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Synthesis of all Possible Regioisomers of *scyllo*-Inositol Phosphate

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Abstract—*scyllo*-Inositol is the all equatorial stereoisomer of *myo*-inositol. All possible 12 regioisomers of *scyllo*-inositol phosphate were synthesized for the first time via a *scyllo*-inositol benzoate intermediate, which was derived from a *myo*-inositol derivative. The stereoinversion of *myo*-inositol into *scyllo*-inositol was accomplished by Mitsunobu reaction of the vicinal *cis*-diol. The requisite intermediates, *scyllo*-inositol benzoates were obtained by benzoyl migration or random benzoylation, and phosphorylated to give *scyllo*-IP_n.

Introduction

Since the discovery that D-*myo*-inositol 1,4,5-trisphosphate [I(1,4,5)P_3] acts as an important intracellular calcium mobilizing molecule in transmembrane signalling events, a number of related *myo*-inositol phosphates have been found in living systems that are also distinct bioactive ligands.[1] One of the major metabolites, D-*myo*-inositol 1,3,4,5-tetrakisphosphate [I(1,3,4,5)P_4], has been suggested to act as a second messenger mobilizing Ca^{2+} ions from extra-[2] or intracellular[3] sources. One of the binding proteins of I(1,3,4,5)P_4 was also identified as a member of the GAP1 family.[4] D-*myo*-Inositol 3,4,5,6-tetrakisphosphate was identified as a novel mediator which uncouples chloride secretion from intracellular calcium ion levels in intestinal epithelial cells.[5] *myo*-Inositol hexakisphosphate (IP_6, phytic acid), a house-keeping molecule in plant seeds and one of the oldest known *myo*-inositol phosphates, has recently shown to be a promising anticancer agent.[6–8] Among all possible 63 regioisomers (15 meso and 24 enantiomeric pairs) of *myo*-inositol phosphates (IP_1–IP_6), more than half were found in nature and prepared by various synthetic routes.[9] We previously reported the systematic and divergent syntheses of all possible optically inactive regioisomers of *myo*-inositol phosphates using the acyl migration as the key strategy[10–14] and tested them on I(1,4,5)P_3 receptors,[15–17] I(1,3,4,5)P_4 binding proteins,[18,19] I(1,4,5)P_3 3-kinase[20,21] and as an iron binding motif.[22] Although we could obtain much useful information on the structure–activity relationships (SAR) of these biomacromolecules, availability of IP_n molecules of other stereoisomers than *myo*- are highly desired in order to obtain more detailed pictures.

In this context, *scyllo*-inositol with all equatorial hydroxyl groups was chosen as our synthetic target, since it represents the simplest isomer in terms of symmetry. Although *myo*-inositol is the most abundant inositol in nature and its derivatives have been studied extensively, the occurrence of *scyllo*-inositol in animals[23,24] and in plants[25,26] has also been known. It has been suggested that a certain human disease is associated with *scyllo*-inositol depletion.[27] There are 12 regioisomers of *scyllo*-inositol phosphate: 3 enantiomeric pairs and 9 meso forms (Fig. 1). Of these 12 isomers only *scyllo*-I(1,2,4)P_3, I(1,2,4,5)P_4 and I(1,2,3,4)P_4 have previously been synthesized.[28–31] We report herein the first complete synthesis of all possible regioisomers of *scyllo*-inositol phosphates by employing the benzoyl migration strategy, which has previously been demonstrated in the synthesis of all regioisomers of *myo*-inositol phosphates.

Results and Discussion

scyllo-Inositol, in which the stereochemistry of 2-OH in *myo*-inositol is inverted to the equatorial orientation, is

Key words: *scyllo*-Inositol; inositol phosphates; Mitsunobu reaction; benzoyl migration.

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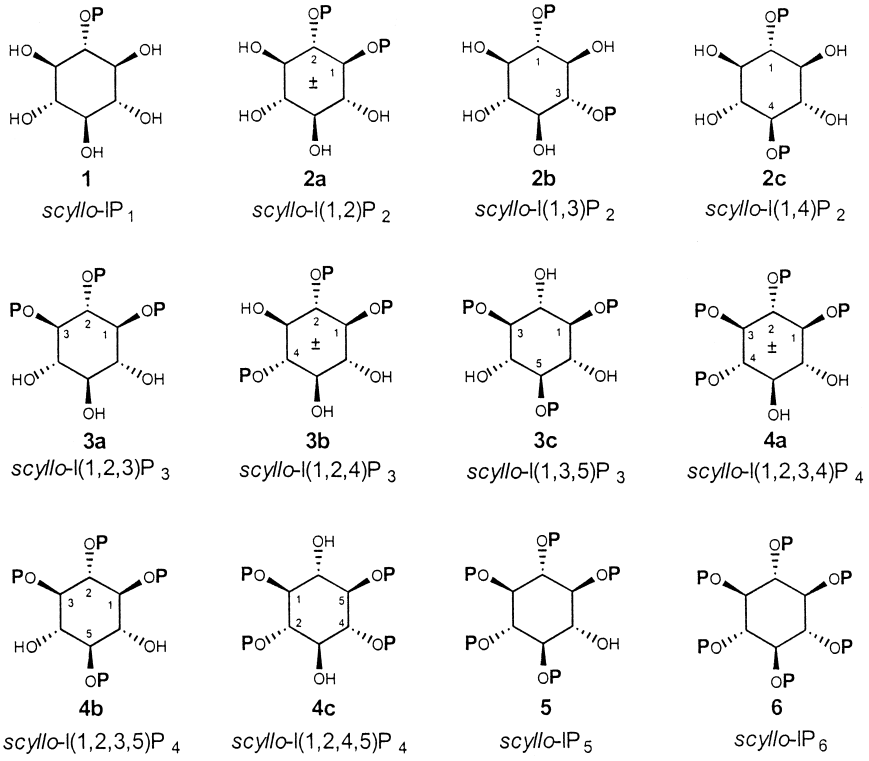
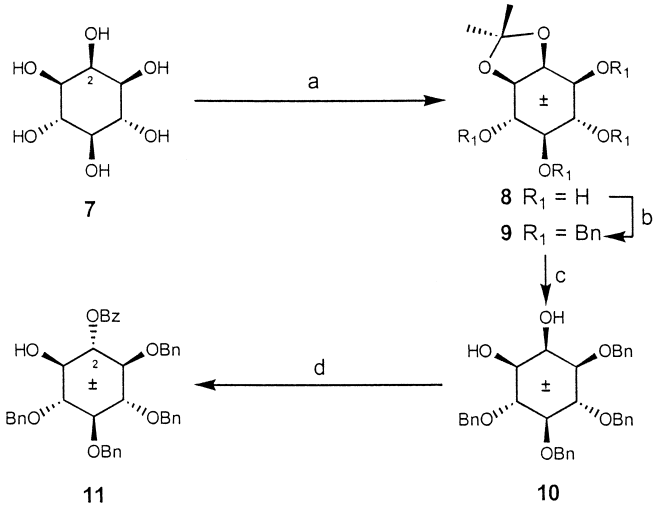


Figure 1. All possible regioisomers of *scyllo*-IP_n ($P = PO_3^{2-}$).

highly symmetric. Thus there are only 12 regioisomers of *scyllo*-IP_n as opposed to 39 optically inactive forms of *myo*-IP_n regioisomers. The key problems in the *scyllo*-IP_n synthesis are (i) the preparation of *scyllo*-inositol itself and suitably protected derivatives, (ii) efficient phosphorylation, and (iii) removal of the protecting groups under mild conditions. The vicinal *cis*-diol (**10**),[32,33] obtained in three steps from *myo*-inositol,[34] was successfully converted to *scyllo*-inositol derivative **11** under Mitsunobu conditions (Scheme 1).[35]

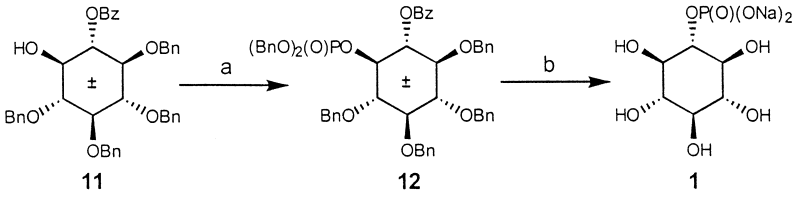


Scheme 1. Reagents and conditions: a. (i) 2,2-dimethoxypropane, *p*-TSA, (ii) EtOH/ether (1/5), (iii) TEA, 69%; b. NaH, BnBr, 89%; c. 80% aq AcOH, quant.; d. PPh_3, DEAD, BzOH, MS (3 Å), 72%.

