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Orthogonally Protected Cyclohexanehexols by a "One Reaction – One Product" Approach: Efficient Access to Cyclitols and Their Analogs

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Differentially protected *myo*-inositol derivatives were prepared from commercially available *myo*-inositol through regioselective *O*-alkylation reactions, which give a single product in each step. These derivatives were converted into six isomeric inositol derivatives carrying orthogonal hydroxy protecting groups. For all these reactions, conditions were chosen to prevent the formation of isomeric products, which obviates the need for separation of isomers and provides the required cyclitol derivative in very good yields. The synthetic potential of these derivatives was illustrated by the conversion of some of the orthogonally protected inositol derivatives into other cyclitol derivatives. Isomeric inositols were also prepared by the global deprotection of all the hydroxy groups.

Introduction

Cyclohexane polyols (cyclitols, inositols, pseudosugars, and carbasugars) and their derivatives constitute a group of organic compounds that are crucial for the well-being of living cells or are capable of intervention in the biological process of diseased cells or pathogens.[1] Involvement of phosphoinositols in cellular signal transduction pathways is an example of the former,[2] whereas the presence of aminocyclitol moieties in antibiotics is an example of the latter.[3] Apart from these, cyclitols and their derivatives are also interesting due to their potential as starting materials for the synthesis of natural products,[4] their ability to complex metal ions,[5] and because of their unusual structure and properties in the crystalline state.[6] Methodologies for the synthesis of cyclitols and their derivatives from different kinds of starting materials, such as naturally occurring inositols (*myo*- and *chiro*-inositols and their derivatives),[7] sugars (glucose, galactose, xylose etc.),[8] benzene and its derivatives (toluene, naphthalene, benzoquinone),[9] and norbornyl derivatives[10] have been reported. By and large, formation of isomeric cyclitol derivatives is a common shortcoming of the known synthetic methodologies and separation of the desired isomer is often required. These limitations result in reduction in the overall yield of the desired product and wastage of chemicals, reagents and (often) laboriously prepared synthetic intermediates. Naturally occurring *myo*-inositol is a convenient starting material for the synthesis of cyclitol derivatives because methods for the preparation of its protected derivatives have been well investigated.[11] However, the scope of most of these methods are narrow as they were developed for the preparation of one or just a few inositol derivatives (predominantly phosphoinositols) and hence are not flexible enough to provide a large number of isomeric cyclitol derivatives. Due to subtle differences in reactivity between the secondary hydroxy groups in *myo*-inositol (or its derivatives), most of the reactions used for the protection of its hydroxy groups result in the formation of isomeric products, and there are few exceptions to this rule.[12] Although investigations on the chemistry of *myo*-inositol (and its derivatives) helped to qualitatively understand the relative reactivity of their hydroxy groups,[11] the actual reaction conditions required to react any one of their hydroxy groups exclusively were seldom realized in the laboratory. Enzyme-mediated regio- and enantiospecific reactions of *myo*-inositol (or its derivatives)[13] are known, but they are not yet viable for organic synthesis, because most of these involve acylation or phosphorylation reactions, both of which are prone to migration among the hydroxy groups. The availability of methods for exclusive reaction at any one hydroxy group (Scheme 1) in *myo*-inositol and its derivatives would be of immense utility to access cyclitol derivatives and many other kinds of compounds that can be obtained from cyclitols.

The shortcomings mentioned above can be addressed if orthogonally protected isomeric inositol derivatives, such as **5**–**7** (Scheme 1), can be synthesized in a few steps, avoiding the formation of isomers during the reaction of the six hydroxy groups of *myo*-inositol. We herein reveal methods for the preparation of orthogonally protected isomeric inositol derivatives that can be used to prepare a variety of cyclitol derivatives. This methodology is based on the fact that *O*-alkylation of partially protected *myo*-inositol derivatives in the presence of lithium-derived bases gives better regioselectivity compared to bases derived from sodium

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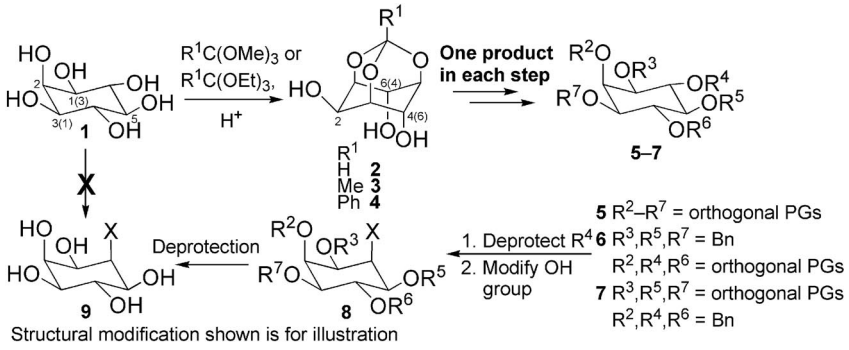
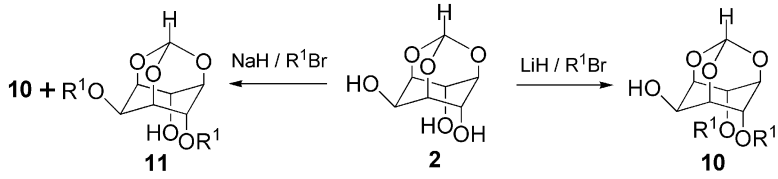


Scheme 1. Synthetic sequence for the preparation of a structurally modified cyclitol or its orthogonally protected derivative.



Scheme 2. Contrast in the *O*-alkylation by using sodium and lithium bases.

(Scheme 2).[14] In most of the reactions reported here, we obtained a single product, which obviates the need for the separation of regio/stereoisomers.

