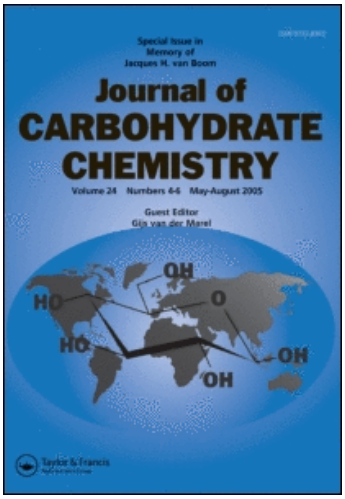

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Divergent Synthesis of All Possible Optically Active Regioisomers of *Myo*-Inositol Mono- and Bisphosphates

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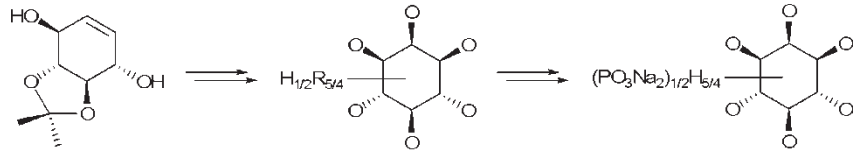
All possible optically active regioisomers of *myo*-inositol mono- and bisphosphates were synthesized using inositol derivatives suitably protected with various protecting groups (IR_ns) as key intermediates. A series of procedures including Novozym 435 catalyzed enzymatic resolution of (3a*R*,4*S*,7*S*,7a*R*)-*rel*-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,7-diol diacetate, several protection and deprotection reactions, and acyl migration afforded two enantiomeric pairs of IR_5 and six enantiomeric pairs of IR_4. Phosphorylation of these key intermediates by the phosphitylation and oxidation procedure gave the target products after removal of the protecting groups.



Keywords *Myo*-inositol, Inositol phosphates, divergent synthesis, Protecting groups, Phosphorylation

INTRODUCTION

Although inositol phosphates had long been known, renewed interests began to rise only after the discovery in 1983 that D-*myo*-inositol-1,4,5-trisphosphate

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[D-I(1,4,5)P_3] is a Ca^{2+}-mobilizing second messenger in the cytosol.[1] It was soon found that D-I(1,4,5)P_3 and its dephosphorylated products, D-I(1,4)P_2 and D-IP_1s as well as D-I(1,3,4)P_3 and D-I(1,3,4,5)P_4, emerged as metabolites when cells were stimulated. Furthermore, $InsP_5$ and $InsP_6$, previously thought to be present only in plants and erythrocytes of a few animals, were also found to be components of mammalian cells. Now the phospholipase C (PLC)-catalyzed hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to D-I(1,4,5)P_3 and diacylglycerol, a PKC activator, is one of the best established signaling pathways in cells. More recently, nuclear counterparts of similar inositol signaling pathways also have been found.[2] *myo*-Inositol phosphates other than D-I(1,3,4)P_3 and D-I(1,3,4,5)P_4 have become quite prominent with newly discovered important biological functions. For example, D-I(3,4,5,6)P_4 was shown to be a physiologically important inhibitor of Ca^{2+}-regulated Cl^- channels, whereas D-IP_6 (phytic acid) was found to regulate mRNA export in mammalian cells through its interaction with synaptotagmin[3] as well as to play a key role in RNA editing.[4]

Mathematically, there are 39 possible optically inactive regioisomers of *myo*-inositol phosphates (IP_n: n = 1 to 6), or 63 regioisomers, if enantiomers are considered. Many inositol kinases and phosphatases have been identified in the course of studying the metabolism of inositol phosphates. For instance, one of the major metabolic pathways of D-I(1,4,5)P_3 is removal of the 5-phosphate group by a specific 5-phophatase located in plasma membrane as well as in the cytosol of stimulated cells to give I(1,4)P_2. Other phosphatases are responsible for the further degradation of the IP_2 formed in this hydrolysis, via I(1)P_1 or I(4)P_1, to give finally free inositol, which is then recycled in the biosynthesis of PIP_2.

Although the conversion of I(1,4,5)P_3 into $I(1,4)_2$ had been regarded as merely a terminating step of the Ca^{2+} mobilization signal, the novel activities of I(1,4)P_2 reported as a DNA polymerase α activator[5] and cytoskeletal actin inducer[6] suggested that IP_2 might be another interesting signaling molecule. Several other IP_2s were also detected in nature, but the biological functions of IP_2s have not yet been thoroughly examined. The mammalian enzyme, *myo*-inositol monophosphatase, which hydrolyzes the naturally occurring IP_1 isomers D-I(1)P_1, I(3)P_1, and I(4)P_1 to free inositol with a low substrate selectivity, is inhibited by lithium ion in an uncompetitive manner.[7] Blockade of this enzyme would be expected to reduce the overall available inositol and thus PIP_2 production, and it was hypothesized that the lithium ion effect in the treatment of manic depression and its accompanying CNS toxicity might be due to the inhibition of inositol monophosphatase.[8] Studies of lithium's effect on *myo*-inositol monophosphatase polymorphisms and bipolar disorder is a current research topic in molecular psychiatry.[9] Some of IP_1 analogs have been prepared and mechanistic studies with them as either substrate or inhibitor have been carried out by several groups.[10] In these connections,

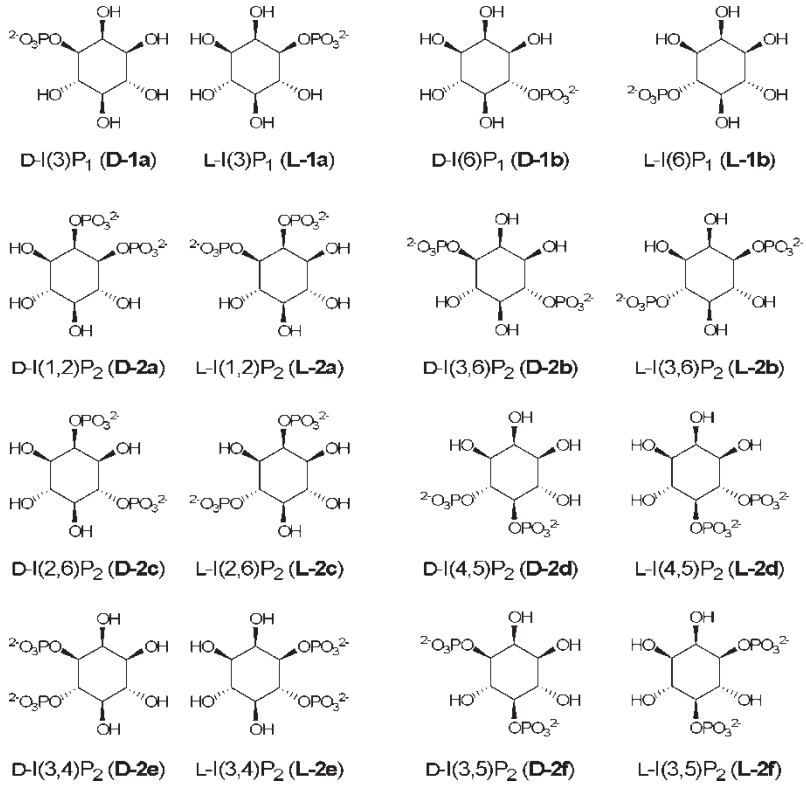


Figure 1: Two enantiomeric pairs of IP_1 and six enantiomeric paris of IP_2.

availability of all possible optically active IP_1 and IP_2 regioisomers would be highly desirable.

We previously reported the systematic and divergent syntheses of all possible 39 optically inactive regioisomers of *myo*-inositol phosphates using the acyl migration as the key strategy[11] and 32 optically active regioisomers of *myo*-inositol tris-, tetrakis-,[12] and pentakis-phosphates[13] using the CRL-catalyzed enzymatic resolution and the acyl migration. Herein we describe the synthesis of optically active *myo*-inositol mono- and bisphosphate regioisomers (Fig. 1) via application of the divergent as well as specific synthetic methods at the stage of various intermediates, thus now completing the syntheses of all possible 63 (15 meso and 24 enantiomeric pairs) regioisomers of *myo*-inositol phosphates.

