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Synthesis of optically active *myo*-inositol derivatives starting from phytic acid

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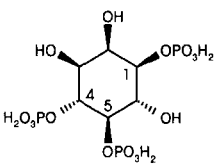
Abstract

Phytic acid treated with Baker's yeast gave D-*myo*-inositol-1,2,6-tris(phosphate) (α-trinositol) which was transformed into (+)-D-1,2-*O*-isopropylidene-*myo*-inositol and (−)-D-3,4,5-tri-*O*-benzyl-*myo*-inositol, two key intermediates in the synthesis of optically active *myo*-inositol derivatives and related compounds. © 1997 Elsevier Science Ltd.

Keywords: *myo*-Inositol; Inositol phosphate; Phytic acid; Chiral inositol

1. Introduction

myo-Inositol phosphates show various interesting biological properties [1–5]. D-*myo*-Inositol-1,4,5-tris(phosphate) (**1**) is a well-known second messenger [1], and D-*myo*-inositol-1,2,6-tris(phosphate) (α-trinositol) (**2**), a regioisomer of the former, possesses anti-inflammatory properties [5]. Structure–activity relationships have been developed, and several analogues of α-trinositol have been prepared and reported [6–12]. Structure–activity relationships usually involve stereospecific interactions between the tested molecules and receptors or enzymes. In the case of chiral ligands, such investigations require the synthesis of optically active compounds.



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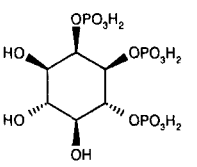

2

Phytic acid **3**, an abundant polyphosphorylated *meso* *myo*-inositol derivative, could be a starting material of choice in the preparation of new inositol derivatives. Here we report how phytic acid was used for the synthesis of optically pure D-1,2-*O*-isopropylidene-*myo*-inositol (**7**) and D-3,4,5-tri-*O*-benzyl-*myo*-inositol (**11**). These compounds are key intermediates for the preparation of reported and new optically active inositols and related compounds.

2. Results

Baker's yeast contains phosphatases which selectively hydrolysed the phosphates in positions 3, 4,

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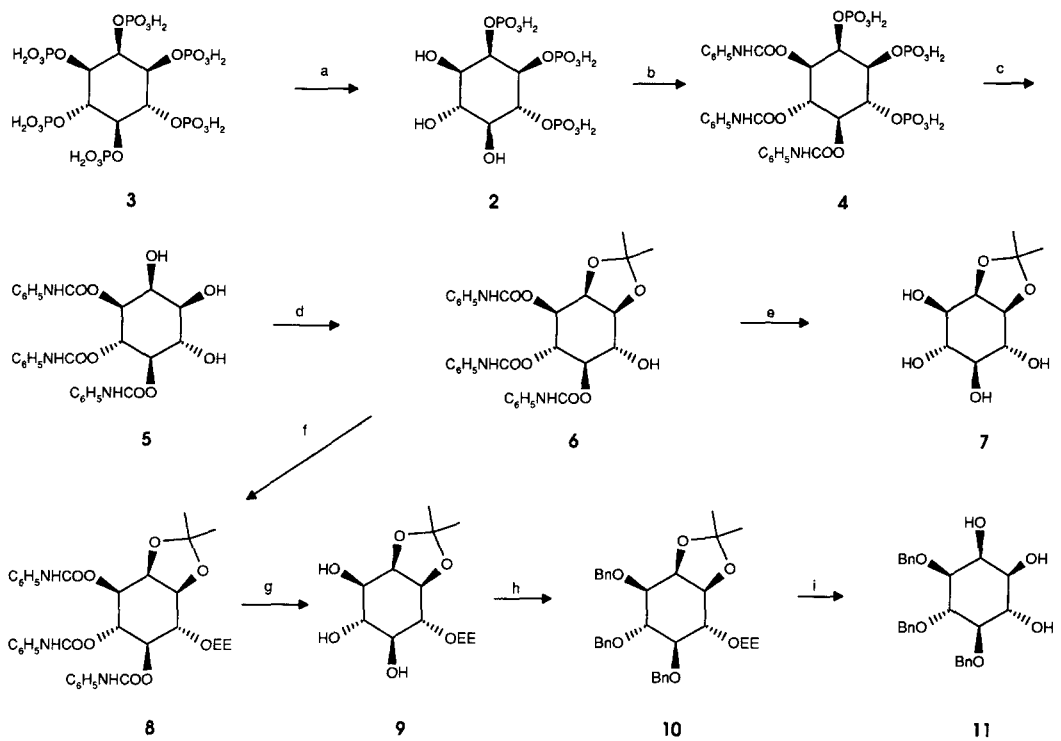
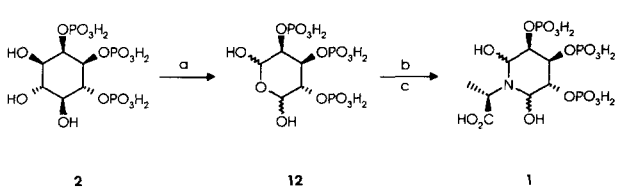