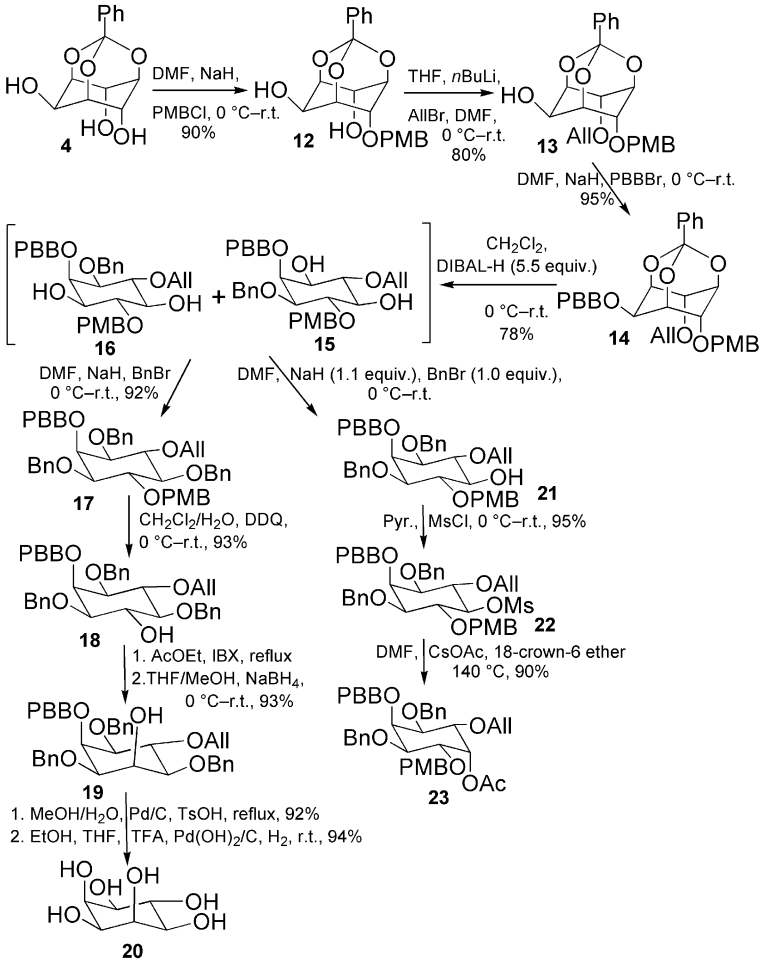
Results and Discussion

We chose to use orthoesters of *myo*-inositol as the starting point, because they can be obtained as single products (in contrast to acetals) in high yield, and these reactions can be performed on 5–100 g scales.[12a,12b,15] Due to strong intramolecular hydrogen bonding between the 4- and 6-hydroxy groups of *myo*-inositol orthoesters, and due to their ability to form chelates with metal ions, reaction of the three hydroxy groups of these orthoesters with alkyl halides can be controlled to obtain mono-, di- or triethers exclusively.[12b,16] Accordingly, the reaction of *myo*-inositol orthobenzoate with 4-methoxybenzyl chloride (assisted by sodium hydride), allyl bromide (assisted by butyllithium) and 4-bromobenzyl bromide (assisted by sodium hydride), in that sequence, provided the orthogonally protected *myo*-inositol orthobenzoate **14** (Scheme 3). Reduction of the orthobenzoate moiety with an excess of diisobutylaluminum hydride (DIBAL-H) gave a mixture of isomeric diols **15** and **16**. Selective benzylation at the 1(3)-hydroxy group provided the corresponding dibenzyl ether **21**, whereas benzylation by using an excess of benzyl bromide gave the tribenzyl ether **17** carrying orthogonal protecting groups at the 2-, 4- and 6-positions of *myo*-inositol. The hydroxy groups at these positions could then be released and modified as desired. The 5-hydroxy group in the dibenzyl ether **21** could be inverted through the mesylate **22** to obtain *neo*-inositol carrying orthogonal protecting groups (**23**). Cleavage of the *p*-methoxybenzyl (PMB) ether in the tribenzyl ether **17**, followed by inversion of the 4-hydroxy group, provided the orthogonally protected *epi*-inositol derivative **19**. Global deprotection of this derivative gave *epi*-inositol (**20**) in an overall yield of 33% from *myo*-inositol. For comparison, the reported yields of *epi*-inositol by using previously developed methods was in the range 6–15% from *myo*-inositol[7a,7b,7d] and 1–21% from other starting materials.[8a,8b,9a,9b,9g,10a,17]

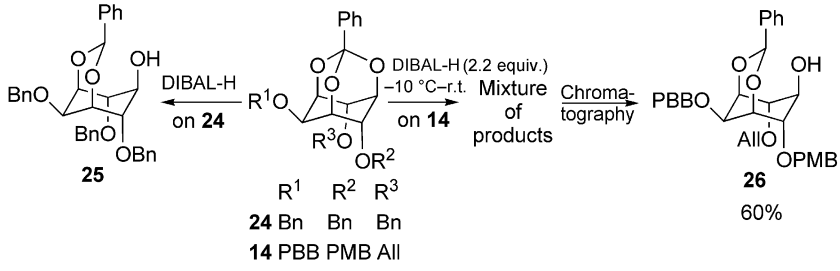
Initially, we attempted to release the 5-hydroxy group in the orthobenzoate **14** by its reduction with DIBAL-H. However, this reaction resulted in the formation of a mixture of products from which the benzylidene acetal **26** (Scheme 4) could be isolated in 60% yield. Reduction of the orthobenzoate moiety in the tribenzyl ether **24** with 1 equiv. of DIBAL-H is known to result in the release of the 5-hydroxy group exclusively.[18] Attempts at inversion of the 5-hydroxy group of benzylidene acetal **26** (by S_N2 substitution on its triflate with cesium acetate, to obtain *neo*-inositol derivatives), resulted in a mixture of products consisting of *myo* and *neo* isomers.

The orthogonally protected *scyllo*-inositol orthobenzoate derivative could be obtained by the sequential oxidation and reduction of the 2-hydroxy group in **13** (Scheme 5), followed by *O*-alkylation with 4-bromobenzyl bromide. Reduction of the orthobenzoate moiety of *scyllo*-inositol orthobenzoate, followed by benzylation, provided *scyllo*-inositol derivative **28** carrying three orthogonal protecting groups.

The synthesis of a *chiro*-inositol derivative carrying orthogonal protecting groups started from the tribenzyl ether **29**, which was prepared from *myo*-inositol orthoformate as reported earlier.[18a] Allylation of **29**, followed by hydrolysis of the acetal, gave the symmetric diol **30**. Alkylation of one



Scheme 3.

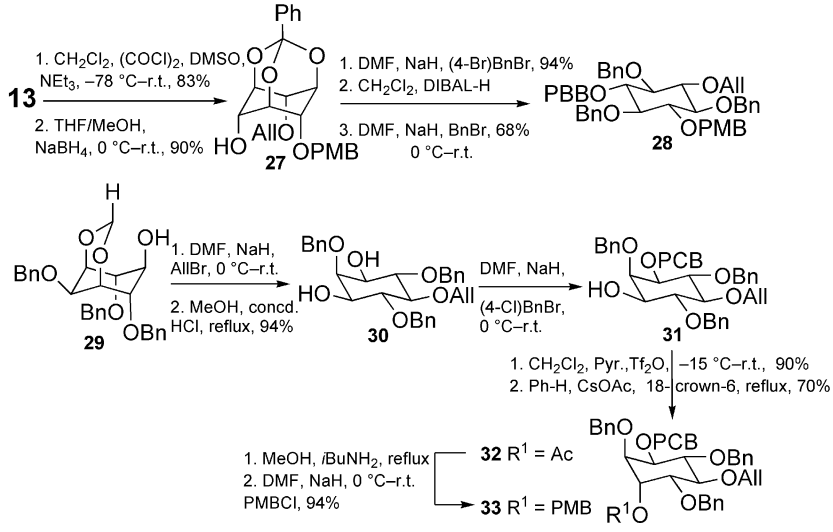


Scheme 4.

