Electronic Supplementary Information Part 1: Experimental Procedures

Development of a Solid Phase Synthesis Strategy for Soluble Phosphoinositide Analogues

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1 General Methods

All the chemicals and anhydrous solvents used were obtained from commercial suppliers (Sigma-Aldrich, VWR). The chiral starting material D-2,3-cyclohexylidene myo-inositol was purchased from SiChem GmbH, Bremen, Germany. The Wang resin (200-400 mesh, 0.97 mmol/g) was obtained from Bachem. The resin intermediates were dried properly on high vacuum before subjecting to the reactions.

$^1$H, $^{13}$C and $^{31}$P nuclear magnetic Resonance (NMR) spectra were recorded on a 400 MHz Bruker Avance DPX. Chemical shifts ($\delta$) are measured in ppm and coupling constants ($J$) are given in Hz. ($^1$H and $^{13}$C chemical shifts were referenced to the solvent peaks (7.26 and 77.0 ppm for CDCl$_3$, 4.84 and 49.05 for CD$_2$OD). Splitting patterns are designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet and dt = doublet of triplet. $^{13}$C and $^{31}$P spectra were broadband hydrogen decoupled. For $^1$H-assignment COSY and HMQC spectra were recorded. Assignment abbreviations for chemical groups: Ph = phenyl, cy = cyclohexylidene, myo = myo-inositol, MEM = methoxyethoxymethyl.

HPLC analysis and purifications were carried out on a Shimadzu High Performance Liquid Chromatograph/Mass Spectrometer LCMS-2010EV with a UV/Vis Photodiode array detector SPD-M20A Prominence. For the analytical and semi-preparative injections the solvent delivery module LC-20AD was used. And for the preparative injections the LC pump unit LC-8A was used. The analytical column was a Macherey Nagel C18 EC 250/4.0 NUCLEODUR 100-5 C18 ec. For semi-preparative separations the column was a Macherey Nagel C18 VP 250/10 NUCLEODUR 110-5 C18 ec. And for preparative separations a Macherey Nagel C18 VP 250/21 NUCLEODUR 100-5 C18 ec column was used.

Mass spectra (ESI) were recorded using a Waters Micromass ZQ mass spectrometer. High resolution mass spectra were recorded using a MaXis II Q-Tof mass spectrometer (Bruker Daltonics) and at the University of Heidelberg with a Bruker ApexQe hybrid 9.4 T FT-ICR. Masses are given as m/z (% intensity)

Optical rotations values were measured at the sodium D-line in a 10 cm cell with a Schmidt + Haensch Polartronic H532 polarimeter at room temperature.

TLC analyses were conducted on Merck precoated silica gel (Merck, 60 F$_{254}$) using UV light (254nm) or a solution of ceric ammonium molybdate (prepared by addition
of 40 mL conc. H$_2$SO$_4$, 360 mL H$_2$O, 10 g ammonium molybdate and 4 g ceric sulfate). Preparative column chromatography was performed using silica gel from Merck, (silica 60, grain size 0.063-0.200 mm, 70-230 mesh ASTM) or silica gel from Sigma-Aldrich (silica 60, 230-400 mesh).

Phosphoramidites were purified on deactivated silica. Prior to use the silica was treated with the eluent containing 10% of dimethylethylamine. For the purification 1% of dimethylethylamine was added to the eluent.

Melting points were determined on a Büchi B-540 and are uncorrected.

The release of phosphate from lipid substrates was monitored using a commercially available phosphatase assay kit, EnzChek, according to the manufacturer's instructions. The EnzChek phosphatase assay kit was purchased from Molecular Probes.

The assay was conducted in 96-well plate format and phosphate release was monitored by absorbance at 360 nm over time.

PRL-3 (6 µM) or Type IV 5-phosphatase (2 µM) in buffer (50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM MgCl$_2$, and 4 mM DTT) was incubated with 200 µM phosphoinositide substrates in 96-well plates. The assay was conducted at 37 °C with shaking in a Tecan Safire TM plate reader.

Assays in the absence of enzyme were included in the 96-well plate setup in triplicate for all the substrates analyzed. The measurements in the absence of enzyme were averaged and subtracted from the data to account for nonspecific hydrolysis of the substrates and for background absorption. In all phosphatase assays, measurements were in triplicate and the standard deviation of the measurements is represented as error bars. Data were plotted using SigmaPlot11.

Supplementary Scheme 1. Synthesis and numbering of all compounds on solid phase and final products. The reaction conditions and the stereochemistry of the compounds have been omitted for clarity.
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was concentrated and subjected to aqueous work-up. Reaction mixture was stirred at 4°C for 24 hrs. After completion the reaction mixture was subjected to aqueous work-up. Extraction with ethyl acetate

Supplementary Scheme 2. Solid phase synthesis of 23b and 23c. Reagents and conditions: (a) TASF, DMF, 32h, RT; (b) 3-Cbz-aminopropanoyl phosphoramidite or (BnO)2P(Br)2, DCI, CH2Cl2, CH3CN, 24 h followed by peracetic acid, -30°C to RT, 1h; (c) TFA, CH2Cl2, H2O, RT, 1h; (d) TMSBr, RT, 1h or overnight when 3-Cbz-aminopropanoyl phosphoramidite is used.

2 Synthetic procedures and analytical data:


1-O-t-Butyldiphenylsilyl-2,3-O-cyclohexylidene-myoinositol 8: To the solution of tetro 46 (1 g, 3.80 mmol, 1 equiv) and imidazole (393 mg, 5.70 mmol, 1.5 equiv.) in pyridine (23 mL) at -10°C was added TBDPS-Cl (1 g, 3.65 mmol, 0.96 equiv.). The reaction mixture was stirred at 4°C for 24 hrs. After completion the reaction mixture was concentrated and subjected to aqueous work-up. Extraction with ethyl acetate

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gave the crude product, which was purified with column chromatography (cyclohexane: ethyl acetate 30:70) giving pure product (1.5g, 3.01mmol, 79%) as a colorless solid. Rf 0.59 (cyclohexane: ethyl acetate 50:50)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) δ 7.78-7.76 (m, 2H), 7.73-7.71 (m, 2H), 7.45-7.36 (m, 6H), 3.91-3.87 (m, 2H), 3.74-3.66 (m, 2H), 3.64-3.59 (m, 1H), 3.12 (t, J = 9.69 Hz, 1H), 3.03 (brs, 1H), 2.88 (brs, 1H), 2.57 (brs, 1H), 1.75-1.66 (m, 5H), 1.52-1.40 (m, 5H), 1.32 (m, 1H), 1.10 (s, 9H)

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) δ 135.9, 133.7, 133.1, 129.8, 129.7, 127.7, 127.5, 78.08, 75.6, 75.5, 73.0, 72.5, 72.4, 38.2, 34.7, 26.9, 24.8, 23.9, 23.6, 19.4

Mp: 88-90 ºC

MS (ESI+): m/z (%): 521.2 (100) [M+Na]⁺

\([\alpha]_{D}^{20} = -19.4° \) (c = 1.0 in CH\(_3\)Cl), Literature: –22.7° (c = 1.5 in CHCl\(_3\)).


2.1 Benzoylation and MEM protection of 8 to obtain compounds 9-12

All the intermediates 9-12 were synthesized from intermediate 8 following a one-pot, two-step protocol.

Supplementary Scheme 4. Synthesis of compounds 9-12.

The solution of triol 8 (2.6 g, 5.22 mmol, 1 equiv.) in pyridine (27 mL) was cooled down to -40°C. A solution of BzCl (605 µL, 5.22 mmol, 1 equiv.) in CH\(_2\)Cl (27 mL)
was added dropwise to the mixture. The system was stirred at this temperature for 1h. After this time the solvent was evaporated and the crude mixture was used without further purification. Supplementary Figure 1 shows the HPLC trace of the reaction mixture.

For the HPLC analytical injection the following conditions were used: C18 column, 70-100% acetonitrile in water, flow rate: 1.5 mL/min, 22 min, \( \lambda = 215 \) nm.

The crude mixture (5.22 mmol) was then dissolved in CHCl\(_3\) (30 mL). Diisopropylethyl amine was added to this solution (13.8 mL, 78.30 mmol, 15 equiv.) followed by addition of methoxyethoxymethyl chloride (6 mL, 52.2 mmol, 10 equiv.). The reaction mixture was refluxed for 72h. The reaction was then quenched with NaHCO\(_3\) and extracted with ethyl acetate. The HPLC trace of the mixture is shown in Supplementary Figure 2.

For the HPLC analytical injection the following conditions were used: C18 column, 90-100% acetonitrile in water, flow rate: 1.5 mL/min, 22 min, \( \lambda = 215 \) nm.

The four intermediates were then purified with flash column chromatography (cyclohexane: ethyl acetate from 90:10 to 60:40).
Supplementary Figure 2. HPLC of the mixture after the reaction of the benzoylated derivatives with MEMCl (9-12).

1-O-t-Butyldiphenylsilyl-2,3-O-cyclohexyldiene-4,5-di-O-benzoyl-6-O-methoxyethoxymethyl-myoinositol 9: Colorless oil; 830 mg, 1.05 mmol, 20%. Rf 0.65 (cyclohexane: ethyl acetate 70:30).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.95-7.83 (m, 6H, Ph), 7.75-7.74 (m, 2H, Ph), 7.53-7.28 (m, 12H, Ph), 5.92 (m, 1H, CH-4-myoinositol), 5.24-5.20 (dd, J = 9.7, 6.9 Hz, 1H, CH-5-myoinositol), 5.0 (d, J = 5.9 Hz, 1H, CH$_2$MEM), 4.74 (d, J = 6.8 Hz, 1H, CH$_2$MEM), 4.35-4.32 (dd, J = 7.8, 3.8 Hz, 1H, CH-1-myoinositol), 4.15-4.12 (m, 2H, CH-6-myoinositol, CH-3-myoinositol), 4.01 (brs, 1H, CH$_2$-myoinositol), 3.50-3.46 (m, 1H, CH$_2$MEM), 3.41-3.35 (m, 1H, CH$_2$MEM), 3.21 (s, 3H, CH$_3$MEM), 3.17-3.12 (m, 1H, CH$_2$MEM), 3.06-3.03 (m, 1H, CH$_2$MEM), 1.99 (m, 1H, cy), 1.84 (m, 1H, cy), 1.74 (m, 2H, cy), 1.52-1.31 (m, 6H, cy), 1.15 (s, 9H, CH$_3$ TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) δ 165.8, 165.5, 136.1, 135.8, 133.5, 133.3, 133.0, 132.8, 129.9, 129.8, 129.7, 129.6, 128.2, 128.1, 127.8, 127.5, 96.7, 75.1, 74.8, 74.2, 71.2, 67.4, 58.8, 37.2, 34.3, 27.0, 26.9, 25.0, 23.9, 23.8, 19.3

MS (ESI+): m/z (%): 817.5 (100) [M+Na]$^+$

$[^{13}	ext{C}]_{D}^{20} = +9.71^\circ$ (c = 1.3 in CH$_3$Cl with 4% MeOH)
1-Ο-t-Butyldiphenylsilyl-2,3-cyclohexylidene-4-Ο-benzoyl-5,6-di-Ο-methoxyethoxymethyl-myoinositol 10: Colorless oil; 1.83 g, 2.35 mmol, 45%. Rf 0.53 (cyclohexane: ethyl acetate 70:30).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 8.02-8.00 (m, 2H, Ph), 7.83-7.77 (m, 4H, Ph), 7.54-7.51 (m, 1H, Ph), 7.43-7.34 (m, 8H, Ph), 5.68 (bs, 1H, CH-4-mylo), 4.88 (s, 1H, CH$_2$ MEM), 4.79-4.74 (m, 2H, CH$_2$ MEM), 4.67 (d, J = 7.0 Hz, 1H, CH$_2$ MEM), 4.19-4.16 (m, 1H, CH$_2$ MEM), 4.19-4.16 (m, 1H, CH$_2$ MEM), 4.0 (m, 1H, CH-3/5-mylo), 3.92 (bs, 2H, CH$_2$-2-mylo and CH$_2$-6-mylo), 3.72-3.70 (m, 1H, CH$_2$ MEM), 3.65-3.57 (m, 2H, CH-3/5-mylo and CH-1-mylo), 3.52-3.42 (m, 3H, CH$_2$ MEM), 3.39-3.37 (m, 1H, CH$_2$ MEM), 3.34 (s, 3H, CH$_3$ MEM), 3.21 (s, 3H, CH$_3$ MEM), 3.16-3.11 (m, 2H, CH$_2$ MEM), 1.93-1.90 (m, 1H, cy), 1.77-1.64 (m, 3H, cy), 1.49 (m, 4H, cy), 1.31-1.22 (m, 2H, cy), 1.12 (s, 9H, CH$_3$ TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) δ 165.0, 135.8, 135.7, 132.6, 129.9, 129.6, 129.5, 127.9, 127.4, 127.2, 96.3, 95.2, 78.0, 75.1, 75.0, 74.3, 71.4, 71.0, 67.3, 66.8, 58.6, 58.4, 36.7, 34.0, 26.8, 26.6, 24.8, 23.7, 23.5, 18.9

