Enantio- and Diastereodivergent Synthetic Route to Multifarious Cyclitols from D-Xylose via Ring-Closing Metathesis

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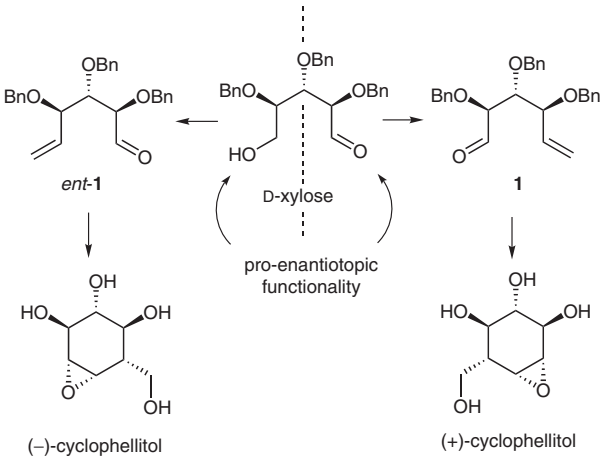
Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Abstract: Short stereoselective syntheses of various cyclitols, including the derivatives of conduritol B, conduritol F, *myo*-inositol, and *chiro*-inositol have been accomplished. The key steps in the syntheses are a ring-closing metathesis process and a diastereodivergent organometallic addition to a D-xylose-derived aldehyde.

Key words: conduritol, inositol, Grignard, stereochemistry model, chelation, Felkin–Anh, cyclophellitol, latent symmetry

The realization that inositols (hexahydroxycyclohexanes), conduritols (tetrahydroxycyclohexenes) and their numerous derivatives play important biological roles has made their study an important endeavor in health-related sciences.[1] Thus, *myo*-inositol phosphates have been intensively investigated for their role in intracellular signal transduction and calcium mobilization.[1d,2] Both *myo*- and *chiro*-inositols have been studied as components of inositolphosphoglycans (IPGs), believed to be important in insulin signaling.[3] It was discovered that various conduritols act as modulators of insulin release[4] and possess antifeedant, antibiotic, anticancer, and growth-regulating activities.[5] Conduritol epoxides, and more prominently fungal metabolite cyclophellitol, are potent glycosidase inhibitors and are under investigation as inhibitors of HIV infection and cancer metastasis.[6]

These and related research activities have generated considerable synthetic effort directed at developing practical preparations of the numerous biologically important cyclitols and their derivatives. Commercially available, inexpensive *myo*-inositol has been a common starting point in the syntheses of *myo*-inositol derivatives,[7] while significantly more expensive naturally occurring methylated *chiro*-inositols, pinitol, and quebrachitol, have been utilized to prepare cyclitols with D- and L-*chiro*-inositol stereochemical configurations, respectively.[8] However, labor-intensive selective hydroxyl protection/deprotection strategies and the necessity of optical resolution of racemic *myo*-inositol derivatives have led to utilization of chiral pool starting materials for cyclitol syntheses. Of these, carbohydrates represent a logical choice due to their availability in optically pure form and stereochemically complex oxygenation patterns that can be relayed to their target destinations in the desired cyclitols. Thus, D-glucose,[9] D-galactose,[10] D-mannitol,[11] and L-iditol,[12] among others, have served as starting points in efficient syntheses of cyclitol derivatives. One of our research groups has recently reported an enantiodivergent synthesis of (+)- and (–)-cyclophellitol from D-xylose.[13] Utilizing the latent plane of symmetry present in the starting carbohydrate, aldehydes **1** and *ent*-**1** were prepared as key intermediates for this enantiodivergent strategy (Scheme 1). In this paper, we show that this chemistry has a much broader scope and provide a full account of the investigation resulting in the development of synthetic pathways to diverse cyclitols starting from D-xylose and utilizing a ring-closing metathesis reaction for carbocycle formation.[14,15]



Scheme 1 Enantiodivergent strategy utilized in the synthesis of (+)- and (–)-cyclophellitol from D-xylose