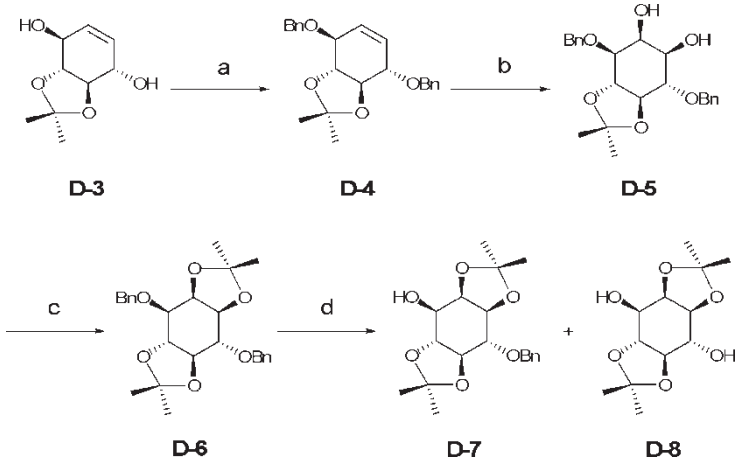
RESULTS AND DISCUSSION

The key issues in the synthesis of optically active regioisomers of IP_1 and IP_2 are (1) how to obtain enantiomerically pure inositol derivatives and (2) how

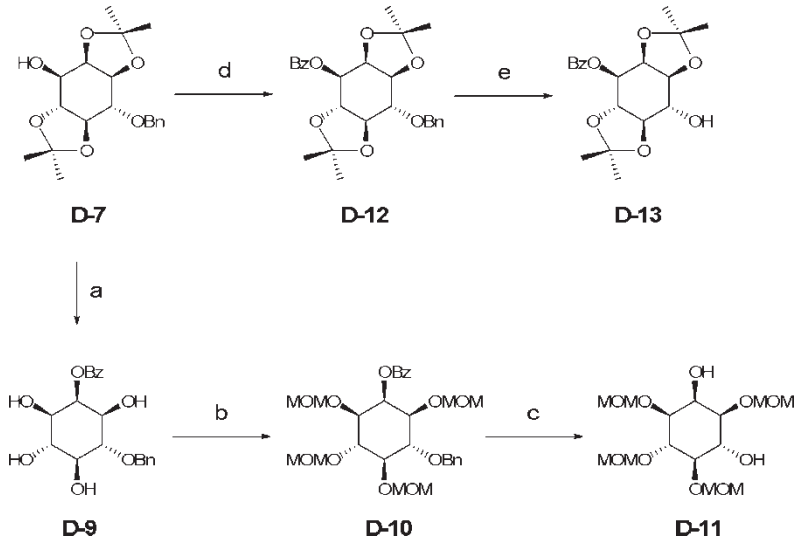
to efficiently prepare IR_5s and IR_4s, the key intermediates. Our synthetic approaches to homochiral regioisomers of IP_1 and IP_2 are based on the enzyme-catalyzed optical resolution of (3a*R*,4*S*,7*S*,7a*R*)-rel-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,7-diol diacetate with Novozym 435 (immobilized lipase from *Candida antarctica*, Novo Nordisk).[14] The conversions of the enantiomeric diols, **D-3** and **L-3**, to two enantiomeric pairs of all possible IP_1 and IP_2 regioisomers involve the identical series of reactions except that the corresponding substrates and products along the synthetic route have opposite configurations. Therefore, the procedure starting from **D-3** only is described as the representative procedure.

Chiral IR_5s and IR_4s, the key synthetic precursors for phosphorylation, were prepared as follows. *cis*-Dihydroxylation of compound **D-4**, which was prepared by simple benzylation of **D-3** with BnBr, NaH, and TBAI in THF, exclusively gave D-3,6-di-*O*-benzyl-4,5-isopropylidene-*myo*-inositol (**D-5**), the synthetic precursor to D-I(1,2)P_2. Treatment of the chiral diol **D-5** with 2-methoxypropene and an acid catalyst gave the di-*O*-benzyl-di-*O*-isopropylidene derivative **D-6**, and catalytic hydrogenolysis of **D-6** in the presence of $NaHCO_3$ gave the monool **D-7** (53.8%) and the diol **D-8** (11.6%),[15] which served as the synthetic precursor to D-I(3)P_1 and D-I(3,6)P_2, respectively (Sch. 1).

The tetraol **D-9**, derived from **D-7** by treatment with aq AcOH, followed by selective monobenzoylation at the axial hydroxy group through the orthobenzoate intermediate,[11d] was treated with MOMCl and DIPEA in 1,2-dichloroethane to afford compound **D-10**. Benzyl and benzoyl groups of **D-10** were removed by hydrogenolysis with $Pd(OH)_2$ on charcoal and subsequent



Scheme 1: a. BnBr, NaH, TBAI; b. OsO_4, NMO; c. 2-methoxypropene, TSA; d. H_2, 10% Pd-C, $NaHCO_3$.

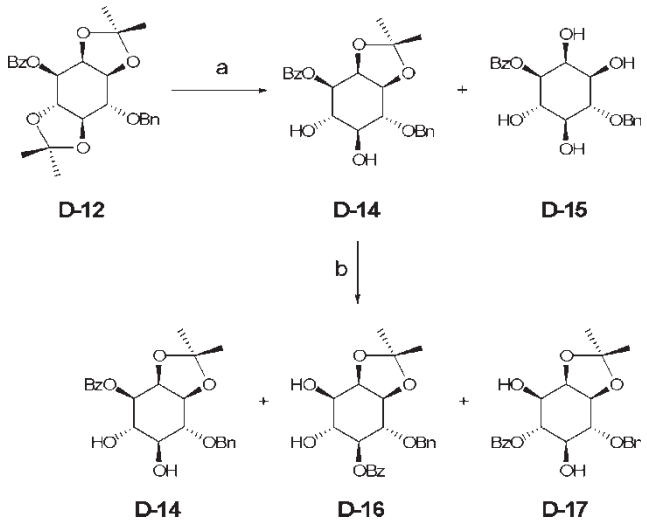


Scheme 2: a. (i) 80% aq AcOH, (ii) triethyl orthobenzoate, TSA; b. MOMCl, DIPEA; c. (i) H_2, 20% $Pd(OH)_2$-C, (ii) NaOMe; d. BzCl, DMAP; e. H_2, 10% Pd-C, $NaHCO_3$.

treatment with NaOMe to give the diol **D-11**, which served as the precursor to D-I(2,6)P_2. After protection of 3-OH of compound **D-7** as benzoyl ester by treatment with BzCl and DMAP, subsequent deprotection of the benzyl group by hydrogenolysis in a basic condition gave **D-13** as the D-I(6)P_1 precursor (Sch. 2).

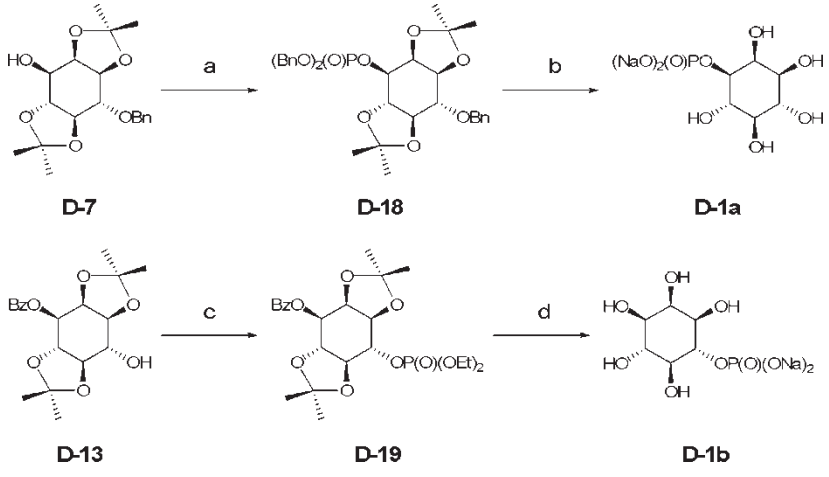
Acid-catalyzed partial solvolysis of compound **D-12** with a catalytic amount of TSA in MeOH-CH_2Cl_2 gave the diol **D-14** (68.5%) and the tetraol **D-15** (25.1%). When the diol **D-14** was subjected to the acyl migration condition (60% aq. pyridine, 90°C), a mixture of three regioisomers was generated. Each of these regioisomers was readily separated and purified by silica gel chromatography. The ratio of the regioisomers on the basis of the isolated yields was as follows; **D-14**:**D-16**:**D-17** = 31:25:44 (Sch. 3).

Compound **D-7** was phosphorylated by successive treatments with dibenzyl diisopropylphosphoramidite and 1H-tetrazole, and then mCPBA to yield **D-18**. Compound **D-13** was phosphitylated with diethyl phosphochloridite and DIPEA, and then oxidized with 30% H_2O_2 to give **D-19**. The two enantiomeric pairs of inositol monophosphate in the protected forms (**18** and **19**) were obtained in 70% to 82% yields (Sch. 4), and their ^{31}P NMR chemical shifts and optical rotations are shown in Table 1. In the final steps, all protecting groups were removed by hydrogenolysis, treatment with TMSBr, and hydrolysis with LiOH to give the desired four optically active regioisomers of IP_1 (**1a** and **1b**) in the sodium salt form. They were fully characterized by ^1H and ^{31}P NMR spectroscopy (Sch. 4).



Scheme 3: a. TSA, MeOH/CH_2Cl_2; b. 60% aq pyridine.

All six enantiomeric pairs of IP_2s in the sodium salt form (**2a**–**f**) were prepared by phosphorylating the corresponding precursors as described for IP_1 regioisomers (Sch. 5 and 6). The ^{31}P NMR chemical shifts and optical rotations of the six enantiomeric pairs of IP_2 in their protected form (**20**–**25**) are listed in Table 1.



