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$Yb(OTf)_3$-Catalyzed Desymmetrization of *myo*-Inositol-1,3,5-Orthoformate and Its Application in the Synthesis of Chiral Inositol Phosphates

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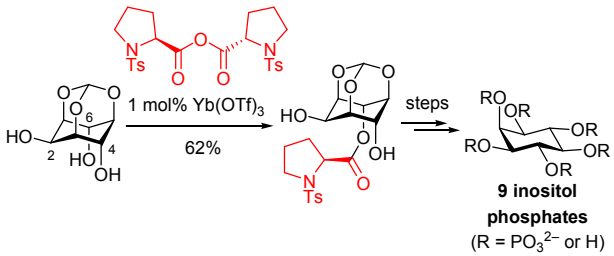


ABSTRACT

A variety of inositol phosphates including *myo*-inositol-1,4,5-trisphosphate, which is a secondary messenger in transmembrane signaling, were selectively synthesized *via* $Yb(OTf)_3$-catalyzed desymmetrization of *myo*-inositol-1,3,5-orthoformate using a proline-based chiral anhydride as an acylation precursor. The investigated catalytic system could regioselectively differentiate the enantiotopic hydroxy groups of *myo*-inositol-1,3,5-orthoformate in the presence of a chiral auxiliary. This key step to generate a suitably protected chiral *myo*-inositol derivatives is described here as a unified approach to access inositol phosphates.

INTRODUCTION

The phosphate esters of *myo*-inositol and its derivatives have multitude of biological functions through the regulation of diverse signal transduction pathways (Figure 1).[1] D-*myo*-Inositol-1,4,5-trisphosphate [Ins(1,4,5)P_3 (**1**)], for instance, is a secondary messenger that affects many cellular processes by eliciting internal calcium channel signals.[2] The secondary messengers Ins(1,4,5)P_3 and diacylglycerol are obtained from agonistic stimulative hydrolysis of phosphatidylinositol phospholipase-C precursor in the plasma membrane. Ins(1,4,5)P_3 regulates the release of Ca^{+2} from internal stores by specific interaction with its receptor located in the endoplasmic reticulum.[3] Currently, Ins(1,4,5)P_3 and its immediate phosphorylated metabolites are much needed compounds especially in eukaryotic cell biology due to their applications in ion-channel physiology, membrane dynamics, and nuclear signaling.[1]

Owing to their broad range of implicated applications, the chemical synthesis and biological properties of inositol phosphates and their analogues have been comprehensively reviewed.[1,2,4] However, while the biomedical importance of inositol phosphates are well-documented, their mechanisms of action in various physiological events have not yet been fully elucidated. As an example in this context, D-*myo*-inositol-1,3,4,5,6-pentakisphosphate [Ins(1,3,4,5,6)P_5 (**6**)] specifically inhibit phosphoinositide 3-kinase protein activity by selectively binding to the pleckstrin homology domain, which inherently induces apoptosis and suppresses tumorigenicity in the human cancer cell lines.[5] It was further shown that Ins(1,3,4,5,6)P_5 restrains serine phosphorylation on protein kinase B *in vivo* similar to the effect of cisplatin and etoposide, proving its importance in cancer therapy. However, the general concern in the use of inositol polyphosphates is associated with their cellular uptake due to the presence of multiple negatively charged phosphate groups. In order to illustrate the dogma of inositol polyphosphate

internalization to get access to cytosol, Potter and co-workers[7] synthesized a fluorescent Ins(1,3,4,5,6)P_5 conjugate and demonstrated the visualization of its uptake by various malignant cell types and further postulated the underlying mechanism of non-receptor mediated endocytosis.

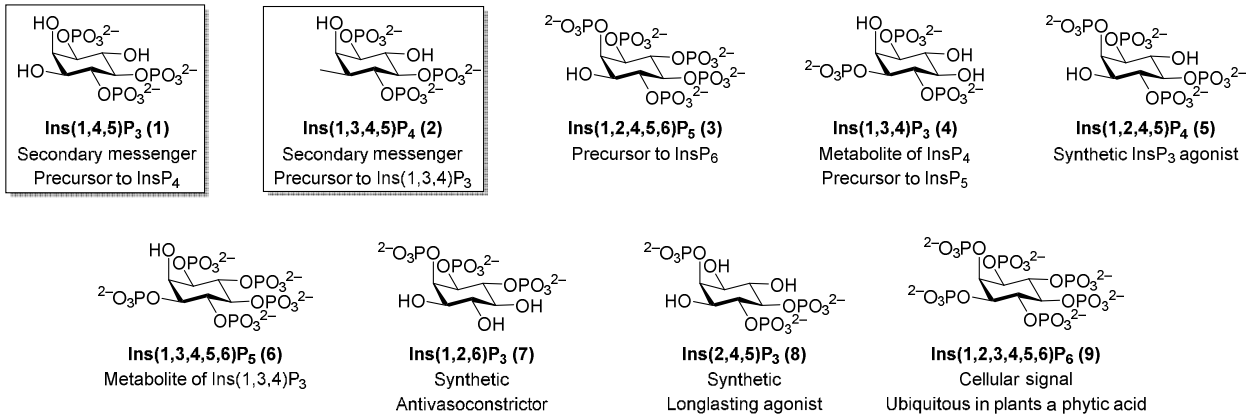


Figure 1. Some important representative examples of naturally occurring and synthetic inositol polyphosphates. The compounds enclosed in squares are synthesized in the current study along with other inositol phosphates.

Due to their ubiquitous presence in a wide variety of flora and fauna,[7] researchers both from academia and industry try to unravel the biological roles of inositol phosphates. Nevertheless, lack of enantiomerically pure forms of inositol phosphates hampers further *in vivo* biochemical investigations due to their difficult isolation from natural sources. Because of this, the demand for the development of rapid and efficient scalable synthetic strategies for the preparation of optically active pure *myo*-inositol phosphate derivatives is high. Hence, much interest has centered upon new synthetic avenues of access, posing challenging tasks to chemists.

D-*myo*-Inositol-1,3,5-orthoformate (**10**) was first studied by Kishi *et al*.[8] in the preparation of *scyllo*-inositol. From its inception, D-*myo*-inositol-1,3,5-orthoesters have been

extensively explored for its utility as rudimentary synthons for the synthesis of phosphoinositols and their analogues. These orthoesters have rigid, conformationally locked adamantane-like structures, enabling the possible regioselective differentiation of the equivalent 1,3-diaxial hydroxy groups from the equatorial 2-hydroxyl.[9] There are constant efforts to expand and exploit the desymmetrization or resolution of *myo*-inositol orthoesters to uncover the latent precursor for inositol phosphates and its congeners of biological relevance.[9a,10] In pursuit of site-selective functionalization of *meso* compounds, desymmetrization processes are underscored for the synthesis of stereochemically complex molecules.[11] For example, phosphorylated histidyl peptides were synthesized as a mimic of phosphohistidine intermediate in proteins[12] and utilized in the desymmetrization of enantiotopic 1,3-positions of *myo*-inositol derivatives via catalytic asymmetric phosphorylation.[13] Using a peptide catalyst containing nonproteinogenic amino acid, this methodology was further exploited in the stereo-differentiation of the more challenging and chemically equivalent enantiotopic 4- and 6-positions for the enantioselective synthesis of D-*myo*-inositol-6-phosphate through kinetic resolution of racemic monophosphate.[14] Moreover, serendipitous regioselective conversion of *myo*-inositol-1,3,5-orthobenzoate to the corresponding 2-*O*-benzoyl cyclitol under acid-catalyzed hydrolysis of orthobenzoate was reported as a novel route to the anticancer agent Ins(1,3,4,5,6)P_5 (**6**).[15] Very recently, a C_2-symmetrical chiral phosphoramidite reagent was developed for chiral resolution via phosphitylation to synthesize chiral inositol bisphosphates.[16] However, the aforementioned synthetic routes have limitations such as multiple orthogonal protection and deprotection manipulations, phosphate functionality migration within the inositol frame work, tedious isolation of densely charged inositol phosphates and require multiple intermediates.

Our previous endeavors to extend the synthetic toolbox toward inositol derivatives included the desymmetrization of orthoformate **10** with mannosyl donor for the preparation of biologically relevant phosphatidylinositol mannosides.[17] Furthermore, we reported the metal triflate [$M(OTf)_3$]-catalyzed desymmetrization of **10** using (+)-camphanic anhydride (Figure 2).[18] We now report the extension of this desymmetrization methodology using various chiral acylating agents and its application in the synthesis of various inositol phosphates.

RESULTS AND DISCUSSION

Initially, we sought to use the conformational rigidity of orthoformate **10** as a structural platform to regioselectively introduce an acyl group at either of the chemically equivalent and axially oriented C-4 or C-6 hydroxy group while leaving the equatorial 2-OH untouched. This manner of regioselective acylation should offer a short, direct, and unified synthetic route toward several chiral D-*myo*-inositol phosphates of interest. With $M(OTf)_3$ as catalyst, the asymmetric acylation of **10** could possibly occur according to the cycle depicted in Figure 2. Here, $M(OTf)_3$ coordinates preferably with the axial hydroxy groups of **10** and simultaneously activates the acid anhydride to assemble the intermediate complex. Such coordination enables the acid anhydride to be properly positioned for nucleophilic attack at either 4-O (path I) or 6-O (path II) of **10** to furnish the 2,6-diol **11** and the 2,4-diol **12**, respectively. The capability of using chiral acid anhydrides in the presence of $M(OTf)_3$ to provide a level of selectivity between the 4- and 6-hydroxyls was realized in our preliminary data.[18] Rare-earth metal triflates are considered as new class of Lewis acids, which occupied much space in the field of enantioselective catalysis with respect to their exquisite features such as water compatibility, environmentally benign nature, and recyclability.[19] Of these late transition metal triflates, $Yb(OTf)_3$ is well-studied in

organic synthesis and carbohydrate chemistry due to its higher catalytic activity attributed to its small ionic radius.[19,20]

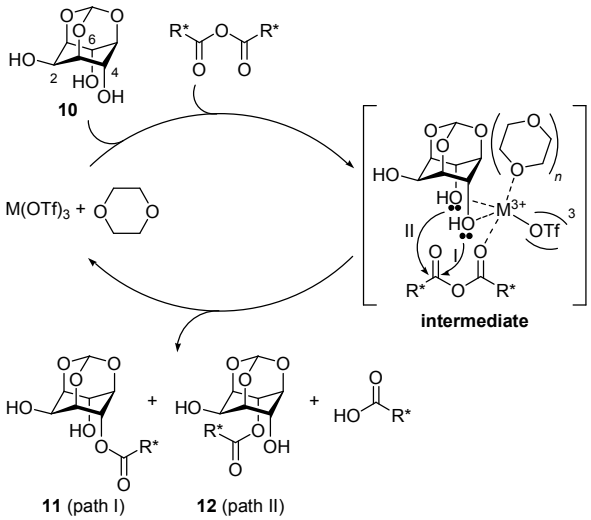
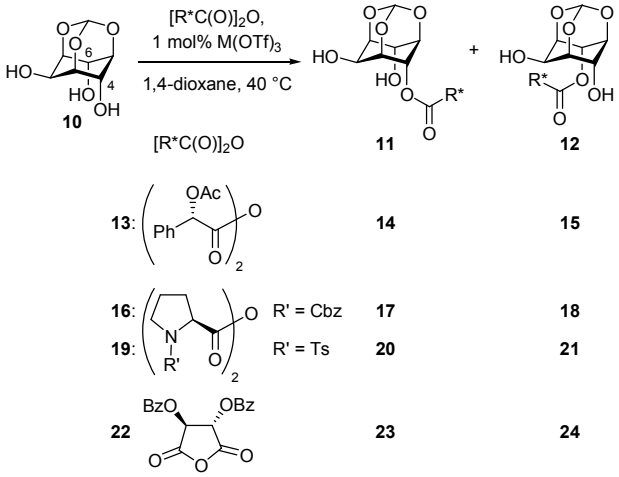


Figure 2. Proposed catalytic cycle for the $M(OTf)_3$-catalyzed asymmetric acylation of *myo*-inositol-1,3,5-orthoformate.

Table 1. Late Transition Metal Trifluoromethanesulfonate-Catalyzed Asymmetric Acylation of *myo*-Inositol-1,3,5-Orthoformate



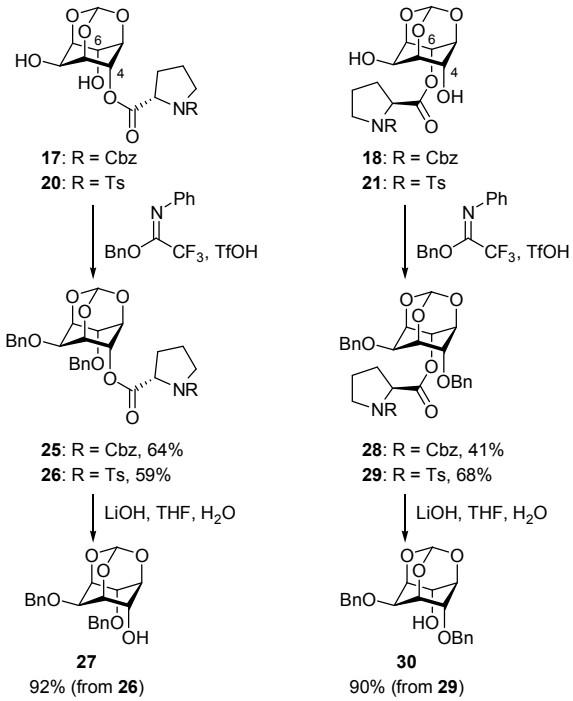
entry	$M(OTf)_3$	anhydride	t (h)	product (yield)[a]
1	$Yb(OTf)_3$	**13**	24	**14** (49%) + **15** (35%)
2	$Yb(OTf)_3$	**16**	72	**17** (30%) + **18** (50%)
3	$Yb(OTf)_3$	**19**	48	**20** (24%) + **21** (62%)
4	$Yb(OTf)_3$	**22**	48	**23** (0%) + **24** (0%)
5	$Yb(OTf)_3$[b]	**19**	48	**20** (17%) + **21** (35%)
6	$La(OTf)_3$	**19**	48	**20** (22%) + **21** (59%)
7	$Pr(OTf)_3$	**19**	48	**20** (23%) + **21** (60%)
8	$Nd(OTf)_3$	**19**	48	**20** (21%) + **21** (51%)
9	$Sm(OTf)_3$	**19**	48	**20** (24%) + **21** (54%)
10	$Eu(OTf)_3$	**19**	48	**20** (23%) + **21** (54%)
11	$Gd(OTf)_3$	**19**	48	**20** (27%) + **21** (54%)

[a] Isolated yields. [b] 5 mol% was used.