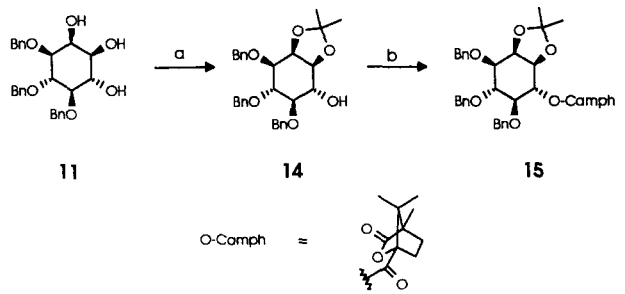
Scheme 1. a: Baker's yeast; b: C_6H_5NCO, CH_2Cl_2, rt, 48 h; c: HCO_2H–HCOONa, pH 4.2, Δ, 31 h, 48% (from **2** to **5**); d: $(CH_3)_2C(OCH_3)_2$, H^+, 2 h, 90%; e: EtONa, MeOH, Δ, 5 h, 95%; f: EVE, CF_3COOH, DMF, rt, 2 h, 97%; g: as for d, 5 h, 100%; h: BnBr, NaH, DMF, 4 h, 46%; i: MeOH, HCl, CH_2Cl_2, Δ, 1 h, 100%.

and 5 of phytic acid, leading to optically active D-*myo*-inositol-1,2,6-tris(phosphate), also named α-trinositol (**2**) (Scheme 1). This reaction can be run on a kilogram scale [13]. The optical purity, expressed as ee, was better than 99.7%. The ee was determined by transforming α-trinositol into *N*-[(1*R*)-1-carboxyethyl]-1,5-dideoxy-1,5-imino-D-arabinitol 2,3,4-tris(phosphate) (**13**) [14]. Thus, α-trinositol **2** was oxidised with $NaIO_4$, giving **12** which was engaged in an aminoreduction involving D-alanine leading to **13** (Scheme 2). Compared to reference compounds, only *N*-[(1*R*)-1-carboxyethyl]-1,5-dideoxy-1,5-imino-D-arabinitol 2,3,4-tris(phosphate) **13** was detected by HPLC (detection limit < 0.15%). Treatment of the Hünig salt of α-trinositol with phenylisocyanate led to the tricarbamate **4** [15]. The three phosphate moieties were then chemically hydrolysed by means of a formic acid–sodium formate buffer (pH 4.2) yielding the triol **5**. The *cis* orientation of the hydroxyl groups in positions 1 and 2 of triol **5** enabled the selective formation of acetonide **6** [16]. The carbamate protective groups were hydrolysed to give the known, optically active isopropylidene inositol **7**. The observed optical activity, $[\alpha]_D^{25}$ −39.9° (*c* 1, MeOH), was opposite to that observed by Schneider for 2,3-isopropylidene-D-*myo*-inositol, the enantiomer of **7** ($[\alpha]_D^{20}$ +44.8° (*c* 2, MeOH) [17]). This derivative is a key intermediate for the preparation of different inositol-phosphates such as L-*myo*-inositol-1,4,5-tris(phosphate), L-*myo*-inositol-1,4,6-tris(phosphate) following Ozaki's procedures [18,19], or L-*myo*-inositol-1,4,5,6-tetrakis(phosphate) according to the scheme published by Meek et al. [20].