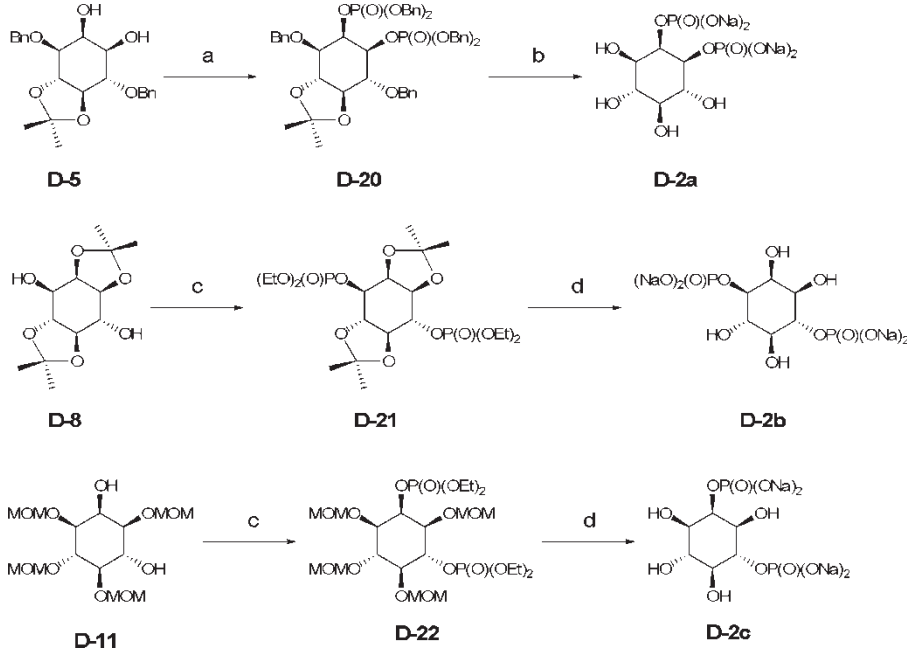
Scheme 4: a. (i) Dibenzyl disopropylphosphoramidite, 1H-tetrazole, (ii) mCPBA; b. (i) H_2, 10% Pd-C, AcOH, (ii) pH 10 (1N NaOH); c, (i) diethyl phosphorochloridite, DIPEA, (ii) 30% H_2O_2; d. (i) TMSBr, (ii) 1M LiOH, (iii) H^+ ion exchange, (iv) pH 10 (1N NaOH).

Table 1: ^{31}P NMR chemical shifts and optical rotations of $IP_nR_{(6-n)}$s.

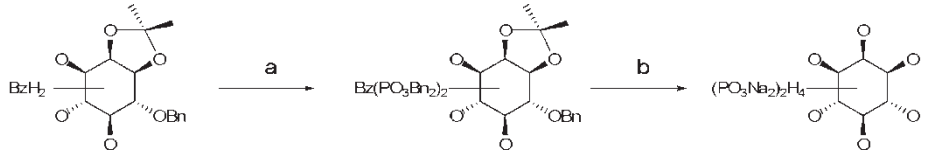
		$(\alpha)_D^{25}$ (in CH_2Cl_2)	
	^{31}P (δ, ppm)	**D-form**	**L-form**
18 (I(3)P′(6)Bn(1,2:4,5)Ace_2)	0.63	−22.8 (*c* 1.10)	+20.8 (*c* 0.50)
19 (I(6)P″(3)Bz(1,2:4,5)Ace_2)	0.89	+30.1 (*c* 1.22)	−30.0 (*c* 0.60)
20 (I(1,2)P''_2(3,6)Bn_2(4,5)Ace)	1.81, 0.93	−13.0 (*c* 1.83)	+12.4 (*c* 1.83)
21 (I(3,6)P'_2(1,2:4,5)Ace_2)	0.86, 0.72	−3.3 (*c* 1.27)	+3.0 (*c* 1.40)
22 (I(2,6)P'_2(1,3:4,5)MOM_4)	1.63, 0.24	+9.9 (*c* 0.57)	−10.0 (*c* 0.77)
23 (I(4,5)P''_2(3)Bz(6)Bn(1,2)Ace)	0.93, 0.63	+18.9 (*c* 1.49)	−20.1 (*c* 1.47)
24 (I(3,4)P''_2(5)Bz(6)Bn(1,2)Ace)	1.28, 0.65	−0.9 (*c* 1.40)	+0.6 (*c* 1.56)
25 (I(3,5)P''_2(4)Bz(6)Bn(1,2)Ace)	1.02, 0.42	+6.7 (*c* 1.37)	−6.4 (*c* 1.69)

P′, $PO(OEt)_2$; P″, $PO(OBn)_2$.

In conclusion, we have synthesized all optically active *myo*-inositol mono- and bisphosphate regioisomers by application of the divergent as well as specific synthetic methods at the level of various intermediates as described herein, and now reported the complete syntheses of all possible 63 (15 meso and 24 enantiomeric pairs) regioisomers of *myo*-inositol phosphates.



Scheme 5: a. (i) Dibenzyl disopropylphosphoramidite, 1H-tetrazole, (ii) mCPBA; b. (i) H_2, 10% Pd-C, AcOH, (ii) pH 10 (1N NaOH); c. (i) diethyl phosphorochloridite, DIPEA, (ii) 30 % H_2O_2; d. (i) TMSBr, (ii) pH 10 (1N NaOH).



D-14. D-I(3)Bz(6)Bn(1,2)Ace
D-16. D-I(5)Bz(6)Bn(1,2)Ace
D-17. D-I(4)Bz(6)Bn(1,2)Ace

D-23
D-24
D-25

D-2d. D-I(4,5)P_2
D-2e. D-I(3,4)P_2
D-2f. D-I(3,5)P_2

Scheme 6: a. (i) Dibenzyl diisopropylphosphoramidite, 1H-tetrazole, (ii) mCPBA; b. (i) H_2 10% Pd-C, AcOH, (ii) 1M LiOH, (iii) H^+ ion exchange, (iv) pH 10 (1N NaOH).

EXPERIMENTAL

General Methods

All nonhydrolytic reactions were carried out in oven-dried glassware under anhydrous nitrogen atmosphere. All commercial reagents were used as obtained without further purification. Solvents were purified and dried by standard methods prior to use. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Analytical TLC was carried out on Merck 60 F254 silica gel plate (0.25 mm thickness) and visualization was done with UV light and/or spraying with a 5% solution of phosphomolybdic acid followed by charring with a heat gun. Column chromatography was performed on Merck 60 silica gel (230–400 mesh). NMR spectra were recorded on a Bruker AM 300, DPX 300, or DRX 500 spectrometer. Tetramethylsilane and phosphoric acid (85%) were used as internal and external standards for ^{1}H NMR and ^{31}P NMR, respectively. Mass spectra (FAB) were recorded on a VG platform II system with 3-NBA and NaCl as matrices. Optical rotations were measured with a JASCO DIP-360 digital polarimeter.

General Procedure for the Preparation of the Compounds (4–17)

*(3aR,4S,7S,7aR)- and (3aR,4S,7R,7aS)-3a,4,7,7a-Tetrahydro-2,2-dimethyl-4,7-dibenzyl-1,3-bezodioxole-4,7-diol (**D-4** and **L-4**)*

To a solution of compound **D-3** (2.98 g, 16.0 mmol)[14] and NaH (4.19 g, 96.0 mmol) in THF (76 mL) at 0°C were added BnBr (5.60 mL, 48.0 mmol) and then TBAI (1.80 g, 4.8 mmol). After 30 min, the mixture was warmed to rt and stirred overnight. The mixture was diluted with EtOAc and successively washed with aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$),

concentrated, and chromatographed to give compound **D-4** (5.36 g, 91.3%) as a solid. Similarly, compound **L-4** was prepared from compound **L-3**.

D-4: R_f 0.56 (n-hexane:EtOAc, 4:1); mp. 55.5–56.5°C; $[\alpha]_D^{25}$ +49.4 (*c* 1.15, CH_2Cl_2) {lit.[14] $[\alpha]_D^{20} + 19.0$ (*c* 2.29, $CHCl_3$), lit.[16] $[\alpha]_D^{20} + 6.1$ (*c* 1.46, $CHCl_3$)}; MS(FAB) = m/z 367 $(M + H)^+$, 389 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.26 (m, 10H, Ar-H), 5.67 (s, 2H, H-5, H-6), 4.82 (d, $J = 11.8$ Hz, 2H, C**H$_A$**H$_B$Ph), 4.65 (d, $J = 11.8$ Hz, 2H, CH$_A$**H$_B$**Ph), 4.24 (dd, $J = 5.3$, 2.2 Hz, 2H, H-1, H-4), 3.63 (dd, $J = 5.3$, 2.2 Hz, 2H, H-2, H-3), 1.46 (s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 128.6, 127.4, 127.2 (Ar-H, C-5, C-6) 110.5 (**C**Me$_2$), 79.9 (2C), 76.6 (2C) [C-1, C-2, C-3, C-4], 71.3 (2C, **C**H$_2$Ph), 26.7 (2C, C**Me$_2$**).

L-4: mp. 56.0–56.5°C; $[\alpha]_D^{25}$ −51.0 (*c* 1.12, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-4**.

*D- and L-3,6-Di-O-benzyl-4,5-O-isopropylidene-myo-inositol (**D-5** and **L-5**)*

To a solution of compound **D-4** (4.93 g, 13.5 mmol) in a mixture of acetone and water (3.6:1, 215 mL) were added 4-methoxylmorpholine *N*-oxide (NMO) (9.95 g, 73.6 mmol) and then OsO_4 (~300 mg). After being stirred for 12 h at rt, the reaction mixture was quenched with 10% $NaHSO_3$, and the solvents were evaporated under reduced pressure. The crude material was dissolved in MeOH and filtered through a bed of silica gel. After removal of the solvent by evaporation, a flash column chromatography on silica gel gave compound **D-5** (4.80 g, 89.2%) as a solid. Similarly, compound **L-5** was prepared from compound **L-4**.

