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Unified Total Syntheses of the Inositol Polyphosphates: D-I-3,5,6P_3, D-I-3,4,5P_3, D-I-3,4,6P_3, and D-I-3,4,5,6P_4 via Catalytic Enantioselective and Site-Selective Phosphorylation

Adam J. Morgan, Shio Komiya, Yingju Xu, and Scott J. Miller*,†

Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02467

scott.miller@yale.edu

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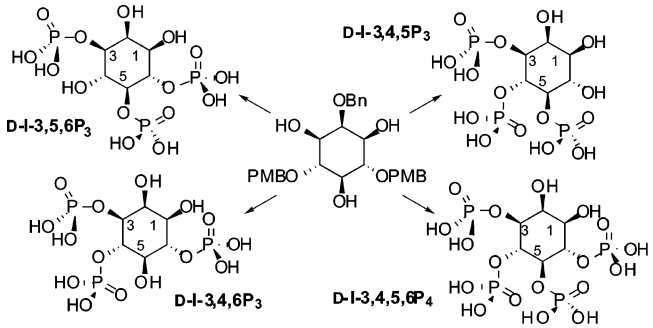

Synthetic routes to various inositol polyphosphates have been discovered utilizing catalytic enantioselective and site-selective phosphorylation reactions. The syntheses described herein exploit a common intermediate to gain efficient access to eight unique inositol polyphosphates.

Introduction

The inositol phosphates comprise a class of biologically active molecules implicated in signal transduction pathways throughout biochemistry.[1] D-*myo*-Inositol-1,4,5-trisphosphate (D-I-1,4,5P_3), for example, has been shown to serve as a secondary messenger modulating the concentration of Ca^{2+} in cells.[2] For this reason, D-I-1,4,5-P_3 (L-I-3,5,6P_3) has become one of the most thoroughly studied molecules in this class. Although these and other inositol phosphates have been the subject of many synthetic and biochemical research endeavors, in-depth studies could be greatly expanded if synthetic access to these compounds and their analogues could be improved.[3] In that regard, concise synthetic routes to several of the inositol polyphosphates, including D-I-3,5,6P_3 (L-I-1,4,5-P_3), employing peptide-catalyzed asymmetric phosphorylation are presented herein (Figure 1).

We anticipated that our recently described enantiodivergent syntheses of D-I-1P and D-I-3P could be used as a conduit to the synthesis of many of the inositol polyphosphates (Figure 2).[4,5] In this work, we discovered peptides **1P** and **3P** that effectively desymmetrized compound **1** to deliver either monophosphate **2** or ***ent*-2** in essentially optically pure form. In more recent studies, we applied these catalysts to the synthesis of members of the phosphatidylinositol class of natural products.[6] This work culminated in the synthesis of phosphatidylinositol-3-phosphate and phosphatidylinositol-3,5-bis(phosphate), as well as related analogues. In several respects, application of these

† Present address: Department of Chemistry, Yale University, P.O. Box 208107, New Haven, CT 06520.

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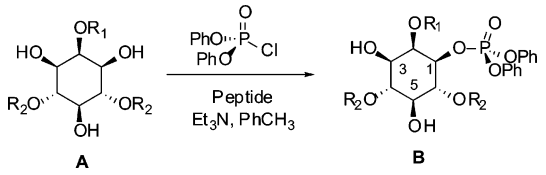
TABLE 1. Survey of Protecting Groups for Phosphorylation



			ee (%)	
entry	R_1	R_2	peptide 1P	peptide 3P
1	Bn	Bn	98	−98
2	Bn	allyl	94	−97
3	PMB	PMB	98	−98
4	Bn	PMB	97	−98

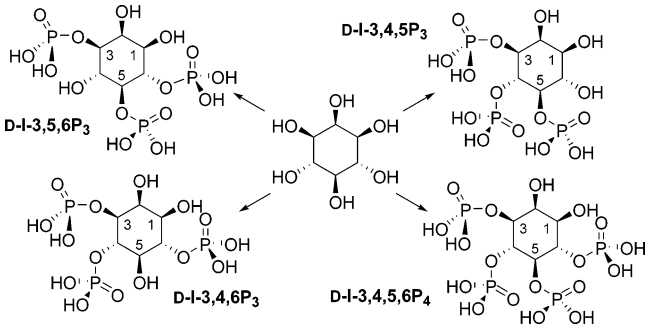


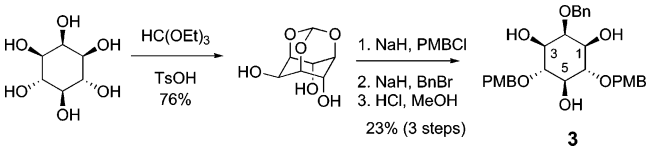
FIGURE 1. Inositol polyphosphates targeted for synthesis.

catalysts to the synthesis of various inositol polyphosphates is a more challenging objective. For example, to achieve the synthesis of unique polyphosphates with positional selectivity on the *myo*-inositol ring, we required a suitably protected derivative of **1** such that positions 4, 5, and 6 could be accessed for functionalization at a later stage.

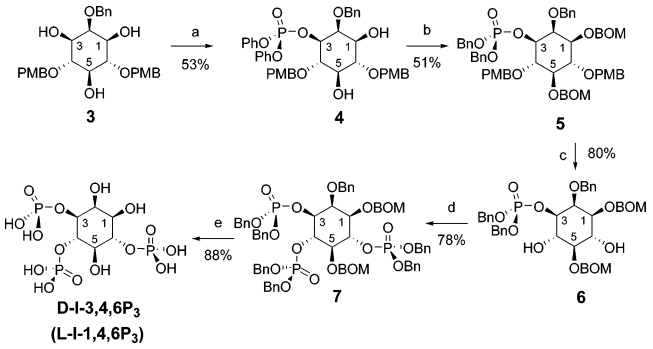
Results and Discussion

To identify a proper analogue, a series of differentially protected *myo*-inositol derivatives were screened as substrates for the asymmetric phosphorylation using peptide **1P** and peptide **3P** (Table 1). This screen revealed that catalysts **1P** and **3P** maintain high enantioselectivity profiles with a variety of protecting groups at the 4- and 6-positions. As shown in entries 1−4, various arrays of benzyl, allyl, and *p*-methoxybenzyl (PMB) substituents were suitable for obtaining the products in high ee (94−98% ee). 2-*O*-Benzyl-4,6-bis(*p*-methoxybenzyl)-*myo*-inositol (entry 4) emerged as a particularly useful compound, as high enantioselectivity was observed within a substrate that possesses orthogonal protection between the 2- and the 4,6-positions. Therefore, this triol was ultimately chosen as the common intermediate that would deliver various inositol polyphosphates (entry 4).

SCHEME 1



SCHEME 2[a]



[a] (a) peptide 3P, DPCP, Et_3N, CH_2Cl_2, 53%, 98% ee; (b) (i) BOMCl, Hunig's base, DMF; (ii) NaH, BnOH, 51% for two steps; (c) DDQ, CH_2Cl_2, 80%; (d) $(i\text{-}Pr)_2NP(OBn)_2$, dicyanoimidazole, H_2O_2, 78%; (e) $Pd(OH)_2/C$, H_2, 88%.

Our work thus began with the identification of a common precursor upon which we might devise schemes for the synthesis of multiple inositol polyphosphates. Our strategy began with a multigram synthesis of 2-*O*-benzyl-4,6-bis(*p*-methoxybenzyl)-D-*myo*-inositol (**3**), which was achieved in a manner similar to that for tribenzyl inositol (**1**) (Scheme 1).[7]

With an appropriately protected derivative of *myo*-inositol identified (**3**), we began investigating synthetic strategies toward D-I-3,4,6P_3 (L-I-1,4,6P_3), which would pave the way for other polyphosphates (Scheme 2). Asymmetric phosphorylation of triol **3** was then achieved using peptide **3P**, affording mono-