The last free hydroxyl group of the acetonide **6** when treated with ethyl vinyl ether (EVE) yielded the fully protected derivative **8** as a diastereoisomeric mixture (1:1). The protective carbamates were selectively removed by treatment with sodium ethoxide to give the triol **9** (1:1 diastereoisomeric mixture). These hydroxyls were benzylated giving another totally protected inositol **10**. An acidic treatment simultaneously removed the ethoxyethyl ether and the acetonide group, giving the optically active (−)-D-3,4,5-tri-*O*-benzyl-*myo*-inositol (**11**). The optical purity of this



Scheme 2. a; $NaIO_4$, HIO_4, H_2O; b: D-alanine, c: $NaBH_4$.



Scheme 3. a: 2,2-Dimethoxypropane, $C_6H_5SO_3H$, THF, CH_3CN, 99%; b: ω-camphanic acid chloride, Et_3N, DMAP, THF, 60%.

compound was determined by preparing the 6-ω-camphanate derivative **15** (see Scheme 3). No diastereoisomers could be seen by NMR. The NMR analyses are in agreement with those described by Gigg [21]. Inositol derivative **11** enables the preparation of new optically active inositol derivatives, particularly isosteres of α-trinositol.

This is the first example involving an optically active inositol-phosphate, obtained from phytic acid, leading to optically active unphosphorylated inositol derivatives which can be transformed into new optically active inositol analogues. This is also, to the best of our knowledge, the first example of phosphatases being used to obtain optically pure compounds.

3. Experimental

General methods.—Melting points were measured on a Mettler PF62 apparatus and are uncorrected. $[\alpha]_D^{25}$ were recorded on a Perkin–Elmer 241 MC Polarimeter. NMR spectra were recorded on a Bruker AC 200 spectrometer (otherwise notified) using the δ scale. Coupling constants are given in Hz.

(+)-D-myo-Inositol-1,2,6-tris(phosphate) or α-trinositol (**2**).—The preparation was similar to that reported in refs [13,15]. Sodium phytate (70 g) was dissolved in 600 mL of NaOAc buffer (pH 4.6). Baker's yeast (50 g) was added and the mixture stirred for 7 h at 45 °C. The enzymatic reaction was quenched by adding ammonia to pH 12. After centrifugation, the supernatant was collected and passed through an ion-exchange column (Dowex 1 chloride form), eluted with a linear gradient of 0–0.7 M HCl. Fractions containing the expected product were neutralised to pH 7.0 with an aq soln of NaOH. An equiv vol of EtOH was added and the volume was reduced by evaporation. The sodium salt was centrifuged, recrystallised (water–EtOH), and dried in vacuum. Enantiomeric excess higher than 99.7%. $[\alpha]_D^{25}$ −26.9° (as pentasodium salt, H_2O); ^1H NMR (300 MHz, D_2O): δ 3.28 (t, *J* 9.1 Hz, 1 H, H-5), 3.31 (dd, *J* 10.0, *J* 2.2 Hz, 1 H, H-3), 3.60 (t, *J* 9.8 Hz, 1 H, H-4), 3.88 (br t, *J* 9.0 Hz, 1 H, H-1), 4.08 (*q*, *J* 9.0 Hz, 1 H, H-6), 4.49 (br d, *J* 8.5 Hz, 1 H, H-2); ^{13}C NMR (75 MHz, D_2O): δ 74.1 (C-3), 75.5 (C-4), 76.6 (C-1), 77.5 (C-5), 77.8 (C-2), 79.6 (C-6); the assignment used two-dimensional H–C correlation; ^{31}P NMR (D_2O): δ 0.0 (P-2), 0.8 (P-1, P-6); the assignment is based on two-dimensional H–P correlation.

