An Effective Strategy for the Synthesis of 6-*O*-(2-Amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*- and -D-*myo*-inositol 1-Phosphate Related to Putative Insulin Mimetics

Carlos Jaramillo, Jose-Luis Chiara, and Manuel Martín-Lomas*

Instituto de Química Orgánica, C.S.I.C., Juan de la Cierva 3, E-28006 Madrid, Spain

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Two glycosylinositol phosphates related to putative insulin mimetics, 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol 1-phosphate (1) and 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol 1-phosphate (2), have been synthesized from selectively protected and enantiomerically pure D-*chiro*- and *myo*-inositol derivatives. The D-*chiro*-inositol unit was prepared in a multigram scale from D-glucose using the Ferrier's carbocyclization route, and it was transformed into the corresponding *myo* epimer by an oxidation–reduction sequence. The trichloroacetimidate method was applied efficiently for the key glycosylation of the inositol derivatives.

It has been proposed that the plasma membrane contains glycosylphosphatidylinositols (GPIs) which are cleaved by phosphatidylinositol specific phospholipase C (PI-PLC) or D (PI-PLD) to release phosphoinositol phosphoglycans or inositol phosphoglycans, respectively. These released glycans may act as mediators of a variety of enzyme pathways.[1] The most thoroughly studied system is the cleavage of GPI after binding of insulin in hepatocytes, adipocytes, or myocytes.[2] Binding of insulin to these target cells results in the PI-PLC or PI-PLD mediated cleavage of a GPI to release a phosphoinositol phosphoglycan or inositol phosphoglycan, respectively, which seem to act as second messengers of insulin action.[2] These compounds have also been reported to mediate the action of interleukine 2,[3] insulin-like growth factor,[4] and nerve growth factor.[5]

The precise chemical structure of these putative mediators has not been elucidated yet, but present evidence indicates that it could be related to those of the GPIs which anchor proteins, polysaccharides, or small oligosaccharides to the outer face of cellular membranes through a covalent linkage.[6] At least two structurally distinct mediators have been reported.[2i,7] The first one inhibited cAMP-dependent protein kinase and contained *myo*-inositol and *chiro*-inositol, 2-amino-2-deoxy-D-glucose, galactose, and phosphate.[2i] The second type stimulated pyruvate dehydrogenase kinase and contained D-*chiro*-inositol, 2-amino-2-deoxy-D-galactose, mannose, and phosphate.[7] These results have been taken as an indication of the existence of a family of compounds with different biological activities rather than a unique phosphoglycan mediator.[2i,7] In agreement with this, we have recently determined partial structures of insulin mediators from bovine liver which contained a variable number of phosphorylated α-galactose residues, *N*-acetylglucosamine or -galactosamine, non-*N*-acetylated glucosamine, and inositol.[8]

The determination of the structure of this potentially important family of compounds is seriously hampered by the minute amounts of active material present in the biological sources from which they have to be isolated. The development of effective and versatile strategies for the preparation of building blocks which could be used for the synthesis of different structures required for biological experiments is, therefore, necessary. In this context, we are involved in work directed to establish these strategies[9,10] and have reported on an efficient route leading to glycosyl-*myo*-inositol 1-phosphate starting from *myo*-inositol.[10a] We have developed a different route for the synthesis of glycosyl-D-*chiro*-inositol 1-phosphates, that can also be used for the synthesis of glycosyl-*myo*-inositol 1-phosphates, in which the inositol unit is prepared from D-glucose.[9] We now report the synthesis of 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol 1-phosphate (1) and 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol 1-phosphate (2) following this synthetic strategy. The complete sequence leading to 1 has been optimized and permits the preparation of sufficient material to be used in biological investigation. Synthesis of several fragments and the complete glycosylphosphatidylinositol anchor of the variant surface glycoprotein of *Trypanosoma*

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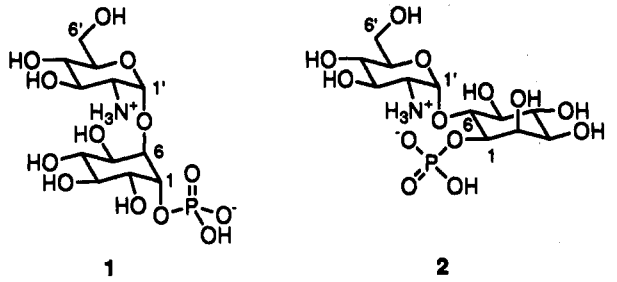
Chart 1



1 2

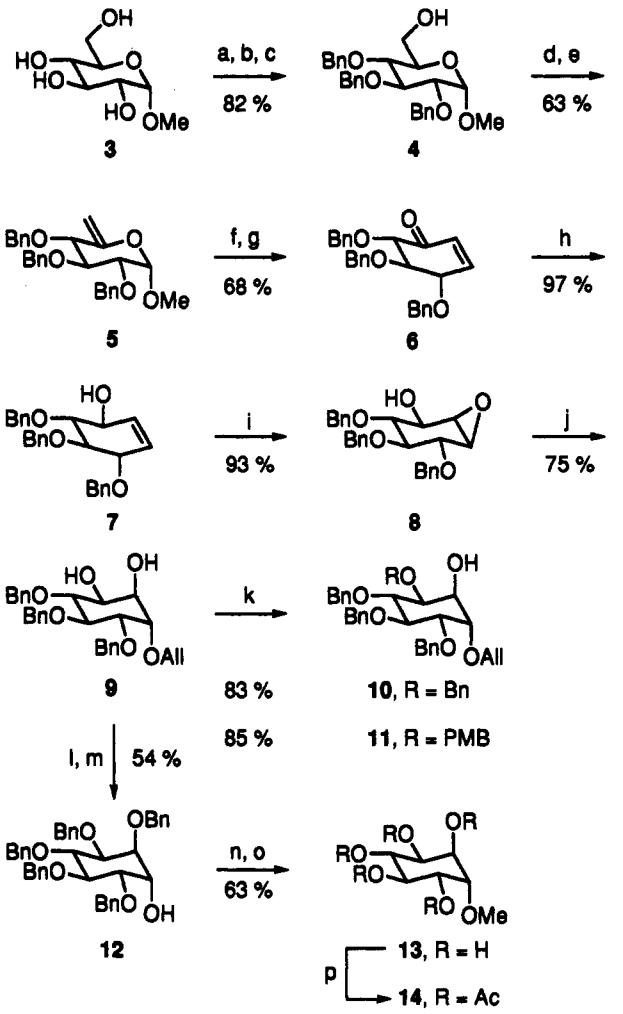
brucei and of rat liver Thy-1 glycoprotein[11] as well as of related oligosaccharide fragments[12] containing *myo*- or D-*chiro*-inositol have been described.

Results and Discussion

The synthesis of the conveniently functionalized D-*chiro*-inositol derivative (**10**) is shown in Scheme 1. Enone **6**,[9] available in multigram amounts from methyl α-D-glucopyranoside by modification of a known procedure,[13,14] was further transformed into the key epoxide **8** as reported by us.[9a] Acid-catalyzed *trans*-diaxial opening[15] of the epoxide ring of **8** with allyl alcohol in the presence of boron trifluoride etherate afforded the D-*chiro*-inositol derivative **9**, which was transformed into **10** and **11** through tin-mediated regioselective alkylation.[16] In compound **10** positions 1 and 6 appear differentiated for further phosphorylation and glycosylation. The complete sequence constitutes an effective method for the multigram-scale preparation of conveniently substituted D-*chiro*-inositol derivatives in which the nature and position of the protecting groups can be varied at will and represents a further example of the usefulness of the Ferrier's carbocyclization reaction.[17] The stereochemistry of **9** was unequivocally established (Scheme 1) by transformation into the previously known[18] 1-*O*-methyl-D-*chiro*-inositol (**13**) and its penta-*O*-acetate **14**.

