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Relative reactivity of hydroxyl groups in inositol derivatives: role of metal ion chelation

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ABSTRACT

O-Alkylation of *myo*-inositol derivatives containing more than one hydroxyl group *via* their alkali metal alkoxides (sodium or lithium) preferentially occurs at a hydroxyl group having a vicinal *cis*-oxygen atom. In general the observed selectivity is relatively higher for lithium alkoxides than for the corresponding sodium alkoxide. The observed regioselectivity is also dependent on other factors such as the solvent and reaction temperature. A perusal of the results presented in this article as well as those available in the literature suggests that chelation of metal ions by inositol derivatives plays a significant role in the observed regioselectivity. Steric factors associated with the axial or equatorial disposition of the reacting hydroxyl groups do not contribute much to the outcome of these O-alkylation reactions. These results could serve as guidelines in planning synthetic strategies involving other carbohydrates and their derivatives.

1. Introduction

Achieving selective reaction at one hydroxyl group in polyhydroxy compounds such as carbohydrates and cyclitols or their partially protected derivatives is a challenge and is a topic of current research interest.[1–5] This has implications for the synthesis of several classes of biologically or medicinally important compounds as exemplified by antibiotics, oligosaccharides, inositols and their derivatives as well as natural products that can be synthesized from these polyols.[6–14] Classical methods for the discrimination of hydroxyl groups in polyols include (a) selective reaction of primary alcohols (with electrophiles), in the presence of secondary and tertiary alcohols; (b) preferential O-substitution of an equatorial hydroxyl group over that of an axial hydroxyl group in cyclohexane-derived alcohols; (c) preferential formation of *cis*-acetals over *trans*-acetals in vicinal cyclic diols; (d) preferential hydrolysis of *trans* acetals over *cis* acetals of vicinal cyclic diols;[15–18] and (e) preferential formation of *trans*-acetals over *cis*-acetals in vicinal diols.[19–22] Hydrolysis and reduction of orthoesters[23–28] and ketals[29–31] of diols and triols are also reported to be specific although their use in synthesis is limited. However, when all the non-equivalent hydroxyl groups in a molecule are secondary or tertiary in nature (as in cyclitols), obtaining selectively derivatized products is a formidable task, due to subtle differences in their reactivity and/ or difficulty in separation of isomeric products.

Chemistry of inositols has been the subject of intense investigation by chemists due to the biological significance of its phosphorylated derivatives and potential medicinal and pharmacological applications of inositol derivatives as enzyme inhibitors and leads for drug discovery.[10,32–37] Inositols and their derivatives have also shown promise as viable starting materials for the synthesis of natural products,[9,11,12,14] as scaffolds for the construction of specific metal ion complexing agents,[38–42] and as synthons for supramolecular assemblies with unusual physical and chemical properties.[43–49] The selective functionalization of *myo*-inositol, a cyclohexane hexol having six secondary hydroxyl groups with more or less similar chemical environment, is one of the main challenges in synthetic inositol chemistry. Often, partially protected ketals or orthoesters of inositol are used for further selective functionalization during phosphoinositol synthesis. Such a modification usually perturbs the chemical environment of different hydroxyl groups unevenly making them prone to better discrimination during synthetic manipulations.

We had observed earlier that the specificity and the facility of complexation of alkali metal ions with inositol derivatives strongly depend on the relative orientation of the oxygen atoms involved in binding of the metal ions.[42,50] This prompted us to examine the regioselectivity of O-substitution reactions in *myo*-inositol orthoesters in the presence of strong bases derived from sodium and lithium.[51] These experiments revealed that the use of lithium alkoxides allows better discrimination (as compared to the corresponding sodium alkoxide) of *myo*-inositol orthoester hydroxyl groups during their reaction with electrophiles (Scheme 1).[†] For instance, the sequential reaction of *myo*-inositol orthoformate (**1**) with

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[†] All the asymmetrically substituted inositol derivatives shown in schemes are racemic, however only one of the enantiomers is shown for simplicity.

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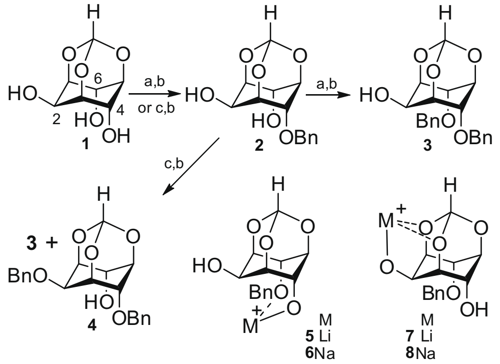


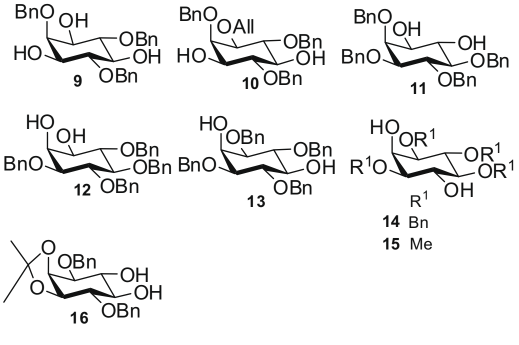
Scheme 1. Reagents and conditions: (a) BuLi/THF, 0 °C; (b) BnBr / DMF, 0 °C–rt; and (c) NaH, DMF.

sodium hydride followed by benzyl bromide gives a mixture of two dibenzyl ethers **3** and **4**, while the use of lithium hydride (or butyllithium) instead of sodium hydride for the same reaction, provides the symmetrical dibenzyl ether **3** exclusively.[51] This difference in reactivity between lithium and sodium alkoxides could be exploited to sequentially react the three hydroxyl groups in *myo*-inositol orthoesters in the order C4–C6–C2. The improvement in the regioselectivity on going from sodium to lithium alkoxides was attributed to the differences in the relative stability of the corresponding chelates **5**–**8**.