(+)-D-3,4,5-Tri-O-(N-phenylcarbamoyl)-myo-inositol-1,2,3-tris(phosphate) (**4**).—Hünig's salt of α-trinositol **2** (70 g, 0.087 mol), DMAP (0.70 g) and *N*-ethyldiisopropylamine (90 mL, 0.52 mol) were dissolved in anhyd CH_2Cl_2 (700 mL) under argon. Phenylisocyanate (85 mL, 0.78 mol) was slowly added and the reaction mixture stirred at room temperature for 48 h. The volume was reduced to 1/4th and then quickly poured into crushed ice (250 mL). The precipitate was filtered and the remaining organic solvents were evaporated. The water layer was washed with EtOAc (3 × 100 mL). Dowex 50W-8 (H^+) was added until a stable pH of 2.35 was reached. After filtration of the ion exchanger, the pH was adjusted to 6.0 by means of 1 M NaOH, and finally the aq phase was evaporated giving crude tris(carbamate) **4** which was used as such for the next step. ^1H NMR (D_2O): δ 4.35 (t, *J* 7.3 Hz, 1 H, H-1), 4.68 (*q*, *J* 7.3 Hz, 1 H, H-6), 4.8–5.0 (m, 1 H, H-2), 5.17 (t, *J* 8.0 Hz, 1 H, H-5), 5.23 (dd, *J* 8.0, *J* 1.4 Hz, 1 H, H-3), 5.45 (t, *J* 7.9 Hz, 1 H, H-4), 7.0–7.6 [m, 15 H, $(C_6H_5)_3$].

(+)-D-3,4,5-Tri-O-(N-phenylcarbamoyl)-myo-inositol (**5**).—The phosphate **4** (15 g, 0.014 mol) was dissolved in an aq soln buffered with a mixture of formic acid and sodium formate (450 mL). The pH was adjusted to 4.2 by means of 150 mL of a 1 M NaOH soln. The reaction mixture was refluxed for 31 h and then cooled to room temperature. The precipitate was filtered, washed with water, and dried under vacuum. Column chromatography on silica gel (2:2:0.1 AcOEt–CH_2Cl_2–MeOH) gave a brown powder (3.53 g, 48%) melting at 207 °C: $[\alpha]_D^{25}$ 34.4° (*c* 0.018, THF); ^1H NMR (Me_2SO-d_6): δ 3.46 (dd, *J* 9.4, *J* 2.1 Hz, 1 H, H-1), 3.75 (t, *J* 9.7 Hz, 1 H, H-6), 4.02 (br s, 1 H, H-2), 4.82 (dd, *J* 10.5, *J* 2.4 Hz, 1 H, H-3), 4.86 (t, *J* 10.1 Hz, 1 H, H-5), 5.15 [br s, $(OH)_3$], 5.45 (t, *J* 7.0 Hz, 1 H, H-4), 6.9–7.6 [m, 15 H, $(C_6H_5)_3$], 9.60 [br s, 2 H, $(NH)_2$], 9.75 (br s, 1 H, NH). Anal. Calcd for $C_{27}H_{27}N_3O_9 \cdot 1/2H_2O$: C,

59.34; H, 4.98; N, 7.68. Found: C, 59.02; H, 5.05; N, 7.82.

(+)-D-1,2-O-Isopropylidene-3,4,5-tri-O-(N-phenylcarbamoyl)-myo-inositol (**6**).—3,4,5-Tri-*O*-(*N*-phenylcarbamoyl)-*myo*-inositol **5** (1.0 g, 1.86 mmol) was dissolved in a 2:1 THF–acetonitrile mixture (30 mL). 2,2-Dimethoxypropane (1.37 mL, 11.2 mmol) and a few crystals of benzene sulfonic acid were added. After stirring for 2 h, Et_3N (1 mL) was added to adjust the pH to 7.0 and the solvents were evaporated under reduced pressure. The crude material was dissolved in ether, washed with satd aq $NaHCO_3$ soln (50 mL), water (2 × 50 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. A white powder (0.97 g, 90%) melting at 139 °C was obtained: $[\alpha]_D^{25}$ +76.8° (*c* 0.017, THF); ^{1}H NMR ($CDCl_3$): δ 1.38 and 1.64 [2 s, 6 H, $C(CH_3)_2$], 3.66 (s, 1 H, O*H*), 4.08 (dt, *J* 8.3, *J* 6.5 Hz, 1 H, H-6), 4.36 (t, *J* 5.7 Hz, 1 H, H-1), 4.60 (dd, *J* 5.3, *J* 4.1 Hz, 1 H, H-2), 5.16 (t, *J* 8.7 Hz, 1 H, H-5), 5.46 (dd, *J* 10.3, *J* 3.8 Hz, 1 H, H-3), 5.55 (dd, *J* 10.3, *J* 9.0 Hz, 1 H, H-4), 7.0–7.5 [m, 15 H, $(C_6H_5)_3$]. Anal. Calcd for $C_{30}H_{31}N_3O_9 \cdot 1/2H_2O$: C, 61.44; H, 5.32; N, 7.16. Found: C, 61.84; H, 5.67; N, 7.04.