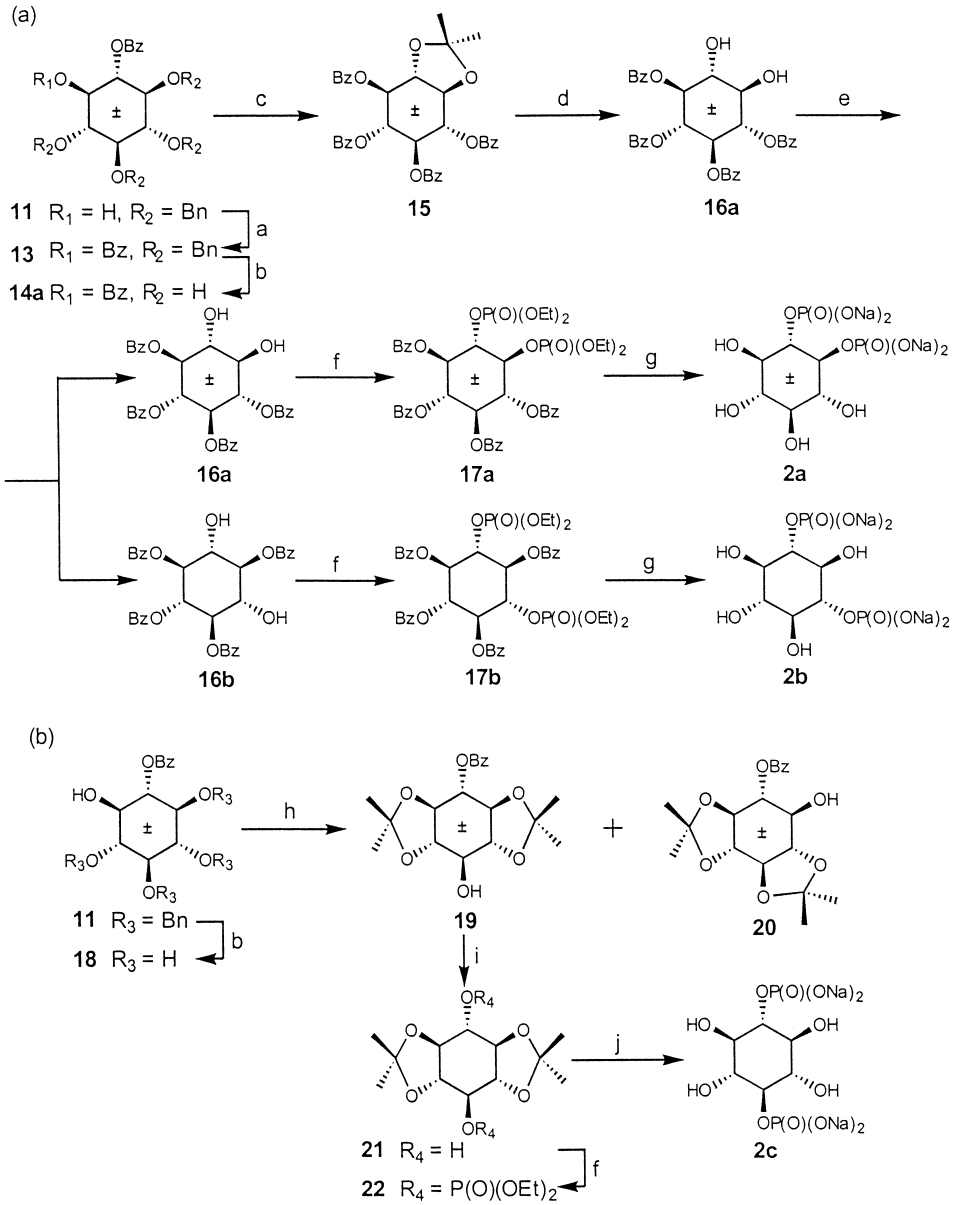
scyllo-I(1)Bz(2,3,4,5)Bn_4 (**11**) was phosphorylated with the phosphoramidite reagent and a weak acid, 1*H*-tetrazole to give **12**, which showed the phosphorous resonance at δ 1.44 ppm. The protecting groups of **12** were removed by hydrogenolysis and treatment with LiOH. The target compound *scyllo*-IP_1 (**1**) was obtained after chromatography on Dowex 50WX8-100 (H^+), pH adjustment to 10 with NaOH, and then lyophilization (Scheme 2).

Synthesis of *scyllo*-IP_2s requires *scyllo*-IBz_4s as intermediates. Thus, benzoylation of *scyllo*-I(1)Bz(2,3,4,5)Bn_4 (**11**), followed by hydrogenolysis provided *scyllo*-I(1,2)Bz_2 (**14a**). Acetonation of **14a** with 2-methoxypropene under standard reaction conditions, followed by benzoylation furnished **15**, which was then hydrolyzed to give the vicinal diol, **16a** (Scheme 3a). Generation of the 3 possible isomers of *scyllo*-IBz_4 was attempted by the benzoyl migration method. However, when **16a** was subjected to 60% aq pyridine at 100°C, only **16a** and **16b** were produced; the 3,6-diol, *scyllo*-I(1,2,4,5)Bz_4, was not produced in a significant amount under these conditions.

Instead, *scyllo*-Inositol diacetonide was used as the *scyllo*-I(1,4)P_2 precursor. Acetonation of **18**, which was prepared by hydrogenolysis of **11**, gave a mixture of **19** (51%) and **20** (34%). Compound **19** was easily crystallized and separated from **20** which could be recycled by hydrolysis, and **19** was debenzoylated to give **21** (Scheme 3b). *scyllo*-Inositol tetrabenzoates (**16a** and **16b**) and diacetonide (**21**) were phosphorylated by successive treatments with diethyl chlorophosphite and



Scheme 2. Reagents and conditions: a. (i) $iPr_2NP(OBn)_2$, 1*H*-tetrazole, (ii) mCPBA, 94%; b. (i) H_2 (50 psi), $NaHCO_3$, Pd/C, (ii) 1 N LiOH, (iii) Dowex 50WX8-100 (H^+), (iv) pH 10 (NaOH), 80%.



Scheme 3. Reagents and conditions: a. BzCl, pyridine, 99.7%; b. H_2 (50 psi), $Pd(OH)_2/C$, 95% for **14a**, 96% for **18**; c. (i) 2-methoxypropene, *p*-TSA, (ii) TEA, (iii) BzCl, pyridine, 92%; d. 80% aq AcOH, quant.; e. 60% aq pyridine, 60% for **16a**, 25% for **16b**; f. (i) $(EtO)_2PCl$, $(i\text{-}Pr)_2NEt$, (ii) 30% aq H_2O_2, 84% for **17a**, 88% for **17b**, 72% for **22**; g. (i) TMSBr, (ii) 1 N LiOH, (iii) Dowex 50WX8-100 (H^+), (iv) pH 10 (NaOH), 90% for **2a**, 92% for **2b**; h. 2-methoxypropene, *p*-TSA, 51% for **19**, 34% for **20**; i. NaOMe, MeOH, quant.; j. (i) TMSBr, (ii) pH 10 (NaOH), 95%.

N,N-diisopropylethylamine in DMF, and then 30% hydrogen peroxide to yield **17a**, **17b** and **22**, respectively. The protecting groups of **17a** and **17b** were removed by successive reactions with TMSBr and then LiOH. Chromatography on Dowex 50WX8-100 (H^+), pH adjustment to 10 with NaOH, and lyophilization gave the two *scyllo*-IP_2 **2a** and **2b**. Treatment of **22** with TMSBr and the spontaneous acid-catalyzed hydrolysis with addition of water (1 day at rt) removed all protecting groups, thus giving the Na

salt of *scyllo*-I(1,4)P_2 (**2c**) after pH adjustment with NaOH.

Random benzoylation of **14a** with BzCl (2 eq) provided the tribenzoates, **23a** (20%), **23b** (22%), *scyllo*-IBz_4 mixture (22%), and the unreacted starting material (22%) (Scheme 4a). Tribenzoate (**23c**) was obtained from **18** via the orthoformate intermediate (**25**). Thus, treatment of **18** with trimethyl orthoformate, *p*-TSA in DMF at 100°C resulted in the formation of monobenzoyl orthoformate, in which the 2, 4 and 6 hydroxyl groups were protected, and the normally equatorial hydroxyl groups were inverted to the axial orientations. Complete benzoylation of the remaining hydroxyl groups required the harsh conditions of excess BzCl and heating at 100°C presumably because of the steric hindrance. Hydrolysis of **25** with a catalytic amount of *p*-TSA in MeOH at reflux removed the orthoformate group to give crystalline **23c** in 87% yield (Scheme 4b). Tribenzoates, **23a–c** were phosphorylated as previously described to afford **24a–c**, which were deprotected to give **3a–c** (Scheme 4).

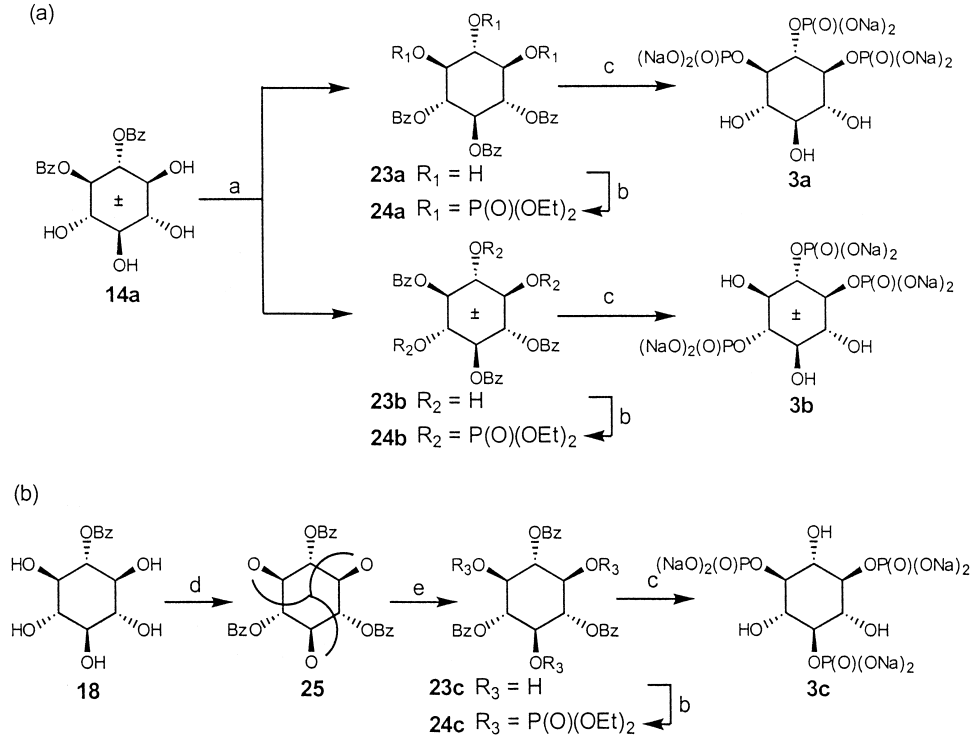
scyllo-IP_4s were similarly prepared via *scyllo*-IBz_2 intermediates. *scyllo*-I(1,2)Bz_2 (**14a**) was subjected to the acyl migration conditions to generate three *scyllo*-IBz_2 regioisomers (Scheme 5). Each *scyllo*-IBz_2 isomer was separated by chromatography and phosphorylated as previously described to yield all 3 regioisomers of *scyllo*-IP_4 (**26a–c**), which were fully characterized by ^1H, ^{13}C, ^{31}P NMR and FAB mass spectrometry. In the final steps, the protecting groups of **26** were removed by successive treatments with TMSBr and then LiOH. The products, **4a–c** were obtained after chromatography on Dowex 50WX8-100 (H^+), pH adjustment to 10 with NaOH, and then lyophilization (Scheme 5).

There is only one regioisomer for *scyllo*-IP_5, and it has been synthesized as follows. The intermediate *scyllo*-IBz_1 (**18**) was phosphorylated by the phosphoramidite method to give **27**. However, in this case the phosphorylation yield (35%) was not as high as those for *scyllo*-IP_{2-4}, even with a large excess of the phosphorylating agent over an extended reaction time. This might be due to the unfavorable steric hindrance or interaction between the vicinal phosphite groups. In any case, deprotection of the phosphate and subsequent handling as previously described provided the Na salt form of *scyllo*-IP_5, **5** (Scheme 6).