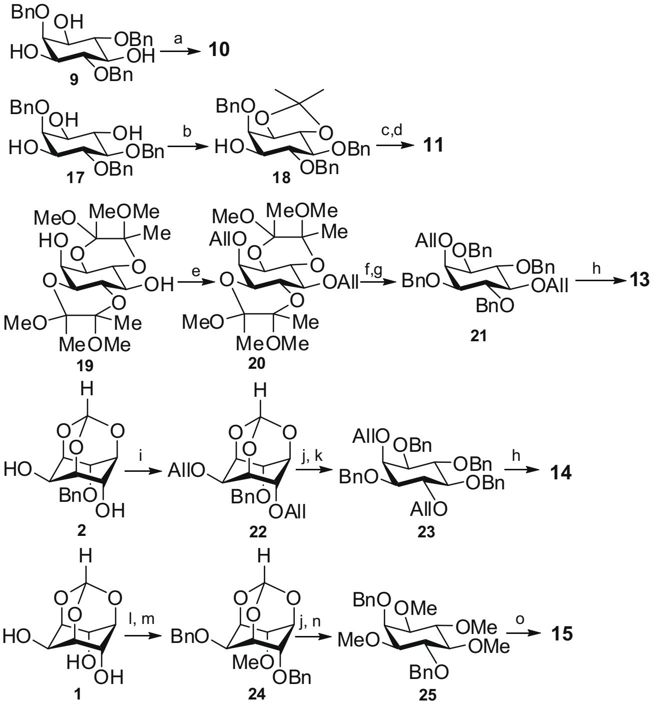
Hence we postulated that if such effects due to chelation of metal ions prevail during the reaction of partially protected inositol derivatives (without the orthoester cage) they would help discriminate between hydroxyl groups with different relative orientations, toward O-substitution. A comparison of the results of the sequential reaction of *myo*-inositol derivatives (Scheme 2) with butyllithium or sodium hydride followed by an electrophile showed that relatively higher selectivity at a hydroxyl group *cis* to a vicinal oxygen could be achieved using butyllithium as the base to generate the alkoxide. The results presented here also support that chelation of metal ions by inositol derivatives plays a major role in deciding the outcome of these O-substitution reactions in terms of the observed regioselectivity.

2. Results and discussion

Sequence of reactions for the preparation of the diols **10**, **11**,[52,53] **13**,[54] **14**,[55] and **15** are shown in Scheme 3. The triol **9**,[56] the diols **12**[57] and **16**[58] were prepared by known methods. Results of the O-alkylation reaction of *myo*-inositol-derived diols and triol are summarized in Scheme 4 and Table 1. Same experimental conditions for the reaction of sodium alkoxides and lithium alkoxides with alkyl halides were maintained to allow comparison of the results.



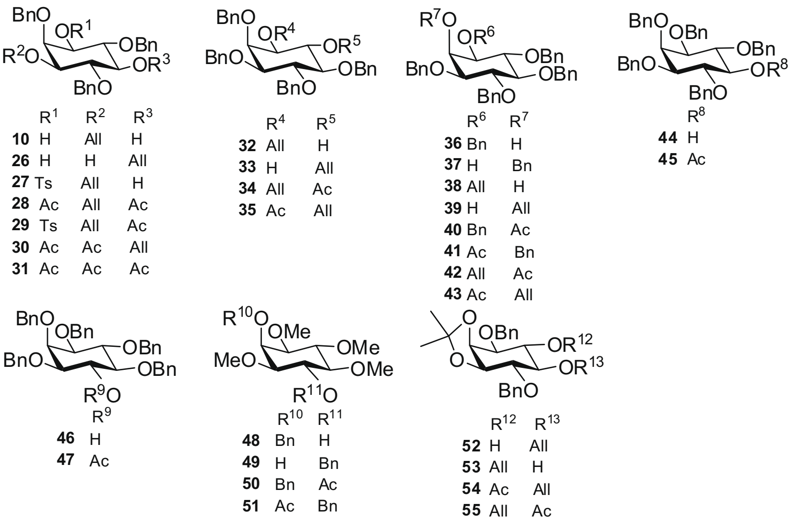
Scheme 2.



Scheme 3. Reagents and conditions: (a) BuLi, THF, AllBr, DMF, 28 h, 71%; (b) 2,2-dimethoxypropane, camphorsulfonic acid, dichloromethane, reflux, 3 h, 75%; (c) DMF, NaH, BnBr, 1 h; (d) dichloromethane, concd HCl, MeOH, 3 h, 74% (for two steps); (e) DMF, NaH, AllBr, rt, 3 h., 71%; (f) aq trifluoroacetic acid, rt, 2 h; (g) DMF, NaH, BnBr, rt, 24 h, 87% (for two steps); (h) MeOH/H_2O, 10% Pd–C, TsOH, reflux, 24 h (39% for **13**), (35% for **14**); (i) DMF, NaH, AllBr, rt, 12 h, 86%; (j) MeOH, TsOH (3 equiv), rt, 14 h; (k) DMF, NaH, BnBr, rt, 24 h, 80% (two steps); (l) DMF, NaH (1.1 equiv), MeI (1.1 equiv); (m) NaH, BnBr, 70% (two steps); (n) DMF, NaH, MeI, rt, 24 h, 74% (two steps); and (o) MeOH, 10% Pd–C, H_2, rt, 24 h, 85%.

A comparison of the results on O-substitution of the triol **9** and the diols **10**, **11**, and **16** (see below) clearly shows that the observed regioselectivity for O-substitution at a hydroxyl group that has a neighboring (vicinal) *cis*-oxygen atom is better in reactions involving lithium alkoxide than in reactions involving the corresponding sodium alkoxide. The highly selective reaction at the C1-hydroxyl group in the triol **9** and the diol **10** in the presence of lithium ions allows the sequential substitution of both C-1 and C-3 hydroxyl groups (in **9**) that are *cis* to the C-2 oxygen leaving the C-5 hydroxyl group undisturbed. It is pertinent to note that the reaction of lithium alkoxide of the diol **16** (entry 15), in which there is no adjacent *cis*-oxygen to either of the hydroxyl groups resulted in a mixture of products[‡] consisting of equal amounts of the mono-allylethers **52** and **53**.[59] Alkylation of the racemic 1,2-diol **12** in DMF at different temperatures, using butyllithium to generate the alkoxide revealed that the proportion of the axial C2-ether can be increased at lower temperature. At a given temperature (0 °C) the proportion of the equatorial C1-benzyl ether formed was higher when sodium alkoxide (64:36) was used instead of the lithium alkoxide (52:48). Hence opposite regio-selectivities can be obtained by using judicious combination of the reaction temperature and the base used to generate the alkoxide of **12**.

[‡] We did not carry out the alkylation of the diol **16** using the corresponding sodium alkoxide since the reaction of its lithium alkoxide yielded a mixture of products. However, alkylation of a 5,6-diol (1-deoxy-1-fluoro-2,3-isopropylidene-4-O-benzyl-*myo*-inositol) which is structurally similar to **16**, using sodium hydride is reported[59] to give a mixture of both the possible isomeric ethers (C5-ether:C6-ether = 1:2).



Scheme 4.