Glycosylation of the axial hydroxyl group of a D-*chiro*-inositol derivative has not been reported in the literature. However, a low reactivity was anticipated toward glycosyl donors bearing a nonparticipating nitrogen function at position 2, as required for the preparation of **1**. According to previous experience,[10b] preliminary experiments indicated that the trichloroacetimidate procedure[19] gave the best yield and α-selectivity, and therefore, glycosyl donor **15** was used.[12b] This trichloroacetimidate was readily

Scheme 1



[a] Reagents and conditions: (a) 1.3 equiv of TrCl, 0.16 equiv of DMAP, pyridine, rt, 16 h; (b) 7.2 equiv of NaH, 6.1 equiv of BnBr, DMF, rt, 3 h; (c) *p*-TsOH until pH < 4, MeOH/CH_2Cl_2 (2:1), rt, 12 h; (d) 2.9 equiv of Ph_3P, 1.4 equiv of CI_4, pyridine, rt, 12 h; (e) 5.7 equiv of NaH, DMF, 20 h; (f) 1.1 equiv of $HgCl_2$, Me_2CO/H_2O (2:1), 100 °C, 1.5 h; (g) 2.7 equiv of MsCl, 0.14 equiv of DMAP, pyridine, rt, 4 h; (h) 1.1 equiv of $CeCl_3 \cdot 7H_2O$, 6.3 equiv of $NaBH_4$, MeOH, −50 °C, 5 h; (i) 1.5 equiv of *m*-CPBA, CH_2Cl_2, rt, 24 h; (j) 6.5 equiv of allyl alcohol, 2.1 equiv of $BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 3.5 h; (k) 1.1 equiv of Bu_2SnO, 1.1 equiv Bu_4NBr, 5.0 equiv of BnBr or 4.1 equiv of PMBCl, 3-Å MS, MeCN, 80 °C, 5 h; (l) 5.0 equiv of NaH, 5.0 equiv of BnBr, DMF, rt, 90 min; (m) cat. 10% Pd/C, cat. *p*-TsOH, 95% aqueous EtOH, 80 °C, 2 h; (n) 2.0 equiv of NaH, 2.5 equiv of MeI, DMF, rt, 15 min; (o) cat. 10% Pd/C, H_2 (1 atm), MeOH, rt, 14 h; (p) 50 equiv of Ac_2O, pyridine, rt, 16 h.

available in multigram quantities from 1,6-anhydromannose.[20,21] Reaction of **10** with **15** using trimethylsilyl triflate as promotor gave the corresponding α-glycoside **16** in 55% yield (Scheme 2). Deallylation[22] and subsequent phosphorylation using the phosphoramidite procedure[23] gave **18** which, after deacetylation and hydrogenation, afforded **1**. This is the first synthesis of a 6-*O*-glycosyl-D-*chiro*-inositol 1-phosphate. The preliminary synthesis by Falk *et al.*[12f] gave a 2-*O*-glycosyl 1-phosphate compound and that reported by Shen *et al.*[12c] gave a 4-*O*-glycosyl 1-phosphate.

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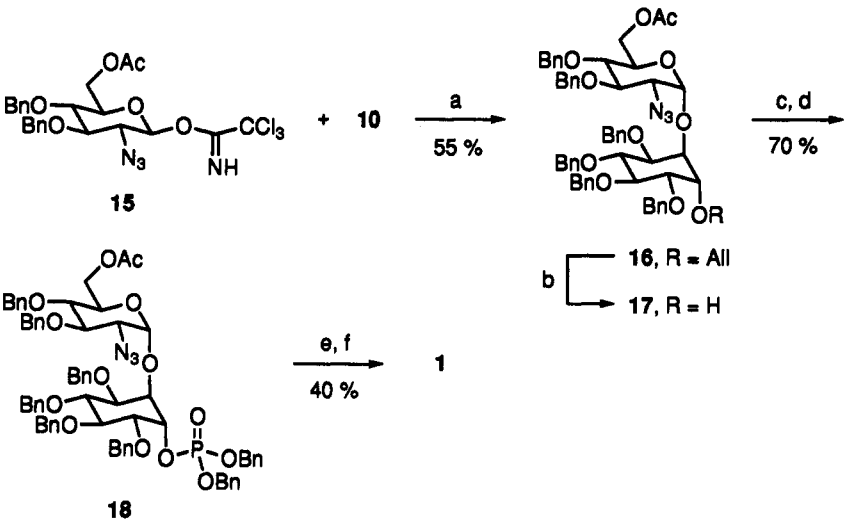
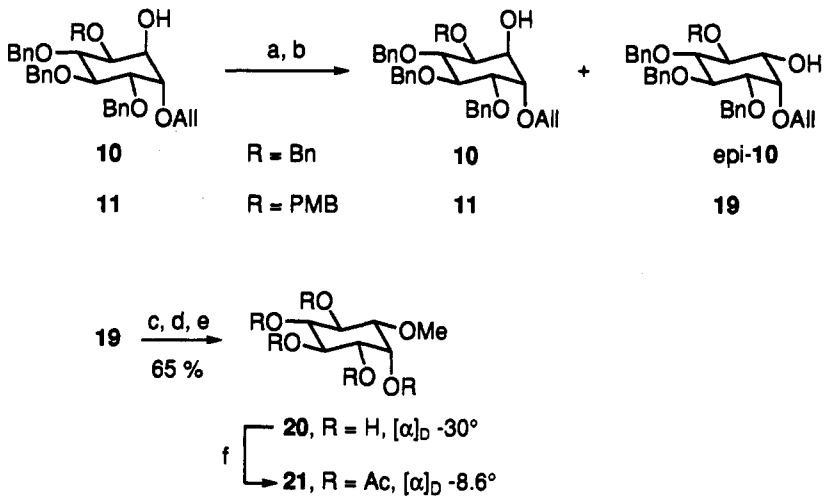
Scheme 2



[a] Reagents and conditions: (a) 1.0 equiv of **10**, 1.6 equiv of **15**, 0.08 equiv of TMSOTf, CH_2Cl_2, −25 °C → 23 °C, 3 h; (b) 0.04 equiv of $[Ir(COD)(Ph_2MeP)_2]PF_6$, H_2 (1 atm), THF, rt, 5 min; argon, 30 min, and then 2.3 equiv of I_2, THF/H_2O (4:1), rt, 2 h; (c) 2.2 equiv of *i*-$Pr_2NP(OBn)_2$, 4.5 equiv of tetrazole, MeCN/CH_2Cl_2 (1:1), rt, 1 h; (d) cat. $RuCl_3 \cdot 3H_2O$, 4.5 equiv of $NaIO_4$, CH_2Cl_2/MeCN/H_2O (1:1:1), rt, 1 h; (e) THF/10% NH_3 in MeOH (1:3.2), 0 °C, 72 h; (f) cat. 10% Pd/C, MeOH–0.2 M NaOAc/HOAc pH 5 buffer (1:1), rt, 18 h.

Scheme 3



[a] Reagents and conditions: (a) 2.3 equiv of PCC, CH_2Cl_2, rt, 13 h; (b) see Table 1; (c) 2.0 equiv of NaH, 3.2 equiv of MeI, DMF, rt, 1 h; (d) cat. *p*-TsOH, cat. 10% Pd/C, 95% aqueous EtOH, 80°C, 90 min; (e) H_2 (1 atm), 95% aqueous EtOH, rt, 90 min; (f) 52 equiv of Ac_2O, pyridine, rt, 16 h.