We prepared various chiral anhydrides from their corresponding acid precursors[21] and utilized those in the resolution of **10** in the presence of catalytic $Yb(OTf)_3$ (Table 1). The acid precursors used herein are relatively cheaper and more readily accessible than (1*S*)-(–)-camphanic acid that we used previously.[18] The insight as well as inputs from our previous work prompted us to choose 1,4-dioxane as solvent at moderate temperatures. Treatment of **10** with acid anhydride **13** in the presence of 1.0 mol% $Yb(OTf)_3$ generated the chiral esters **14** and **15** in 49% and 35% yields, respectively (entry 1). Isomer **14** was isolated as a crystalline solid and its structure was confirmed by X-ray analysis as a 4-O-substituted ester (CCDC 934229, see Supporting Information). To further expand the scope of this desymmetrization methodology, two N-substituted L-proline anhydrides were prepared as chiral auxiliaries, and their efficacy were studied in this chelation-assisted regioselective acylation of orthoformate **10**. When *N*-Cbz-L-proline anhydride (**16**) was used as desymmetrization agent, the formation of **17** (30%) and **18** (50%) was observed, showing a reversal of regioselectivity in comparison to that of the acid anhydride **13** (entry 2). Similarly, when *N*-tosyl-L-proline anhydride (**19**, entry 3) was employed, the desymmetrization process yielded the 6-O-acylated derivative **21** as major product. The best regioselectivity in terms of product ratio and reaction yield was observed in this case. The acylated derivatives **17** and **18** existed as rotamers and showed complex NMR spectra. To determine their structures, we relied on chemical correlation methods (Scheme 1). Compound **17** was treated with benzyl *N*-phenyl-2,2,2-trifluoroacetimidate in the presence of trifluoromethanesulfonic acid (TfOH) followed by basic hydrolysis to form the dibenzyl derivative **27**, whose spectral and analytical data are in good agreement with the literature.[22] The alternative Williamson etherification to properly install the dibenzyl groups did not proceed as planned due to concomitant hydrolysis of the ester linkage. The structures of **18**, **20**, and **21**

were established in the same manner. The rigid backbone of the cyclic anhydride **22** derived from D-tartaric acid probably prevented proper chelation during the $M(OTf)_3$ catalytic cycle, and thus, **22** failed to provide any products with 1.0 mol% $Yb(OTf)_3$ (entry 4). Increasing the catalyst loading to 5.0 mol% provided the desired 4-O and 6-O esters albeit in low yields because of orthoformate hydrolysis (entry 5). Subsequently, other late transition metal triflates, such as $La(OTf)_3$, $Pr(OTf)_3$, $Nd(OTf)_3$, $Sm(OTf)_3$, $Eu(OTf)_3$, and $Gd(OTf)_3$ were screened in the presence of anhydride **19** (entries 6–11). In all these cases, the regioselective acylation results are comparable to $Yb(OTf)_3$, with ester **21** being the major product.

Scheme 1. Structure Confirmation by Chemical Correlation

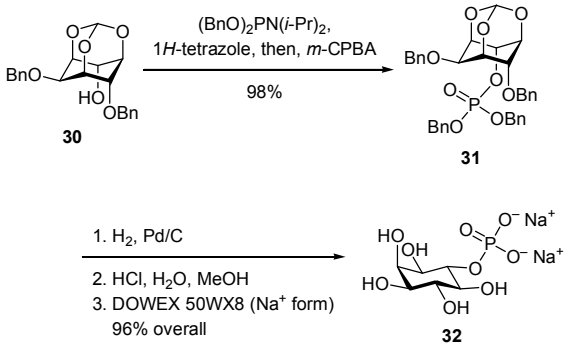


With the asymmetric inositol derivative **21** in hand, we continued further to install the phosphate functionality selectively to afford various inositol phosphates. The inositol phosphate

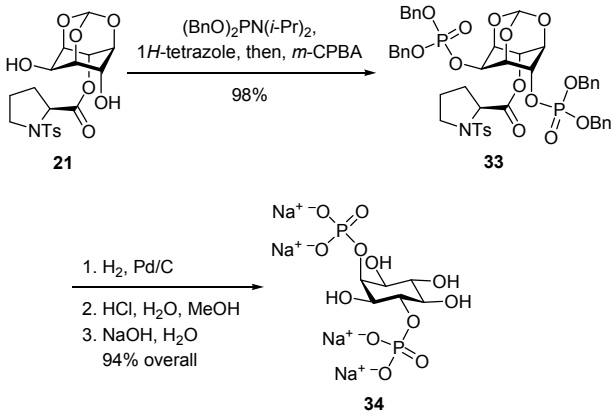
structures prepared herein were specifically chosen to demonstrate the utility of our desymmetrization approach and the opportunity it presents in providing ready access to such compounds. To start with, orthoformate **21** was transformed to compound **30** as outlined in Scheme 1. Phosphitylation using dibenzyl-*N,N*-diisopropyl phosphoramidite/1*H*-tetrazole and subsequent *m*-CPBA[23] oxidation of the resulting phosphite delivered the fully protected dibenzylphosphate **31** (Scheme 2). Further hydrogenolysis removed all the benzyl groups and acidic hydrolysis cleaved the orthoformate protection to give a compound that was passed through a Na^+ ion exchange resin to afford Ins(6)P (**32**). The presence of phosphate in **32**, as with all other inositol phosphates prepared in this paper, was verified by ^{31}P NMR (see Supporting Information).

The synthesis of Ins(2,4)P_2 (**34**) was carried out by reacting the same key diol **21** with the phosphorylation reagent followed by oxidation, leading to the formation compound **33** in excellent yield (Scheme 3). Hydrogenolysis, acid hydrolysis of the orthoformate, and NaOH-mediated *N*-tosyl-L-proline ester cleavage in water provided the target bisphosphate **34**.

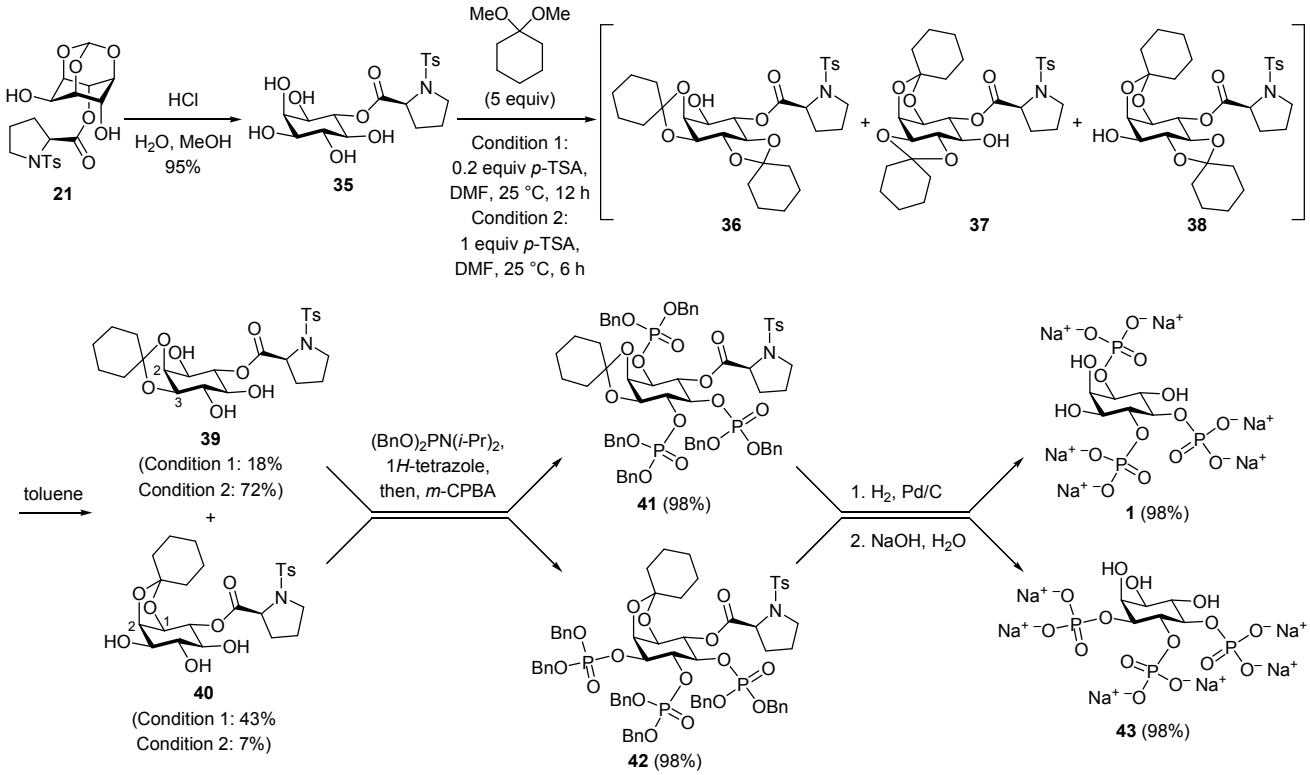
Scheme 2. Synthesis of Ins(6)P (**32**)



Scheme 3. Synthesis of Ins(2,4)P_2 (**34**)



Scheme 4. Synthesis of Ins(1,4,5)P_3 (**1**) and Ins(3,4,5)P_3 (**43**)



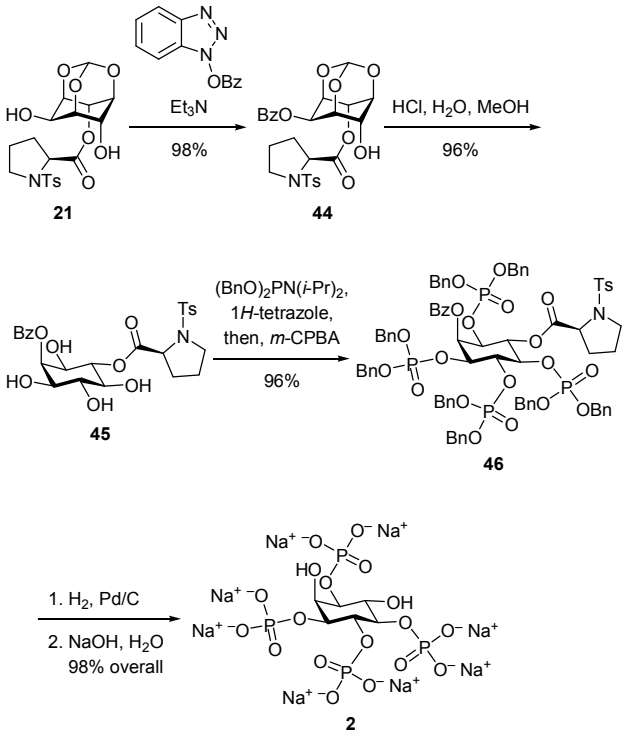
We next turned our attention toward the synthesis of the trisphosphates. Acid hydrolysis of the orthoformate in **21** supplied the pentaol **35** with the chiral auxiliary at 6-O position

(Scheme 4). Compound **35** needed to be regioselectively protected at 2-O and 3-O positions to acquire the triol that could be further transformed into the trisphosphate **1**. Treatment of *myo*-inositol with excess 1,1-dimethoxycyclohexane is known to produce a mixture of ketal derivatives, and selective cleavage of the more strained *trans*-ketal in the presence of its *cis* counterpart is well-documented.[24] From the inherent asymmetric nature of **35**, we speculated that ketal formation using 1,1-dimethoxycyclohexane in the presence of *p*-toluenesulfonic acid (*p*-TSA) followed by selective cleavage of the *trans*-ketal could provide the 2,3- and 1,2-cyclohexylidene derivatives **39** and **40**, respectively, with some degree of regioselectivity. Our ketalization of pentaol **35** provided a mixture of mono- and di-cyclohexylidene derivatives (**36-40**) upon NMR inspection. Further exposure to *p*-TSA with added toluene in an open flask also promoted the cleavage of the *trans*-ketals and produced the mono-cyclohexylidene derivatives **39** and **40**. The yields and ratio of **39** and **40** varied depending on the amount of *p*-TSA, with 1 equiv. of *p*-TSA providing **39** as major product (72%) and 0.2 equiv. of *p*-TSA providing **40** as major product (43%). The structures of **39** and **40** were confirmed by extensive NMR experiments (see Supporting Information), where the free hydroxyls clearly showed correlation with the respective carbon-bound protons. As anticipated, phosphorylation of **39** with dibenzyl-*N,N*-diisopropyl phosphoramidite in CH_2Cl_2 followed by oxidation with *m*-CPBA gave compound **41** in excellent yield. The trisphosphate **41** was then subjected to successive hydrogenolysis in the presence of Pd/C and saponification with NaOH. It is worth mentioning that the cyclohexylidene ketal in **41** was also removed during hydrogenolysis, most likely due to the formation of phosphoric acid, which could promote the cleavage. Being more soluble in methanol, the hydrolyzed *N*-tosylated L-proline was easily separated by methanol elution through a cellulose column. Subsequent elution with deionized water gave Ins(1,4,5)P_3 (**1**). Following

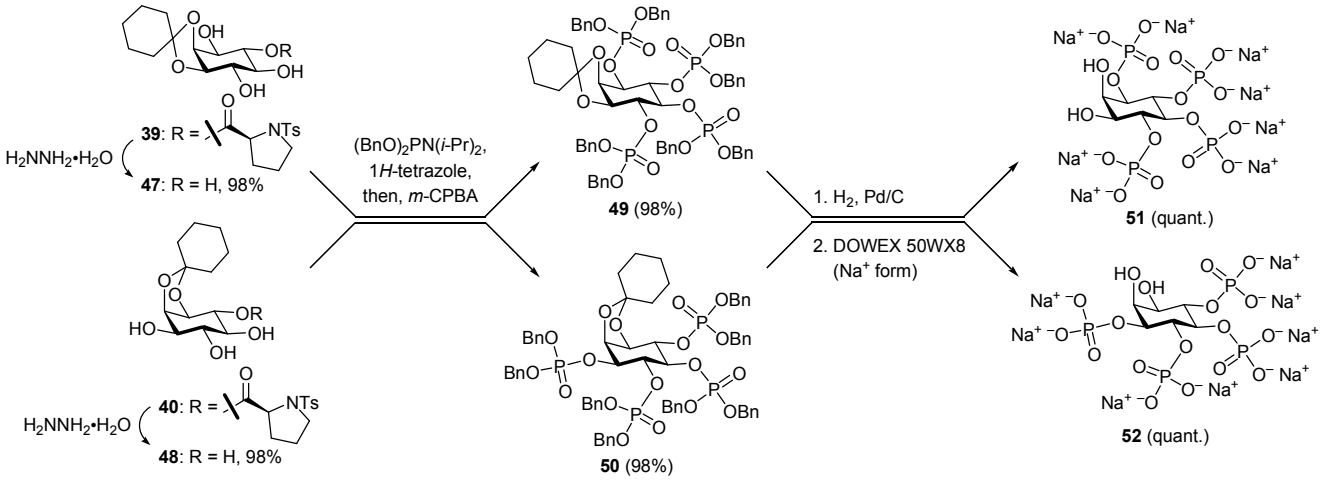
similar synthetic transformations as **39**, the regioisomer **40** was converted to another trisphosphate, Ins(3,4,5)P_3 (**43**).

