Diastereoselective Synthesis of D- and L-*myo*-Inositol 3,4,5,6-Tetrakisphosphates from D-Glucose *via* Dihydroxylation of (+)-Conduritol B Derivatives

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Syntheses of D- and L-*myo*-inositol 3,4,5,6-tetrakisphosphates were achieved *via* diastereoselective 1,2-addition of vinylcopper reagent with the chiral aldehyde prepared from 1,2,5,6-diisopropylidene-D-glucose, ring-closing metathesis of 1,7-diene with Grubbs catalyst followed by catalytic OsO_4 dihydroxylation of (+)-conduritol B derivatives.

Key words I(3,4,5,6)P4; ring-closing metathesis; dihydroxylation; total synthesis

Phosphorylated phosphatidyl-*myo*-inositols and *myo*-inositol phosphates play important roles as second messengers in intracellular signal transduction.[1)] We have previously reported on the synthesis of various lipid analogs as artificial second messengers and biochemical probes.[2—12)]

Recently, D- and L-*myo*-inositol 3,4,5,6-tetrakisphosphates (**D-1** and **L-1**) were identified as novel bioactive molecules (Fig. 1), which play distinct but critical roles in cellular signaling.[13—23)] **D-1** is responsible for the inhibition of the calcium-mediated chloride section. It may have therapeutic implications for diseases like cystic fibrosis and secretory diarrhea. In contrast, **L-1** inhibits insulin-like growth factor 1 (IGF-1) induced thymidine incorporation in human breast cancer cells and thus prevents the ability of these cells to grow. Recent studies have revealed that **L-1** is also involved in nuclear processes since it is required for gene regulation and may control gene expression. Their mechanisms of action are far from being elucidated but appear to be closely related to the number and position of the phosphate groups on the inositol ring. Thus, a new area of design of anticancer drugs can be envisaged for the future.

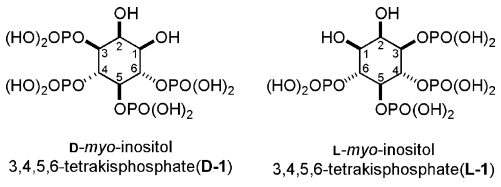

Fig. 1

In order to synthesize suitably protected optically active *myo*-inositol derivatives with appropriate stereogenic centers, Ferrier rearrangement,[24,25)] pinacol coupling[26—30)] and ring-closing metathesis (RCM)[12,31)] of chiral intermediates derived from precursors such as carbohydrates and tartaric acid derivatives, have been performed in addition to optical resolution[32—34)] of racemic *myo*-inositol derivatives. In this article, we describe the efficient syntheses of both enantiomers of *myo*-inositol 3,4,5,6-tetrakisphosphates *via* ring-closing metathesis of 1,7-diene with Grubbs catalyst followed by catalytic OsO_4 dihydroxylation of (+)-conduritol B derivatives (Chart 1).

The 1,2-addition of vinylcopper to the known aldehyde (**3**)[35)] derived from D-glucose gave the desired allyl alcohol (**4**) with high diastereoselectivity (>99%de).[36)] In order to synthesize both **D-1** and **L-1** from common intermediate **4**, its hydroxyl group was protected as 4-methoxybenzyl ether (R^1=PMB, **5a**) for **D-1** and 2-methoxybenzyl ether (R^1=OMB, **5b**) for **L-1**. Acidic hydrolysis of isopropylidene acetal with aqueous 3 N-H_2SO_4 in THF, gave an anomeric mixture of the hemiacetal (**6a**, **b**), which was subjected to Wittig methylenation to give the 1,7-diene (**7a**, **b**). RCM of **7a** or **7b** using Grubbs catalyst gave the conduritol B derivatives (**8a**, **b**) in good yield. To confirm the relative and absolute stereochemistry of **8a**, PMB ether was hydrolyzed

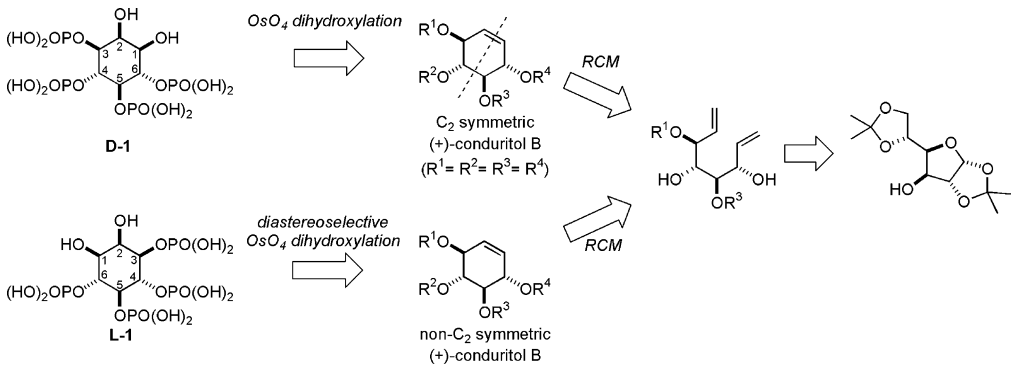

Chart 1

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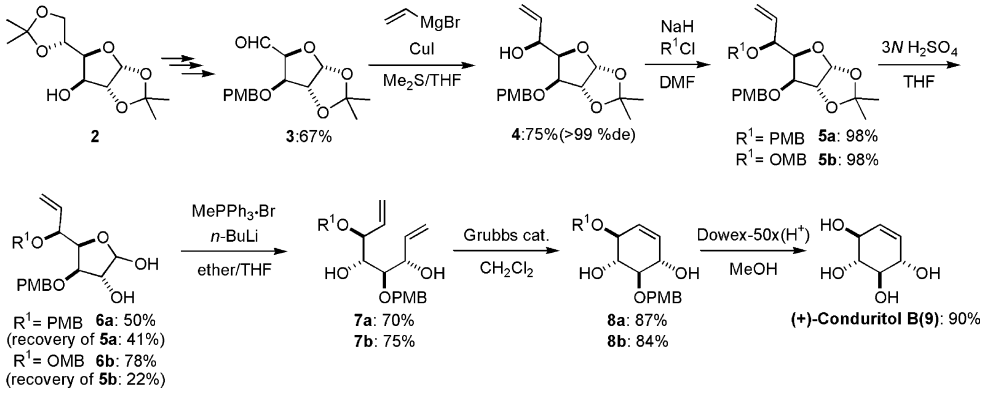