Table 1
Results on O-alkylation of partially protected *myo*-inositol derivatives[a]

Entry	Diol/triol	Reaction conditions	Products (ratio;% yield)[b]
1	**9**	a, b	**10** (71)
2	**9**	c, b	**10:26** (1:1, 95)
3	**9**	NaH, b,[4]	**10** (61)
4	**10**	a, d	**27** (53)
5	**11**	a, b	**32:33** (4:1; 67)
6	**11**	c, b	**32:33** (2:1; 75)
7	**12**	a, e, −78 °C	**36:37** (45:55; 69)
8	**12**	a, e, 0 °C	**36:37** (52:48; 70)
9	**12**	a, e, 76 °C	**36:37** (71:29; 74)
10	**12**	c, e, 0 °C	**36:37** (64:36; 76)
11	**12**	a, b, 0 °C	**38:39** (67:33; 66)
12	**13**	c, e	**44:36** (19:1, 59)
13	**14**	c, e	**46:36** (19:1, 47)
14	**15**	c, e	**48:49** (18:1, 60)
15	**16**	a, b	**52:53** (1:1; 76)

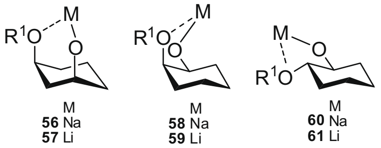
(a) THF, *n*-BuLi; previous experience[51] on the O-alkylation of *myo*-inositol orthoesters had shown that although other bases such as lithium hydride could be used for the O-substitution reactions, butyllithium worked best. Hence in the present work butyllithium was used to generate lithium alkoxides from diols and triols. Reactions carried out with lithium hydride were much slower than the corresponding reactions with butyllithium.
(b) DMF, AllBr.
(c) THF, NaH.
(d) DMF, TsCl.
(e) DMF, BnBr.

[a] See Schemes 2 and 4 for the structure of reactants and products. The molar ratio of the diol/triol:base:alkyl halide in all the experiments was 1:1:1.

[b] Isolated yields. The ratio of the products for entries 2 and 5–15 was estimated from the ^{1}H NMR spectra of acetates obtained after acetylation of the mixture of isomeric products.

Benzylation of the 2,5- and 2,4-diols **13**, **14**, and **15** gave the corresponding C2-benzyl ether as the major product. This was unexpected based on the fact that equatorial hydroxyl groups normally undergo O-substitution with better facility than the axial hydroxyl groups in cyclohexanols. However, such reasoning may not be accurate[60] in reactions under discussion since inositols have many (protected) hydroxyl groups which could influence the reactivity of each other.[§] We wondered whether this could be an outcome of several benzyl groups present in the tetrabenzyl ethers **13** and **14** and hence we carried out the benzylation of the corresponding tetramethyl ether **15**. However, major O-substitution at the C2-axial hydroxyl group was observed again showing that the observed regioselectivity was not dependent on the inositol hydroxyl protecting groups. X-ray crystal structure (see Supplementary data) of these diols did not show any unusual feature in the molecular structures of **13**, **14**, and **15** that could provide clues for the unexpected observed regioselectivity. Preferential substitution at an axial hydroxyl group over an equatorial hydroxyl group has earlier been reported.[55] Since high regioselectivity was observed for these diols on using sodium hydride as the base, there was no need to carryout the corresponding reactions with butyllithium.

The results presented in Table 1 can be explained based on the relative stability of the alkoxides generated by the reaction of the diols with butyllithium or sodium hydride. Some of the experiments which suggested the involvement of alkali metal chelates (Scheme 5) in the reactions described so far are given below. Use of THF alone as a solvent for the reaction resulted in a reduction in the rate of the reaction and the yield of the products did not appear to be of practical utility. Increase in the temperature of the reaction (to decrease the reaction time), resulted in poorer regioselectivity. Since alkali metal alkoxides of the diols under study appeared to be less soluble in dry THF than in dry DMF, a mixture of these two solvents was essential to achieve good regioselectivity and conversion. Use of DMF as a co-solvent drove the reaction to completion at lower temperatures with higher regioselectivity. Hence it appears that DMF helps to solubilize the alkoxide and facilitates the reaction with electrophiles. The factors that could contribute to the stability of the alkoxides **56**–**61** are (a) the metal ion involved; (b) relative orientation of the vicinal oxygen atom which could chelate with the metal ion; (c) the solvent in which the alkoxide exists, and (d) the temperature of the reaction medium. In reactions involving lithium alkoxides, it is conceivable that



Scheme 5. Structure of possible alkali metal chelates involved in the O-alkylation reactions (R^1 = alkyl). All the hydroxyl groups of inositol are not shown for clarity.

[§] This is similar to the fact that while cyclohexane rings carrying a few substituents adopt a chair conformation with minimum number of axial substituents (or maximum number of equatorial substituents), inositol derivatives carrying bulky substituents are known to adopt chair conformation with maximum number of axial substituents.

the chelation from a vicinal *cis*-oxygen atom is better than the chelation from a vicinal *trans*-oxygen atom. This is analogous to the relative strength of intramolecular hydrogen bonding in polyhydroxy cyclohexanes which is known to decrease in the order 1,3-diaxial diols > 1,2-*cis* diols > 1,2-*trans* diols.[61,62] Intramolecular hydrogen bonds in *cis*-1,3 (diaxial) diols have been observed in their crystals.[61,63,64] Hence the relative stability of alkali metal chelates is expected to decrease in the order **56**,**57** > **58**,**59** > **60**,**61**.[65] For a given diol, the lithium chelate would be expected to be more stable than the corresponding sodium chelate due to the ability of lithium to form chelates better. This difference in the facility of chelation would translate in the preferential O-substitution at a hydroxyl group having a vicinal *cis*-oxygen atom. In reactions involving sodium alkoxides, although chelates **56**, **58**, and **60** are formed, their relative stability may not be very different since sodium ion is not a chelator as good as lithium ion. Hence the reactions using sodium alkoxides show poorer selectivity (as compared to lithium alkoxides) under similar experimental conditions. However, when one of the two hydroxyl groups in a diol has two adjacent *cis*-oxygen atoms while the other has two *trans*-oxygen atoms (as in **13–15**), O-substitution preferentially takes place at the former, since the corresponding alkoxide is stabilized by two neighboring *cis*-oxygen atoms while the equatorial hydroxyl group is stabilized by two *trans*-oxygen atoms. Similarly during the reaction of the alkoxides of the 1,2 *cis* diol **12** the alkoxide derived from the C2-axial hydroxyl group is stabilized by two *cis*-oxygen atoms while the alkoxide derived from the C1-equatorial hydroxyl group is stabilized by one *cis* and one *trans*-oxygen atom. This implies relatively greater stabilization of the C2-lithium alkoxide and hence higher yield of the C2-ether (especially as the temperature decreases). Chelation-assisted regioselective O-substitution of vicinal diols (using heavier metals)[66,67] and *myo*-inositol orthoesters (using lithium alkoxides)[51] has been reported earlier.