MS (ESI+): 801.5 [M+Na]$^+$

[$\alpha$]$_D^{20}$ = −3.84º (c = 1 in CH$_3$Cl)

1-Ο-t-Butyldiphenylsilyl-2,3-cyclohexylidene-5-Ο-benzoyl-4,6-di-Ο-methoxyethoxymethyl-myoinositol 11: Colorless oil; 590 mg, 0.75 mmol, 15%. Rf 0.37 (cyclohexane: ethyl acetate 70:30).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 8.0 (m, 2H, Ph), 7.82-7.80 (m, 2H, Ph), 7.71 (m, 2H, Ph), 7.61-7.58 (m, 1H, Ph), 7.42-7.28 (m, 8H, Ph), 5.0 (dd, J = 8.9, 5.9 Hz, 1H, CH-5-mylo), 4.91 (d, J = 6.8 Hz, 1H, CH$_2$-MEM), 4.86-4.84 (m, 1H, CH$_2$-MEM), 4.79-4.77 (d, J = 6.8 Hz, 1H, CH$_2$-MEM), 4.68-4.66 (d, J = 6.8 Hz, 1H, CH$_2$-MEM), 4.3 (brs, 1H, CH-4/6-mylo), 4.27-4.24 (m, 1H, CH-3/1-mylo), 4.0 (m, 2H, CH-2-mylo, CH1/3-mylo), 3.89 (brs, 1H, CH-4/6-mylo), 3.59-3.46 (m, 3H, CH$_2$-MEM), 3.39-3.32 (m, 3H, CH$_2$-MEM), 3.29 (s, 3H, CH$_3$-MEM), 3.21 (s, 3H, CH$_3$-MEM), 3.16-3.12 (m, 2H,
CH$_2$-MEM), 1.88 (m, 1H, cy), 1.77-1.70 (m, 3H, cy), 1.56-1.51 (m, 4H, cy), 1.39-1.33 (m, 2H, cy), 1.13 (s, 9H, CH$_3$ TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 165.4, 136.0, 135.7, 133.4, 133.3, 132.9, 129.8, 129.7, 129.6, 128.1, 127.6, 127.3, 95.0, 77.5, 77.4, 75.5, 74.3, 71.3, 71.1, 70.9, 67.2, 66.7, 58.7, 58.6, 33.8, 33.8, 26.9, 26.8, 26.7, 25.0, 23.9, 23.6, 19.1

MS (ESI+): m/z (%): 801.6 (100) [M+Na]$^+$

$[\alpha]_D^{20} = +19.72^\circ$ (c = 1.5 in CH$_3$Cl)

$1$-O-$\alpha$-Butyldiphenylsilyl-$2,3$-O-cyclohexyldiene-$4,5,6$-tri-$O$-methoxyethoxymethyl-xy-inositol 12: Colorless oil; 780 mg, 1.02 mmol, 20%. R$_f$ 0.16 (cyclohexane: ethyl acetate 70:30).

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.83-7.79 (m, 2H; Ph), 7.76-7.73 (m, 2H; Ph), 7.44-7.39 (m, 3H; Ph), 7.37-7.33 (m, 3H; Ph), 4.89 (dd, J = 14.7, 6.43 Hz, 2H, CH$_2$-MEM), 4.77 (dd, J = 13.9, 6.7 Hz, 2H, CH$_2$-MEM), 4.70 (bs, 1H, CH$_2$-MEM), 4.60 (bs, 1H, CH$_2$-MEM), 4.17-4.15 (m, 1H, CH-myo), 3.96-3.89 (m, 2H, CH-myo), 3.81-3.76 (m, 1H, CH$_2$-MEM), 3.75-3.67 (m, 3H, CH-myo and CH$_2$-MEM), 3.61-3.56 (m, 2H, CH$_2$-MEM), 3.54 (t, J=4.8 Hz, 3H, CH$_2$-MEM), 3.50-3.40 (m, 6H, CH-myo and CH$_2$-MEM), 3.38 (s, 3H, CH$_3$-MEM), 3.36 (s, 3H, CH$_3$-MEM), 3.32 (s, 3H, CH$_3$-MEM), 1.81-1.78 (m, 1H, cy), 1.72-1.65 (m, 3H, cy), 1.50-1.25 (m, 6H, cy), 1.09 (s, 9H, CH$_3$ TBDPS)

In this case the myo-inositol ring protons can be identified but not assigned. The identification is done with the HMQC and the APT spectra. However, the COSY spectra doesn’t allow for assignment.

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 136.2, 136.1, 133.8, 133.7, 129.8, 129.6, 127.7, 127.4, 110.0, 95.7, 95.5, 92.3, 79.0, 78.6, 78.3, 77.1, 74.3, 71.8, 71.8, 71.7, 71.0, 67.5, 67.4, 67.3, 59.0, 58.9, 36.8, 34.0, 27.1, 25.3, 24.1, 23.8, 19.2

MS (ESI+): m/z (%): 785.5 (100) [M+Na]$^+$

$[\alpha]_D^{20} = +4.16^\circ$ (c = 0.9 in CH$_3$Cl with 4% MeOH)
2.2 Cleavage of the cyclohexylidene ketal in 9-12

Supplementary Scheme 5. Cleavage of the cyclohexylidene ketal in 9 to yield 28a

1-\textit{O}-t-Butyldiphenylsilyl-4,5-di-\textit{O}-benzoyl-6-\textit{O}-methoxethoxymethyl-\textit{myo}-inositol 28a: 6 mL 65% formic acid in methanol were added to compound 9 (635 mg, 0.80 mmol) and it was stirred at room temperature for 48h. After completion of reaction (monitored by HPLC), it was quenched with saturated solution of NaHCO₃. Extraction with ethyl acetate gave the crude product. Percent conversion to product (by HPLC) 88%. Rᵥ 0.33 (cyclohexane: ethyl acetate 80:20).

HPLC conditions: C18 column, 70-100 acetonitrile in water, flow rate: 1.5 mL/min., λ = 215nm.

\[ t_R = 8.51 \text{ min; } m/z (\%) : 737 [M+Na]^+ \]

Supplementary Figure 3. Analytical run of the crude reaction product.

This compound was used without purification but a small amount was isolated for characterization.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.97-7.95 (m, 2H, Ph), 7.88-7.86 (m, 2H, Ph), 7.77-7.75 (m, 4H, Ph), 7.49-7.43 (m, 8H, Ph), 7.38-7.28 (m, 4H, Ph), 5.63 (t, $J = 9.9$ Hz, 1H, CH-4-myo), 5.41 (t, $J = 9.8$ Hz, 1H, CH-5-myo), 5.03 (d, $J = 7.0$ Hz, 1H, CH$_2$ MEM), 4.68 (d, $J = 7.0$ Hz, 1H, CH$_2$ MEM), 4.33 (t, $J = 9.4$ Hz, 1H, CH-6-myo), 4.0-3.97 (dd, $J = 9.3$, 2.5 Hz, 1H, CH-1-myo), 3.67 (m, 1H, CH-2-myo), 3.54-3.49 (dt, $J = 9.3$, 2.6 Hz, 1H, CH-3-myo), 3.46-3.41 (m, 1H, CH$_2$ MEM), 3.33-3.27 (m, 1H, CH$_2$ MEM), 3.14 (s, 3H, CH$_3$ MEM), 2.99-2.90 (m, 2H, CH$_2$ MEM), 2.71 (m, 1H, OH), 2.52 (m, 1H, OH), 1.12 (s, 9H, CH$_3$ from TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 166.9, 165.9, 135.8, 135.6, 133.4, 133.1, 133.0, 132.4, 130.3, 130.1, 129.8, 129.7, 129.2, 128.3, 128.2, 128.0, 127.9, 97.8, 78.2, 74.5, 74.1, 72.3, 71.8, 71.0, 70.6, 67.6, 58.7, 27.0, 26.9, 19.3

MS (ESI+): m/z (%): 737.3 (100) [M+Na]$^+$

$\left[\alpha\right]$_D$^{20} = +19.41^\circ$ (c = 1 in CH$_3$Cl)

**1-O-t-Butyldiphenylsilyl-4-O-benzoyl-5,6-di-O-methoxyethoxymethyl-myoinositol 28b**: To the compound 10 (510 mg, 0.65 mmol) 11mL 75% formic acid in methanol were added dropwise at -6°C. This reaction was stirred at -6°C for 40 h (reaction monitored by HPLC). The reaction was quenched with saturated solution of NaHCO$_3$. Extraction with ethyl acetate gave the crude product (410 mg), which was used for the next step without further purification. Percent conversion to product (by HPLC) 82%. $R_f$ 0.43 (cyclohexane: ethyl acetate 50:50)

HPLC conditions: C18 column, 70-100 acetonitrile in water, flow rate: 1.5 mL/min., $\lambda$ = 215nm.

t$_R$ = 6.8 min; m/z (%):721 [M+Na]$^+$. 
This compound was used without purification but a small amount was isolated and purified for characterization.

\[ ^1H-NMR \ (400 \text{ MHz, CDCl}_3) \delta 8.02-8.00 \text{ (m, 2H, Ph), 7.76-7.70} \text{ (m, 4H, Ph), 7.55-7.52} \text{ (m, 1H, Ph), 7.46-7.38} \text{ (m, 8H, Ph), 5.43} \text{ (t, J = 9.3 Hz, 1H, CH-4-myo), 5.0} \text{ (d, J = 6.4 Hz, 1H, CH2 MEM), 4.90} \text{ (d, J = 6.8 Hz, 1H, CH2 MEM), 4.85} \text{ (d, J = 6.3 Hz, 1H, CH2 MEM), 4.78} \text{ (d, J = 6.8 Hz, 1H, CH2 MEM), 4.0} \text{ (t, J = 9.0 Hz, 1H, CH-2/6-myo), 3.87-3.84} \text{ (dd, J = 9.1, 2.5 Hz, 1H, CH-1-myo), 3.81-3.76} \text{ (m, 1H, CH2 MEM), 3.69-3.64} \text{ (m, 1H, CH2 MEM), 3.65-3.61} \text{ (t, J = 9.0 Hz, 1H, CH-3/5-myo) 3.52-3.42} \text{ (m, 5H, 4H from CH2 MEM plus CH-2/6-myo), 3.36} \text{ (s, 3H, CH3 MEM), 3.32} \text{ (m, 1H, CH-3/5-myo), 3.19} \text{ (s, 3H, CH3 MEM), 3.12-3.10} \text{ (m, 2H, CH2 MEM), 2.44} \text{ (d, J = 9.7 Hz, 1H, OH), 2.35} \text{ (brs, 1H, OH), 1.10} \text{ (s, 9H, CH3 TBDPS)} \]

\[ ^{13}C-NMR \ (100 \text{ MHz, CDCl}_3) \delta 166.4, 135.7, 135.4, 133.4, 132.8, 132.4, 130.0, 129.8, 129.6, 128.1, 127.7, 127.6, 97.8, 96.9, 78.7, 76.9, 74.7, 74.1, 71.7, 71.6, 71.1, 70.7, 67.9, 67.4, 58.8, 58.5, 26.9, 26.7, 19.1 \]

MS (ESI+): m/z (%): 721.5 (100) [M+Na]+

\[ [\alpha]_D^{20} = -6.83^\circ \text{ (c = 0.95 in CH}_3\text{Cl)} \]

**1-O-t-Butyldiphenylsilyl-5-O-benzoyl-4,6-di-O-methoxyethylmethyl-myo-inositol 28c:** Same reaction conditions as 28b but the reaction time was 24h (reaction monitored by HPLC). Percent conversion to product (by HPLC) 88%; R\textsubscript{f} 0.43 (cyclohexane: ethyl acetate 50:50).
HPLC conditions: C18 column, 70-100 acetonitrile in water, flow rate: 1.5 mL/min., \( \lambda = 215 \text{nm} \).

\( t_R = 7.0 \text{ min} \); m/z (%): 721 [M+Na]⁺.

**Supplementary Figure 5.** Analytical run of the crude reaction product.

This compound was used without purification but a small amount was isolated and purified for characterization.