Next, we focused on the selective functionalization of 2-OH in the chiral derivative **21** to synthesize other optically active D-*myo*-inositol polyphosphates. In this direction, the diol **21** was subjected to benzylation using benzyl-*N*-phenyl-2,2,2-trifluoroacetimidate, which afforded the corresponding 2-O-benzylated derivative in very low yield (50%). When Ac_2O in the presence of $Sc(OTf)_3$ was used to study the regioselective esterification, a mixture of 2-O-acylated (65%) and 2,4-di-O-acylated (13%) derivatives were produced. The traditional benzoylation with BzCl in pyridine mainly provided the desired 2-*O*-benzoyl derivative **44** in 58% yield. Alternatively, when 1-*N*-(benzoyloxy)-benzotriazole (BzOBt)[25] was employed as benzoylation reagent in the presence of Et_3N, the ester **44** was obtained exclusively in an excellent yield (Scheme 5). With **44** in hand, the orthoformate protection was removed under acid hydrolysis to give tetraol **45** in 96% yield. The hydroxy groups in **45** were then phosphorylated to provide the protected tetrakisphosphate **46**, which was readily converted as described to Ins(1,3,4,5)P_4 (**2**).

Scheme 5. Synthesis of Ins(1,3,4,5)P_4 (**2**)



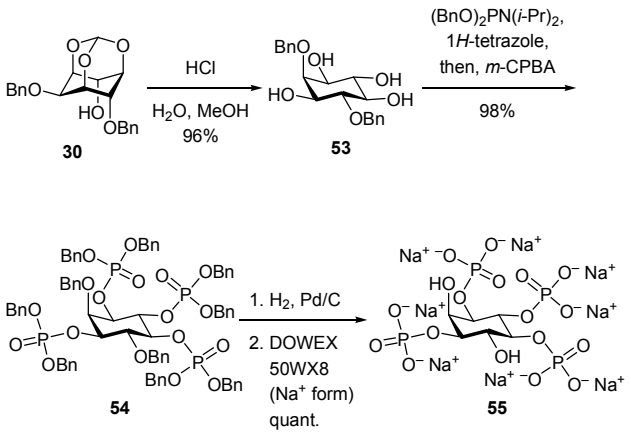
Scheme 6. Synthesis of Ins(1,4,5,6)P_4 (**51**) and Ins(3,4,5,6)P_4 (**52**)



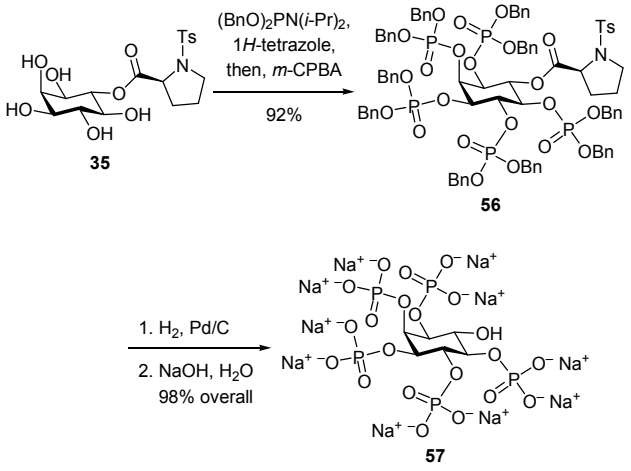
To make the tetrakisphosphates Ins(1,4,5,6)P_4 (**51**) and Ins(3,4,5,6)P_4 (**52**), we started from the monocyclohexylidene derivatives **39** and **40**, respectively (Scheme 6). Treatment of **39**

and **40** with hydrazine hydrate in methanol provided the respective tetraols **47** and **48** in excellent yields. Phosphitylation followed by oxidation of the respective phosphite with *m*-CPBA furnished the tetrakisphosphates **49** and **50**, which were subjected to hydrogenolysis to remove all benzyl groups, and subsequently, the ketal protection. Final Na^+ ion exchange delivered the target tetrakisphosphates **51** and **52**.

Scheme 7. Synthesis of Ins(1,3,5,6)P_4 (**55**)



Scheme 8. Synthesis of Ins(1,2,3,4,5)P_5 (**57**)



To afford another tetrakisphosphate, we converted the dibenzylated **30** into compound **53** by acid hydrolysis (Scheme 7). Phosphitylation of **53** and concomitant oxidation of the polyphosphite delivered the fully protected **54**. Palladium-catalyzed hydrogenolysis followed by ion exchange chromatography gave Ins(1,3,5,6)P_4 (**55**).

Finally, our effort was extended to the synthesis of Ins(1,2,3,4,5)P_5 (**57**) from the 6-O-acylated **35**, which was phosphorylated to form the corresponding fully protected pentakisphosphate **56** (Scheme 8). The target compound **57** was obtained after hydrogenolysis and alkaline hydrolysis of the ester.

CONCLUSIONS

We described an efficient Yb(OTf)$_3$-catalyzed desymmetrization strategy for the site-selective functionalization of D-*myo*-inositol-1,3,5-othoformate using a chiral auxiliary. The desymmetrization strategy further enabled a short and direct synthetic access to a wide range of chiral D-*myo*-inositol phosphates. These compounds and their derivatives may find widespread applications in field of organic synthesis and chemical biology.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, materials and all other reagents obtained from commercial sources were used without further purification. All reactions were conducted in glassware that was dried in an oven and cooled under argon atmosphere. CH_2Cl_2 was dried from a safe purification system filled with anhydrous Al_2O_3. Water was either distilled or Milli-Q-purified. Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). Cotton linters and cellulose powder for column chromatography were purchased from

Sigma-Aldrich. TLC was performed on glass plates pre-coated with Silica Gel 60 F_{254} (0.25 mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, and H_2SO_4 in water followed subsequent heating on a hot plate. Specific rotations were taken at ambient conditions. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on 400 and 600 MHz spectrometers. Proton peaks were assigned with the aid of 2D NMR techniques (^1H-^1H COSY, HMQC, and NOESY). The hydrogen multiplicities of carbon peaks were determined using DEPT-90 and DEPT-135 experiments, the spectra of which were provided in the Supporting Information together with the power-gated-decoupled ^{13}C NMR spectrum. The high resolution mass spectra (HRMS) were obtained using either a FAB–double focusing, MALDI–TOF, or ESI–quadrupole ion trap mass analyzer.

General procedure for $M(OTf)_3$-catalyzed regioselective acylation of *myo*-inositol-1,3,5-orthoformate. A mixture of compound **10** (190 mg, 1.00 mmol), $M(OTf)_3$ (1 mol%), and chiral anhydride (**13**, **16**, **19**, and **22**) (1.2 mmol) was dried under vacuum for 1 h. Anhydrous 1,4-dioxane (8 mL) was added to the mixture under N_2 atmosphere, and the solution was stirred at 40 °C. After the triol **10** was consumed, 1,4-dioxane was removed *in vacuo*, the crude residue was dissolved in CH_2Cl_2 (15 mL), and the mixture was sequentially washed with saturated $NaHCO_{3(aq)}$ and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2% MeOH in $CHCl_3$) to afford the diols. With **13** (444 mg, 1.20 mmol) as chiral anhydride, diols **14** (166 mg, 49%) and **15** (119 mg, 35%) were obtained. With **16** (576 mg, 1.20 mmol) as chiral anhydride, diols **17** (126 mg, 30%) and **18** (210 mg, 50%) were obtained. With **19** (624 mg, 1.20 mmol) as chiral anhydride, diols **20** (106 mg, 24%) and **21** (273 mg, 62%) were obtained.

4-*O*-[(*S*)-*O*-Acetylmandeloyl]-D-*myo*-inositol-1,3,5-orthoformate (14). $[\alpha]^{25}_{D}$ +78.5 (*c* 1.0, $CHCl_3$); mp 163–165 °C; IR (KBr, thin film): ν 3466, 2957, 1745, 1375, 1161, 990, 748 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.44–7.39 (m, 5H, Ar-H), 5.70 (s, 1H), 5.46–5.45 (m, 2H, H-6, 1H; orthoformate-H), 4.60 (br s, 1H, H-6), 4.46–4.44 (m, H, H-5), 4.19–4.18 (m, 1H, H-1), 4.10–4.08 (m, 1H, H-3), 3.95 (br s, 1H, H-2), 3.17 (br s, 1H, 2-OH), 2.98 (br s, 1H, 6-OH), 2.19 (s, 1H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.4 (C), 167.4 (C), 132.0 (C), 129.9 (CH), 129.1 (CH), 127.5 (CH), 102.9 (CH), 74.9 (CH), 73.6 (CH), 71.4 (CH), 69.5 (CH), 67.3 (CH), 66.9 (CH), 60.7 (CH), 20.6 (CH_3); HRMS (ESI): *m/z* calcd for $C_{17}H_{18}O_9Na$ ($[M + Na]^+$) 389.0849, found 389.0848. An X-ray analysis of the crystal confirmed the structure of **14** (CCDC 934229).

6-*O*-[(*S*)-*O*-Acetylmandeloyl]-D-*myo*-inositol-1,3,5-orthoformate (15). $[\alpha]^{25}_{D}$ +44.0 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3479, 2965, 1746, 1374, 1161, 1005, 992, 752 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.43–7.39 (m, 5H, Ar-H), 5.88 (s, 1H), 5.55 (td, J = 3.9, 1.9 Hz, 1H, H-6), 5.44 (d, J = 1.3 Hz, 1H, orthoformate-H), 4.42 (td, J = 3.9, 1.9 Hz, 1H, H-5), 4.24–4.21 (m, 2H, H-1, H-3), 4.13–4.11 (m, 1H, H-4) 3.97 (br s, 1H, H-2), 2.18 (s, 1H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.0 (C), 167.0 (C), 132.6 (C), 129.7 (CH), 129.1 (2 × CH), 127.4 (2 × CH), 102.8 (CH), 74.3 (CH), 73.8 (CH), 71.4 (CH), 69.3 (CH), 67.6 (CH), 66.9 (CH), 60.6 (CH), 20.6 (CH_3); HRMS (FAB): *m/z* calcd for $C_{17}H_{19}O_9$ ($[M + H]^+$) 367.1029, found 367.1000.

4-*O*-(*N*-Benzyloxycarbonyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (17). $[\alpha]^{25}_{D}$ –8.4 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3430, 2960, 1750, 1688, 1424, 1357, 1161, 994, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): (two rotamers present) δ 7.38–7.29 (m, 5H, Ar-H), 5.53, 5.32 (2 × br s, 1H, H-4), 5.48, 5.41 (2 × s, 1H, orthoformate-H), 5.21 (d, J = 12.4 Hz, 0.2 H), 5.13, 5.07 (ABq, J = 12.4 Hz, 1.7 H), 4.95 (d, J = 12.4 Hz, 0.2 H), 4.61 (br s, 0.8H), 4.45 (br s, 0.8H), 4.25–4.19 (m, 3.7H), 4.05–3.89 (m, 0.6 H), 3.59–3.55. (m, 1H), 3.50–3.46 (m, 1H), 2.24–

2.18 (m, 1H), 2.07–1.98 (m, 2H), 1.92–1.87 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): (two rotamers present) δ 171.5, 171.0 (C), 155.1, 154.1 (C), 136.1 (C) 128.7 (CH),128.6 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 103.1, 102.9 (CH), 73.9, 73.7 (CH), 72.0, 71.6 (CH), 69.1, 68.7 (CH), 67.6.61, 67.60 (CH_2), 67.4, 67.0, 66.8 (CH), 61.0, 60.6 (CH), 59.3, 58.7 (CH), 47.0, 46.8 (CH_2), 30.7, 29.6 (CH_2), 24.7, 23.4 (CH_2); HRMS (ESI): *m/z* calcd for $C_{20}H_{23}NO_9Na$ ([M + Na]$^+$) 444.1271, found 444.1278.