D-5: R_f 0.58 (n-hexane:EtOAc, 1:2); mp. 125.5–127.0°C {lit.[14] mp. 125–126°C, lit.[17] mp. 104–106°C}; $[\alpha]_D^{25}$ −43.8 (*c* 1.10, $CHCl_3$) {lit.[14] $[\alpha]_D^{20}$ −67.0 (*c* 1.02, $CHCl_3$), lit.[17] $[\alpha]_D$ −55 (*c* 1.0, $CHCl_3$)}; MS(FAB) = m/z 401 $(M + H)^+$, 423 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 10H, Ar-H), 4.89–4.66 (m, 4H, CH_2Ph), 4.10 (t, $J = 3.2$ Hz, 1H, H-2), 3.98 (t, $J = 9.9$ Hz, 1H, H-4), 3.71 (t, $J = 9.2$ Hz, 1H, H-6), 3.50 (dd, $J = 10.1$, 3.0 Hz 1H, H-3), 3.42 (dd, $J = 8.8$, 3.1 Hz, 1H, H-1), 3.29 (t, $J = 9.6$ Hz, 1H, H-5), 2.60 (br s, 2H, OHs), 1.39, 1.36 (2s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 129.2, 129.1, 128.68, 128.66 (Ar-H) 112.6 (**C**Me$_2$), 80.0, 78.8, 78.3, 76.9, 74.2, 73.7, 72.5, 71.9 (inositol ring carbons, 2**C**H$_2$Ph), 27.7 (2C, C**Me$_2$**).

L-5: mp. 126–127°C; $[\alpha]_D^{20} + 45.1$ (*c* 0.93, $CHCl_3$); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-5**.

*D- and L-1,2: 4.5-Di-O-isopropylidene-4-O-benzyl-myo-inositol (**D-7** and **L-7**), D- and L-1,2: 4.5-di-O-isopropylidene-myo-inositol (**D-8** and **L-8**)*

To a solution of **D-5** (4.60 g, 11.5 mmol) and TSA (495 mg, 2.9 mmol) in CH_2Cl_2 (230 mL) was added 2-methoxypropene (5.5 mL, 57.5 mmol) by syringe. After being stirred for 1 h at rt, the reaction mixture was quenched with triethylamine (0.4 mL), diluted with EtOAc, and successively washed

with aq $NaHCO_3$ and brine. Concentration of organic layer gave a crystalline solid, compound **D-6** (5.03 g, 99.4%). A mixture of the compound **D-6** (4.66 g, 10.6 mmol), Pd on charcoal (10%, 2.80 g), $NaHCO_3$ (470 mg), and THF (100 mL) was hydrogenated (1 atm) at rt. After 3 d, the catalyst was filtered off through Celite and washed with CH_2Cl_2. The filtrate was evaporated, and the residue was chromatographed on silica gel to give the major **D-7** (2.0 g, 53.8%), the minor **D-8** (320 mg, 11.6%), and the starting material **D-6** (1.35 g, 28.9%). Similarly, compounds **L-7** and **L-8** were prepared from compound **L-5**.

D-7: R_f 0.45 (n-hexane:EtOAc, 1:1); mp. 131–132°C; $[\alpha]_D^{25}$ −72.3 (*c* 0.74, $CHCl_3$); MS(FAB) = *m/z* 351 $(M+H)^+$, 373 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H, Ar-H), 4.80 (s, 2H, C**H$_2$**Ph), 4.44 (t, *J* = 4.8 Hz, 1H, H-2), 4.17 (t, *J* = 5.7 Hz, 1H, H-1), 3.97 (dd, *J* = 10.1, 4.5 Hz, 1H, H-3), 3.76 (t, *J* = 9.7 Hz, 1H, H-4), 3.66 (dd, *J* = 10.5, 6.2 Hz, 1H, H-6), 3.39 (t, *J* = 9.9 Hz, 1H, H-5), 1.46, 1.44, 1.37, 1.34 (4s, 12H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 127.8, 127.1 (Ar-H), 111.9, 109.5 (**C**Me_2), 81.2, 79.8, 77.4, 77.2, 71.5, 69.3 (inositol ring carbons, **C**H_2Ph), 27.31, 26.53 (2C), 25.41 [C**Me$_2$**].

D-8: R_f 0.40 (EtOAc); mp. 166.0–167.5°C {lit.[18] mp. 169–170°C}; $[\alpha]_D^{25}$ −40.1 (*c* 0.95, CH_2Cl_2) {lit.[18] $[\alpha]_D$ −41.7 (*c* 1.58, CH_2Cl_2)}; MS(FAB) = *m/z* 261 $(M+H)^+$, 283 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.46 (t, *J* = 4.8 Hz, 1H, H-2), 4.06 (t, *J* = 5.8 Hz, 1H, H-1), 4.02 (dd, *J* = 10.5, 4.3 Hz, 1H, H-3), 3.88 (dd, *J* = 10.7, 6.4 Hz, 1H, H-6), 3.82 (t, *J* = 9.8 Hz, 1H, H-4), 3.31 (t, *J* = 10.0 Hz, 1H, H-5), 1.52, 1.46, 1.44, 1.36 (4s, 12H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.7, 110.3 (**C**Me_2), 81.9, 78.0, 77.6, 75.0, 71.5, 70.0 (inositol ring carbons), 28.1, 26.9 (2C), 25.4 [C**Me$_2$**].

L-7: mp. 131.5–133.0°C {lit.[15] mp. 132–134°C}; $[\alpha]_D^{25}$ +74.0 (*c* 1.11, $CHCl_3$) {lit.[15] $[\alpha]_D^{25}$ +66.5 (*c* 1.0, $CHCl_3$)}; R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-7**.

L-8: mp. 167.0–167.5°C; $[\alpha]_D^{25}$ +38.9 (*c* 0.93, $CHCl_3$); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-8**.

*D- and L-2-O-Benzoyl-6-O-benzyl-myo-inositol (**D-9** and **L-9**)*

Compound **D-7** (300 mg, 0.86 mmol) in 80% aq AcOH (85 mL) was heated at reflux for 5 h and evaporated to dryness to give a crude product. To a solution of crude product (60.0 mg, 0.22 mmol) and triethyl orthobenzoate (77.8 mL, 0.44 mmol) in DMF (1.8 mL) at rt was added TSA (2.0 mg, 11.1 μmol). After being stirred for 4 h at rt, the reaction was quenched with a few drops of 80% aq AcOH, and the solvents were removed under a stream of N_2. The product mixture was chromatographed to give compound **D-9** (58.9 mg, 70.9%). Similarly, compound **L-9** was prepared from compound **L-7**.

D-9: R_f 0.23 (EtOAc); mp. 135–137°C; $[\alpha]_D^{25}$ +62.6 (*c* 0.82, MeOH); MS(FAB) = *m/z* 375 $(M+H)^+$; ^{1}H NMR (300 MHz, CD_3OD): δ 8.06–7.21 (m, 10H, Ar-H), 5.66 (t, *J* = 2.7 Hz, 1H, H-2) 4.88 (d, *J* = 10.8 Hz, 1H, C**H$_A$**H$_B$Ph), 4.82 (d, *J* = 10.8 Hz, 1H, CH$_A$**H$_B$**Ph), 3.78 (dd, *J* = 9.8, 2.8 Hz,

1H, H-1), 3.73 (t, $J = 9.7$ Hz, 1H, H-6), 3.68 (t, $J = 9.4$ Hz, 1H, H-5), 3.61 (dd, $J = 9.9$, 2.7,Hz 1H, H-3), 3.42 (t, $J = 9.1$ Hz, 1H, H-4); ^{13}C NMR (75 MHz, CD_3OD): δ 167.9 (**C**OPh), 140.5, 134.3, 132.0, 130.9, 129.6, 129.4, 129.3, 128.7 (Ar-H), 83.5, 77.1, 76.7, 76.3, 75.1, 72.0, 71.9 (inositol ring carbons, **C**H_2Ph).

L-9: mp. 134.0–135.5°C; $[\alpha]_D^{25}$ −59.6 (*c* 0.78, MeOH); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-9**.

*D- and L-2-O-Benzoyl-6-O-benzyl-1,3,4,5-tetra-O-methoxymethyl-myo-inositol (**D-10** and **L-10**)*

A mixture of the compound **D-9** (50.0 mg, 0.13 mmol), chloromethyl methyl ether (432 μL, 5.4 mmol), DIPEA (751 μL, 5.4 mmol), and 1,2-dichloroethane (2 mL) was heated at 50°C for 12 h. The mixture was diluted with EtOAc and successively washed with aq $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), concentrated, and chromatographed to give compound **D-10** (65.2 mg, 88.7%) as a colorless oil. Similarly, compound **L-10** was prepared from compound **L-9**.

D-10: R_f 0.60 (n-hexane:EtOAc, 1:1); $[\alpha]_D^{25}$ −12.5 (*c* 0.25, CH_2Cl_2); MS(FAB) = *m/z* 551 $(M + H)^+$, 573 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06–7.26 (m, 10H, Ar-H), 5.85 (t, $J = 2.6$ Hz, 1H, H-2) 4.95–4.63 (m, 10H, C**H$_2$**Ph, OC**H$_2$**OCH_3), 3.98 (t, $J = 9.7$ Hz, 1H, H-4), 3.87 (t, $J = 9.6$ Hz, 1H, H-5), 3.77 (dd, $J = 10.0$, 2.6 Hz, 1H, H-3), 3.69 (dd, $J = 10.0$, 2.6 Hz, 1H, H-1), 3.60 (t, $J = 9.3$ Hz, 1H, H-6), 3.43, 3.40, 3.38, 3.31 (4s, 12H, OCH_2OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5 (**C**OPh), 139.0, 133.9, 130.7, 130.6, 129.2, 129.0, 128.3 (Ar-H), 99.5, 99.2, 96.6, 96.4 (O**C**H_2OCH_3), 81.6, 80.2, 78.7, 76.4, 75.6, 75.4, 70.4 (inositol ring carbons, **C**H_2Ph), 57.4, 57.1, 56.7, 56.6 (OCH_2O**C**H_3).

L-10: $[\alpha]_D^{25}$ +12.4 (*c* 0.20, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-10**.