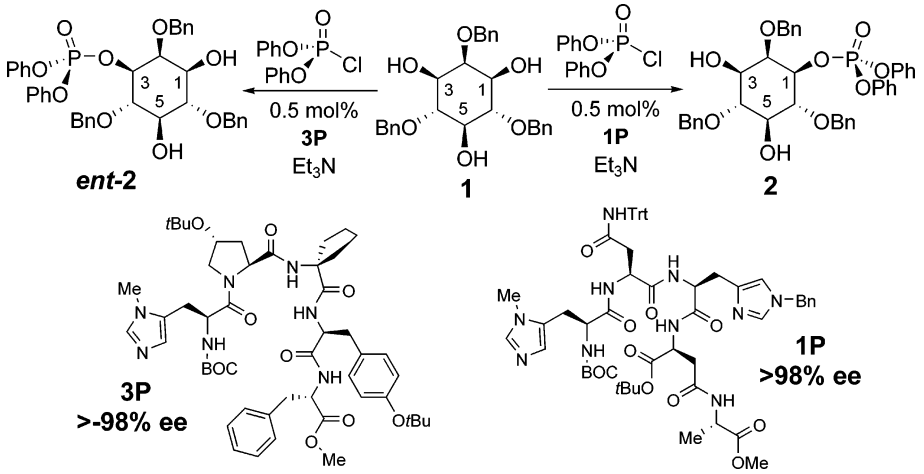
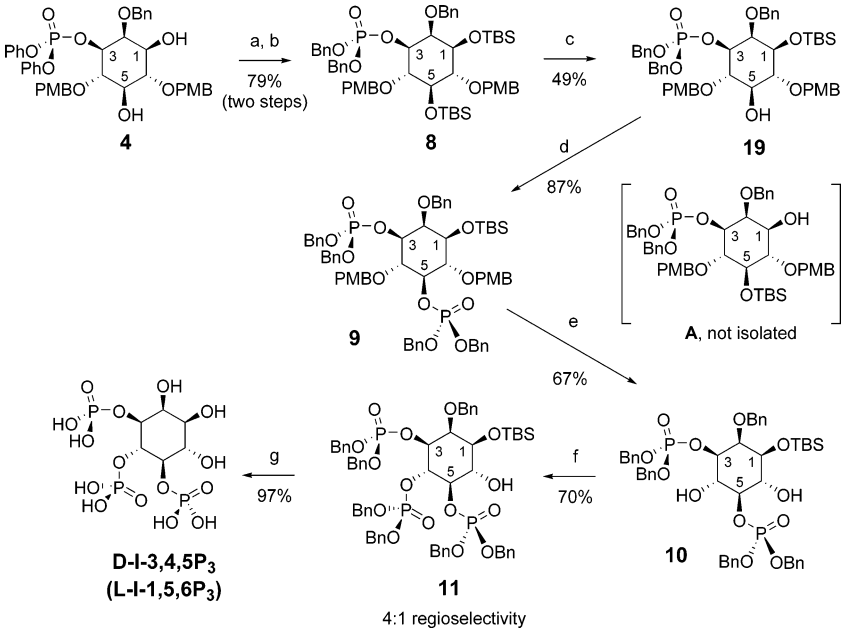


FIGURE 2. Peptide-catalyzed phosphorylation.

SCHEME 3[a]



[a] (a) TBSCl, imidazole, DMF; (b) NaH, BnOH; 79%, two steps; (c) cat. AcCl, MeOH; (d) (*i*-Pr)$_2$NP(OBn)$_2$, dicyanoimidazole, H_2O_2; 43%, two steps; (e) DDQ, CH_2Cl_2/H_2O 67%; (f) (*i*-Pr)$_2$NP(OBn)$_2$, dicyanoimidazole, H_2O_2; 4:1 regioselectivity, 70% isolated; (g) $Pd(OH)_2/C$, H_2, 97%.

phosphate **4** in 53% yield with 98% ee. Protection of the 1- and 5-hydroxyl groups as BOM ethers followed by transesterification of the *diphenyl* phosphate provides *dibenzyl* phosphate **5**. It is important to note that all attempts to facilitate PMB deprotection in the presence of an adjacent *diphenyl* phosphate results in phosphate migration.[8] Deprotection of the PMB ethers was then accomplished with dichlorodicyanobenzoquinone (DDQ) affording 4,6-diol **6**. The synthesis of D-I-3,4,6P$_3$ (L-I-1,4,6P$_3$) was then completed by simultaneous phosphorylation of the 4- and 6-hydroxyl groups followed by global hydrogenolysis with $Pd(OH)_2$ to give the target, isolated as the sodium salt (Scheme 2).

With the development of a successful synthesis of one of the inositol triphosphates, we turned our focus to the synthesis of D-I-3,4,5P$_3$ (L-I-1,5,6P$_3$). The approach is reminiscent of the synthetic plan described in Scheme 2, but this case requires a critical differentiation of the 4- and 6-hydroxyl groups. Our approach utilizes a TBS group at the 1-position of diol **10** (Scheme 3), which created the expectation that the steric and electronic environments would be sufficiently different such that preferential reaction would occur at either the 4- or the 6-position. Thus, compound **4** was subjected to per-silylation, followed by phosphate ester transesterification to deliver intermediate **8** (79% yield; 2 steps). Selective hydrolysis of the 5-TBS ether, followed by conventional phosphorylation gave **9**, which was then exposed to DDQ to give key diol **10**. Notably, the desilylation of the TBS-protected ether at the 5-position of compound **8** is faster than the TBS-ether at the 1-position. Thus, compound **19** is produced in 49% yield, along with recovered starting material (14%) and diol (23%). Perhaps surprisingly, isolation of the regioisomeric TBS-protected ether **A**, resulting from desilylation at the 1-position is difficult, because of its formation in minute quantities. Since the 5-position is presumed to be sterically more encumbered, we presume that there may be issues of steric relief that lead to selectivity for this step. At the same time, the free hydroxyl group of **19** may provide cooperativity in the desilylation of the TBS-ether at the 1-position, leading to the observation.

In the key phosphorylation event, exposure of **10** to phosphoramidite coupling conditions led to the formation of **11**, with 4:1 regioselectivity.[9] Our current contention is that this is a sterically controlled process, with the spatial requirements of the TBS ether exceeding that of the dibenzyl phosphate group. Isolation of the major product was then followed by hydrogenolysis to deliver D-I-3,4,5P$_3$ (L-I-1,5,6P$_3$). Notably, the TBS-ether at the 1-position appears to undergo autodeprotection once the phosphoric diacid functionality is revealed.

Our synthetic strategy outlined for D-I-3,4,5P$_3$ (L-I-1,5,6P$_3$) stimulated a parallel approach to D-I-3,4,5,6P$_4$ (L-I-1,4,5,6P$_4$, Scheme 4). This synthesis was initiated with selective desilylation of common intermediate **8** followed by PMB-group deprotection with DDQ to afford 4,5,6-triol **12**. Exhaustive phosphorylation and subsequent global hydrogenolysis rapidly provided D-I-3,4,5,6P$_4$ (L-I-1,4,5,6P$_4$).

We then turned our attention to the synthesis of D-I-3,5,6P$_3$ (L-I-1,4,5P$_3$). Analysis of our synthesis of D-I-3,4,5P$_3$ (L-I-1,5,6P$_3$) led to the hypothesis that the sterically demanding TBS ethers were responsible for direction of the observed regioselectivity in the phosphorylation of **10** to deliver **11**. We therefore examined 1-OH substituents that are less sterically demanding. Thus, substrate **13** was synthesized employing a benzyloxy methyl ether (BOM) protecting group in place of TBS as outlined in Scheme 5. In this case, the reaction produced a

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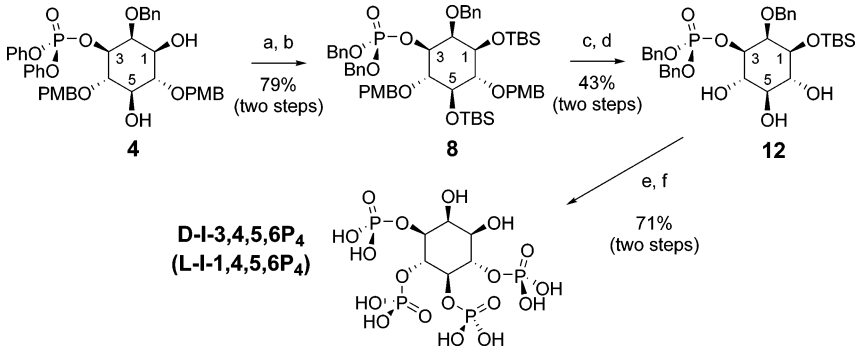
(8) The migratory behavior of diphenyl phosphates within the inositol framework is known; see ref 1b.

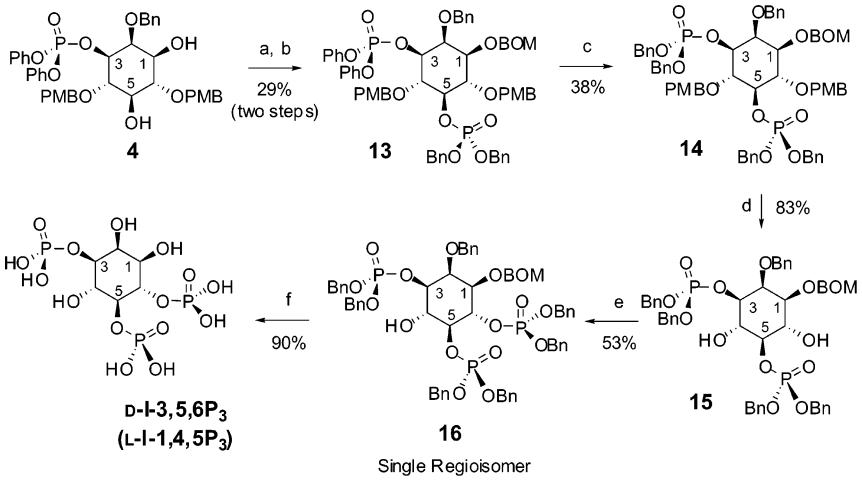
(9) Notably, catalytic P(V)-phosphorylation conditions with substrate **10** failed to give appreciable yields of either regioisomeric product.