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.08-8.06 (m, 2H, Ph), 7.76-7.71 (m, 4H, Ph), 7.59-7.55 (m, 1H, Ph), 7.46-7.36 (m, 8H, Ph), 5.15 (t, \( J = 9.6 \text{ Hz} \), 1H, CH-5-myo), 5.0 (d, \( J = 7.0 \text{ Hz} \), 1H, CH\(_2\) MEM), 4.7 (d, \( J = 6.4 \text{ Hz} \), 2H, CH\(_2\) MEM), 4.23 (t, \( J = 9.5 \text{ Hz} \), 1H, CH-4/6-myo), 4.15 (brs, 1H, OH), 3.89 (t, \( J = 9.5 \text{ Hz} \), 1H, CH-4/6-myo), 3.85-3.82 (dd, \( J = 9.4, 2.4 \text{ Hz} \), 1H, CH-1/3-MEM), 3.75-3.70 (m, 1H, CH\(_2\) MEM), 3.69-3.67 (m, 1H, CH-2-myo), 3.54-3.50 (m, 1H, CH\(_2\) MEM), 3.42-3.38 (m, 3H, CH\(_2\) MEM), 3.27 (s, 3H, CH\(_3\) MEM), 3.30-3.24 (m, 2H, CH\(_2\) MEM plus CH-1/3-myo), 3.10 (s, 3H, CH\(_3\) MEM), 2.91-2.88 (m, 2H, CH\(_2\) MEM), 2.42 (brs, 1H, OH), 1.06 (s, 9H, CH\(_3\) TBDPS)

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \( \delta \) 165.6, 135.7, 135.6, 133.6, 133.0, 132.5, 130.0, 129.9, 129.8, 129.6, 128.3, 127.7, 97.7, 96.8, 82.0, 78.3, 74.3, 73.5, 71.7, 71.2, 70.9, 70.1, 67.7, 67.4, 58.7, 58.6, 26.9, 19.2

MS (ESI+): m/z (%): 721.5 (100) [M+Na]⁺

\([\alpha]_D^{20} = +37.11^\circ \) (c = 1 in CH\(_3\)Cl)
**1-O-t-Butyldiphenylsilyl-4,5,6-tri-O-methoxyethoxymethyl-myoinositol 28d:** Same reaction conditions as 28c. Percent conversion to product (by HPLC) 75%; R_f 0.34 (cyclohexane: ethyl acetate 30:70).

HPLC conditions: C18 column, 70-100 acetonitrile in water, flow rate: 1.5 mL/min., λ = 215nm.

t_R = 5.4 min; m/z (%): 705 [M+Na]^+.

**Supplementary Figure 6.** Analytical run of the crude reaction product.

This compound was used without purification but a small amount was isolated and purified for characterization.

**^1H-NMR (400 MHz, CDCl3)** δ 7.76-7.72 (m, 4H, Ph), 7.45-7.34 (m, 6H, Ph), 5.04 (d, J=6.4 Hz, 1H, CH2 MEM), 4.96 (d, J=6.6 Hz, 1H, CH2 MEM), 4.91-4.83 (m, 3H, CH2 MEM), 4.77 (d, J=7.1 Hz, 1H, CH2 MEM), 4.03 (t, J=9.5 Hz, 1H, CH myo-4), 3.86-3.77 (m, 4H, CH2 MEM), 3.71-3.66 (m, 3H, CH2 MEM plus CH myo-5), 3.63-3.58 (m, 3H, CH2 MEM plus CH myo-6), 3.55-3.49 (m, 5H, CH2 MEM plus CH myo-2), 3.37 (s, 6H, CH3 MEM), 3.36-3.35 (m, 1H, CH myo-3), 3.33 (s, 3H, CH3 MEM), 3.08 (d, J=8.9 Hz, 1H, CH myo-1), 1.07 (s, 9H, CH3 TBDPS)

**^13C-NMR (100 MHz, CDCl3)** δ 135.9, 135.8, 133.8, 132.8, 130.0, 129.9, 127.8, 127.8, 98.1, 97.8, 97.2, 78.8, 78.2, 74.4, 71.9, 71.9, 71.5, 71.4, 70.5, 68.1, 67.7, 67.6, 59.0, 27.1, 19.3

**MS (ESI):** m/z (%): 705.5 (100) [M+Na]^+
[α]D\textsubscript{20} = +20.49° (c = 1.35 in CH\textsubscript{3}OH)

2.3 Synthesis of 4-(dimethoxymethyl)phenol (48):

$$
\text{HO} \xrightarrow{\text{LiBF}_4, \text{CH(OMe)}_3, \text{MeOH, 65°C, 70 min}} \text{HO} \xrightarrow{\text{OMe}}
$$

Supplementary Scheme 6. Synthesis of 4-(dimethoxymethyl)phenol 48

4-(dimethoxymethyl)phenol 48: To the solution of 4-hydroxybenzaldehyde 47 (1 g, 8.19 mmol) and LiBF\textsubscript{4} (23.0 mg, 0.25 mmol) in anhydrous methanol (5 mL) was added trimethyl orthoformate (1.12 g, 10.6 mmol). After the reaction mixture was stirred at 65°C for 30 min, it was followed by addition of LiBF\textsubscript{4} (23.0 mg, 0.25 mmol) again and stirred the reaction at same temperature for further 40 minutes. After cooling to room temperature the reaction was quenched with saturated solution of NaHCO\textsubscript{3} and extracted with ethyl acetate. The vacuum dried crude product was directly used for the next step without purification, because the compound was observed to be unstable. The \textsuperscript{1}H NMR spectrum of the crude product shows the acetal aldehyde ratio as 2.5:1.

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) δ 9.86 (s, 0.40H, CHO from S.M.), 7.80 (d, J=8.7 Hz, 0.80H, Ar from S.M.), 7.32 (d, J=8.7 Hz, 2H, Ar), 6.94 (d, J=8.7 Hz, 0.80H, Ar from S.M.), 6.82 (d, J=8.7 Hz, 2H, Ar), 5.35 (s, 1H, CH acetal), 3.33, (s, 6H, CH\textsubscript{3})

2.4 Representative procedure for coupling of the acetal 48 with diols 28a-d:

1-O-\textit{t}-Butyldiphenylsilyl-2,3-O-p-hydroxybenzylidene-4,5-di-O-benzoyl-6-O-methoxyethoxymethyl-\textit{myo}-inositol 29a:
Supplementary Scheme 7. Coupling of the acetal 48 with diol 28a to obtain 29a.

29a. To the solution of diol 28a (88%, purity by HPLC), 400 mg, 0.56 mmol) and acetal 48 (71%, purity by NMR, 140 mg, 0.67 mmol) in dichloromethane (4 mL) was added molecular sieves (4Å) followed by addition of pyridinium p-toluenesulfonate (PPTS, 140 mg, 0.56 mmol). The reaction mixture was stirred at room temperature for overnight and at 40°C for 5 hrs. The reaction mixture was then cooled to room temperature and quenched with water. Extraction with ethyl acetate and purification with flash column chromatography (cyclohexane: ethyl acetate 80:20) gave the pure product as a foam (364 mg, 0.44 mmol, 64 % over two steps). Rf 0.23 (cyclohexane: ethyl acetate 80:20).

These compounds are obtained as a mixture of two diastereomers. The HPLC retention times and NMR data are included for each case.

For the HPLC analytical injection the following conditions were used: C18 column, 70-100% acetonitrile in water, flow rate: 1.5 mL/min, 22min, λ = 215nm. HMQC was used for identification of the protons from the different diastereomers. The proton from the aromatic acetal was used as reference for calculating the rest of integrals.

HPLC:

HPLC: $t_R = 10.55$ min; m/z (%) = 841 (100) [M+Na]$^+$

$t_R = 11.08$ min; m/z (%) = 841 (100) [M+Na]$^+$

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.01-7.99 (m, 1H, Ph), 7.94-7.91 (m, 2H, Ph), 7.80-7.78 (m, 2H, Ph), 7.73 (d, J = 6.8 Hz, 1H, Ph), 7.69 (d, J = 6.8 Hz, 1H, Ph), 7.56-7.47 (m, 4H, Ph), 7.43-7.29 (m, 10H, Ph), 7.19 (t, J = 7.6 Hz, 1H, Ph), 6.87-6.82 (m, 2H, Ph), 6.62 (t, J = 9.2Hz, 0.6H), 6.39 (s, 0.6H, acetal), 6.36 (bs, 1H), 5.64 (s, 0.4H,
acetal), 5.38-5.37 (m, 1H), 5.25 (dd, J = 4.9, 9.2, 0.4H), 5.18 (dd, J = 2.4, 9.5, 0.6H), 5.00 (q, J = 6.2 Hz, 2H), 4.81-4.82 (m, 0.4H), 4.71-4.64 (m, 1H), 4.61-4.57 (m, 1.6H), 4.49 (t, J=4.3 Hz, 0.6H), 4.45 (dd, J = 4.0, 6.7, 0.4H), 4.37-4.32 (m, 0.4H), 4.20 (bs, 0.4H), 3.98 (bs, 0.4H), 3.61 (s, 0.6H), 3.52-3.40 (m, 2H), 3.32-3.25 (m, 1H), 3.23 (s, 1.8H, CH$_3$ MEM), 3.21 (s, 1.2H, CH$_3$ MEM), 1.30 (s, 6H, CH$_3$ TBDPS), 1.22 (s, 3H, CH$_3$ TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 165.9, 157.4, 153.3, 136.2, 136.1, 133.2, 132.2, 132.1, 132.0, 131.8, 129.9, 129.8, 129.6, 128.6, 128.5, 128.2, 128.3, 127.7, 127.8, 115.3, 104.6, 104.2, 95.8, 77.9, 76.4, 76.0, 75.4, 74.9, 71.4, 71.2, 70.1, 67.4, 58.9, 27.2, 22.0

HRMS (ESI+): m/z pos.: [M+Na]$^+$ calculated 841.30146, found 841.30096 +0.6ppm

Mp: 85.1-88.0 °C

The other three compounds 29b, 29c and 29d were synthesized following the same procedure used for synthesis of 29a. And the same conditions used for 29a were used for the HPLC injections.

1-O-t-Butyldiphenylsilyl-2,3-O-p-hydroxybenzyldiene-4-O-benzoyl-5,6-di-O-methoxyethoxymethyl-myoinositol 29b.

White solid; 350 mg, 0.43 mmol, 61% over two steps. $R_f$ 0.22 (cyclohexane: ethyl acetate 60:40).

HPLC: $t_R$ = 8.72 min; m/z (%) = 825 (100) [M+Na]$^+$

$^{1}$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.08-8.05 (m, 2H, Ph), 7.82-7.79 (m, 4H, Ph), 7.56-7.52 (m, 1H, Ph), 7.46-7.28 (m, 10H, Ph), 6.81-6.76 (m, 2H, Ph), 6.34-6.32 (m, 1H, CH-4-myio), 6.30 (s, 1H, acetal), 4.59-4.55 (m, 2H, CH$_2$ MEM), 4.46-4.52 (m, 4H, CH$_2$ MEM plus CH-3/5 and CH-2/6-myio), 4.41 (t, J = 3.9 Hz, 1H, CH-1-myio), 4.15 (bres, 1H, CH-2/6-myio), 3.81 (dd, J = 9.2, 2.1 Hz, 1H, CH-3/5-myio), 3.50-3.45 (m, 3H, CH$_2$ MEM), 3.42-3.31 (m, 3H, CH$_2$ MEM), 3.28 (s, 3H, CH$_3$ MEM), 3.24 (s, 3H,
CH$_3$ MEM), 3.19-3.14 (m, 2H, CH$_2$ MEM), 1.43 (s, 3H, CH$_3$ TBDPS), 1.18 (s, 6H, CH$_3$ TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 165.8, 156.4, 136.4, 136.2, 133.6, 133, 132.8, 130.1, 129.9, 129.7, 128.4, 128.3, 127.8, 127.6, 115.1, 103.8, 95.3, 94.0, 78.0, 77.6, 76.9, 74.9, 72.9, 71.5, 71.4, 70.9, 67.4, 67.0, 59.0, 58.9, 27.2, 19.1

HRMS (ESI+): m/z pos.: [M+Na]$^+$ calculated 825.32767, found 825.32739 +0.3ppm

Mp: 115.4-118.8 ºC

1-O-t-Butyldiphenylsilyl-2,3-O-p-hydroxybenzylidene-5-di-O-benzoyl-4,6-di-O-methoxyethoxymethyl-myoinositol 29c. Yellowish oil; 400 mg, 0.50 mmol, 67% over two steps. $R_f$ 0.33 (cyclohexane: ethyl acetate 60:40).

HPLC: $t_R$ = 8.95 min (broad peak at 8.5-9.3 min.); m/z (%) = 825 (100) [M+Na]$^+$

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 8.01-7.97 (m, 2H, Ph), 7.74-7.64 (m, 4H, Ph), 7.62-7.56 (m, 1H, Ph), 7.47-7.36 (m, 4H, Ph), 7.30-7.19 (m, 6H, Ph), 6.84-6.80 (m, 2H, Ph), 6.24 (s, 0.6H, acetal), 5.58 (s, 0.4H, acetal), 5.31 (bs, 1H), 5.10 (dd, J = 4.9, 8.7, 0.4H), 5.05-4.99 (m, 1.4H), 4.87-4.80 (m, 2H), 4.59-4.54 (m, 1.4H), 4.41-4.34 (m, 2.6H), 4.14-4.07 (m, 0.6H), 3.68-3.62 (m, 1H), 3.60-3.54 (m, 1.6H), 3.52-3.38 (m, 2.6H), 3.33-3.30 (m, 1.6H), 3.27 (s, 1.8H, CH$_3$ MEM), 3.24 (s, 1.2H, CH$_3$ MEM), 3.23-3.22 (m, 2H), 3.20 (s, 1.8H, CH$_3$ MEM), 3.19 (s, 1.2H, CH$_3$ MEM), 1.14 (s, 6H, CH$_3$ TBDPS), 1.05 (s, 3H, CH$_3$ TBDPS)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 165.4, 156.9, 136.2, 136.0, 133.2, 132.7, 132.4, 130.0, 129.9, 128.6, 128.4, 128.2, 127.8, 127.7, 115.2, 103.5, 100.0, 95.3, 78.3, 78.0, 75.0, 74.8, 71.4, 70.9, 67.4, 66.9, 58.9, 58.9, 27.2, 19.3

HRMS (ESI+): m/z pos.: [M+Na]$^+$ calculated 825.32767, found 825.32722 +0.6ppm

1-O-t-Butyldiphenylsilyl-2,3-O-p-hydroxybenzylidene-4,5,6-tri-O-methoxyethoxymethyl-myoinositol 29d.
Yellowish oil; 530 mg, 0.67 mmol, 55% over two steps. \( R_f \) 0.40 (cyclohexane: ethyl acetate 30:70).