*D- and L-1,3,4,5-Tetra-O-methoxymethyl-myo-Inositol (**D-11** and **L-11**)*

A mixture of the compound **D-10** (58.0 mg, 0.11 mmol), $Pd(OH)_2$ on charcoal (20%, 58 mg), and EtOH (1.5 mL) was hydrogenated (45 psi) at rt overnight. The catalyst was filtered off through Celite and washed with CH_2Cl_2, and the filtrate was evaporated. To a solution of the residue in MeOH (1 mL) was added NaOMe (25% solution in MeOH, 2.4 μL, 11.0 μmol). After being stirred for 19 h at rt, the solution was concentrated and chromatographed to afford compound **D-11** (31.9 mg, 85.0%) as an oil. Similarly, compound **L-11** was prepared from compound **L-10**.

D-11: R_f 0.15 (EtOAc), 0.31 (CH_2Cl_2:MeOH, 9:1); $[\alpha]_D^{25}$ +29.0 (*c* 0.65, $CHCl_3$); MS(FAB) = *m/z* 357 $(M + H)^+$, 379 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.87–4.74 (m, 8H, OC**H$_2$**OCH_3), 4.21 (t, $J = 2.6$ Hz, 1H, H-2), 3.94 (t, $J = 9.6$ Hz, 1H, H-4), 3.89 (t, $J = 9.3$ Hz, 1H, H-5), 3.52–3.40 (m, 14H, OCH_2OC**H$_3$**, H-1, H-3), 3.24 (t, $J = 9.2$ Hz, 1H, H-6); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 99.4, 98.9, 97.2 (2C) [O**C**H_2OCH_3], 86.0, 77.9, 77.0, 71.8, 70.6 (inositol ring carbons), 56.82, 56.78, 56.52, 56.45 (OCH_2O**C**H_3).

L-11: $[\alpha]_D^{25}$ −28.4 (*c* 1.10, $CHCl_3$); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-11**.

*D- and L-1,2: 4.5-Di-O-isopropylidene-3-O-benzoyl-6-O-benzyl-myo-inositol (**D-12** and **L-12**)*

Benzoylation of compound **D-7** (1.0 g, 2.85 mmol) was carried out with BzCl (1.67 mL, 14.3 mmol) and DMAP (35.6 mg, 0.29 mmol) in pyridine (50 mL). After being stirred for 6 h at rt, the reaction mixture was treated with water (10 mL) for 30 min, diluted with EtOAc, and washed with aq $NaHCO_3$ and brine. The organic layer was separated, dried ($MgSO_4$), and concentrated to give a solid product, which was chromatographed to give compound **D-12** (1.27 g, 97.7%). Similarly, compound **L-12** was prepared from compound **L-7**.

D-12: R_f 0.86 (n-hexane:EtOAc, 1:1); mp. 158.0–159.5°C; $[\alpha]_D^{25}$ +13.2 (*c* 1.26, CH_2Cl_2); MS(FAB) = *m/z* 455 $(M+H)^+$, 477 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–7.24 (m, 10H, Ar-H), 5.31 (dd, *J* = 10.6, 4.4 Hz, 1H, H-3), 4.84 (s, 2H, C**H$_2$**Ph), 4.70 (t, *J* = 4.7 Hz, 1H, H-2), 4.23 (t, *J* = 5.6 Hz, 1H, H-1), 4.16 (t, *J* = 10.0 Hz, 1H, H-4), 3.74 (dd, *J* = 10.5, 6.3 Hz, 1H, H-6), 3.56 (t, *J* = 10.0 Hz, 1H, H-5), 1.48, 1.44, 1.36, 1.26 (4s, 12H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (**C**OPh), 137.6, 132.8, 129.6, 129.2, 127.9, 127.8, 127.6, 127.1 (Ar-H), 112.1, 109.6 (**C**Me_2), 80.7, 79.3, 78.4, 74.8, 74.2, 71.6, 71.0 (inositol ring carbons, **C**H_2Ph), 27.4, 26.6, 26.5, 25.4 (C**Me$_2$**).

L-12: mp. 159–161°C; $[\alpha]_D^{25}$ −13.8 (*c* 0.55, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR were identical to those of **D-12**.

*D- and L-1,2: 4.5-Di-O-isopropylidene-3-O-benzoyl-myo-inositol (**D-13** and **L-13**)*

A mixture of the compound **D-12** (136 mg, 0.30 mmol), Pd on charcoal (10%, 274 mg), $NaHCO_3$ (6 mg), and EtOH (3 mL) was hydrogenated (45 psi) at rt. After 1 d, the catalyst was filtered off through Celite and washed with CH_2Cl_2. The filtrate was evaporated, and the residue was chromatographed on silica gel to give compound **D-13** (90.0 mg, 82.0%). Similarly, compound **L-13** was prepared from compound **L-12**.

D-13: R_f 0.52 (n-hexane:EtOAc, 1:1); mp. 183–185°C {lit.[19] mp. 183–184°C}; $[\alpha]_D^{25}$ +35.7 (*c* 0.30, CH_2Cl_2); MS(FAB) = *m/z* 365 $(M+H)^+$, 387 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12–7.41 (m, 5H, Ar-H), 5.35 (dd, *J* = 10.6, 4.3 Hz, 1H, H-3), 4.72 (t, *J* = 4.6 Hz, 1H, H-2), 4.19 (t, *J* = 10.0 Hz, 1H, H-4), 4.11 (t, *J* = 5.7 Hz, 1H, H-1), 3.96 (dd, *J* = 10.7, 6.6 Hz, 1H, H-6), 3.48 (t, *J* = 10.0 Hz, 1H, H-5), 1.60, 1.52, 1.49, 1.23 (4s, 12H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8 (**C**OPh), 134.0, 130.8, 129.2 (Ar-H), 113.6, 111.1 (**C**Me_2), 82.5, 79.1, 76.0, 75.5, 75.2, 71.6 (inositol ring carbons), 28.9, 27.7, 27.5, 26.5 (C**Me$_2$**).

L-13: mp. 184–185°C; $[\alpha]_D^{25}$ –37.2 (*c* 0.92, CH_2Cl_2); R_f, MS(FAB), ^1H NMR, ^{13}C NMR were identical to those of **D-13**.

*D- and L-1,2-O-Isopropylidene-3-O-benzoyl-6-O-benzyl-myo-inositol (**D-14** and **L-14**)*

Compound **D-12** (640 mg, 1.41 mmol) and TSA (34.4 mg, 0.28 mmol) in a mixed solvent (MeOH:CH_2Cl_2 = 1:5, 20 mL) were stirred at 0°C for 15 h. The reaction mixture was treated with aq $NaHCO_3$, concentrated under reduced pressure, and chromatographed to give compound **D-14** (400 mg, 68.5%) and a minor product, compound **D-15** (133 mg, 25.1%). Similarly, compound **L-14** was prepared from compound **L-12**.

D-14: R_f 0.34 (n-hexane:EtOAc, 1:1); mp. 190.0–191.5°C; $[\alpha]_D^{25}$ +32.2 (*c* 1.50, CH_2Cl_2); MS(FAB) = *m/z* 415 $(M+H)^+$, 437 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–7.24 (m, 10H, Ar-H), 5.22 (dd, J = 9.3, 3.9 Hz, 1H, H-3), 4.97 (d, J = 11.5 Hz, 1H, C$\mathbf{H_A}$$H_B$Ph), 4.68 (d, J = 11.5 Hz, 1H, $CH_A$$\mathbf{H_B}$Ph), 4.56 (t, J = 4.6 Hz, 1H, H-2), 4.24 (t, J = 6.0 Hz, 1H, H-1), 4.07 (t, J = 9.1 Hz, 1H, H-4), 3.61 (dd, J = 9.8, 7.0 Hz, 1H, H-6), 3.49 (t, J = 9.3 Hz, 1H, H-5), 1.47, 1.31 (2s, 6H, C$\mathbf{Me_2}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8 (**C**OPh), 137.5, 132.9, 129.6, 129.1, 128.0, 127.9, 127.7, 127.4 (Ar-H), 109.8 (**C**Me_2), 81.1, 78.8, 73.6, 72.9, 72.8, 71.9, 70.1 (inositol ring carbons, **C**H_2Ph), 27.5, 26.5 (C$\mathbf{Me_2}$).

D-15: R_f 0.31 (n-hexane:EtOAc, 1:2); mp. 165–167°C; $[\alpha]_D^{25}$ +27.1 (*c* 0.50, MeOH); MS(FAB) = *m/z* 375 $(M+H)^+$, 397 $(M+Na)^+$; ^1H NMR (300 MHz, CD_3OD): δ 8.12–7.23 (m, 10H, Ar-H), 3H (H-3, C$\mathbf{H_2}$Ph) disappeared behind the solvent peak around 4.8 ppm, 4.16 (t, J = 2.6 Hz, 1H, H-2), 4.02 (t, J = 9.8 Hz, 1H, H-6), 3.69 (t, J = 9.2 Hz, 1H, H-4), 3.62 (dd, J = 9.6, 2.5 Hz, 1H, H-1), 3.43 (t, J = 9.0 Hz, 1H, H-5); ^{13}C NMR (75 MHz, CD_3OD): δ 166.0 (**C**OPh), 132.3, 129.8, 129.0, 127.5, 127.31, 127.27, 126.6 (Ar-H), 81.1, 74.6, 74.5, 74.2, 71.1, 70.4, 70.2 (inositol ring carbons, **C**H_2Ph).

L-14: mp. 188.5–190.0°C; $[\alpha]_D^{25}$ –31.2 (*c* 0.99, CH_2Cl_2); R_f, MS(FAB), ^1H NMR, ^{13}C NMR were identical to those of **D-14**.