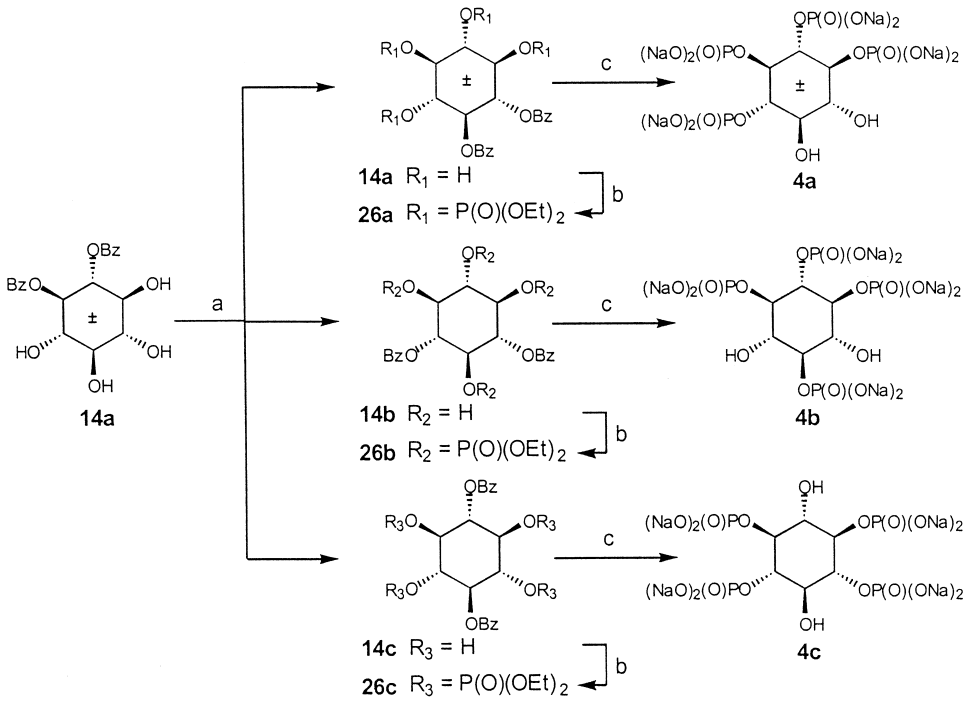
The monobenzoate **18** was hydrolyzed with a catalytic amount of NaOMe in MeOH at reflux to obtain *scyllo*-inositol,[36] which was phosphorylated by the phosphoramidite method to give **29**. Hydrogenolysis of **29** over Pd/C, pH adjustment to 10 with NaOH, and lyophilization afforded the Na salt of *scyllo*-IP_6, **6** (Scheme 7).

We have thus synthesized all possible 12 regioisomers of *scyllo*-IP_n using variously protected *scyllo*-inositol intermediates. These regioisomers were fully characterized by ^1H, ^{13}C and ^{31}P NMR, and the ^{31}P NMR data for the fully protected and the Na-salt forms of *scyllo*-IP_ns ($n = 1–6$) are listed in Table 1.

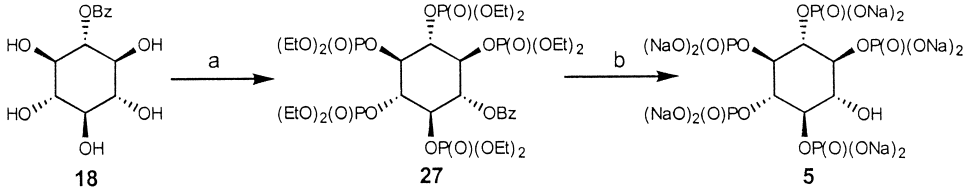
scyllo-IP_ns are the stereoisomers of *myo*-IP_ns with the only difference being the inverted 2-OH stereochemistry.



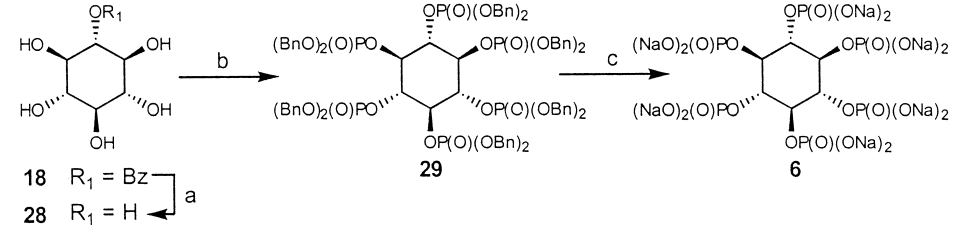
Scheme 4. Reagents and conditions: a. BzCl (2 eq), pyridine, 20% for **23a**, 22% for **23b**; b. (i) $(EtO)_2PCl$, $(i\text{-}Pr)_2NEt$, (ii) 30% aq H_2O_2, 75% for **24a**, 77% for **24b**, 85% for **24c**; c. (i) TMSBr, (ii) 1 N LiOH, (iii) Dowex 50WX8-100 (H^+), (iv) pH 10 (NaOH), 92% for **3a**, 90% for **3b**, 93% for **3c**; d. (i) trimethyl orthoformate, *p*-TSA, (ii) TEA, (iii) BzCl, pyridine, 42%; e. *p*-TSA, MeOH, reflux, 87%.



Scheme 5. Reagents and conditions: a. 60% aq pyridine, 48% for **14a**, 28% for **14b**, 16% for **14c**; b. (i) $(i\text{-}Pr)_2NEt$, $(EtO)_2PCl$, (ii) 30% aq H_2O_2, 70% for **26a**, 74% for **26b**, 75% for **26c**; c. (i) TMSBr, (ii) 1 N LiOH, (iii) Dowex 50WX8-100 (H^+), (iv) pH 10 (NaOH), 90% for **4a**, 87% for **4b**, 88% for **4c**.



Scheme 6. Reagents and conditions: a. (i) $(i\text{-}Pr)_2NEt$, $(EtO)_2PCl$, (ii) 30% aq H_2O_2, 35%; b. (i) TMSBr, (ii) 1 N LiOH, (iii) Dowex 50WX8-100 (H^+), (iv) pH 10 (NaOH), 85%.



Scheme 7. a. NaOMe, MeOH, 88%; b. (i) $iPr_2NP(OBn)_2$, tetrazole, (ii) 30% aq H_2O_2, 44%; c. (i) H_2 (50 psi), $NaHCO_3$, Pd/C, (ii) pH 10 (NaOH), 94%.

It is instructive to compare the corresponding geometries of *scyllo*-IP_ns and *myo*-IP_ns whose biological activities are known (Fig. 2). For example, D-*myo*-I(1,4,5)P_3 and D-*myo*-I(1,3,4,5)P_4 are well known second messengers, and *scyllo*-I(1,2,4)P_3 and *scyllo*-I(1,2,3,5)P_4 may be viewed as the stereoisomers with inverted configuration at C-2. Their binding affinities with relevant biomacromolecules may be compared in order to gain information on the geometry of the binding domains (Fig. 2a and b). Similarly, *scyllo*-I(1,2,3)P_3 may be viewed as the C-2 stereoisomer of D-*myo*-I(1,2,6)P_3 (α-trinositol), which was found to possess an inhibitory effect on neuropeptide Y-evoked vasoconstriction in many vascular assays, and a potent anti-inflammatory property (Fig. 2c).[37] Finally, *scyllo*-I(1,2,3,4)P_4 may also be compared to D-*myo*-I(3,4,5,6)P_4, which was shown to be a novel mediator uncoupling the chloride secretion from intracellular calcium levels in intestinal epithelial cells (Fig. 2d).[5] There are many other such comparisons possible between *scyllo*-IP_ns and *myo*-IP_ns for which novel biological activities have been demonstrated. In this context various binding studies are in progress with the synthetic set of the *scyllo*-IP_n regioisomers.

Table 1. ^{31}P NMR chemical shift of *scyllo*-IP_ns

δ (ppm)	*scyllo*-IP_ns (protected form) (in $CDCl_3$)	*scyllo*-IP_ns (Na salt) (in D_2O, pH 10)
scyllo-IP_1	1.44	6.98
DL-*scyllo*-I(1,2)P_2	0.70 (2P)	7.30 (2P)
scyllo-I(1,3)P_2	1.08 (2P)	7.13 (2P)
scyllo-I(1,4)P_2	0.28 (2P)	7.01 (2P)
scyllo-I(1,2,3)P_2	0.61 (2P), 0.85	6.38, 7.30 (2P)
DL-*scyllo*-I(1,2,4)P_3	0.73, 0.77, 1.01	7.00, 7.33 (2P)
scyllo-I(1,3,5)P_3	1.10 (3P)	7.07 (3P)
DL-*scyllo*-I(1,2,3,4)P_4	0.48 (4P)	5.98 (2P), 6.84 (2P)
scyllo-I(1,2,3,5)P_4	0.70 (2P), 0.95, 0.98	6.12, 6.75 (2P), 7.08
scyllo-I(1,2,4,5)P_4	0.75 (4P)	6.85 (4P)
scyllo-IP_5	0.04, 0.29 (2P), 0.53 (2P)	5.79 (2P), 6.08, 6.55 (2P)
scyllo-IP_6	0.66 (6P)	5.99 (6P)

Experimental

General

All reactions except hydrolyses were performed in oven-dried glassware under inert atmosphere of dry argon or nitrogen. All commercial chemicals were used as obtained without further purification except for solvents, which 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 by spraying with a 5% solution of phosphomolybdic acid followed by charring with a heat gun. Column chromatography was performed on Merck 60 silica gel (70–230 mesh or 230–400 mesh). NMR spectra were recorded on a Bruker AM 300 or DPX 300 spectrometer. Chemical shifts are reported in ppm, and tetramethylsilane and phosphoric acid (80%) were used as internal and external standard for ^1H NMR and ^{31}P NMR, respectively. Mass spectra (EI or FAB) were determined on a micromass PLATFORM II. HRMS (FAB) were performed by Korea Basic Science Center, Taejeon, Korea.