Chart 2

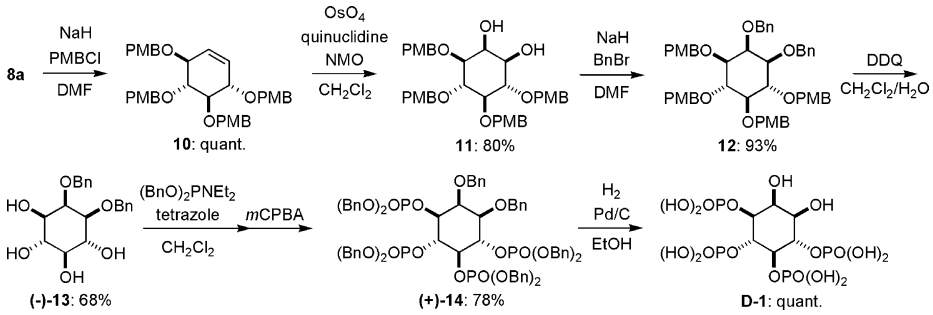

Chart 3

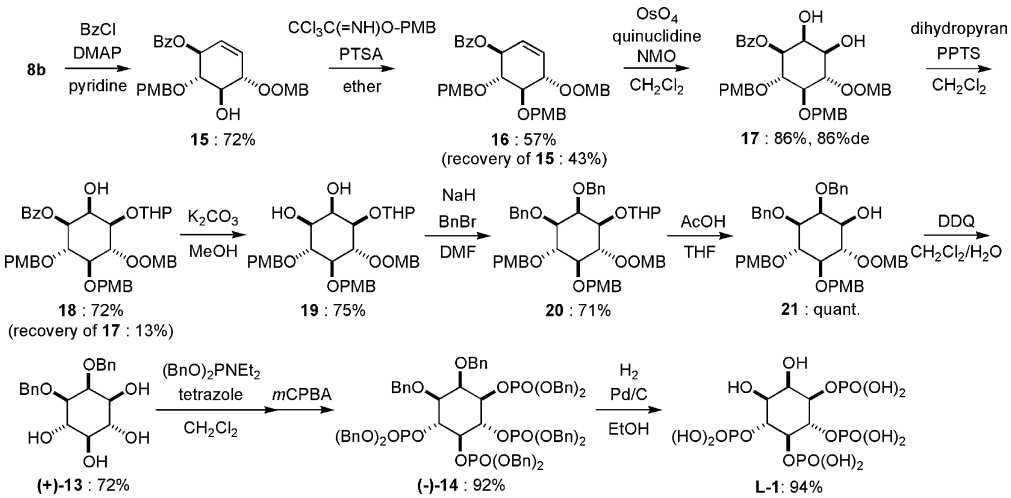

Chart 4

with the Dowex-50X^{TM}(H^+) in MeOH to give (+)-conduritol B (**9**)[37] (Chart 2).

As the syntheses of the chiral conduritol B derivatives (**8a**, **b**) were successfully completed, the dihydroxylation of conduritol B derivative to *myo*-inositol derivatives by osmium tetroxide was investigated. Two hydroxyl groups of **8a**, a precursor of **D-1**, were protected as PMB ether to give the C_2-symmetric conduritol B derivative (**10**), which was dihydroxylated utilizing a catalytic amount of osmium tetroxide, to give *myo*-inositol derivative as the sole product **11**. The resulting 1,2-diol was protected as benzyl ether, and all PMB groups were oxidatively removed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Then, the four hydroxyl groups of (−)-**13** were phosphorylated by the amidite method[38] to give the fully protected (+)-**14**. Finally, hydrogenolysis of (+)-**14** with Pd–C as a catalyst gave **D-1**[39] (Chart 3).

Next, the synthesis of **L-1**, an enantiomer of **D-1**, was achieved by diastereoselective and regioselective transformation of intermediate **8b**. As predicted, the OsO_4 oxidation of non-C_2 symmetric (+)-conduritol B derivatives (**8b)**, having two ether-type protective groups at both allylic hydroxyl groups, showed no diastereofacial selectivity.[12] However, when one allylic alcohol was protected as benzoate and another was protected as 2-methoxybenzyl ether, dihydroxylation took place from the same side of benzoate in 86%de to

give the diol **17**, which was easily purified by silica gel column chromatography. Regioselective protection of the equatorially oriented C-1 hydroxyl group as THP ether, followed by methanolysis of the benzoate, gave **18**. The benzylation of 1,2-diol and the removal of THP and PMB gave the *myo*-inositol derivative ((+)-**13**), an enantiomer of (−)-**13**. Finally, (+)-**13** was successfully converted to **L-1** the same as (−)-**13** gave **D-1**.

In conclusion, we have achieved efficient syntheses of both enantiomers of *myo*-inositol 3,4,5,6-tetrakisphosphates (**D-1**, **L-1**), *via* the RCM of 1,7-diene with Grubbs catalyst followed by catalytic OsO_4 dihydroxylation of (+)-conduritol B derivatives. The synthesis is not only a series of inositol analogs, but also various six-membered cyclitols.

Experimental

General Methods IR spectra were recorded on a Jasco IR report-100 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-AL300N (300 MHz) or a JNM-ECP500 (500 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a JEOL JNM-AL300N (75 MHz) or a JNM-ECP500 (125 MHz) spectrometer. ^{31}P-NMR spectra were recorded on a JEOL JNM-ECP400 (162 MHz) with 80% phosphoric acid as an external standard. Mass spectrometry were reading on a JEOL JMS-700 and a JMS-HX110 mass spectrometer. The melting point was determined using a yanaco MP-S3 macro melting point apparatus and were uncorrected. Optical rotation was obtained with a Jasco P-1020 polarimeter. Column chromatography was carried out on silica gel 60 (40—100 mesh, Spherical, Kanto). The elemental analysis was obtained with a PE2400 CHNS/O.

1,2-*O*-Isopropylidene-3-*O*-(4′-methoxybenzyl)-5-*C*-vinyl-β-L-*ido*-pentofuranose 4 To a solution of copper iodide (9.43 g, 49.5 mmol) in dimethylsulfide (26 ml) and tetrahydrofuran (130 ml) was added vinylmagnesium bromide (45.0 ml, 43.7 mmol) at −40 °C. After 5 min, a solution of **3** (4.49 g, 14.6 mmol) in tetrahydrofuran (24 ml) was added to the mixture at −40 °C and the reaction mixture was allowed to stand at room temperature for 3 h. Then, the reaction mixture was diluted with aqueous ammonium hydrochloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2/AcOEt=30/1 to 4/1) to afford **4** (3.69 g, 75%) as a colorless oil and the recovered **3** (666 mg, 15%). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H), 1.48 (s, 3H), 2.81 (br, 1H), 3.81 (s, 3H), 3.94 (d, J=3.5 Hz, 1H), 4.05 (dd, J=3.5, 6.4 Hz, 1H), 4.40 (d, J=11.6 Hz, 1H), 4.49 (tdd, J=1.6, 5.7, 6.4 Hz, 1H), 4.62 (d, J=11.6 Hz, 1H), 4.63 (d, J=3.8 Hz, 1H), 5.20 (td, J=1.7, 10.7 Hz, 1H), 5.41 (td, J=1.7, 16.9 Hz, 1H), 5.81 (ddd, J=5.7, 10.7, 16.9 Hz, 1H), 5.98 (d, J=3.8 Hz, 1H), 6.89 (d, J=8.8 Hz, 2H), 7.24 (d, J=8.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 26.30, 26.78, 55.27, 60.37, 70.93, 71.63, 82.16, 82.88, 105.01, 111.86, 113.96 (2C), 116.94, 128.84, 129.53 (2C), 135.73, 159.56. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{18}H_{24}O_6Na$ $(M+Na)^+$ 359.1471, Found 359.1469. IR (neat) cm^{-1}: 3600, 3500, 3000, 2930, 1730, 1610, 1580, 1510, 1450. $[\alpha]_D$ −59.7 (c=1.0, $CHCl_3$).