of the hydroxy groups in **30** with (4-chloro)benzyl bromide, followed by inversion of the second hydroxy group via its triflate, gave the *chiro*-inositol derivative **32** (Scheme 5). A perusal of the earlier reports reveals that much time and effort has been invested in attempts to prepare protected *chiro*-inositol derivatives such as **33** (starting from *chiro*-inositol), with little success.[7c,7e]

This synthetic approach provides isomeric inositol derivatives that are amenable to manipulation to obtain a variety of cyclitol derivatives. Inositol isomers (Figure 1) other than the *myo* isomer are not readily available (or relatively expensive if commercially available) in quantities large enough to be used as starting materials for the preparation of differentially protected derivatives. Furthermore, such an approach[19] would require standardizing the reaction conditions for selective reactions of the six hydroxy groups in each of these isomeric cyclohexanehexols and their partially protected derivatives. An illustration of the utility of the isomeric inositol derivatives carrying orthogonal protecting groups to prepare other cyclitol derivatives is provided below.

The *epi*-inositol derivative **19** (Scheme 6) could be transformed into the *cis*-inositol derivative **42** by protection of the axial hydroxy group followed by cleavage of the allyl



Scheme 5.

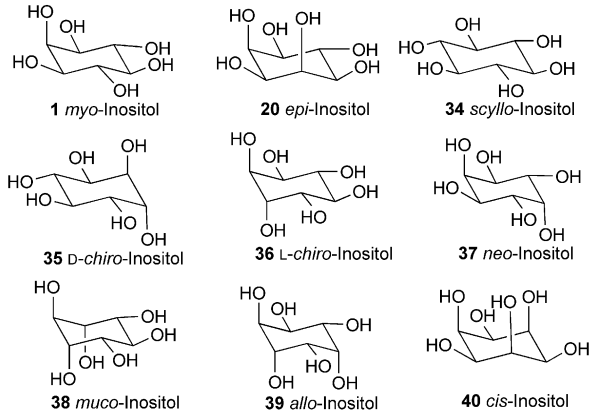
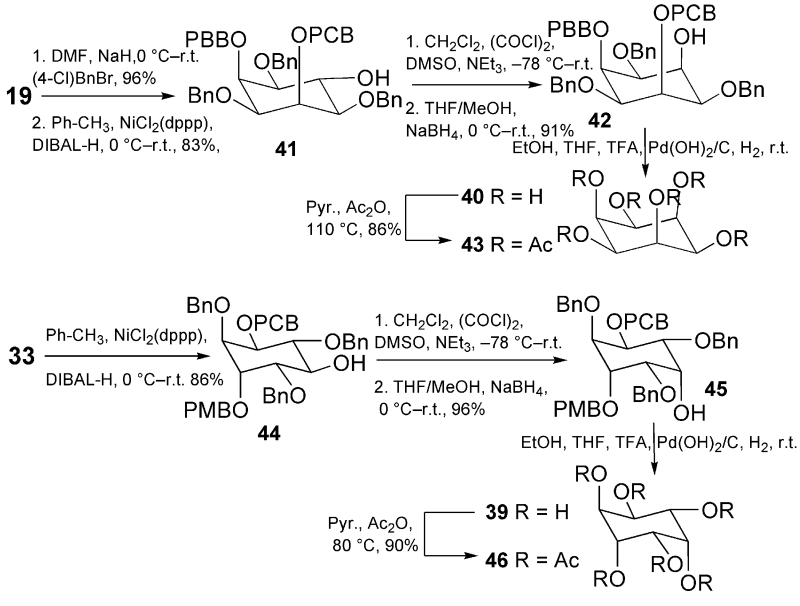
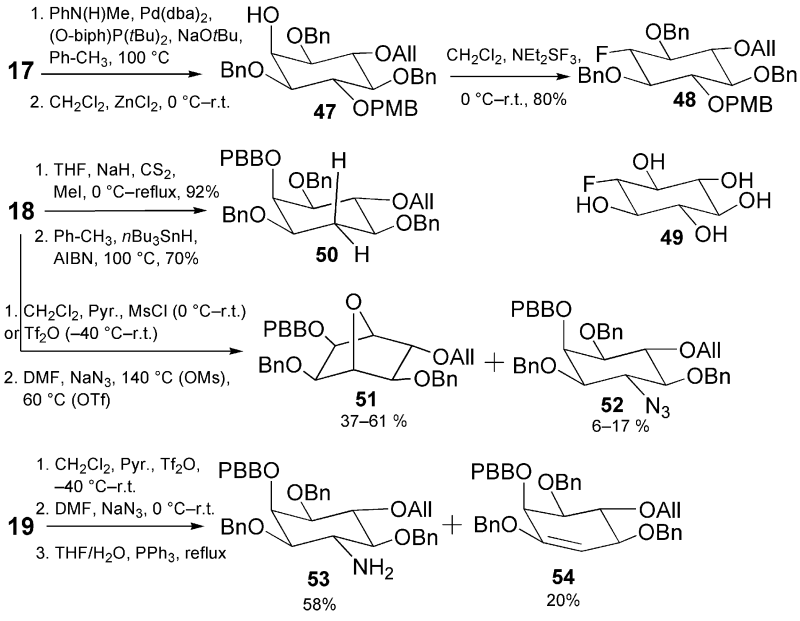


Figure 1. Structures of all nine possible inositol isomers.

ether and inversion of the resulting hydroxy group. Global deprotection of all the hydroxy groups provided *cis*-inositol (**40**, isolated as its hexaacetate **43**) in an overall yield of 25% from *myo*-inositol; for comparison, the yields in most of the methods reported previously[7b,9b,19c,20] were lower or required separation of isomeric inositols. Similarly, the *allo*-inositol derivative **45** could be obtained from the racemic *chiro*-inositol derivative **33**. *allo*-Inositol (isolated as its hexaacetate **46**) was prepared by global deprotection of the hydroxy groups in an overall yield of 28% from *myo*-inositol. Free *cis*- and *allo*-inositols can be generated by the aminolysis of the hexaacetates **43** and **46**, respectively.[15b] For comparison, yields of *allo*-inositol prepared in methods reported earlier was 15% from *myo*-inositol[7g] and 2–16% from other starting materials.[7b,8a,9c,9d,9e,21]



Scheme 6. Preparation of inositol diastereoisomers from orthogonally protected inositols.