DL-1,4,5,6-Tetra-*O*-benzyl-2,3-*O*-isopropylidene-*myo*-inositol (9). To a solution of compound **8**[34] (2 g, 9.08 mmol) and NaH (3.7 g, 146 mmol) in DMF (100 mL) at 0°C was added BnBr (11 mL, 90.6 mmol). After 30 min, the mixture was warmed up to rt and stirred for 20 h. The mixture was diluted with EtOAc and successively washed with aq $NaHSO_4$, aq $NaHCO_3$ and brine. The organic layer was separated, dried (anhydrous $MgSO_4$), filtered and concentrated. A column chromatography gave compound **9** (4.67 g, 89%) as an oil. R_f 0.23 (EtOAc:hexane = 1:10); ^1H NMR ($CDCl_3$) δ 1.35, 1.51 (2s, 6H, CMe_2), 3.42 (app. t, J = 9.0 Hz, 1H, H-5), 3.70 (dd, J = 3.8, 8.8 Hz, 1H, H-1), 3.79 (dd, J = 6.9, 9.4 Hz, 1H, H-4), 3.95 (app. t, J = 8.6 Hz, 1H, H-6), 4.10 (app. t, J = 6.2 Hz, 1H, H-3), 4.27 (dd, J = 3.8, 5.5 Hz, 1H, H-2), 4.72–4.88 (m, 8H, $4CH_2Ph$), 7.24–7.39 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$) δ 26.39, 28.33 [CMe_2], 73.83, 74.40, 75.79, 75.84 [$4CH_2Ph$], 75.08, 77.70, 79.66, 81.45, 82.71, 83.01 [inositol ring carbons], 110.33 (CMe_2), 128.11–139.19 [4Ph]; MS (FAB) m/z = 579 ($M^+ + H$).

DL-1,4,5,6-Tetra-*O*-benzyl-*myo*-inositol (10). A solution of compound **9** (2.9 g, 5 mmol) in 80% aq acetic acid (50 mL) was heated at 100°C for 4 h, and then concentrated under reduced pressure to give a solid product

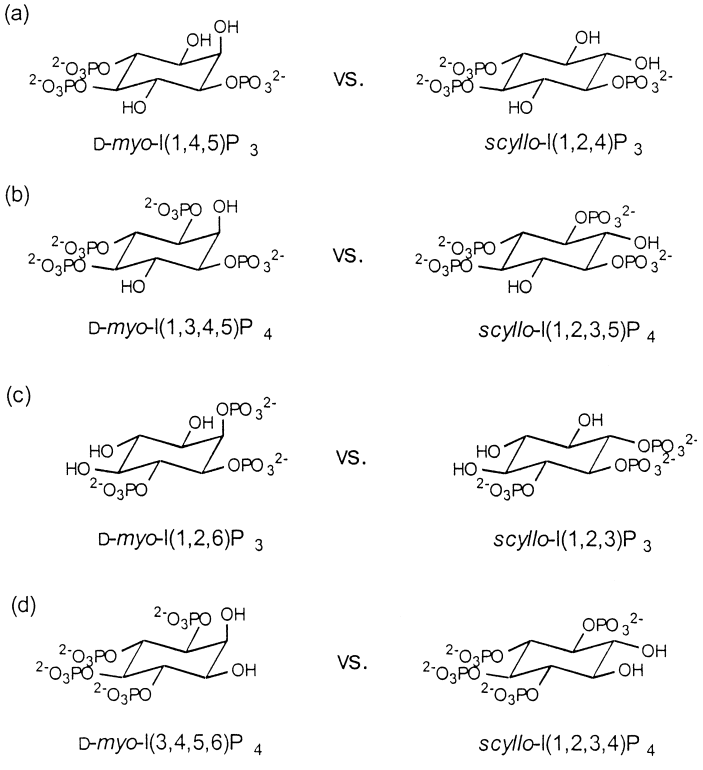


Figure 2. Comparison of several *myo*-IP_ns with *scyllo*-IP_ns.

10. Recrystallization of the crude product from EtOAc:hexane gave a pure product **10** (2.46 g, 91%). R_f 0.2 (EtOAc:hexane = 1:2); mp 126.5–127.5°C (lit. mp 127.5–128°C[32] and 114–115°C[33]); ^{1}H NMR ($CDCl_3$) δ 2.41 (d, J = 4.5 Hz, 1H, OH), 2.48 (s, 1H, OH), 3.44–3.51 (m, 3H, H-1, H-3 and H-5), 3.84 (app. t, J = 9.5 Hz, 1H, H-4 or H-6), 3.97 (app. t, J = 9.5 Hz, 1H, H-4 or H-6), 4.21 (br. s, 1H, H-2), 4.71–4.97 (m, 8H, 4CH_2Ph), 7.25–7.35 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$) δ 69.74, 72.27, 80.45, 81.89, 82.09, 83.71 [inositol ring carbons], 73.15, 76.08, 76.20, 76.42 [4CH_2Ph], 128.11–139.14 [4Ph]; MS (FAB) m/z = 560 (M^+ + Na).

DL-1-*O*-Benzoyl-2,3,4,5-tetra-*O*-benzyl-*scyllo*-inositol (11). A mixture of diol **10** (1 g, 1.85 mmol), PPh_3 (0.587 g, 2.01 mmol), benzoic acid (0.25 g, 2.05 mmol) DEAD (0.352 mL, 2.2 mmol) and 3 Å molecular sieve in benzene (20 mL) was stirred at 80°C for 4 h. The reaction mixture was filtered and the filtrate was evaporated to give a crude product, which was chromatographed on silica gel to afford compound **11** (0.86 g, 72%). R_f 0.42 (EtOAc:hexane = 1:2); mp 134–135°C; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 1H, 6-OH), 3.55–3.77 (m, 5H, H-2, H-3, H-4, H-5 and H-6), 4.65–4.98 (m, 8H, 4CH_2Ph), 5.34 (app. t, J = 9.7 Hz, 1H, H-1), 7.08–8.05 (m, 25H, 5Ph); ^{13}C NMR ($CDCl_3$) δ 73.08, 75.19, 80.85, 82.98, 83.06, 83.46 [inositol ring carbons], 76.05, 76.28 (2C), 76.44 [4CH_2Ph], 128.06–138.64 [5Ph], 166.58 [COPh]; MS (FAB) m/z = 645 (M^+ + H).

DL-1-Mono-*O*-benzoyl-2,3,4,5-tetra-*O*-benzyl-*scyllo*-inositol 6-mono(dibenzyl phosphate) (12). To a solution of compound **11** (130 mg, 0.2 mmol) and 1*H*-tetrazole (72 mg, 1 mmol) in CH_2Cl_2 (5 mL) at rt was added dibenzyl diisopropylphosphoramidite (0.25 mL, 0.73 mmol). After 12 h, an excess amount of mCPBA (640 mg) was added to the mixture. After standing 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 over $MgSO_4$, concentrated and chromatographed to give **12** (171 mg, 94%). R_f 0.5 (EtOAc:hexane = 1:2); mp 132–134°C; ^{1}H NMR ($CDCl_3$) δ 3.65–3.77 (m, 4H, H-2, H-3, H-4 and H-5), 4.44 (dd, J = 8.4, 11.9 Hz, 1H, H-6), 4.53–4.90 (m, 12H, 6 CH_2Ph), 5.50 (app. t, J = 9.5 Hz, 1H, H-1), 6.83–8.06 (m, 35H, 7Ph); ^{13}C NMR ($CDCl_3$) δ 69.42 (2C), 75.60, 76.06, 76.34, 76.41 [6CH_2Ph], 73.23, 78.55, 80.28, 81.14, 82.70, 83.04 [inositol ring carbons], 127.62–138.56 [7Ph], 166.07 [COPh]; ^{31}P NMR ($CDCl_3$) δ 1.44; HRMS (FAB): calcd for $C_{55}H_{54}O_{10}P$ m/z 905.3455, found, 905.3459 (M^+ + H).

Sodium salt of *scyllo*-inositol 1-monophosphate (1). To a solution of compound **12** (58 mg, 0.064 mmol) and $NaHCO_3$ (5 mg) in a mixed solvent (H_2O:MeOH = 1:10, 11 mL) was added 10% Pd/C (50 mg). The mixture was stirred under H_2 (50 psi). After 1 day, the catalyst was filtered off and the solution was concentrated under reduced pressure. The reaction mixture was treated with 1 N LiOH (5 mL) 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) and pH was adjusted to 10 with NaOH and lyophilized again to give the sodium salt of *scyllo*-inositol monophosphate (**1**, 14 mg, 80%). ^{1}H NMR (D_2O, pH 10) δ 3.33–3.49 (m, 5H, H-2, H-3, H-4, H-5 and H-6), 3.82 (app. q, J = 8.2 Hz, 1H, H-1); ^{13}C NMR (D_2O, pH 10) δ 73.71 (2C), 73.75 (2C), 73.88, 77.47 [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 6.98.

DL-1,2-Di-*O*-benzoyl-3,4,5,6-tetra-*O*-benzyl-*scyllo*-inositol (13). To a solution of compound **11** (748 mg, 1.16 mmol) in pyridine (20 mL) at 0°C was added dropwise benzoyl chloride (0.4 mL, 3.41 mmol), and the solution was stirred at rt for 3 h. The reaction mixture was treated with water and extracted with EtOAc. The organic layer was washed with water four times, dried over $MgSO_4$ and concentrated to give a solid product. The crude solid was recrystallized from CH_2Cl_2:hexane to give **13** (860 mg, 99%). R_f 0.38 (EtOAc:hexane = 1:3); mp 203–204°C; ^{1}H NMR ($CDCl_3$) δ 3.80–3.84 (m, 4H, H-3, H-4, H-5 and H-6), 4.66 (d, J = 10.9 Hz, 2H, 2CH_aCH_bPh), 4.80 (d, J = 10.9 Hz, 2H, 2CH_aCH_bPh), 4.91–4.97 (m, 4H, 2CH_2Ph), 5.56–5.59 (m, 2H, H-1 and H-2), 7.06–7.91 (m, 30H, 6Ph); ^{13}C NMR ($CDCl_3$) δ 72.83 (2C), 80.64 (2C), 83.24 (2C) [inositol ring carbons], 76.06 (2C), 76.47 (2C) [4CH_2Ph], 126.29–137.95 [6Ph], 166.11 (2C) [2COPh]; MS (FAB) m/z = 749 (M^+ + H).

DL-1,2-Di-*O*-benzoyl-*scyllo*-inositol (14a). A mixture of compound **13** (750 mg, 1 mmol) and 20% $Pd(OH)_2$/C (0.5 g) in a mixed solvent (EtOAc:EtOH = 1:5, 24 mL) was stirred under H_2 (50 psi). After 1 day, the catalyst was filtered off and the solvent was evaporated under reduced pressure. A column chromatography gave crystalline **14a** (388 mg, 95%). R_f 0.13 (EtOAc:hexane = 3:1); mp 114–116°C; ^{1}H NMR (CD_3OD) δ 3.44–3.48 (m, 2H), 3.67–3.72 (m, 2H), 5.34–5.38 (m, 2H, H-1 and H-2), 7.32–7.89 (m, 10H, 2Ph); ^{13}C NMR (CD_3OD) δ 72.58 (2C), 74.29 (2C), 74.57 (2C) [inositol ring carbons], 128.35–133.20 [2Ph], 166.52 (2C) [2COPh]; MS (FAB) m/z = 389 (M^+ + H), 411 (M^+ + Na).