L-15: mp. 164–167°C; $[\alpha]_D^{25}$ –25.1 (*c* 0.71, MeOH); R_f, MS(FAB), ^1H NMR, ^{13}C NMR were identical to those of **D-15**.

*D- and L-1,2-O-Isopropylidene-5-O-benzoyl-6-O-benzyl-myo-inositol (**D-16** and **L-16**), D-and L-1,2-O-isopropylidene-4-O-benzoyl-6-O-benzyl-myo-inositol (**D-17** and **L-17**)*

Compound **D-14** (168 mg, 0.41 mmol) in a mixed solvent (pyridine: water = 6:4, 6 mL) was heated at 90°C for 10 h. The reaction mixture was cooled and concentrated under reduced pressure, and the crude mixture was chromatographed on silica gel to yield **D-14** (50.2 mg, 29.9%), **D-16** (40.0 mg, 23.8%), and **D-17** (70.3 mg, 41.8%). Similarly, compounds **L-16** and **L-17** were prepared from compound **L-14**.

D-16: R_f 0.41 (n-hexane:EtOAc, 1:1); mp. 159–161°C; $[\alpha]_D^{25}$ +15.9 (*c* 0.6, $CHCl_3$); MS(FAB) = *m/z* 415 $(M+H)^+$, 437 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02–7.24 (m, 10H, Ar-H), 5.08 (t, $J = 7.6$ Hz, 1H, H-5), 4.75 (s, 2H, C**H$_2$**Ph), 4.47 (dd, $J = 6.2$, 3.7 Hz, 1H, H-2), 4.34 (t, $J = 6.1$ Hz, 1H, H-1), 4.01 (t, $J = 8.2$ Hz, 1H, H-4), 3.92 (dd, $J = 8.9$, 3.6 Hz, 1H, H-3), 3.87 (dd, $J = 7.6$, 6.0 Hz, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (**C**OPh), 138.5, 134.0, 130.6, 130.4, 129.1, 128.9, 128.7, 128.4 (Ar-H), 110.7 (**C**Me$_2$), 79.4, 78.9, 77.6, 75.8, 73.4, 72.6, 70.7 (inositol ring carbons, **C**H$_2$Ph), 27.9, 25.8 (C**Me$_2$**).

D-17: R_f 0.65 (n-hexane:EtOAc, 1:2); mp. 162–163°C; $[\alpha]_D^{25}$ +8.9 (*c* 2.0, $CHCl_3$); MS(FAB) = *m/z* 415 $(M+H)^+$, 437 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 8.07–7.28 (m, 10H, Ar-H), 4.95 (dd, $J = 6.1$, 4.1 Hz, 1H, H-2), 4.86 (d, $J = 11.6$ Hz, 1H, C**H$_A$**H$_B$Ph), 4.69 (d, $J = 11.6$ Hz, 1H, CH$_A$**H$_B$**Ph), 4.33 (t, $J = 6.1$ Hz, 1H, H-1), 4.04 (dd, $J = 8.9$, 4.0 Hz, 1H, H-3), 3.83–3.74 (m, 2H, H-5, H-6), 1.55, 1.38 (2s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8 (**C**OPh), 138.5, 133.9, 130.6, 130.4, 129.2, 129.1, 128.8, 128.7 (Ar-H), 110.9 (**C**Me$_2$), 81.8, 78.7, 77.0, 76.3, 73.9, 73.2, 69.7 (inositol ring carbons, **C**H$_2$Ph), 28.0, 25.9 (C**Me$_2$**).

L-16: mp. 158–160°C; $[\alpha]_D^{25}$ −15.9 (*c* 1.90, $CHCl_3$); R_f, MS(FAB), ^1H NMR, ^{13}C NMR were identical to those of **D-16**.

L-17: mp. 159–160°C; $[\alpha]_D^{25}$ −9.6 (*c* 0.88, $CHCl_3$); R_f, MS(FAB), ^1H NMR, ^{13}C NMR were identical to those of **D-17**.

General Procedure for the Preparation of the Compounds (18–25)

Phosphorylation Method A

To a solution of each regioisomer and 1H-tetrazole (10 eq) in a mixed solvent (DMF:CH_2Cl_2 = 1:1) at rt was added dibenzyl diisopropyl-phosphoramidite (6 eq). After 7 h, an excess amount of mCPBA (20 eq) was added to the mixture at 0°C. After being stirred overnight at rt, the mixture was diluted with CH_2Cl_2 and washed with aq Na_2SO_3, aq $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed to give phosphorylated regioisomers in 71% to 82% yields.

Method B

To a solution of each regioisomer in DMF at −42°C were added dropwise DIPEA (30 eq) and then diethyl phosphorochloridite (11 eq) with vigorous stirring. After 20 min, the reaction mixture was allowed to slowly warm up to rt and stirred for additional 5 h. The mixture was cooled in an ice bath and sodium phosphate buffer (1 M, pH 7) and excess 30% H_2O_2 were added. After standing overnight at rt, the mixture was diluted with EtOAc and

washed with water and brine. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed to give phosphorylated regioisomers in 70% to 85% yields.

*D- and L-1,2: 4.5-Di-O-isopropylidene-4-O-benzyl-myo-inositol 3-mono(dibenzyl-phosphate) (**D-18** and **L-18**)*

Compounds **D-18** and **L-18** were prepared from **D-7** and **L-7**, respectively, by the method A.

D-18: R_f 0.43 (n-hexane:EtOAc, 2:1); mp. 130–132°C; $[\alpha]_D^{25}$ −22.8 (*c* 1.10, CH_2Cl_2); MS(FAB) = *m/z* 611 $(M+H)^+$, 633 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.26 (m, 15H, Ar-H), 5.10–5.07 (m, 4H, POC**H$_2$**Ph), 4.80 (s, 2H, OC**H$_2$**Ph), 4.72 (m, 1H, H-3), 4.55 (t, $J = 4.5$ Hz, 1H, H-2), 4.13 (t, $J = 5.5$ Hz, 1H, H-1), 4.02 (t, $J = 9.8$ Hz, 1H, H-4), 3.67 (dd, $J = 10.6$, 6.3 Hz, 1H, H-6), 3.43 (t, $J = 10.0$ Hz, 1H, H-5), 1.44, 1.41, 1.36, 1.24 (4s, 12H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 135.3, 135.2, 128.0, 127.8, 127.5, 127.4, 127.1 (Ar-H), 112.1, 109.7 (**C**Me_2), 81.1, 79.2, 78.0, 76.2, 74.8, 74.1, 71.6 (inositol ring carbons, **C**H_2Ph), 69.1, 68.8 (PO**C**H_2Ph), 27.4, 26.5 (2C), 25.4 [C**Me$_2$**]; ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.63.

L-18: mp. 129.0–130.5°C; $[\alpha]_D^{25}$ +20.8 (*c* 0.50, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-18**.

*D- and L-1,2: 4.5-Di-O-isopropylidene-3-O-benzoyl-myo-inositol 6-mono(diethyl-phosphate) (**D-19** and **L-19**)*

Compounds **D-19** and **L-19** were prepared from **D-13** and **L-13**, respectively, by the method B.

D-19: R_f 0.25 (n-hexane:EtOAc, 1:1); mp. 216–218°C; $[\alpha]_D^{25}$ +30.1 (*c* 1.20, CH_2Cl_2); MS(FAB) = *m/z* 501 $(M+H)^+$, 523 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11–7.41 (m, 5H, Ar-H), 5.33 (dd, $J = 10.6$, 4.2 Hz, 1H, H-3), 4.70 (t, $J = 4.5$ Hz, 1H, H-2), 4.67–4.58 (m, 1H, H-6), 4.25–4.12 (m, 6H, POC**H$_2$**Ph, H-1, H-4), 3.57 (t, $J = 10.1$ Hz, 1H, H-5), 1.57, 1.47, 1.42, 1.28 (4s, 12H, C**Me$_2$**), 1.36–1.31 (m, 6H, OCH_2C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (**C**OPh), 132.9, 129.6, 128.9, 127.9 (Ar-H), 112.5, 110.2 (**C**Me_2), 79.7, 78.9, 76.9, 74.8, 74.2, 70.5 (inositol ring carbons), 63.5, 63.4 (O**C**H_2CH_3), 27.4, 26.5, 26.4, 25.5 (C**Me$_2$**), 15.6, 15.5 (OCH_2**C**H_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.89.

L-19: mp. 218–219°C; $[\alpha]_D^{25}$ −30.0 (*c* 0.60, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-19**.

*D- and L-3,6-Di-O-benzyl-4,5-O-isopropylidene-myo-inositol 1,2,-bis(dibenzyl-phosphate) (**D-20** and **L-20**)*

Compounds **D-20** and **L-20** were prepared from **D-5** and **L-5**, respectively, by the method A.

D-20: R_f 0.54 (n-hexane:EtOAc, 1:1); $[\alpha]_D^{25}$−13.0 (*c* 1.83, CH_2Cl_2); MS(FAB) = *m/z* 921 $(M+H)^+$, 943 $(M+Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.43–7.15 (m, 30H, Ar-H), 5.36 (d, $J = 9.4$ Hz, 1H, H-1), 5.13 (d, $J = 6.9$ Hz, 2H, C**H$_2$**Ph), 5.04–4.81 (m, 8H, C**H$_2$**Ph), 4.68 (t, $J = 10.6$ Hz, 2H, OC**H$_2$**Ph), 4.46 (t, $J = 9.0$ Hz, 1H, H-2), 3.98 (t, $J = 9.4$ Hz, 1H, H-4), 3.95 (t, $J = 9.4$ Hz, 1H, H-5), 3.68 (d, $J = 10.2$ Hz, 1H, H-3), 3.45 (t, $J = 9.6$ Hz, 1H, H-6), 1.49, 1.46 (2s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5–127.1 (Ar-H), 111.9 (**C**Me$_2$), 78.7, 76.3, 75.3, 74.5, 72.3, 71.2 (inositol ring carbons), 69.0, 68.94, 68.88, 68.81, 68.80, 68.7 (O**C**H$_2$Ph), 29.5 (2C, C**Me$_2$**); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.81, 0.93.