(+)-D-1,2-O-Isopropylidene-myo-inositol (**7**).—(+)-1,2-*O*-Isopropylidene-3,4,5-tri-*O*-(*N*-phenylcarbamoyl)-*myo*-inositol **6** (100 mg, 0.17 mmol) was dissolved in MeOH (10 mL) containing $NaOCH_2CH_3$ (106 mg, 1.6 mmol). The reaction mixture was refluxed for 5 h. The crude material was poured into water (20 mL) and washed with CH_2Cl_2 (2 × 10 mL). The aq phase was evaporated to dryness. The crude product was crystallised from EtOH–water to give **7** as a white powder (36 mg, 95%) melting at 158 °C (lit. 157–158 °C [22]): $[\alpha]_D^{25}$ +16.5° (*c* 10, H_2O), −39.9° (*c* 1, MeOH); ^{1}H NMR (D_2O): δ 1.26 and 1.40 [2 s, 6 H, $C(CH_3)_2$], 3.06 (dd, *J* 10.5, *J* 9.7 Hz, 1 H, H-5), 3.43 (dd, *J* 10.2, *J* 7.9 Hz, 1 H, H-4), 3.52 (t, *J* 9.6 Hz, 1 H, H-6), 3.65 (dd, *J* 9.8, *J* 4.2 Hz, 1 H, H-1), 3.87 (dd, *J* 7.9, *J* 4.9 Hz, 1 H, H-3), 4.29 (t, *J* 4.5 Hz, H-2). Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.76; H, 7.14.

6-O-(1'-Ethoxyethyl)-1,2-O-isopropylidene-4,5,6-tri-O-(N-phenylcarbamoyl)-myo-inositol (**8**).—The alcohol **6** (1.5 g, 2.6 mmol) in a soln of 2:1 ethyl vinyl ether–DMF (45 mL) was stirred at room temperature for 2 h after adding CH_3COOH (0.15 mL, 2 mmol). Triethylamine was added to neutral pH, followed by water (100 mL). The aq phase was extracted with EtOAc (100 mL) which was washed with water (3 × 100 mL), dried over Na_2SO_4, and evaporated. Column chromatography on silica gel (1:3 AcOEt–hexane) gave **8** (1,64 g, 97%) as a white powder melting at 92–93 °C: ^{1}H NMR ($CDCl_3$) (1:1 diastereoisomeric mixture): δ 1.1–1.3 (m, 6 H, CH_3CH_2O, CH_3CH_2O'), 1.36 (d, *J* 5.3 Hz, 6 H, CH_3CH, CH_3CH'), 1.40 and 1.64 [2 s, 12 H, $C(CH_3)_2$, $C(CH_3)'_2$], 3.5–3.6 (m, 2 H, CH_3CH_2O), 3.6–3.8 (m, 2 H, CH_3CH_2O'), 4.06 (t, *J* 5.3 Hz, 1 H, H-6), 4.12 (t, *J* 4.9 Hz, 1 H, H-6'), 4.38 (t, *J* 5.5 Hz, 1 H, H-1), 4.55 (t, *J* 5.5 Hz, 1 H, H-1'), 4.6–4.8 (m, 2 H, H-2, H-2'), 5.0–5.2 (m, 4 H, H-5, H-5', CH_3CH, CH_3CH'), 5.38 and 5.41 (2 dd, *J* 3.7, *J* 1.9 Hz, 2 H, H-3, H-3'), 5.5–5.7 (m, 2 H, H-4, H-4'), 6.9–7.1 [m, 6 H, $(NH)_3$, $(NH)'_3$], 7.2–7.4 [m, 30 H, $(C_6H_5)_3$, $(C_6H_5)'_3$]. Anal. Calcd for $C_{34}H_{39}N_3O_{10}$: C, 62.86; H, 6.05; N, 6.47. Found: C, 62.90; H, 6.24; N, 6.29.