Transformation of aldehyde **1** to biologically important conduritols and inositols can be achieved using a short synthetic sequence that starts with a Grignard addition of a vinylmetal reagent to generate an inseparable epimeric mixture of alcohols **2** and **3** (Scheme 2). The ratio of the two is highly dependent on the nature of the vinylmetal reagent, solvent and the presence of chelating salts. The highest selectivity for *syn*-alcohol **2** (**2**:**3** = 4.3:1) is attained using vinylmagnesium bromide in CH_2Cl_2 at –78 °C,[16] whereas a preponderance of *anti*-alcohol **3** is ob-

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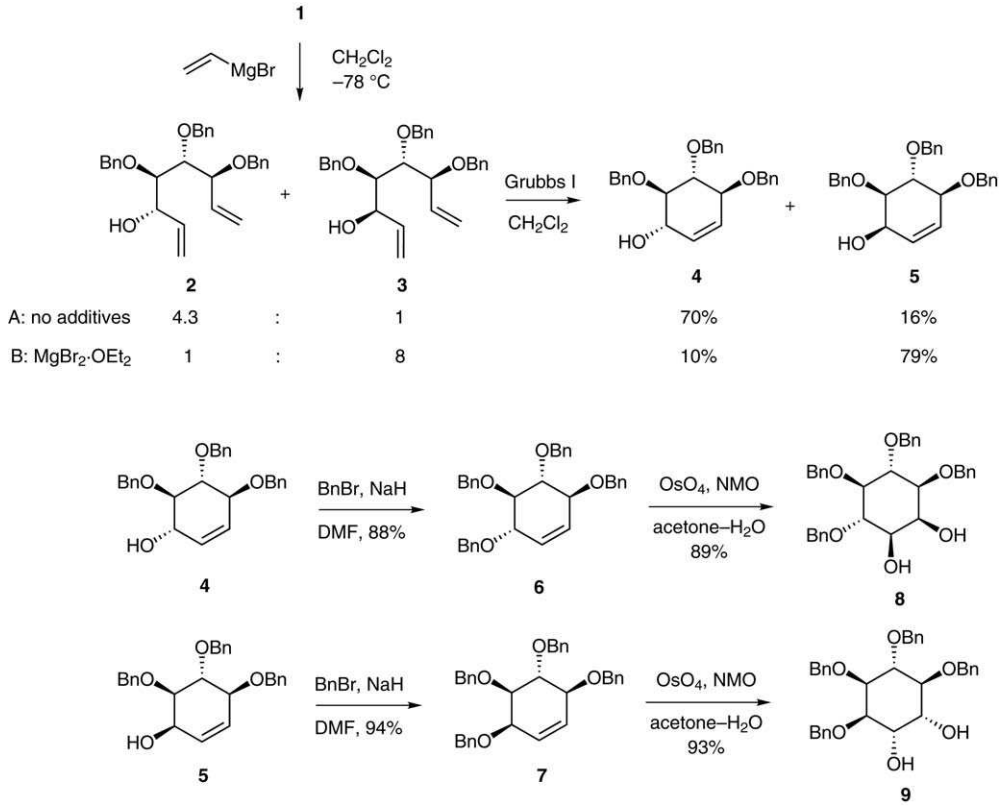


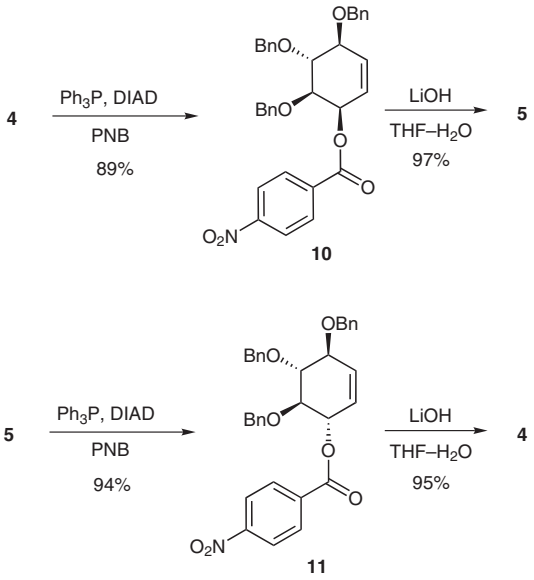
Scheme 2 Syntheses of benzylated derivatives of conduritol B, conduritol F, *myo*-inositol, and *chiro*-inositol

served in the presence of 3 equivalents of $MgBr_2$·OEt_2 under the otherwise similar conditions (**2**:**3** = 1:8).