We have reported a method for the preferential O-substitution of hydroxyl groups that have an adjacent *cis* oxygen atom in *myo*-inositol-derived diols and triols. A comparison of the O-alkylation of partially protected inositol derivatives via their lithium and sodium alkoxides presented here (also see Supplementary data), clearly shows that the use of lithium alkoxides generally leads to better discrimination between the hydroxyl groups in diols and triols (Scheme 3 and 4) and minimizes the formation of diethers. These results could serve as guidelines in planning synthetic strategies with other polyols and their derivatives as well as molecules containing polyol moieties. We did not carry out acylation in the present study due to the potential of hydroxyl esters to undergo inter or intra molecular acyl migration,[3,68,69] which would hamper conclusions on the observed regioselectivity. Also, since esterification of alcohols proceeds by addition elimination (at a carbonyl group) mechanism whereas ether formation proceeds by direct nucleophilic substitution at a tetrahedral carbon atom, outcome of the two reactions may not be a fair measure to conclude whether chelates are involved in these two reactions which proceed by different mechanisms.[55]

3. Experimental

3.1. General methods

All the reactions were carried out in an atmosphere of argon. Dry DMF and dry THF were used as solvents in all the experiments involving metal hydrides or *n*-butyllithium. Sodium hydride used in experiments was 60% suspension in mineral oil. A stock solution of *n*-butyllithium (0.6–1.62 M) in dry hexanes was prepared and used in all the experiments. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates with concd H_2SO_4 or chromic acid. 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. 'Usual work-up' implies washing of the organic layer with water followed by brine, drying over anhydrous sodium sulfate, and removal of the solvent under reduced pressure using a rotary evaporator. IR spectra were recorded (in $CHCl_3$ solution or as Nujol mull or as neat film) on a Shimadzu FTIR-8400 or Perkin Elmer 16 spectrophotometer. NMR spectra were recorded on Bruker ACF 200 spectrometer (200 MHz for ^1H and 50.3 MHz for ^{13}C) unless otherwise mentioned. Chemical shifts (δ) reported are referred to internal tetramethylsilane. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. All the melting points reported are uncorrected and were recorded using a Büchi B-540 electro-thermal 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.

3.2. Racemic 1,6-*O*-isopropylidene-2,4,5-tri-*O*-benzyl-*myo*-inositol (18)

The racemic triol **17**[58] (2.00 g, 4.44 mmol), 2,2-dimethoxypropane (1.101 g, 10.57 mmol), and camphorsulfonic acid (0.516 g, 2.22 mmol) were refluxed in dichloromethane (60 mL) for 3 h. The resulting solution was cooled to room temperature and neutralized with triethylamine. Solvents were evaporated and the solid obtained was purified by column chromatography to obtain the racemic acetal **18** (1.784 g, 82%) as a colorless solid. Mp 78–80 °C; IR (nujol, cm^{-1}) 3115–3489; ^1H NMR ($CDCl_3$) δ 7.20–7.45 (m, 15H), 4.60–5.10 (m, 6H), 4.15–4.30 (m, 2H), 3.56–3.74 (m, 3H), 3.49 (dd, J = 2, 10 Hz, 1H), 2.40–2.50 (br s, 1H, D_2O exchangeable), 1.49 (s, 3H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 138.5, 138.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.6, 127.4, 111.8, 84.0, 80.2, 77.8, 76.9, 75.9, 74.4, 74.2, 73.5, 72.9, 27.1, 26.7; Anal. Calcd for $C_{30}H_{34}O_6$.1.2 H_2O; C, 70.34; H, 7.16. Found: C, 70.03; H, 7.33.

3.3. Racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol (11)

To a solution of the racemic ketal **18** (1.500 g, 3.06 mmol) in DMF (15 mL) sodium hydride (0.184 g, 4.59 mmol) was added and stirred for 20 min. The reaction mixture was cooled to 0 °C and benzyl bromide (1.047 g, 6.12 mmol) was added drop-wise and the mixture was stirred for 1 h. The reaction was quenched by the addition of ice and worked up as usual with ethyl acetate. The residue obtained (1.020 g) after evaporation of ethyl acetate was dissolved in dichloromethane (16 mL) and methanol (8 mL) and stirred with concd HCl (0.25 mL) for 4 h. Triethylamine was added to the reaction mixture and the solvents were evaporated under reduced pressure. The solid residue was purified by column chromatography to get the racemic 1,6-diol **11** (0.761 g, 80%) as a colorless solid. Mp 167–169 °C, Lit.[53] mp 162–164 °C; ^1H NMR ($CDCl_3$) δ 7.20–7.40 (m, 20H), 4.63–5.10 (m, 8H), 3.96–4.10 (m, 2H), 3.76–3.91 (m, 1H), 3.48 (dd, J = 2, 10 Hz, 1H), 3.25–3.39 (m, 2H), 2.47 (br s, 1H, D_2O exchangeable), 2.30 (d, 1H, J = 8 Hz, D_2O exchangeable). Anal. Calcd for $C_{34}H_{36}O_6$; C, 75.53; H, 6.71. Found: C, 75.55; H, 6.59.

3.4. 1,6:3,4-Bis-[*O*-(2,3-dimethoxybutane-2,3-diyl)]-2,5-di-*O*-allyl-*myo*-inositol (20)

To an ice-cooled solution of **19**[70] (2.478 g, 6.07 mmol) in dry DMF (40 mL), sodium hydride (2.50 g, 62.5 mmol) was added followed by allyl bromide (7.34 g, 60.6 mmol) and the mixture was stirred at room temperature for 24 h. Excess of sodium hydride was quenched by the addition of ice and the solvents were removed under reduced pressure. The residue was worked up 'as usual' with dichloromethane; the crude product was purified by flash column chromatography to afford **20** (2.10 g, 71%) as a gum. ^{1}H NMR ($CDCl_3$) δ 6.08–5.84 (m, 2H), 5.36 (q, J = 1.7 Hz, 1H), 5.27 (q, J = 1.63, 2.05 Hz, 1H), 5.2–5.0 (m, 2H), 4.36–4.26 (m, 4H), 4.06 (t, J = 9.4 Hz, 2H), 3.74 (t, J = 2.3 Hz, 1H), 3.50 (dd, J = 2.4, 9.4 Hz, 2H), 3.38 (t, J = 9.3 Hz, 1H), 3.27 (s, 6H), 3.23 (s, 6H), 1.28 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 136.0, 135.7, 115.7, 115.2, 99.4, 98.9, 78.3, 75.4, 73.4, 72.4, 69.7, 69.2, 47.8, 47.6, 17.8, 17.5. Anal. Calcd for $C_{24}H_{40}O_{10}$: C, 58.99; H, 8.24. Found C, 58.65; H, 8.46.