6-O-(1'-Ethoxyethyl)-1,2-O-isopropylidene-myo-inositol (**9**).—The carbamate **8** (1.3 g, 2.0 mmol) was dissolved in MeOH (50 mL) and treated with $NaOCH_2CH_3$ (613 mg, 8 mmol). The mixture was stirred under reflux for 5 h. The MeOH was evaporated. Water (50 mL) was added and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was dried over Na_2SO_4 and evaporated to give triol **9** as an oil (585 mg, 100%); ^{1}H NMR (D_2O) (1:1 diastereoisomeric mixture): δ 1.06 and 1.15 (2 t, *J* 7.3 Hz, 6 H, CH_3CH_2O, CH_3CH_2O'), 1.24 (d, *J* 5.1 Hz, 6 H, CH_3CH, CH_3CH'), 1.28 and 1.44 [2 s, 12 H, $C(CH_3)_2$, $C(CH_3)'_2$], 3.1–3.2 (m, 2 H, H-5, H-5'), 3.4–3.8 (m, 10 H, H-1, H-1', H-4, H-4', H-6, H-6', CH_3CH_2O, CH_3CH_2O'), 3.9–4.1 (m, 2 H, H-3, H-3'), 4.35 (t, 2 H, *J* 4.4 Hz, H-2, H-2'), 4.93 (*q*, 2 H, *J* 5.1 Hz, CH_3CH, CH_3CH'). Anal. Calcd for $C_{13}H_{24}O_7 \cdot 1/2H_2O$: C, 53.41; H, 8.28. Found: C, 52.70; H, 8.57.

6-O-(1'-Ethoxyethyl-1,2-O-isopropylidene-3,4,5-tri-O-benzyl-myo-inositol (**10**).—The triol **9** (500 mg, 1.7 mmol) dissolved in DMF (50 mL) was treated with benzyl bromide (0.74 mL, 6.2 mmol) and NaH (185 mg, 7.7 mmol). The mixture was stirred at room temperature for 4 h. Ethanol (2–3 mL) was added. The product was precipitated with water (100 mL) and extracted with ether (100 mL). The organic phase was washed with water (4 × 100 mL), dried over Na_2SO_4, and evaporated. Column chromatography on silica gel (1:6 AcOEt–hexane) gave a viscous oil **10** (443 mg, 46%): ^{1}H NMR ($CDCl_3$) (1:1 diastereoisomeric mixture): δ 1.08 and 1.20 (2 t, *J* 6.9 Hz, 6 H, CH_3CH_2O, CH_3CH_2O'), 1.29 and 1.35 (2 d, *J* 5.1 Hz, 6 H, CH_3CH, CH_3CH'), 1.36 and 1.57 [2 s, 12 H, $C(CH_3)_2$, $C(CH_3)'_2$], 3.3–4.1 (m, 14 H,

H-1, H-1′, H-3, H-3′, H-4, H-4′, H-5, H-5′, H-6, H-6′, CH_3CH_2O, CH_3CH_2O'), 4.2–4.3 (m, 2 H, H-2, H-2′), 4.7–4.9 [m, 12 H, $(OCH_2C_6H_5)_3$, $(OCH_2C_6H_5)'_3$], 4.9–5.0 (m, 2 H, CH_3CH, CH_3CH'), 7.3–7.4 [m, 30 H, $(C_6H_5)_3$, $(C_6H_5)'_3$]. Anal. Calcd for $C_{34}H_{42}O_7$: C, 72.56; H, 7.53. Found: C, 72.53; H, 7.67.