For the synthesis of the *myo*-inositol derivative **2**, several attempts were made to invert the configuration of the free hydroxyl group of **10** or **11** conventionally, either through a Mitsunobu reaction[24] or by treatment of the corresponding triflate with benzoyl nucleophiles[25] with unsatisfactory results. Similarly, the attempted osmylation of **7** did not provide a convenient route for the gram-scale preparation of the desired *myo*-inositol compound. Therefore, a two-step oxidation–reduction sequence was preferred (Scheme 3). Thus, oxidation of either **10** or **11** gave the corresponding ketones whose reduction was strongly dependent on steric and electronic factors. Lithium reagents seemed to favor α-delivery of hydride and only reducing agents bearing very large alkyl substituents favored β-attack, away from the vicinal allyloxy group in axial position, providing the desired stereochemistry (Table 1). Most likely, the orientation of the substituents α to the carbonyl function in the ketones allows complexation of these molecules by both faces. The configuration of **19** was unequivocally established by conversion into the previously known (−)-bornesitol (**20**) and its penta-*O*-acetate **21** (Scheme 3).[26] Phosphorylation of **19** gave **22** and subsequent acidolysis of the *p*-methoxybenzyl group afforded the *myo*-inositol derivative **23**, which is ready for glycosylation at position 6 (Scheme 4). Reaction of **23** with trichloroacetimidate **15**, using TMSOTf as promotor, afforded glycoside **24** in 65% yield, which was completely deprotected to give **2**[12a,d,e] in moderate yield (Scheme 4).

Experimental Section

General. NMR spectra were recorded at 30 °C on Varian XL-300 (300 MHz) or Bruker AM-200 (200 MHz) instruments. Melting points were determined on a Kofler hot-stage apparatus

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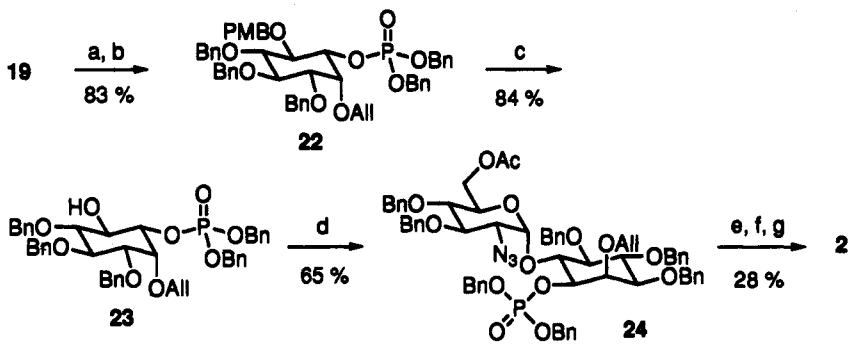
Table 1. OH Inversion of 10 and 11 through an Oxidation–Reduction Sequence (see Scheme 3)

substrate	reduction conditions after PCC oxidation of substrate: reagents	solvent	T (°C)	products (ratio)[a]
10	$NaBH_4$	MeOH	0	**10**/epi-**10** (1:1)
10	$NaBH_4$	MeOH	−78	**10**/epi-**10** (1:1)
10	$NaBH_4/CeCl_3$	MeOH	−78	**10**/epi-**10** (3:2)
10	L-Selectride	THF	0	**10**/epi-**10** (10:1)
10	DIBAL	THF	0	**10**/epi-**10** (5:1)
10	$LiBH_4$	THF	−78	**10**/epi-**10** (7:1)
10	$LiAlH_4$	THF	−78	**10**/epi-**10** (2.2:1)
10	LiAl(O-*t*-Bu)$_3$H	THF	−78	**10**/epi-**10** (1.6:1)
11	$NaBH_4/CeCl_3$	MeOH	−78	**11**/**19** (1.2:1)
11	$LiAlH_4$	THF	−78	**11**/**19** (2.1:1)
11	LiAl(O-*t*-Bu)$_3$H	THF	−78	**11**/**19** (2.1:1)
11	LiAl(O-*t*-Bu)$_3$H	Et_2O	−78	**11**/**19** (1.8:1)
11	LiAl(O-*t*-Bu)$_3$H/$HgCl_2$	Et_2O	−78	**11**/**19** (2.7:1)
11	(*R*)-Alpine hydride	THF	0	**11**/**19** (1:4.2)
11	(*R*)-Alpine hydride	THF	−90	**11**/**19** (1:6)
11	(*S*)-Alpine hydride	THF	0	**11**/**19** (1:3)
11	(*S*)-Alpine hydride	THF	−90	**11**/**19** (1:5)

[a] Determined from the ^1H NMR of the crude.

Scheme 4



[a] Reagents and conditions: (a) 2.5 equiv of *i*-$Pr_2NP(OBn)_2$, 3.0 equiv of tetrazole, $MeCN/CH_2Cl_2$ (1:1), rt, 1 h; (b) cat. $RuCl_3 \cdot 3H_2O$, 2.5 equiv of $NaIO_4$, $CH_2Cl_2/MeCN/H_2O$ (1:1:1), rt 1 h; (c) CF_3CO_2H 2.5% v/v in CH_2Cl_2, rt, 1 h; (d) 1.0 equiv of **23**, 2.6 equiv of **14**, 0.08 equiv of TMSOTf, CH_2Cl_2, −20 °C → 23 °C, 2.5 h; (e) THF/10% NH_3 in MeOH (1:3.4), 0 °C, 68 h; (f) 0.04 equiv of $[Ir(COD)(Ph_2MeP)_2]PF_6$, H_2 (1 atm), THF, rt, 5 min; argon 30 min, and then 2.0 equiv of I_2, THF/H_2O (4.2:1), rt, 2 h; (g) cat. 10% Pd/C, H_2 (1 atm), 95% aqueous EtOH, rt, 18 h.

and are uncorrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Elemental analyses were obtained with a Perkin-Elmer 240 instrument. Separation and purification of products was performed by flash chromatography using silica gel Merck (230–400 mesh). Silica gel plates (Merck, GF_{254}) were used for analytical thin-layer chromatography (TLC). Tetrahydrofuran (THF) and ethyl ether were distilled under argon from sodium–benzophenone, methylene chloride from calcium hydride, and dimethylformamide from barium oxide. All reactions were performed under an argon atmosphere with anhydrous, freshly distilled solvents, unless otherwise indicated.

Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside (4).[13] To a solution of methyl α-D-glucopyranoside (**3**, 19.40 g, 100.00 mmol) in pyridine (200 mL) were added TrCl (35.00 g, 125.67 mmol) and DMAP (2.00 g, 16.37 mmol). After 16 h, the solvent was evaporated, and the residue was crystallized (EtOH, 200 mL). The resulting crystalline methyl 6-*O*-trityl-α-D-glucopyranoside (36.34 g, 83%) was dissolved in DMF (400 mL) and treated with 95% NaH (15.00 g, 606.25 mmol) and BnBr (60 mL, 86.34 g, 504.91 mmol) at rt. After 3 h, the reaction was quenched with MeOH (150 mL), and the solvents were evaporated at reduced pressure. The residue was dissolved in Et_2O (900 mL) and washed with H_2O (500 mL). The aqueous phase was extracted with Et_2O (2 × 250 mL), and the combined organics were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. The resulting residue was dissolved in $MeOH–CH_2Cl_2$ (2:1, 500 mL), and *p*-TsOH was added until pH < 4. After 12 h of stirring, the reaction was neutralized with Et_3N, and the solvents were evaporated. Et_2O (400 mL) was added, and the organic phase was washed with H_2O (500 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL), and the combined organics were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (hexane/AcOEt 10:1 → 2:1), yielding **4**[13] (36.70 g, 79% from **3**).