3.5. Preparation of 2,5-di-*O*-allyl-1,3,4,6-tetra-*O*-benzyl-*myo*-inositol (21)

A solution of **20** (2.10 g, 4.30 mmol) in TFA–H_2O (9:1, 40 mL), was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue co-evaporated with toluene to get crude 2,5-di-*O*-allyl-*myo*-inositol (1.25 g) as a white solid. The tetrol so obtained was suspended in dry DMF (30 mL), cooled with ice, sodium hydride (2.80 g, 70 mmol) was added, followed by benzyl bromide (7.97 g, 46.6 mmol); the mixture was stirred at room temperature for 48 h. Excess of sodium hydride was quenched by the addition of ice, the solvents were removed under reduced pressure and the residue was worked up 'as usual' with ethyl acetate. The crude product was purified by flash column chromatography to obtain the tetrabenzyl ether **21** (2.319 g, 87%) as a white solid. Mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.27 (m, 20H), 6.10–5.86 (m, 2H), 5.34–5.12 (m, 4H), 4.84 (AB q, J = 10.4 Hz, 4H), 4.66 (s, 4H), 4.36–4.32 (m, 4H), 4.01–3.92 (m, 3H), 3.34–3.24 (m, 3H);. ^{13}C NMR ($CDCl_3$) δ 138.8, 138.3, 135.7, 135.3, 128.2, 128.0, 127.5, 116.7, 116.5, 83.3, 81.6, 80.5, 75.8, 74.6, 73.8, 73.3, 72.7. Anal. Calcd. For $C_{40}H_{44}O_6$: C, 77.39; H, 7.14. Found C, 76.98; H, 6.91.

3.6. 1,3,4,6-Tetra-*O*-benzyl-*myo*-inositol (13)

A mixture of the diallyl ether **21** (0.500 g, 0.806 mmol), 10% Pd/C (0.051 g), *p*-toluenesulfonic acid (0.023 g, 0.13 mmol), methanol (13 mL), and water (1.6 mL) was heated (75–80 °C) for 24 h. Excess of 10% Pd/C (0.010 g) was added and the mixture was stirred at room temperature for 2 days. The reaction mixture was then diluted with methanol and passed through Celite to remove Pd/C. The filtrate was concentrated under reduced pressure; the residue was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, and then worked up 'as usual'. The crude product was purified by flash column chromatography to obtain **13** (0.170 g, 39%) as a white solid. In several trials the yield of **13** varied; the best yield obtained was 39%. Mp 129–131 °C (crystals from warm light petroleum–dichloromethane), lit[54] mp 125 °C.

3.7. Racemic 1,3,4,5-tetra-*O*-benzyl-2,6-di-*O*-allyl-*myo*-inositol (23)

To an ice-cooled solution of the benzyl ether **2**[56] (1.085 g, 3.88 mmol) in dry DMF (10 mL), sodium hydride (0.465 g, 11.6 mmol) was added, followed by the addition of a solution of allyl bromide (1.641 g, 13.6 mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by the addition of ice to the reaction mixture, solvents were removed under reduced pressure and then worked up 'as usual' with ethyl acetate to afford the crude product, which was purified by flash column chromatography to obtain **22** as a gum (1.203 g, 86%). ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 6.09–5.77 (m, 2H), 5.52 (d, J = 1.3 Hz, 1H), 5.37–5.17 (m, 4H), 4.63 (AB q, J = 12 Hz, 4H), 4.45–4.40 (m, 1H), 4.35–4.28 (m, 4H), 4.16–4.06 (m, 4H), 3.93–3.98 (m, 1H).

A mixture of **22** (1.125 g, 3.12 mmol), *p*-toluenesulfonic acid monohydrate (1.781 g, 9.36 mmol), and methanol (15 mL) was stirred at room temperature overnight. Solvents were removed under reduced pressure; the residue was taken in ethyl acetate, washed with saturated sodium bicarbonate solution, and worked up 'as usual' to afford crude racemic 2,4-di-*O*-allyl-6-*O*-benzyl-*myo*-inositol (1.050 g) as a pale yellow gum.

To an ice-cooled solution of the crude triol (1.050 g) obtained above in dry DMF (20 mL), sodium hydride (0.980 g, 24.5 mmol) was added followed by a solution of benzyl bromide (4.190 g, 24.5 mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature for 40 h. Excess of sodium hydride was quenched with ice, solvents were removed under reduced pressure, and worked up 'as usual' with ethyl acetate to afford the crude product, which was purified by flash column chromatography to obtain the tetrabenzyl ether **23**[55] as a colorless solid (1.549 g, 80%); mp 62–64 °C (crystals from methanol).

3.8. Racemic 1,3,4,5-tetra-*O*-benzyl-*myo*-inositol (14)

A mixture of **23** (0.420 g, 0.68 mmol), 10% Pd/C (0.126 g), *p*-toluenesulfonic acid (0.126 g, 0.732 mmol), methanol (12 mL), and water (2.5 mL) was heated (70–80 °C) for 30 h. The reaction mixture was diluted with methanol and passed through Celite to remove Pd/C. The filtrate was concentrated under reduced pressure and the residue was taken in ethyl acetate, washed with saturated sodium bicarbonate solution, and worked up 'as usual'. The crude product was purified by flash column chromatography to obtain **14** (0.130 g, 35%) as a colorless solid. In several trials the yield of **14** varied; maximum yield obtained was 35%; mp 116–118 °C (from ethyl acetate–light petroleum), lit.[71] mp 111–113 °C (crystals obtained by slow evaporation of methanol solution, at ambient temperature).

3.9. Racemic 2,4-di-*O*-benzyl-6-*O*-methyl-*myo*-inositol 1,3,5 orthoformate (24)

To an ice-cooled solution of **1** (0.380 g, 2.00 mmol) in dry DMF (5 mL), sodium hydride (0.088 g, 2.20 mmol) was added followed by a solution of methyl iodide (0.312 g, 2.20 mmol) in dry DMF (1 mL) and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled with ice, sodium hydride (0.500 g, 12.5 mmol) was added followed by benzyl bromide (1.725 g, 10.0 mmol). The resulting mixture was stirred at room temperature overnight. Excess sodium hydride was quenched by adding ice, the solvents were removed under reduced pressure and the residue was worked up with ethyl acetate 'as usual'. The crude product obtained was purified by flash column chromatography to obtain the dibenzyl ether **24** (0.540 g, 70%) as a gum. ^{1}H NMR ($CDCl_3$) δ 7.43–7.28 (m, 10H), 5.52 (d, J = 1.3 Hz, 1H), 4.67 (s, 2H), 4.55 (AB q, 2H), 4.44–4.39 (m, 1H), 4.36–4.27 (m, 2H), 4.24–4.19 (m, 1H), 4.16–4.11 (m, 1H), 3.97–3.92 (m, 1H), 3.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.7, 137.5, 128.18, 128.21, 127.7, 127.56, 127.64, 127.2, 102.9, 75.7, 73.6, 71.3, 70.2, 70.0, 67.4, 67.2, 57.0. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 69.11; H, 6.24.