1,2-*O*-Isopropylidene-3,5-*O*-di-(4′-methoxybenzyl)-5-*C*-vinyl-β-L-*ido*-pentofuranose 5a A solution of **4** (399 mg, 1.19 mmol) in *N*,*N*-dimethylformamide (4 ml) was cooled in an ice bath and slowly mixed with 60% sodium hydride (71.1 mg, 1.78 mmol). The reaction mixture was stirred at the same temperature for 2 h. Then, 4-methoxybenzyl chloride (0.21 ml, 1.54 mmol) was added dropwise while cooling in an ice bath. The reaction mixture was stirred at room temperature overnight, poured onto ice, diluted with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4) to afford **5a** (529 mg, 98%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (s, 3H), 1.48 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.92 (d, J=1.8 Hz, 1H), 4.17 (d, J=1.8 Hz, 1H), 4.18 (d, J=2.7 Hz, 1H), 4.35 (d, J=11.1 Hz, 1H), 4.48 (d, J=11.1 Hz, 1H), 4.53 (d, J=11.1 Hz, 1H), 4.54 (d, J=11.1 Hz, 1H), 4.56 (d, J=3.8 Hz, 1H), 5.26 (dd, J=2.0, 10.5 Hz, 1H), 5.36 (dd, J=2.0, 17.1 Hz, 1H), 5.72 (ddd, J=2.7, 10.5, 17.1 Hz, 1H), 5.98 (d, J=3.8 Hz, 1H), 6.84 (d, J=8.1 Hz, 2H), 6.87 (d, J=8.1 Hz, 2H), 7.20 (d, J=8.6 Hz, 2H), 7.25 (d, J=8.6 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 26.36, 26.78, 55.23, 55.26, 70.63, 71.55, 78.64, 81.68, 82.17, 82.86, 105.29, 111.64, 113.60 (2C), 113.80 (2C), 118.96, 129.29 (2C), 129.35, 129.42 (2C), 130.79, 134.39, 158.93, 159.37. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{26}H_{32}O_7Na$ $(M+Na)^+$ 479.2046, Found 479.2059. IR (neat) cm^{-1}: 2950, 1730, 1610, 1580, 1520, 1460, 1370, 1300. $[\alpha]_D$ −26.9 (c=1.02, $CHCl_3$).

1,2-*O*-Isopropylidene-3-*O*-(4′-methoxybenzyl)-5-*O*-(2′-methoxybenzyl)-5-*C*-vinyl-β-L-*ido*-pentofuranose 5b A solution of **4** (1.47 g, 4.38 mmol) in *N*,*N*-dimethylformamide (10 ml) was cooled in an ice bath and slowly mixed with 60% sodium hydride (316 mg, 7.89 mmol). The reaction mixture was stirred at the same temperature for 2 h. Then, 2-methoxybenzyl chloride (0.73 ml, 5.26 mmol) was added dropwise while cooling in an ice bath. The reaction mixture was stirred at room temperature overnight, poured onto ice, diluted with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4) to afford **5a** (1.96 g, 98%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 3H), 1.50 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 3.84 (d, J=5.1 Hz, 1H), 4.19—4.27 (m, 2H), 4.35 (d, J=11.1 Hz, 1H), 4.44 (d, J=11.1 Hz, 1H), 4.58 (d, J=11.1 Hz, 1H), 4.58 (d, J=3.9 Hz, 1H), 4.62 (d, J=11.1 Hz, 1H), 5.25 (dd, J=1.9, 10.5 Hz, 1H), 5.40 (dd, J=1.9, 17.2 Hz, 1H), 5.74 (ddd, J=6.3, 10.5, 17.2 Hz, 1H), 6.00 (d, J=3.9 Hz, 1H), 6.8—7.0 (m, 4H), 7.2—7.3 (m, 3H), 7.53 (d, J=7.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 26.36, 26.79, 55.20, 55.26, 65.84, 71.53, 79.09, 81.69, 82.19, 82.85, 105.30, 109.79, 111.61, 113.77 (2C), 118.81 (2C), 120.39, 127.35, 127.94, 128.53, 129.39 (2C), 134.41, 156.62, 159.33. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{26}H_{32}O_7Na$ $(M+Na)^+$ 479.2046, Found 479.2053. IR (neat) cm^{-1}: 2900, 1740, 1610, 1590, 1520, 1490, 1460, 1370, 1300, 1240, 1170, 1050. $[\alpha]_D$ −26.6 (c=1.25, $CHCl_3$).

3,5-*O*-Di-(4′-methoxybenzyl)-5-*C*-vinyl-β-L-*ido*-pentofuranose 6a To a solution of **5a** (232 mg, 0.51 mmol) in tetrahydrofuran (20 ml) was added 3 N sulfuric acid (2 ml) and stirred at 40 °C for 40 h. The reaction mixture was neutralized with anhydrous sodium carbonate, diluted water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=2/3 to 2/1) to afford **6a** (106 mg 50%) as a colorless oil and the recovered **5a** (96.1 mg, 41%). ^{1}H-NMR ($CDCl_3$) δ: 3.78—3.82 (m, 6H), 3.84—4.62 (m, 8H), 5.00—5.54 (m, 3H), 5.68—5.93 (m, 1H), 6.81—6.91 (m, 4H), 7.15—7.28 (m, 4H). HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{23}H_{28}O_7Na$ $(M+Na)^+$ 439.1733, Found 439.1728.

3-*O*-(4′-Methoxybenzyl)-5-*O*-(2-methoxybenzyl)-5-*C*-vinyl-β-L-*ido*-pentofuranose 6b To a solution of **5b** (228 mg, 0.50 mmol) in tetrahydrofuran (16 ml) was added 3 N sulfuric acid (1.6 ml) and stirred at 60 °C for 30 h. The reaction mixture was neutralized with anhydrous sodium carbonate, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=2/3 to 2/1) to afford **6b** (163 mg 78%) as a colorless oil and the recovered **5b** (53.0 mg, 22%). ^{1}H-NMR ($CDCl_3$) δ: 3.76—3.79 (m, 6H), 3.84—4.70 (m, 8H), 4.91—5.52 (m, 3H), 5.67—6.04 (m, 1H), 6.78—6.95 (m, 4H), 7.17—7.45 (m, 4H). HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{23}H_{28}O_7Na$ $(M+Na)^+$ 439.1733, Found 439.1723.