Methyl 2,3,4-Tri-*O*-benzyl-α-D-*xylo*-hex-5-enopyranoside (5).[14] To a solution of **3** (42.10 g, 90.73 mmol) in pyridine (500 mL) were added Ph_3P (68.00 g, 259.54 mmol) and CI_4 (68.00 g, 130.77 mmol). After 12 h, MeOH (120 mL) was added and the solvents were evaporated. The residue was dissolved in Et_2O (500 mL) and washed with H_2O (300 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organics were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (hexane/AcOEt 20:1 → 5:1), affording methyl 2,3,4-tri-*O*-benzyl-6-iodo-6-deoxy-α-D-glucopyranoside (38.50 g, 74%). This product was dissolved in DMF (350 mL) and treated with 95% NaH (9.60 g, 380.00 mmol). After 20 h, MeOH (200 mL) was added, the solvent was evaporated at reduced pressure, and the resulting residue was suspended in H_2O (200 mL). The aqueous phase was extracted with Et_2O (2 × 300 mL), the combined organics were washed with brine (200 mL), dried (Na_2SO_4), and concentrated, and the resulting residue was purified by flash chromatography (hexane/AcOEt 15:1 → 10:1), affording **5**[14] (25.50 g, 63% from **3**).

(2*S*,3*R*,4*S*)-2,3,4-Tris(benzyloxy)cyclohex-5-enone (6).[14] To a solution of **5** (12.00 g, 26.91 mmol) in $Me_2CO–H_2O$ (2:1, 800 mL) was added $HgCl_2$ (7.90 g, 29.10 mmol), and the resulting solution was heated at 100 °C for 90 min. The reaction was then cooled, and the solvent was evaporated at reduced pressure. The residue was dissolved in Et_2O (300 mL) and washed with 10% aqueous KI (300 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organics were washed with brine (200 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (hexane/AcOEt

3:1), affording a mixture of epimers (9.88 g, 85%, α/β = 3.5:1 by ^{1}H NMR). To a solution of this mixture (6.30 g, 14.58 mmol) in pyridine (120 mL) were added MsCl (3 mL, 38.8 mmol) and DMAP (250 mg, 2.05 mmol). After 4 h, ice (100 g) was added, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The solvents were evaporated at reduced pressure, and the resulting residue was purified by flash chromatography (hexane/AcOEt 10:1 → 4:1), affording **6**[14] (4.86 g, 68% from **5**).

1,2,3-Tri-*O*-benzylconduritol B (7). To a solution of **6** (4.86 g, 11.74 mmol) in MeOH (450 mL) at −50 °C was added $CeCl_3 \cdot 7H_2O$ (4.60 g, 12.35 mmol). After 10 min of stirring, $NaBH_4$ (700 mg, 18.42 mmol) was added, and the reaction mixture was stirred at −50 °C for 5 h. The reaction mixture was treated with Me_2CO (5 mL) at −50 °C and allowed to warm to rt. The solvents were evaporated at reduced pressure and the resulting residue was dissolved in Et_2O (100 mL) and washed with H_2O (100 mL). The aqueous phase was washed with Et_2O (100 mL), and the combined organics were concentrated, affording an epimeric mixture of alcohols (4.70 g, 97%, 14:1 by ^{1}H NMR), which was submitted to epoxidation without further purification. A pure sample of **7** was obtained by flash chromatography (hexane/AcOEt 4:1 → 2:1): mp 116–119 °C; $[\alpha]^{23}_D$ +117° (*c* 0.9, $CHCl_3$), lit.[27] +114.6°; ^{1}H NMR (200 MHz, C_6D_6) δ 7.40–7.20 (m, 15 H), 5.23 (m, 2 H), 4.67–4.38 (m, 4 H), 4.19 (s, 2 H), 3.92 (m, 1H), 3.83 (m, 1 H), 3.47 (dd, 1 H, *J* = 10.3, 7.5 Hz), 3.17 (dd, 1H, *J* = 10.3, 7.7 Hz), 1.44 (d, 1 H, *J* = 4.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 129.4, 128.6, 128.4, 127.9, 127.8, 127.7, 127.6, 127.0, 84.3, 83.3, 80.5, 75.3, 72.2, 71.9, 71.8. Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.87; H, 6.78. Found: C,77.60; H, 6.70.

4,5,6-Tri-*O*-benzyl-1,2-anhydro-*myo*-inositol (8). To a solution of **7** (4.70 g, 11.30 mmol) in CH_2Cl_2 (120 mL) was added 55% *m*-CPBA (5.32 g, 16.97 mmol) at rt. After 24 h, CH_2Cl_2 (80 mL) was added, and the organic phase was washed with 10% $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The solvent was evaporated at reduced pressure, and the resulting residue was purified by flash chromatography (hexane/AcOEt 3:1 → 1:1) to give **8** as a white solid (4.55 g, 93%): mp 147–150 °C; $[\alpha]^{23}_D$ +78° (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 15 H), 4.94–4.63 (m, 6 H), 4.02 (dd, 1 H, *J* = 8.1, 1.7 Hz), 3.93 (d, 1 H, *J* = 7.4 Hz), 3.48 (m, 2 H), 3.41 (m, 1 H), 3.23 (d, 1 H, *J* = 3.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 138.2, 127.9, 127.8, 127.8, 127.7, 127.6, 83.3, 79.5, 79.3, 75.6, 75.2, 73.2, 71.9, 56.2, 53.6. Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.52. Found: C, 75.10; H, 6.86.

1-*O*-Allyl-2,3,4-tri-*O*-benzyl-D-*chiro*-inositol (9). To a solution of **8** (4.55 g, 10.53 mmol) in CH_2Cl_2 (100 mL) were added allyl alcohol (4.69 mL, 68.81 mmol) and $BF_3 \cdot OEt_2$ (2.70 mL, 21.94 mmol). After 3.5 h, the reaction was neutralized with Et_3N, CH_2Cl_2 (100 mL) was added, and the organic phase was washed with water (150 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure, and the resulting residue was purified by flash chromatography (hexane/AcOEt 2:1 → 1:1) to give **9** as a syrup (3.87 g, 75%): $[\alpha]^{23}_D$ + 40° (*c* 0.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.15 (m, 15 H), 5.84–5.71 (m, 1 H), 5.18–5.03 (m, 2 H), 4.91–4.52 (m, 6 H), 4.15–3.94 (m, 3 H), 3.84–3.72 (m, 4 H), 3.52 (t, 1 H, *J* = 8.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 138.7, 138.5, 135.0, 128.6, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 117.1, 81.6, 81.5, 80.2, 75.6, 75.5, 75.3, 73.1, 72.5, 71.3, 69.5. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.12; H, 6.87.

1-*O*-Allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (10). To a solution of **9** (275 mg, 0.561 mmol) in MeCN (20 mL) were added Bu_2SnO (145 mg, 0.582 mmol), Bu_4NBr (185 mg, 0.574 mmol), powdered 3-Å molecular sieves (2.0 g), and BnBr (0.33 mL, 2.77 mmol), and the resulting solution was heated at 80 °C. After 5 h, the reaction was cooled and filtered through a pad of Celite. The filter was washed with CH_2Cl_2 (2 × 10 mL), and the filtrate and washings combined were evaporated at reduced pressure. The resulting residue was purified by flash chromatography (hexane/AcOEt 4:1, 2.7 × 14.0 cm) to give **10** as a syrup (270 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.15 (m, 20 H), 5.81–5.70 (m, 1 H), 5.17–5.03 (m, 2 H), 4.86-4.54 (m, 8 H), 4.17–3.90 (m, 3 H), 3.84–3.66 (m, 5 H); ^{13}C (50 MHz, $CDCl_3$) δ 139.0, 138.95, 138.7, 138.1, 135.1, 128.5, 128.3, 128.0, 127.9, 127.7, 127.4, 116.8, 81.9, 81.6, 80.3, 79.9, 75.8, 75.7, 75.6, 73.3, 72.5, 68.2.