3.10. Racemic 1,3,4,5-tetra-*O*-methyl-2,6-di-*O*-benzyl-*myo*-inositol (25)

A mixture of **24** (0.500 g, 1.30 mmol), *p*-toluenesulfonic acid monohydrate (0.740 g, 3.89 mmol), and methanol (10 mL) was stirred at room temperature for 10 h, the solvent was removed under reduced pressure. The residue was taken in ethyl acetate, washed with a saturated solution of sodium carbonate, and then worked up 'as usual' to obtain the crude triol as a gum (0.540 g).

To an ice-cooled solution of the triol (0.540 g) obtained above, in dry DMF (8 mL), sodium hydride (0.577 g, 14.4 mmol) was added followed by a solution of methyl iodide (2.0 g, 14.1 mmol) in dry DMF (2 mL) and the mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of ice to the reaction mixture, solvents were removed under reduced pressure, and the residue was worked up 'as usual' using ethyl acetate. The product was subjected to flash column chromatography to isolate **25** (0.400 g, 74%) as gum which turned into a solid on storing at room temperature. Mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 7.44–7.27 (m, 10H), 4.84 (s, 2H), 4.81 (AB q, $J = 10.7$ Hz, 2H) 4.08 (t, $J = 2.3$ Hz, 1H), 3.83 (t, $J = 9.4$ Hz), 3.65–3.53 (m, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 3.44 (s, 3H), 3.42 (s, 3H), 3.11–3.02 (m, 2H), 2.96 (dd, $J = 2.2$, 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.88, 138.78, 128.17, 127.93, 127.50, 127.38, 127.16, 85.37, 83.04, 82.72, 82.38, 81.46, 75.48, 73.79, 72.41, 61.04, 60.78, 58.34, 58.17. Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.07; H, 7.76.

3.11. Racemic 1,3,4,5-tetra-*O*-methyl-*myo*-inositol (15)

A mixture of **25** (1.15 g, 2.76 mmol), 10% Pd/C (0.064 g), and methanol (15 mL) was stirred at room temperature under H_2 atmosphere for 24 h. The catalyst was removed by passing the reaction mixture through Celite. The filtrate was evaporated under reduced pressure to obtain the diol **15** (0.550 g, 85%) as a colorless solid. Mp 137–138 °C (crystals obtained by cooling a warm solution of ethyl acetate to room temperature), Lit.[72] mp 130–132 °C. IR ($CHCl_3$, cm^{-1}) 3300–3550 (OH); ^{1}H NMR ($CDCl_3$) δ 4.36 (t, $J = 2.7$ Hz, 1H), 3.86 (t, $J = 9.6$, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.55–3.45 (2s and m, 7H), 3.09–2.93 (m, 3H), 2.69 (br s, OH), 2.41 (br s, OH); ^{13}C NMR ($CDCl_3$) δ 84.4, 82.5, 82.0, 81.3, 71.6, 65.2, 60.8, 58.3, 57.8. Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 50.98; H, 8.89.

3.12. O-Alkylation of *myo*-inositol-derived triol and diols

3.12.1. General procedure

The required *myo*-inositol-derived triol or diol (0.5–1 mmol) was dissolved in dry THF (3–6 mL) and cooled to 0 °C. *n*-Butyllithium (1.0–1.2 mmol) was added drop-wise using a syringe followed by a solution of the required alkyl halide or sulfonyl halide (1.2–1.5 mmol) in DMF (0.5–1 mL) at 0 °C. The reaction mixture was stirred for 20–56 h at room temperature and worked up as usual with ethyl acetate. The products were separated by column chromatography using 10–20% ethyl acetate–light petroleum (80% for mixture of monobenzyl ethers **48** and **49**) or light petroleum–dichloromethane mixtures as eluent. In some experiments, the ratio of the mixture of ethers formed was estimated by ^{1}H NMR spectroscopy of their acetate derivatives. The same procedure was followed in the case of reactions where sodium hydride was used to generate the alkoxides.

3.12.2. Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-*myo*-inositol (10)

The 1,3,5-triol **9** (0.450 g, 1 mmol) was allylated as in the general procedure (reaction time 28 h), using butyllithium (1.46 mL, 1.20 mmol) and allyl bromide (0.182 g, 1.50 mmol) to obtain the racemic 1-allyl ether **10** (0.351 g, 71%) as a gum after column chromatography. A small amount of the symmetric diallyl ether (0.089 g, 17%) was also obtained as a solid. IR (neat, cm^{-1}) 3196–3641. ^{1}H NMR ($CDCl_3$) δ 7.20–7.45 (m, 15H), 5.80–6.05 (m, 1H), 5.26–5.39 (m, 1H), 5.14–5.24 (m, 1H), 4.68–5.04 (m, 6H), 4.10–4.18 (m, 2H), 4.04 (t, $J = 2.4$ Hz, 1H), 3.85 (t, $J = 9.4$ Hz, 1H), 3.68 (t, $J = 9.4$ Hz, 1H), 3.51 (t, $J = 9.0$ Hz, 2H), 3.35 (dd, $J = 2.4$ and 9.8 Hz, 1H), 2.52 (s, 1H, D_2O exchangeable), 3.33 (d, 1H, J = 5.9 Hz, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 134.6, 130.5, 124.3, 124.2, 123.9, 123.6, 123.5, 112.8, 73.5, 72.9, 72.3, 71.3, 70.8, 68.0, 67.3. Anal. Calcd for $C_{30}H_{34}O_6$ C: 73.45; H, 6.99. Found: C, 73.07; H, 6.89.

3.12.3. Allylation of 2,4,6-tri-*O*-benzyl-*myo*-inositol (9) with sodium hydride/allyl bromide

The 1,3,5-triol **9** (0.100 g, 0.22 mmol) was allylated as in the general procedure (reaction time 2 h), using sodium hydride (0.011 g, 0.27 mmol) and allyl bromide (0.040 g, 0.33 mmol) to obtain a mixture of allyl ethers. This mixture was acetylated using acetic anhydride (0.3 mL) and pyridine (0.6 mL) overnight at room temperature. Usual work-up with ethyl acetate gave mixture (0.121 g) of acetates **28** and **30**. ^{1}H NMR spectrum of the mixture of acetates showed that **28** and **30** were present in the ratio 1:1.

The acetate **28** was prepared from **10** for comparison with NMR spectra of the mixture of acetates **28** and **30**.