6-*O*-(*N*-Benzyloxycarbonyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (18). $[\alpha]^{25}_D$ –28.0 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3419, 2925, 1751, 1682, 1424, 1355, 1161, 993, 755 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): (two rotamers present) δ 7.35–7.30 (m, 5H, Ar-H), 5.54, 5.33 (2 × br, 1H, H-6), 5.46, 5.42 (2 × s, 1H, orthoformate-H), 5.18 (d, *J* = 12.3 Hz, 0.3 H), 5.12, 5.10 (ABq, *J* = 12.3 Hz, 2 H), 4.98 (d, *J* = 12.3 Hz, 0.3 H), 4.48 (br s, 0.6H), 4.40–4.38 (m, 1H), 4.35 (br s, 0.6 H), 4.31 (dd, *J* = 8.3, 3.2 Hz, 0.3 H), 4.18 (dd, *J* = 15.5, 1.3 Hz, 1.3 H), 4.09 (br, 0.3 H), 3.98 (br s, 1H), 3.92 (d, *J* = 12 Hz, 0.6 H), 3.56–3.47 (m, 2H), 2.22–2.12 (m, 2H), 1.93–1.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): (two rotamers present) δ 171.0, 170.5 (C), 155.6, 154.3(C), 136.2 (C) 128.5 (CH),128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 103.0 (CH), 74.2, 74.1 (CH), 71.6 (CH), 69.0, 68.7 (CH), 67.9 (CH), 67.5, 67.3 (CH_2), 66.9 (CH), 60.7 (CH), 59.4, 58.9 (CH), 46.9, 46.6 (CH_2), 30.6, 29.3 (CH_2), 24.4, 23.5 (CH_2); HRMS (ESI): *m/z* calcd for $C_{20}H_{23}NO_9Na$ ([M + Na]$^+$) 444.1271, found 444.1263.

4-*O*-(*N*-Tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (20). White foam; $[\alpha]^{22}_D$ –75.4 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3494, 2962, 1747, 1339, 1161, 1095, 952, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.2 Hz, 2H, Ar-H), 5.55 (td, *J* = 3.6, 2 Hz, 1H, H-4), 5.49 (s, 1H, orthoformate-H), 4.59 (br, 1H, H-6), 4.46–4.45 (m, 1H, H-5), 4.24–4.22 (m, 3H, H-1, H-2, H-3), 4.12–4.08 (m, 1H, proline-H) 3.52, 3.47 (m,

1H), 3.38–3.33 (m, 2H, 2-OH, 6-OH), 3.17–3.11 (m, 1H), 2.42 (s, 3H), 2.04–1.90 (m, 3H), 1.71–1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C), 144.3 (C), 133.9 (C), 129.9 (CH), 127.4 (CH), 103.0 (orthoformate-CH), 73.9 (CH), 71.7 (CH), 69.3 (CH), 67.8 (CH), 67.1 (CH), 60.7 (CH), 60.4 (CH), 48.6 (CH_2), 30.6 (CH_2), 24.8 (CH_2), 21.5 (CH_3); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_9SNa$ ([M + Na]$^+$) 464.0991; found 464.0997.

6-*O*-(*N*-Tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (21). White foam; $[\alpha]^{22}_D$ –71.1 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3480, 2961, 1755, 1339, 1161, 955, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.30 (d, *J* = 8.2 Hz, 2H, Ar-H), 5.58 (td, *J* = 3.6, 1.6 Hz, 1H; H-6), 5.48 (s, 1H; orthoformate-H), 4.58 (br s, 1H; H-4), 4.41–4.39 (m, 1H; H-5), 4.24–4.21 (m, 2H; H-1, H-3), 4.15–4.12 (m, 2H; H-2, proline-H), 3.51–3.46 (m, 1H), 3.14–3.08 (m, 1H), 2.40 (s, 3H), 2.09–2.00 (m, 1H), 1.94–1.83 (m, 2H), 1.71–1.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 (C), 144.2 (C), 133.8 (C), 129.9 (CH), 127.4 (CH), 102.9 (orthoformate-CH), 74.0 (CH), 71.6 (CH), 69.1 (CH), 68.0 (CH), 67.1 (CH), 60.7 (CH), 48.6 (CH_2), 30.3 (CH_2), 24.6 (CH_2), 21.5 (CH_3); HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_9SNa$ ([M + Na]$^+$) 464.0991, found 464.0986.

General procedure for dibenzylation. A solution of the *myo*-inositol orthoformate-derived ester (1 equiv.) and *N*-phenyl-2,2,2-trifluoroacetimidate (4 equiv.) in 1,4-dioxane (20 mL per total gram of the benzyl donor and acceptor) in the presence of flame dried 3 Å molecular sieves was stirred for 30 min at room temperature. TfOH (0.4 equiv.) was then added and the resulting solution was stirred at room temperature for further 1 h. The reaction was quenched with Et_3N and filtered through Celite. The filtrate was concentrated *in vacuo*, and the crude mass was purified by flash column chromatography (hexane/EtOAc = 3/1) to afford the dibenzylated compounds.

2,6-Di-*O*-benzyl-4-*O*-(*N*-benzyloxycarbonyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (25). Compound **17** (86 mg, 0.20 mmol) was transformed into compound **25** (78 mg, 64%) as a gum, following the general procedure for dibenzylation. $[\alpha]^{25}_{D}$ –10.2 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 2925, 1751, 1750, 1416, 1355, 1164, 949, 744 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): (two rotamers present) δ 7.39–7.25 (m, 13H, Ar-H), 7.18–7.16 (m, 1H), 7.02-7.01 (m, 1H), 5.53 (d, *J* = 1 Hz, 0.5H, orthoformate-H), 5.50 (d, *J* = 1.1 Hz, 0.5H, orthoformate-H), 5.45(td, *J* = 3.8, 1.2 Hz, 0.5H, H-4), 5.23 (d, *J* = 12.2 Hz, 0.5H), 5.17(td, *J* = 3.8, 1.5 Hz, 0.5H), 5.10, 5.06 (ABq, *J* = 12.4 Hz, 1H), 4.88 (d, *J* = 12.2 Hz, 0.5H), 4.67 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 12.6 Hz, 0.5H), 4.57 (d, *J* = 11.8 Hz, 0.5H), 4.53–4.51 (m, 1H), 4.41 (d, *J* = 11.8 Hz, 0.5H), 4.30-4.25 (m, 2.5H), 4.23-4.17 (m, 1.5H), 4.16 (dd, *J* = 8.8, 4.5 Hz, 0.5H), 4.05 (dd, *J* = 8.5, 4.7 Hz, 0.5 H), 3.82–3.81 (m, 0.5H), 3.75–3.74 (m, 0.5H), 3.68–3.67 (m, 0.5H), 3.40–2.21 (m, 1.5H), 3.22–3.21 (m, 0.5H), 1.89–1.85 (m, 1H), 1.65–1.38 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): (two rotamers present) δ 171.2, 171.1 (C), 154.7, 153.9 (C), 137.6, 137.5 (C) 137.2, 136.9 (C), 136.5, 136.4 (C), 128.6 (CH), 128.53 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.14 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 103.1, 103.0 (CH), 73.5, 73.2 (CH), 71.8, 71.6 (CH_2), 71.0 (CH_2) 70.0, 69.9 (CH), 69.2, 68.9 (CH), 68.7, 68.5 (CH), 67.2, 67.1(CH), 67.01, 67.0 (CH_2), 66.4, 65.8 (CH), 59.1, 58.8 (CH), 46.8, 46.3 (CH_2), 30.2, 29.4 (CH_2), 24.2, 23.3 (CH_2); HRMS (ESI): *m/z* calcd for $C_{34}H_{35}NO_9Na$ ($[M + Na]^+$) 624.2210, found 624.2202.

2,6-Di-*O*-benzyl-4-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (26). Compound **20** (100 mg, 0.23 mmol) was transformed into compound **26** (84 mg, 59%) as a gum, following the general procedure for dibenzylation. $[\alpha]^{27}_{D}$ –39.3 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 1745, 1454, 1346, 1164, 1096, 949, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*

= 8.2 Hz, 2H, Ar-H), 7.46–7.44 (m, 2H, Ar-H), 7.38–7.26 (m, 9H, Ar-H), 7.17–7.15 (m, 2H, Ar-H), 5.54 (d, J = 1.2 Hz,1H, orthoformate-H), 5.40 (td, J = 3.8, 1.5 Hz, 1H, H-4),4.76, 4.70 (ABq, J = 12.5 Hz, 2H), 4.49, 4.40 (ABq, J = 11.6 Hz, 2H), 4.48–4.46 (m, 1H, H-5), 4.28 (td, J = 3.8, 1.5 Hz, 1H, H-6), 4.26–4.21 (m, 2H, H-1, H-3), 3.99 (dd, J = 8.7, 4.5 Hz, 1H, proline-H), 3.94-3.92 (m, 1H, H-2), 3.13–3.03 (m, 2H), 2.40 (s, 3H), 1.74–1.65 (m, 1H), 1.60–1.42 (m, 2H), 1.37–1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (C), 143.7 (C), 137.8 (C), 137.1 (C), 134.9 (C), 129.6 (CH), 128.4 (CH),128.2 (CH), 128.0 (CH), 127.8 (CH), 127.2 (CH), 103.1 (orthoformate-CH), 73.7 (CH), 72.0 (CH_2), 71.2 (CH_2), 70.2 (CH), 69.1 (CH), 68.8 (CH), 67.4 (CH), 66.3 (CH), 60.5 (CH), 48.2 (CH_2), 30.2 (CH_2), 24.3 (CH_2), 21.4 (CH_3); HRMS (ESI): *m/z* calcd for $C_{33}H_{35}NO_9SNa$ ($[M + Na]^+$) 644.1930, found 644.1932.

2,6-Di-*O*-benzyl-D-*myo*-inositol-1,3,5-orthoformate (27). Compound **26** (100 mg, 0.16 mmol) was dissolved in THF/H_2O (1/1) (2 mL). $LiOH \cdot H_2O$ (13 mg, 0.32 mmol) was then added and the resulting solution stirred for 2 h at room temperature. The reaction mixture was diluted with Et_2O and washed with water and brine. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography to afford **27** (54 mg, 92%) as a colorless gum. $[\alpha]^{26}_D$ –4.8 (*c* 1.0, EtOH) [lit.[22] $[\alpha]^{25}_D$ –8.0 (*c* 1,EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.30 (m, 8 H, Ar-H), 7.16 (dd, J = 3.6, 6.5, 2H, Ar-H), 5.49 (d, J = 1 Hz, 1H, orthoformate-H), 4.74, 4.64 (ABq, J = 12.4 Hz, 2H, Bn-H), 4.52, 4.47 (ABq, J = 11.6 Hz, 2H, Bn-H), 4.46–4.41 (m, 1H), 4.37–4.32 (m, 2H), 4.26–4.23 (m, 2H), 3.87–3.86 (m, 1H), 3.59 (d, 1H, J = 10.3 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5 (C), 135.9 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 102.6 (CH), 74.5 (CH), 72.9 (CH_2), 72.1 (CH), 71.3 (CH_2), 69.9 (CH), 68.0 (CH), 67.6 (CH), 66.1 (CH); HRMS (ESI): *m/z* calcd for $C_{21}H_{22}O_6Na$ ($[M + Na]^+$) 393.1314, found 393.1320.

2,4-Di-*O*-benzyl-6-*O*-(*N*-benzyloxycarbonyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (28). Compound **18** (120 mg, 0.28 mmol) was converted to compound **28** (70 mg, 41%) as a gum, following the general procedure for dibenzylation. $[\alpha]^{25}_{D}$ –28.2 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 2958, 1754, 1705, 1416, 1354, 1163, 949, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): (two rotamers present) δ 7.42–7.11 (m, 15H, Ar-H), 5.53, 5.50 (2 x s, 1H, orthoformate-H) 5.45, 5.21, (2 x br, 1H, H-6), 5.17 (d, *J* = 12.2 Hz, 0.5 H), 5.14, 5.08, (ABq, *J* = 12.4 Hz, 1 H),4.97 (d, *J* = 12.2 Hz, 0.5 H), 4.76, 4.67 (ABq, *J* = 12.4 Hz, 1 H), 4.63, 4.54 (ABq, *J* = 12.4 Hz, 1 H), 4.45-4.30 (m, 3.5H), 4.26 (br, 1 H), 4.23 (br, 1H), 4.19 (dd, *J* = 7.6, 3.3 Hz, 0.5 H), 4.09 . (dd, *J* = 4.2, 3.3 Hz, 0.5 H), 4.01 (br, 0.5 H), 3.95 (br, 0.5H), 3.75 (br, 0.5H), 3.42-3.31 (m, 2H), 1.71-1.62(m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): (two rotamers present) δ 171.43, 171.4 (C), 154.8, 154.0(C), 137.7, 137.5 (C) 137.15, 137.1 (C), 136.6, 136.4 (C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.04 (CH), 128.0 (CH), 127.90 (CH), 127.85 (CH), 127.7 (CH), 103.2, 103.1 (CH), 73.8, 73.6 (CH), 72.1, 71.9 (CH_2), 71.3, 71.0 (CH_2) 70.2, 69.8 (CH), 69.1 (CH), 68.9, 68.7 (CH), 67.4, 67.2 (CH), 67.15, 67.1 (CH_2), 66.5, 66.2 (CH), 59.0–58.6 (CH), 46.8, 46.3 (CH_2), 30.0, 29.0 (CH_2), 24.4, 23.4 (CH_2); HRMS (ESI): *m/z* calcd for $C_{34}H_{35}NO_9Na$ ($[M+Na]^+$) 624.2210, found 624.2219.

