	6.54	3.72

^{13}C-NMR (major isomer, $CDCl_3$): δ = 11.36 ($J_{C,P}$ = 143.50 Hz, CH_3), 66.52 ($J_{C,P}$ = 5.86 Hz, OCH_2, benzyl), 72.71, 74.84, 75.22, 75.69, 75.77 (5 × OCH_2, benzyl), 75.95 ($J_{C,P}$ = 5.86 Hz, C-1), 77.29 (C-2), 79.91 ($J_{C,P}$ = 4.40 Hz, C-6), 80.56, 81.23, 83.16 (C-3, C-4, C-5), 127.17–128.39 (30 × CH_{arom}), 136.04 (Cq, $J_{C,P}$ = 5.86 Hz, benzyl), 137.97, 138.20, 138.35, 138.44, 138.58 (5 × Cq, benzyl).

^{31}P-NMR (CH_2Cl_2): δ = 31.13/32.91 (1:3).

D-*myo*-Inositol 1-(Sodium Methylphosphonate) (9):

2,3,4,5,6-Penta-*O*-benzyl-D-*myo*-inositol 1-(benzyl methylphosphonate) (**8**; 197 mg, 0.25 mmol) is dissolved in a mixture of MeOH and H_2O (25 mL, 4:1), and hydrogenated over 10% Pd–C (200 mg) 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, 1.1 g, 2.53 mmol) cation-exchange and lyophilization, D-*myo*-inositol 1-(sodium methylphosphonate) **(9)** is obtained as a white solid; yield: 63 mg (91%).

$C_7H_{14}O_8PNa$	calc.	P 11.06	
(280.1)	found	10.85	

^{1}H-NMR (D_2O, pH = 2.00): δ = 1.40 (d, 3H, $J_{H,P}$ = 17.0 Hz, CH_3), 3.33 (dd, 1H, $J_{5,6}$ = 9.5 Hz, H-5), 3.56 (dd, 1H, $J_{3,4}$ = 10.0 Hz, H-3), 3.65 (dd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 3.73 (dd, 1H, $J_{6,1}$ = 10.0 Hz, H-6), 3.99 (ddd, 1H, $J_{1,2}$ = 3.0 Hz, $J_{H,P}$ = 9.0 Hz, H-1), 4.19 (dd, 1H, $J_{2,3}$ = 2.5 Hz, H-2).

^{31}P-NMR (D_2O, pH = 2.00): δ = 29.12.

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