*(−)-D-3,4,5-Tri-O-benzyl-*myo*-inositol* (**11**).—The fully protected inositol **10** (443 mg, 0.78 mmol) dissolved in a soln of 2:2:0.5 CH_2Cl_2–MeOH–2 M HCl was stirred under reflux for 1 h. The solvents were evaporated. Column chromatography (2:2:0.1 AcOEt–CH_2Cl_2–MeOH) gave compound **11** as a white powder (285 mg, 81%): $[\alpha]_D^{25}$ −13.1° (*c* 0.022, THF); ^{1}H NMR ($CDCl_3$): δ 2.73 and 2.79 [2 s, 2 H, $(OH)_2$], 2.92 (d, *J* 5.4 Hz, 1 H, O*H*), 3.32 (t, *J* 9.5 Hz, 1 H, H-5), 3.40 (dd, *J* 9.5, *J* 2.6 Hz, 1 H, H-1), 3.48 (dd, *J* 9.5, *J* 2.6 Hz, 1 H, H-3), 3.87 (t, *J* 9.8 Hz, 1 H, H-6), 3.94 (t, *J* 9.5 Hz, 1 H, H-4), 4.20 (t, *J* 2.4 Hz, 1 H, H-2), 4,93 (AB, J_{AB} 10.9 Hz, Δδ 0.09, 2 H, $OCH_2C_6H_5$), 4,95 (AB, J_{AB} 11.3 Hz, Δδ 0.20, 2 H, $OCH_2C_6H_5$), 4.70 (s, 2 H, $OCH_2C_6H_5$), 7.2–7.4 [m, 15 H, $(C_6H_5)_3$]. Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.97; H, 6.72. Found: C, 71.71; H, 6.71.

*N-[(1R)-Carboxyethyl]-1,5-dideoxy-1,5-imino-*D*-arabinitol 2,3,4-tris(phosphate) calcium salt* (**13**).—α-Trinositol (5.00 g, 90%, 8.50 mmol) was added to a stirred soln of periodic acid (2.03 g, 8.91 mmol) and sodium periodate (1.91 g, 8.93 mmol) in water (150 mL). After 48 h in the dark, a sample (14 mL, 0.79 mmol) was withdrawn. To this, D-alanine (0.707 g, 7.94 mmol) and aq NaOH (2 M, 4 mL) was added. After 10 min, aq $NaBH_4$ (1.6 M, 5 mL) was added. After 1 day, pH was lowered to 5.0 by addition of an acidic resin (AG 50W-X8, 100–200 mesh). The solvent was removed and the residue was dissolved in a minimal amount of water and poured into a large volume of EtOH. The precipitate was collected and purified by ion-exchange chromatography (Dowex 1-X8, 200–400 mesh, 1 × 100 cm) with a linear gradient of HCl (0–0.3 M, 100 mL/h). Calcium hydroxide was added to fractions containing product, and the precipitated calcium salt was filtered and dried. Yield 42%. $[\alpha]_D^{21}$ −17.1° (*c* 0.6, 1.2 M HCl, H_2O); ^{1}H NMR (0.4% DCl, D_2O): δ 1.65 (d, *J* 7.1 Hz, 3 H, CH_3), 3.4–3.6 (m, 4 H, H-2, H-5), 4.34 (*q*, *J* 1.1 Hz, 1 H, C*H*N), 4.6–4.9 (m, 3 H, H-2, H-3, H-4); ^{13}C NMR (0.4% DCl, D_2O): δ 12.7, 50.8, 51.7, 65.9, 69.4, 71.5, 73.0, 173.1.