(3*S*,4*R*,5*R*,6*S*)-3,5-Di-(4′-methoxybenzyloxy)-4,6-dihydro-octa-1,7-diene 7a Methyltriphenylphosphonium bromide (6.83 g, 19.1 mmol) was suspended in ether (20 ml). Then the reaction mixture was treated with *n*-butyllithium (10.0 ml, 15.6 mmol) and stirred at room temperature for 2 h. A solution of **6a** (1.33 g, 3.19 mmol) in tetrahydrofuran (20 ml) was added to the reaction mixture, and stirred at the same temperature overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4 to 1/2) to afford **7a** (931 mg, 70%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.6—2.9 (br, 2H), 3.48 (dd, J=3.6, 4.5 Hz, 1H), 3.72 (dd, J=3.6, 6.2 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.98 (dd, J=6.2, 7.6 Hz, 1H), 4.26—4.33 (m, 1H), 4.30 (d, J=11.1 Hz, 1H), 4.53 (d, J=10.8 Hz, 1H), 4.59 (d, J=11.1 Hz, 1H), 4.65 (d, J=10.8 Hz, 1H), 5.20 (td, J=1.5, 10.5 Hz, 1H), 5.27—5.41 (m, 3H), 5.79 (ddd, J=7.6, 10.2, 17.4 Hz, 1H), 5.91 (ddd, J=5.7, 10.5, 17.4 Hz, 1H), 6.8—7.0 (m, 4H), 7.2—7.3 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 55.27 (2C), 70.09, 73.11, 73.80, 74.21, 80.07, 80.66, 113.86 (2C), 113.90 (2C), 116.42, 120.19, 129.58 (2C), 129.76 (2C), 130.18, 130.2, 134.87, 137.88, 159.35, 159.38. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{24}H_{30}O_6Na$ $(M+Na)^+$ 437.1940, Found 437.1926. IR (neat) cm^{-1}: 3470, 2900, 1610, 1580, 1515, 1490, 1460,

1440, 1240. $[\alpha]_D$ +18.7 (c=1.03, $CHCl_3$).

(3*S*,4*R*,5*R*,6*S*)-3-(2′-Methoxybenzyloxy)-5-(4′-methoxybenzyloxy)-4,6-dihydro-octa-1,7-diene 7b Methyltriphenylphosphonium bromide (5.59 g, 15.7 mmol) was suspended in ether (20 ml). Then the reaction mixture was treated with *n*-butyllithium (8.20 ml, 12.8 mmol) and stirred at room temperature for 1.5 h. A solution of **6b** (1.09 g, 2.16 mol) in tetrahydrofuran (20 ml) was added to the reaction mixture, and stirred at the same temperature overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4 to 1/2) to afford **7b** (810 mg, 75%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.8—3.3 (br, 2H), 3.45 (dd, J=3.5, 4.8 Hz, 1H), 3.72 (dd, J=3.5, 6.8 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 4.02 (dd, J=6.8, 7.6 Hz, 1H), 4.36 (tdd, J=1.5, 4.8, 5.8 Hz, 1H), 4.45 (d, J=11.1 Hz, 1H), 4.51 (d, J=11.1 Hz, 1H), 4.61 (d, J=11.1 Hz, 1H), 4.65 (d, J=11.1 Hz, 1H), 5.19 (td, J=1.5, 10.6 Hz, 1H), 5.31—5.40 (m, 3H), 5.78 (ddd, J=7.6, 10.8, 16.9 Hz, 1H), 5.92 (ddd, J=5.8, 10.6, 17.2 Hz, 1H), 6.83—6.96 (m, 4H), 7.20—7.33 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 55.08, 55.10, 66.56, 73.11, 73.84, 74.06, 80.39, 80.83, 110.26 (2C), 113.63 (2C), 116.06, 119.59, 120.26, 125.75, 129.18, 129.40 (2C), 129.61, 129.78, 130.22, 134.59, 137.85, 157.43, 159.11. HR-FAB-MS (NBA+NaCl) m/z: Calcd $C_{24}H_{30}O_6Na$ $(M+Na)^+$ 437.1940, Found 437.1942. IR (neat) cm^{-1}: 3470, 2900, 1610, 1580, 1515, 1490, 1460, 1440, 1240. $[\alpha]_D$ +8.93 (c=1.04, $CHCl_3$).

(+)-3,5-*O*-Di-(4′-methoxybenzyl)-conduritol B 8a To a solution of **7a** (50.0 mg, 0.12 mmol) in methylene chloride (10 ml) was added benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (1st Grubbs catalyst) (9.9 mg, 0.012 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/1) to afford **8a** (40.5 mg, 87%) as a colorless solid. mp 130—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.39 (dd, J=7.9, 10.3 Hz, 1H), 3.80 (s, 6H), 3.80 (dd, J=7.9, 10.3 Hz, 1H), 4.08 (tdd, J=1.8, 3.2, 7.9 Hz, 1H), 4.29 (td, J=1.8, 7.9 Hz, 1H), 4.64 (d, J=11.4 Hz, 1H), 4.68 (d, J=11.4 Hz, 1H), 4.77 (d, J=11.4 Hz, 1H), 4.83 (d, J=11.4 Hz, 1H), 5.61 (td, J=1.8, 10.3 Hz, 1H), 5.68 (td, J=1.8, 10.3 Hz, 1H), 6.86—6.93 (m, 4H), 7.27—7.34 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 55.28 (2C), 71.82, 72.82, 74.71, 75.01, 79.43, 84.13, 113.89 (2C), 114.12 (2C), 127.32 (2C), 129.47 (2C), 129.67 (2C), 130.38, 130.47, 159.30, 159.50. IR (KBr) cm^{-1}: 1610, 1510, 1460, 1300, 1250. HR-FAB-MS (NBA+NaCl) m/z: Calcd $C_{22}H_{26}O_6Na$ $(M+Na)^+$ 409.1627, Found 409.1613. $[\alpha]_D$: +96.2° (c=0.52, $CHCl_3$).

(+)-3-*O*-(2′-Methoxybenzyl)-5-*O*-(4′-methoxybenzyl)-conduritol B 8b To a solution of **7b** (3.43 g, 8.28 mmol) in methylene chloride (140 ml) was added benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (1st Grubbs catalyst) (681 mg, 0.83 mmol, 10 mol%) and stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/1) to afford **8a** (2.69 m, 84%) as a colorless solid. mp 134—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (br, 1H), 3.05 (br, 1H), 3.43 (dd, J=7.8, 10.3 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 3.84 (dd, J=7.8, 10.3 Hz, 1H), 4.09—4.15 (m, 1H), 4.26—4.31 (m, 1H), 4.72 (s, 2H), 4.74 (d, J=11.4 Hz, 1H), 4.88 (d, J=11.4 Hz, 1H), 5.62 (td, J=2.0, 10.3 Hz, 1H), 5.75 (td, J=2.0, 10.3 Hz, 1H), 6.88—6.98 (m, 4H), 7.26—7.39 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 55.19, 55.35, 67.52, 72.06, 74.42, 74.80, 80.58, 83.78, 110.32, 113.97 (2C), 120.51, 126.32, 127.17, 129.10, 129.29, 129.57, 129.63 (2C), 130.60, 157.23, 159.31. *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.13; H, 6.70. IR (KBr) cm^{-1}: 3350, 2900, 1610, 1580, 1510, 1490, 1460, 1390, 1360. $[\alpha]_D$ +125 (c=1.03, $CHCl_3$).