**HPLC:** \( t_R = 6.95 \text{ min} \); m/z (%) = 809 \( [\text{M} + \text{Na}]^+ \)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.78-7.70 (m, 4H, Ph), 7.45-7.25 (m, 8H, Ph), 6.81-6.76 (m, 2H, Ph), 6.19 (s, 0.6H, acetal), 5.57 (s, 0.4H, acetal), 5.38 (bs, 1H), 5.00-4.92 (m, 1H), 4.90 (s, 1H), 4.77 (dd, \( J = 6.8, 11.3, 1 \)H), 4.70 (dd, \( J = 6.9, 16.0, 1 \)H), 4.60 (t, \( J = 8.9, 1 \)H), 4.46 (dd, \( J = 6.7, 13.7, 1 \)H), 4.35-4.24 (m, 3H), 3.86-3.81 (m, 1H), 3.76-3.65 (m, 3H), 3.60-3.45 (m, 8H), 3.43-3.41 (m, 2H), 3.37 (s, 3H, CH\(_3\) MEM), 3.34 (s, 1.8H, CH\(_3\) MEM), 3.32 (s, 1.2H, CH\(_3\) MEM), 3.31 (s, 1.2H, CH\(_3\) MEM), 3.28 (s, 1.8H, CH\(_3\) MEM), 1.12 (s, 6H, CH\(_3\) TBDPS) 1.04 (s, 3H, CH\(_3\) TBDPS)

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 156.5, 136.3, 136.2, 136.1, 133.5, 133.0, 129.9, 129.7, 128.7, 128.1, 127.7, 127.6, 127.5, 127.3, 115.1, 114.9, 103.7, 103.4, 95.6, 95.5, 94.9, 79.2, 78.9, 78.5, 78.4, 78.3, 77.6, 75.6, 74.9, 71.8, 71.7, 71.6, 71.4, 67.5, 67.4, 67.3, 67.2, 59.0, 27.2, 27.1, 19.2

**HRMS (ESI\(^+\)):** m/z pos.: \([\text{M} + \text{Na}]^+\) calculated 809.35389, found 809.35349 +0.5 ppm

### 2.5 Representative procedure for loading on solid phase:

1-\(O\)-t-Butyldiphenylsilyl-2,3-\(O\)-(\(p\)-Wang-resin-oxy-)-benzylidene-4,5-di-\(O\)-benzoyl-6-\(O\)-methoxyethoxymethyl-\(\text{myo}\)-inositol 13:

![Supplementary Scheme 8](image)

**Supplementary Scheme 8.** Solid phase loading of compound 29a to obtain resin 13

The Wang resin (450 mg, 0.50 mmol, loading 1.1 mmol/g) was swollen in anhydrous THF (5 mL) for 30 min. A solution of alcohol 29a (1.22 g, 1.50 mmol, racemic) and triphenyl phosphine (393 mg, 1.50 mmol) in anhyd. THF was added to the swollen
Diisopropyl azodicarboxylate (303 mg, 1.50 mmol) was dissolved in anhyd. THF (2 mL) and was added dropwise to the resin mixture at room temperature. The resin was allowed to shake for 48 h. The mixture was then filtered and the resin was washed with THF (2 X), DMF (3 X), MeOH (3 X), again THF (2 X) and finally dichloromethane (3 X) and was then dried overnight in vacuo.

The weight of the resin after overnight in vacuum was 754 mg. That means that 304 mg of alcohol 29a (0.37 mmol) are loaded (754 mg – 450 mg). The amount of alcohol loaded represents 75% yield with respect to the Wang resin starting material.

20mg of this resin were treated with 10% TFA in DCM:MeOH (see also p.16 “Test cleavage”) to cleave the compound from the resin. The loading was 70%. Calculated from the resulting amount of compound.

Since the determination of the amount of alcohol loaded is very similar by both methods, for the rest of the resins the loading was calculated by weight difference.

The theoretical loading of all the product resins, also the following ones, was calculated using the formula described below, assuming 100% loading yield. These loadings were used to calculate the amount of materials required for the corresponding next reactions.

\[ L_2 = \frac{L_1}{1+(M_2-M_1)x L_1} \]

**Supplementary Equation 1.** \( L_2 \) = loading of product resin, \( L_1 \) = loading of reactant resin, \( M_2 \) = molecular weight of product, \( M_1 \) = molecular weight of reactant.

Accordingly for resin 13

\[ L_2 = 0.0011/1+(818.98-18)x0.0011 = 0.585 \text{ mmol/g} \]

This reaction was performed with the chiral and with the racemic material.

The following resins were obtained through the same reaction procedure.

Resin 14: **1-O-t-Butyldiphenylsilyl-2,3-O-(p-Wang-resin-oxy-)benzylidene-4-O-benzoyl-5,6-di-O-methoxyethoxymethyl-myoinositol**, 67% loading, corresponding to 0.127 mmol compound, chiral material.

\[ L_2 \] for Resin 14 and Resin 15
L_2 = 0.0011/(1+(802.98-18))x0.0011 = 0.591 mmol/g

Resin 15: 1-\textit{O-\textit{t-Butyldiphenylsilyl-2,3-O-(\textit{p-Wang-resin-oxy-})benzylidene-5-O-benzoyl-4,6-di-O-methoxyethoxymethyl-\textit{myo-inositol}}, 83% loading, corresponding to 0.130 mmol compound, chiral material.

Resin 16: 1-\textit{O-\textit{t-Butyldiphenylsilyl-2,3-O-(\textit{p-Wang-resin-oxy-})benzylidene-4,5,6-tri-O-methoxyethoxymethyl-\textit{myo-inositol}}, 84% loading, corresponding to 0.129 mmol compound, chiral material.

L_2 for Resin 16

L_2 = 0.0012/(1+(786.2-18))x0.0012 = 0.624 mmol/g

To load the inositol material 29a-d to the resin it has to be used in 3 fold excess. This however is no disadvantage, because excess chiral material can be recovered, purified and re-loaded to fresh resin (by using the same protocol described for the loading of 29a) without a decrease in the loading. It was observed that drying the resin and the alcohol overnight in vacuo is very important to get a good loading.

**Test Cleavage**

A small amount of all resins was cleaved to check the success of the loading reaction. Representative procedure:


To the preswelled resin 13 (5 mg) in \textit{CH}_2\textit{Cl}_2 was added a mixture of 10% TFA in \textit{CH}_2\textit{Cl}_2 containing 1% water. The resin was allowed to shake for 1 h, filtered and washed with \textit{CH}_2\textit{Cl}_2 for several times. All the washings were combined and evaporated to give the crude product, which was analyzed with ESI-MS. The MEM protecting group gets partially cleaved under these conditions.
Resin 13

**MS (ESI):** m/z (%): 649.4 (100) [M-MEM+Na]+, 737.5 (90) [M+Na]+

Resin 14:

**MS (ESI):** m/z (%): 633.4 (100) [M-MEM+Na]+

Resin 15:

**MS (ESI):** m/z (%): 633.2 (100) [M-MEM+Na]+, 721.5 (40) [M+Na]+

Resin 16:

**MS (ESI):** m/z (%): 617.3 (100) [M-MEM+Na]+, 529.2 (80) [M-2MEM+Na]+

### 2.6 Representative procedure for debenzoylation:

**1-O-t-Butyldiphenylsilyl-2,3-O-(p-Wang-resin-oxy-)benzylidene-6-O-methoxyethoxymethyl-myoinositol 17:**

Supplementary Scheme 10. Debenzoylation of resin 13 to yield resin 17

Resin 13 (300 mg, 0.15 mmol, loading 0.59 mmol/g) was swollen in anhyd. THF (8 mL) for 30 min., followed by the addition of 30% NaOMe in methanol (2 mL). The resin mixture was then allowed to shake for 24 h. The mixture was filtered and the resin was washed with THF (3 X), methanol (3 X), methanol:water (3:1, 3 X), methanol (3 X), DMF (3 X) and finally DCM (3 X). The resin was dried overnight in vacuo.

The formation of the product was confirmed by test cleavage using the same procedure as described for resin 13 (Supplementary Scheme 9).

Resin 17

HPLC:
C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., λ = 215nm.

\[ t_R = 10.13 \text{ min}; \ m/z (\%) : 441 \ [M-\text{MEM+Na}]^+ \]

\[ t_R = 11.95 \text{ min}; \ m/z (\%) : 529 \ [M+Na]^+ \]

The other derivatives 19 and 21 were synthesized using the same method described above.

Resin 19: 1\text{-}O\text{-}t\text{-}Butyldiphenylsilyl\text{-}2,3\text{-}O\text{-(p-Wang-resin-oxy-)}\text{benzylidene-5,6-di-}
\text{O\text{-}methoxyethoxymethyl\text{-}myo\text{-}inositol}

MS (ESI): m/z (%): 529.4 (100) [M-\text{MEM+Na}]^+, 617.4 (100) [M+Na]^+

Resin 21: 1\text{-}O\text{-}t\text{-}Butyldiphenylsilyl\text{-}2,3\text{-}O\text{-(p-Wang-resin-oxy-)}\text{benzylidene-4,6-di-}
\text{O\text{-}methoxyethoxymethyl\text{-}myo\text{-}inositol}

HPLC:

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., λ = 215nm.

\[ t_R = 11.72 \text{ min}; \ m/z (\%) : 529 \ [M-\text{MEM+Na}]^+ \]

\[ t_R = 12.72 \text{ min}; \ m/z (\%) : 617 \ [M+Na]^+ \]

### 2.7 Representative procedure for the regioselective opening of the 3-position:

Resin 18: 1\text{-}O\text{-}t\text{-}Butyldiphenylsilyl\text{-}2\text{-(p-Wang-resin-oxy-)}\text{benzyl-6-}
\text{O\text{-}methoxyethoxymethyl\text{-}myo\text{-}inositol}

\[
\begin{array}{c}
\text{BzO} \quad \text{O} \\
\text{OTBDPS} \\
\text{BzO} \quad \text{OBzMEM}
\end{array}
\quad \xrightarrow{\text{DIBAL-H, DCM}}
\quad
\begin{array}{c}
\text{OH} \quad \text{O} \\
\text{OTBDPS} \\
\text{OMEM}
\end{array}
\]

\[-78^\circ \text{C 1h, to rt} \]

Supplementary Scheme 11. Regioselective opening of resin 13 with DIBAL-H.
The resin 13 (200 mg, 0.10 mmol, loading 0.58 mmol/g) was placed in a Schlenk tube and was swelled in anhyd. toluene (2 mL) for 30 min. After this time the solvent was evaporated and the resin was dried under vacuum overnight to remove the traces of water. After this time the resin was swelled in anhyd. DCM (2 mL) for 30 min and the system was cooled to -78°C. At this temperature DIBAL-H 1.0 M in DCM (1 mL, 1 mmol) was added dropwise. The resin was stirred at the same temperature for 1 h, then stirred at -65°C for 1 h and at -30°C for 1 h. The reaction was then quenched with the addition of MeOH. The mixture was filtered and the resin was washed with THF (3 X), THF:water (1:1, 5 X), MeOH (3X) and DCM (3X). The resin was dried overnight in vacuo.

Resin 22: 1-\textit{O-t-}Butyldiphenylsilyl-2-\textit{O-(p-Wang-resin-oxy-)}benzyl-4,5,6-tri-\textit{O-methoxyethoxymethyl-\textit{myo-inositol} was prepared as described above for 18a.}

2.7.1 Butyrylation of intermediate 18 to determine selective opening

![Diagram](image_url)

**Supplementary Scheme 12.** Butyrylation and DDQ cleavage of resin 18.

The regioselective opening at 3-position was proven by butyrylation of intermediate 18. This reaction also proved that for intermediate 18 the DIBAL-H opening also debenzoylated 4 and 5 positions of compound 13.

Resin 18 (30.0 mg, 0.02 mmol, loading 0.67 mmol/g, 1 equiv.) was swelled in pyridine for 30 min. DMAP (5 mg, catalytic) was added to the system followed by addition of Bt\(_2\)O (110 \(\mu\)L, 0.66 mmol, 33 equiv.). The resin was then stirred slowly at rt for 48 h. The mixture was then filtered and the resin was washed with DCM (3 X), MeOH (3 X), MeOH:H\(_2\)O (3 X), MeOH (3X), DCM (3X). It was then dried overnight in vacuum.
For the DDQ test cleavage 20 mg of this resin (33) was swelled in DCM (0.9 mL) for 30 min, DDQ was then added (15 mg) followed by addition of H₂O (0.1 mL). The resin was shaken for 1h. After this time water was added to the system, and the resin was filtered. The product was extracted with DCM and concentrated in vacuo. For compound 34 the ESI-MS analysis confirmed the debenzoylation at positions 4 and 5 since a mass of 739 m/z corresponding to the tri-butyrylated derivative (+Na⁺) was observed. NMR analysis (Supplementary Figure 7) of compound 34 confirmed the regioselective opening at 3-position as only reaction product.