The stereochemical assignment of the *syn* and *anti* addition products was confirmed by their conversion into the corresponding tetrabenzyl ethers, whose NMR analysis revealed the symmetry of the *syn*-alcohol-derived compound. Although **2** and **3** can in principle be separated, for example, by converting them into the corresponding TIPS ethers and then desilylating,[17] direct treatment of their mixture with the first-generation Grubbs' ruthenium catalyst gives chromatographically separable conduritols B (**4**) and F (**5**). The facility of the metathesis process is remarkable. TLC monitoring of the reaction progress reveals complete conversion seconds after the catalyst is added to the reaction mixture. The overall yields of the conduritol mixtures from aldehyde **1** are in the range of 85–90%, but the individual yields vary depending on the conditions used to perform the Grignard reaction and they are dependent on the ratio of intermediate alcohols **2** and **3**.

Conduritols **4** and **5** are further benzylated and dihydroxylated to give *myo*- and *chiro*-inostiol derivatives **8** and **9** in good yields. While the C_2-symmetry of **6** accounts for the formation of only one possible *cis*-dihydroxy compound **8**, the facial preference of the dihydroxylation reaction leading to the exclusive formation of **9** is noteworthy. Evidently, the two vicinal benzyloxy substituents flanking the olefin in **7** provide a strong steric bias resulting in the observed stereochemical outcome. The NMR spectra of **8** and **9** are consistent with those previously reported for these compounds by us[18] and others.[19]

We also found that conduritols **4** and **5** are excellent substrates for Mitsunobu inversion. Thus, the yield of a desired conduritol, regardless of whether it is **4** or **5**, can be further improved by treating the minor unwanted epimer with Ph_3P, *p*-nitrobenzoic acid (PNB), and diisopropyl azodicarboxylate (DIAD) in diethyl ether to afford 4-ni-



Scheme 3 Mitsunobu inversion interconverting conduritols **4** and **5**

trobenzoates **10** and **11**, which are smoothly hydrolyzed to **5** and **4** respectively (Scheme 3).

The diastereodivergence of this synthetic pathway arises from the stereocontrol in the Grignard reaction of aldehyde **1** with vinylmagnesium bromide. Before the conditions favoring the formation of **2** over **3** and vice versa were found, extensive experimentation had been performed and the observed general trends warrant a discussion. Factors controlling the stereochemistry of organometallic addition reactions with α-alkoxy, and even α,β-dialkoxy aldehydes have been investigated in some detail.[20] However, such processes are considerably more complicated in the case of carbohydrate-derived aldehydes, which may contain additional alkoxy groups capable of chelation.

Generally, researchers have interpreted the stereochemical outcomes of such reactions in terms of Felkin–Anh (Figure 1a, transition state **A**), α-chelation (Figure 1b, transition state **C**), and β-chelation (Figure 1c, transition state **E**) models.[20a] When applied to aldehyde **1**, these models will be represented by transition states **B**, **D** and **F**, which will lead to the formation of *anti*-, *syn*- and *anti*-alcohols **3**, **2**, and **3**, correspondingly.