(+)-Conduritol B 9 To a solution of **8a** (100 mg, 0.26 mmol) in MeOH (5 ml) was added water (5 ml) and Dowex-50xw8^{TM}(H^+). Then, the reaction mixture was refluxed for 5 h. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was dissolved in the water, and washed with $CHCl_3$. The aqueous layer was lyophilized to afford **9** (33.6 mg, 90%) as a colorless solid. mp 172—173 °C. ^{1}H-NMR (CD_3OD) δ: 3.36 (d, J=7.5 Hz, 2H), 4.19 (d, J=7.5 Hz, 2H), 5.53 (s, 2H). ^{13}C-NMR (CD_3OD) δ: 77.63 (2C), 77.43 (2C), 130.70 (2C). $[\alpha]_D$ +183 (c=1.1, CH_3OH).

(+)-3,4,5,6-*O*-Tetra-(4′-methoxybenzyl)-conduritol B 10 A solution of **8a** (138 mg, 0.35 mmol) in *N*,*N*-dimethylformamide (5 ml) was cooled in an ice bath and slowly mixed with 60% sodium hydride (49.9 mg, 1.25 mmol). The reaction mixture was stirred at the same temperature for 2 h. Then, 4-methoxybenzyl chloride (0.15 ml, 1.07 mmol) was added dropwise while cooling in an ice bath. The reaction mixture was stirred at room temperature overnight, poured onto ice, diluted with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/9 to 2/1) to afford **10** (228 mg, quant.) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (td, J=5.1, 7.7 Hz, 2H), 3.60 (s, 6H), 3.62 (s, 6H), 4.04 (td, J=5.1, 7.7 Hz, 2H), 4.45 (d, J=11.1 Hz, 2H), 4.50 (d, J=11.1 Hz, 2H), 4.66 (d, J=10.5 Hz, 2H), 4.73 (d, J=10.5 Hz, 2H), 5.54 (s, 2H), 6.71 (d, J=8.4 Hz, 4H), 6.72 (d, J=8.4 Hz, 4H), 7.13 (d, J=8.4 Hz, 4H), 7.15 (d, J=8.4 Hz, 4H). ^{13}C-NMR ($CDCl_3$) δ: 54.92 (4C), 71.82 (2C), 74.92 (2C), 79.65 (2C), 83.22 (2C), 113.46 (4C), 113.53 (4C), 127.45 (2C), 129.16 (4C), 129.30 (4C), 130.25 (2C), 130.77 (2C), 158.88 (2C), 158.96 (2C). *Anal.* Calcd for $C_{38}H_{42}O_8$: C, 72.82; H, 6.75. Found: C, 72.54; H, 6.79. IR (neat) cm^{-1}: 3000, 2950, 2400, 1610, 1580, 1510, 1460, 1300. $[\alpha]_D$ +65.9 (c=1.04, $CHCl_3$).

3,4,5,6-*O*-Tetra-(4′-methoxybenzyl)-D-*myo*-inositol 11 To an ice-cooled solution of **10** (470 mg, 0.72 mmol) in methylene chloride (15 ml) was added quinuclidine (4.2 mg, 0.036 mmol, 5 mol%), 4-methylmorpholine *N*-oxide (252 mg, 2.15 mmol) and 2% osmium tetroxide in water (0.46 ml, 0.036 mmol, 5 mol%). The reaction mixture was stirred at room temperature for 4 d, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4 to 2/1) to afford **11** (379 mg, 80%) as a colorless solid. mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (br, 2H), 3.39—3.45 (m, 3H), 3.78 (s, 3H), 3.78 (t, J=9.5 Hz, 1H), 3.80 (s, 3H), 3.91 (t, J=9.5 Hz, 1H), 4.13 (t, J=2.4 Hz, 1H), 4.59—4.89 (m, 8H), 6.85 (d, J=8.4 Hz, 4H), 7.23—7.27 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 55.21 (2C), 55.23 (2C), 69.09, 71.63, 72.34, 75.18, 75.32, 75.55, 79.70, 80.89, 81.41, 82.98, 113.73 (2C), 113.76 (2C), 113.84 (2C), 113.94 (2C), 129.38 (2C), 129.48 (2C), 129.52 (2C), 129.57 (2C), 129.87, 130.63, 130.74, 130.87, 159.10 (2C), 159.28, 159.32. *Anal.* Calcd for $C_{38}H_{42}O_8$: C, 69.07; H, 6.71. Found: C, 68.94; H, 6.69. IR (KBr) cm^{-1}: 3400, 2900, 1610, 1580, 1520, 1460, 1350, 1300. $[\alpha]_D$ −22.6 (c=1.04, $CHCl_3$).

1,2-*O*-Dibenzyl-3,4,5,6-*O*-tetra-(4′-methoxybenzyl)-D-*myo*-inositol 12 A solution of **11** (379 mg, 0.57 mmol) in *N*,*N*-dimethylformamide (5 ml) was cooled in an ice bath and slowly mixed with 60% sodium hydride (73.4 mg, 1.84 mmol). The reaction mixture was stirred at the same temperature for 2 h. Then, benzyl bromide (0.18 ml, 1.55 mmol) was added dropwise while cooling in an ice bath. The reaction mixture was stirred at room temperature overnight, poured onto ice, diluted with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4) to afford **12** (446 mg, 93%) as a colorless solid. mp 90—91 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.30 (dd, J=2.4, 9.9 Hz, 1H), 3.34 (dd, J=2.4, 9.9 Hz, 1H), 3.42 (t, J=9.2 Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.99 (m, 1H), 4.03 (dd, J=9.2, 9.9 Hz, 1H), 4.04 (dd, J=9.2, 9.9 Hz, 1H), 4.51 (d, J=11.4 Hz, 1H), 4.58 (d, J=11.4 Hz, 1H), 4.59 (d, J=11.4 Hz, 1H), 4.65 (d, J=11.4 Hz, 1H), 4.73—4.86 (m, 8H), 6.79—6.87 (m, 8H), 7.20—7.42 (m, 18H). ^{13}C-NMR ($CDCl_3$) δ: 55.23 (2C), 55.25 (2C), 72.42, 72.73, 74.03, 74.40, 75.46, 75.49, 75.53, 80.72, 80.97, 81.44 (2C), 83.49, 113.68 (4C), 113.73 (4C), 127.26, 127.48 (2C), 127.53, 127.72 (2C), 128.09 (2C), 128.34 (2C), 129.14 (2C), 129.32 (2C), 129.67 (2C), 129.69 (2C), 130.53, 131.07, 131.12, 131.16, 138.47, 139.01, 159.02, 159.06 (2C), 159.10. *Anal.* Calcd for $C_{52}H_{56}O_{10}$: C, 74.26; H, 6.71. Found: C, 74.03; H, 6.69. IR (KBr) cm^{-1}: 2900, 1610, 1580, 1510, 1450, 1350, 1300, 1250. $[\alpha]_D$ +0.80 (c=1.03, $CHCl_3$).