3.12.4. Racemic 1-*O*-allyl-2,4,6-tri-*O*-benzyl-3-*O*-(*p*-toluenesulfonyl)-*myo*-inositol (27)

The racemic allyl ether **10** (0.254 g, 0.52 mmol) was sulfonylated as in the general procedure (reaction time 15 h), using butyllithium (0.76 mL, 0.62 mmol) and *p*-toluenesulfonyl chloride (0.148 g, 0.78 mmol) to obtain the racemic 3-tosylate **27** (0.179 g, 53%) as a gum, after column chromatography. IR (neat, cm^{-1}) 3216–3630; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 2H, $J = 8$ Hz), 7.05–7.48 (m, 17H), 5.75–6.01 (m, 1H), 5.24–5.37 (m, 1H), 5.13–5.23 (m, 1H), 4.66–4.96 (m, 4H), 4.55 (AB q, $J = 11.4$ Hz, 2H), 4.37 (dd, $J = 2.3$, 10.2 Hz, 1H), 4.25 (t, $J = 2.4$ Hz, 1H), 4.08 (dt, $J = 1.5$, 5.5 Hz, 2H), 3.84 (AB q, $J = 9.3$ Hz, 2H), 3.44 (t, $J = 9.4$ Hz, 1H), 3.32 (dd, $J = 2.3$, 9.8 Hz, 1H), 2.43 (s, 1H, D_2O exchangeable), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.3, 136.3, 135.1, 131.1, 130.4, 126.3, 125.0, 124.8, 124.4, 124.2, 124.1, 113.5, 75.3, 74.0, 73.6, 73.3, 73.2, 71.9, 71.8, 71.6, 71.3, 68.1, 18.1. The racemic tosylate **27** was characterized as its acetate **29**: The racemic tosylate **27** (0.020 g, 0.03 mmol) was acetylated using acetic anhydride (0.04 mL, 0.46 mmol) and pyridine (0.7 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave the acetate **29** (0.021 g, 99%) as a gum. IR (neat, cm^{-1}) 3193–3520, 1747. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2H, $J = 8.4$ Hz), 7.02–7.54 (m, 17H), 5.82–6.01 (m, 1H), 5.29–5.41 (m, 1H), 5.19–5.28 (m, 1H), 4.80–5.06 (m, 4H), 4.56–4.65 (m, 1H), 4.32–4.46 (m, 4H), 4.14 (dt, $J = 1.5$, 5.5 Hz, 2H), 3.93 (AB q, $J = 9.9$ Hz, 2H), 3.44 (dd, $J = 2.2$, 9.6 Hz, 1H), 2.34 (s, 3H), 1.75 (s, 3H). Anal. Calcd for $C_{39}H_{42}O_9S.H_2O$; C, 66.46; H, 6.29. Found: C, 66.78; H, 6.04.

3.12.5. Allylation of racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol (11)

3.12.5.1. Procedure A (with butyllithium/allyl bromide). The racemic diol **11** (0.280 g, 0.52 mmol) in THF (3 mL) was allylated at 0 °C using butyllithium (0.41 mL, 0.57 mmol) and allyl bromide (0.082 g, 0.68 mmol) in DMF (0.8 mL) over 56 h as in the general procedure. The mixture of monoethers **32** and **33** (0.194 g, 65%) was separated by column chromatography using 10% ethyl acetate – light petroleum as eluent. This mixture (0.194 g) was acetylated using acetic anhydride (0.6 mL) in pyridine (2 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **34** and **35** (0.203 g). The ^{1}H NMR spectrum of the mixture showed that **34** and **35** were present in the ratio 4:1.

3.12.5.2. Procedure B (with sodiumhydride/allyl bromide). The racemic diol **11** (0.100 g, 0.19 mmol) in THF (1 mL) was allylated at 0 °C, using sodium hydride (0.008 g, 0.21 mmol) and a solution of allyl bromide (0.030 g, 0.25 mmol) in DMF (0.3 mL) as mentioned above. The reaction mixture was worked up with ethyl acetate and the mixture of monoethers (**32** and **33**, 0.083 g, 77%) was separated by column chromatography using 10% ethyl acetate–light petroleum as eluent. The mixture of monoethers (0.083 g) was acetylated using acetic anhydride (0.2 mL) and pyridine (1 mL) at room temperature overnight. Usual work-up of the reaction mixture with ethyl acetate gave the mixture of acetates (**34** and **35**, 0.086 g). The ^{1}H NMR spectrum of the mixture of acetates showed that **34** and **35** were present in the ratio 2:1.

3.12.6. Alkylation of racemic 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (12)

3.12.6.1. Procedure A. The racemic diol **12** (0.200 g, 0.37 mmol) was benzylated as in the general procedure (reaction time 26 h, −78 °C), using butyllithium (0.23 mL, 0.37 mmol) and benzyl bromide (0.076 g, 0.44 mmol) to obtain a mixture of pentabenzyl ethers **36**[57] and **37** (0.161 g, 69%) and hexa-*O*-benzyl-*myo*-inositol[57] (0.048 g, 18%). The mixture of pentaethers (0.040 g) was acetylated using acetic anhydride (0.03 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **40**[57] and **41** (0.041 g). The ^{1}H NMR spectrum of the mixture showed that **40** and **41** were present in the ratio 45:55.

3.12.6.2. Procedure B. The racemic diol **12** (0.100 g, 0.19 mmol) was benzylated as in the general procedure (reaction time 26 h, 0 °C–rt), using butyllithium (0.12 mL, 0.20 mmol) and benzyl bromide (0.076 g, 0.44 mmol) to obtain the mixture of pentabenzyl ethers **36** and **37** (0.084 g, 72%) and hexa-*O*-benzyl-*myo*-inositol (0.020 g, 15%). The mixture of pentaethers (0.050 g) was acetylated using acetic anhydride (0.04 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **40** and **41** (0.053 g). The ^{1}H NMR spectrum of the mixture showed that **40** and **41** were present in the ratio 52:48.

3.12.6.3. Procedure C. The racemic diol **12** (0.200 g, 0.37 mmol) was benzylated as in the general procedure (reaction time 26 h at reflux ~76 °C), using butyllithium (0.45 mL, 0.37 mmol, added at 0 °C) and benzyl bromide (0.076 g, 0.44 mmol, added at reflux temperature) to obtain a mixture of pentabenzyl ethers **36** and **37** (0.172 g, 74%) and hexa-*O*-benzyl-*myo*-inositol (0.051 g, 19%). The mixture of pentaethers (0.100 g) was acetylated using acetic anhydride (0.15 mL) and pyridine (2 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **40** and **41** (0.103 g). The ^{1}H NMR spectrum of the mixture showed that **40** and **41** were present in the ratio 71:29.