DL-1,2,3,4-Tetra-*O*-benzoyl-5,6-*O*-isopropylidene-*scyllo*-inositol (15). To a solution of compound **14a** (690 mg, 1.78 mmol) and *p*-TSA (110 mg) in DMF (8 mL) at rt was added 2-methoxypropene (1 mL, 10 mmol). After 1 day, the reaction mixture was treated with triethylamine (5 mL), and then the low-boiling substance evaporated. To the resulting mixture in pyridine (12 mL) at 0°C were added dropwise DMAP (55 mg) and BzCl (1 mL, 8.6 mmol). After 15 h at rt, the reaction mixture was stirred with H_2O (3 mL) for 30 min and diluted with EtOAc, and washed with aq $NaHSO_4$, aq $NaHCO_3$ and then brine. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel to give **15** (1.044 g, 92%). R_f 0.62 (EtOAc:hexane = 1:1); mp 321–324°C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 6H, CMe_2), 4.16 (dd, J = 2.6, 6.9 Hz, 2H, H-5 and H-6), 5.84–5.93 (m, 4H, H-1, H-2, H-3 and H-4), 7.26–7.98 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$) δ 27.17 (2C) [CMe_2], 71.58 (2C), 73.56 (2C), 76.75 (2C) [inositol ring carbons], 114.41 [CMe_2], 128.70–133.68 [4Ph], 165.76(2C), 165.83 (2C) [4COPh]; MS (FAB) m/z = 637 (M^+ + H).

DL-1,2,3,4-Tetra-*O*-benzoyl-*scyllo*-inositol (16a). A solution of **15** (790 mg) in 80% aq AcOH (50 ml) was refluxed for 4 h, and evaporated to dryness to give **16a** quantitatively. R_f 0.15 (EtOAc:hexane = 1:1); mp 257–260°C; ^{1}H NMR (DMSO-d_6) δ 4.05–4.08 (m, 2H, H-5 and H-6), 5.67–5.74 (m, 2H, H-1 and H-4), 5.81 (d, J = 4.1 Hz, 2H, 2OH), 5.98 (dd, J = 2.8, 7.1 Hz, 2H, H-2 and H-3), 7.44–7.98 (m, 20H, 4Ph); ^{13}C NMR (DMSO-d_6) δ 72.00 (2C), 72.52 (2C), 74.31 (2C) [inositol ring carbons], 126.29–134.41 [4Ph], 165.84(2C), 166.06 (2C) [4COPh]; MS (FAB) m/z = 597 ($M^+ + H$).

1,2,3,5-Tetra-*O*-benzoyl-*scyllo*-inositol (16b). Compound **16a** (400 mg) in pyridine:water (6:4, 75 ml) was stirred at 100°C for 1.5 h. The solution was cooled, and concentrated under reduced pressure. Addition of acetone and evaporation of the solvents were repeated twice. The crude mixture was chromatographed on silica gel. The first eluted compound was 1,2,3,5-tetra-*O*-benzoyl-*scyllo*-inositol (**16b**) (100 mg), and the second eluted material was **16a** (240 mg). **16b**: R_f 0.4 (EtOAc:hexane = 1:1); mp 246–248°C; ^{1}H NMR (DMSO-d_6) δ 4.18 (app. dt, J = 5.9, 9.5 Hz, 2H, H-4 and H-6), 5.34 (t, J = 9.6 Hz, 1H, H-5), 5.59 (app. t, J = 9.8 Hz, 2H, H-1 and H-3), 5.74 (d, J = 5.7 Hz, 2H, 2OH), 5.77 (t, J = 9.9 Hz, 1H, H-2), 7.35–8.03 (m, 20H, 4Ph); ^{13}C NMR (DMSO-d_6) δ 69.94 (2C), 72.63, 74.34 (2C), 76.54 [inositol ring carbons], 129.47–134.38 [4Ph], 165.90 (2C), 165.94 (2C) [4COPh]; MS (FAB) m/z = 597 ($M^+ + H$).

Phosphorylation of *scyllo*-IBz$_4$ regioisomers (16a and b). To a solution of compound **16a** (60 mg, 0.1 mmol) in DMF (5 mL) at −42°C were added dropwise excess diisopropylethylamine (1.5 mL, 8.5 mmol) and then diethyl chlorophosphite (0.25 mL, 1.7 mmol) with vigorous stirring. After 30 min, the reaction mixture was allowed to slowly warm up to rt and stirred for additional 8 h. The mixture was cooled in an ice bath, and sodium phosphate buffer (1 N, pH 7, 5 mL) and excess 30% H_2O_2 (5 mL) were added. After standing overnight at rt, the mixture was diluted with water, and extracted extensively with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and chromatographed to give **17a** (73 mg, 84%). Compound **16b** (60 mg, 0.1 mmol) was similarly phosphorylated to give **17b** (76.5 mg, 88%).

DL-1,2,3,4-Tetra-*O*-benzoyl-*scyllo*-inositol 5,6-bis(diethyl phosphate) (17a). R_f 0.31 (EtOAc:hexane = 2:1); mp 227–228.5°C; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 6H, 2CH$_2$CH$_3$), 1.25 (t, J = 7.1 Hz, 6H, 2CH$_2$CH$_3$), 3.58–4.19 (m, 8H, 4CH$_2$CH$_3$), 4.98–5.05 (m, 2H, H-5 and H-6), 5.83 (m, 4H, H-1, H-2, H-3 and H-4), 7.25–8.01 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$) δ 15.79 (2C), 16.23 (2C) [4CH$_2$CH$_3$], 64.39 (2C), 64.92 (2C) [4CH$_2$CH$_3$], 70.63 (2C), 71.09 (2C), 76.50 (2C) [inositol ring carbons], 128.66–133.69 (4Ph), 165.67(4C) [4COPh]; ^{31}P NMR ($CDCl_3$) δ 0.70 (2P); HRMS (FAB): calcd for $C_{42}H_{47}O_{16}P_2$ m/z 869.2339, found, 869.2355 ($M^+ + H$).

1,2,3,5-Tetra-*O*-benzoyl-*scyllo*-inositol 4,6-bis(diethyl phosphate) (17b). R_f 0.24 (EtOAc:hexane = 2:1); mp 240–242°C; ^{1}H NMR ($CDCl_3$) δ 0.74–0.79 (m, 12H, 4CH$_2$CH$_3$), 3.47–3.72 (m, 8H, 4CH$_2$CH$_3$), 5.09 (app. q, J = 9.5 Hz, 2H, H-4 and H-6), 5.74–5.79 (m, 4H, H-1, H-2, H-3 and H-5), 7.25–8.22 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$) δ 15.68 (2C), 15.77 (2C) [4CH$_2$CH$_3$], 64.29 (2C), 64.35 (2C) [4CH$_2$CH$_3$], 70.56, 71.14 (2C), 71.78, 75.63 (2C) [inositol ring carbons], 128.65–133.82 (4Ph), 165.62, 165.72 (2C), 165.77 [4COPh]; ^{31}P NMR ($CDCl_3$) δ 1.08 (2P); MS (FAB) m/z = 869 ($M^+ + H$).

Preparation of sodium salts of *scyllo*-inositol bisphosphate (2a and b). To compound **17a** (40 mg, 0.046 mmol) in CH_2Cl_2 (2 mL) at rt was added TMS-Br (1 mL), and the solution was stirred overnight. The solvent and excess reagent were evaporated, and the residue was dissolved in MeOH (5 mL), then treated with drops of water at 0°C. The reaction mixture was slowly warmed up to rt, concentrated to dryness, and treated with 1 N LiOH (5 mL) 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) and pH was adjusted to 10 with NaOH and lyophilized again to give the sodium salt of *scyllo*-inositol 1,2-bisphosphate (**2a**, 17.7 mg, 90%) in quantitative yield. Compound **2b** (22.5 mg, 92%) was similarly prepared from **17b** (50 mg).

Sodium salt of DL-*scyllo*-inositol 1,2-bisphosphate (2a). ^{1}H NMR (D_2O, pH 10) δ 3.39 (dd, J = 2.7, 6.7 Hz, 2H, H-4 and H-5), 3.49–3.56 (m, 2H, H-3 and H-6), 3.82–3.92 (m, 2H, H-1 and H-2); ^{13}C NMR (D_2O, pH 10) δ 73.85 (2C), 74.43 (2C), 76.41 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 7.30 (2P).

Sodium salt of *scyllo*-inositol 1,3-bisphosphate (2b). ^{1}H NMR (D_2O, pH 10) δ 3.33–3.42 (m, 4H, H-2, H-4, H-5 and H-6), 3.73 (app. t, J = 8.1 Hz, 2H, H-1 and H-3); ^{13}C NMR (D_2O, pH 10) δ 73.15, 73.75, 73.88 (2C), 77.28 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 7.13 (2P).

1-*O*-Benzoyl-*scyllo*-inositol (18). A mixture of compound **11** (645 mg, 1 mmol) and 20% $Pd(OH)_2$/C (0.35 g) in a mixed solvent (CH_2Cl_2:EtOH = 1:2, 21 mL) was stirred under H_2 (50 psi). After 1 day, the catalyst was filtered off and the solvent was evaporated under reduced pressure. A column chromatography gave crystalline compound **18** (273 mg, 96%). Mp 244–246°C; ^{1}H NMR (CD_3OD) δ 3.29–3.39 (m, 3H), 3.52 (app. t, J = 9.2 Hz, 2H), 5.06 (t, J = 9.7 Hz, 1H, H-1), 7.45–8.09 (m, 5H, Ph); ^{13}C NMR (CD_3OD) δ 72.86 (2C), 74.48, 74.67 (2C), 76.59 (inositol ring carbons), 128.41–133.11 (Ph), 166.96 (COPh); MS (EI) m/z = 284 (M^+).