Scheme 7. Preparation of inositol derivatives from orthogonally protected inositols.

The reactions shown in Scheme 7 leading to the synthesis of ring-modified cyclitol derivatives, a deoxyinositol, a deoxyfluoroinositol, an azidoinositol, and an aminocyclitol, illustrate the synthetic potential and flexibility of orthogonally protected inositol derivatives. Compound **49**, which can be prepared by global deprotection of **48**, has shown promise as a potential therapeutic agent for Alzheimer's disease.[22] When the use of one of the intermediates (e.g., **18**) for the preparation of a particular inositol derivative (**52**) results in lower yield (the bicyclic derivative **51** arises from the debenzylative cycloetherification reaction),[23] the same product can be obtained in higher yield by using an alternative intermediate (**19**). Perhaps, in this case, the nucleophilic substitution in the mesylate of **18** proceeds through an S_N1 mechanism, which facilitates the formation of the bicyclic derivative **51**. This view is supported by the observed retention of configuration at C-4 upon formation of the azide **52**. Here, inversion at C-4 is prevented by participation of the 1-benzyloxy group (formation of **51**).

These newly synthesized cyclitol derivatives carry protecting groups that can be cleaved in the presence of each other to release the desired hydroxy group, which can be further modified to give second-generation (with two modifications) cyclitol derivatives. Hence, this methodology can be used to prepare a large number of cyclitols and their derivatives starting from commercially available *myo*-inositol. In addition, phosphorylation and glycosylation reactions can be carried out on orthogonally protected cyclitol derivatives (since all the protecting groups can be cleaved by hydrogenolysis) to obtain the corresponding cyclitol phosphate or glycoside conjugates.

Conclusions

An understanding of the relative reactivities of the *myo*-inositol hydroxy groups[11,14,16,18b] and differences in their ability to chelate with metal ions[5] helped us to develop reaction conditions for the selective derivatization of these hydroxy groups. Judicious choice of alkyl halides[24] for the preparation of *myo*-inositol ethers provided *myo*-inositol derivatives carrying orthogonal protecting groups. Since any of these ethers could be cleaved in the presence of other ethers present in the same derivative, the desired *myo*-inositol hydroxy group can be released and inverted to obtain six (of the eight possible isomers) isomeric inositol derivatives carrying orthogonal protecting groups. Also, since most of the ethers used are (substituted) benzyl ethers, they can all be cleaved simultaneously by hydrogenation to release all the hydroxy groups in one step, if necessary. These compounds can now be used for the preparation of a variety of cyclitol derivatives. Although, methods for the preparation of isomeric inositols have been reported in the literature, none of these approaches provide access to differentially protected isomeric inositol derivatives. Chiral cyclitol derivatives can be obtained by resolution of the intermediates; we are currently working on the desymmetrization of some of the intermediates reported here to obtain differentially protected chiral inositol derivatives.

Experimental Section

General Methods: Sodium hydride was a 60% suspension in mineral oil. Thin layer chromatography was performed with E. Merck pre-coated 60 F_{254} plates, and the spots were rendered visible either by UV light or by charring the plates with chromic acid solution. Column chromatographic separations (silica gel, 100–200 mesh) and flash column chromatographic separations (silica gel, 230–400 mesh) were carried out with light petroleum/ethyl acetate mixtures as eluent (v/v%). For column chromatographic separation of compounds containing the PMB group or benzylidene acetal or triflate, the silica gel used was pre-eluted with a triethylamine/light petroleum (1:49, 3–5 mL/g) mixture. "Usual workup" implies wash-

ing of the organic layer with water followed by brine, drying with anhydrous sodium sulfate and removal of the solvent under reduced pressure using a rotary evaporator. IR spectra were recorded (in $CHCl_3$ solution, as a Nujol mull or as a neat film) with a Shimadzu FTIR-8400 or Perkin–Elmer spectrophotometer. NMR spectra were recorded with a Bruker ACF 200 spectrometer (200 MHz for ^1H and 50.3 MHz for ^{13}C) unless otherwise mentioned. Chemical shifts (δ, ppm) reported are referred to internal tetramethylsilane. Microanalytical data were obtained with a FLASH 1112 Series EA or Elementar Vario EL elemental analyzer. All the melting points were recorded with a Büchi B-540 electrothermal melting-point apparatus. Compounds previously reported in the literature were characterized by comparison of their melting points and/or ^1H NMR spectra with the reported data.

Preparation of Racemic 4-*O*-(4-Methoxybenzyl)-*myo*-inositol 1,3,5-Orthobenzoate (12): To an ice-cooled solution of *myo*-inositol 1,3,5-orthobenzoate (**4**)[15c,25] (10 g, 37.59 mmol) in DMF (80 mL), sodium hydride (1.50 g, 37.59 mmol) was added followed by a solution of 4-methoxybenzyl chloride (5.09 g, 37.59 mmol) in DMF (20 mL). The reaction mixture was stirred at room temp. for 4 h. The reaction mixture was then decomposed by the addition of ice, solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane as solvent. The crude product obtained was purified by flash column chromatography (ethyl acetate/light petroleum, 2:3) on silica gel to obtain **12** (13.0 g, 90%) as a colorless solid. R_f = 0.38 (ethyl acetate/light petroleum, 2:3); m.p. 126–128 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.70–7.55 (m, 2 H, Ar-H), 7.45–7.32 (m, 3 H, Ar-H), 7.31–7.20 (m, 2 H, Ar-H), 7.00–6.80 (m, 2 H, Ar-H), 4.64 [q, J = 11.5 Hz, 2 H, CH_2Ph(OCH$_3$)], 4.61–4.48 (m, 2 H), 4.44–4.32 (m, 3 H), 4.14 (m, 1 H), 3.82 (s, 3 H, OCH_3), 3.80 (d, J = 10 Hz, 1 H, D_2O exchangeable, OH), 3.15 (d, J = 12 Hz, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 159.8 (C_{ipso}), 136.5 (C_{ipso}), 129.7 (C_{arom}), 129.5 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{ipso}), 125.1 (C_{arom}), 114.1 (C_{arom}), 107.2 ($PhCO_3$), 75.9 (Ins C), 73.4 (Ins C), 72.5 (CH_2), 68.0 (Ins C), 67.6 (Ins C), 59.7 (Ins C), 55.1 (OCH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600–3550, 3550–3400 (OH) cm^{-1}. $C_{21}H_{22}O_7$ (386.4): calcd. C 65.28, H 5.74; found C 64.92, H 5.62.