1,2-*O*-Dibenzyl-D-*myo*-inositol (−)-13 To a solution of **12** (161 mg, 0.19 mmol) in methylene chloride (3 ml) was added water (0.3 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (261 mg, 1.15 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with water and methanol and filtered by Dowex-1X4-50^{TM}(OH^-). The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography ($MeOH/CHCl_3$=1/3) to afford (−)-**13** (46.8 mg, 68%) as a colorless solid. mp 200—201 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (t, J=9.3 Hz, 1H), 3.19—3.20 (m, 1H), 3.28 (dd, J=2.7, 9.9 Hz, 1H), 3.56 (t, J=9.3 Hz, 1H), 3.73 (t, J=9.3 Hz, 1H), 3.93 (t, J=2.7 Hz, 1H), 4.53 (d, J=12.3 Hz, 1H), 4.58 (d, J=12.3 Hz, 1H), 4.68 (d, J=12.3 Hz, 1H), 4.73 (d, J=12.3 Hz, 1H), 7.14—7.30 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 73.58, 73.77, 74.19, 74.62, 75.84, 76.80, 79.12, 81.94, 128.32, 128.62, 128.88 (2C), 129.01 (2C), 129.08 (2C), 129.32 (2C), 139.98, 140.57. HR-FAB-MS (NBA+NaCl) m/z: Calcd $C_{20}H_{24}O_6Na$ $(M+Na)^+$ 383.1471, Found 383.1482. IR (KBr) cm^{-1}: 3400, 30250, 2920, 2500, 1490, 1410, 1370. $[\alpha]_D$ −39.5 (c=0.26, MeOH).

1,2-*O*-Dibenzyl-D-*myo*-inositol 3,4,5,6-tetrakisphoric acid dibenzyl

ester (+)-14 To a solution of (−)-**13** (60.3 mg, 0.17 mmol) in methylene chloride (6 ml) was added 1*H*-tetrazole (117 mg, 1.67 mmol) and dibenzyl diethylphosphoramidite (0.56 ml, 1.59 mmol). Then the reaction mixture was stirred at room temperature overnight. To the reaction mixture was added water (1.0 ml) and 3-chloroperbenzoic acid (618 mg, 2.5 mmol) at −78 °C. Then the reaction mixture was allowed to stand at room temperature for 40 min, diluted with aqueous 10% sodium sulfite, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/9 to 1/4) to afford (+)-**14** (173 mg, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (dd, J=2.0, 9.8 Hz, 1H), 4.23 (ddd, J=2.1, 7.5, 9.5 Hz, 1H), 4.40—4.56 (m, 4H), 4.68 (d, J=11.7 Hz, 1H), 4.79 (d, J=11.7 Hz, 1H), 4.81—5.09 (m, 18H), 7.06—7.32 (m, 50H). ^{31}P-NMR ($CDCl_3$) δ: −0.65, −0.78, −1.45, −1.58. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{76}H_{77}O_{18}P_4$ $(M+H)^+$ 1401.4060, Found 1401.4064. IR (neat) cm^{-1}: 3480, 3060, 3030, 2950, 2900, 1960, 1890, 1810, 1740, 1610, 1500, 1460. $[\alpha]_D$ +0.91 (c=1.08, $CHCl_3$).

D-*myo*-Inositol 3,4,5,6-Tetrakisphosphate D-1 To a solution of (+)-**14** (152 mg, 0.11 mmol) in ethanol (5 ml) was added 10% palladium on carbon (25 mg) and the mixture was stirred under hydrogen atmosphere at room temperature for 27 h. The catalyst was removed by filtration and washed with water. The filtrate was washed with chloroform and lyophilized to afford **D-1** (33.6 mg, 90%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (dd, J=2.1, 9.6 Hz, 1H), 3.98—4.08 (m, 3H), 4.17 (dt, J=9.0, 9.3 Hz, 1H), 4.29 (dt, J=9.0, 9.3 Hz, 1H). ^{31}P-NMR (D_2O) δ: 0.16, 0.78 (2P), 1.05. HR-FAB-MS (Gly) *m/z*: Calcd $C_6H_{17}O_{18}P_4$ $(M+H)^+$ 500.9365, Found 500.9368. $[\alpha]_D$ +2.26 (c=1.12, H_2O).

(+)-3-*O*-Benzoyl-4-*O*-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-conduritol B 15 To an ice-cooled stirred solution of **8b** (792 mg, 2.05 mmol) and 4-dimethylaminopyridine (1 portion) in pyridine (10 ml) was added benzoyl chloride (0.264 ml, 2.25 mmol). The reaction mixture was stirred at room temperature for 4 h, diluted with water, and extracted with ethyl acetate. The organic layer was washed with aqueous hydrochloric acid and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4 to 2/1) to afford **15** (729 mg, 72%) as a colorless oil and 5-*O*-benzoate (210 mg, 17%). ^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H) 3.83 (dd, J=7.6, 10.3 Hz, 1H), 3.86 (s, 3H), 3.94 (dd, J=7.6, 10.3 Hz, 1H), 4.19 (ddd, J=2.3, 4.6, 7.6 Hz, 1H), 4.73 (d, J=11.2 Hz, 1H), 4.75 (d, J=11.2 Hz, 1H), 4.75 (d, J=11.7 Hz, 1H), 4.80 (d, J=11.7 Hz, 1H), 5.67 (td, J=2.3, 10.5 Hz, 1H), 5.75 (ddd, J=2.3, 4.6, 7.8 Hz, 1H), 5.88 (td, J=2.3, 10.5 Hz, 1H), 6.74 (d, J=6.7 Hz, 2H), 6.89 (d, J=8.1 Hz, 2H), 6.98 (t, J=7.5 Hz, 1H), 7.18 (d, J=8.7 Hz, 2H), 7.29 (dt, J=1.8, 7.8 Hz, 1H), 7.39—7.47 (m, 3H), 7.58 (t, J=7.5 Hz, 1H), 8.00 (d, J=7.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 55.14, 55.39, 67.61, 74.30, 74.82, 75.07, 79.66, 80.54, 110.33, 113.75 (2C), 125.96 (2C), 126.34, 128.37 (2C), 129.10, 129.50, 129.53, 129.62, 129.65 (2C), 129.88 (2C), 130.08, 133.13, 157.24, 159.20, 165.83. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{29}H_{30}O_7Na$ $(M+Na)^+$ 513.1889, Found 513.1884. IR (neat) cm^{-1}: 3500, 2930, 1720, 1610, 1580, 1515, 1495, 1480. $[\alpha]_D$ +193 (c=1.00, $CHCl_3$).