*(−)-D-1,2-O-Isopropylidene-3,4,5-tri-*O*-benzyl-*myo*-inositol* (**14**).—3,4,5-Tri-*O*-benzyl-*myo*-inositol **11** (30 mg, 0.066 mmol) was dissolved in a 2:1 THF–acetonitrile mixture (6 mL). 2,2-Dimethoxypropane (41.6 mg, 0.4 mmol) and a few crystals of benzene sulfonic acid were added. After stirring for 2 h at room temperature, Et_3N (0.1 mL) was added to adjust the pH at 7.0. The solvents were evaporated under reduced pressure. The crude material was dissolved in ether (5 mL), washed with satd aq $NaHCO_3$ soln (5 mL), then with water (2 × 5 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. Column chromatography on silica gel treated with a 10% TEA in ether soln (1:3 AcOEt–hexane) gave an oil (32 mg, 99%): $[\alpha]_D^{25}$ −27.4° (*c* 0.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.38 and 1.58 [2 s, 6 H, $C(CH_3)_2$], 2.64 (br s, 1 H, -OH), 3.29 (dd, 1 H, *J* 9.8, *J* 8.3 Hz, H-5), 3.76 (dd, 1 H, *J* 7.5, *J* 4.1 Hz, H-3), 3.9–4.0 (m, 3 H, H-4, H-6, H-1), 4.31 (dd, 1 H, *J* 5.3, *J* 4.1 Hz, H-2), 4.80 (s, 2 H, $OCH_2C_6H_5$), 4,80 (AB, J_{AB} 10.9 Hz, Δδ 0.25, 2 H, $OCH_2C_6H_5$), 4,81 (AB, J_{AB} 10.9 Hz, Δδ 0.11, 2 H, $OCH_2C_6H_5$), 7.2–7.4 [m, 15 H, $(C_6H_5)_3$].

(−)-ω-Camphanate of (−)-D-1,2-O-isopropylidene-3, 4, 5 - tri - O - benzyl - myo - inositol (**15**).—Dry (−)-ω-camphanic acid (200 mg, 1 mmol) was dissolved in anhyd benzene (5 mL). Oxalyl chloride (512 mg, 4 mmol) and 2 drops of DMF were added to the soln at 0 °C. After 6 h at room temperature, the solvent was evaporated. The mixture was washed with anhyd benzene (2 × 5 mL) and dried under reduced pressure overnight. The obtained ω-camphanic acid chloride was used as such in the next step.

To a soln of the alcohol (**14**) (97 mg, 0.19 mmol) was added anhyd Et_3N (40 mg, 0.39 mmol), camphanic acid chloride (107 mg, 0.49 mmol), and dimethylaminopyridine (24 mg, 0.19 mmol) in anhyd THF (2 mL). After 3 days at room temperature, the solvent was evaporated under reduced pressure. The crude material was dissolved in CH_2Cl_2 (10 mL), washed with water, and a satd H_2CO_3 soln (10 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. Column chromatography on silica gel treated with a 10% TEA in ether soln (1:3 AcOEt–hexane) afforded a white powder (76 mg, 60%): mp 176–177 °C, lit. 177–179 °C [21]; $[\alpha]_D^{25}$ −45.5° (*c* 1, $CHCl_3$), lit. −47° [21]; ^{1}H NMR ($CDCl_3$): δ 0.97, 1.02 and 1.12 [3 s, 9 H, $C(CH_3)_2$, CH_3 *camph*], 1.34 and 1.61 [2 s, 6 H, $C(CH_3)_2$], 1.6–1.65 (m, 1 H, CH_2 *camph*), 1.65–1.7 (m, 2 H, CH_2 *camph*), 2.3–2.4 (m, 1 H, CH_2 *camph*), 3.47 (dd, *J* 10.2, *J* 8.7 Hz, 1 H, H-5), 3.73 (dd, *J* 9.0, *J* 4.1 Hz, 1 H, H-3), 4.02 (dd, *J* 9.0, *J* 8.7 Hz, 1 H, H-3), 4.05 (dd, *J* 7.5, *J* 4.9 Hz, 1 H,

H-1), 4.25 (dd, *J* 4.9, *J* 4.1 Hz, 1 H, H-2), $\overline{4,74}$ (AB, J_{AB} 11.3 Hz, $\Delta\delta$ 0.16, 2 H, $OCH_2C_6H_5$), $\overline{4,82}$ (AB, J_{AB} 12.4 Hz, $\Delta\delta$ 0.08, 2 H, $OCH_2C_6H_5$), $\overline{4,83}$ (AB, J_{AB} 10.5 Hz, $\Delta\delta$ 0.08, 2 H, $OCH_2C_6H_5$) 5.46 (dd, *J* 10.2, *J* 7.5 Hz, 1 H, H-6), 7.1–7.5 [m, 15 H, $(C_6H_5)_3$]. The other diastereoisomer was not detected by NMR. Anal. Calcd for $C_{40}H_{46}O_9$: C, 71.62; H, 6.91. Found: C, 71.26; H, 6.88.

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