Preparation of Racemic 6-*O*-Allyl-4-*O*-(4-methoxybenzyl)-*myo*-inositol 1,3,5-Orthobenzoate (13): To a cooled (0 to –5 °C) solution of **12** (4.03 g, 10.44 mmol) in dry THF (40 mL), was added *n*BuLi (7.83 mL, 12.53 mmol, 1.6 M in cyclohexane) followed by a solution of allyl bromide (0.95 mL, 10.96 mmol) in dry DMF (20 mL). The reaction mixture was stirred at room temp. for 30 h and then decomposed by the addition of ice. The solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane. The crude product obtained was purified by flash column chromatography (ethyl acetate/light petroleum, 5:17) on silica gel to obtain **13** (3.55 g, 80%) as a gum. R_f = 0.35 (ethyl acetate/light petroleum, 5:17). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.70–7.55 (m, 2 H, Ar-H), 7.44–7.23 (m, 5 H, Ar-H), 6.94–6.82 (m, 2 H, Ar-H), 6.02–5.80 (m, 1 H, CH=CH_2), 5.38–5.14 (m, 2 H, CH=CH_2), 4.70–4.31 (m, 7 H), 4.25–4.05 (m, 3 H), 3.81 (s, 3 H, Ar-OCH_3), 3.10 (d, J = 12 Hz, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 159.2 (C_{ipso}), 136.9 (C_{ipso}), 134.0, 129.6 (C_{ipso}), 129.4, 129.1, 127.9, 125.1, 117.5 (C=CH$_2$), 113.7, 107.8 ($PhCO_3$), 74.2 (Ins C), 74.2 (Ins C), 73.4 (Ins C), 73.0 (Ins C), 71.1 (CH_2), 70.7 (CH_2), 68.5 (Ins C), 60.4 (Ins C), 55.1 (OCH_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3584–3320 (OH) cm^{-1}. $C_{24}H_{26}O_7$ (426.46): calcd. C 67.59, H 6.15; found C 67.40, H 5.80.

Preparation of Racemic 6-*O*-Allyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-*myo*-inositol 1,3,5-Orthobenzoate (14): To an ice-cooled solution of **13** (7.90 g, 18.54 mmol) in dry DMF (50 mL) was added sodium hydride (1.48 g, 37.09 mmol) followed by a solution of 4-bromobenzyl bromide (5.10 g, 20.40 mmol) in DMF (20 mL), and the reaction mixture was stirred at room temp. for 12 h. Excess of sodium hydride was destroyed by adding ice to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane. The crude product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:4) on silica gel to obtain **14** (10.5 g, 95%) as a gum. R_f = 0.38 (ethyl acetate/light petroleum, 5:17). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.70–7.59 (m, 2 H, Ar-H), 7.50–7.43 (m, 2 H, Ar-H), 7.37–7.18 (m, 7 H, Ar-H), 6.91–6.84 (m, 2 H, Ar-H), 5.95–5.76 (m, 1 H, CH=CH_2), 5.31–5.16 (m, 2 H, CH=CH_2), 4.64 (s, 2 H), 4.59–4.35 (m, 7 H), 4.17–3.97 (m, 3 H), 3.82 (s, 3 H, Ar-OCH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 159.2 (C_{ipso}), 137.1 (C_{ipso}), 134.0 (C_{arom}), 131.3 (C_{arom}), 129.6 (C_{ipso}), 129.3 (C_{arom}), 129.2 (C_{arom}), 129.0 (C_{arom}), 127.8 (C_{arom}), 125.2 (C_{arom}), 121.4 (C_{ipso}), 117.4 (C=CH$_2$), 113.7 (CH=C), 107.7 ($PhCO_3$), 73.6 (Ins CH), 73.4 (Ins CH), 71.8 (Ins CH), 71.7 (Ins CH), 71.1 (CH_2), 70.5 (CH_2), 70.2 (CH_2), 68.8 (Ins CH), 66.5 (Ins CH), 55.1 (OCH_3) ppm. $C_{31}H_{31}BrO_7$ (594.13): calcd. C 62.53, H 5.25; found C 62.29, H 4.86.

Preparation of Racemic 6-*O*-Allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-*myo*-inositol (17): To an ice-cooled solution of the orthobenzoate **14** (4.5 g, 7.56 mmol) in dichloromethane (50 mL), DIBAL-H (42 mL, 42 mmol, 1 M in toluene) was added, and the reaction mixture was stirred at room temp. for 4 h. The reaction mixture was diluted with dichloromethane (150 mL) and rapidly poured into a mixture of saturated solutions of ammonium chloride (90 mL) and sodium potassium tartarate (120 mL) with stirring and cooling. The stirring was continued at room temp. until two layers separated. The aqueous layer was washed with dichloromethane (2 × 60 mL), and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to afford the crude product, which was purified by flash column chromatography (ethyl acetate/light petroleum, 7:15) on silica gel to obtain a mixture of diastereoisomeric diols **15** and **16** (3.3 g, 73%) as a gum. To an ice-cooled solution of **15** and **16** (3.3 g, 5.51 mmol) in dry DMF (30 mL), sodium hydride (1.10 g, 27.55 mmol) was added, followed by benzyl bromide (3.27 mL, 27.55 mmol), and the reaction mixture was stirred at room temp. for 12 h. Excess of sodium hydride was destroyed by adding ice to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane. The crude product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:9) on silica gel to obtain **17** (4.15 g, 97%) as a colorless solid. R_f = 0.36 (ethyl acetate/light petroleum, 1:9); m.p. 66–68 °C. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.17 (m, 21 H, Ar-H), 6.84–6.77 (m, 2 H, Ar-H), 6.07–5.88 (m, 1 H, CH=CH_2), 5.33–5.09 (m, 2 H, CH=CH_2), 4.86 (s, 2 H), 4.79–4.53 (m, 8 H), 4.44–4.26 (m, 2 H), 4.06–3.83 (m, 3 H), 3.78 (s, 3 H, Ar-OCH_3), 3.47–3.23 (m, 3 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 158.9 (C_{ipso}), 138.7 (C_{ipso}), 138.2 (C_{ipso}), 138.1 (C_{ipso}), 137.8 (C_{ipso}), 135.3, 131.0, 130.8 (C_{ipso}), 129.5, 129.2, 128.2, 128.1, 127.7, 127.5, 127.3, 120.9 (C_{ipso}), 116.3 (C=CH$_2$), 113.5, 83.5 (Ins C), 81.2 (Ins C), 81.1 (Ins C), 80.6 (Ins C), 80.5 (Ins C), 75.7 (CH_2), 75.3 (CH_2), 74.8 (Ins CH), 74.3 (CH_2), 73.2 (CH_2), 72.75 (CH_2), 72.69 (CH_2), 55.0 (CH_3) ppm. $C_{45}H_{47}BrO_7$ (779.75): calcd. C 69.31, H 6.08; found C 69.18, H 6.10.