**Supplementary Figure 7.** ¹H,¹H COSY spectra of compound 34.

¹H-NMR (400 MHz, CDCl₃) δ 7.78-7.74 (m, 1H, Ph), 7.69-7.66 (m, 3H, Ph), 7.44-7.35 (m, 6H, Ph), 5.49-5.44 (t, J = 10.1 Hz, 1H, CH-4-myo), 4.94 (t, J = 9.6 Hz, 1H, CH-5-myo), 4.79 (d, J = 6.86 Hz, 1H, CH-MEM), 4.72-4.70 (m, 1H, CH-OH), 4.66-4.63 (dd, J = 10.5, 10.2 Hz, 1H, CH-3-myo), 4.54-4.52 (d, J = 6.86 Hz, 1H, CH-MEM), 4.44-4.40 (m, 1H, CH-MEM), 4.30-4.28 (m, 1H, CH-MEM), 4.07-4.02 (t, J = 9.33 Hz, 1H, CH-6-myo), 3.86-3.83 (dd, J = 9.2, 2.5 Hz, 1H, CH-1-myo), 3.64 (m, 2H, CH-2-myo and CH-MEM), 3.43 (m, 1H, CH-MEM), 3.34 (s, 3H, CH-MEM),
2.19-2.10 (m, 6H, CH-MEM), 1.54-1.50 (m, 6H, CH-MEM), 1.06 (s, 9H, CH$_3$-TBDPS), 0.90-0.85 (m, 9H, CH$_3$-MEM)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 146.8, 144.7, 135.6, 130.0, 127.9, 129.8, 97.7, 79.0, 73.7, 72.0, 71.4, 70.1, 69.6, 67.7, 35.9, 35.8, 29.6, 29.3, 29.0, 27.0, 19.2, 18.3, 18.2, 18.0

MS (ESI): m/z (%): 739.3 (100) [M+Na]$^+$

2.7.2 Butyrylation of intermediate 22 to determine selective opening

Supplementary Scheme 13. Butyrylation and DDQ cleavage of resin 22.

Resin 22 (37.0 mg, 0.02 mmol, loading 0.62 mmol/g, 1 equiv) was swelled in pyridine for 30 min. DMAP (5 mg, catalytic) was added to the system followed by addition of Bt$_2$O (50 µL, 0.30 mmol, 13 equiv.). The resin was then stirred slowly at rt for 48h. The mixture was then filtered and the resin was washed with DCM (3 X), MeOH (3 X), MeOH:H$_2$O (3 X), MeOH (3X), DCM (3X). It was then dried overnight in vacuum.

For the DDQ test cleavage 30 mg of this resin (49) was swelled in DCM (1.5 mL) for 30 min, DDQ was then added (15 mg) followed by addition of H$_2$O (150 µL). The resin was shaken for 1.5h. After this time water was added to the system, and the resin was filtered. The product was extracted with DCM and concentrated in vacuo. NMR analysis (Supplementary Figure 8a and b) of compound 50 confirmed the regioselective opening at 3-position as only reaction product.
Supplementary Figure 8a. HMQC spectra of compound 50, measured for the identification of myo-inositol protons.

Supplementary Figure 8b. $^1$H,$^1$H COSY spectra of compound 50.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.72-7.67 (m, 4H, Ph), 7.46-7.35 (m, 6H, Ph), 5.04 (d, J=6.3 Hz, 1H, CH$_2$ MEM), 4.98 (d, J=6.4 Hz, 1H, CH$_2$ MEM), 4.88 (dd, J = 2.5, 6.4 Hz, 2H, CH$_2$ MEM), 4.78 (dd, J=6.4, 13.0 Hz, 2H, CH$_2$ MEM), 4.43 (dd, J=2.8, 10.2 Hz, 1H, CH myo-3), 3.97-3.90 (m, 2H, CH$_2$-myo-2, CH$_2$-myo-6), 3.85-3.79 (m, 2H, CH-myö-5 plus CH$_2$ MEM), 3.78-3.75 (m, 1H, CH$_2$ MEM), 3.73-3.65 (m, 2H, CH$_2$ MEM), 3.64-3.61 (m, 1H, CH$_2$ MEM), 3.54-3.52 (m, 4H), 3.50-3.47 (m, 2H), 3.38-3.35 (m, 1H, CH myo-1), 3.37 (s, 6H, CH$_3$ MEM), 3.37-3.33 (m, 1H, CH myo-4), 3.35 (s, 3H, CH$_3$ MEM), 2.20 (t, J = 7.4 Hz, 2H, CH$_2$(α) Bt), 1.57-1.52 (m, 2H, CH$_2$(β) Bt), 1.08 (s, 9H, CH$_3$ TBDPS), 0.85 (t, J = 7.4 Hz, 3H, CH$_3$(γ) Bt)

$^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 135.8, 135.5, 133.7, 130.2, 130.1, 128.1, 127.9, 98.0, 97.4, 97.1, 78.4, 78.1, 76.0, 74.4, 72.1, 71.9, 71.1, 69.8, 62.8, 68.0, 67.7, 59.0, 36.0, 29.7, 27.2, 18.4, 13.1

MS (ESI): m/z (%): 775.7 (100) [M+Na]$^+$

2.8 DIBAL-H opening of an analogue in solution phase:

2.8.1 Synthesis of 4-(dimethoxymethyl)anisole (51):

4-(dimethoxymethyl)anisole (51): Same experimental procedure as for the synthesis of compound 48 but using as starting material 4-methoxybenzaldehyde. The product was used unpurified in the next step as it is unstable. NMR showed 70% conversion.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 9.89 (s, 0.46H, CHO from S.M.), 7.84 (d, J=8.7 Hz, 0.90H, Ar from S.M.), 7.35 (d, J=8.7 Hz, 2H, Ar), 7.02 (d, J=8.7 Hz, 0.90H, Ar from S.M.), 6.88 (d, J=8.7 Hz, 2H, Ar), 5.35 (s, 1H, CH acetal), 3.90 (s, 1.3H, OCH$_3$ from S.M.), 3.81 (s, 3H, OCH$_3$), 3.29 (s, 6H, CH$_3$).
2.8.2 Procedure for coupling of the acetal 51 with diol 28b:

1-O-t-Butyldiphenylsilyl-2,3-O-p-methoxybenzylidene-4-O-benzoyl-5,6-di-O-methoxethoxymethyl-myoinositol 35:

same experimental procedure as for the synthesis of compounds 29a-d but with acetal 51. Colorless oil; 100mg, 0.12 mmol, 66%. R<sub>f</sub> 0.5 (cyclohexane: ethyl acetate 60:40). Diastereomeric mixture of compounds (3:1).

HPLC: t<sub>R</sub> = 13.45 min; m/z (%) = 839 (100) [M+Na]<sup>+</sup>

t<sub>R</sub> = 13.78 min; m/z (%) = 839 (100) [M+Na]<sup>+</sup>

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 8.08-8.02 (m, 2.6H, Ph), 7.83-7.76 (m, 5.2H, Ph), 7.55-7.51 (m, 4H, Ph), 7.44-7.26 (m, 10.4H, Ph), 6.91-6.86 (m, 2.6H, Ph), 6.32 (m, 0.6H), 6.0 (m, 1H), 5.60 (s, 1.3H), 4.75-4.70 (m, 2H), 4.68-4.66 (m, 2H), 4.57 (m, 1H), 4.49 (m, 1.3H), 4.44 (m, 0.3H), 4.32 (m, 1H), 4.21 (m, 1H), 4.11 (brs, 1H), 3.81 (s, 3H, Ar-OCH<sub>3</sub>), 3.80 (s, 1H, Ar-OCH<sub>3</sub>), 3.78-3.76 (m, 2.3H), 3.66-3.52 (m, 2.6H), 3.52-3.34 (m, 6H), 3.32 (s, 3H, CH<sub>3</sub>-MEM), 3.28 (s, 1H, CH<sub>3</sub> MEM), 3.24 (s, 1H, CH<sub>3</sub> MEM), 3.22 (s, 3H, CH<sub>3</sub> MEM), 3.20-3.12 (m, 2H), 1.19 (s, 3H, CH<sub>3</sub> TBDPS), 1.09 (s, 9H, CH<sub>3</sub> TBDPS).

<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 165.3, 160.5, 136.4, 136.2, 132.9, 132.8, 129.9, 129.8, 129.7, 128.7, 128.2, 127.7, 127.4, 113.6, 104.3, 95.3, 95.2, 78.7, 75.9, 75.2, 71.6, 71.3, 70.8, 70.4, 67.6, 67.2, 59.0, 58.8, 55.3, 27.2, 19.1

MS (ESI): m/z (%): 839 (100) [M+Na]<sup>+</sup>

2.8.3 DIBAL-H opening of compound 35:

In order to get a better understanding of the DIBAL-H opening reaction in solid phase an analogy in solution was carried out. Therefore the DIBAL-H opening was conducted in parallel under the same conditions in solid phase and for the analogue in solution. In both cases the conditions used to prepare compound 18 were followed.
2.8.3.1 Solid Phase opening

**Supplementary Scheme 14.** DIBAL-H opening in solid phase, phosphorylation of the obtained product and cleavage from the resin.

**Supplementary Figure 9.** HPLC trace of the crude reaction product after the DIBAL-H opening in solid phase, subsequent phosphorylation and cleavage from the resin.

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., λ = 215nm.

\[ t_R = 16.6 \text{ min}; \quad m/z \text{ (%}: 1138 \left[ M + Na \right]^+. \]

2.8.3.2 Opening of an analogue in solution

**Supplementary Scheme 15.** DIBAL-H opening of an analogue in solution phase.
Supplementary Figure 10. HPLC trace of the crude reaction product after the DIBAL-H opening of the analogue in solution phase.

C18 column, 70-100 acetonitrile in water, flow rate: 1.5 mL/min., λ = 215nm.

$t_R = 7.78$ min; m/z (%): 737 [37 or 38 + Na]. Not isolated, too little amount.

$t_R = 8.65$ min; m/z (%): 737 [37 or 38 + Na]. Not isolated, too little amount.

$t_R = 9.38$ min; m/z (%): 735 [36 + Na].

37 and 38 were identified only by mass spec. and their polarity corresponds to an earlier retention time.

1-O-t-Butyldiphenylsilyl-2,3-O-p-methoxybenzyliden-5,6-di-$O$-methoxyethoxymethyl-$m$-inositol 36:

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.76-7.71 (m, 5H, Ph), 7.45-7.26 (m, 12H, Ph), 6.89-6.85 (m, 2H, Ph), 6.19 (s, 0.3H$_2$), 5.5 (s, 1H), 4.85-4.78 (m, 3H), 4.75-4.71 (m, 1H), 4.62-4.55 (m, 1H), 4.26 (m, 0.6H), 4.14 (m, 2H), 3.99-3.96 (m, 1.6H), 3.90-3.83 (m, 4H), 3.82 (s, 1H, Ar-OCH$_3$), 3.82 (s, 3H, Ar-OCH$_3$), 3.76-3.40 (m, 11H), 3.38 (s, 1H, CH$_3$-MEM), 3.35 (s, 6H, CH$_3$ MEM), 3.32 (s, 1H, CH$_3$ MEM), 3.30-3.28 (m, 2H), 1.08 (s, 9H, CH$_3$ TBDPS), 1.04 (s, 9H, CH$_3$ TBDPS).

MS (ESI): m/z (%): 735 (100) [M+Na]$^+$
2.9 Representative procedure for phosphorylation:

1-O-\text{-Butyldiphenylsilyl}-2,3-O-(p-Wang-resin-oxy)benzyldene-4,5-di-O-dibenzylphosphoryl-6-O-methoxyethoxymethyl-\text{-myo-inositol} 30a

Supplementary Scheme 16. Phosphorylation of resin 17 to yield resin 30a.

Resin 17 (180 mg, 0.11 mmol, loading 0.67 mmol/g) was swollen in anhyd. dichloromethane (3 mL) for 30 min. in a round bottom flask under argon atmosphere. This was followed by addition of dicyanoimidazole (147 mg, 1.24 mmol) in 1.5 mL acetonitrile and immediate addition of phosphoramidite (431 mg, 1.25 mmol) in acetonitrile (1.5 mL). The resin mixture was then allowed to shake for 24 h. It was then cooled to -30°C followed by addition of peracetic acid (40% in acetic acid, 296 µL, 1.56 mmol) in dichloromethane (1 mL). The resin was stirred at the same temperature for 1 h and filtered. Washings were carried out with DCM (3 X), DMF (3 X), MeOH (3 X), and finally DCM (3 X). The resin was dried overnight in vacuo. The formation of the product was confirmed by test cleavage.

HPLC:
C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., λ = 215nm.

\[ t_R = 16.1 \text{ min}; \quad m/z \%: 961 \text{ [M-MEM+Na]}^+ \text{ (TFA test cleavage)} \]

The other derivatives 30b, 30c, 40a and 40b were synthesized following the same method described above.