1,2,3,4,5-Penta-*O*-benzyl-D-*chiro*-inositol (12). To a solution of **9** (590 mg, 1.20 mmol) in DMF (20 mL) were added 80% NaH (180 mg, 6.00 mmol) and BnBr (0.72 mL, 6.06 mmol) at rt. After 90 min, MeOH (0.5 mL) was added and the solvents were evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with H_2O (20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude was dissolved in 95% EtOH (60 mL), treated with 10% Pd/C (320 mg) and *p*-TsOH (65 mg), and heated at 80 °C.[28] After being stirred for 2 h at 80 °C, the reaction was cooled to rt and filtered through a pad of Celite, washing with CH_2Cl_2 (20 mL) and MeOH (20 mL). The filtrate and the washings combined were evaporated at reduced pressure, and the resulting residue was purified by flash chromatography (hexane/AcOEt 5:1) to give **12** (410 mg, 54%).

1-*O*-Methyl-D-*chiro*-inositol (13).[18] To a solution of **12** (410 mg, 0.651 mmol) in DMF (15 mL) were added 80% NaH (39 mg, 1.30 mmol) and MeI (0.1 mL, 1.62 mmol). After 15 min, MeOH (0.1 mL) was added, and the solvents were evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) and the solution was washed with H_2O (15 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The crude was dissolved in MeOH (40 mL), 10% Pd/C (168 mg) was added, and the mixture was stirred under H_2 (1 atm) at rt. After 14 h, the reaction mixture was filtered through a pad of Celite, the filter was washed with MeOH (2 × 15 mL), and the filtrate and washings combined were evaporated at reduced pressure. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 2:1, 2.7 × 10.5 cm) to give **13** (80 mg, 63%): $[\alpha]^{23}_D$ +59° (*c* 1.3, D_2O), lit.[18] +61°; ^{1}H-NMR (300 MHz, D_2O) δ 4.02 (t, 1 H, *J* = 3.4 Hz), 3.57 (dd, 1H, *J* = 9.5, 3.4 Hz), 3.46 (dd, 1 H, *J* = 3.4, 8.1 Hz), 3.44 (t, 1 H, *J* = 3.4 Hz), 3.35 (t, 1 H, *J* = 9.5 Hz) and 3.33 (dd, 1 H, *J* = 9.5, 8.1 Hz).

1,2,3,4,5-Penta-*O*-acetyl-6-*O*-methyl-D-*chiro*-inositol (14).[18] **13** (40 mg, 0.206 mmol) was acetylated (pyridine, 2 mL; Ac_2O, 1 mL) to give **14** as a white solid: mp 106–110 °C, lit.[18] mp 110.5–111.5 °C; $[\alpha]^{23}_D$ + 26.0° (*c* 1.7, $CHCl_3$), lit.[18] +29.1°; ^{1}H NMR (200 MHz, C_6D_6) δ 5.91 (dd, 1H, *J* = 10.0, 9.5 Hz), 5.82 (dd, 1 H, *J* = 10.0, 9.5 Hz), 5.76 (dd, 1 H, *J* = 4.0, 3.6 Hz), 5.59 (dd, 1 H, *J* = 10.0, 3.6 Hz), 5.53 (dd, 1 H, *J* = 10.0, 3.2), 3.03 (s, 3 H), 3.59 (dd, 1 H, *J* = 4.0, 3.2), 1.73, 1.69, 1.68, 1.64 and 1.52 (5 s, 3 H each); ^{13}C (50 MHz, C_6D_6) δ 169.6, 169.55, 169.5, 169.35, 169.3, 76.9, 71.3, 70.9, 70.5, 69.7, 67.6, 59.0, 20.2, 19.9.

6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl Trichloroacetimidate (15).[12b] To a solution of 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose[20,21] (200 mg, 0.47 mmol) and CCl_3CN (680 mg, 4.71 mmol) in 3 mL of CH_2Cl_2 was added powdered, flame-dried K_2CO_3 (65 mg, 0.47 mmol) at 23 °C. After 1 h of stirring, the suspension was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure. The residue was quickly purified by flash chromatography (hexane/EtOAc 3:1) to give **15** as a white solid (262 mg, 98%, >95% β anomer by ^{1}H NMR).

1-(6-*O*-Acetyl-2-azido-2-deoxy-3,4-dibenzyl-α-D-glucopyranosyl)-6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (16). A mixture of **10** (214 mg, 0.37 mmol) and **15** (137 mg, 0.23 mmol), azeotroped with freshly distilled benzene (2 × 10 mL), was dissolved in CH_2Cl_2 (3 mL). The solution was cooled to −25 °C and treated with $CF_3SO_2SiMe_3$ (95 μL of a 0.2 M solution in CH_2Cl_2, 0.019 mmol). After being stirred at −25 °C for 30 min, the solution was allowed to warm to rt over 3 h, and Et_3N (0.6 mL), Ac_2O (0.2 mL), and DMAP (5 mg) were added. After 4 h of stirring, MeOH (0.5 mL) was added, the solution was stirred for 5 min, and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 9:1 → 5:1) to give **16** as a colorless syrup (124 mg, 55%): $[\alpha]^{23}_D$ +40.8° (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.42–7.07 (m, 30 H), 5.82 (m, 1 H, *J* = 17.2, 10.6, 5.5 Hz), 5.21 (m, 1 H, *J* = 17.2, 1.7 Hz), 5.04 (m, 1 H, *J* = 10.6, 1.5 Hz), 5.01–4.68 (m, 10H), 4.57–4.47 (m, 4 H), 4.34–4.27 (m, 1 H), 4.19–3.92 (m, 6 H), 3.80 (dd, 1 H *J* = 4.1, 1.3 Hz), 3.57 (dd, 1 H *J* = 9.9, 9.0 Hz), 3.15 (dd,

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1 H, J = 10.1, 3.5), 1.67 (s, 3 H); ^{13}C (50 MHz, C_6D_6) δ 169.6, 139.8, 139.7, 138.8, 138.4, 135.4, 128.5–127.5 (obscured by solvent signals), 116.6, 96.5, 82.4, 80.6, 80.5, 78.6, 78.5, 76.0, 75.7, 75.3, 75.0, 74.6, 74.5, 73.7, 73.6, 73.1, 69.7, 64.3, 62.6, 20.4. Anal. Calcd for $C_{59}O_{11}H_{63}N_3$: C, 71.57; H, 6.41; N, 4.24. Found: C, 71.28; H, 6.70; N, 4.45.

1-(6-*O*-Acetyl-2-azido-2-deoxy-3,4-dibenzyl-α-D-glucopyranosyl)-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (17). To a solution of **16** (124 mg, 0.125 mmol) in THF (4 mL) under argon was added $[Ir(COD)(Ph_2MeP)_2]PF_6$ (4 mg, 4.8×10^{-3} mmol) at rt. The argon atmosphere was replaced with H_2 and the solution was stirred for 5 min, during which time the initially slightly red suspension becomes colorless. The H_2 was replaced with argon again, the solution was stirred for 1 h, and water (1.0 mL) and I_2 (74 mg) were added. After 2 h of stirring, the reaction mixture was diluted with EtOAc (25 mL), washed with 10% aqueous $Na_2S_2O_3$ (20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 3:1 → 3:2) to give **17** as a colorless oil (101 mg, 85%): ^{1}H NMR (300 MHz, C_6D_6) δ 7.40–7.04 (m, 30 H), 5.04–4.48 (m, 12 H), 4.44 (d, 1 H, J = 3.5 Hz), 4.29–3.88 (m, 10 H), 3.55 (dd, J = 10.1, 9.0 Hz), 3.09 (dd, 1 H, J = 10.2, 3.5 Hz), 2.36 (bs, 1 H), 1.66 (s, 3 H).