2,4-Di-*O*-benzyl-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (29). Compound **21** (200 mg, 0.45 mmol) was transformed to compound **29** (191 mg, 68%) as a gum, following the general procedure for dibenzylation. $[\alpha]^{23}_{D}$ –39.9 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 1756, 1454, 1347, 1164, 1096, 949, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.42–7.40 (m, 2H, Ar-H), 7.35–7.23 (m, 9H, Ar-H), 7.17–7.15 (m, 2H, Ar-H), 5.54 (d, *J* = 1 Hz,1H, orthoformate-H), 5.41 (app. t, *J* = 4.2, 3.3 Hz, 1H, H-6), 4.76, 4.61 (ABq, *J* = 12.4 Hz, 2H), 4.49, 4.43 (ABq, *J* = 11.8 Hz, 2H), 4.45–4.40 (m, 2H, H-5, H-1), 4.28

(br, 2H, H-3, H-4), 4.03 (dd, J = 8.2, 4.2 Hz, 1H, proline-H), 3.95 (br, 1H, H-2), 3.25–3.20 (m, 1H), 3.12–3.06 (m, 1H), 2.40 (s, 3H), 1.70–1.53 (m, 3H), 1.51–1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (C), 143.7 (C), 137.7 (C), 137.2 (C), 135.0 (C), 129.6 (CH), 128.4 (CH),128.1 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 103.1 (orthoformate-CH), 73.7 (CH), 71.8 (CH_2), 71.3 (CH_2), 70.2 (CH), 69.1 (CH), 69.0 (CH), 67.2 (CH), 66.4 (CH), 60.1 (CH), 48.2 (CH_2), 30.0 (CH_2), 24.5 (CH_2), 21.5 (CH_3); HRMS (ESI): *m/z* calcd for $C_{33}H_{35}NO_9SNa$ ($[M + Na]^+$) 644.1930, found 644.1932.

2,4-Di-*O*-benzyl-D-*myo*-inositol-1,3,5-orthoformate (30). Compound **29** (100 mg, 0.16 mmol) was dissolved in THF/H_2O (1/1) (2 mL). $LiOH \cdot H_2O$ (13 mg, 0.32 mmol) was then added and the resulting solution stirred for 2 h at room temperature. The reaction mixture was diluted with Et_2O and washed with water and brine. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography to afford **30** (53 mg, 90%) as a colorless gum. $[\alpha]^{23}_D$ +7.5 (*c* 1.0, EtOH) [lit.[22] $[\alpha]^{25}_D$ +8.8 (*c* 1.1, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.30 (m, 8 H, Ar-H), 7.16 (dd, J = 3.6, 6.3, 2H, Ar-H), 5.49 (d, J = 1.1 Hz, 1H, orthoformate-H), 4.74, 4.63 (ABq, J = 12.3 Hz, 2H, Bn-H), 4.52, 4.48 (ABq, J = 11.5 Hz, 2H, Bn-H), 4.46–4.42 (m, 1H), 4.37–4.32 (m, 2H), 4.26–4.23 (m, 2H), 3.87–3.86 (m, 1H), 3.59 (d, 1H, J = 10.3 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5 (C), 135.9 (C), 128.8 (CH), 128.6 (CH), 128.0 (CH), 102.6 (CH), 74.5 (CH), 72.9 (CH_2), 72.1 (CH), 71.4 (CH_2), 69.9 (CH), 68.0 (CH), 67.7 (CH), 66.1 (CH); HRMS (ESI): *m/z* calcd for $C_{21}H_{22}O_6Na$ ($[M + Na]^+$) 393.1314, found 393.1322.

General procedure for phosphorylation. A mixture of the alcohol compound (1 equiv.) and 1*H*-tetrazole (3 equiv. per phosphorylation site) was dissolved in CH_2Cl_2 (10 mL, unless otherwise stated) and allowed to stir for 10 min. Dibenzyl *N*,*N*-

diisopropylphosphoramidite (1.5 equiv. per phosphorylation site) was then added and the reaction mixture was stirred at room temperature for 1 h. The reaction flask was then cooled to –40 °C and *m*-CPBA (77% purity, 2.25 equiv. per phosphorylation site) was added in one portion. The reaction mixture was gradually warmed to room temperature over a period of 2 h. CH_2Cl_2 (10 mL) was then added to the mixture, the organic layer was washed with saturated $NaHCO_{3(aq)}$, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The so-obtained crude compound was purified by flash column chromatography (2% MeOH in $CHCl_3$) to afford the phosphorylated inositol derivative.

2,4-Di-*O*-benzyl-D-*myo*-inositol-1,3,5-orthoformate-6-dibenzylphosphate (31). Compound **30** (150 mg, 0.40 mmol) was transformed into the monophosphate **31** (250 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{28}_{D}$ +12.5 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3032, 1455, 1280, 1166, 1097, 1000, 950, 891, 737, 698, 603, 510 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.33–7.19 (m, 21H, Ar-H), 7.16–7.15 (m, 2H, Ar-H), 5.48 (d, J = 1.3 Hz, 1H, orthoformate-H), 5.02–4.99 (m, 1H, H-6), 4.90–4.85 (m, 4H, CH_2), 4.61, 4.55 (ABq, J = 12.2 Hz, 2H, CH_2-Ar), 4.53, 4.36 (ABq, J = 11.6 Hz, 2H, CH_2-Ar), 4.40–4.38 (m, 1H, H-5), 4.26–4.25 (m, 2H, H-3, H-1), 4.24–4.22 (m, 1H, H-4), 3.90 (br, 1H, H-2); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.5 (C), 137.2 (C), 135.41 (C), 135.36 (C), 128.8 (CH), 128.7 (CH), 128.64 (CH), 128.60 (CH), 128.4 (CH), 128.0 (CH), 127.97 (CH), 127.93 (CH), 127.89 (CH), 127.5 (CH), 102.9 (orthoformate-CH), 73.4 (CH), 71.6 (CH_2), 71.3 (CH_2), 71.0 (CH), 70.9 (CH), 70.3 (CH), 70.0 (CH), 69.9 (CH), 69.7 (CH_2), 69.6 (CH_2), 67.8 (CH), 67.7 (CH), 66.2 (CH); ^{31}P NMR (121 MHz, $CDCl_3$): δ –1.34; HRMS (ESI): *m/z* calcd for $C_{35}H_{35}O_9PNa$ ($[M + Na]^+$) 653.1916, found 653.1919.

D-*myo*-Inositol-6-monophosphate disodium salt (32). To a solution of compound **31** (100 mg, 0.16 mmol) in MeOH (5 mL) was added 10% Pd/C (50 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, dissolved in a solution of 1 N $HCl_{(aq)}$/MeOH, (1/1, 1 mL) and stirred at ambient temperature overnight. The solvents were evaporated, and the residue was eluted through Dowex 50WX8 ion exchange resin (Na^+ form) using deionized water as the eluent. The fractions containing the product were combined and lyophilized to afford (**32**) (46 mg, 96%) a white fluffy solid. $[\alpha]^{27}_D$ +0.93 (*c* 2.1, H_2O, pH 9.2) [lit.[26] $[\alpha]^{20}_D$ +1.1 (*c* 5, H_2O, pH 9)]; ^1H NMR (600 MHz, D_2O): δ 4.15 (q, J = 9.2 Hz, 1H, H-6), 4.06 (t, J = 2.8 Hz, 1H, H-2), 3.69 (t, J = 9.7 Hz, 1H, H-4), 3.67 (dd, J = 9.7, 2.8 Hz, 1H, H-1), 3.55 (dd, J = 10.0, 2.6 Hz, 1H, H-3), 3.44 (t, J = 9.3 Hz, 1H, H-5); ^{13}C NMR (150 MHz, D_2O): δ 77.7 (CH), 77.6 (CH), 73.64 (CH), 73.62 (CH), 72.1 (CH), 71.8 (CH), 70.9 (CH), 70.8 (CH), 70.7 (CH); ^{31}P NMR (121 MHz, D_2O): δ 2.48; HRMS (ESI): *m/z* calcd for $C_6H_{12}O_9PNa_2$ ($[M - H + 2Na]^+$) 305.0014, found 305.0015.

6-*O*-(*N*-Tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate-2,4-bis(dibenzyl phosphate) (33). Diol **21** (150 mg, 0.34 mmol) was transformed into the bisphosphate **33** (319 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{25}_D$ –36.8 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 2960, 1761, 1456, 1348, 1283, 1163, 998, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.72–7.70 (m, 2H, Ar-H), 7.33–7.27 (m, 22H, Ar-H), 5.50 (d, J = 1.2 Hz, 1H, orthoformate H), 5.47–5.46 (app m, 1H, H-6), 5.08–4.94 (m, 9H, 4 × CH_2, H-2), 4.86–4.84 (m, 1H, H-4), 4.36–4.34 (m, 2H, H-3, H-5), 4.30–4.28 (m, 1H, H-1), 4.06 (dd, J = 8.5, 4.7 Hz,

1H, proline-H), 3.44–3.41 (m, 1H), 3.15–3.11 (m, 1H), 1.93–1.88 (m, 1H), 1.82–1.69 (m, 2H), 1.51–1.45 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8 (C), 143.7 (C), 135.5 (C), 135.4 (C), 135.2 (C), 135.1 (C), 134.7 (C), 129.8 (C), 128.9 (C), 128.8 (C), 128.7 (C), 128.6 (C), 128.24 (C), 128.20 (C), 128.0 (C), 127.5 (C), 102.8 (orthoformate-CH), 70.6 (CH), 70.5 (CH), 70.3 (CH), 70.04 (CH_2), 70.0 (CH_2), 69.9 (CH_2), 69.73 (CH_2), 69.70 (CH_2), 69.6 (CH_2), 69.49 (CH), 69.45 (CH), 68.1 (CH), 66.80 (CH), 66.77 (CH), 66.19 (CH), 66.16 (CH), 48.5 (CH_2), 30.3 (CH_2), 24.7 (CH_2), 21.5 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ –1.08, –1.13; HRMS (ESI): *m/z* calcd for $C_{47}H_{49}NO_{15}P_2SNa$ ($[M + Na]^+$) 984.2196, found 984.2196.

D-*myo*-Inositol-2,4-bisphosphate tetrasodium salt (34). To a solution of compound **33** (100 mg, 0.10 mmol) in MeOH (5 mL) was added 10% Pd/C (50 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, dissolved in a solution of 1 N $HCl_{(aq)}$/MeOH (1/1, 1 mL) and stirred at ambient temperature overnight. The solvents were evaporated, and the residue was dissolved in a cold solution of 1 N NaOH (0.62 mmol) and stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by cellulose column chromatography, first eluting with MeOH, then MeOH/water, 1/1, and finally with water. The fractions containing product were concentrated and lyophilized to afford the bisphosphate **34** (42 mg, 94%) as a white fluffy solid. $[\alpha]^{27}_D$ +9.03 (*c* 0.77, H_2O, pH 11.5) [lit.[27] for the enantiomer $[\alpha]^{27}_D$ –4.3 (*c* 0.7, H_2O, pH 10)]; ^{1}H NMR (600 MHz, D_2O): δ 4.37 (dt, J = 7.2, 2.2 Hz, 1H, H-2), 4.03 (q, J = 9.2 Hz, 1H, H-4), 3.66 (t, J = 9.7 Hz, 1H, H-6), 3.46 (dt, J = 9.7, 2.0 Hz, 1H, H-

3), 3.34–3.29 (m, 2H, H-1, H-5); ^{13}C NMR (150 MHz, D_2O): δ 76.7 (CH), 75.2 (CH), 74.7 (CH), 73.0 (CH), 71.6 (CH), 70.94 (CH); ^{31}P NMR (121 MHz, D_2O): δ 5.49, 5.45; HRMS (ESI): *m/z* calcd for $C_6H_{10}O_{12}P_2Na_3$ ($[M - 4H + 3Na]^-$) 404.9341, found 404.9332.

6-*O*-(*N*-Tosyl-L-prolinoyl)-D-*myo*-inositol (35). Compound **21** (450 mg, 1 mmol) was dissolved in 1 N $HCl_{(aq)}$/MeOH (1/10 v/v, 10 mL) and allowed to reflux for 30 min. After completion of the reaction monitored by TLC, the mixture was allowed to cool to room temperature. The solvents were removed *in vacuo* to obtain a white solid. The crude solid was filtered, washed with water, then, with acetone, and dried to give **35** (417 mg, 95%) as a fluffy white solid. $[\alpha]^{25}_D$ –95.5 (*c* 1.0, DMF); mp 233–235 °C; IR (KBr, thin film): ν 3338, 1719, 1344, 1156, 1091, 724 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.74 (d, J = 8.1 Hz, 2H, Ar-H), 7.42 (d, J = 8.1 Hz, 2H, Ar-H), 4.94 (t, J = 9.8 Hz, 1H, H-6), 4.81 (d, J = 3.4 Hz, 1H, OH) 4.76(d, J = 5.5 Hz, 1H, OH), 4.71 (d, J = 4.7 Hz, 1H, OH), 4.54 (d, J = 6.7 Hz, 1H, OH), 4.51 (d, J = 5.7 Hz, 1H, OH), 4.33 (dd, J = 8.3, 2.7 Hz, 1H, proline-H), 3.75–3.74 (m, 1H, H-2), 3.44–3.39 (m, 2H, H-1, H-4), 3.34–3.29 (m, 1H), 3.19–3.13 (m, 3H, H-3, H-5), 2.40 (s, 3H), 2.05–2.03 (m, 1H), 1.77–1.72 (m, 2H), 1.62–1.59 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.0 (C), 143.4 (C), 134.9 (C), 129.8 (CH), 127.2 (CH), 76.4 (CH), 72.9 (CH), 72.7 (CH), 71.5 (CH), 69.3 (CH), 60.7 (CH), 48.2 (CH_2), 30.3 (CH_2), 23.9 (CH_2), 21.0 (CH_3); HRMS (ESI): *m/z* calcd for $C_{18}H_{25}NO_9SNa$([M + Na]$^+$) 454.1148, found 454.1146.

Ketalization of pentaol 35. A mixture of the pentaol **35** (100 mg, 0.23 mmol) and *p*-TSA (8 mg, 0.05 mmol) was dissolved in anhydrous DMF (1 mL). After a clear solution was obtained, 1,1-dimethoxycyclohexane (0.176 mL, 1.16 mmol) was added dropwise, and the reaction mixture was allowed to stir at 25 °C. After completion of the reaction monitored by TLC, the solvents were removed under reduced pressure at 35 °C. Regular solvent grade toluene

(5 mL) was then added, and the reaction mixture was allowed to stir at room temperature for 2 h in an open flask. The reaction was then quenched with Et_3N (1 mL) and the solvents were removed *in vacuo*. The so-obtained crude residue was purified by flash column chromatography (5% MeOH in $CHCl_3$) to afford the compounds **39** (0.084 mg, 72%) and **40** (0.008 mg, 7%).