DL-1-Mono-*O*-benzoyl-(2,3;5,6)-di-*O*-isopropylidene-*scyllo*-inositol (19) and DL-1-mono-*O*-benzoyl-(2,3;4,5)-di-*O*-isopropylidene-*scyllo*-inositol (20). To a solution of compound **18** (285 mg, 1 mmol) and *p*-TSA (100 mg) in DMF (5 mL) at rt was added 2-methoxypropene (1 mL, 10 mmol). After 1 day, the reaction mixture was poured

into aq $NaHCO_3$ with vigorous stirring, and extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel to give **19** (184 mg, 51%) and **20** (122 mg, 34%). **19**: R_f 0.25 (EtOAc:hexane = 1:2); mp 284–285°C; ^{1}H NMR ($CDCl_3$) δ 1.44, 1.47 (each s, each 6H, 2C$\underline{Me}_2$), 2.46 (d, J = 2.7 Hz, 1H, O$\underline{H}$), 3.76 (app. t, J = 9.3 Hz, 2H, H-3 and H-5), 3.85 (app. t, J = 9.3 Hz, 2H, H-2 and H-6), 4.13 (dt, J = 2.7, 8.9 Hz, 1H, H-4), 5.60 (t, J = 9.2 Hz, 1H, H-1), 7.26–8.10 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 27.06 (4C) [2C$\underline{Me}_2$], 69.37, 70.07, 78.70 (2C), 80.73 (2C) [inositol ring carbons], 113.99 (2C) [2$\underline{C}Me_2$], 128.71 (2C), 130.02, 130.46 (2C), 133.65 [Ph], 165.72 [$\underline{C}$OPh]; MS (FAB) m/z = 365 ($M^+ + H$). **20**: R_f 0.40 (EtOAc:hexane = 1:2); mp 206–207°C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 6H), 1.49 (s, 3H), 1.51 (s, 3H) [2C$\underline{Me}_2$], 2.87 (d, J = 4.1 Hz, 1H, OH), 3.67–3.95 (m, 4H, H-2, H-3, H-4 and H-5), 4.13 (ddd, J = 4.1, 7.9, 10.2 Hz, 1H, H-6), 5.43 (dd, J = 7.9, 10.4 Hz, 1H, H-1), 7.44–8.11 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.99, 27.02, 27.10 (2C) [2C$\underline{Me}_2$], 73.03, 75.62, 75.84, 76.30, 79.26, 81.75 [inositol ring carbons], 114.36, 114.44 [2$\underline{C}Me_2$], 128.87 (2C), 129.66, 130.49 (2C), 133.99 [Ph], 167.11 [$\underline{C}$OPh]; MS (FAB) m/z = 365 ($M^+ + H$).

(1,2;4,5)-Di-*O*-isopropylidene-*scyllo*-inositol (21). A solution of **19** (114 mg, 0.31 mmol) and NaOMe (cat.) in MeOH (10 mL) was heated at reflux for 4 h. After cooling, the solution was concentrated under reduced pressure. After addition of CH_2Cl_2, the reaction mixture was filtered through silica gel. The filtrate was evaporated to give a solid product **21** in quantitative yield. R_f 0.15 (EtOAc:hexane = 1:1); mp 261–263°C; ^{1}H NMR ($CDCl_3$, with a few drops of DMSO-d_6) δ 1.44 (s, 12H, 2C$\underline{Me}_2$), 3.56 (dd, J = 2.6, 6.5 Hz, 4H, H-1, H-2, H-4 and H-5), 3.90–3.94 (m, 2H, H-3 and H-6), 5.43 (d, J = 4.7 Hz, 2H, 2O$\underline{H}$); ^{13}C NMR ($CDCl_3$, with a few drops of DMSO-d_6) δ 32.02 (4C) [2C$\underline{Me}_2$], 73.44 (2C), 85.82 (4C) [inositol ring carbons], 117.34 (2C) [2$\underline{C}Me_2$]; MS (FAB) m/z = 261 ($M^+ + H$).

(1,2;4,5)-Di-*O*-isopropylidene-*scyllo*-inositol 3,6-bis(diethyl phosphate) (22). To a solution of compound **21** (26 mg, 0.1 mmol) in DMF (5 mL) at −42°C were added dropwise excess diisopropylethylamine (1.5 mL, 8.5 mmol) and then diethyl chlorophosphite (0.25 mL, 1.7 mmol) with vigorous stirring. After 30 min, the reaction mixture was allowed to slowly warm up to rt, and stirred for additional 8 h. The mixture was cooled in an ice bath, and sodium phosphate buffer (1 N, pH 7, 5 mL) and excess 30% H_2O_2 (5 mL) were added. After standing overnight at rt, the mixture was diluted with water, and extracted extensively with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and chromatographed to give **22** (38 mg, 71%). R_f 0.32 (MeOH:CH_2Cl_2 = 1:20); mp 185–186°C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 12H, 4$CH_2C\underline{H}_3$), 1.41 (s, 12H, 2C$\underline{Me}_2$), 3.71 (dd, J = 2.6, 6.6 Hz, 4H, H-1, H-2, H-4 and H-5), 4.15 (app. quin, J = 7.1 Hz, 8H, 4$C\underline{H}_2CH_3$), 4.63–4.70 (m, 2H, H-3 and H-6); ^{13}C NMR ($CDCl_3$) δ 16.37 (4C) [4$CH_2\underline{C}H_3$], 27.05 (4C) [2C$\underline{Me}_2$], 64.41 (4C) [4$\underline{C}H_2CH_3$], 73.74 (2C), 78.99 (4C) [inositol ring carbons], 113.81 (2C) [2$\underline{C}Me_2$]; ^{31}P NMR ($CDCl_3$) δ 0.28 (2P); HRMS (FAB): calcd for $C_{20}H_{39}O_{12}P_2$ m/z 533.1917, found, 533.1907 ($M + + H$).

Sodium salt of *scyllo*-inositol 1,4-bisphosphate (2c). To compound **22** (25 mg, 0.047 mmol) in CH_2Cl_2 (2 mL) at rt was added TMS-Br (1 mL), and the mixture was stirred overnight. The mixture was concentrated and redissolved in MeOH (3 mL), and then treated with drops of water at 0°C. After slowly being warmed up to rt and standing for 1 day, the reaction mixture was concentrated and pH adjusted to 10 with NaOH and lyophilized to give the sodium salt of **2c** (19 mg, 95%). ^{1}H NMR (D_2O, pH 10) δ 3.50 (dd, J = 2.6, 6.4 Hz, 4H, H-2, H-3, H-5 and H-6), 3.78–3.84 (m, 2H, H-1 and H-4); ^{13}C NMR (D_2O, pH 10) δ 73.53 (4C), 77.38 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 7.01 (2P).

1,2,3-Tri-*O*-benzoyl-*scyllo*-inositol (23a) and DL-1,2,4-tri-*O*-benzoyl-*scyllo*-inositol (23b). To a solution of compound **14a** (389 mg, 1 mmol) in pyridine (6 mL) at 0°C was added benzoyl chloride (0.24 mL, 2 mmol) with vigorous stirring, and slowly warmed up to rt. After 14 h, the reaction mixture was stirred with water (1 mL) for 30 min, diluted with EtOAc, and then successively washed with aq $NaHSO_4$, aq $NaHCO_3$ and brine. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. A column chromatography gave 1,2,3-tri-*O*-benzoyl-*scyllo*-inositol (**23a**) (100 mg, 20%), DL-1,2,4-tri-*O*-benzoyl-*scyllo*-inositol (**23b**) (110 mg, 22%), and *scyllo*-IBz_4 mixture (130 mg, 22%) together with the starting material **7a** (85 mg, 22%). **23a**: R_f 0.35 (EtOAc); mp 216–218°C; ^{1}H NMR ($CDCl_3$, with a few drops of CD_3OD) δ 3.67 (t, J = 9.3 Hz, 1H, H-5), 3.78 (app. t, J = 9.3 Hz, 2H, H-4 and H-6), 5.52 (app. t, J = 9.9 Hz, 2H, H-1 and H-3), 5.69 (t, J = 10.0 Hz, 1H, H-2), 7.19–7.90 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$, with a few drops of CD_3OD) δ 71.46, 72.72 (2C), 73.61 (2C), 74.64 [inositol ring carbons], 128.62–133.62 [3Ph], 166.29, 166.67 (2C) [3$\underline{C}$OPh]; MS (FAB) m/z = 493 ($M^+ + H$). **23b**: R_f 0.4 (EtOAc:CH_2Cl_2 = 1:2); mp 169–171°C; ^{1}H NMR ($CDCl_3$, with a few drops of CD_3OD) δ 3.82 (app. t, J = 9.4 Hz, 1H), 3.91 (app. t, J = 9.1 Hz, 1H,), 4.03 (app. t, J = 9.6 Hz, 1H), 5.38 (app. t, J = 9.5 Hz, 1H), 5.50 (app. t, J = 9.6 Hz, 1H), 5.59 (app. t, J = 9.7 Hz, 1H), 7.31–8.12 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$, with a few drops of CD_3OD) δ 71.59, 72.84, 72.94, 73.37, 73.99, 76.02 [inositol ring carbons], 128.67–133.67 [3Ph], 166.79, 166.84, 167.39 [3$\underline{C}$OPh]; MS (FAB) m/z = 493 ($M^+ + H$).

1,3,5-Tri-*O*-benzoyl-*scyllo*-inositol orthoformate (25). A solution of compound **18** (250 mg, 0.88 mmol) and trimethyl orthoformate (2.5 mL, 22.6 mmol) in DMF (5 mL) containing TSA (20 mg) was heated at 100°C. After 12 h, triethylamine (2.5 mL) was added, and the solution was concentrated at 50°C over 2 h. To the reaction residue in pyridine (5 mL) at rt, was added dropwise benzoyl chloride (2.3 mL, 19.6 mmol) with vigorous stirring, and the solution was stirred at 100°C for 1 day. The reaction mixture was cooled and stirred with water (10 mL) for 30 min, diluted with EtOAc, and successively washed with aq $NaHSO_4$, aq $NaHCO_3$ and brine. The organic layer was separated, dried ($MgSO_4$),

filtered, concentrated and chromatographed to give compound **25** (186 mg, 42%). R_f 0.3 (EtOAc:hexane = 1:5); mp 248–250°C; ^{1}H NMR ($CDCl_3$) δ 4.97 (dd, J = 2.9, 4.6 Hz, 3H, H-2, H-4 and H-6), 5.76 (s, 1H, $\underline{H}CO_3$), 5.78 (dd, J = 2.9, 4.6 Hz, 3H, H-1, H-3 and H-5), 6.91–7.72 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 67.45 (3C), 67.71 (3C) [inositol ring carbons], 103.67 [$H\underline{C}O_3$], 128.63–133.73 [3Ph], 166.03 (3C) [3COPh]; MS (FAB) m/z = 503 ($M^+ + H$).