Resin 30b: 1-O-\text{-Butyldiphenylsilyl}-2,3-O-(p-Wang-resin-oxy)benzyldene-4-O-dibenzylphosphoryl-5,6-di-O-methoxyethoxymethyl-\text{-myo-inositol}

MS (ESI): m/z (%): 701.6 (100) [M-2MEM+Na]^+ \text{ (TFA test cleavage)}
Resin 30c: \(1-O-t\text{-Butyldiphenylsilyl}-2,3-O-(p\text{-Wang-resin-oxy})\text{benzylidene}-5-O\text{-dibenzylphosphoryl}-4,6-di-O\text{-methoxyethoxymethyl-\textit{myo}-inositol}

**HPLC:**

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., \(\lambda = 215\) nm.

\[t_R = 14.5\ \text{min};\ \text{m/z (\%): } 701 \ [\text{M-2MEM+Na}]^+.\]

\[t_R = 14.95\ \text{min};\ \text{m/z (\%): } 789 \ [\text{M-MEM+Na}]^+ \text{ (TFA test cleavage)}.\]

Resin 40a: \(1-O-t\text{-Butyldiphenylsilyl}-2-O-(p\text{-Wang-resin-oxy})\text{benzyl-3,4,5-tri-O-dibenzylphosphoryl-6-O\text{-methoxyethoxymethyl-\textit{myo}-inositol}}

**HPLC:**

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., \(\lambda = 215\) nm.

\[t_R = 17.58\ \text{min};\ \text{m/z (\%): } 1310 \ [\text{M+Na}]^+ \text{ (DDQ test cleavage)}.\]

Resin 40b: \(1-O-t\text{-Butyldiphenylsilyl}-2-O-(p\text{-Wang-resin-oxy})\text{benzyl-3-O-dibenzylphosphoryl-4,5,6-tri-O\text{-methoxyethoxymethyl-\textit{myo}-inositol}}

**HPLC:**

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., \(\lambda = 215\) nm.

\[t_R = 15.8\ \text{min};\ \text{m/z (\%): } 966 \ [\text{M+Na}]^+ \text{ (DDQ test cleavage)}.\]
2.10 Representative procedure for TBDPS cleavage:

2,3-O-(p-Wang-resin-oxy-)benzylidene-4,5-di-O-dibenzylphosphoryl-6-O-methoxyethoxymethyl-myoinositol Resin 43a

To the preswelled resin 30a (190 mg, 0.08 mmol, loading 0.49 mmol/g) in anhyd. DMF (3 mL) was added TASF (100 mg, 0.363 mmol) in 1mL DMF and it was allowed to shake for 32 h. The resin was then filtered and washed with DMF (3 X), DCM (3 X), MeOH (3 X), MeOH: H2O (3 X), again DCM (3 X) and dried overnight. The formation of the product was confirmed by test cleavage.

HPLC:

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., λ = 215nm.

$\text{t}_R = 11.48 \text{ min;} \quad \text{m/z (\%): } 723 \text{ [M-MEM+Na]}.^+

$\text{t}_R = 12.18 \text{ min;} \quad \text{m/z (\%): } 811 \text{ [M+Na]}.^+ \text{ (TFA test cleavage)}.$

The other derivatives 43b, 43c, 43d, 43d and 43e were synthesized following the same method described above.

Resin 43b: 2,3-O-(p-Wang-resin-oxy)benzylidene-4-O-dibenzylphosphoryl-5,6-di-O-methoxyethoxymethyl-myoinositol

MS (ESI): m/z (%): 462.9 (20) [M-2MEM+Na]+, 551.0 (100) [M-MEM+Na]+ (TFA test cleavage)
Resin 43c: 2,3-O-(p-Wang-resin-oxy)benzylidene-5-O-dibenzyldiphosphoryl-4,6-di-O-methoxyethoxymethyl-myro-inositol

HPLC:

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., \( \lambda = 215\text{nm} \).

\[ t_R = 6.25 \text{ min}; \quad m/z \text{ (%):} \quad 551 \ [M-\text{MEM+Na}]^+. \]

\[ t_R = 7.51 \text{ min}; \quad m/z \text{ (%):} \quad 639 \ [M+Na]^+ \text{ (TFA test cleavage)}. \]

Resin 43d: 2-O-(p-Wang-resin-oxy)benzyl-3,4,5-tri-O-dibenzyldiphosphoryl-6-O-methoxyethoxymethyl-myro-inositol

HPLC:

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., \( \lambda = 215\text{nm} \).

\[ t_R = 14.61 \text{ min}; \quad m/z \text{ (%):} \quad 1071 \ [M+Na]^+ \text{ (DDQ test cleavage)}. \]

Resin 43e: 2-O-(p-Wang-resin-oxy)benzyl-3-O-dibenzyldiphosphoryl-4,5,6-tri-O-methoxyethoxymethyl-myro-inositol

HPLC:

C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min., \( \lambda = 215\text{nm} \).

\[ t_R = 8.38 \text{ min}; \quad m/z \text{ (%):} \quad 727 \ [M-\text{MEM+Na}]^+ \text{ (DDQ test cleavage)}. \]
2.11 Representative procedure for the attachment of lipid chains:

1-O-[(1’,2’-di-octanoyl-sn-glycero)benzyl]phosphoryl-2,3-O-(p-Wang-resin-oxy)benzylidene-4,5-di-O-(di-O-benzyl-phosphate)-6-O-methoxyethoxymethyl-myo-inositol 31a:

Supplementary Scheme 18. Attachment of lipid chain 53 to resin 43a to yield resin 31a.

To the preswelled resin 43a (150 mg, 0.07 mmol, loading 0.55 mmol/g) in anhydrous CH₂Cl₂ (2 mL) was added dicyanoimidazole (39 mg, 0.33 mmol) in acetonitrile (1 mL), followed by immediate addition of dioctanoyl (diC8) glycerol diester phosphoramidite 53 (192 mg, 0.331 mmol) in acetonitrile (1 mL). The resin was then allowed to shake for 40 h at room temperature, which was then cooled to -30°C, followed by addition of peracetic acid (70 µL, 0.41 mmol, 40% in acetic acid). After stirring the resin for 1 h at the same temperature, it was filtered and washed with DCM (3 X), DMF (3 X), MeOH (3 X), and finally DCM (3 X). The resin was dried overnight in vacuo. The formation of the product was confirmed by test cleavage using the same procedure described for resin 13 (Supplementary Scheme 9). The diC8 glycerol diester phosphoramidite 53 was prepared according to the previously described procedure (S. F. Martin, J. A. Josey, Y.-L. Wong, D.W. Dean, J. Org. Chem., 1994, 59, 4805-4820).

MS (ESI): m/z (%): 1219.6 (90) [M-MEM+Na]^+, 1307.6 (100) [M+Na]^+ (TFA test cleavage)

The other derivatives 31b, 31c and 41a were synthesized following the method described above.

MS (ESI): m/z (%): 1047.6 (100) [M-MEM+Na]^+ (TFA test cleavage)


MS (ESI): m/z (%): 1047.8 (100) [M-MEM+Na]^+ (TFA test cleavage)


MS (ESI): m/z (%): 795 [M+2Na]^2+ (DDQ test cleavage)

The derivative 44b was synthesized following the method described for the obtention of 30a.

Resin 44b: 1,4,5-O-[di-O-benzyl-phosphate]-2,3-O-(p-Wang-resin-oxo)benzylidene-6-O-methoxyethoxymethyl-myo-inositol


Derivates 44a, 41b and 41c were prepared using an analogous protocol with (benzyloxy)[(N-Cbz-3-aminopropyl-1-oxy)(N’,N’-diisopropylamino)phosphoramidite 54 which was prepared as previously reported (V. A. Estevez, G. D. Prestwich, J. Am. Chem. Soc., 1991, 113, 9885-9887).

**MS (ESI):** $m/z$ (%): 1084 [M–MEM+Na]^+, 1173 [M+Na]^+ (TFA test cleavage)


**MS (ESI):** $m/z$ (%): 728.0 (100) [M+Na]^{2+}, 1433.0 (20) [M+Na]^+ (DDQ test cleavage)

Resin 41c: 1-O-[(N-Cbz-3-aminopropyl)benzyl]phosphoryl-2-O-(p-Wang-resin-oxo)benzyl-3-O-dibenzylphosphoryl-4,5,6-tri-O-methoxyethoxymethyl-myoinositol

**MS (ESI):** $m/z$ (%): 1088.6 (100) [M+Na]^+ (DDQ test cleavage)
2.12 Representative procedure for TFA-mediated cleavage from the solid support:

1-\(O\)-(1',2'-di-\(O\)-octanoyl-\(sn\)-glycero)benzyl\(\!\!\!\!]\)phosphoryl-\(4,5\)-di-\(O\)-(di-\(O\)-benzylphosphate)-6-\(O\)-methoxyethoxymethyl-\(myo\)-inositol 32a:

Supplementary Scheme 20. Cleavage from the solid support to yield compound 32a (l.c. = lipid chain).

To the preswelled resin 31a (168 mg, 0.068 mmol, loading 0.469 mmol/g) in CH\(_2\)Cl\(_2\) was added a mixture of 10\% TFA in CH\(_2\)Cl\(_2\) containing 1\% water. The resin was shaken for 1 h, filtered and washed with CH\(_2\)Cl\(_2\) for several times. All the washings were combined and evaporated to give the crude product, which was purified by HPLC yielding a mixture of free hydroxyl and MEM protected hydroxyl group at the 6-position. This mixture was used directly for the next step.

32 mg (0.025 mmol using the weighted averaged mass of products having into account the area under the peak) were obtained after purification by HPLC, which corresponds to 37\% overall yield of the mixture of the two species (OH/MEM) for six steps on solid phase. This compound was obtained as chiral and racemic version.

HPLC conditions: C18 column, 90-100 methanol in water, flow rate: 1.5 mL/min., \(\lambda\) = 215nm.

\(t_R = 8.9\) min; \(m/z\) (%):1219 [M-MEM+Na]\(^+\). The area under the peak represents 1.

\(t_R = 9.4\) min; \(m/z\) (%):1308 [M+Na]\(^+\). The area under the peak represents 0.5.
Supplementary Figure 11. Analytical run of the crude reaction product after cleaving the compound from the resin 31a.

The data is given for the chiral compound 1-\textit{O-}[(1',2'-\textit{di-O-octanoyl-sn-glycero})benzyl]phosphoryl-4,5-\textit{di-O-(di-benzyl-phosphate)-myo-inositol} 32a1

\begin{align*}
\text{\textsuperscript{1}H-NMR} (400 \text{ MHz, CDCl}_3) & \delta 7.38-7.17 \ (m, \ 25H, \ Ph), \ 5.25-5.21 \ (m, \ 1H, \ CH(\beta)), \ 5.18-5.10 \ (m, \ 2H, \ CH_2-OBn), \ 5.04-4.97 \ (m, \ 8H, \ CH_2-OBn), \ 4.61-4.50 \ (m, \ 1H, \ CH-4-my), \ 4.33-4.29 \ (m, \ 1H, \ CH_2(\alpha)), \ 4.27-4.11 \ (m, \ 6H, \ CH-1-my, \ CH-2-my, \ CH-5-my, \ H-CH_2(\alpha), \ CH_2(\gamma)), \ 3.63-3.59 \ (m, \ 2H, \ CH-3-my, \ CH-6-my), \ 2.34-2.26 \ (m, \ 4H, \ l.c. \ CH_2(\alpha)), \ 1.70-1.55 \ (m, \ 4H, \ l.c. \ CH_2(\beta)), \ 1.27-1.25 \ (m, \ 16H, \ l.c. \ CH_2), \ 0.89-0.86 \ (m, \ 6H, \ l.c. \ CH_3) \\
\text{\textsuperscript{31}P-NMR} (162 \text{ MHz, CDCl}_3) & \delta 0.79 \ (0.5P), \ 0.70 \ (0.5P), \ 0.16 \ (0.5P), \ 0.01 \ (0.5P), \ -1.39 \ (0.5P), -1.54 \ (0.5P) \\
[\alpha]_{D}^{20} & = -11.6^\circ \ (c = 0.3 \ \text{in CHCl}_3) \\
\text{MS (ESI+): m/z (\%):} & 1219 \ (100) \ [\text{M+Na}]^+ 
\end{align*}

The other derivatives 32b, 32c, 45a and 45b were synthesized using the procedure described above. It was observed that the MEM groups were partly cleaved in all cases.
HPLC conditions: C18 column, 90-100 methanol in water, flow rate: 1.5 mL/min., λ = 215nm.

$t_R = 5.1$ min; m/z (%): 959 [M-2MEM+Na]$^+$, The area under the peak represents 0.3.

$t_R = 5.9$ min; m/z (%): 1048 [M-MEM+Na]$^+$, The area under the peak represents 1.

Overall yield: 40%

This compound was obtained as chiral version.

Supplementary Figure 12. Analytical run of the crude reaction product after cleaving the compound from the resin 31b.

HPLC conditions: C18 column, methanol:water 85:100, flow rate: 1.5 mL/min.