2,3-*O*-Cyclohexylidene-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol (39). Colorless solid; $[\alpha]^{26}_D$ –78.0 (*c* 1.0, DMF); mp 202–204 °C; IR (KBr, thin film): ν 3428, 3335, 2352, 1696, 1344, 1155, 1095, 1002, 926 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 7.75 (d, J = 8.3 Hz, 2H, Ar-H), 7.43 (d, J = 8.3 Hz, 2H, Ar-H), 5.15 (d, J = 6.0 Hz, 1H, 1-OH), 5.11 (d, J = 5.0 Hz, 1H, 4-OH), 4.88 (m, 2H, H-6, 5-OH), 4.35 (dd, J = 8.4, 2.3 Hz, 1H, proline-H), 4.20 (t, J = 4.6 Hz, 1H, H-2), 3.85 (dd, J = 7.1, 5.3 Hz, 1H, H-3), 3.79–3.76 (m, 1H, H-1), 3.42–3.39 (m, 1H, H-4), 3.33–3.12 (m, 1H), 3.15–3.12 (m, 2H, H-5), 2.40 (s, 3H), 1.79–1.72 (m, 2H), 1.69–1.59 (m, 5H), 1.54–1.47 (m, 4H), 1.37–1.31 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 171.0 (C), 143.4 (C), 134.9 (C), 129.8 (CH), 127.2 (CH), 108.9 (Spiro C), 78.5 (CH) 76.1 (CH), 75.4 (CH), 75.00 (CH), 71.9 (CH), 60.6 (CH), 48.2 (CH_2), 37.6 (CH_2), 34.9 (CH_2), 30.3 (CH_2), 24.6 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 23.3 (CH_2), 21.0 (CH_3); HRMS (ESI): *m/z* calcd for $C_{24}H_{33}NO_9SNa$ ($[M + Na]^+$) 534.1774, found 534.1767.

1,2-*O*-Cyclohexylidene-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol (40). Colorless solid; $[\alpha]^{26}_D$ –120.2 (*c* 1.0, DMF); mp 159–161 °C; IR (KBr, thin film): ν 3377, 2936, 1748, 1338, 1159, 1097, 1002, 927, 752 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 7.73 (d, J = 8.3 Hz, 2H; Ar-H), 7.40 (d, J = 8.3 Hz, 2H; Ar-H), 5.01 (d, J = 5.5 Hz, 1H; 3-OH) 4.98 (d, J = 4.6 Hz, 1H; 4-OH), 4.97 (d, J = 5.5 Hz, 1H; 5-OH), 4.22 (t, J = 4.4 Hz, 1H; H-2), 4.06 (dd, J = 8.0, 5.0 Hz, 1H; H-1), 3.55-3.52 (m, 1H; H-3), 3.40 (td, J = 9.0, 4.2 Hz, 1H; H-4), 3.31–3.29 (m, 1H;), 3.15–3.09 (m, 1H; H-5), 2.40 (s, 3H), 2.03–1.99 (m, 1H), 1.82–1.61 (m, 5H),1.57–1.45 (m, 6H), 1.38–1.31

(m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 170.9 (C), 143.4 (C), 135.0 (C), 129.8 (CH), 127.2 (CH), 109.2 (Spiro-C), 77.1 (CH), 76.3 (CH), 75.4 (CH), 72.5 (CH), 71.4 (CH), 69.5 (CH), 60.5 (CH), 48.1 (CH_2), 37.2 (CH_2), 35.0 (CH_2), 30.4 (CH_2), 24.5 (CH_2), 23.9 (CH_2), 23.5 (CH_2), 23.2 (CH_2), 21.0 (CH_3); HRMS (ESI): *m/z*: calcd for $C_{24}H_{33}NO_9SNa$ ($[M + Na]^+$) 534.1774; Found 534.1768.

2,3-*O*-Cyclohexylidene-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol-1,4,5-tris(dibenzyl phosphate) (41). Triol **39** (150 mg, 0.3 mmol) was transformed into the trisphosphate **41** (370 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{25}_D$ –34.9 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 2939, 1765, 1455, 1339, 1279, 1162, 1017, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.37 (d, *J* = 7.02 Hz, 2H, Ar-H), 7.32–7.20 (m, 28 H, Ar-H), 5.68 (dd, *J* = 9.3, 5.9 Hz, 1H, H-6), 5.17–4.96 (m, 12H, CH_2), 4.85–4.82 (m, 1H, H-2), 4.75–4.72 (m, 1H, H-5), 4.68 (dd, *J* = 6.5, 3.7, 1H, H-4), 4.64–4.61 (m, 1H, H-1), 4.25 (t, *J* = 5.8, 1H, H-3), 3.21–3.18 (m, 1H), 3.13–3.09 (m, 1H), 2.34 (s, 3H), 2.14–2.08 (m, 1H), 1.77–1.65 (m, 4H),1.58–1.53 (m, 2H), 1.51–1.45 (m, 5H), 1.33–1.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.7 (C), 143.4 (C), 135.83 (C), 135.78 (C), 135.73 (C), 135.66 (C), 135.61 (C), 135.56 (C), 135.52 (C), 135.49 (C), 135.4 (C), 129.5 (CH), 128.5 (CH), 128.46 (CH), 128.41 (CH), 128.4 (CH), 128.30 (CH), 128.26 (CH), 128.1 (CH), 128.04 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 111.7 (Spiro-C), 78.0 (CH), 75.2 (CH), 72.9 (CH), 72.5 (CH), 72.4 (CH), 72.0 (CH), 69.74 (CH_2), 69.71 (CH_2), 69.65 (CH_2), 69.61 (CH_2), 69.57 (CH_2), 69.53 (CH_2), 60.4 (CH), 48.2 (CH_2), 35.9 (CH_2), 33.7 (CH_2), 30.2 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 23.8 (CH_2), 23.5 (CH_2), 21.4 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ –1.39, –1.56 (2 × P); HRMS (ESI): *m/z* calcd for $C_{66}H_{72}NO_{18}P_3SNa$ ($[M + Na]^+$) 1314.3581, found 1314.3572.

D-*myo*-Inositol-1,4,5-trisphosphate hexasodium salt (1). To a solution of compound **41** (100 mg, 0.07 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg). The mixture was placed under vacuum and the atmosphere was replaced with nitrogen and then with hydrogen gas. The suspension was allowed to stir under hydrogen atmosphere for 16 h. The heterogeneous mixture was filtered through a pad of Celite, the residue was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, and the residue was dissolved in cold 1 N NaOH (0.54 mmol) and stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by cellulose column chromatography, first eluting with MeOH, then with MeOH/water (1/1), and finally with water. The fractions containing the product were combined, concentrated, and lyophilized to obtain the trisphosphate **1** (41 mg, 98%). $[\alpha]^{25}_{D}$ –27.9 (*c* 1.0, H_2O, pH 8.9) [lit.[28] $[\alpha]^{25}_{D}$ –24.1 (*c* 0.28, H_2O, pH 10); ^{1}H NMR (600 MHz, D_2O): δ 4.17–4.16 (m, 1H, H-2), 4.08 (q, J = 8.5 Hz, 1H, H-4), 3.83–3.77 (m, 3H, H-1, H-5, H-6), 3.63 (dd, J = 9.8, 2.9 Hz, 1H, H-3); ^{13}C NMR (150 MHz, D_2O): δ 78.0 (CH), 75.9 (CH), 75.4 (CH), 73.4 (CH), 72.6 (CH), 71.4 (CH); ^{31}P NMR (121 MHz, D_2O): δ 5.49, 5.37, 3.78; HRMS (ESI): *m/z* calcd for $C_6H_{13}NaO_{15}P_3$ ([M – 2H + Na]$^-$) 440.9365, found 440.9370.

1,2-*O*-Cyclohexylidene-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol-3,4,5-tris(dibenzyl phosphate) (42). Triol **40** (100 mg, 0.19 mmol) was transformed into the trisphosphate **42** (246 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{25}_{D}$ –17.3 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 2938, 1763, 1456, 1279, 1161, 1015, 738 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2H, Ar-H), 7.30–7.20 (m, 33 H, Ar-H), 5.51 (t, J = 5.3 Hz, 1H, H-6), 5.15 (td, J = 9.3, 5.3 Hz, 1H, H-2), 5.11–5.00 (m, 12H, CH_2), 4.85–4.82 (m, 1H, H-3), 4.78 (dd, J = 6.5, 3.7, 1H, H-4), 4.67 (dt, J = 9.3, 5.3, 4.0 Hz, 1H, H-1), 4.35 (t, J = 6.5, 5.3 Hz,

1H, H-5), 4.19 (dd, J = 8.0, 4.1 Hz, 1H, proline-H), 3.43–3.39 (m, 1H), 3.22–3.18 (m, 1H), 2.38 (s, 3H), 2.05–1.99 (m, 2H), 1.89–1.82 (m, 2H), 1.76–1.74 (m, 2H), 1.62–1.51 (m, 4H), 1.48–1.47 (m, 3H), 1.35–1.30 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4 (C), 143.5 (C), 135.84 (C), 135.80 (C), 135.77 (C), 135.72 (C), 135.68 (C), 135.65 (C), 135.60 (C), 135.55 (C), 135.1 (C), 129.7 (CH), 128.43 (CH), 128.36 (CH), 128.32 (CH), 128.27 (CH), 128.20 (CH), 128.0 (CH), 127.92 (CH), 127.87 (CH), 127.80 (CH), 127.6 (CH), 111.6 (Spiro-C), 78.5 (CH), 76.42 (CH), 76.38 (CH), 73.9 (CH), 73.4 (CH), 72.9 (CH), 72.4 (CH), 69.7 (CH_2), 69.60 (CH_2), 69.56 (CH_2), 69.5 (CH_2), 69.44 (CH_2), 69.41 (CH_2), 60.2 (CH), 48.4 (CH_2), 35.8 (CH_2), 33.6 (CH_2), 30.4 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 21.4 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ –0.76, –1.36, –1.63; HRMS (MALDI): *m/z*: calcd for $C_{66}H_{73}NO_{18}P_3S$ ($[M + H]^+$) 1292.3760, found 1292.3788.

D-*myo*-Inositol-3,4,5-trisphosphate hexasodium salt (43). To a solution of compound **42** (100 mg, 0.07 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, the residue dissolved in a cold solution of 1 N NaOH (0.54 mmol), and stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by cellulose column chromatography, first eluting with MeOH, then MeOH/water, 1/1, and finally with water. The fractions containing product were concentrated and lyophilized to afford the trisphosphate **43** (41 mg, 98%) as a white fluffy solid. $[\alpha]^{26}_D$ –7.5 (*c* 1.0, H_2O, pH 10.3) [lit.[29] $[\alpha]^{20}_D$ –4.6 (*c* 1.4, H_2O, pH 6); ^{1}H NMR (600 MHz,

D_2O): δ 4.21 (brs, 1H, H-2), 4.14 (q, J = 8.9 Hz, 1H, H-6), 3.81 (t, J = 7.7 Hz, 1H, H-5), 3.73–3.68 (m, 2H, H-4, H-5), 3.45 (dd, J = 8.4, 2.4 Hz, 1H, H-3); ^{13}C NMR (150 MHz, D_2O): δ 78.2 (CH), 76.9 (CH), 75.1 (CH), 73.6 (CH), 72.1 (CH), 71.7 (CH); ^{31}P NMR (121 MHz, D_2O): δ 5.07, 3.91, 2.83; HRMS (ESI): *m/z* calcd for $C_6H_{13}O_{15}P_3Na$ ([M – 2H + Na]$^-$) 440.9365, found 440.9384; *m/z* calcd for $C_6H_{12}O_{15}P_3Na_2$ [M – 3H + 2Na]$^-$ 462.9184, found 462.9182.

2-*O*-Benzoyl-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,5-orthoformate (44). The diol **21** (100 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (10 mL), and Et_3N (3 mL) was added. The flask was cooled to 0 °C using ice-bath and 1-(benzoyloxy)benzotriazole (59 mg, 0.25 mmol) was added in one portion. The reaction mixture was allowed to stir at 0 °C and gradually warmed up to room temperature over a period of 1 h. The solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography (EtOAc/hexane = 1/1) to afford the benzoyl derivative **44** (118 mg, 98%) as a white foam. $[\alpha]^{25}_D$ –62.5 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): δ 3501, 2976, 1756, 1723, 1340, 1271, 1164, 1092, 958, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 8.1, 0.8 Hz, 2H, Ar-H), 7.00 (d, J = 8.2 Hz, 2H, Ar-H), 7.59–7.56 (m, 1H, Ar-H), 7.44 (t, J = 8.1, 7.7 Hz, 2H, Ar-H), 7.32 (d, J = 8.2 Hz, 2H, Ar-H), 5.70 (td, J = 3.9, 1.7 Hz, 1H, H-6), 5.60 (d, J = 1.1 Hz, 1H, orthoformate-H), 5.55–5.53 (m, 1H, H-2), 4.70 (td, J = 6.1, 1.7 Hz, 1H, H-4) 4.50–4.47 (m, 2H, H-5, H-1), 4.47–4.45 (m, 1H, H-3), 4.19 (dd, J = 8.7, 3.8 Hz, 1H, proline-H), 3.66–3.62 (m, 1H), 3.46 (d, J = 4.9 Hz, 1H, 4-OH), 3.15–3.11 (m, 1H), 2.42 (s, 3H), 2.20–2.15 (m, 1H), 2.13–2.06 (m, 1H), 2.02–1.96 (m, 1H), 1.80–1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 (C), 166.1 (C), 144.2 (C), 134.0 (C), 133.4 (CH), 129.9 (CH), 129.5 (CH), 128.5 (CH), 127.4 (CH), 102.9 (orthoformate-CH), 71.7 (CH), 69.1 (CH_2), 68.7 (CH), 68.5 (CH), 67.4 (CH), 63.6 (CH), 61.0 (CH), 48.5 (CH_2), 30.7

(CH_2), 24.6 (CH_2), 21.6 (CH_3); HRMS (ESI): *m/z* calcd for $C_{26}H_{27}NO_{10}SNa$ ($[M + Na]^+$) 568.1253, found 568.1251.