1,3,5-Tri-*O*-benzoyl-*scyllo*-inositol (23c). A solution of compound **25** (152 mg, 0.3 mmol) and TSA (50 mg) in MeOH (10 mL) was stirred at reflux overnight. After the low boiling solvents were evaporated off, the mixture was diluted with EtOAc, and successively washed with aq $NaHCO_3$, aq $NaHSO_4$ and brine. The organic layer was separated, dried ($MgSO_4$), filtered, concentrated and chromatographed to give compound **23c** (130 mg, 87%). R_f 0.55 (EtOAc:CH_2Cl_2 = 1:2); mp 226–228°C ^{1}H NMR ($CDCl_3$) δ 2.84 (d, J = 6.4 Hz, 3H, 3O$\underline{H}$), 4.06 (dt, J = 6.1, 9.7 Hz, 3H, H-2, H-4 and H-6), 5.47 (t, J = 9.7 Hz, 3H, H-1, H-3 and H-5), 7.41–8.08 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 70.91 (3C), 75.91 (3C) [inositol ring carbons], 128.22–133.17 [3Ph], 166.84 (3C) [3$\underline{C}$OPh]; HRMS (FAB): calcd for $C_{27}H_{25}O_9$ m/z 493.1499, found, 493.1487 ($M^+ + H$).

Phosphorylation of *scyllo*-IBz$_3$ regioisomers (23a–c). To a solution of compound **23a** (50 mg, 0.1 mmol) in DMF (5 mL) at −42°C were added dropwise excess diisopropylethylamine (1.5 mL, 8.5 mmol) and then diethyl chlorophosphite (0.2 mL, 1.35 mmol) with vigorous stirring. After 30 min, the reaction mixture was allowed to slowly warm up to rt, and stirred for additional 8 h. The mixture was cooled in an ice bath, and sodium phosphate buffer (1 N, pH 7, 5 mL) and excess 30% H_2O_2 (5 mL) were added. After standing overnight at rt, the mixture was diluted with water, and extracted extensively with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and chromatographed to give **24a** (67.5 mg, 75%). Similarly, **24b** and **c** were prepared in 77 and 85% yields, respectively.

1,2,3-Tri-*O*-benzoyl-*scyllo*-inositol 4,5,6-tris(diethyl phosphate) (24a). R_f 0.2 (EtOAc); mp 129–131°C; ^{1}H NMR ($CDCl_3$) δ 0.87–1.40 (m, 18H, 6$CH_2\underline{C}H_3$), 3.62–4.29 (m, 12H, 6$\underline{C}H_2CH_3$), 4.76–4.95 (m, 3H, H-4, H-5 and H-6), 5.70–5.79 (m, 3H, H-1, H-2 and H-3), 7.23–8.00 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 15.81–16.54 [6$CH_2\underline{C}H_3$], 64.35–64.90 [6$\underline{C}H_2CH_3$], 70.84, 71.13 (2C), 76.04 (2C), 76.63 [inositol ring carbons], 128.64–133.66 [3Ph], 165.61 (3C) [3$\underline{C}$OPh]; ^{31}P NMR ($CDCl_3$) δ 0.61 (2P), 0.85; MS (FAB) m/z = 901 ($M^+ + H$).

DL-1,2,4-Tri-*O*-benzoyl-*scyllo*-inositol 3,5,6-tris(diethyl phosphate) (24b). R_f 0.32 (EtOAc); mp 172–173°C; ^{1}H NMR ($CDCl_3$) δ 0.72–1.26 (m, 18H, 6$CH_2\underline{C}H_3$), 3.47–4.16 (m, 12H, 6$\underline{C}H_2CH_3$), 4.85–5.04 (m, 3H, H-3, H-5 and H-6), 5.66–5.77 (m, 3H, H-1, H-2 and H-4), 7.29–8.23 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 15.88–16.58 [6$CH_2\underline{C}H_3$], 64.52–65.16 [6$\underline{C}H_2CH_3$], 70.94, 71.17, 71.54, 75.60, 76.32, 76.39 [inositol ring carbons], 128.91–133.96 [3Ph], 165.82, 165.89, 165.93 [3$\underline{C}$OPh]; ^{31}P NMR ($CDCl_3$) δ 0.73, 0.77, 1.01; MS (FAB) m/z = 901 ($M^+ + H$).

1,3,5-Tri-*O*-benzoyl-*scyllo*-inositol 2,4,6-tris(diethyl phosphate) (24c). R_f 0.37 (MeOH:CH_2Cl_2 = 1:10); mp 212–213 C; ^{1}H NMR ($CDCl_3$) δ 0.73 (t, J = 7.1 Hz, 18H, 6$CH_2\underline{C}H_3$), 3.42–3.67 (m, 12H, 6$\underline{C}H_2CH_3$), 4.93 (app. q, J = 9.7 Hz, 3H, H-2, H-4 and H-6), 5.74 (t, J = 10.0 Hz, 3H, H-1, H-3 and H-5), 7.40–8.18 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$) δ 15.70 [6$CH_2\underline{C}H_3$], 64.29 [6$\underline{C}H_2CH_3$], 71.40 (3C), 75.31 (3C) [inositol ring carbons], 128.83–133.80 [3Ph], 165.75 (3C) [3$\underline{C}$OPh]; ^{31}P NMR ($CDCl_3$) δ 1.10 (3P); HRMS (FAB): calcd for $C_{39}H_{52}O_{18}P_3$ m/z 901.2367, found, 901.2377 ($M^+ + H$).

Preparation of sodium salts of *scyllo*-inositol trisphosphate (3a–c). To compound **24a** (45 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) at rt was added TMS-Br (1 mL), and the solution was stirred overnight. The solvent and excess reagent were evaporated, and the residue was dissolved in MeOH (5 mL), then treated with drops of water at 0°C. The reaction mixture was slowly warmed up to rt, evaporated to dryness, and treated with 1 N LiOH (5 mL) 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) and pH was adjusted to 10 with NaOH and lyophilized to give the sodium salt of *scyllo*-inositol 1,2,3-trisphosphate (**3a**, 46 mg, 92%). Similarly, **3b and c** were prepared in 90 and 93% yields, respectively.

Sodium salt of *scyllo*-inositol 1,2,3-trisphosphate (3a). ^{1}H NMR (D_2O, pH 10) δ 3.45–3.58 (m, 3H, H-4, H-5 and H-6), 3.87–4.04 (m, 3H, H-1, H-2 and H-3); ^{13}C NMR (D_2O, pH 10) δ 74.33, 74.61 (2C), 75.70, 77.25 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 6.38, 7.30 (2P).

Sodium salt of DL-*scyllo*-inositol 1,2,4-trisphosphate (3b). ^{1}H NMR (D_2O, pH 10) δ 3.54–3.60 (m, 3H, H-3, H-5 and H-6), 3.84–3.91 (m, 3H, H-1, H-2 and H-4); ^{13}C NMR (D_2O, pH 10) δ 73.81, 74.20, 74.35, 76.16, 76.28, 77.28 [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 7.00, 7.33 (2P).

Sodium salt of *scyllo*-inositol 1,3,5-trisphosphate (3c). ^{1}H NMR (D_2O, pH 10) δ 3.54 (t, J = 9.2 Hz, 3H, H-2, H-4 and H-6), 3.89 (app. q, J = 8.6 Hz, 3H, H-1, H-3 and H-5); ^{13}C NMR (D_2O, pH 10) δ 73.49 (3C), 77.28 (3C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 7.07 (3P).

Preparation of 14b–c by acyl migration of 14a. Compound **14a** (250 mg) in the solvent mixture of pyridine: water (6:4, 30 mL) was heated at 100°C for 1.5 h. The solution was cooled, and concentrated under reduced pressure. Addition of acetone and evaporation of the solvents were repeated twice. The crude mixture was chromatographed on silica gel to give 3 regioisomers. The first eluted was 1,4-di-*O*-benzoyl-*scyllo*-inositol (**14c**) (40 mg). The second and third eluted were 1,3-di-*O*-benzoyl-*scyllo*-inositol (**14b**) (70 mg) and **14a** (120 mg), respectively.

1,3-Di-*O*-benzoyl-*scyllo*-inositol (14b). R_f 0.27 (EtOAc:hexane = 3:1); mp 242–243°C; ^{1}H NMR (CD_3OD) δ 3.47 (t, J = 9.9 Hz, 1H, H-5), 3.62 (app. t, J = 9.5 Hz, 2H, H-4 and H-6), 3.87 (t, J = 9.8 Hz, 1H, H-2), 5.21 (app. t, J = 9.6 Hz, 2H, H-1 and H-3), 7.44–8.10 (m, 10H, 2Ph); ^{13}C NMR (CD_3OD) δ 71.02, 72.72 (2C), 74.62, 76.41 (2C) [inositol ring carbons], 128.40–133.11 [2Ph], 166.73 (2C) [2COPh]; HRMS (FAB): calcd for $C_{20}H_{21}O_8$ m/z 389.1236, found, 389.1234 ($M^+ + H$).

1,4-Di-*O*-benzoyl-*scyllo*-inositol (14c). R_f 0.41 (EtOAc:hexane = 3:1); mp 253–254°C; ^{1}H NMR (DMSO-d_6) δ 3.47 (m, 4H, 4-OH), 4.93 (m, 2H, H-1 and H-4), 5.25 (m, 4H, H-2, H-3, H-5 and H-6), 7.49–8.00 (m, 10H, 2Ph); ^{13}C NMR (DMSO-d_6) δ 72.74 (4C), 77.20 (2C) [inositol ring carbons], 129.34–133.80 [2Ph], 166.16 (2C) [2COPh]; MS (FAB) m/z = 389 ($M^+ + H$).

Phosphorylation of *scyllo*-IBz$_2$ regioisomers (14a–c). To a solution of compound **14a** (39 mg, 0.1 mmol) in DMF (5 mL) at −42°C were added dropwise excess diisopropylethylamine (1.5 mL, 8.5 mmol) and then diethyl chlorophosphite (0.2 mL, 1.35 mmol) with vigorous stirring. After 30 min, the reaction mixture was allowed to slowly warm up to rt, and stirred for additional 8 h. The mixture was cooled in an ice bath, and sodium phosphate buffer (1 N, pH 7, 5 mL) and excess 30% H_2O_2 (5 mL) were added. After standing overnight at rt, the mixture was diluted with water, and extracted extensively with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, concentrated and chromatographed to give **26a** (65 mg, 70%). Similarly, compounds **14b** and **c** were phosphorylated to give **26b** (69 mg, 74%) and **26c** (70 mg, 75%), respectively.

DL-1,2-Di-*O*-benzoyl-*scyllo*-inositol 3,4,5,6-tetrakis(diethyl phosphate) (26a). R_f 0.4 (MeOH:CH_2Cl_2 = 1:10); mp 74–75.5°C; ^{1}H NMR ($CDCl_3$) δ 0.93–1.37 (m, 24H, 8$CH_2C\underline{H}_3$), 3.70–4.26 (m, 16H, 8$C\underline{H}_2CH_3$), 4.77–4.84 (m, 2H), 4.88–4.95 (m, 2H), 5.68 (dd, J = 2.4, 5. Hz, 2H, H-1 and H-2), 7.33–7.98 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 15.83–16.68 [8$CH_2\underline{C}H_3$], 64.43–65.14 [8$\underline{C}H_2CH_3$], 71.98 (2C), 76.37 (2C), 76.57 (2C) [inositol ring carbons], 128.85–133.85 [2Ph], 165.75 (2C) [2COPh]; ^{31}P NMR ($CDCl_3$) δ 0.48 (4P); MS (FAB) m/z = 933 ($M^+ + H$).