$t_R = 10.19$ min; m/z (%): 960 [M-2MEM+Na]$^+$, The area under the peak represents 0.06.

$t_R = 11.00$ min; m/z (%): 1048 [M-MEM+Na]$^+$, The area under the peak represents 0.65.

$t_R = 11.61$ min; m/z (%): 1136 [M +Na]$^+$, The area under the peak represents 1.
Overall yield: 38%

This compound was obtained as chiral version.

**Supplementary Figure 13.** Analytical run of the crude reaction product after cleaving the compound from the resin 31c.

The data is given for the chiral compound 1-O-[(1’,2’-di-O-octanoyl-sn-glycero)benzyl]phosphoryl-5-O-(di-O-benzyl-phosphate)-4,6-di-O-methoxyethoxymethyl-myo-inositol 32c1

\[ \text{1H-NMR (400 MHz, CDCl}_3\text{)} \ \delta \ 7.41-7.34 \text{ (m, 15H, Ph), 5.22-5.17 \text{ (m, 1H, CH(\beta))}, 5.15-5.05 \text{ (m, 6H, CH}_2\text{-OBn), 4.67-4.58 \text{ (m, 4H, CH}_2\text{-MEM), 4.39-4.27 \text{ (m, 4H, CH}_2\text{(\alpha), CH-myo), 4.18-4.01 \text{ (m, 3H, CH}_2(\gamma)\text{, CH-myo), 3.80-3.70 \text{ (m, 4H, CH}_2\text{-MEM, CH-myo), 3.61-3.56 \text{ (m, 3H, CH}_2\text{-MEM), 3.51-3.42 \text{ (m, 4H, CH}_2\text{-MEM, CH-myo), 3.32 \text{ (s, 3H, CH}_3\text{-MEM), 3.28 \text{ (s, 3H, CH}_3\text{-MEM), 2.30-2.25 \text{ (m, 4H, l.c. CH}_2(\alpha), 1.62-1.55 \text{ (m, 4H, l.c. CH}_2(\beta), 1.29-1.24 \text{ (m, 16H, l.c. CH}_2), 0.88-0.85 \text{ (m, 6H, l.c. CH}_3) } \]

\[ \text{31P-NMR (162 MHz, CDCl}_3\text{)} \ \delta \ -0.79 \text{ (0.5P), -0.86 \text{ (0.5P), -1 \text{ (0.5P), -1.03 \text{ (0.5P) }} \]

\[ \alpha \] = +2.5° (c = 0.4 in CHCl3)

MS (ESI+): m/z (%): 1136 (100) [M+Na]^+
1-O-[(N-Cbz-3-aminopropyl)benzyl]phosphoryl-4,5-di-O-(di-O-benzyl-phosphate)-6-O-methoxyethoxymethyl-myoinositol 45a:

HPLC conditions: C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min, λ = 215nm.

t_R = 13.89 min; m/z (%): 1084 [M-MEM+Na]^+, The area under the peak represents 1.

t_R = 14.15 min; m/z (%): 1173 [M+Na]^+, The area under the peak represents 0.40.

Overall yield: 33%

This compound was obtained as chiral and racemic version.

The data is given for the chiral compound 1-O-[(N-Cbz-3-aminopropyl)benzyl]phosphoryl-4,5-di-O-(di-O-benzyl-phosphate)- myo-inositol 45a1

1H-NMR (400 MHz, CDCl3) δ 7.38-7.17 (m, 30H, Ph), 5.44 (d, J = 5.5 Hz, 1H, NH-Cbz), 5.17-4.95 (m, 12H, CH2-OBn), 4.58-4.50 (m, 1H, CH-myo), 4.24-4.10 (m, 5H, CH-myo, CH2(α)), 3.62-3.58 (m, 2H, CH-myo), 3.31-3.26 (m, 2H, CH2(γ)), 1.84-1.81 (m, 2H, CH2(β)).

31P-NMR (162 MHz, CDCl3) δ 0.67 (0.5P), 0.61 (0.5P), 0.09 (0.5P), 0.03 (0.25P), -0.05 (0.25P), -0.99 (0.5P), -1.37 (0.5P)

\[ \alpha \] \text{D}^{20} = -12.8^\circ (c = 0.95 \text{ in CHCl}_3)

**MS (ESI+):** m/z (%): 1084 (100) [M+Na]⁺

1,4,5-tri-O-(di-O-benzyl-phosphate)-6-O-methoxyethoxymethyl-myoinositol 45b:

HPLC conditions: C18 column, 70-100 methanol in water, flow rate: 1.5 mL/min, \( \lambda = 215 \text{nm} \).

\( t_R = 12.10 \text{ min}; \) m/z (%): 983 [M-MEM+Na]⁺, The area under the peak represents 0.29.

\( t_R = 12.45 \text{ min}; \) m/z (%): 1071 [M+Na]⁺, The area under the peak represents 1.

Overall yield: 34%

This compound was obtained as chiral and racemic version.

**Supplementary Figure 15.** Analytical run of the crude reaction product after cleaving the compound from the resin 44b.

The data is given for the chiral compound 1,4,5-tri-O-(di-O-benzyl-phosphate)-myoinositol 45b1.

\(^1\text{H-NMR (}400 \text{ MHz, CDCl}_3\) δ 7.35-7.16 (m, 30H, Ph), 5.14-4.96 (m, 12H, CH₂-OBn), 4.57-4.51 (m, 1H, CH-myo), 4.19-4.15 (m, 3H, CH-myo), 3.59-3.56 (m, 2H, CH-myo).

$^{31}$P-NMR (162 MHz, CDCl$_3$) δ 0.81 (s, 1P), 0.02 (s, 1P), -1.17 (s, 1P)

$[\alpha]_{D}^{20} = -16.55^\circ$ (c = 0.35 in CHCl$_3$)

MS (ESI+): m/z (%): 961.2557 (100) [M+H]$^+$

2.13 DDQ-mediated cleavage from the solid support:

For the derivatives where the position 3 is functionalized (42a, 42b and 42c) the cleavage from the resin was performed using dicyanobenzoquinone (DDQ). In order to facilitate the removal of excess DDQ and DDQH from cleavage products, a mixed-bed ion exchange scavenger analogous to the one developed by J.A. Porco Jr. and co-workers was used (T. L. Deegan, O. W. Gooding, S. Baudart, J. A. Porco Jr., Tetrahedron Lett. 1997, 28, 4973-4976).

1-O-[(N-Cbz-3-aminopropyl)benzyl]phosphoryl-3-O-dibenzylphosphoryl-4,5,6-tri-O-methoxyethoxymethyl-\textit{myo}-inositol 42c.

Supplementary Scheme 21. Cleavage of the solid support to yield compound 42c

Resin 41c (108 mg, 0.05 mmol, loading 0.50 mmol/g) was swelled in 5 mL of DCM for 30 minutes. After this time solid DDQ (30 mg, 0.14 mmol, 2 equiv.) was added to the system followed by addition of 500 µL of water. The reaction was then stirred at rt for 2h. The mixed-bed scavenger resin Dowex 1X8-200 Ascorbate resin (200 mg) and Dowex 1X8-200 OH$^-$ resin 55 (400 mg) were weighted into a 10 mL solid phase reactor syringe. The cleavage solution was then filtered onto the mixed-bed resin. The filtrate was agitated with the mixed-bed resin for 2h. The solution and 3 X 2 mL DCM resin washes were collected by filtration, concentrated and purified by HPLC.
The derivatives 42a and 42b were synthesized using the procedure described above.

1-O-[(1’,2’-di-O-octanoyl-sn-glycero)benzyl]phosphoryl-3,4,5-tri-O-dibenzylphosphoryl-6-O-methoxyethoxymethyl-\textit{myo}-inositol 42a:

HPLC conditions: C18 column, 90-100 methanol in water, flow rate: 1.5 mL/min, $\lambda$ = 215nm.

t$_R$ = 12.56 min; m/z (%): 795 [M+2Na]$_{2+}$.

Overall yield: 16%

This compound was obtained as chiral version.

Supplementary Figure 16. Analytical run of the crude reaction product after cleaving the compound from the resin 41a.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.16 (m, 35H, Ph), 5.21-5.17 (m, 1H, CH($\beta$)), 5.13-4.93 (m, 14H, CH$_2$-OBn), 4.81-4.76 (m, 3H, CH$_2$-MEM), 4.36-4.31 (m, 1H, CH$_2$-MEM), 4.29-4.25 (m, 1H, CH$_2$(\alpha)), 4.21-4.08 (m, 5H, CH$_2$(\gamma), CH$_2$(\alpha), CH$_2$-MEM), 3.78-3.73 (m, 1H, CH-myo), 3.70-3.66 (m, 1H, CH-myo), 3.64-3.58 (m, 1H, CH-myo), 3.59-3.54 (m, 1H, CH-myo), 3.40-3.37 (m, 1H, CH-myo), 3.33-3.29 (m, 1H, CH-myo), 3.25 (s, 3H, CH$_3$-MEM), 2.31-2.25 (m, 4H, l.c. CH$_2$(\alpha)), 1.57-1.56 (m, 4H, l.c. CH$_2$(\beta)), 1.25 (bs, 16H, l.c. CH$_2$), 0.88-0.85 (m, 6H, l.c. CH$_3$).

\[^{31}\text{P}-\text{NMR}\,(162\text{ MHz}, \text{CDCl}_3)\delta\ -1.09\ (1\text{P}),\ -1.26\ (1\text{P}),\ -1.58\ (0.5\text{P}),\ -1.95\ (0.5\text{P}),\ -2.34\ (0.5\text{P}),\ -2.40\ (0.5\text{P})\]

\([\alpha]_D^{20}\ =\ -15.6^\circ\ (c = 0.45\text{ in CHCl}_3)\)

**MS (ESI+): m/z (%): 1567.54 (100) [M+Na]^{+}\]**

**1-O-[(N-Cbz-3-aminopropyl)benzyl]phosphoryl-3,4,5-tri-O-dibenzylphosphoryl-6-O-methoxyethoxymethyl-myoinositol 42b.**

HPLC conditions: C18 column, 80-100 methanol in water, flow rate: 1.5 mL/min, \(\lambda = 215\text{nm}\).

\(t_R = 11.3\text{ min};\ m/z\ (%): 728\ [M+2Na]^{2+}.\) Overall yield: 18%

This compound was obtained as racemic version.

**Supplementary Figure 17.** Analytical run of the crude reaction product after cleaving the compound from the resin 41b.

\[^{1}\text{H}-\text{NMR}\,(400\text{ MHz}, \text{CDCl}_3)\ δ\ 7.37-7.15\ (m, 40\text{H, Ph}),\ 5.74\ (bs, 1\text{H, NH l.c.}),\ 5.13-4.92\ (m, 16\text{H, O-CH}_2\text{-Ph}),\ 4.81-4.73\ (m, 2\text{H, CH}_2\text{-MEM}),\ 4.38-4.30\ (m, 1\text{H, CH}_2\text{-MEM}),\ 4.20-4.01\ (m, 5\text{H, CH}_2\text{-MEM, CH}_2\ l.c. (\alpha)),\ 3.79-3.69\ (m, 2\text{H, CH-mylo}),\ 3.79-3.69\ (m, 2\text{H, CH-mylo}),\ 3.62-3.54\ (m, 2\text{H, CH-mylo}),\ 3.45-3.37\ (m, 2\text{H, CH-mylo}),\ 3.27-3.21\ (m, 5\text{H, CH}_3\text{-MEM, CH}_2\ l.c. (\gamma)),\ 1.80\ (bs, 2\text{H, CH}_2\ l.c. (\beta))\]

\[^{31}\text{P}-\text{NMR}\,(162\text{ MHz}, \text{CDCl}_3)\ δ\ -1.06\ (d, 1\text{P}),\ -1.26\ (d, 1\text{P}),\ -1.36\ (s, 0.5\text{P}),\ -1.94\ (s, 0.5\text{P}),\ -2.36\ (d, 0.5\text{P}),\ -2.51\ (s, 0.5\text{P})\]

**MS (ESI+): m/z (%): 1410.4144 (100) [M+Na]^{+}\**
1-O-[(N-Cbz-3-aminopropyl)benzyl]phosphoryl-3-O-dibenzylphosphoryl-4,5,6-tri-O-methoxyethoxymethyl-myoinositol 42c:

HPLC conditions: C18 column, 60-100 methanol in water, flow rate: 1.5 mL/min, $\lambda = 215$ nm.

$t_R = 12.32$ min; m/z (%): 1088 $[M+Na]^+$. Overall yield: 26%

This compound was obtained as chiral version.