SCHEME 4[a]



[a] (a) TBSCl, imidazole, DMF; (b) NaH, BnOH; 79%, two steps (c) cat. AcCl, MeOH; (d)DDQ, CH_2Cl_2/H_2O 43%, two steps; (e) $(i\text{-Pr})_2NP(OBn)_2$, Dicyanoimidazole, H_2O_2; (f) $Pd(OH)_2/C$, H_2, 71%, two steps.

SCHEME 5[a]



[a] (a) BOMCl, Hunig's base, THF; (b) $(i\text{-Pr})_2NP(OBn)_2$, dicyanoimidazole, H_2O_2; 29%, two steps; (c) NaH, BnOH; 38%; (d) DDQ, CH_2Cl_2/H_2O, 83%; (e) $(i\text{-Pr})_2NP(OBn)_2$, dicyanoimidazole, H_2O_2; 53% isolated; (f) $Pd(OH)_2/C$, H_2, 90%.

mixture of the monoprotected BOM-ethers, along with bis-(protected) material as well as recovered starting material. Although compound **13** is isolated in only 29% yield after two steps, the desired monoprotected material is the major product of the BOM-protection reaction (~2:1 over the alternative regioisomer), and this procedure proved operationally convenient. Nonetheless, desymmetrized diol **4**, upon treatment with BOMCl and subsequent phosphorylation, affords diphosphate **13**. Transesterification of the diphenyl phosphate followed by PMB deprotection with DDQ provides 4,6-diol **15**. Phosphorylation of **15** under standard conditions provides 3,5,6-trisphosphate **16** *as a single regioisomer*, supporting our hypothesis for selectivity. Global hydrogenolysis with $Pd(OH)_2$ ultimately provides D-I-3,5,6,P_3.

Conclusions

The syntheses of four inositol polyphosphates (D-I-3,4,6P_3, D-I-3,4,5P_3, D-I-3,4,5,6P_4, and D-I-3,5,6P_3) has thus been achieved with excellent efficiency from common intermediate **4**. This intermediate is obtained through desymmetrization of **3** by peptide-catalyzed asymmetric phosphorylation employing peptide **3P**. Alternatively, peptide **1P** provides access to ***ent*-4** with high levels of selectivity, allowing formal access to each enantiomer of the inositol polyphosphates described above (D-I-1,4,6P_3, D-I-1,5,6P_3, D-I-1,4,5,6P_4, and D-I-1,4,5P_3). Regioselective manipulation of the desymmetrized ring was achieved through selective functionalization of the remaining hydroxyl groups. In all, eight unique *myo*-inositol polyphosphates are accessible via this approach. Further studies directed toward the development of inositol polyphosphate analogues as well as studies of their behavior on biological systems are ongoing.[10]

Experimental Section

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol (3). To a solution of 4,6-di-*O*-*p*-methoxybenzyl-*myo*-inositol-1,3,5-*O*-orthoformate[11] (930 mg, 2.16 mmol) in DMF (30 mL) was added sodium hydride (104 mg, 4.32 mmol). The reaction was stirred at room temperature for 15 min at which time benzyl bromide (257 μL, 2.16 mmol) was added. The reaction continued to stir at room temperature for 2 h and was then quenched by slow addition of water. The reaction was then concentrated in vacuo and extracted with dichloromethane (3 × 200 mL) and washed repeatedly with water followed by brine. The organic layers were then dried ($MgSO_4$), filtered, and concentrated to afford 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate as a clear

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oil (1.03 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.26 (m, 5H), 7.12 (d, J = 8.1 Hz, 4H), 6.81 (d, J = 8.1 Hz, 4H), 5.52 (s, 1H), 4.63, (s, 2H), 4.57−4.35 (m, 5H), 4.30 (t, J = 3.7 Hz, 2H), 4.26 (s, 2H), 4.01 (s, 1H), 3.80 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 137.7, 129.5, 129.2, 128.3, 127.9, 127.6, 113.7, 103.1, 73.8, 71.5, 71.2, 70.6, 68.2, 67.4, 55.3; IR (film, cm^{-1}) 2955, 1615, 1583, 1508, 1457, 1382; TLC R_f 0.50 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{30}H_{32}O_8P + Na]^+$ requires m/z 543.1995, found 543.1983 (ESI+). This material (500 mg, 0.960 mmol) was then dissolved in methanol (18.0 mL) and 2 N HCl (1.00 mL) was added. Precipitate immediately formed upon addition, and dichloromethane was added until the precipitate completely dissolved. The reaction was then allowed to stir at room temperature for 18 h at which time the solution was brought to pH = 8 with concentrated ammonium hydroxide. The reaction was then concentrated to provide an oil containing ammonium chloride precipitate. Ethyl acetate (200 mL) was then added, and the resulting solution was filtered to remove ammonium chloride. The ethyl acetate was then removed in vacuo to afford an oil. The crude material was then purified via column chromatography eluting with a gradient of 40−50% ethyl acetate/hexanes to afford pure triol **3** as a clear oil (271 mg, 55%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.28 (m, 9H), 6.90 (d, J = 8.8 Hz, 4H), 4.84 (s, 2H), 4.79 (s, 4H), 4.00 (t, J = 2.9 Hz, 1H), 3.81 (s, 6H), 3.68−3.46 (m, 5H), 2.49 (s, 1H), 2.35 (d, J = 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 138.4, 130.5, 129.6, 128.9, 128.3, 127.7, 113.9, 81.5, 79.3, 75.2, 74.9, 74.6, 72.5, 55.3; IR (film, cm^{-1}) 3547, 2937, 1621, 1583, 1527, 1457, 1363, 1300; TLC R_f 0.13 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{29}H_{34}O_8 + Na]^+$ requires m/z 533.2151, found 533.2158 (ESI+).

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-1-diphenyl Phosphate (*ent*-4). 2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol (**3**) was phosphorylated under standard peptide catalyzed conditions using Peptide 1P.[4] Product was obtained in 46% yield and 97% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.11 (m, 19H), 6.87 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 8.1 Hz, 2H), 4.89−4.52 (m, 7H), 4.22 (t, J = 2.2 Hz, 1H), 3.92 (t, J = 8.8 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.72−3.47 (m, 3H), 2.46 (s, 1H), 2.26 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 138.3, 130.4, 130.1, 129.6, 129.5, 128.1, 127.4, 127.2, 125.3, 125.2, 119.9, 119.8, 113.8, 113.7, 80.4, 79.8, 79.8, 79.7, 79.7, 78.9, 75.2, 74.8, 74.6, 74.5, 71.7, 55.2; ^{31}P NMR ($CDCl_3$, 162 Hz) δ −11.2; IR (film, cm^{-1}) 3427, 3056, 2936, 2829, 1608, 1598, 1508, 1489, 1250; TLC R_f 0.20 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{41}H_{43}O_{11}P + Na]^+$ requires m/z 765.2441, found 765.2439 (ESI+). HPLC t_R 15.4 min employing a normal phase Chiralcel OD column (Alltech), eluting with 30% ethanol/hexanes $[\alpha]_D$ = +5.4 (c 1.0, CH_2Cl_2, at 97% ee).

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl Phosphate (4). 2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol (**3**) was phosphorylated under standard peptide-catalyzed conditions using Peptide 3P.[4] Product was obtained in 53% yield and 98% ee. Spectral data matched that for 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-1-diphenyl phosphate above. HPLC t_R 12.9 min employing a normal phase Chiralcel OD column (Alltech), eluting with 30% ethanol/hexanes $[\alpha]_D$ = −4.2 (c 1.0, CH_2Cl_2, at 98% ee).