2,3,4,5-Tri-*O*-benzyl-1-(6-*O*-acetyl-2-azido-2-deoxy-3,4-di-*O*-benzyl-α-D-glucopyranosyl)-6-(dibenzylphosphono)-D-*chiro*-inositol (18). To a solution of **17** (85 mg, 0.089 mmol) in MeCN–CH_2Cl_2 (1 mL, 1:1) were added dibenzyl *N,N*-diisopropylphosphoramidite (69 mg, 0.20 mmol) and tetrazole (28 mg, 0.40 mmol). After being stirred for 1 h at rt, the reaction mixture was diluted with water (0.5 mL) and treated with $NaIO_4$ (68 mg, 0.40 mmol) and $RuCl_3 \cdot 3H_2O$ (0.5 mg). After being stirred vigorously for 1 h, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated at reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 3:1 → 3:2) to give **18** as a colorless oil (88 mg, 82%): $[\alpha]^{23}_D$ +58.1° (*c* 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.54–7.04 (m, 40 H), 5.20 (m, 1H, J = 7.2, 3.9, 3.1 Hz), 5.08–4.28 (m, 20 H), 4.56 (d, 1 H, J = 3.6 Hz), 4.12–3.93 (m, 5 H), 3.55 (t, 1 H, J = 9.2 Hz), 3.07 (dd, 1 H, J = 10.1, 3.5 Hz), 1.69 (s, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 169.7, 139.5, 138.7, 138.6, 138.4, 128.9–127.5 (obscured by solvent signals), 97.1, 81.9, 81.6, 80.7, 78.4, 77.9, 76.1, 75.8, 75.3, 75.0, 74.2 (d, J_{CP} = 2.0 Hz), 73.1, 72.7 (d, J_{CP} = 5.5 Hz), 69.9, 69.8 (d, J_{CP} = 5.8 Hz), 69.4 (d J_{CP} = 5.5 Hz), 64.3, 62.6, 20.4. Anal. Calcd for $C_{70}H_{72}N_3O_{14}P$: C, 69.47; H, 6.00; N, 3.47. Found: C, 69.71; H, 6.30; N, 3.71.

Sodium 1-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*chiro*-inositol 1-Hydrogen Phosphate (1). A solution of **18** (80 mg, 0.066 mmol) in THF (2.5 mL) and 10% NH_3 in MeOH (8 mL) was kept at 0 °C for 72 h. The solvent was removed at reduced pressure and the residue was purified by flash chromatography to give unreacted **18** (13 mg, 16%) and its deacetylated derivative (52 mg, 67%): ^{1}H NMR (300 MHz, C_6D_6) δ 7.52–7.01 (m, 40 H,), 5.23 (m, 1 H, J = 8.5, 3.2 Hz), 5.12-4.52 (m, 17 H), 4.47 (t, 1 H, J = 3.6 Hz), 4.31 (m, 1 H, J = 9.6, 2.8 Hz), 4.26 (m, 1 H, J = 10.0, 2.7 Hz), 4.15–3.94 (m, 4 H), 3.60 (t, 1 H, J = 9.6 Hz), 3.58 (bs, 3 H), 3.10 (dd, 1 H, J = 10.1, 3.6 Hz). A solution of the latter compound (147 mg, 0.126 mmol) in MeOH (15 mL) and 0.2 M NaOAc/HOAc pH 5 buffer (15 mL) was stirred under H_2 (1 atm) in the presence of 10% Pd/C (100 mg) at rt. After 18 h of stirring, the suspension was filtered through a pad of Celite and the filtrate was passed through a column of Na-exchanged Amberlite IR-120. The resultant solution was lyophilized and the residue was purified by column chromatography on Sephadex G-15 (H_2O) to give **1** as a white solid (34 mg, 40% from **18**): $[\alpha]^{23}_D$ +99.9° (*c* 1.022, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 5.23 (d, 1 H, J = 3.7 Hz), 4.41 (m, 1 H), 4.23 (t, 1 H, J = 3.4 Hz), 3.97 (dt, 1 H, J = 10.0, 2.9 Hz), 3.85–3.64 (m, 5 H), 3.58–3.49 (m, 2 H), 3.44 (Ψt, 1H, J = 9.9 Hz), 3.31 (dd, 1H, J = 10.7, 3.7 Hz); ^{13}C NMR (50 MHz, D_2O) δ 95.4 (br), 76.9, 74.1, 73.6, 73.5, 71.4 (br), 70.9, 70.5, 70.3, 61.2, 55.0 (br).

1-*O*-Allyl-2,3,4-tri-*O*-benzyl-5-*O*-(*p*-methoxybenzyl)-D-*chiro*-inositol (11). To a solution of **9** (3.50 g, 7.14 mmol) in MeCN (120 mL) were added Bu_2SnO (1.92 g, 7.71 mmol), Bu_4NBr (2.42 g, 7.52 mmol), powdered 3-Å molecular sieves (15.0 g), and PMBCl (4.00 mL, 29.52 mmol), and the resulting solution was heated at 80 °C. After 5 h, the reaction was cooled and filtered through a pad of Celite. The filter was washed with CH_2Cl_2 (2 × 40 mL), and the filtrate and washings combined were evaporated at reduced pressure. The resulting residue was purified by flash chromatography (hexane/AcOEt 5:1 → 2:1) to give **11** as a colorless syrup (3.70 g, 85%): $[\alpha]^{23}_D$ + 1.5° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.33–6.62 (m, 19 H), 5.78–5.65 (m, 1 H), 5.12–4.80 (m, 6 H), 4.55 (d, 1 H), 4.45 (d, 1 H), 4.41 (d, 1 H), 4.29 (d, 1 H), 4.18–4.07 (m, 2 H), 4.03 (dd, 1 H, J = 2.6, 9.8 Hz), 3.91–3.78 (m, 5 H), and 3.18 (s, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 159.9, 140.0, 140.0, 139.5, 135.7, 130.0, 129.8, 129.5, 128.9, 128.5, 128.4, 128.3, 128.0, 127.8, 127.5, 127.4, 116.8, 114.1, 82.6, 82.2, 80.7, 80.4, 76.7, 75.85, 75.8, 73.4, 73.1, 69.1, 54.7. Anal. Calcd for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93. Found: C, 74.57; H, 6.99.