3.12.6.4. Procedure D. The racemic diol **12** (0.200 g, 0.37 mmol) was benzylated as in the general procedure (reaction time 26 h, 0 °C), using sodium hydride (0.015 g, 0.37 mmol) and benzyl bromide (0.076 g, 0.44 mmol) to obtain the mixture of pentabenzyl ethers **36** and **37** (0.177 g, 76%) and hexa-*O*-benzyl-*myo*-inositol (0.058 g, 22%). The mixture of pentaethers (0.100 g) was acetylated using acetic anhydride (0.15 mL) and pyridine (2 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave the mixture of acetates **40** and **41** (0.105 g). The ^{1}H NMR spectrum of the mixture showed that **40**[57] and **41** were present in the ratio 64:36.

3.12.6.5. Procedure E. The racemic diol **12** (0.150 g, 0.28 mmol) was allylated as in the general procedure (reaction time 20 h, 0 °C), using butyllithium (0.19 mL, 0.28 mmol) and allyl bromide (0.044 g, 0.36 mmol) to obtain a mixture of allyl ethers **38** and **39** (0.107 g, 66%). The mixture of allyl ethers (0.032 g) was acetylated using acetic anhydride (0.03 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **42** and **43** (0.034 g). The ^{1}H NMR spectrum of the mixture showed that **42** and **43** were present in the ratio 67:33.

3.12.7. Benzylation of 1,3,4,6-tetra-*O*-benzyl-*myo*-inositol (13)

The racemic diol **13** (0.075 g, 0.138 mmol) was benzylated as in the general procedure (reaction time 18 h, rt) using sodium hydride (0.006 g, 0.165 mmol) and benzyl bromide (0.0258 g, 0.151 mmol) to obtain a mixture of penta-*O*-benzyl *myo*-inositols **44** and **36** (0.051 g, 59%) as a colorless solid, the starting diol **13** (0.016 g, 22%), and hexa-*O*-benzyl-*myo*-inositol (0.011 g, 11%). The mixture of benzyl ethers (0.025 g) was acetylated using acetic anhydride (0.05 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **45** and **40**[57] (0.024 g). The ^{1}H NMR spectrum of the mixture showed that major product is **45** (~95%).

3.12.8. Benzylation of racemic 1,3,4,5 tetra-*O*-benzyl-*myo*-inositol (14) with sodium hydride and benzyl bromide

The racemic diol **14** (0.100 g, 0.19 mmol) was benzylated as in the general procedure (reaction time 16 h, rt) using sodium hydride (0.008 g, 0.20 mmol) and benzyl bromide (0.035 g, 0.20 mmol) to obtain a mixture of penta-*O*-benzyl *myo*-inositols **46**[55] and **36** (0.054 g, 47%) and the starting diol **14** (0.047 g, 47%). The mixture of benzyl ethers (0.020 g) was acetylated using acetic anhydride (0.04 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **47** and **40**[57] (0.021 g). The ^{1}H NMR spectrum of the mixture showed that major product is **47** (~95%).

3.12.9. Benzylation of racemic 1,3,4,5-tetra-*O*-methyl-*myo*-inositol (15) using sodium hydride and benzyl bromide

The racemic diol **15** (0.100 g, 0.42 mmol) was benzylated as in the general procedure (reaction time 24 h, rt) using sodium hydride (0.021 g, 0.50 mmol) and benzyl bromide (0.079 g, 0.46 mmol) to obtain a mixture of monobenzyl ethers **48** and **49** (0.083 g, 60%), the dibenzyl ether **25** (0.040 g, 23%), and the starting diol **15** (0.010 g, 10%). The mixture of benzyl ethers (0.035 g) was acetylated using acetic anhydride (0.05 mL) and pyridine (1 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **50** and **51** (0.034 g). The ^{1}H NMR spectrum of the mixture showed that **50** and **51** were present in the ratio 18:1. The acetate **50** was made from **48** (see below) for comparison with the NMR spectrum of the mixture of **50** and **51**.

3.12.10. Racemic 2-*O*-benzyl-1,3,4,5-tetra-*O*-methyl-*myo*-inositol (48)

A mixture of **25** (0.344 g, 0.82 mmol), 10% Pd/C (0.026 g), and ethyl acetate (5 mL), was stirred under hydrogen atmosphere at room temperature for 48 h. Analysis of the reaction mixture by TLC showed the presence of the starting material **25**. Excess of 10% Pd/C (0.050 g) and methanol (3 mL) were added and the mixture was stirred under hydrogen atmosphere at room temperature for another 3 h. The catalyst was removed by passing the reaction mixture through a bed of Celite. The filtrate was evaporated under reduced pressure and the residue was flash chromatographed on a column of silica gel to afford the monobenzyl ether **48** (0.130 g, 48%) as a gum (which turned into a solid on storing at room temperature) and the diol **15** (0.096 g, 49%) as a colorless solid. Data for **48**; mp 55–57 °C. IR (CHCl$_3$, cm^{-1}) 3250–3550 (OH). ^{1}H NMR (CDCl$_3$) δ 7.42–7.27 (m, 5H), 4.81 (AB q, J = 12 Hz, 2H), 4.12 (t, J = 2.2 Hz, 1H), 3.95 (t, J = 9.5 Hz, 1H), 3.64 (s, 3H), 3.62–3.54 (m, 4H, Ins H), 3.46 (s, 3H), 3.37 (s, 3H), 3.04–2.90 (m, 3H), 2.59 (bs, OH); ^{13}C NMR (CDCl$_3$) δ 138.8, 128.2, 127.7, 127.4, 84.84, 83.1, 83.0, 82.1, 74.0, 72.1, 71.5, 60.8, 60.7, 58.4, 57.7. Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.86; H, 8.34.

3.12.11. Allylation of racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol (16) with butyllithium/allyl bromide

The racemic diol **16** (0.200 g, 0.50 mmol) was allylated as in the general procedure (reaction time 52 h, 0 °C), using butyllithium (0.67 mL, 0.55 mmol) and allyl bromide (0.091 g, 0.75 mmol) to obtain a mixture of mono-allylethers **52** and **53** (0.166 g, 76%). The mixture of mono-allylethers (0.166 g) was acetylated using acetic anhydride (0.4 mL) and pyridine (3 mL) overnight at room temperature. Usual work-up of the reaction mixture with ethyl acetate gave a mixture of acetates **54** and **55** (0.181 g). The ^{1}H NMR spectrum of the mixture showed that **54** and **55** were present in the ratio 1:1.

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Supplementary data

Literature reports on O-alkylation of inositol derivatives involving alkali metal alkoxide, single crystal X-ray diffraction analysis data for compounds **13**–**15**, ^{1}H NMR spectra for the mixture of acetates obtained (by acetylation) from the products of O-alkylation reactions in Table 1 (for entries 2, 5–15) and rationale for their (isomeric acetate peaks) assignment. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.04.007.

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