2-*O*-Benzoyl-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol (45). Compound **44** (100 mg. 0.18 mmol) was dissolved in 1 N $HCl_{(aq)}$/MeOH (1/10 v/v, 5 mL) and allowed to reflux for 30 min. The reaction mixture was allowed to cool to room temperature, and the solvents were removed *in vacuo*. The crude residue was preadsorbed on silica gel and purified by flash column chromatography (2% MeOH in $CHCl_3$) to afford compound **45** (94 mg, 96%) as a white solid. $[\alpha]^{25}_D$ –120.4 (*c* 1.0, $CHCl_3$); mp 118–120 °C; IR (KBr, thin film): ν 3445, 2924, 1715, 1560, 1451, 1337, 1278, 1157, 1098, 1012, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 8.0, 1.0 Hz, 2H, Ar-H), 7.73 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.68 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.57 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.39 (d, *J* = 8.2, Hz, 2H, Ar-H), 5.48 (t, *J* = 2.8 Hz, 1H, H-2), 5.24 (d, *J* = 5.9 Hz, 1H, 1-OH), 5.08–5.01 (m, 4H, H-6 + 3,4,5-OH), 4.34 (dd, *J* = 8.2, 2.5 Hz, 1H, proline-H), 3.78 (ddd, *J* = 10.0, 6.1, 2.8 Hz, 1H, H-1), 3.57–3.51 (m, 2H, H-3, H-5), 3.33–3.30 (m, 1H), 3.25 (td, *J* = 9.0, 6.2 Hz, 1H, H-4), 3.15–3.12 (m, 1H), 2.37 (s, 3H), 2.08–2.03 (m, 1H), 1.81–1.73 (m, 2H), 1.65–1.63 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9 (C), 165.1 (C), 143.4 (C), 134.9 (C), 133.1 (CH), 130.5 (C), 129.8 (CH), 129.3 (CH), 128.6 (CH), 127.2 (CH), 79.2 (CH), 76.1 (CH), 75.9 (CH), 73.1 (CH), 72.6 (CH), 69.6 (CH), 61.0 (CH), 67.3 (CH), 60.6 (CH), 48.2 (CH_2), 30.3 (CH_2), 23.9 (CH_2), 21.0 (CH_3); HRMS (ESI): *m/z* calcd for $C_{25}H_{29}NO_{10}SNa$ ($[M + Na]^+$) 558.1410, found 558.1406.

2-*O*-Benzoyl-6-*O*-(*N*-tosyl-L-prolinoyl)-D-*myo*-inositol-1,3,4,5-tetrakis(dibenzyl phosphate) (46). Tetraol **45** (100 mg, 0.19 mmol) was transformed into the tetrakisphosphate **46** (289 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{25}_D$ –25.0 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3034, 2959, 1766, 1737, 1456, 1265, 966, 739 cm^{-1}; ^1H NMR

(600 MHz, $CDCl_3$): δ 8.02 (dd, J = 8.0, 0.8 Hz, 2H, Ar-H), 7.70 (d, J = 8.3 Hz, 2H, Ar-H), 7.61 (t, J = 8.0 Hz, 1H, Ar-H), 7.46 (t, J = 8.0 Hz, 2H, Ar-H), 7.23–7.06 (m, 43H, Ar-H), 6.32 (t, J = 2.6 Hz, 1H, H-2), 5.63 (d, J = 9.5 Hz, 1H, H-6), 5.06–4.82 (m, 17H, 8 × CH_2, H-4), 4.52 (dd, J = 8.7, 3.1 Hz, 1H, proline-H), 4.49–4.41 (m, 3H, H-5, H-3, H-1), 3.09–3.02 (m, 2H), 2.36–2.32 (m, 1H), 2.30 (s, 3H), 1.64–1.52 (m, 2H), 1.39–1.34 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8 (C), 164.9 (C), 143.1 (C), 135.81 (C), 135.77 (CH), 135.70 (C), 135.67 (C), 135.61 (C), 135.53 (C), 135.50 (C), 134.46 (C), 135.4 (C), 133.7 (CH), 130.0 (CH), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.44 (CH), 128.41 (CH), 128.44 (CH), 128.33 (CH), 128.30 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.99 (CH), 127.86 (CH), 127.7 (CH), 75.6 (CH), 75.4 (CH), 73.1 (CH), 72.4 (CH), 72.3 (CH), 71.49 (CH), 71.46 (CH), 70.11 (CH_2), 70.07 (CH_2), 70.0 (CH_2), 69.91 (CH_2), 69.87 (CH_2), 69.7 (CH_2), 69.64 (CH_2), 69.61 (CH_2), 69.58 (CH_2), 69.54 (CH_2), 60.7 (CH), 48.2 (CH_2), 29.3 (CH_2), 24.3 (CH_2), 21.4 (CH_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ –0.80, –0.87, –1.16, –1.34; HRMS (FAB): *m/z* calcd for $C_{81}H_{82}NO_{22}P_4S$ ($[M + H]^+$) 1576.4010, found 1576.4000.

D-*myo*-inositol-1,3,4,5-tetrakisphosphate octasodium salt (2). To a solution of compound **46** (100 mg, 0.06 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, and the residue dissolved in a cold solution of 1 N NaOH (0.76 mmol) and stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by cellulose column chromatography, first eluting with

MeOH, then MeOH/water (1/1), and finally with water. The fractions containing the product were concentrated and lyophilized to afford the tetrakisphosphate **2** (41 mg, 98%) as a white fluffy solid. $[\alpha]^{27}_{D}$ –2.7 (*c* 1.0, H_2O, pH 10.0) [lit.[28] $[\alpha]^{25}_{D}$ –4.08 (*c* 2.02, H_2O, pH 10.0)]; ^{1}H NMR (600 MHz, D_2O): δ 4.49 (t, *J* = 2.4 Hz, 1H, H-2), 4.33 (q, *J* = 9.4 Hz, 1H, H-4), 4.02–3.86 (m, 4H, H-1, H-3, H-5, H-6); ^{13}C NMR (150 MHz, D_2O): δ 77.6 (CH), 75.9 (CH), 73.7 (CH), 72.1 (CH), 70.6 (CH); ^{31}P NMR (121 MHz, D_2O): δ 4.67, 4.12, 3.94, 2.26; HRMS (ESI): *m/z* calcd for $C_6H_{15}O_{18}P_4$ ($[M - H]^-$) 498.9209, found 498.9225; calcd for $C_6H_{12}O_{18}P_4Na_3$ [M – 4H + 3Na]$^-$) 564.8667, found 564.8664.

2,3-*O*-Cyclohexylidene-D-*myo*-inositol (47). A solution of compound **39** (150 mg, 0.29 mmol) and hydrazine monohydrate (29 mg, 0.59 mmol) in MeOH (3 mL) was stirred at room temperature for 2 h. The volatile materials were removed under reduced pressure, and the residue was purified by flash column chromatography ($CHCl_3$) to afford the tetraol **47** (75 mg, 98%) as a white solid. $[\alpha]^{27}_{D}$ +31.3 (*c* 0.7, MeOH); mp 187–189 °C; [lit.[30] $[\alpha]^{21}_{D}$ +36.9 (*c* 1.3, MeOH); mp 188–189 °C]; IR (KBr, thin film): ν 3391, 2936, 1449, 1368, 1164, 1101, 998, 724 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.84 (d, *J* = 4.8 Hz, 1H, OH), 4.81 (d, *J* = 5.3 Hz, 1H, OH), 4.74 (d, *J* = 4.3 Hz, 1H, OH), 4.69 (d, *J* = 4.5 Hz, 1H, OH), 4.15 (dd, *J* = 5.0, 4.1 Hz, 1H, H-2), 3.78 (dd, *J* = 7.3, 5.3 Hz, 1H, H-3), 3.47 (ddd, *J* = 9.1, 5.0, 4.1 Hz, 1H, H-1), 3.33-3.29 (m, 2H, H-4, H-6), 2.89 (td, *J* = 9.3, 4.4 Hz, 1H, H-5), 1.60–1.52 (m, 4H), 1.52–1.46 (m, 4H), 1.36–1.32 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 108.5 (Spiro-C), 78.8 (C), 76.0 (C), 75.0 (C), 74.1 (CH), 72.2 (CH), 69.9 (CH), 37.7 (CH_2), 34.9 (CH_2), 24.6 (CH_2), 23.6 (CH_2), 23.3 (CH_2); HRMS (ESI): *m/z* calcd for $C_{12}H_{21}O_6$ ($[M + H]^+$) 261.1338, found 261.1345.

1,2-*O*-Cyclohexylidene-D-*myo*-inositol (48). A solution of compound **40** (200 mg, 0.39 mmol) and hydrazine monohydrate (39 mg, 0.78 mmol) in MeOH (3 mL) was stirred at room

temperature for 2 h. The volatile materials were removed under reduced pressure and the residue was purified by flash column chromatography ($CHCl_3$) to afford the tetraol **48** (98 mg, 98%) as a white solid. $[\alpha]^{26}_D$ –27.3 (*c* 0.75, MeOH); mp 184–185 °C [lit.[30] $[\alpha]^{22}_D$ –36.0 (*c* 1.05, MeOH), mp 188–190 °C]; IR (KBr, thin film): ν 3391, 2936, 1450, 1368, 1278, 1164, 1101, 997, 764 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 4.84 (d, J = 4.8 Hz, 1H, OH), 4.80 (d, J = 5.2 Hz, 1H, OH), 4.74 (d, J = 4.4 Hz, 1H, OH), 4.69 (d, J = 4.5 Hz, 1H, OH), 4.15 (dd, J = 5.0, 4.2 Hz, 1H, H-2), 3.78 (dd, J = 7.3, 5.3 Hz, 1H, H-1), 3.47 (ddd, J = 9.1, 5.0, 4.2 Hz, 1H, H-3), 3.33–3.29 (m, 2H, H-4, H-6), 2.89 (td, J = 9.4, 4.4 Hz, 1H, H-5), 1.60–1.52 (m, 4H), 1.52–1.46 (m, 4H), 1.36–1.32 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 108.5 (Spiro-C), 78.8 (C), 76.0 (C), 75.0 (C), 74.1 (CH), 72.2 (CH), 69.9 (CH), 37.7 (CH_2), 34.9 (CH_2), 24.6 (CH_2), 23.6 (CH_2), 23.3 (CH_2); HRMS (ESI): *m/z* calcd for $C_{12}H_{21}O_6$ ($[M + H]^+$) 261.1338, found 261.1340.

2,3-*O*-Cyclohexylidene-D-*myo*-inositol-1,4,5,6-tetrakis(dibenzyl phosphate) (49). Tetraol **47** (50 mg, 0.19 mmol), using CH_2Cl_2/DMF (9/1, 5mL) as solvent, was transformed into the tetrakisphosphate **49** (243 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{27}_D$ –9.4 (*c* 1.0, CH_2Cl_2) [lit.[30] $[\alpha]^{23}_D$ –8.7 (*c* 5.77, CH_2Cl_2)]; IR (KBr, thin film): ν 2939, 1456, 1279, 1016, 737 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.29–7.18 (m, 42H, Ar-H), 5.10 (td, J = 9.1, 5.3 Hz, 1H, H-2), 5.06–4.92 (m, 17H), 4.79–4.74 (m, 2H, H-1, H-3), 4.67 (dd, J = 6.7, 3.7 Hz, 1H, H-6), 4.25 (dd, J = 6.7, 5.3 Hz, 1H, H-5), 1.73–1.67 (m, 2H), 1.53 (m, 2H), 1.46–1.43 (m, 2H), 1.29(m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.8 (C), 135.73 (C), 135.69 (C), 135.63(C), 128.49 (CH), 128.44 (CH), 128.40 (CH), 128.37 (CH), 128.25 (CH), 128.01 (CH), 128.96 (CH), 128.91 (CH), 128.8 (CH), 111.7 (Spiro-C), 78.7 (CH), 76.4 (CH), 76.3 (CH), 74.9 (CH), 73.2 (CH), 72.2 (CH), 69.71 (CH_2), 69.65 (CH_2), 69.59 (CH_2), 69.55 (CH_2), 69.47 (CH_2), 69.44 (CH_2), 35.8 (CH_2), 33.3 (CH_2), 24.9 (CH_2), 23.8 (CH_2), 23.5 (CH_2);

^{31}P NMR (121 MHz, $CDCl_3$): δ –0.88, –1.40, –1.47, –1.56; HRMS (ESI): *m/z* calcd for $C_{68}H_{72}O_{18}P_4Na$ ($[M + Na]^+$) 1323.3567, found 1323.3556.

1,2-*O*-Cyclohexylidene-D-*myo*-inositol-3,4,5,6-tetrakis(dibenzyl phosphate) (50). Tetraol **48** (50 mg, 0.19 mmol) was transformed into the tetrakisphosphate **50** (245 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{25}_D$ +9.0 (*c* 1.0, CH_2Cl_2); [lit.[30] $[\alpha]^{25}_D$ +8.7 (*c* 6.80, CH_2Cl_2)]; IR (KBr, thin film): ν 2938, 1455, 1279, 1215, 1014, 737 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28–7.16 (m, 40H, Ar-H), 5.10 (td, *J* = 9.1, 5.3 Hz 1H, H-2), 5.06–4.92 (m, 17H), 4.78–4.73 (m, 2H, H-1, H-3), 4.67 (dd, *J* = 6.7, 3.6 Hz, 1H, H-4), 4.25 (dd, *J* = 6.8, 5.2 Hz, 1H, H-5), 1.70–1.68 (m, 2H), 1.52–1.50 (m, 2H), 1.45–1.41 (m, 2H), 1.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.8 (C), 135.73 (C), 135.69 (C), 135.63 (C), 135.57 (C), 128.49 (CH), 128.44 (CH), 128.40 (CH), 128.37 (CH), 128.25 (CH), 128.01 (CH), 127.96 (CH), 127.91 (CH), 127.85 (CH), 111.7 (Spiro-C), 78.7 (CH), 76.4 (CH), 76.3 (CH), 74.9 (CH), 73.2 (CH), 72.2 (CH), 69.71 (CH_2), 69.65 (CH_2), 69.59 (CH_2), 69.55 (CH_2), 69.47 (CH_2), 69.44 (CH_2), 35.8 (CH_2), 33.6 (CH_2), 24.9 (CH_2), 23.8 (CH_2), 23.5 (CH_2)); ^{31}P NMR (121 MHz, $CDCl_3$): δ –0.87, –1.39, –1.46, –1.56; HRMS (ESI): *m/z* calcd for $C_{68}H_{72}O_{18}P_4Na$ ($[M + Na]^+$) 1323.3567, found 1323.3579.