2-*O*-Benzyl-1,5-di-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl Phosphate (17). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate (**4**, 535 mg, 0.720 mmol) in DMF (15.0 mL) was added diisopropyl ethylamine (878 μL, 5.04 mmol) followed by BOMCl (601 μL, 4.32 mmol). The reaction was stirred at room temperature for 18 h and then concentrated in vacuo to remove DMF. The resulting residue was then purified by column chromatography eluting with 20% ethyl acetate/hexanes to afford pure 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate as a clear oil (465 mg, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.02 (m, 29H), 6.77 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 4.99 (s, 2H), 4.87−4.48 (m, 13H), 4.29 (br. s, 1H), 4.07 (t, J = 9.4 Hz, 1H), 3.99 (t, J = 9.6 Hz, 1H), 3.78−3.65 (m, 1H), 3.74 (s, 3H overlaps with multiplet at 3.78), 3.71 (s, 3H overlaps with multiplet at 3.78), 3.61 (t, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 158.7, 150.3, 138.5, 137.8, 137.3, 130.5, 130.2, 129.6, 129.5, 129.3, 129.1, 128,4 128.3, 128.0, 128.0, 127.5, 127.4, 127.3, 127.2, 126.8, 125.2, 125.1, 120.0, 120.0, 119.9, 119.8, 113.5, 113.4, 96.4, 94.5, 80.2, 79.9, 79.3, 79.2, 77.7, 75.2, 75.1, 74.9, 70.2, 69.7, 65.3, 55.2, 55.2; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −11.5; IR (film, cm^{-1}) 3031, 2949, 1608, 1513, 1489, 1451, 1363, 1300, 1250, 1193, 1136, 1029, 960, 828; TLC R_f 0.47 (30% ethyl acetate/hexanes); exact mass calcd for $[C_{57}H_{59}O_{13}P + Na]^+$ requires m/z 1005.3591, found 1005.3588 (ESI+); $[\alpha]_D$ = +18.6 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1,5-di-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-dibenzyl Phosphate (5). To a stirred solution of 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate (**17**, 290 mg, 0.295 mmol) in THF (6.00 mL) was added benzyl alcohol (93.0 μL, 0.885 mmol) followed by sodium hydride (28.0 mg, 1.18 mmol). The reaction was stirred at room temperature for 35 min and was then quenched with saturated NH_4Cl. The THF was then removed in vacuo and the resulting residue was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an orange oil. This crude material was then purified by column chromatography (10−36% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-dibenzyl phosphate (**5**) as a clear thick oil (230 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.08 (m, 29H), 6.76 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 5.04−4.66 (m, 14H), 4.56 (s, 2H), 4.54−4.49 (m, 2H), 4.32−4.19 (m, 3H), 3.98 (ABq, J = 9.9 Hz, 2H), 3.75 (s, 3H), 3.71 (s, 3H), 3.57 (ABq, J = 9.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 138.6, 137.8, 137.4, 135.6, 135.5, 130.5, 130.3, 129.2, 129.0, 128.3, 128.3, 128.2, 128.0, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 127.2, 113.5, 113.5, 96.4, 93.9, 80.2, 79.5, 79.4, 79.3, 78.8, 78.7, 75.2, 75.1, 75.0, 70.1, 69.4, 69.4, 69.2, 69.2, 55.2, 55.2; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −0.6; IR (film, cm^{-1}) 3031, 2936, 2892, 2357, 2332, 1608, 1514, 1457, 1376, 1250, 1168, 1124, 1023; TLC R_f 0.22 (30% ethyl acetate/hexanes); exact mass calcd for $[C_{59}H_{63}O_{13}P + Na]^+$ requires m/z 1033.3904, found 1033.3887 (ESI+); $[\alpha]_D$ = +12.0 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1,5-di-*O*-benzyloxymethyl-D-*myo*-inositol-3-dibenzyl Phosphate (6). To a stirred solution of 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-dibenzyl phosphate (**5**, 220 mg, 0.218 mmol) in a 9:1 mixture of DCM/water (6.00 mL total) was added DDQ (148 mg, 0.653 mmol). The reaction was stirred at room temperature for 2 h at which time the reaction was diluted with excess DCM and saturated $NaHCO_3$ was added. The reaction was then extracted with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography (12−50% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-D-*myo*-inositol-3-dibenzyl phosphate (**6**) as a white solid (134 mg, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60−7.17 (m, 25H), 5.11 (d, J = 7.8 Hz, 2H), 5.05 (dd, J = 5.1, 8.0 Hz, 2H), 4.88−4.51 (m, 8H), 4.23 (ddd, J = 2.3, 7.6, 9.9 Hz, 1H), 4.16−4.01 (m, 3H), 3.77 (d, J = 2.3 Hz, 1H), 3.54 (d, J = 1.6 Hz, 1H), 3.48 (dd, J = 2.3, 9.9 Hz, 1H), 3.26 (t, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 137.2, 136.6, 135.7, 135.6, 135.6, 135.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.6, 127.5, 127.5, 127.4, 127.3, 127.3, 96.5, 94.2, 85.5, 78.9, 78.8, 77.8, 77.4, 77.3, 75.0, 71.0, 70.9, 70.9, 70.4, 69.8, 69.7, 69.7, 69.4; ^{31}P NMR ($CDCl_3$, 121 Hz) δ 0.2; IR (film, cm^{-1}) 3502, 3352, 3031, 2986, 1495, 1457, 1382, 1250, 1155, 1117, 1086, 1023; TLC R_f 0.14 (40% ethyl acetate/hexanes); exact mass calcd for $[C_{43}H_{47}O_{11}P + Na]^+$ requires m/z 793.2754, found 793.2779 (ESI+); $[\alpha]_D$ = −1.8 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1,5-di-*O*-benzyloxymethyl-D-*myo*-inositol-3,4,6-tris(dibenzyl) Phosphate (7). To a stirred solution of 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-D-*myo*-inositol-3-dibenzyl phosphate (**6**, 65.0 mg, 0.0840 mmol) in DCM (4.00 mL) was added dibenzyl diisopropylphosphoramidite (141 μL, 0.420 mmol) followed by 4,5-dicyanoimidazole (60.0 mg, 0.504 mmol). The reaction was stirred at room temperature for 15 h at which time the reaction was cooled to 0 °C and 1 mL 30% H_2O_2 was added. The reaction continued to stir at 0 °C for 1 h at which time the reaction was quenched with saturated Na_2SO_3 until bubbling ceased. The reaction was then extracted with DCM (5 × 100 mL) and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was then purified by column chromatography (20−40% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-D-*myo*-inositol-3,4,6-tris(dibenzyl) phosphate (**7**) as a thick oil (85.0 mg, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.11 (m, 45H), 5.09−4.84 (m, 15H), 4.84−4.70 (m, 2H), 4.67−4.54 (m, 4H), 4.53−4.38 (m, 4H), 4.22 (ddd, J = 2.1, 7.3, 9.6 Hz, 1H), 3.70 (t, J = 9.2 Hz, 1H), 3.61 (dd, J = 2.3, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8, 143.4, 138.0, 138.0, 137.2, 135.8, 135.7, 135.6, 135.4, 135.3, 133.0, 128.6, 128.5, 128.5, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.4, 127.3, 127.1, 126.8, 126.8, 126.3, 126.0, 125.8, 124.8, 123.9, 120.8, 120.3, 119.7, 118.8, 113.6, 110.5, 109.2, 104.3, 101.9, 101.1, 96.1, 94.4, 91.8, 87.1, 78.4, 78.4, 77.7, 76.5, 76.4, 76.2, 75.8, 75.7, 75.1, 70.6, 69.8, 69.8, 69.6, 69.5, 69.4, 69.3, 69.3, 58.8, 58.1; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −0.2, −0.4, −0.8; IR (film, cm^{-1}) 3064, 3032, 2956, 2924, 1497, 1455, 1380, 1275, 1214, 1023; exact mass calcd for $[C_{71}H_{73}O_{17}P_3 + H]^+$ requires m/z 1291.4139, found 1291.4186 (ESI+); $[\alpha]_D$ = +14.3 (c 1.0, CH_2Cl_2).