2-*O*-Allyl-3,4,5-tri-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-*myo*-inositol (19). To a solution of **11** (3.39 g, 5.56 mmol) in CH_2Cl_2 (80 mL) was added PCC (2.72 g, 12.62 mmol) at rt. After being stirred for 13 h, the reaction mixture was filtered through a pad of Celite, the filter was washed with CH_2Cl_2 (2 × 25 mL), and the filtrate and washings combined were evaporated at reduced pressure. The resulting residue was purified by flash chromatography (hexane/AcOEt 8:1 → 4:1) to give the ketone as a colorless syrup (3.00 g, 89%). To a solution of the ketone (3.00 g, 4.93 mmol) in THF (100 mL), at −90 °C, was added a solution of (*R*)-Alpine hydride (0.5 M in THF, 21.0 mL, 10.50 mmol) in THF (40 mL). After 30 min, the reaction was warmed to 0 °C, and water (46 mL), 3 M NaOH (14 mL), and 30% H_2O_2 (30 mL) were added. After 30 min, the reaction was warmed to 22 °C, H_2O (250 mL) was added, the aqueous phase was extracted with Et_2O (2 × 250 mL), and the solvent was evaporated at reduced pressure. The resulting residue was purified by flash chromatography (hexane/AcOEt 4:1 → 3:1) to give **11** (0.70 g) and **19** as a white solid (1.95 g, 58% from starting **11**). **19**: mp 89–91 °C; $[\alpha]^{23}_D$ - 8.0° (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–6.81 (m, 19 H), 5.96–5.85 (m, 1 H), 5.28–5.12 (m, 2 H), 4.91–4.66 (m, 8 H), 4.45–4.15 (m, 2 H), 3.97 (t, 1 H, J = 9.5 Hz), 3.91 (t, 1 H, J = 2.6 Hz), 3.76 (s, 3 H), 3.74 (t, 1 H, J = 9.5 Hz), 3.45–3.36 (m, 3 H), and 2.19 (d, 1 H, J = 6.2 Hz); ^{13}C (50 MHz, C_6D_6) δ 159.3, 138.7, 138.2, 135.3, 129.6, 128.4, 128.0, 127.7, 127.6, 127.5, 116.7, 113.9, 83.6, 81.9, 81.1, 77.2, 76.7, 75.9, 75.7, 75.2, 73.7, 73.0, 72.3, 55.3. Anal. Calcd for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93. Found: C, 74.36; H, 7.15.

2-*O*-Allyl-3,4,5-tri-*O*-benzyl-1-*O*-(dibenzylphosphono)-6-*O*-(*p*-methoxybenzyl)-D-*myo*-inositol (22). To a solution of **19** (340 mg, 0.56 mmol) in CH_2Cl_2/MeCN (1:1, 5 mL) were added tetrazole (120 mg, 1.67 mmol) and *N,N*-dibenzyldiisopropylphosphoramidite (480 mg, 1.39 mmol). After being stirred for 1.5 h at rt, the reaction mixture was cooled to 0 °C and H_2O (2.5 mL), $NaIO_4$ (300 mg, 1.39 mmol) and $RuCl_3 \cdot 3H_2O$ (1 mg) were added. The resulting mixture was vigorously stirred at 0 °C for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 (60 mL), washed with 10% aqueous $Na_2S_2O_3$ (10 mL), and brine (10 mL), dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 3:1) to give **22** as a white solid (397 mg, 83%): mp 85–87 °C; $[\alpha]^{23}_D$ +6.0° (*c* 0.905, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.36 (m, 27 H), 6.76-6.72 (m, 2 H), 5.92 (m, 1 H, J = 17.2, 10.4, 5.6, 5.3 Hz), 5.25 (m, 1 H, J = 17.2, 1.8, 1.6 Hz), 5.11 (m, 1 H, J = 10.4, 10.4, 1.8, 1.5 Hz), 5.05–4.57 (m, 12 H), 4.37 (m, 1 H, J = 12.9, 5.6, 1.6 Hz), 4.27–4.17 (m, 3 H), 4.03 (t, J = 9.4 Hz), 4.01 (t, 1 H, J = 9.6 Hz), 3.74 (s, 3 H), 3.44 (t, 1 H, J = 9.2 Hz), 3.37 (dd, 1 H, J = 9.9, 2.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 138.5, 138.0, 135.7 (d, J_{CP} = 7.2 Hz), 135.2, 130.6, 129.3, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127,4, 116.3, 113.6, 83.1, 81.2, 80.4, 79.9 (d, J_{CP} = 7.2 Hz), 78.5, (d, J_{CP} = 6.2 Hz), 77.6, 77.0, 76.4, 75.8, 75.2, 73.9, 72.6, 69.3 (d, J_{CP} = 5.4 Hz), 69.2 (d, J_{CP} = 5.2 Hz), 55.1. Anal. Calcd for $C_{52}H_{55}O_{10}P$: C, 71.70; H, 6.37. Found: C, 71.51; H, 6.60.

2-*O*-Allyl-3,4,5-tri-*O*-benzyl-1-*O*-(dibenzylphosphono)-D-*myo*-inositol (23). To a solution of **22** (100 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added CF_3CO_2H (2 mL of a 2.5% v/v solution in CH_2Cl_2) at 23 °C. After being stirred for 1 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated aqueous $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined

organic extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 2:1) to give **23** as a white solid (72 mg, 84%): mp 102–104 °C; $[\alpha]^{23}_D$ +6.3° (*c* 0.238, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.13 (m, 25 H), 5.75 (m, 1 H, *J* = 17.2, 10.4, 5.5, 5.2 Hz), 5.09 (m, 1 H, *J* = 17.2, 1.7, 1.6 Hz), 5.01–4.88 (m, 5 H), 4.81–4.66 (m, 4 H), 4.50 (m, 2 H), 4.15 (m, 1 H, *J* = 12.9, 5.5, 1.7 Hz), 4.06–3.98 (m, 3 H), 3.90 (t, 1 H, *J* = 2.1 Hz, H-2), 3.85 (t, 1 H, *J* = 9.5 Hz), 3.23 (dd, 1 H, *J* = 9.8, 2.3 Hz), 3.20 (t, 1 H, *J* = 9.1 Hz), 2.68 (bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 138.0, 135.7 (d, J_{CP} = 7.0 Hz), 135.6 (d, J_{CP} = 7.1 Hz), 135.1, 128.6, 128.5, 128.4, 128.35, 128.3, 128.2, 128.0, 127.95, 127.9, 127.7, 127.6, 127.5, 116.4, 82.9, 80.9, 80.4, 78.8 (d, J_{CP} = 6 Hz), 77.6, 77.0, 76.4, 75.85 (d, J_{CP} = 2.7 Hz), 75.7, 75.5, 73.9, 72.7, 72.1 (d, J_{CP} = 4.9 Hz), 69.65 (d, J_{CP} = 5.9 Hz), 69.4 (d, J_{CP} = 5.6 Hz). Anal. Calcd for $C_{44}H_{47}O_9P$: C, 70.39; H, 6.31. Found: C, 70.30; H, 6.12.

(−)-D-Bornesitol (20).[26a] To a solution of **19** (305 mg, 0.500 mmol) in DMF (10 mL) were added 97% NaH (25 mg, 1.00 mmol) and MeI (0.10 mL, 1.62 mmol). After 1 h of stirring, MeOH (1 mL) and H_2O (30 mL) were added, the aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The resulting residue was purified by flash chromatography (hexane/AcOEt 4:1) to give the pure methyl ether (250 mg, 80%). A solution of this product in 95% EtOH (20 mL) was treated with *p*-TsOH (40 mg) and 10% Pd/C (150 mg) at 80 °C for 90 min. The reaction was allowed to cool to rt and was stirred under H_2 (1 atm). After 90 min, the reaction mixture was filtered through a pad of Celite, the filter was washed with MeOH (2 × 20 mL), and the filtrate and washings combined were evaporated at reduced pressure. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 2:1) to give **20**[26a] (63 mg, 65% from **19**): $[\alpha]^{23}_D$ −30° (*c* 0.25, D_2O), lit.[26a] −32°; ^1H NMR (200 MHz, D_2O) δ 4.21 (t, 1 H, *J* = 2.7 Hz), 3.55 (dd, 1 H, *J* = 10.0, 9.5 Hz), 3.52 (dd, 1 H, *J* = 10.0, 9.0 Hz), 3.39 (dd, 1 H, *J* = 10.0, 2.7 Hz), 3.33 (s, 3 H), 3.17 (dd, 1 H, *J* = 9.5, 9.0 Hz), 3.11 (dd, 1 H, *J* = 10.0, 2.8 Hz).