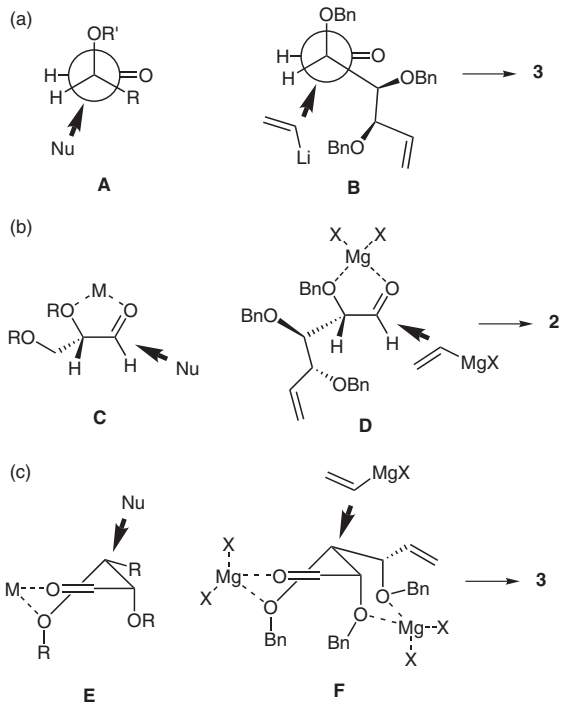


Figure 1 Possible transition states governing the stereocontrol in vinylmetal addition to aldehyde **1**

It appears that the reaction can be channeled through **B**, **D**, or **F** by adjusting the chelating power of the reaction medium.[21] Nonchelating reagents would be expected to react through the Felkin–Anh transition state **B**, leading to the selective formation of *anti*-alcohol **3**. Our results with vinyllithium (Table 1, entries 1–4) are consistent with this interpretation and can be explained by the low chelating ability of organolithium reagents in ethereal solvents. Macdonald, Reetz, and more recently Evans and co-workers, have reached similar conclusions in their investigations of Li- and Ti-based organometallic addition reactions to α,β-dialkoxy aldehydes.[20b,22] Literature reports indicate that the selectivity can be switched from *anti* to *syn* by replacing organolithium reagents with their organomagnesium counterparts.[20b,23] Due to the higher chelating ability of Mg^{2+} the operative transition state for these addition reactions should be **D** and the results of our experiments with aldehyde **1** (entries 5, 6) are consistent with this proposal. The replacement of Lewis basic ethereal solvents with CH_2Cl_2 should further strengthen the metal coordination in transition state **D** and this is also well-precedented in the literature.[22a,24] Indeed complete removal of THF from the commercial vinylmagnesium bromide reagent and its substitution by CH_2Cl_2 gives the highest *syn* selectivity we have been able to attain (entry 9).[16]

Finally, we propose that the *syn* to *anti* switch that occurs with increasing amounts of $MgBr_2{\cdot}OEt_2$ (entries 10–12), should be interpreted in terms of the β-chelation controlled transition state **E**. Here, the second metal coordination event with the participation of α- and γ-alkoxyl groups leads to the reactive conformer **F**, in which the perpendicular geometry of Cα–OBn bond and coordination of this α-alkoxyl to the metal would enhance the 'Anh effect'. This hypothesis is in agreement with the results reported by Martin and co-workers, who found that the selectivity of organometallic addition to a α,β,γ-trialkoxyaldehyde was crucially dependent on the protecting group on the γ-oxygen.[25] The reaction stereochemistry was completely reversed when the nonchelating γ-TBDPS ether was replaced by the benzyloxy moiety, arguing in favor of an α- to β-chelation switch similar to the one proposed in this work.

Although we found that the highest selectivities favoring both *syn*- and *anti*-alcohols **2** and **3** are obtained in CH_2Cl_2, the practicality of these procedures, especially performed on a large scale, are somewhat undermined by the side-reaction of the Grignard reagent with the solvent and, therefore, the necessity to use a large excess of the reagent (20 equiv). The procedures involving the use of vinyllithium in diethyl ether (**2**:**3** = 1:3.5) and vinylmagnesium bromide in CH_2Cl_2–THF (5:1) (**2**:**3** = 3:1) may be recommended for large-scale preparations.

In conclusion, a short synthetic route to a diverse group of cyclitol derivatives has been developed. The synthesis is enantiodivergent and allows for the preparation of various derivatives of conduritols B and F as well as *myo*- and *chiro*-inositols in both enantiomeric series. In addition, conduritol B derivative *ent*-**4** served as a penultimate intermediate in the synthesis of (+)-cyclophellitol by Trost and co-workers.[26] Therefore, our route provides another strategy for an enantiodivergent synthesis of this intensively researched anti-HIV and antimetastic agent and, more importantly, a library of its analogues in both enantiomeric series. Finally, we believe that our studies of the