D-*myo*-Inositol-3,4,6-triphosphate Hexasodium Salt (D-I-3,4,-6P$_3$). To a stirred solution of 2-*O*-benzyl-3,5-di-*O*-benzyloxymethyl-D-*myo*-inositol-3,4,6-tris(dibenzyl) phosphate (**7**, 40.0 mg, 0.031 mmol) in methanol (2.50 mL) was added 20% palladium hydroxide on carbon (30.0 mg). The reaction was sealed and then purged with hydrogen several times. The reaction continued to stir at room temperature under hydrogen atmosphere (balloon pressure) for 24 h. The reaction was then filtered through Celite into a round-bottom flask and prerinsed (3 × H_2O) Chelex 100 resin (sodium form) was added to afford the crude product as the hexasodium salt. Minor impurities were removed by converting this material to the free acid form via treatment with Dowex 50X2-200 followed by conversion back to the hexasodium salt as described above. The light brown solid obtained upon lyophilization was then washed several times with methanol to afford pure D-*myo*-inositol-3,4,6-triphosphate hexasodium salt (D-I-3,4,6P$_3$) (15 mg, 88%). ^{1}H NMR (D_2O, pD 10, 300 MHz) δ 4.34 (br. s, 1H), 4.26−4.09 (m, 2H), 3.89 (ddd, J = 2.5, 7.6, 9.9 Hz, 1H), 3.68 (dd, J = 3.0, 9.6 Hz, 1H), 3.53 (t, J = 9.0 Hz, 1H); ^{13}C NMR (D_2O, pD 10, 126 MHz) δ 76.9 (d, J = 5.4 Hz, 1C), 75.9 (t, J = 6.0 Hz, 1C), 75.0 (d, J = 6.3 Hz, 1C), 74.0 (t, J = 5.5 Hz, 1C), 71.6 (s, 1C), 70.9 (s, 1C); ^{31}P NMR (D_2O, pD 10, 121 Hz) δ 6.0, 5.5, 4.4; exact mass calcd for $[C_6H_{15}O_{15}P_3 - H]^-$ requires m/z 418.9546, found 418.9530 (ESI−). $[\alpha]_D$ = +5.3 (c 0.8, H_2O, pH 8) [lit. (D-I-1,4,6P$_4$) $[\alpha]_D$ = −10.1 (c 0.78, H_2O),[12] $[\alpha]_D$ = −8.9 (c 0.90, H_2O, sodium salt).[13]

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-1,5-di-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-diphenyl Phosphate (18). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate (**4**, 240 mg, 0.323 mmol) in DMF (4.50 mL) was added imidazole (440 mg, 6.46 mmol) followed by *tert*-butyl dimethylsilyl chloride (487 mg, 3.23 mmol). The reaction was stirred at 50 °C for 48 h at which time the reaction was quenched with methanol and continued to stir for 30 min. The reaction was then cooled to room temperature and concentrated in vacuo to remove DMF. The resulting residue was then extracted with dichloromethane and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated to afford a clear thick oil. The product was then purified by column chromatography eluting with 10% ethyl acetate/hexanes to afford pure 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1,5-di-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-diphenyl phosphate as a clear oil (284 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.05 (m, 19H), 6.82 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 4.94−4.84 (m, 2H), 4.76−4.63 (m, 3H), 4.58 (ddd, J = 2.5, 7.8, 10.1 Hz, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.12−4.07 (m, 1H), 3.90 (t, J = 9.2 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.71−3.62 (m, 2H), 3.53 (t, J = 8.7 Hz, 1H), 0.82 (s, 9H), 0.80 (s, 9H), 0.09 (s, 3H), −0.01 (s, 3H), −0.07 (s, 3H), −0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 158.0, 150.2, 138.9, 133.2, 132.1, 131.1, 130.6, 129.6, 129.4, 128.6, 128.0, 127.3, 127.2, 127.1, 125.3, 125.1, 124.9, 123.7, 119.9, 119.7, 113.1, 113.0, 81.4, 80.7, 80.2, 80.1, 79.8, 75.3, 75.0, 74.8, 74.6, 73.9, 55.1, 26.1, 26.0, 18.1, −3.7, −4.1, −4.7; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −11.1; IR (film, cm^{-1}) 3064, 3032, 3001, 2953, 2929, 2895, 2856, 1614, 1589, 1490, 1472, 1463, 1387, 1359, 1295, 1248, 1220, 1191, 1170, 1127, 1072, 1037, 957; exact mass calcd for $[C_{53}H_{71}O_{11}PSi_2 + H]^+$ requires m/z 971.4351, found 971.4376 (ESI+). $[\alpha]_D$ = +21.2 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-1,5-di-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl Phosphate (8). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1,5-di-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3-diphenyl phosphate (**18**, 280 mg, 0.288 mmol) in THF (5.80 mL) was added benzyl alcohol (89.0 μL, 0.864 mmol) followed by sodium hydride (27.6 mg, 1.15 mmol). The reaction was stirred at room temperature for 1 h at which time saturated ammonium chloride solution was added slowly to quench any remaining sodium hydride. The reaction was then extracted (3 × 200 mL EtOAc) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography eluting with 15% ethyl acetate/hexanes to afford pure 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1,5-di-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl phosphate (**8**) as a clear oil (254 mg, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.12 (m, 19H), 7.82 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 5.00−4.80 (m, 6H), 4.79−4.63 (m, 4H), 4.24 (ddd, J = 2.5, 7.6, 10.1 Hz, 1H), 4.13 (br s, 1H), 3.85 (t, J = 9.2 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.68 (d, J = 9.2 Hz, 1H), 3.57 (dd, J = 2.3, 9.6 Hz, 1H), 3.46 (t, J = 9.0 Hz, 1H), 0.81 (s, 18H), 0.03 (s, 3H), −0.03 (s, 6H), −0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5, 158.0, 139.1, 131.2, 130.7, 128.8, 128.4, 128.3, 128.3, 128.0, 127.7, 127.6, 127.3, 127.2, 127.1, 126.8, 113.2, 113.0, 81.5, 80.7, 80.1, 80.0, 78.9, 78.9, 75.5, 75.0, 74.9, 74.6, 73.9, 69.3, 69.2, 69.1, 55.2, 26.1, 26.0, 18.1, 18.0, −3.7, −4.2; ^{31}P NMR ($CDCl_3$, 162 Hz) δ −0.4; IR (film, cm^{-1}) 3065, 3033, 2953, 2929, 2895, 2856, 1614, 1514, 1463, 1386, 1248, 1127, 1076, 1035, 1016; exact mass calcd for $[C_{55}H_{75}O_{11}PSi_2 + H]^+$ requires m/z 999.4664, found 999.4689 (ESI+). $[\alpha]_D$ = +19.4 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl Phosphate (19). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate (**8**, 1.44 g, 1.44 mmol) in methanol (29.0 mL) was added acetyl chloride (10.0 μL, 0.144 mmol). The reaction was stirred at 0 °C for 12 h at which time saturated aqueous sodium bicarbonate was added. The reaction was then concentrated in vacuo and extracted (5 × 200 mL DCM). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a clear oil. This crude material was then purified by column chromatography eluting with a gradient of 20−35% ethyl acetate/hexanes to afford pure 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl phosphate as a clear oil (630 mg, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.18 (m, 19H), 6.86 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.3 Hz, 2H), 5.10−4.60 (m, 10H), 4.23 (ddd, J = 2.5, 7.8, 9.9 Hz, 1H), 4.09