(+)-3-*O*-Benzoyl-4,5-*O*-di-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-conduritol B 16 To an ice-cooled solution of **15** (60.0 mg, 0.12 mmol) in ether (3 ml) was added 4′-methoxybenzyl 2,2,2-trichloroacetimidate (104 mg, 0.36 mmol) and 4-toluenesulufonic acid (11.6 mg, 0.061 mmol). The reaction mixture was stirred at room temperature for 10 d, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by repeated silica gel column chromatography (AcOEt/CH_2Cl_2=1/19 to 1/4) and (AcOEt/hexane=1/9 to 1/2) to afford **16** (64.3 mg, 57%) as a colorless oil and the recovered **15** (26.6 mg, 43%). ^{1}H-NMR ($CDCl_3$) δ: 3.67 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.80—3.87 (m, 2H), 4.30 (m, 1H), 4.65 (d, J=11.0 Hz, 2H), 4.74 (d, J=11.7 Hz, 1H), 4.80 (d, J=11.0 Hz, 1H), 4.80 (d, J=11.7 Hz, 1H), 4.85 (s, 2H), 5.65 (td, J=2.2, 10.5 Hz, 1H), 5.74—5.80 (m, 1H), 5.84 (td, J=2.2, 10.5 Hz, 1H), 6.66 (d, J=8.4 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.88 (d, J=8.1 Hz, 1H), 6.95 (dt, J=1.0, 7.5 Hz, 1H), 7.11 (d, J=8.7 Hz, 2H), 7.25—7.31 (m, 3H), 7.39—7.44 (m, 3H), 7.56 (t, J=7.2 Hz, 1H), 7.94 (d, J=7.2 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 55.06, 55.22, 55.24, 67.26, 74.77, 74.92, 75.17, 80.12, 80.94, 83.17, 110.13, 113.68 (2C), 113.94 (2C), 120.43, 126.01, 126.50, 128.26 (2C), 128.84, 129.24, 129.52, 129.60 (2C), 129.64 (2C), 129.75 (2C), 129.98, 130.41, 130.84, 132.98, 157.02, 159.00, 159.12, 165.89. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{37}H_{38}O_8Na$ $(M+Na)^+$ 633.2464, Found 633.2478. IR (neat) cm^{-1}: 2900, 1720, 1610, 1580, 1515, 1495, 1460, 1250. $[\alpha]_D$ +163° (c=1.03, $CHCl_3$).

3-*O*-Benzoyl-4,5-*O*-di-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-D-*myo*-inositol 17 To an ice-cooled solution of **16** (108 mg, 0.18 mmol) in methylene chloride (2.5 ml) was added quinuclidine (0.98 mg, 0.0088 mmol, 5 mol%), 4-methylmorpholine *N*-oxide (62.1 mg, 0.53 mmol) and 2% osmium tetroxide in water (0.11 ml, 0.0088 mmol, 5 mol%). The reaction mixture was stirred at room temperature for 2 d, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4 to 2/1) to afford **17** (97.6 mg, 80%, 86%de) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (t, J=9.3 Hz, 1H), 3.63 (dd, J=2.4, 9.3 Hz, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.88 (t, J=9.3 Hz 1H), 4.21 (dd, J=9.3, 9.8 Hz, 1H), 4.35 (t, J=2.4 Hz 1H), 4.67—4.88 (m, 6H), 5.11 (dd, J=2.4, 9.8 Hz, 1H), 6.65 (d, J=8.1 Hz, 2H), 6.87 (d, J=7.8 Hz, 1H), 6.89 (d, J=7.8 Hz, 2H), 6.94 (t, J=7.5 Hz, 1H), 7.04 (d, J=8.7 Hz, 2H), 7.20 (d, J=6.3 Hz, 1H), 7.21—7.41 (m, 5H), 7.52 (t, J=7.2 Hz, 1H), 8.05 (d, J=8.1 Hz, 2H). ^{13}C-NMR ($CDCl_3$) δ: 55.11, 55.26, 55.44, 69.34, 71.50, 72.82, 73.90, 75.36, 75.39, 79.51, 81.95, 82.91, 110.82, 113.63 (2C), 113.85 (2C), 120.94, 125.76, 128.40 (2C), 129.52 (2C), 129.57 (2C), 129.76 (2C), 129.80, 130.13, 130.30, 130.75, 130.80, 133.16, 157.69, 159.05, 159.23, 165.72. HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{37}H_{39}O_{10}$ $(M-H)^+$ 643.2543, Found 643.2538. IR (KBr in $CHCl_3$) cm^{-1}: 3480, 3020, 2940, 1725, 1615, 1585, 1515, 1495, 1465, 1360. $[\alpha]_D$ +52.2 (c=1.07, $CHCl_3$).

1-*O*-Tetrahydropyranyl-3-*O*-benzoyl-4,5-*O*-di-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-D-*myo*-inositol 18 To a solution of **17** (209 mg, 0.32 mmol) in methylene chloride (5 ml) was added pyridinium 4-toluenesulfonate (8.1 mg, 0.032 mmol) and dihydropyran (51 μl, 0.59 mmol) and was stirred at room temperature for 9 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/9 to 1/2) to afford **18** (168 mg, 72%) as a colorless oil and the recovered **17** (26.9 mg, 13%). ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.9 (m, 6H), 3.3—4.3 (m, 7H), 3.70, 3.71 (s, 3H), 3.76, 3.77 (s, 3H), 3.78 (s, 3H), 4.36—4.39 (m, 1H), 4.6—5.03 (m, 6H), 5.09—5.17 (m, 1H), 6.63—7.56 (m, 16H), 8.03—8.08 (m, 11H). HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{42}H_{48}O_{11}Na$ $(M+Na)^+$ 751.3094, Found 751.3097. IR (KBr in $CHCl_3$) cm^{-1}: 3450, 3000, 2950, 2820, 1720, 1610, 1580, 1510, 1495, 1460, 1440, 1360.

1-*O*-Tetrahydropyranyl-4,5-*O*-di-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-D-*myo*-inositol 19 A solution of **18** (34.4 mg, 0.047 mmol) and potassium carbonate (26.0 mg, 0.19 mmol) in methanol (5 ml) was refluxed overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/4 to 2/1) to afford **19** (22.0 mg, 75%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.9 (m, 6H), 3.3—4.0 (m, 8H), 3.75, 3.76 (s, 3H), 3.77—3.78 (m, 3H), 3.79—3.80 (m, 3H), 4.23—4.24 (m, 1H), 4.60—5.01 (m, 6H), 6.77—6.95 (m, 6H), 7.17—7.39 (m, 6H). HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{35}H_{44}O_{10}Na$ $(M+Na)^+$ 647.2832, Found 647.2821. IR (KBr in $CHCl_3$) cm^{-1}: 3560, 3450, 3000, 2950, 2820, 1720, 1610, 1580, 1510, 1495, 1460, 1440, 1360, 1300.