Preparation of Racemic 6-*O*-Allyl-1,3-di-*O*-benzyl-2-*O*-(4-bromobenzyl)-4-*O*-(4-methoxybenzyl)-*myo*-inositol (21): To an ice-cooled solution of a mixture of diasteroisomeric diols **15** and **16** (1.16 g,

1.94 mmol) in DMF (12 mL), was added sodium hydride (0.086 g, 2.13 mmol) followed by benzyl bromide (0.23 mL, 1.94 mmol), and the mixture was stirred at ambient temperature for 20 min. The reaction was quenched by the addition of ice, solvents were removed under reduced pressure, and the residue was taken into dichloromethane and worked up as usual. The products were separated by flash column chromatography (ethyl acetate/light petroleum, 1:3) on silica gel to obtain *myo*-alcohol **21** (0.75 g, 57%) as a gum, which turned into a colorless solid on storing at ambient temperature. The triether **17** (0.15 g, 20%) and the starting diols **15** and **16** (0.11 g, 10%) were also obtained. R_f = 0.32 (ethyl acetate/light petroleum, 1:3); m.p. 66–69 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.46–7.28 (m, 13 H, Ar-H), 7.25–7.19 (m, 3 H, Ar-H), 6.88–6.78 (m, 2 H, Ar-H), 6.07–5.88 (m, 1 H, C*H*=CH_2), 5.33–5.12 (m, 2 H, CH=CH_2), 4.90–4.50 (m, 8 H), 4.45–4.23 (m, 2 H), 3.96 (t, *J* = 2.4 Hz, 1 H), 3.87 (t, *J* = 9.5 Hz, 1 H), 3.79 (s, 3 H, Ar-OCH_3), 3.80–3.70 (m, 1 H), 3.44 (t, *J* = 9.2 Hz, 1 H), 3.36–3.26 (m, 2 H), 2.52 (br. s, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 159.1 (C_{ipso}), 138.2 (C_{ipso}), 138.1 (C_{ipso}), 137.9 (C_{ipso}), 135.2, 131.1, 130.9 (C_{ipso}), 129.6, 129.3, 128.3, 127.6, 127.4, 127.38, 121.0 (C_{ipso}), 116.7 (C=*C*H_2), 113.7, 80.63 (Ins C), 80.6 (Ins C), 80.5 (Ins C), 80.4 (Ins C), 75.0 (Ins C), 74.9 (CH_2), 74.8 (Ins C), 74.1 (CH_2), 73.3 (CH_2), 72.7 (CH_2), 72.6 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 3603–3344 cm^{-1}. $C_{38}H_{41}BrO_7$ (689.63): calcd. C 66.18, H 5.99; found C 66.16, H 6.35.

Preparation of 5-*O*-Allyl-2,4,6-tri-*O*-benzyl-*myo*-inositol (30): To an ice-cooled solution of **29**[18a] (8.50 g, 18.39 mmol) in DMF (50 mL), was added sodium hydride (2.20 g, 55.17 mmol) followed by allyl bromide (3.18 mL, 36.78 mmol), and the mixture was stirred at ambient temperature for 4 h. Excess of sodium hydride was destroyed by the addition of ice, the solvents were removed under reduced pressure, and the residue was worked up with ethyl acetate as usual to obtain the crude product (10.2 g). To the crude allyl ether (10.2 g), methanol (25 mL) and concd. HCl (5 mL) were added, and the mixture was refluxed for 5 h. The reaction mixture was cooled to ambient temperature, acid was neutralized by the addition of solid sodium hydrogen carbonate, and the mixture was filtered through a bed of Celite. The filtrate was concentrated under reduced pressure and worked up with ethyl acetate as usual. The product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:3) to afford the 1,3-diol **30** (8.5 g, 94%) as a gum. R_f = 0.36 (ethyl acetate/light petroleum, 3:7). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.42–7.30 (m, 15 H, Ar-H), 6.09–5.90 (m, 1 H, C*H*=CH_2), 5.36–5.15 (m, 2 H, CH=CH_2), 4.92 (d, *J* = 11 Hz, 2 H), 4.81 (s, 2 H), 4.75 (d, *J* = 11 Hz, 2 H), 4.36 (dt, *J* = 5.7, 1.4 Hz, 2 H), 4.00 (t, *J* = 2.7 Hz, 1 H), 3.75 (t, *J* = 9.3 Hz, 2 H), 3.60–3.45 (m, 2 H), 3.34 (t, *J* = 9.2 Hz, 1 H), 2.28 (d, *J* = 5.4 Hz, 2 H, D_2O exchangeable, 2 OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 138.5 (C_{ipso}), 138.4 (C_{ipso}), 134.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 116.7 (C=*C*H_2), 83.2 (Ins C), 82.0 (Ins C), 78.9 (Ins C), 75.4 (CH_2), 75.1 (CH_2), 74.2 (CH_2), 72.3 (Ins C) ppm. IR (Nujol): $\tilde{\nu}$ = 3594–3233 (OH) cm^{-1}. $C_{30}H_{34}O_6$ (490.59): calcd. C 73.45, H 6.99; found C 73.30, H 7.29.

Preparation of Racemic 5-*O*-Allyl-1-*O*-(4-chlorobenzyl)-2,4,6-tri-*O*-benzyl-*myo*-inositol (31): To an ice-cooled solution of **30** (6.00 g, 12.24 mmol) in dry DMF (30 mL), was added sodium hydride (0.54 g, 13.47 mmol) followed by a solution of 4-chlorobenzyl bromide (2.64 g, 12.86 mmol) in DMF (20 mL), and the reaction mixture was stirred at room temp. for 12 h. Excess of sodium hydride was destroyed by the addition of ice, solvents were removed under reduced pressure, and the residue was worked up with ethyl acetate as usual. The product was separated by flash column chromatography (ethyl acetate/light petroleum, 1:4) on silica gel to obtain **31** (3.6 g, 48%; 78% based on recovered **30**) as a gum, which turned into a sticky solid on cooling under light petroleum (in a refridgerator); unreacted starting diol **30** (2.3 g, 38%) was also recovered. R_f = 0.37 (ethyl acetate/light petroleum, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.28 (m, 15 H, Ar-H), 7.24–7.18 (m, 4 H, Ar-H), 6.08–5.89 (m, 1 H, C*H*=CH_2), 5.35–5.14 (m, 2 H, CH=CH_2), 5.00–4.87 (m, 2 H), 4.84 (s, 2 H), 4.78–4.69 (dd, *J* = 2.5, 11.0 Hz, 2 H), 4.61 (s, 2 H), 4.44–4.27 (m, 2 H), 4.05–3.94 (m, 2 H), 3.77 (t, *J* = 9.5 Hz, 1 H), 3.48–3.28 (m, 3 H), 2.24 (br. s, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 138.43 (C_{ipso}), 138.4 (C_{ipso}), 136.6 (C_{ipso}), 134.9, 133.0 (C_{ipso}), 128.5, 128.3, 128.1, 127.83, 127.8, 127.5, 127.39, 127.36, 116.4 (CH=*C*H_2), 83.0 (Ins C), 81.6 (Ins C), 81.5 (Ins C), 80.5 (Ins C), 76.6 (Ins C), 75.6 (CH_2), 75.2 (CH_2), 74.4 (CH_2), 74.2 (CH_2), 71.9 (Ins C), 71.6 (CH_2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3559, 3455 (OH) cm^{-1}. $C_{37}H_{39}ClO_6$ (615.15): calcd. C 72.24, H 6.39; found C 72.58, H 6.55.