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(br. s, 1H), 3.89 (t, J = 9.4 Hz, 1H), 3.80−3.68 (m, 7H), 3.56 (dd, J = 1.8, 9.4 Hz, 1H), 3.43 (t, J = 9.2 Hz, 1H), 2.34 (br. s, 1H), 0.92 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 158.9, 138.8, 135.6, 130.8, 130.5, 129.4, 129.2, 128.3, 128.3, 128.2, 128.2, 128.0, 127.7, 127.6, 127.1, 127.0, 113.7, 113.5, 81.0, 80.9, 79.5, 79.4, 78.3, 78.2, 75.5, 75.0, 74.8, 74.6, 73.5, 69.3, 69.3, 69.1, 69.0, 55.2, 55.2, 26.0, 18.1, −4.4; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −0.5; IR (film, cm^{-1}) 3428, 2954, 2927, 2855, 1652, 1636, 1615, 1514, 1457, 1249, 1117, 1021; exact mass calcd for $[C_{49}H_{61}O_{11}PSi + Na]^+$ requires m/z 907.3618, found 907.3615 (ESI+). $[\alpha]_D$ = +28.4 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3,5-bis(dibenzyl) Phosphate (9). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3-dibenzyl phosphate (**19**, 530 mg, 0.599 mmol) in DCM (29.5 mL) was added dibenzyl diisopropyl phosphoramidite (1.00 mL, 3.00 mmol) followed by 4,5-dicyanoimidazole (424 mg, 3.59 mmol). The reaction was stirred at room temperature for 15 h at which time the reaction was cooled to 0 °C and 3 mL of 30% H_2O_2 was added. The reaction continued to stir at 0 °C for 1 h at which time the reaction was quenched slowly with saturated aqueous Na_2SO_3 until bubbling ceased. The reaction was then extracted with DCM (5 × 100 mL) and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was then purified by column chromatography (15−30% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3,5-bis(dibenzyl) phosphate (**9**) as a thick oil (600 mg, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.09 (m, 25H), 7.07−6.93 (m, 4H), 6.77 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 5.00−4.57 (m, 14H), 4.40 (ABq, J = 9.2 Hz, 1H), 4.25 (ddd, J = 2.5, 7.6, 9.9 Hz, 1H), 4.13 (br. s, 1H), 4.05 (t, J = 9.5 Hz, 1H), 3.90 (t, J = 9.4 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.59 (dd, J = 2.1, 9.4 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 158.3, 138.7, 135.9, 135.8, 135.4, 130.6, 130.2, 129.0, 128.3, 128.2, 128.1, 128.0, 128.0, 127.8, 127.7, 127.6, 127.4, 127.2, 127.0, 113.3, 113.2, 80.6, 80.3, 79.3, 78.1, 78.0, 77.9, 75.5, 74.4, 74.1, 73.4, 69.4, 69.2, 69.1, 69.0, 69.0, 68.9, 55.1, 25.9, 18.0, −4.4, −4.7; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −0.3, −0.6; IR (film, cm^{-1}) 3064, 3033, 2953, 2929, 2855, 1679, 1613, 1586, 1514, 1498, 1456, 1381, 1360, 1249, 1214, 1174, 1157, 1129, 1082, 1011; TLC R_f 0.15 (30% ethyl acetate/hexanes); exact mass calcd for $[C_{63}H_{74}O_{14}P_2Si + H]^+$ requires m/z 1145.4401, found 1145.4454 (ESI+). $[\alpha]_D$ = +9.7 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3,5-bis(dibenzyl) Phosphate (10). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3,5-bis(dibenzyl) phosphate (**9**, 300 mg, 0.262 mmol) in a 9:1 mixture of DCM/water (7.00 mL) was added DDQ (178 mg, 0.786 mmol). The reaction was stirred at room temperature for 12 h and then diluted with excess DCM (100 mL). The reaction was then washed several times with saturated aqueous $NaHCO_3$ until the organic layer became clear. The organic layer was then dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was then purified by column chromatography eluting with 40% ethyl acetate/hexanes to afford pure 2-*O*-benzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3,5-bis(dibenzyl) phosphate (**10**) as a white solid (158 mg, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.20 (m, 25H), 5.14−4.93 (m, 8H), 4.71 (ABq, J = 11.2 Hz, 2H), 4.30−4.03 (m, 3H), 4.01−3.81 (m, 3H), 3.49 (d, J = 9.2 Hz, 1H), 2.98 (d, J = 2.5 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 135.6, 135.5, 128.4, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.2, 127.1, 82.8, 82.7, 80.2, 78.3, 75.5, 73.3, 72.0, 72.1, 71.0, 71.0, 69.7, 69.8, 69.4, 69.4, 29.8, 25.9, 18.3, −4.4, −4.5; ^{31}P NMR ($CDCl_3$, 121 Hz) δ 0.9, 0.1; IR (film, cm^{-1}) 3390, 3091, 3065, 3034, 2953, 2928, 2897, 2855, 1498, 1456, 1386, 1360, 1260, 1216, 1157, 1016; TLC R_f 0.54 (60% ethyl acetate/hexanes); exact mass calcd for $[C_{47}H_{58}O_{12}P_2 + Na]^+$ requires m/z 927.3071, found 927.3057 (ESI+). $[\alpha]_D$ = +6.2 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3,4,5-tris(dibenzyl) Phosphate (11). To a stirred solution of 2-*O*-benzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3,5-bis(dibenzyl) phosphate (**10**, 50.0 mg, 0.0550 mmol) in DCM (2.50 mL) was added dibenzyl diisopropylphosphoramidite (28.0 μL, 0.083 mmol) followed by 4,5-dicyanoimidazole (13.0 mg, 0.110 mmol). The reaction was stirred at room temperature for 11 h at which time starting material was still present, so another 10.0 μL dibenzyl diisopropyl phosphoramidite was added and the reaction continued to stir for 4 h. The reaction was then cooled to 0 °C, 30% H_2O_2 (600 μL) was added, and the mixture stirred for 1 h. The reaction was then quenched with saturated aqueous Na_2SO_3 until bubbling ceased. The mixture was then extracted with DCM (5 × 50 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography (15−35% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3,4,5-tris(dibenzyl) phosphate (**11**) as a white solid (45.0 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.07 (m, 35H), 5.20−4.82 (m, 14H), 4.64 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 2.3 Hz, 1H), 4.27−4.15 (m, 2H), 4.14−3.96 (m, 2H), 3.49 (br. d, J = 7.1 Hz, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 135.9, 135.8, 135.7, 135.6, 135.5, 135.5, 135.4, 135.4, 135.4, 135.3, 135.3, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 127.2, 81.8, 79.6, 77.2, 75.8, 75.7, 73.1, 72.3, 70.1, 70.0, 69.8, 69.7, 69.5, 69.4, 69.3, 69.3, 69.2, 32.0, 30.2, 29.8, 29.4, 26.0, 22.8, 18.4, 14.2, −4.1, −4.7; ^{31}P NMR ($CDCl_3$, 121 Hz) δ 0.9, −0.4, −1.0; IR (film, cm^{-1}) 3356, 2954, 2924, 2853, 1659, 1632, 1456, 1377, 1271, 1012; TLC R_f 0.50 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{61}H_{71}O_{15}P_3Si + Na]^+$ requires m/z 1187.3673, found 1187.3705 (ESI+). $[\alpha]_D$ = +11.6 (c 1.0, CH_2Cl_2).

D-*myo*-Inositol-3,4,5-triphosphate Hexasodium Salt (D-I-3,4,-5P$_3$). To a stirred solution of 2-*O*-benzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3,4,5-tris(dibenzyl) phosphate (**11**, 37 mg, 0.032 mmol) in HPLC grade methanol (1.0 mL) was added 20% palladium hydroxide on carbon (30 mg). The mixture was stirred under hydrogen (atmospheric pressure) for 24 h and then filtered through a syringe filter (Millex-HV 0.45 μm) to remove the catalyst. Solvent was then removed under reduced pressure to afford D-I-3,5,6P$_3$ in free acid form. This material was redissolved in H_2O and Chelex 100 (sodium form) was added and the mixture stirred for 3 min then filtered. The solvent was then removed via lyophilization and the resulting solid was rinsed several times with HPLC grade methanol to afford D-I-3,4,5P$_3$ as the hexasodium salt (13 mg, 97%). ^{1}H NMR (D_2O, sodium salt, pD ∼8, 300 MHz) δ 4.32 (q, J = 9.4 Hz, 1H), 4.22 (t, J = 3.0 Hz, 1H), 3.99 (td, J = 2.8, 9.4 Hz, 1H), 3.90 (q, J = 8.7 Hz, 1H), 3.81 (t, J = 9.4 Hz, 1H), 3.61 (dd, J = 2.8, 9.6 Hz, 1H); ^{13}C NMR (D_2O, pD 10, 100 MHz) δ 78.9, 77.3, 74.9, 74.9, 74.6, 73.6, 73.5, 71.8, 70.3, 70.2; ^{31}P NMR (D_2O, sodium salt, pD ∼8, 121 Hz) δ 4.8, 3.8, 2.1; exact mass calcd for $[C_6H_{15}O_{15}P_3 + H]^+$ requires m/z 420.9702, found 420.9696 (ESI+). $[\alpha]_D$ = +0.4 (c 2.4, H_2O, pH 9) [lit. (D-I-1,5,-6P$_4$) $[\alpha]_D$ = −2.57 (c 1.01, H_2O),[11] $[\alpha]_D$ = +2.2 (c 2.30, H_2O, free acid),[14] $[\alpha]_D$ = −2.8 (c 1.43, H_2O, sodium salt)[15]].

2-*O*-Benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl Phosphate (12). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl phosphate (**19**, 220 mg, 0.249 mmol) in a 9:1 mixture of DCM/water (9.00 mL) was added DDQ (170 mg, 0.747 mmol). The reaction was stirred at room temperature for 1.5 h and then diluted