1-*O*-Tetrahydropyranyl-2,3-*O*-dibenzyl-4,5-*O*-di-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-D-*myo*-inositol 20 A solution of **19** (96.1 mg, 0.15 mmol) in *N*,*N*-dimethylformamide (1 ml) was cooled in an ice bath and slowly mixed with 60% sodium hydride (18.5 mg, 0.46 mmol). The reaction mixture was stirred at the same temperature for 2 h. Then, benzyl bromide (49.3 μl, 0.42 mmol) was added dropwise while cooling in an ice bath. The reaction mixture was stirred at room temperature overnight, poured onto ice, diluted with aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/19 to 1/4) to afford **20** (85.8 mg, 71%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.9 (m, 6H), 3.3—4.3 (m, 7H), 3.70, 3.71 (s, 3H), 3.76—3.77 (m, 3H), 3.77—3.78 (m, 3H), 4.36—4.39 (m, 1H), 4.6—5.03 (m, 6H), 5.09—5.17 (m, 1H), 6.63—7.56 (m, 16H), 8.03—8.08 (m, 16H). HR-FAB-MS (NBA+NaCl) *m/z*: Calcd $C_{42}H_{48}O_{11}Na$ $(M+Na)^+$ 751.3094, Found 751.3097. IR (KBr in $CHCl_3$) cm^{-1}: 3450, 3000, 2950, 2820, 1720, 1610, 1580, 1510, 1495, 1460, 1440, 1360.

2,3-*O*-Dibenzyl-4,5-*O*-di-(4′-methoxybenzyl)-6-*O*-(2′-methoxybenzyl)-D-*myo*-inositol 21 To a solution of **20** (9.70 mg, 0.012 mmol) in tetrahy-

drofuran (0.2 ml) was added 80% acetic acid (1 ml) and stirred at 45 °C for 17 h. The reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/9 to 1/2) to afford **21** (8.7 mg, quant.) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.41 (dd, J=2.1, 9.6 Hz, 1H), 3.44 (t, J=9.6 Hz, 1H), 3.51 (m, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 3.89 (t, J=9.6 Hz, 1H), 4.04 (t, J=9.6 Hz, 1H), 4.07 (t, J=2.1 Hz, 1H), 4.64 (s, 2H), 4.74—4.94 (m, 8H), 6.80—6.92 (m, 6H), 7.21—7.40 (m, 16H). ^{13}C-NMR ($CDCl_3$) δ: 55.18, 55.21, 55.33, 72.18, 72.53, 74.50, 75.25, 75.50, 76.14, 81.01, 81.94, 82.14, 83.37, 110.61, 113.68 (2C), 113.77 (2C), 120.74, 126.14, 127.21, 127.51 (3C), 127.59 (2C), 128.07 (2C), 128.30 (2C), 129.44 (2C), 129.66 (2C), 129.76, 130.64, 131.01, 131.05, 138.38, 139.12, 157.62, 159.06, 159.62, 159.10. HR-FAB-MS (NBA+NaCl) m/z: Calcd $C_{44}H_{48}O_9Na$ $(M+Na)^+$ 743.3196, Found 743.3201. IR (KBr in $CHCl_3$) cm^{-1}: 3475, 3010, 3000, 2930, 2830, 1610, 1580, 1510, 1495, 1460, 1450, 1360. $[\alpha]_D$ +5.4 (c=0.54, $CHCl_3$).

1,2-*O*-Dibenzyl-D-*myo*-inositol (+)-13 To a solution of **21** (55.3 mg, 0.077 mmol) in methylene chloride (2 ml) was added water (0.2 ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (78.4 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 6 h, diluted with water and methanol, and filtered by Dowex-1X4-50^{TM}(OH^-). The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (MeOH/$CHCl_3$=1/10 to 1/4) to afford (+)-**13** (19.9 mg, 72%) as a colorless solid. mp 201—202 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.17 (t, J=9.3 Hz, 1H), 3.28—3.24 (m, 1H), 3.36 (dd, J=2.5, 9.9 Hz, 1H), 3.66 (dd, J=9.3, 9.9 Hz, 1H), 3.83 (dd, J=9.3, 9.9 Hz, 1H), 4.02 (t, J=2.5 Hz 1H), 4.64 (m, 2H), 4.80 (m, 2H), 7.21—7.39 (m, 10H). ^{13}C-NMR ($CDCl_3$): δ: 73.58, 73.77, 74.17, 74.62, 75.84, 76.80, 79.09, 81.94, 128.32, 128.62, 128.87 (2C), 129.00 (2C), 129.08 (2C), 129.32 (2C), 139.97, 140.56. HR-FAB-MS (NBA+NaCl) m/z: Calcd $C_{20}H_{24}O_6Na$ $(M+Na)^+$ 383.1471, Found 383.1464. IR (KBr) cm^{-1}: 3300, 3025, 2920, 2500, 1490, 1450, 1410, 1360. $[\alpha]_D$ +37.9 (c=0.26, MeOH).

1,2-*O*-Dibenzyl-L-*myo*-inositol 3,4,5,6-tetrakisphoric acid dibenzyl ester (−)-14 To a solution of (+)-**13** (13.1 mg, 0.036 mmol) in methylene chloride (2 ml) was added 1*H*-tetrazole (25.5 mg, 0.36 mmol) and dibenzyl diethylphosphoramidite (0.12 ml, 0.035 mmol). Then the reaction mixture was stirred at room temperature overnight. To the reaction mixture was added water (0.2 ml) and 3-chloroperbenzoic acid (134 mg, 0.55 mmol) at −78 °C. Then, the reaction mixture was allowed to stand at room temperature for 40 min, diluted with aqueous 10% sodium sulfite, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (AcOEt/hexane=1/9 to 1/4) to afford (−)-**14** (46.5 mg, 92%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (dd, J=2.1, 9.8 Hz, 1H), 4.22 (ddd, J=2.1, 7.3, 9.6 Hz, 1H), 4.40—4.56 (m, 4H), 4.72 (d, J=11.7 Hz, 1H), 4.82 (d, J=11.7 Hz, 1H), 4.83—5.10 (m, 18H), 7.07—7.29 (m, 50H). ^{31}P-NMR ($CDCl_3$) δ: −0.69, −0.81, −1.50, −1.67. HR-FAB-MS (NBA+NaCl) m/z: Calcd $C_{76}H_{76}O_{18}P_4Na$ $(M+Na^+)$ 1423.3880, Found 1423.3882. IR (neat) cm^{-1}: 3000, 2920, 1730, 1495, 1455, 1370, 1270. $[\alpha]_D$ −0.66 (c=1.10, $CHCl_3$).

L-*myo*-Inositol 3,4,5,6-tetrakisphosphate L-1 To a solution of (−)-**14** (44.9 mg, 0.032 mmol) in ethanol (3 ml) was added 10% palladium on carbon (10 mg) and the mixture was stirred under hydrogen atmosphere at room temperature for 27 h. The catalyst was removed by filtration and washed with water. The filtrate was washed with chloroform and lyophilized to afford **L-1** (15.1 mg, 94%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (dd, J=2.1, 9.6 Hz, 1H), 3.98—4.08 (m, 3H), 4.17 (dt, J=9.0, 9.3 Hz, 1H), 4.29 (dt, J=9.0, 9.3 Hz, 1H). HR-FAB-MS (Gly) m/z: Calcd $C_6H_{17}O_{18}P_4$ $(M+H)^+$ 500.9365, Found 500.9367. $[\alpha]_D$ −4.78 (c=0.70, H_2O).

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