**Supplementary Figure 18.** Analytical run of the crude reaction product after cleaving the compound from the resin 41c.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.30 (m, 20H, Ph), 5.11-4.98 (m, 8H, O-CH$_2$-Ph), 4.91 (s, 2H, CH$_2$ MEM), 4.89-4.80 (m, 4H, CH$_2$ MEM), 4.13-4.07 (m, 2H, CH$_2$ l.c. ($\alpha$)), 4.04-3.95 (m, 4H, CH$_2$ MEM), 3.76-3.71 (m, 4H, CH$_2$ MEM), 3.69-3.62 (m, 2H, 2 CH myo), 3.54-3.48 (m, 4H, CH$_2$ MEM), 3.46-3.39 (m, 2H, 2 CH myo), 3.37 (s, 3H, CH$_3$ MEM), 3.34-3.31 (m, 6H, CH$_3$ MEM plus 2 CH myo), 3.29 (s, 3H, CH$_3$ MEM), 3.26-3.20 (m, 2H, CH$_2$ l.c. ($\gamma$)), 1.84 (bs, 2H, CH$_2$ l.c. ($\beta$))

$^{31}$P-NMR (162 MHz, CDCl$_3$) $\delta$ -1.31 (s, 0.25P), -1.63 (s, 0.5P), -1.68 (s, 0.25P), -1.77 (s, 0.5P), -1.86 (s, 0.5P)

$[\alpha]_D^{20} = -2.8^\circ$ (c = 1 in CHCl$_3$

MS (ESI+): m/z (%): 1088.3880 (100) $[M+Na]^+$
2.14 Representative procedure for TMSBr-mediated global deprotection:

Supplementary Scheme 22. TMSBr global deprotection of compound 32a to yield compound 23a.

To compound 32a (18 mg, 0.015 mmol) in a Schlenk flask was added bromotrimethylsilane (0.5 mL, excess) and the reaction was stirred for 1 h at room temperature. The reaction was then concentrated under vacuum to remove excess TMSBr and other byproducts. The residue was then stirred with methanol (1 mL) for 1 h followed by removal of the solvent under vacuum to give pure product as white solid (9.5 mg, quantitative).

This compound was obtained as chiral and racemic version.

\[ ^1H-\text{NMR (400 MHz, CD}_2\text{OD}) \delta 5.18 \text{ (brs, 1H, CH(\beta), 4.45-4.38 (q, J = 9.2 Hz, 1H, CH-4-myo), 4.35-4.31 (dd, J = 11.7, 3.2 Hz, 1H, H-CH}_2(\alpha), 4.13-4.05 (m, 5H, CH-2-myo, CH-5-myo, H-CH}_2(\alpha), H-CH}_2(\gamma), 4.02-4.0 (m, 1H, CH-1-myo), 3.93-3.88 (m, 1H, CH-6-myo), 3.57-3.54 (m, 1H, CH-3-myo), 2.29-2.22 (m, 4H, l.c. CH}_2(\alpha), 1.55-1.50 (m, 4H, l.c. CH}_2(\beta), 1.23 (m, 16H, l.c. CH}_2), 0.83-0.80 (m, 6H, l.c. CH}_3) \]

\[ ^13C-\text{NMR (100 MHz, CD}_2\text{OD}) \delta 174.9, 174.6, 72.6, 72.2, 71.6, 71.5, 71.4, 71.3, 35.0, 34.9, 32.9, 30.1, 26.0, 23.7, 15.0, 14.4 \]

\[ ^31P-\text{NMR (162 MHz, CD}_2\text{OD}) \delta 0.91 (1P), 0.60 (1P), -1.0 (1P) \]

MS (ESI\(^+\)): m/z (%): 769.2 (100) [M+Na\(^+\)]

**S54**

MS (ESI–): m/z (%): 745.3 (100) [M-H]⁻

[α]D₂⁰ = −12.2° (c = 0.3 in CH₃OH)

**Mp**: 72.7–74.9 °C

The other compounds 25, 26, 24a, and 23c were synthesized following the method described above.

1-O-(1',2'-di-O-octanoyl-sn-glycero)phosphatidylmyo-inositol-4-phosphate, diC₈-PtdIns(4)P 25:
white solid; 8.5 mg, 0.01, quantitative

This compound was obtained as chiral version.

**¹H-NMR (400 MHz, CD₃OD)** δ 5.22-5.20 (m, 1H, CH(β)), 4.40-4.36 (dd, J = 12.0, 3.4, 1H, CH-H(CH₂(α))), 4.33-4.26 (m, 1H, CH-4-mylo), 4.16-4.12 (m, 4H, CH-2-mylo, H-CH₂(α), CH₂(γ)), 3.99-3.94 (m, 1H, CH-1-mylo), 3.79 (t, J = 9.5, 1H, CH-6-mylo), 3.57-3.54 (m, 1H, CH-3-mylo), 3.39-3.34 (m, 1H, CH-5-mylo), 2.30 (m, 4H, lipid chain CH₂(α)), 1.57 (m, 4H, lipid chain CH₂(β)), 1.26 (m, 1H, lipid chain the rest of CH₂), 0.85 (m, 6H, lipid chain CH₃);

**¹³C-NMR (100 MHz, CD₃OD)** δ 175.0, 174.6, 81.2, 79.2, 75.4, 72.7, 71.9, 71.0, 65.9, 63.4, 35.1, 34.9, 32.9, 30.1, 26.0, 23.7, 14.4;

**³¹P-NMR (162 MHz, CD₃OD)** δ 1.36 (1P), -0.85 (1P)

**MS (ESI+): m/z (%):** 689.3 (100) [M+Na]⁺

**MS (ESI–): m/z (%):** 665.4 (100) [M-H]⁻

HRMS (ESI–): m/z neg.: [M-H]⁻ calculated 665.23448, found 665.23434 +0.2ppm

[α]D₂⁰ = +2.5° (c = 0.8 in CH₃OH)

**Mp**: 59.7-61.2 °C
1-O-(1’,2’-di-O-octanoyl-sn-glycero)phosphatidyl-myoinositol-5-phosphate, diC8-PtdIns(5)P 26: white solid, 8 mg, 0.01 mmol, quantitative

This compound was obtained as chiral version.

$^1$H-NMR (400 MHz, CD$_3$OD) δ 5.25 (bs, 1H, CH(β)), 4.40-4.45 (m, 1H, H-CH$_2$(α)), 4.22-4.17 (m, 3H, H-CH$_2$(α), CH$_2$(γ)) 4.06 (bs, 1H, CH-5-my o), 3.97 (bs, 2H, CH-6-my o, CH-1-my o), 3.80 (bs, 1H, CH-3-my o), 3.55-3.60 (m, 1H, CH-2-my o), 3.42-3.45 (m, 1H, CH-4-my o), 2.31-2.37 (m, 4H, lipid chain CH$_2$(α)), 1.31 (m, 16H, lipid chain the rest of CH$_2$), 0.90 (t, J = 6.3 Hz, 6H, lipid chain CH$_3$);

$^{13}$C-NMR (100 MHz, CD$_3$OD) δ 174.9, 174.6, 71.7, 71.6, 71.0, 70.4, 70.0, 69.9, 62.9, 61.9, 33.5, 31.5, 30.2, 28.7, 26.4, 22.3, 13.0;

$^{31}$P-NMR (162 MHz, CD$_3$OD): δ 0.78 (1P), 0.11 (1P)

HRMS (ESI–): m/z neg.: [M-H]– calculated 665.23448, found 665.23462 –0.2ppm

$[\alpha]_D^{20} = +3.5º$ (c = 0.8 in CH$_3$OH)

Mp: 60.3-62.4 ºC

1-O-(1’,2’-di-O-octanoyl-sn-glycero)phosphatidyl-myoinositol-3,4,5-triphosphate, diC8-PtdIns(3,4,5)P$_3$ 24a:

clear oil, 4.5 mg, 0.005 mmol, quantitative

This compound was obtained as chiral version.

$^1$H-NMR (400 MHz, Na salt D$_2$O) δ 5.22-5.16 (bs, 1H, CH(β)), 4.33-4.28 (m, 2H), 4.22-4.16 (m, 2H), 4.01-3.95 (m, 2H), 3.91-3.85 (m, 2H), 3.82-3.75 (m, 2H), 2.29-2.24 (m, 4H, lipid chain CH$_2$(α)), 1.46 (m, 4H, lipid chain CH$_2$(β)), 1.14 (m, 16H, lipid chain the rest of CH$_2$), 0.73 (m, 6H, lipid chain CH$_3$).

$^{31}$P-NMR (162 MHz, Na salt D$_2$O): δ 1.52 (1P), 1.16 (1P), 0.57 (1P), −0.75 (1P)
$[\alpha]_D^{20} = +2.4$ (c=0.16 in CH$_3$OH)

**myo-inositol-1,4,5-triphosphate, IP$_3$ 23c:**

oil, 3 mg, 0.007 mmol, quantitative

This compound was obtained as chiral and racemic version.

$^1$H-NMR (400 MHz, CD$_3$OD) $\delta$ 4.47 (q, J = 9.3 Hz, 1H, CH-4-myo), 4.19 (bs, 1H, CH-2-myo), 4.16-4.11 (m, 1H, CH-5-myo), 4.07 (t, J = 9.5 Hz, 1H, CH-1-myo), 3.97 (t, J = 9.3 Hz 1H, CH-6-myo), 3.60 (d, J = 8.2, 1H, CH-3 myo)

$^{31}$P-NMR (162 MHz, Na salt D$_2$O): $\delta$ 4.86 (1P), 4.72 (1P), 3.08 (1P)

$[\alpha]_D^{20} = –2.8$ (c=0.15)

And for compounds 23b, 24b and 27, having Cbz group on the chain, the reaction with bromotrimethylsilane was stirred 24h (Y. Xu, X. H. Liu, G. D. Prestwich, Tetrahedron Lett 2005, 46, 8311-8314).

**1-O-(aminopropyl)phosphatidyl-myoinositol-4,5-diphosphate, aminopropyl-PtdIns(4,5)P$_2$ 23b**

clear oil, 7.5 mg, 0.01 mmol, quantitative

This compound was obtained as chiral and racemic version.

$^1$H-NMR (400 MHz, CD$_3$OD) $\delta$ 4.45 (q, J = 9.5 Hz, 1H, CH-4-myo), 4.17 (s, 1H, CH-2-myo), 4.11 (d, J = 9.5 Hz ,1H, CH-5-myo), 4.04 (t, J = 8.8 Hz, 1H, CH-1-myo), 3.94 (t, J = 9.1 Hz, 1H, CH-6-myo), 3.58 (d, 1H, J = 8.7 Hz, CH-3-myo), 3.49 (t, 2H, J = 6.2 Hz, l.c. CH$_2$), 3.03 (t, 2H, J = 7.1 Hz, l.c. CH$_2$), 2.18-2.11 (m, 2H, l.c. CH$_2$)

$^{31}$P-NMR (162 MHz, CD$_3$OD): $\delta$ 2.16 (1P), 1.82 (1P), 1.31 (1P)

$^{13}$C-NMR (100 MHz, CD$_3$OD) $\delta$ 80.9, 79.9, 78.2, 72.4, 71.5, 39.5, 31.4, 29.8

$[\alpha]_D^{30} = –1.6$ (c=0.75)
**1-O-(aminopropyl)phosphatidyl-myoinositol-3,4,5-triphosphate, aminopropyl-PtdIns(3,4,5)P₃ 24b:** oil, 5mg, 0.009 mmol quantitative. This compound is racemic.

**¹H-NMR (400 MHz, CD₃OD)** \(\delta\) 4.64 (q, J = 9.3, 1H, CH-4-myo), 4.39 (bs, 1H, CH-2-myo), 4.26-4.19 (m, 1H, CH-3-myo), 4.16 (d, J = 9.1, 1H, CH-5-myo), 4.13-4.07 (m, 1H, CH-1-myo), 3.98 (t, J = 9.3, 1H, CH-6 myo), 3.52 (t, J = 6.3, 2H, CH₂(α)), 3.07 (t, J = 7.1, 2H, CH₂(γ)), 2.22-2.14 (m, 2H, CH₂(β))

**¹³C-NMR (100 MHz, CD₃OD) δ** 80.7, 78.1, 77.6, 76.7, 71.8, 71.5, 39.5, 31.5, 29.9

**³¹P-NMR (162 MHz, CD₃OD):** δ 2.12 (1P), 1.97 (1P), 1.54 (1P), 1.28 (1P)

**HRMS (ESI–): m/z neg.: [M–H]⁻ calculated 555.977905, found 555.84214**

**1-O-(aminopropyl)phosphatidyl-myoinositol-3-phosphate aminopropyl-PtdIns(3)P 27:** White solid, 8 mg, 0.02 mmol, quantitative. This compound is chiral.

**¹H-NMR (400 MHz, CD₃OD) δ** 4.37 (s, 1H, CH-3-myo), 3.89-3.84 (m, 2H, CH-2-myo, CH-4-myo), 3.69-3.63 (m, 2H, CH-1-myo, CH-5-myo), 3.38 (t, J = 6.3, 2H, CH₂(α)), 3.4 (m, 1H, CH-6 myo), 2.92 (t, J = 6.9, 2H, CH₂(γ)), 2.02-2.09 (m, 2H, CH₂(β))

**¹³C-NMR (100 MHz, CD₃OD) δ** 78.9, 78.9, 76.0, 73.0, 73.0, 71.7, 39.8, 31.7, 30.0

**³¹P-NMR (162 MHz, CD₃OD) δ -1.64**

\([\alpha]₀^{20} = -1.7 \ (c=0.73)\)

**HRMS (ESI–): m/z neg.: [M-H]⁻ calculated 396.04662, found 396.04683 –0.5ppm**

**Mp:** 81.0-82.5 °C