Preparation of Racemic 1-*O*-Acetyl-3-*O*-allyl-2,4,6-tri-*O*-benzyl-5-*O*-(4-chlorobenzyl)-*chiro*-inositol (32): To a cooled solution (–15 °C) of **31** (1.43 g, 2.32 mmol) in pyridine/dichloromethane (5:15 mL) was added trifluoromethanesulfonic anhydride (0.58 mL, 3.49 mmol), and the reaction mixture was stirred for 2 h, during which time the mixture was allowed to warm to ambient temperature. The reaction mixture was decomposed by the addition of ice, then solvents were removed under reduced pressure, and the residue was worked up with dichloromethane as usual. The product was purified by column chromatography on silica gel to obtain the corresponding triflate (1.6 g, 90%) as a gum. The triflate (1.6 g), benzene (12 mL), cesium acetate (1.23 g, 6.43 mmol) and 18-crown-6 (1.13 g, 4.28 mmol), were refluxed for 2 h. The reaction mixture was cooled to ambient temperature and decomposed by the addition of ice, then diluted with dichloromethane and worked up as usual. The product was purified by flash column chromatography (ethyl acetate/light petroleum, 1.5:8.5) to afford the *chiro*-acetate **32** (0.98 g, 70%) as a gum and 4-*O*-allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)cyclohex-1(6)-ene-1,2,3,4,5-pentol (ethyl acetate/light petroleum, 1:13) as a colorless solid (0.32 g, 25%).

Data for 32: R_f = 0.40 (ethyl acetate/light petroleum, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.39–7.27 (m, 17 H, Ar-H), 7.24–7.17 (m, 2 H, Ar-H), 6.10–5.90 (m, 1 H, C*H*=CH_2), 5.36–5.14 (m, 3 H, CH=CH_2, 1-H), 4.84 (q, *J* = 12.8 Hz, 2 H), 4.74–4.47 (m, 6 H), 4.45–4.23 (m, 2 H), 3.95–3.79 (m, 2 H), 3.73 (t, *J* = 3.6 Hz, 1 H), 3.66–3.55 (m, 2 H), 1.99 (s, 3 H, OC-CH_3) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 169.6 (C=O), 138.6 (C_{ipso}), 137.9 (C_{ipso}), 137.7 (C_{ipso}), 136.7 (C_{ipso}), 135.2, 133.2 (C_{ipso}), 128.9, 128.34, 128.29, 128.27, 128.2, 128.1, 127.8, 127.63, 127.6, 116.4 (CH=*C*H_2), 81.5 (Ins C), 81.3 (Ins C), 79.2 (Ins C), 77.3 (Ins C), 76.0 (CH_2), 74.5 (CH_2), 74.0 (Ins CH), 73.1 (CH_2), 72.6 (CH_2), 72.1 (CH_2), 67.8 (Ins C), 20.8 (OC-*C*H_3) ppm. IR (neat): $\tilde{\nu}$ = 1747 (C=O) cm^{-1}. $C_{39}H_{41}ClO_7$ (657.19): calcd. C 71.28, H 6.29; found C 71.32, H 6.49.

Data for 4-*O*-Allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-chloro)benzylcyclohex-1(6)-ene-1,2,3,4,5-pentol: R_f = 0.38 (ethyl acetate/light petroleum, 1:9); m.p. 87–89 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.45–7.28 (m, 15 H, Ar-H), 7.24–7.15 (m, 4 H, Ar-H), 6.10–5.90 (m, 1 H), 5.37–5.30 (m, 2 H), 5.00–4.57 (m, 9 H), 4.50–4.30 (m, 2 H), 4.28–4.16 (m, 2 H), 3.72 (dd, *J* = 7.3, 7.5 Hz, 1 H), 3.56 (dd, *J* = 7.3, 7.2 Hz, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 153.7 (C_{ipso}), 138.52 (C_{ipso}), 138.46 (C_{ipso}), 136.9 (C_{ipso}), 136.4 (C_{ipso}), 135.1, 133.2 (C_{ipso}), 129.5, 128.5, 128.4, 128.34, 128.30, 128.1, 127.9, 127.8, 127.7, 127.6, 116.8 (CH=*C*H_2), 96.9 (Ins C), 83.2 (Ins C), 82.5 (Ins C), 80.2 (Ins C), 78.4 (Ins C), 75.6 (CH_2),

74.12 (CH_2), 74.06 (CH_2), 72.4 (CH_2), 69.7 (CH_2) ppm. $C_{37}H_{37}ClO_5$ (597.14): calcd. C 74.42, H 6.25; found C 74.46, H 5.86.