2,3,4,5,6-Penta-*O*-acetyl-1-*O*-methyl-*myo*-inositol (21).[26b] **22** (63 mg, 0.101 mmol) was acetylated (pyridine, 1 mL; Ac_2O, 0.5 mL) to give **21**:[26b] mp 143–146 °C, lit.[26b] mp 142–143.5 °C; $[\alpha]_D$ −8.6° (*c* 1.1, $CHCl_3$), lit.[26b] −9.3°; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (t, 1 H, *J* = 2.8 Hz), 5.48 (dd, 1H, *J* = 10.5, 10.0 Hz), 5.37 (dd, 1 H, *J* = 10.1, 9.9 Hz), 5.12 (dd, 1 H, *J* = 10.0 Hz), 4.96 (dd, 1 H, *J* = 10.5, 2.8 Hz), 3.41 (dd, 1 H, *J* = 10.1, 2.8 Hz), 3.35 (s, 3 H), 2.19 (s, 3 H), 2.05 (s, 6 H), 2.01 (s, 6 H).

2-*O*-Allyl-3,4,5-tri-*O*-benzyl-1-*O*-(dibenzylphosphono)-6-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol (24). A mixture of **23** (151 mg, 0.20 mmol) and **15** (293 mg, 0.51 mmol) was azeotroped with freshly distilled benzene (2 × 10 mL) and dissolved in CH_2Cl_2 (3 mL). The solution was cooled to −20 °C and treated with $CF_3SO_2SiMe_3$ (85 μL of a 0.2 M solution in CH_2Cl_2, 0.017 mmol). After being stirred for 2 h at −20 °C, the reaction mixture was allowed to warm to rt over a period of 0.5 h, diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The resulting residue was purified by flash chromatography (hexane/EtOAc 4:1) to give **24** as a clear oil (151 mg, 65%): $[\alpha]^{23}_D$ +47.4° (*c* 0.527, $CHCl_3$); ^1H NMR (300MHz, C_6D_6) δ 7.37–7.05 (m, 35 H,), 6.03–5.87 (m, 1 H), 5.69 (d, 1 H, *J* = 3.6 Hz), 5.35–5.24 (m, 1 H), 5.17–4.17 (m, 24 H), 3.98 (dd, 1 H *J* = 12.4, 3.7 Hz), 3.49 (dd, 1 H, *J* = 9.8, 8.7 Hz), 3.37 (t, 1 H, *J* = 9.2 Hz), 3.14 (dd, 1 H, *J* = 9.8, 2.1 Hz), 3.00 (dd, 1 H, *J* = 10.2, 3.6 Hz), 1.54 (s, 3 H); ^{13}C NMR (50 MHz, C_6D_6) δ 169.6,139.4, 138.75, 138.7, 138.5, 136.7, 136.6, 136.4, 128.8-127.5 (obscured by solvent signals), 116.3, 97.8, 82.0, 81.3, 80.8, 79.9 (d, J_{CP} = 8.3 Hz), 78.7, 76.6, 76.0, 75.6, 75.1, 74.9 (d, J_{CP} = 9.0 Hz), 74.6, 72.7, 69.9 (d, 74.6, 72.7, 69.9 (d, J_{CP} = 5.3 Hz), 69.6 (d, J_{CP} = 6.1 Hz), 63.8, 63.7, 20.4. Anal. Calcd for $C_{86}H_{70}N_3O_{14}P$: C, 68.32; H, 6.08; N, 3.62. Found: C, 68.48; H, 6.31; N, 3.70.

3,4,5-Tri-*O*-benzyl-1-*O*-(dibenzylphosphono)-6-(2-azido-2-deoxy-3,4-dibenzyl-α-D-glucopyranosyl)-D-*myo*-inositol (25). A solution of **24** (120 mg, 0.103 mmol) in THF (3.5 mL) and 10% NH_3 in MeOH (12 mL) was kept at 0 °C for 68 h. The reaction mixture was concentrated at reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 4:1 → 3:1) to give unreacted **24** (15 mg, 12%) and its deacetylated derivative (65 mg, 56%) as a clear oil. To a solution of the latter compound (65 mg, 0.058 mmol) in 2.5 mL of THF under argon at rt was added $[Ir(COD)(Ph_2MeP)_2]PF_6$ (2 mg, 2.4 × 10^{-3} mmol). The argon atmosphere was replaced with H_2 and the solution was stirred for 5 min. The H_2 was replaced with argon, the solution was stirred 30 min, and I_2 (30 mg) and water (0.6 mL) were added. After stirring for 2 h, the reaction mixture was diluted with EtOAc (80 mL), washed with 10% aqueous $Na_2S_2O_3$ (15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 1:1) to give **25** as a clear oil (34 mg, 54%): ^1H NMR (300 MHz, C_6D_6) δ 7.43–7.00 (m, 35 H), 5.78 (d, 1 H, *J* = 3.8 Hz), 5.25–4.61 (m, 14 H), 4.49–4.31 (m, 3 H), 4.28–4.20 (m, 2 H), 4.16 (t, 1 H, *J* = 9.5 Hz), 3.75 (dd, 1 H, *J* = 9.7, 9.2 Hz), 3.45 (dd, 1 H, *J* = 12.2, 1.9 Hz), 3.43 (dd, 1 H, *J* = 12.2, 2.2 Hz), 3.32 (t, 1 H, *J* = 9.4 Hz), 3.18 (dd, 1 H, *J* = 10.4, 3.8 Hz), 3.11 (dd, 1 H, *J* = 9.5, 2.5 Hz), 2.22 (br, 2 H).

6-(2-Amino-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol 1-Phosphate (2).[12a,d,e] A suspension containing **25** (34 mg, 0.032 mmol) and 10% Pd/C (30 mg) in EtOH (10 mL) was vigoruosly stirred under H_2 (1 atm) at rt. After 18 h, the suspension was filtered through a pad of Celite and the filter was rinsed with EtOH (5 mL) and water (2 × 5 mL). The filtrate and the washings combined were concentrated at reduced pressure and the resulting aqueous solution was lyophilized to give **2** as a white solid (12.2 mg, 91%): $[\alpha]^{23}_D$ +73.2° (*c* 0.608, H_2O), lit.[12e] $[\alpha]^{23}_D$ +62° (*c* 0.3, H_2O); ^1H NMR (300 MHz, D_2O) δ 5.49 (d, 1 H, *J* = 3.8 Hz), 4.08 (bs, 1 H), 4.04 (br d, 1 H, *J* = 9.2 Hz), 3.98 (dt, 1 H, *J* = 10.2, 3.5 Hz), 3.80 (t, 1 H, *J* = 9.2 Hz), 3.78 (dd, 1 H, *J* = 10.4, 9.4 Hz), 3.71–3.70 (m, 2 H), 3.58 (Ψt, 1 H, *J* = 9.7 Hz), 3.44 (br d, 1 H, *J* = 9.7 Hz), 3.42 (t, 1 H, *J* = 9.6 Hz), 3.30 (t, 1 H, *J* = 10.3 Hz), 3.23 (dd, 1 H, *J* = 10.6, 3.8 Hz); ^{13}C NMR (50 MHz, D_2O) δ 96.6, 78.4 (d, J_{CP} = 5.2 Hz), 77.3 (d, J_{CP} = 4.1 Hz), 74.0, 73.6, 73.3, 72.8, 71.7, 71.4, 70.4, 61.2, 55.1; ^{31}P NMR (121.4 MHz, D_2O, pH 11, ext ref H_3PO_4) δ 3.21.

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