Table 1 Stereoselectivities of Vinylmetal Addition to Aldehyde **1**

Entry	Vinylmetal reagent	Solvent	Additive	Chelation	*anti*:*syn* **3**:**2**
1	vinyllithium	THF	12-crown-4	low	1.5:1
2	vinyllithium	THF	none	low	2.2:1
3	vinyllithium	THF	Me_2S	low	2.6:1
4	vinyllithium	Et_2O	none	low	3.5:1
5	vinylmagnesium bromide	THF–Et_2O (1:1)	none	medium	1:2
6	vinylmagnesium bromide	THF	none	medium	1:2
7	vinylmagnesium bromide	CH_2Cl_2–THF (1:1)	none	medium	1:2
8	vinylmagnesium bromide	CH_2Cl_2–THF (5:1)	none	medium	1:3
9	vinylmagnesium bromide	CH_2Cl_2	none	medium	1:4.3
10	vinylmagnesium bromide	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$ (1 equiv)	high	1:1
11	vinylmagnesium bromide	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$ (2 equiv)	high	2:1
12	vinylmagnesium bromide	CH_2Cl_2	$MgBr_2{\cdot}OEt_2$ (3 equiv)	high	8:1

stereochemical outcome of the vinylmetal addition to a carbohydrate-derived aldehyde shed more light on these generally poorly understood processes.

Unless otherwise noted all commercially obtained reagents were used without purification. THF was distilled from sodium benzophenone ketyl prior to use. CH_2Cl_2 was distilled from $CaCl_2$. Reactions were carried out under N_2 in oven-dried glassware using standard syringe, cannula, and septa techniques. Reactions were monitored by TLC (Silica Gel 60 F_{254}, 250 μm) and visualized with UV light and ceric ammonium molybdate solution. Flash chromatography was performed on silica gel (32–63 μm). Optical rotations were measured with an Autopol III automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Jeol 300 MHz spectrometer.

(3*S*,4*R*,5*R*)-Tribenzyloxy-(6*S*)-hydroxycyclohexene (4)

To a 1 M solution of vinylmagnesium bromide in CH_2Cl_2 (23 mL) was added aldehyde **1** (0.5 g, 1.2 mmol) in CH_2Cl_2 (7 mL) dropwise during 30 min at –78 °C. The mixture was stirred at that temperature for 3 h, and MeOH (2 mL) was added to quench the excess of the Grignard reagent. The mixture was warmed up to r.t. and washed with H_2O (10 mL), aq 1 M NH_4Cl (10 mL), H_2O (10 mL), and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue consisted of a 4.3:1 (based on the integration of doublets at 2.64 and 3.25 ppm) mixture of **2** and **3**, which was chromatographed (hexanes–EtOAc, 6:1). To a solution of **2** and **3** (0.46 g, 4.3:1) in CH_2Cl_2 (40 mL) was added $(Cy_3P)_2RuCl_2(CHPh)$ (56 mg, 0.068 mmol) at r.t. The mixture was stirred for 15 min and opened to the atmosphere for 4 h. The solvent was evaporated and the residue chromatographed (hexanes–Et_2O, 1:1 → 1:2) to give 0.35 g (70%) of **4**, followed by 80 mg (16%) of **5**; $[\alpha]_D^{20}$ +123.3 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.25–7.36 (m, 15 H), 5.70 (m, 2 H), 5.03 (d, *J* = 11.3 Hz, 1 H), 4.92–4.25 (m, 5 H), 4.32–4.25 (m, 2 H), 3.79 (dd, *J* = 7.4, 10.2 Hz, 1 H), 3.53 (dd, *J* = 8.0, 10.1 Hz, 1 H), 2.22 (d, *J* = 3.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 138.7, 138.3, 129.5, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.1, 84.4, 83.4, 80.6, 75.4, 72.4, 72.0.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{28}O_4$ + Na (M + Na)$^+$: 439.1885; found: 439.1884.