L-20: $[\alpha]_D^{25}$ +12.4 (*c* 1.83, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-20**.

*D- and L-1,2: 4.5-Di-O-isopropylidene-myo-inositol 3,6-bis(diethylphosphate) (**D-21** and **L-21**)*

Compounds **D-21** and **L-21** were prepared from **D-8** and **L-8**, respectively, by the method B.

D-21: R_f 0.57 (EtOAc); $[\alpha]_D^{25}$–3.3 (*c* 1.27, CH_2Cl_2); MS(FAB) = *m/z* 533 $(M + H)^+$, 555 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76–4.71 (m, 1H, H-6), 4.58–4.53 (m, 2H, H-1, H-3), 4.16–4.12 (m, 9H, OC**H$_2$**CH$_3$, H-2), 4.03 (t, $J = 9.8$ Hz, 1H, H-4), 3.42 (t, $J = 9.8$ Hz, 1H, H-5), 1.57–1.22 (m, 24H, OCH$_2$C**H$_3$**, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.3, 110.1 (**C**Me$_2$), 79.62, 79.57, 78.7, 74.9, 74.8, 73.3 (inositol ring carbons), 63.8, 63.6, 63.4 (2C) [O**C**H$_2$CH$_3$], 27.7, 26.41, 26.37, 25.4 (C**Me$_2$**), 15.5 (2C), 15.49 (2C) [OCH$_2$**C**H$_3$]; ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.86, 0.72.

L-21: $[\alpha]_D^{25}$ +3.0 (*c* 1.40, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-21**.

*D- and L-1,3,4,5-Tetra-O-methoxymethyl-myo-inositol 2,6-bis(diethylphosphate) (**D-22** and **L-22**)*

Compounds **D-22** and **L-22** were prepared from **D-11** and **L-11**, respectively, by the method B.

D-22: R_f 0.06 (EtOAc), 0.39 (CH_2Cl_2:MeOH, 9:1); $[\alpha]_D^{25}$ +9.9 (*c* 0.57, CH_2Cl_2); MS(FAB) = *m/z* 629 $(M + H)^+$, 651 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95–4.55 (m, 10H, OC**H$_2$**OCH$_3$), 4.15–4.05 (m, 9H, OC**H$_2$**CH$_3$, H-3), 3.87 (t, $J = 9.8$ Hz, 1H, H-1), 3.59–3.40 (m, 14H, OCH$_2$C**H$_3$**, H-5, H-6), 1.27 (t, $J = 6.3$ Hz, 12H, OCH$_2$C**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.3, 97.9, 95.8, 95.2 (O**C**H$_2$OCH$_3$), 78.2, 77.9, 75.4, 74.5, 73.4, 73.0 (inositol ring carbons), 63.54, 63.50, 63.4, 63.3 (O**C**H$_2$CH$_3$), 56.3, 55.9, 55.8, 55.6 (OCH$_2$OC**H$_3$**), 15.8, 15.6, 15.55, 15.49 (OCH$_2$**C**H$_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.63, 0.24.

L-22: $[\alpha]_D^{25}$ –10.0 (*c* 0.77, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-22**.

*D- and L-1,2-O-Isopropylidene-3-O-benzoyl-6-O-benzyl-myo-inositol 4,5-bis(dibenzylphosphate) (**D-23** and **L-23**)*

Compounds **D-23** and **L-23** were prepared from **D-14** and **L-14**, respectively, by the method A.

D-23: R_f 0.30 (n-hexane:EtOAc, 1:1); $[\alpha]_D^{25} + 18.9$ (*c* 1.49, CH_2Cl_2); MS(FAB) = *m/z* 935 $(M + H)^+$, 957 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13–6.93 (m, 30H, Ar-H), 5.60 (dd, $J = 9.5$, 3.6 Hz, 1H, H-3), 5.31–4.64 (m, 13H, C**H$_2$**Ph, H-2, H-3, H-4), 4.41 (t, $J = 5.7$ Hz, 1H, H-1), 4.10 (dd, $J = 9.7$, 5.9 Hz, 1H, H-6), 1.47, 1.28 (2s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (**C**OPh), 137.0–127.1 (Ar-H), 109.9 (**C**Me_2), 79.2, 77.2, 76.4, 76.1, 72.6, 72.0 (inositol ring carbons), 69.3, 69.1, 68.9 (2C), 68.7 (2C) [O**C**H_2Ph], 26.0, 24.0 (C**Me$_2$**); ^{31}P NMR (121 MHz, $CDCl_3$): δ 0.93, 0.63.

L-23: $[\alpha]_D^{25}$ −20.1 (*c* 1.47, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-23**.

*D- and L-1,2-O-Isopropylidene-5-O-benzoyl-6-O-benzyl-myo-inositol 3,4-bis(dibenzylphosphate) (*D-24 *and* L-24*)*

Compounds **D-24** and **L-24** were prepared from **D-16** and **L-16**, respectively, by the method A.

D-24: R_f 0.41 (n-hexane:EtOAc, 1:1); $[\alpha]_D^{25}$ −0.9 (*c* 1.4, CH_2Cl_2); MS(FAB) = *m/z* 935 $(M + H)^+$, 957 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06–6.91 (m, 30H, Ar-H), 5.40 (t, $J = 7.2$ Hz, 1H, H-5), 5.27–4.71 (m, 12H, C**H$_2$**Ph, H-2, H-3), 4.57 (dd, $J = 11.7$, 8.4 Hz, 1H, H-4), 4.30 (t, $J = 5.6$ Hz, 1H, H-1), 3.81 (t, $J = 5.9$ Hz, 1H, H-6), 1.51, 1.26 (2s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2 (**C**OPh), 132.7–127.1 (Ar-H), 110.0 (**C**Me_2), 77.0, 76.9, 74.7, 73.7, 73.5, 73.3, 72.1 (inositol ring carbons, O**C**H_2Ph), 69.1, 69.0, 68.8, 60.6 (PO**C**H_2Ph), 26.6, 24.4 (C**Me$_2$**); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.28, 0.65.

L-24: $[\alpha]_D^{25}$ +0.57 (*c* 1.56, CH_2Cl_2); R_f, MS(FAB), ^{1}H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **D-24**.

*D- and L-1,2-O-Isopropylidene-4-O-benzoyl-6-O-benzyl-myo-inositol 3,5-bis(dibenzylphosphate) (**D-25** and **L-25**)*

Compounds **D-25** and **L-25** were prepared from **D-17** and **L-17**, respectively, by the method A.

D-25: R_f 0.40 (n-hexane:EtOAc, 1:2); $[\alpha]_D^{25}$ +6.7 (*c* 1.37, CH_2Cl_2); MS(FAB) = *m/z* 935 $(M + H)^+$, 957 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–6.89 (m, 30H, Ar-H), 5.94 (t, $J = 9.2$ Hz, 1H, H-4), 5.00–4.60 (m, 13H, C**H$_2$**Ph, H-2, H-3, H-5), 4.32 (t, $J = 5.5$ Hz, 1H, H-1), 3.92 (t, $J = 6.1$ Hz, 1H, H-6), 1.52, 1.27 (2s, 6H, C**Me$_2$**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1 (**C**OPh), 137.0–126.9 (Ar-H), 110.2 (**C**Me_2), 78.6, 77.5, 77.2, 73.9, 73.0, 72.4, 70.3 (inositol ring carbons, O**C**H_2Ph), 69.1, 69.0, 68.72, 68.65 (PO**C**H_2Ph), 26.7, 24.7 (C**Me$_2$**); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.02, 0.42.

L-25: $[\alpha]_D^{25}$ −6.4 (*c* 1.69, CH_2Cl_2); R_f, MS(FAB), ^1H NMR, ^{13}C NMR, ^{31}P NMR were identical to those of **L-25**.

General Procedure for the Preparation of the *myo*-Inositol mono- (1) and bisphosphates (2)

*Sodium Salt of D-myo-Inositol 3-Monophosphate (**D-1a**)*

A mixture of compound **D-18** (50.0 mg, 82.0 μmol), Pd on charcoal (10%, 25 mg), and one drop of AcOH in a mixed solvent (EtOH:MeOH = 1:1, 3 mL) was hydrogenated (50 psi) at rt. After 1 d, the catalyst was filtered off on the short pad of Celite and silica gel and the solvent was evaporated under reduced pressure. The reaction mixture was redissolved in a small amount of water and the pH was adjusted to 10 by 1N NaOH and lyophilized to give the sodium salt of D-I(3)P_1 (**D-1a**) as a white powder in approximately 80% yield.

^1H NMR (300 MHz, D_2O, pH 10): δ 4.07 (t, J = 2.5 Hz, 1H, H-2), 3.82 (dt, J = 9.2, 2.7 Hz 1H, H-3), 3.56 (t, J = 9.6 Hz, 1H, H-4), 3.46 (t, J = 9.5 Hz, 1H, H-6), 3.14 (t, J = 9.3 Hz, 1H, H-5); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 6.73.