Preparation of Racemic 4-*O*-Allyl-1,3,5-tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*chiro*-inositol (33): A mixture of *chiro*-acetate **32** (1.75 g, 2.66 mmol), isobutylamine (2 mL) and methanol (12 mL) was refluxed for 4 h. The solvent was removed under reduced pressure, and the residue was worked up with ethyl acetate as usual, to afford the corresponding crude alcohol (1.65 g). To an ice-cooled solution of the alcohol (1.65 g) and tetrabutylammonium iodide (0.02 g) in DMF (15 mL), sodium hydride (0.32 g, 7.98 mmol) was added followed by PMBCl (0.90 g, 6.65 mmol). The mixture was stirred at ambient temperature for 4 h, then the reaction mixture was decomposed by the addition of ice, the solvent was removed under reduced pressure, and the residue was worked up with dichloromethane as usual. The product was purified by column chromatography (ethyl acetate/light petroleum, 2:23) on silica gel to obtain the racemic *chiro*-PMB ether **33** (1.85 g, 95% yield) as a gum. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.17 (m, 17 H, Ar-H), 7.16–7.10 (m, 2 H, Ar-H), 7.05–7.00 (m, 2 H, Ar-H), 6.82–6.77 (m, 2 H, Ar-H), 6.06–5.96 (m, 1 H), 5.32–5.25 (m, 1 H), 5.18–5.13 (m, 1 H), 4.84 (q, J = 10.7 Hz, 2 H), 4.69 (d, J = 11.9 Hz, 1 H), 4.60–4.31 (m, 8 H), 4.25 (d, J = 11.9 Hz, 1 H), 3.85–3.77 (m, 1 H), 3.79 (s, 3 H, Ar-OCH_3), 3.75–3.68 (m, 3 H), 3.61–3.58 (m, 1 H), 3.51 (t, J = 3.36 Hz, 1 H) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$, 25 °C): δ = 159.1 (C_{ipso}), 139.0 (C_{ipso}), 138.8 (C_{ipso}), 138.2 (C_{ipso}), 137.3 (C_{ipso}), 135.6, 133.2 (C_{ipso}), 130.5 (C_{ipso}), 128.3, 129.1, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 116.4 (CH=*C*H_2), 113.7, 82.0 (Ins C), 81.9 (Ins C), 79.6 (Ins C), 79.5 (Ins C), 75.9 (CH_2), 74.9 (Ins C), 74.6 (CH_2), 74.5 (Ins C), 73.3 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 72.3 (CH_2), 55.2 (OCH_3) ppm. $C_{45}H_{47}ClO_7$ (735.30): calcd. C 73.50, H 6.44; found C 73.64, H 6.58.

Preparation of Racemic 1,3,5-Tri-*O*-benzyl-2-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*chiro*-inositol (44): To an ice-cooled solution of the *chiro*-allyl ether **33** (1.85 g, 2.51 mmol) in toluene (20 mL), (dppp)$NiCl_2$ (0.07 g, 0.12 mmol) and DIBAL-H (7.55 mL, 7.55 mmol, 1 M in toluene) were added, and the mixture was stirred at room temp. for 3 h. The reaction mixture was diluted with dichloromethane (80 mL), cooled to 0 °C and methanol (4 mL) and 10% HCl (5 mL) were added. The mixture was stirred at room temp. for 3 h, and the precipitate formed was filtered by passing through a bed of Celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was taken up in dichloromethane, washed successively with aq. sodium hydrogen carbonate, water, brine and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (ethyl acetate/light petroleum, 1:4) to afford the racemic *chiro*-alcohol **44** (1.50 g, 86%) as a gum. R_f = 0.38 (ethyl acetate/light petroleum, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.27 (m, 13 H, Ar-H), 7.25–7.12 (m, 6 H, Ar-H), 7.08–6.99 (m, 2 H, Ar-H), 6.85–6.76 (m, 2 H, Ar-H), 4.86 (q, J = 12.5 Hz, 2 H), 4.65–4.35 (m, 7 H), 4.23 (d, J = 11.7 Hz, 1 H), 3.98 (t, J = 8.5 Hz, 1 H), 3.83–3.72 (m, 2 H), 3.80 (s, 3 H, Ar-OCH_3), 3.71–3.57 (m, 3 H), 2.53 (br. s, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 159.1 (C_{ipso}), 138.9 (C_{ipso}), 138.3 (C_{ipso}), 138.1 (C_{ipso}), 137.1 (C_{ipso}), 133.1 (C_{ipso}), 130.2 (C_{ipso}), 129.2 (C_{arom}), 129.0 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 127.9 (C_{arom}), 127.74 (C_{arom}), 127.7 (C_{arom}), 127.4 (C_{arom}), 113.6 (C_{arom}), 81.6 (Ins C), 79.2 (InsC), 79.1 (InsC), 75.3 (CH_2), 74.8 (InsC), 73.6 (InsC), 73.0 (InsC), 72.9 (CH_2), 72.7 (CH_2), 72.1 (CH_2), 55.1 (OCH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3609–3322 (OH) cm^{-1}. $C_{42}H_{43}ClO_7$ (695.24): calcd. C 72.56, H 6.23; found C 72.83, H 6.08.

Preparation of Racemic 1,3,5-Tri-*O*-benzyl-4-*O*-(4-chlorobenzyl)-6-*O*-(4-methoxybenzyl)-*allo*-inositol (45): Dichloromethane (1.5 mL) and oxalyl chloride (0.18 mL, 2.07 mmol) were taken in a two-necked round-bottomed flask (50 mL) and cooled to –78 °C. A solution of dimethyl sulfoxide (0.18 mL, 2.84 mmol) in dichloromethane (1.5 mL) was added, and the reaction mixture was stirred at –78 °C for 20 min. To the resulting mixture, a solution of the *chiro*-alcohol **44** (0.60 g, 0.86 mmol) in dichloromethane (5.0 mL) was added dropwise, and the mixture was stirred at –78 °C for 2 h. Triethylamine (0.66 mL, 4.73 mmol) was added at –78 °C, and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with dichloromethane and worked up as usual to obtain the crude ketone (0.70 g). To an ice-cooled solution of the crude ketone (0.70 g) in a THF/methanol (8:2 mL) mixture, sodium borohydride (0.16 mL, 4.3 mmol) was added, and the mixture was stirred at ambient temperature for 30 min. Saturated ammonium chloride solution was added to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up as usual with dichloromethane. The product was purified by flash column chromatography (ethyl acetate/light petroleum, 1:4) to afford racemic *allo*-alcohol **45** as a gum (0.58 g, 96%). R_f = 0.37 (ethyl acetate/light petroleum, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.45–7.27 (m, 15 H, Ar-H), 7.24–7.02 (m, 6 H, Ar-H), 6.85–6.77 (m, 2 H, Ar-H), 4.81–4.30 (m, 11 H), 4.05–3.63 (m, 5 H), 3.80 (s, 3 H, Ar-OCH_3), 3.56 (br. s, OH, 1 H, D_2O exchangeable) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ = 159.3 (C_{ipso}), 138.5 (C_{ipso}), 138.1 (C_{ipso}), 137.4 (C_{ipso}), 133.0 (C_{ipso}), 129.4 (C_{arom}), 129.0 (C_{arom}), 128.30 (C_{arom}), 129.27 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 127.4 (C_{arom}), 113.7 (C_{arom}), 78.4 (InsC), 77.8 (InsC), 76.0 (InsC), 75.3 (InsC), 73.6 (CH_2), 73.2 (CH_2), 72.7 (CH_2), 72.2 (CH_2), 55.2 (OCH_3) ppm. IR (Neat): $\tilde{\nu}$ = 3505 (OH) cm^{-1}. $C_{42}H_{43}ClO_7$ (695.24): calcd. C 72.56, H 6.23; found C 72.87, H 6.42.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **18**–**20**, **22**, **23**, **26**–**28**, **41**–**43**, **46**–**48**, and **50**–**54**.

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