(3*S*,4*R*,5*R*)-Tribenzyloxy-(6*R*)-hydroxycyclohexene (5)

To a solution of aldehyde **1** (0.5 g, 1.2 mmol) in CH_2Cl_2 (11 mL) was added $MgBr_2{\cdot}OEt_2$ (0.92 g, 3.6 mmol) in one portion and the mixture was stirred at r.t. for 30 min. To a cold (–78 °C) mixture was added vinylmagnesium bromide in CH_2Cl_2 (24 mL of 1 M solution, 24 mmol) over a period of 30 min. The mixture was stirred at –78 °C for 3 h after which time MeOH (10 mL) was added. The mixture was allowed to warm up to r.t. and treated with aq 1 M NH_4Cl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were washed with H_2O (40 mL), brine (40 mL), and dried ($MgSO_4$). The residue consisted of a 1:8.5 (based on the integration of doublets at 2.61 and 3.15 ppm) mixture of **2** and **3**, which was chromatographed (hexanes–EtOAc, 6:1). To a solution of **2** and **3** (0.44 g, 1:8.5) in CH_2Cl_2 (40 mL) was added $(Cy_3P)_2RuCl_2(CHPh)$ (56 mg, 0.068 mmol) at r.t. The mixture was stirred for 15 min and opened to the atmosphere for 4 h. The solvent was evaporated and the residue chromatographed (hexanes–Et_2O, 1:1 → 1:2) to give 0.39 g (79%) of **5**, preceded by 50 mg (10%) of **4**; $[\alpha]_D^{20}$ +39.3 (*c* 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.35–7.25 (m, 15 H), 5.88 (d, *J* = 1.9 Hz, 2 H), 4.94–4.66 (m, 6 H), 4.29 (m, 1 H), 4.10 (d, *J* = 7.4 Hz, 1 H), 4.50 (dd, *J* = 7.2, 9.7 Hz, 1 H), 3.56 (dd, *J* = 4.1, 9.7 Hz, 1 H), 2.71 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 138.8, 138.6, 138.2, 131.0, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 127.0, 79.7, 79.1, 79.0, 75.2, 73.2, 72.0, 65.7.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{28}O_4$ + Na (M + Na)$^+$: 439.1885; found: 439.1885.

(3*S*,4*R*,5*R*,6*S*)-Tetrabenzyloxycyclohexene (6)[19]

To a solution of **4** (7 mg, 0.017 mmol) in DMF (0.6 mL) was added NaH (4 mg of 60% dispersion in mineral oil, 0.1 mmol) at 0 °C. The mixture was stirred for 15 min after which time BnBr (5 μL, 0.04 mmol) was added and the resulting solution was stirred overnight. Et_2O (3 mL) was added and the excess of NaH was quenched with aq 1 M NH_4Cl (2 mL). The organic layer was washed with H_2O (2 × 2 mL), dried ($MgSO_4$), and evaporated. The residue was subjected to a preparative chromatography plate (hexanes–EtOAc, 9:1) to give 7.5 mg (88%) of **6**, whose ^{1}H NMR spectrum was identical to that reported previously.[19]

(3*S*,4*R*,5*R*,6*R*)-Tetrabenzyloxycyclohexene (7)[27]

To a solution of **5** (8 mg, 0.019 mmol) in DMF (0.6 mL) was added NaH (4 mg of 60% dispersion in mineral oil, 0.1 mmol) at 0 °C. The mixture was stirred for 15 min after which time BnBr (5 μL, 0.04 mmol) was added and the resulting solution was stirred overnight. Et_2O (3 mL) was added and the excess of NaH was quenched with aq 1 M NH_4Cl (2 mL). The organic layer was washed with H_2O (2 × 2mL), dried ($MgSO_4$), and evaporated. The residue was subjected to preparative TLC (hexanes–EtOAc, 9:1) to give 9 mg (94%) of **7**, whose ^1H NMR spectrum was identical to that reported previously.[27]

3,4,5,6-Tetra-*O*-benzyl-D-*myo*-inositol (8)[19]

To a solution of **6** (6 mg, 0.012 mmol) and NMO (2 mg, 0.017 mmol) in acetone–H_2O (9:1, 0.6 mL) was added a catalytic amount of OsO_4. The mixture was stirred for 3 d at r.t. and treated with Et_2O (3 mL). The organic layer was washed with aq 10% $Na_2S_2O_3$ (2 mL), H_2O (2 mL), dried ($MgSO_4$), and evaporated. The residue consisted of **8**, which was >98% pure by TLC and ^1H NMR spectroscopy (5.8 mg, 89%). ^1H NMR spectrum of **8** was identical to that reported previously.[19]