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with excess DCM (100 mL). The reaction was then washed several times with saturated aqueous $NaHCO_3$ until the organic layer became clear. The organic layer was then dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was then purified by column chromatography (50−80% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl phosphate (**12**) as a white solid (140 mg, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−7.10 (m, 15H), 5.10−4.85 (m, 4H), 4.81 (d, J = 11.7 Hz, 1H), 4.60−4.35 (m, 3H), 4.26 (ddd, J = 2.3, 7.8, 10.1 Hz, 1H), 4.00 (t, J = 9.0 Hz, 1H), 3.92−3.276 (m, 2H), 3.56−3.27 (m, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 135.4, 135.4, 128.3, 128.2, 128.2, 127.8, 127.8, 127.6, 127.6, 127.5, 126.9, 80.6, 78.7, 78.6, 75.3, 74.6, 73.5, 72.8, 71.9, 69.7, 69.3, 25.9, 18.2, −4.2, −4.4; ^{31}P NMR ($CDCl_3$, 162 Hz) δ 0.0; IR (film, cm^{-1}) 3427, 3089, 3065, 3033, 2953, 2927, 2894, 2854, 1497, 1456, 1423, 1386, 1335, 1249, 1220, 1159, 1137, 1098, 1077, 1041, 1014, 851, 836; TLC R_f 0.18 (80% ethyl acetate/hexanes); exact mass calcd for $[C_{33}H_{45}O_9PSi + H]^+$ requires m/z 645.2649, found 645.2641 (ESI+). $[\alpha]_D$ = +10.5 (c 2.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3,4,5,6-tetrakis(dibenzyl) Phosphate (20). To a stirred solution of 2-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-*myo*-inositol-3-dibenzyl phosphate (**12**, 100 mg, 0.155 mmol) in DCM (7.00 mL) was added dibenzyl diisopropylphosphoramidite (521 μL, 1.55 mmol) followed by 4,5-dicyanoimidazole (201 mg, 1.71 mmol). The reaction was stirred at room temperature for 14 h. The reaction was then cooled to 0 °C, 30% H_2O_2 (1.20 mL) was added, and the mixture stirred for 1 h. The reaction was then quenched with saturated aqueous Na_2SO_3 until bubbling ceased. The mixture was then extracted with DCM (5 × 50 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography (20−35% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3,4,5,6-tetrakis(dibenzyl) phosphate as a clear thick oil (199 mg, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.04 (m, 45H), 4.15−4.75 (m, 19H), 4.69 (d, J = 11.5 Hz, 1H), 4.41−4.17 (m, 3H), 3.64 (d, J = 9.4 Hz, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1, 136.0, 135.9, 135.9, 132.5, 129.0, 129.0, 128.9, 128.8, 128.8, 128.6, 128.6, 128.3, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.2, 127.1, 126.6, 122.2, 116.4, 102.5, 101.4, 88.6, 84.2, 79.0, 76.3, 76.2, 76.0, 75.8, 75.7, 75.6, 75.5, 75.4, 71.8, 69.7, 69.6, 69.5, 69.5, 69.4, 69.3, 69.1, 44.2, 26.0, 16.0, −2.6, −4.5, −4.6; ^{31}P NMR ($CDCl_3$, 121 Hz) δ 0.3, 0.1, −0.3, −0.8; IR (film, cm^{-1}) 3064, 3032, 2954, 2927, 2895, 2855, 1497, 1456, 1382, 1278, 1215, 1128, 1017, 959, 880, 839; TLC R_f 0.21 (40% ethyl acetate/hexanes); exact mass calcd for $[C_{75}H_{84}O_{18}P_4 + H]^+$ requires m/z 1425.4456, found 1425.4678. (ESI+). $[\alpha]_D$ = +7.2 (c 1.0, CH_2Cl_2).

D-*myo*-Inositol-3,4,5,6-tetraphosphate Octasodium Salt (D-I-3,4,5,6P$_4$). To a stirred solution of 2-*O*-benzyl-1-*O*-*tert*-butyl dimethylsilyl-D-*myo*-inositol-3,4,5,6-tetrakis(dibenzyl) phosphate (**20**, 40 mg, 0.028 mmol) in HPLC grade methanol (2.0 mL) was added 20% palladium hydroxide on carbon (30 mg). The mixture was stirred under hydrogen (atmospheric pressure) for 24 h and then filtered through Celite to remove the catalyst. Chelex 100 (sodium form) was added and the mixture stirred for 3 min and then filtered. The solvent was then removed via lyophilization and the resulting solid was rinsed several times with HPLC grade methanol to afford D-I-3,4,5,6P$_4$ as the octasodium salt (15.0 mg, 79%). ^{1}H NMR (D_2O, sodium salt, pD ∼8, 300 MHz) δ 4.47 (q, J = 9.6 Hz, 1H), 4.34 (q, J = 9.2 Hz, 1H), 4.25 (t, J = 2.3 Hz, 1H), 4.22−4.05 (m, 2H), 3.75 (dd, J = 2.8, 9.6 Hz, 1H); ^{13}C NMR (D_2O, pD 10, 100 MHz) δ 74.8, 74.7, 73.6, 72.4, 65.1; ^{31}P NMR (D_2O, pD 10, 121 Hz) δ 5.3, 4.8, 4.7, 4.4; exact mass calcd for $[C_6H_{14}O_{18}P_4 + H]^+$ requires m/z 498.9209, found 498.9235 (ESI+). $[\alpha]_D$ = +2.0 (c 2.0, H_2O, pH 10) [lit. (D-I-3,4,5,6P$_4$) $[\alpha]_D$ = +10.1 (c 2.23, H_2O, pH 8.9),[11] $[\alpha]_D$ = +9.8 (c 1.43, H_2O, pH 11.1),[16] $[\alpha]_D$ = −6.2 (c 2.15, H_2O, sodium salt)[17]].

2-*O*-Benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl Phosphate (21). To a stirred solution of 2-*O*-benzyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate (**4**, 285 mg, 0.384 mmol) in THF (5.00 mL) was added diisopropyl ethylamine (401 μL, 2.30 mmol) followed by benzyloxymethyl chloride (BOMCl, 267 μL, 1.92 mmol). The reaction was stirred at 50 °C for 24 h and was then quenched with excess methanol and concentrated. The mixture was then extracted with DCM (5 × 100 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography (10−30% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate as a clear oil (120 mg, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.06 (m, 24H), 6.84 (d, J = 8.71 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 4.89−4.48 (m, 11H), 4.26 (t, J = 2.3 Hz, 1H), 3.95 (t, J = 9.4 Hz, 1H), 3.87 (t, J = 9.6 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.67 (dd, J = 2.1, 9.6 Hz, 1H), 3.53 (dt, J = 1.6, 9.0 Hz, 1H), 2.38 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 158.9, 150.4, 150.3, 150.2, 148.1, 142.2, 139.0, 138.5, 137.3, 132.2, 130.6, 130.3, 129.7, 129.6, 129.4, 129.3, 129.3, 128.2, 128.0, 127.6, 127.5, 127.3, 127.2, 125.2, 125.1, 119.9, 119.9, 115.1, 113.7, 113.6, 105.2, 104.5, 104.3, 99.1, 94.3, 80.1, 79.8, 79.7, 79.4, 79.3, 78.0, 77.6, 77.3, 75.0, 74.9, 74.7, 71.3, 69.7, 68.5, 67.6, 57.9, 55.3, 52.4; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −11.5; IR (film, cm^{-1}) 3451, 3063, 3031, 2936, 2904, 2836, 1612, 1588, 1514, 1488, 1454, 1294, 1249, 1214, 1189, 1115, 1072, 1035, 1026, 958; TLC R_f 0.61 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{49}H_{51}O_{12}P + Na]^+$ requires m/z 885.3016, found 885.3008 (ESI+). $[\alpha]_D$ = +12.6 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl Phosphate-5-dibenzyl Phosphate (13). To a stirred solution of 2-*O*-benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate (**21**, 325 mg, 0.377 mmol) in DCM (18.9 mL) was added dibenzyl diisopropylphosphoramidite (633 μL, 1.89 mmol) followed by 4,5-dicyanoimidazole (267 mg, 1.26 mmol). The reaction was stirred at room temperature for 15 h. The reaction was then cooled to 0 °C, 30% H_2O_2 (3.00 mL) was added, and the mixture stirred for 1 h. The reaction was then quenched with saturated aqueous Na_2SO_3 until bubbling ceased. The mixture was then extracted with DCM (5 × 100 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography (15−33% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3-diphenyl phosphate-5-dibenzyl phosphate (**13**) as a clear oil (343 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.03 (m, 34H), 6.76 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 4.95−4.52 (m, 13H), 4.50 (s, 2H), 4.42 (q, J = 9.5 Hz, 1H), 4.31 (t, J = 2.5 Hz, 1H), 4.13 (t, J = 9.5 Hz, 1H), 4.03 (t, J = 9.5 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H),. 3.68 (dd, J = 2.2, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 158.6, 150.2, 150.1, 138.3, 137.2, 135.9, 135.9, 135.8, 130.4, 130.0, 129.5, 129.3, 129.0, 128.2, 128.1, 128.0, 127.9, 127.5, 127.3, 127.2, 125.2, 125.1, 120.0, 119.9, 119.8, 113.4, 113.2, 94.4, 80.6, 80.5, 79.3, 79.2, 78.7, 77.8, 77.8, 77.7, 77.5, 77.2, 76.8, 74.9, 74.7, 74.3, 69.7, 69.2, 55.2; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −0.5, −11.7; IR (film, cm^{-1}) 2956, 2925, 2856, 1611, 1588, 1515, 1490, 1457, 1249, 1191, 1023, 960; TLC R_f 0.65 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{63}H_{64}O_{15}P_2 + H]^+$ requires m/z 1123.3799, found 1123.3848 (ESI+). $[\alpha]_D$ = +8.0 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3,5-bis(dibenzyl) Phosphate (14). To a stirred solution of 2-*O*-benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxy-