D-*myo*-Inositol-1,4,5,6-tetrakisphosphate octasodium salt (51). To a solution of compound **49** (100 mg, 0.07 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, and the residue was dissolved in deionized water and

passed through Dowex 50WX8 ion exchange resin (Na^+ form) using deionized water as the eluent. The fractions containing product were concentrated and lyophilized to afford the tetrakisphosphate **51** (51 mg, 100%) as a white fluffy solid. $[\alpha]^{26}_D$ –10.25 (*c* 2.0, H_2O, pH 9.7) [lit.[28] $[\alpha]^{25}_D$ –8.99 (*c* 1.85, H_2O, pH 10)]; ^1H NMR (600 MHz, D_2O): δ 4.45 (q, J = 9.4 Hz, 1H, H-6), 4.33 (q, J = 9.2 Hz, 1H, H-4), 4.24 (brs, 1H, H-2), 4.17–4.10 (m, 2H, H-1, H-5), 3.75 (dd, J = 9.8, 2.4 Hz, 1H, H-3); ^{13}C NMR (150 MHz, D_2O): δ 77.4 (CH), 76.8 (CH), 76.2 (CH), 74.5 (CH), 70.9 (CH), 70.0 (CH); ^{31}P NMR (121 MHz, D_2O): δ 1.68 (1P), 1.62 (2P), 0.76(1P); HRMS (ESI): *m/z* calcd for $C_6H_{12}O_{18}P_4Na_5$ ($[M - 4H + 5Na]^+$) 610.8463, found 610.8462.

D-*myo*-inositol-3,4,5,6-tetrakisphosphate octasodium salt (52). To a solution of compound **50** (100 mg, 0.07 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg). The mixture was placed under vacuum, and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed with MeOH and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, and the residue dissolved in deionized water and passed through Dowex 50WX8 ion exchange resin (Na^+ form) using deionized water as the eluent. The fractions containing product were concentrated and lyophilized to afford the tetrakisphosphate **52** (51 mg, 100%) as a white fluffy solid. $[\alpha]^{27}_D$ +7.8 (*c* 2.0, H_2O, pH 9.3) [lit.[28] $[\alpha]^{27}_D$ +10.1 (*c* 2.23, H_2O, pH 10); ^1H NMR (600 MHz, D_2O): δ 4.45 (q, J = 9.5 Hz, 1H, H-6), 4.32 (q, J = 9.6 Hz, 1H, H-4), 4.24 (t, J = 2.7 Hz, 1H, H-2), 4.16–4.09 (m, 2H, H-1, H-5), 3.74 (dd, J = 9.6, 2.7 Hz, 1H, H-3); ^{13}C NMR (150 MHz, D_2O): δ 77.4 (CH), 76.8 (CH), 76.2 (CH), 74.5 (CH), 70.9 (CH), 70.0 (CH); ^{31}P NMR (121 MHz, D_2O): δ 1.71 (1P), 1.65 (2P), 0.79 (1P); HRMS (ESI): *m/z* calcd for $C_6H_{12}O_{18}P_4Na_5$ ($[M - 4H + 5Na]^+$) 610.8463, found 610.8463.

2,4-Di-*O*-benzyl-D-*myo*-inositol (53). Compound **30** (150 mg. 0.40 mmol) was dissolved in 1N $HCl_{(aq)}$/MeOH (1/10 v/v, 5 mL) and allowed to reflux for 30 min. The reaction mixture was allowed to cool to room temperature. The solvents were removed *in vacuo*, and the crude residue was preadsorbed on silica gel and purified by flash column chromatography (2% MeOH in $CHCl_3$) to afford compound **53** (140 mg, 96%) as a white solid. $[\alpha]^{27}_D$ +30.4 (*c* 1.0, MeOH); mp 145–147 °C; IR (KBr, thin film): ν 3391, 2948, 1452, 1107, 929, 749 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 7.43–7.41 (m, 4H, Ar-H), 7.34–7.29 (m, 4H, Ar-H), 7.26–7.22 (m, 2H, Ar-H), 4.82–4.76 (m, 6H, CH_2, 2 × OH), 4.73 (d, J = 4.7 Hz, 1H, OH), 4.70 (d, J = 4.7 Hz, 1H, OH), 3.72 (t, J = 2.4 Hz, 1H, H-2), 3.49–3.43 (m, 3H, H-1, H-4, H-6), 3.29 (ddd, J = 10.7, 2.8, 2.4, Hz, 1H, H-3); ^{13}C NMR (150 MHz, DMSO-d_6): δ 139.9 (C), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 82.4 (CH), 82.3 (CH), 75.1 (CH), 74.2 (CH_2), 73.6 (CH_2), 71.8 (CH), 71.6 (CH); HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_6Na$ ($[M + Na]^+$) 383.1471, found 383.1470.

2,4-Di-*O*-benzoyl-D-*myo*-inositol-1,3,5,6-tetrakis(dibenzyl phosphate) (54). Tetraol **53** (60 mg, 0.17 mmol) was transformed into the tetrakisphosphate **54** (228 mg, 98%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{27}_D$ +7.9 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3033, 1497, 1455, 1278, 1215, 1015, 737 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, J = 7.0 Hz, 2H, Ar-H), 7.25–7.07 (m, 48H, Ar-H), 6.94 (d, J = 7.2 Hz, 2H, Ar-H), 4.96–4.82 (m, 15H, CH_2, H-2), 4.79–4.73 (m, 5H, CH_2), 4.66 (t, J = 2.4 Hz, 1H, H-6), 4.61 (dd, J = 11.8, 8.8 Hz, 1H, CH_2), 4.45–4.41(m, 1H, H-3), 4.28 (ddd, J = 9.8, 7.9, 2.4 Hz, 1H, H-5), 4.21 (ddd, J = 9.8, 7.6, 2.4 Hz, 1H, H-1), 4.05 (t, J = 9.5 Hz, 1H, H-4); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.1 (C), 138.0 (C), 136.1 (C), 136.04 (C), 136.02 (C), 135.99 (C), 135.93 (C), 135.88 (C), 135.76 (C), 135.72 (C), 135.59 (C), 135.55 (C), 135.49 (C), 135.47 (C), 135.45 (C), 128.6 (CH), 128.53

(CH), 128.50 (CH), 128.44 (CH), 128.43 (CH), 128.3 (CH), 128.26 (CH), 128.25 (CH), 128.23 (CH), 128.14 (CH), 128.11 (CH), 128.07 (CH), 128.03 (CH), 127.97 (CH), 127.91 (CH), 127.85 (CH), 127.75 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 78.0 (CH), 77.7 (CH), 77.6 (CH), 77.2 (CH), 76.0 (CH), 75.8 (CH_2), 75.4 (CH), 74.6 (CH_2), 69.8 (CH_2), 60.7 (CH_2), 69.61 (CH_2), 69.57 (CH_2), 69.51 (CH_2), 69.48 (CH_2), 69.31 (CH_2), 69.27 (CH_2), 69.24 (CH_2), 69.21 (CH_2)); ^{31}P NMR (121 MHz, $CDCl_3$): δ –0.57, –0.80, –0.98, –1.30; HRMS (ESI): *m/z* calcd for $C_{76}H_{76}O_{18}P_4Na$ ($[M + Na]^+$) 1423.3880, found 1423.3887.

D-*myo*-Inositol-1,3,5,6-tetrakisphosphate octasodium salt (55). To a solution of compound **54** (100 mg, 0.07 mmol) in MeOH (5 mL) was added 10% Pd/C (100 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, and the residue was dissolved in deionized water and passed through Dowex 50WX8 ion exchange resin (Na^+ form) using deionized water as the eluent. The fractions containing product were concentrated and lyophilized to afford the tetrakisphosphate **55** (48 mg, 100%) as a white fluffy solid. $[\alpha]^{26}_D$ +6.04 (*c* 2.1, H_2O, pH 10.7) [lit.[28] $[\alpha]^{25}_D$ +4.68 (*c* 2.11, H_2O, pH 10)]; ^{1}H NMR (600 MHz, D_2O, pD 6.8): δ 4.66 (brs, 1H, H-2), 4.32 (q, J = 9.4 Hz, 1H, H-4), 3.95–3.84 (m, 4H, H-1, H-3, H-5, H6); ^{13}C NMR (150 MHz, D_2O): δ 77.64 (CH), 74.1, 74.0 (CH), 73.3 (CH), 72.7 (CH), 69.8 (CH); ^{31}P NMR (121 MHz, D_2O): δ 5.50, 4.87, 4.54, 3.96; HRMS (ESI) *m/z* calcd for $C_6H_{12}O_{18}P_4Na_5$ ($[M –4H + 5Na]^+$) 610.8463, found 610.8456.

6-*O*-(*N*-Tosyl-L-prolinoyl)-D-*myo*-inositol-1,2,3,4,5-pentakis(dibenzyl phosphate) (56). Pentaol **35** (75 mg, 0.17 mmol), using CH_2Cl_2/DMF (4/1, 10 mL) as solvent, was transformed into the pentakisphosphate **56** (272 mg, 92%) as a gum, following the general procedure for phosphorylation. $[\alpha]^{25}_D$ –19.5 (*c* 1.0, $CHCl_3$); IR (KBr, thin film): ν 3035, 1767, 1497, 1456, 1280, 1160, 1016, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.75–7.74 (m, 2H, Ar-H), 7.28–7.09 (m, 53H, Ar-H), 5.66 (t, *J* = 9.6 Hz, 1H, H-6), 5.55 (dt, *J* = 9.0, 2.2 Hz, 1H, H-2), 5.19 (dd, *J* = 11.7, 6.12 Hz, 1H, CH_2), 5.12–4.89 (m, 18H, CH_2), 4.83–4.81 (m, 2H, CH_2), 4.76 (dd, *J* = 11.4, 6.7 Hz, 1H, CH_2) 4.61 (dd, *J* = 9.1, 3.2 Hz, 1H, proline-H), 4.44 (q, *J* = 9.6 Hz, 1H, H-5), 4.28 (t, *J* = 9.6 Hz, 2H, H-3, H-1), 2.39-2.34 (m, 1H), 2.30 (s, 3H), 1.65–1.60 (m, 1H), 1.58–1.50 (m, 1H), 1.40–1.34 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9 (C), 143.1 (C), 136.0 (C), 135.8 (C), 135.79 (C), 135.75 (C), 135.71 (C), 135.67 (C), 135.60 (C), 135.57 (C), 135.52 (C), 135.46 (C), 135.31 (C), 135.26 (C), 129.4 (CH), 128.53 (CH), 128.50 (CH), 128.45 (CH), 128.39 (CH), 128.36 (CH), 128.31 (CH), 128.23 (CH), 128.21 (CH), 128.16 (CH), 128.08 (CH), 127.97 (CH), 127.91 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 77.2 (CH), 75.7 (CH), 75.0 (CH), 73.2 (CH), 72.5 (CH), 71.0 (CH),70.2 (CH_2), 70.16 (CH_2), 70.13 (CH_2), 70.0 (CH_2), 69.9 (CH_2), 69.88 (CH_2), 69.79 (CH_2), 69.74 (CH_2), 69.70 (CH_2), 69.65 (CH_2), 69.60 (CH_2), 69.56 (CH_2); ^{31}P NMR (121 MHz, $CDCl_3$): δ –0.21, –0.27, –0.91, –1.49, –1.81; HRMS (MALDI): *m/z* calcd for $C_{88}H_{90}NO_{24}P_5SNa$ ($[M + Na]^+$) 1754.4159, found 1754.4196.

D-*myo*-Inositol-1,2,3,4,5-pentakisphosphate decasodium salt (57). To a solution of compound **56** (100 mg, 0.06 mmol) in MeOH (5 mL) was added 10% Pd/C (150 mg). The mixture was placed under vacuum and the atmosphere was replaced first with nitrogen gas and then with hydrogen gas. The suspension was then allowed to stir under hydrogen atmosphere for 16 h. The heterogenous mixture was filtered through a pad of Celite, the residue was washed

with MeOH, and the combined filtrate was concentrated under reduced pressure. The resulting crude product was washed with $CHCl_3$, and the residue was dissolved in a cold solution of 1 N NaOH (0.76 mmol) and stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure and purified by cellulose column chromatography, first eluting with MeOH, then MeOH/water (1/1), and finally with water. The fractions containing product were concentrated and lyophilized to afford the pentakisphosphate **57** (44 mg, 98%) as a white fluffy solid. $[\alpha]^{26}_{D}$ –6.3 (*c* 0.43, H_2O, pH 10.2) [lit.[31] $[\alpha]^{20}_{D}$ –6.2 (*c* 1.29, H_2O, pH 6); ^{1}H NMR (600 MHz, D_2O): δ 4.74 (d, J = 8.8 Hz, 1H, H-2), 4.40 (q, J = 9.2 Hz, 1H, H-6), 4.05–3.96 (m, 4H, H-1, H-3, H-4, H-5); ^{13}C NMR (150 MHz, D_2O): δ 78.1 (CH), 75.5 (2 × CH), 73.6 (CH), 73.4 (CH), 72.1 (CH); ^{31}P NMR (121 MHz, D_2O): δ 4.52, 4.41, 4.34, 3.08 (2P); HRMS (ESI): *m/z* calcd for $C_6H_{11}Na_5O_{21}P_5$ ($[M - 6H + 5Na]^-$) 688.7969; found 688.7957.

ASSOCIATED CONTENT

Supporting Information

X-ray structure data for compound **14** and copies of all relevant ^{1}H, ^{13}C, and ^{31}P spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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