1,3-Di-*O*-benzoyl-*scyllo*-inositol 2,4,5,6-tetrakis(diethyl phosphate) (26b). R_f 0.45 (MeOH:CH_2Cl_2 = 1:10); mp 129–130°C; ^{1}H NMR ($CDCl_3$) δ 0.73–1.36 (m, 24H, 8$CH_2C\underline{H}_3$), 3.41–4.27 (m, 16H, 8$C\underline{H}_2CH_3$), 4.65–4.80 (m, 3H, H-4, H-5 and H-6), 4.92 (app. q, J = 9.5 Hz, 1H, H-2), 5.64 (app. t, J = 9.1 Hz, 2H, H-1 and H-3), 7.43–8.19 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 15.79–16.66 [8$CH_2\underline{C}H_3$], 64.35–65.04 [8$\underline{C}H_2CH_3$], 71.57 (2C), 75.57, 75.78 (2C), 76.04 [inositol ring carbons], 128.89-133.82 [2Ph], 165.82 (2C) [2COPh]; ^{31}P NMR ($CDCl_3$) δ 0.70 (2P), 0.95, 0.98; HRMS (FAB): calcd for $C_{36}H_{57}O_{20}P_4$ m/z 933.2394, found, 933.2392 ($M^+ + H$).

1,4-Di-*O*-benzoyl-*scyllo*-inositol 2,3,5,6-tetrakis(diethyl phosphate) (26c). R_f 0.5 (MeOH:CH_2Cl_2 = 1:10); mp 143–144°C; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.1 Hz, 12H, 4$CH_2C\underline{H}_3$), 1.20 (t, J = 7.1 Hz, 12H, 4$CH_2C\underline{H}_3$), 3.47–4.15 (m, 16H, 8$C\underline{H}_2CH_3$), 4.74–4.82 (m, 4H, H-2, H-3, H-5 and H-6), 5.53–5.60 (m, 2H, H-1 and H-4), 7.43–8.21 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 16.02 (4C), 16.55 (4C) [8$CH_2\underline{C}H_3$], 64.61 (4C), 65.15 (4C) [8$\underline{C}H_2CH_3$], 71.27 (2C), 76.19 (4C) [inositol ring carbons], 128.97–133.86 [2Ph], 165.93 (2C) [2COPh]; ^{31}P NMR ($CDCl_3$) δ 0.75 (4P); MS (FAB) m/z = 933 ($M^+ + H$).

Preparation of sodium salts of *scyllo*-inositol tetrakisphosphate (4a–c). To compound **26a** (47 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) at rt was added TMS-Br (1 mL), and the solution was stirred overnight. The solvent and excess reagent were evaporated, and the residue was dissolved in MeOH (5 mL), then treated with drops of water at 0°C. The reaction mixture was slowly warmed up to rt, evaporated to dryness, and treated with 1 N LiOH (5 mL) 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) and pH was adjusted to 10 with NaOH and lyophilized to give the sodium salt of *scyllo*-inositol tetrakisphosphate (**4a**, 30 mg, 90%). Similarly, compounds **26b** and **26c** were converted to **4b** (29 mg, 87%) and **4c** (29.5 mg, 88%), respectively.

Sodium salt of DL-*scyllo*-inositol 1,2,3,4-tetrakisphosphate (4a). ^{1}H NMR (D_2O, pH 10) δ 3.94 (br. s, 2H, H-5 and H-6), 4.17–4.24 (m, 4H, H-1, H-2, H-3 and H-4); ^{13}C NMR (D_2O, pH 10) δ 74.04 (2C), 76.09 (2C), 80.37 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 5.98 (2P), 6.84 (2P).

Sodium salt of *scyllo*-inositol 1,2,3,5-tetrakisphosphate (4b). ^{1}H NMR (D_2O, pH 10) δ 3.78–3.83 (m, 2H, H-4 and H-6), 4.05–4.13 (m, 4H, H-1, H-2, H-3 and H-5); ^{13}C NMR (D_2O, pH 10) δ 73.49, 75.89 (2C), 76.96, 78.35 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 6.12, 6.75 (2P), 7.08.

Sodium salt of *scyllo*-inositol 1,2,4,5-tetrakisphosphate (4c). ^{1}H NMR (D_2O, pH 10) δ 3.92 (br. s, 2H, H-3 and H-6), 4.05-4.13 (m, 4H, H-1, H-2, H-4 and H-5); ^{13}C NMR (D_2O, pH 10) δ 75.95 (4C), 78.30 (2C) [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 6.85 (4P).

1-Mono-*O*-benzoyl-*scyllo*-inositol 2,3,4,5,6-pentakis(diethyl phosphate) (27). To a solution of compound **18** (43 mg, 0.15 mmol) in DMF (5 mL) at −42°C were added dropwise excess diisopropylethylamine (2 mL, 11.4 mmol) and then diethyl chlorophosphite (0.6 mL, 4.1 mmol) with vigorous stirring. After 30 min, the reaction mixture was allowed to slowly warm up to rt, and stirred for additional 12 h. The mixture was cooled in an ice bath, and sodium phosphate buffer (1 N, pH 7, 5 mL) and excess 30% H_2O_2 (5 mL) were added. After standing overnight at rt, the mixture was diluted with water, and extracted extensively with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, concentrated and chromatographed to give oily **27**

(51 mg, 35%). R_f 0.35 (MeOH:CH_2Cl_2 = 1:10); ^{1}H NMR ($CDCl_3$) δ 0.96–1.38 (m, 30H, 10CH_2CH_3), 3.71–4.26 (m, 20H, 10CH_2CH_3), 4.83–4.93 (m, 5H, H-2, H-3, H-4, H-5 and H-6), 5.67 (t, J = 7.7 Hz, 1H, H-1), 7.34.8.14 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.91–16.49 [10CH_2CH_3], 64.50–65.17 [10CH_2CH_3], 72.71, 76.42, 77.14 (2C), 77.30 (2C) [inositol ring carbons], 128.74 (2C), 129.95, 130.52 (2C), 133.70 [Ph], 165.70 [COPh]; ^{31}P NMR ($CDCl_3$) δ 0.04, 0.29 (2P), 0.53 (2P); HRMS (FAB): calcd for $C_{33}H_{62}O_{22}P_5$ m/z 965.2421, found, 965.2435 ($M^+ + H$).

Sodium salt of *scyllo*-inositol 1,2,3,4,5-pentakisphosphate (5). To compound **27** (45 mg, 0.047 mmol) in CH_2Cl_2 (2 mL) at rt was added TMS-Br (1 mL), and the solution was stirred for 1 day. The solvent and excess reagent were evaporated, and the residue was dissolved in MeOH (5 mL), then treated with drops of water at 0°C. The reaction mixture was slowly warmed up to rt, evaporated to dryness, and treated with 1 N LiOH (5 mL) 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) and pH was adjusted to 10 with NaOH and lyophilized to give the sodium salt of *scyllo*-inositol pentakisphosphate (**5**, 32 mg, 85%). ^{1}H NMR (D_2O, pH 10) δ 4.25 (br. s, 1H, H-6), 4.47 (m, 5H, H-1, H-2, H-3, H-4 and H-5); ^{13}C NMR (D_2O, pH 10) δ 71.03, 72.41–72.73 [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 5.79 (2P), 6.08, 6.55 (2P).

***scyllo*-Inositol (28).** A mixture of **18** (142 mg, 5 mmol) and NaOMe (cat.) in MeOH (10 ml) was heated at reflux for 3 h. After cooling, the resulting solution was concentrated under reduced pressure. Crystallization of the mixture from MeOH–acetone gave a solid, **28** (80 mg, 88%). Mp > 330°C (lit.[36] mp 352°C); ^{1}H NMR (D_2O) δ 3.33 (s, 6H, H-1, H-2, H-3, H-4, H-5 and H-6); ^{13}C NMR (D_2O) δ 73.79 [inositol ring carbons].

***scyllo*-Inositol hexakis(dibenzyl phosphate) (29).** To a solution of compound **28** (18 mg, 0.1 mmol) and 1*H*-tetrazole (215 mg, 3 mmol) in a mixed solvent (CH_2Cl_2:DMF = 1:1, 8 mL) at rt was added dibenzyl diisopropylphosphoramidite (0.8 mL, 2.38 mmol). After 1 day, the mixture was cooled in an ice bath, and sodium phosphate buffer (1 N, pH 7, 5 mL) and excess 30% H_2O_2 (5 mL) were added. After standing overnight at rt, the mixture was diluted with water, and extracted extensively with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, concentrated and chromatographed to give oily **29** (77 mg, 44%). R_f 0.37 (EtOAc:hexane = 1:1); ^{1}H NMR ($CDCl_3$) δ 4.93–5.07 (m, 24H, 12CH_2Ph), 5.18 (br. d, J = 7.4 Hz, 6H, H-1, H-2, H-3, H-4, H-5 and H-6), 7.16–7.25 (m, 60H, 12Ph); ^{13}C NMR ($CDCl_3$) δ 70.32 [12CH_2Ph], 76.95 [inositol ring carbons], 128.49–136.08 [12Ph]; ^{31}P NMR ($CDCl_3$) δ 0.66 (6P); MS (FAB) m/z = 1741 ($M^+ + H$).

Sodium salt of *scyllo*-inositol hexakisphosphate (6). A mixture of compound **29** (31 mg, 0.018 mmol), 10% Pd/C (30 mg) and $NaHCO_3$ (5 mg) in a mixed solvent (H_2O:MeOH = 1:2, 9 mL) was stirred under H_2 (50 psi). After 1 day, the catalyst was filtered off and the solvent was evaporated under reduced pressure. The reaction mixture was redissolved in a small amount of water (1 mL), pH adjusted to 10 with NaOH, and lyophilized to give the sodium salt of *scyllo*-inositol hexakisphosphate (**6**, 15.5 mg, 94%). ^{1}H NMR (D_2O, pH 10) δ 4.57 (d, J = 10.3 Hz, 6H, H-1, H-2, H-3, H-4, H-5 and H-6); ^{13}C NMR (D_2O, pH 10) δ 71.14 [inositol ring carbons]; ^{31}P NMR (D_2O, pH 10) δ 5.99 (6P).

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