*Sodium Salt of L-myo-Inositol 3-Monophosphate (**L-1a**)*

Deprotection of **L-18** (28.5 mg, 49.1 μmol) according to the procedures described for **D-1a** gave L-I(3)P_1 (**L-1a**) as a white powder in approximately 80% yield.

^1H NMR, ^{31}P NMR were identical to those of **D-1a**.

*Sodium Salt of D-myo-Inositol 6-monophosphate (**D-1b**)*

To a solution of **D-19** (50.0 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) at rt was added excess bromotrimethylsilane (1 mL), and the solution was stirred overnight. The solvent and excess reagent were evaporated and the residue was redissolved in MeOH (5 mL) and then treated with drops of water at 0°C. After standing at rt for 10 min, the reaction mixture was evaporated to dryness, treated with 1 M LiOH (3 mL), and stirred at 80°C for 3 h. The basic solution was cooled and loaded on Dowex 50WX8-100 (H^+ form) and eluted with water. The acidic effluent was collected, washed with CH_2Cl_2 three times, and lyophilized to dryness. The residue was redissolved in a small amount of water (1 mL), the pH was adjusted to 10 with 1N NaOH, and the residue was lyophilized again to give sodium salts of D-I(6)P_1 (**D-1b**) as a white powder in approximately 80% yield.

^1H NMR (300 MHz, D_2O, pH 10): δ 3.93 (q, J = 10.5 Hz, 1H, H-6), 3.85 (s, 1H, H-2), 3.59–3.33 (m, 3H, H-1, H-3, H-4), 3.21 (t, J = 9.2 Hz, 1H, H-5); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.19.

*Sodium Salt of L-myo-Inositol 6-Monophosphate (**L-1b**)*

Deprotection of **L-19** (15.5 mg, 31 μmol) according to the procedures described for **D-1b** gave L-I(6)P_1 (**L-1b**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-1b**.

*Sodium Salt of D-myo-Inositol 1,2-Bisphosphate (**D-2a**)*

Deprotection of **D-20** (40.0 mg, 43.4 μmol) according to the procedures described for **D-1a** gave D-I(1,2)P_2 (**D-2a**) as a white powder in approximately 80% yield.

^{1}H NMR (300 MHz, D_2O, pH 10): δ 4.44 (app d, $J = 5.9$ Hz 1H, H-2), 3.86 (t, $J = 8.9$ Hz, 1H, H-1), 3.75 (t, $J = 9.3$ Hz, 1H, H-6), 3.66 (t, $J = 9.6$ Hz, 1H, H-4), 3.32 (d, $J = 9.9$ Hz, 1H, H-3), 3.20 (t, $J = 9.2$ Hz, 1H, H-5); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.42, 7.10.

*Sodium Salt of L-myo-Inositol 1,2-Bisphosphate (**L-2a**)*

Deprotection of **L-20** (50.0 mg, 54.3 μmol) according to the procedures described for **D-1a** gave L-I(1,2)P_2 (**L-2a**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-2a**.

*Sodium Salt of D-myo-Inositol 3,6-Bisphosphate (**D-2b**)*

To a solution of **D-21** (41 mg, 77 μmol) in a CH_2Cl_2 (3 mL) at rt was added excess bromotrimethylsilane (1 mL), and the solution was stirred overnight. The solvent and excess reagent were evaporated and the residue was redissolved in MeOH (4 mL) and then treated with drops of water at 0°C. After standing at rt for 10 min, the reaction mixture was evaporated to dryness. The residue was washed with CH_2Cl_2 three times, lyophilized to dryness, and then redissolved in a small amount of water (1 mL); the pH was adjusted to 10 with 1 N NaOH, and the residue was lyophilized again to give sodium salts of D-I(3,6)P_2 (**D-2b**) as a white powder in approximately 80% yield.

^{1}H NMR (300 MHz, D_2O, pH 10): δ 4.09 (t, $J = 2.4$ Hz, 1H, H-2), 3.99 (q, $J = 8.9$ Hz, 1H, H-6), 3.79 (dt, $J = 9.0$, 2.6 Hz, 1H, H-3), 3.68 (t, $J = 9.5$ Hz, 1H, H-4), 3.53 (dd, $J = 9.7$, 2.7 Hz, 1H, H-1), 3.33 (t, $J = 9.1$ Hz, 1H, H-5); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.27, 6.77.

*Sodium Salt of L-myo-Inositol 3,6-Bisphosphate (**L-2b**)*

Deprotection of **L-21** (13.0 mg, 24 μmol) according to the procedures described for **D-2b** gave L-I(3,6)P_2 (**L-2b**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-2b**.

*Sodium Salt of D-myo-Inositol 2,6-Bisphosphate (**D-2c**)*

Deprotection of **D-22** (19.4 mg, 54 μmol) according to the procedures described for **D-2a** gave D-I(2,6)P_2 (**D-2c**) as a white powder in approximately 80% yield.

^{1}H NMR (300 MHz, D_2O, pH 10): δ 4.39 (app d, $J = 7.2$ Hz, 1H, H-2), 4.06 (q, $J = 8.7$ Hz, 1H, H-6), 3.69 (t, $J = 9.6$ Hz, 1H, H-4), 3.49 (d, $J = 9.7$ Hz, 1H, H-3), 3.35 (d, $J = 9.7$ Hz, 1H, H-3), 3.33 (t, $J = 9.3$ Hz, 1H, H-5); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.36, 7.32.

*Sodium Salt of L-myo-Inositol 2,6-Bisphosphate (**L-2c**)*

Deprotection of **L-22** (13.8 mg, 39 μmol) according to the procedures described for **D-2a** gave L-I(2,6)P_2 (**L-2c**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-2c**.

*Sodium Salt of D-myo-Inositol 4,5-Bisphosphate (**D-2d**)*

A mixture of compound **D-23** (57.0 mg, 61 μmol) and Pd on charcoal (10%, 28.5 mg) in a mixed solvent (AcOH:EtOH:MeOH = 2:1:1, 4 mL) was hydrogenated (50 psi) at rt. After 1 d, the catalyst was filtered off on the short pad of Celite and silica gel and the filtrate was evaporated under reduced pressure. The reaction mixture was treated with 1 M LiOH (6 mL) and stirred at 80°C for 3 h. The basic solution was cooled and loaded on Dowex 50WX8-100 (H^+ form) and eluted with water. The acidic effluent was collected, washed with CH_2Cl_2 three times, and lyophilized to dryness. The residue was redissolved in a small amount of water (1 mL), the pH was adjusted to 10 with 1N NaOH, and the residue was lyophilized again to give sodium salts of D-I(4,5)P_2 (**D-2d**) as a white powder in approximately 80% yield.

^{1}H NMR (300 MHz, D_2O, pH 10): δ 4.01 (q, $J = 8.6$ Hz, 1H, H-4), 3.87 (t, $J = 2.8$ Hz, 1H, H-2), 3.74–3.65 (m, 2H, H-5, H-6), 3.55 (dd, $J = 9.8$, 2.7 Hz, 1H, H-3), 3.45 (dd, $J = 9.6$, 3.6 Hz, 1H, H-1); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.46, 7.30.

*Sodium Salt of L-myo-Inositol 4,5-Bisphosphate (**L-2d**)*

Deprotection of **L-23** (44.8 mg, 48 μmol) according to the procedures described for **D-2d** gave L-I(1,6)P_2 (**L-2d**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-2d**.

*Sodium Salt of D-myo-Inositol 3,4-Bisphosphate (**D-2e**)*

Deprotection of **D-24** (65.0 mg, 69.5 μmol) according to the procedures described for **D-2d** gave D-I(3,4)P_2 (**D-2e**) as a white powder in approximately 80% yield.

^{1}H NMR (300 MHz, D_2O, pH 10): δ 4.29 (s, 1H, H-2), 4.06 (q, J = 8.7 Hz, 1H, H-4), 3.81 (dt, J = 9.7, 2.2 Hz, 1H, H-3), 3.60 (t, J = 9.7 Hz, 1H, H-6), 3.48 (dd, J = 10.0, 2.8 Hz, 1H, H-1), 3.40 (t, J = 9.0 Hz, 1H, H-5); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.58, 6.02.

Sodium Salt of L*-myo-Inositol 3,4-Bisphosphate (**L-2e**)*

Deprotection of **L-24** (45.0 mg, 48 μmol) according to the procedures described for **D-2d** gave L-I(3,4)P_2 (**L-2e**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-2e**.

Sodium Salt of D*-myo-Inositol 3,5-Bisphosphate (**D-2f**)*

Deprotection of **D-25** (39.0 mg, 41.7 μmol) according to the procedures described for **D-2d** gave D-I(3,5)P_2 (**D-2f**) as a white powder in approximately 80% yield.

^{1}H NMR (300 MHz, D_2O, pH 10): δ 4.13 (t, J = 2.7 Hz, 1H, H-2), 3.79 (dt, J = 7.3, 2.6 Hz, 1H, H-3), 3.68–3.57 (m, 3H, H-4, H-5, H-6), 3.50 (dd, J = 9.0, 2.7 Hz, 1H, H-1); ^{31}P NMR (121 MHz, D_2O, pH 10): δ 7.22, 6.48.

Sodium Salt of L*-myo-Inositol 3,5-Bisphosphate (**L-2f**)*

Deprotection of **L-25** (33.5 mg, 35.8 μmol) according to the procedures described for **D-2d** gave L-I(3,5)P_2 (**L-2f**) as a white powder in approximately 80% yield.

^{1}H NMR, ^{31}P NMR were identical to those of **D-2f**.

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