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benzyl-D-*myo*-inositol-3-diphenyl phosphate-5-dibenzyl phosphate (**13**, 343 mg, 0.305 mmol) in THF (6.10 mL) was added benzyl alcohol (95.0 μL, 0.915 mmol) followed by sodium hydride (29.0 mg, 1.22 mmol). The reaction was stirred at room temperature for 30 min at which time saturated ammonium chloride solution was added slowly to quench any remaining sodium hydride. The reaction was then extracted (3 × 100 mL EtOAc) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was then purified by column chromatography (15−35% ethyl acetate/hexanes) to afford pure 2-*O*-benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3,5-bis-(dibenzyl) phosphate (**14**) as a clear oil (135 mg, 38%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.03 (m, 34H), 6.75 (d, J = 8,4 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 4.98−4.63 (m, 16H), 4.46 (q, J = 12.1 Hz, 2H), 3.37 (q, J = 9.2 Hz, 1H), 4.29 (t, J = 2.2 Hz, 1H), 4.23 (ddd, J = 2.6, 7.7, 9.9 Hz, 1H), 4.05 (t, J = 9.5 Hz, 1H), 4.00 (t, J = 9.9 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.60 (dd, J = 2.2, 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 151.9, 149.6, 138.4, 137.3, 135.8, 135.8, 135.4, 130.4, 130.1, 129.1, 128.9, 128.6, 128.3, 128.1, 128.1, 127.9, 127.8, 127.6, 127.5, 127.5, 127.3, 122.8, 113.3, 113.3, 96.5, 93.8, 90.8, 80.5, 78.6, 78.1, 78.0, 77.1, 77.1, 76.8, 76.6, 76.5, 76.3, 76.2, 75.0, 74.6, 74.2, 72.2, 69.4, 69.2, 69.1, 55.1; ^{31}P NMR ($CDCl_3$, 121 Hz) δ −0.4, −0.8; IR (film, cm^{-1}) 3065, 3035, 2953, 2924, 2852, 2358, 2333, 1613, 1513, 1498, 1455, 1380, 1248, 1173, 1082, 1010, 881; TLC R_f 0.30 (50% ethyl acetate/hexanes); exact mass calcd for $[C_{65}H_{68}O_{15}P_2 + Na]^+$ requires m/z 1173.3931, found 1173.3937 (ESI+). $[\alpha]_D$ = +12.3 (c 1.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-benzyloxymethyl-D-*myo*-inositol-3,5-bis(dibenzyl) Phosphate (15). To a stirred solution of 2-*O*-benzyl-1-*O*-benzyloxymethyl-4,6-di-*O*-*p*-methoxybenzyl-D-*myo*-inositol-3,5-bis(dibenzyl) phosphate (**14**, 130 mg, 0.113 mmol) in DCM (2.80 mL) was added distilled water (311 μL) followed by DDQ (77.0 mg, 0.339 mmol). The heterogeneous reaction was stirred at room temperature for 12 h and then diluted with DCM and saturated $NaHCO_3$ solution was added. The reaction was then extracted with DCM (4 × 50 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was purified by column chromatography, eluting with 60% ethyl acetate/hexanes to afford desired diol **15** (85.0 mg, 83%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.18 (m, 30H), 5.18−4.95 (m, 8H), 4.86−4.50 (m, 6H), 4.23−4.08 (m, 4H), 4.05 (s, 1H), 3.87 (d, J = 1.8 Hz, 1H), 3.64 (d, J = 1.6 Hz, 1H), 3.51−3.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 137.0, 135.5, 135.4, 128.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.3, 94.3, 82.6, 82.5, 78.5, 78.4, 77.7, 77.1, 75.0, 70.9, 70.8, 69.9, 69.8, 69.8, 69.6, 69.5; ^{31}P NMR ($CDCl_3$, 121 Hz) δ 1.1, 0.2; IR (film, cm^{-1}) 3397, 3065, 3032, 2954, 2924, 2853, 1456, 1248, 1215, 1119; TLC R_f 0.27 (60% ethyl acetate/hexanes); exact mass calcd for $[C_{49}H_{52}O_{13}P_2 + Na]^+$ requires m/z 933.2781, found 933.2761 (ESI+). $[\alpha]_D$ = +0.5 (c 5.0, CH_2Cl_2).

2-*O*-Benzyl-1-*O*-benzyloxymethyl-D-*myo*-inositol-3,5,6-tris-(dibenzyl) Phosphate (16). To a stirred solution of 2-*O*-benzyl-1-*O*-benzyloxymethyl-D-*myo*-inositol-3,5-bis(dibenzyl) phosphate (**15**, 50 mg, 0.055 mmol) in DCM (2.5 mL) was added dibenzyl diisopropyl phosphoramidite (28 μL, 0.083 mmol) followed by 4,5-dicyanoimidazole (13 mg, 0.11 mmol). The reaction was stirred at room temperature for 12 h and then was cooled to 0 °C and 0.20 mL 30% H_2O_2 solution was added. The reaction then continued to stir at 0 °C for 1 h and was then quenched with saturated Na_2SO_3 solution. The product was then extracted into DCM (5 × 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography eluting with 60% ethyl acetate/hexanes to afford pure 2-*O*-benzyl-1-*O*-benzyloxymethyl-D-*myo*-inositol-3,5,6-tris-(dibenzyl) phosphate (**16**) as a colorless oil that crystallized upon standing (35 mg, 53%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.17 (m, 40H), 5.19−4.87 (m, 12H), 4.74 (ABq, J = 11.9 Hz, 2H), 4.57 (ABq, J = 7.1 Hz, 2H), 4.42 (q, J = 12.2 Hz, 2H), 4.32−4.22 (m, 2H), 4.21−4.07 (m, 2H), 3.60 (dd, J = 2.2, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0, 137.2, 135.7, 135.7, 135.6, 135.5, 135.3, 135.2, 128.3, 128.2, 128.0, 127.9, 127.7, 127.4, 94.4, 77.8, 77.7, 77.1, 75.2, 75.1, 71.0, 70.3, 70.2, 70.2, 70.1, 69.8, 69.7, 69.6, 69.2; ^{31}P NMR ($CDCl_3$, 121 Hz) δ 1.1, −0.3, −0.4; IR (film, cm^{-1}) 3347, 3067, 3032, 2964, 2926, 2856, 1496, 1454, 1380, 1258; TLC R_f 0.25 (60% ethyl acetate/hexanes); exact mass calcd for $[C_{63}H_{65}O_{16}P_3 + H]^+$ requires m/z 1171.3564, found 1171.3589 (ESI+). $[\alpha]_D$ = +0.8 (c 1.0, CH_2Cl_2).

D-*myo*-Inositol-3,5,6-triphosphate Hexasodium Salt (D-I-3,5,-6P$_3$). To a stirred solution of 2-*O*-benzyl-1-*O*-benzyloxymethyl-D-*myo*-inositol-3,5,6-tris(dibenzyl) phosphate (**16**, 12 mg, 0.010 mmol) in HPLC grade methanol (1.0 mL) was added 20% palladium hydroxide on carbon (13 mg). The mixture was stirred under hydrogen (atmospheric pressure) for 24 h and then filtered through a syringe filter (Millex-HV 0.45 μm) to remove the catalyst. Solvent was then removed under reduced pressure to afford D-I-3,5,6P$_3$ in free acid form. This material was redissolved in H_2O and stirred with 1 M NaOH (aq, 80 μL, 0.080 mmol). The solvent was then removed via lyophilization and the resulting solid was rinsed several times with HPLC grade methanol to afford D-I-3,5,-6P$_3$ as the hexasodium salt (5.0 mg, 90%). ^{1}H NMR (D_2O, pD 10, 300 MHz) δ 4.33 (br. s, 1H), 4.14 (q, J = 7.8 Hz, 1H), 3.91−3.81 (m, 3H), 3.70 (dd, J = 2.9, 9.8 Hz, 1H); ^{13}C NMR (D_2O, pD 10, 100 MHz) δ 78.0, 75.8, 75.4, 73.4, 72.6, 71.5; ^{31}P NMR (D_2O, pD 10, 121 Hz) δ 5.8, 5.7, 4.0; exact mass calcd for $[C_6H_{15}O_{15}P_3 + H]^+$ requires m/z 420.9702, found 420.9693 (ESI+); $[\alpha]_D$ = +9.8 (c 1.0, H_2O, pH 10) [lit. (D-I-1,4,5P$_3$) $[\alpha]_D$ = −20 (c 0.05, H_2O, pH 9),[5c] $[\alpha]_D$ = −3.19 (c 0.26, H_2O, sodium salt),[5b] $[\alpha]_D$ = −24.1 (c 0.28, H_2O, sodium salt)[11]]

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Supporting Information Available: Experimental procedures and product characterization for additional intermediates discussed in the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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