1,2,3,4-Tetra-*O*-benzyl-L-*chiro*-inositol (9)[18]

To a solution of **7** (6 mg, 0.012 mmol) and NMO (2 mg, 0.017 mmol) in acetone–H_2O (9:1, 0.6 mL) was added a catalytic amount of OsO_4. The mixture was stirred for 2 h at r.t. and treated with Et_2O (3 mL). The organic layer was washed with aq 10% $Na_2S_2O_3$ (2 mL), H_2O (2 mL), dried ($MgSO_4$), and evaporated. The residue consisted of **9**, which was >98% pure by TLC and ^1H NMR (5.9 mg, 93%). ^1H NMR spectrum of **9** was identical to that reported previously.[18]

Mitsunobu Inversion of Conduritols 4 and 5

To a stirred solution of **4** or **5** (30 mg, 0.072 mmol) in Et_2O (1.25 mL) was added PPh_3 (19 mg, 0.072 mmol) and 4-nitrobenzoic acid (12 mg, 0.072 mmol) at r.t. After the material had dissolved, DIAD (17.7 μL, 0.074 mmol) was added to the mixture. After stirring for 17 h at r.t., the mixture was concentrated under reduced pressure and the residue was chromatographed (hexanes–EtOAc, 9:1) to yield pure **10** (37 mg, 89%) or **11** (39 mg, 94%).

(1*R*,4*S*,5*R*,6*R*)-4,5,6-Tris(benzyloxy)cyclohex-2-enyl 4-Nitrobenzoate (10)

$[\alpha]_D^{20}$ –114.3 (*c* 0.1, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 8.28 (d, *J* = 8.5 Hz, 2 H), 8.18 (d, *J* = 8.5, 2 H), 7.36–7.23 (m, 15 H), 6.04–5.87 (m, 3 H), 4.99–4.67 (m, 6 H), 4.16–4.04 (m, 2 H), 3.73 (dd, *J* = 3.0, 9.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 164.3, 150.6, 138.6, 138.2, 138.0, 135.7, 134.2, 131.0, 128.8, 128.6, 128.4, 128.2, 128.0, 127.8, 123.6, 123.1, 79.8, 78.4, 77.9, 77.3, 75.3, 72.8, 68.3.

HRMS (ESI): *m*/*z* calcd for $C_{34}H_{31}NO_7$ + Na (M + Na)$^+$: 588.1998; found: 588.1982.

(1*S*,4*S*,5*R*,6*R*)-4,5,6-Tris(benzyloxy)cyclohex-2-enyl 4-Nitrobenzoate (11)

$[\alpha]_D^{20}$ +156.8 (*c* 0.05, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 8.24 (d, *J* = 8.8 Hz, 2 H), 8.02 (d, *J* = 8.8 Hz, 2 H), 7.36–7.10 (m, 15 H), 5.83 (m, 2 H), 5.64 (d, *J* = 10.5 Hz, 1 H), 4.98–4.67 (m, 6 H), 4.30 (dd, *J* = 2.8, 4.7 Hz, 1 H), 3.93–3.85 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 164.1, 150.6, 138.5, 138.1, 135.3, 130.9, 130.0, 128.6, 128.5, 128.4, 128.1, 128.1, 127.9, 127.7, 125.4, 123.5, 83.8, 81.1, 79.8, 77.5, 75.8, 75.7, 72.7.

HRMS (ESI): *m*/*z* calcd for $C_{34}H_{31}NO_7$ + Na (M + Na)$^+$: 588.1998; found: 588.1995.

Hydrolysis of Esters 10 and 11

To a stirred solution of **10** or **11** (20 mg, 0.035 mmol) in THF (0.5 mL) was added aq 1 M LiOH (0.5 mL). The reaction mixture was stirred for 3 h at rt. The solvent was evaporated and the residue chromatographed (hexanes–EtOAc, 9:1) to yield pure **5** (14.1 mg, 97%) or **4** (13.8 mg, 95%).

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