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Inositol derived crown ethers: effect of auxiliary protecting groups and the relative orientation of crown ether oxygen atoms on their metal ion binding ability

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Abstract

The binding constants of crown ethers prepared from tetra-*O*-substituted *myo*- and *scyllo*-inositol derivatives and 2-*O*-substituted *myo*- and *scyllo*-inositol-1,3,5-orthoformates, with metal picrates show that the *O*-substituents and the relative orientation of the crown ether oxygen atoms contribute significantly to the binding of crown ethers with metal ions. In particular, the binding efficiency of *myo*-inositol derived crown ethers to silver and potassium ions could be enhanced by introducing benzyl ethers in the inositol ring. Hence binding efficacy and selectivity of metal ions to inositol derived crown ethers can be tuned by varying substituents on the *myo*-inositol ring and/or the relative orientation of crown ether oxygen atoms.

Keywords: Crown ether; Cyclitol; Inositol; Supramolecule; Ligand; Metal complex

1. Introduction

Due to a revival in interest in the chemistry of inositols over the last two decades, naturally occurring inositols and their derivatives have been explored as (i) starting materials for the synthesis of natural products and their analogs,[1] (ii) core molecules for the preparation of cation binding ligands,[2] (iii) chiral auxiliaries for asymmetric synthesis,[3] and (iv) for the study of chemical[4] and physical transformations[5] in single crystals. Although inositols and their derivatives have been known to form complexes[6] or suspected to chelate with metal ions[7] during reactions, inositol derived metal complexing agents were only synthesized and studied in the recent past.[2a,8] Central to these efforts is the availability of methods for the selective protection and deprotection of inositol hydroxyl groups.[9] Based on the selective reactions of hydroxyl groups exhibited by inositol derivatives, we had designed and synthesized *myo*-inositol based podands and crown ethers, which exhibited preferential binding to lithium, potassium, and silver ions.[10] In particular, the relative orientation of the crown-ether oxygen atoms in *myo*-inositol derived crown ethers appeared to play a significant role in their binding to metal picrates.[10b,c] The six secondary hydroxyl groups of inositols allow the construction of isomeric crown ethers as well as the introduction of pendant groups that can affect the binding of ions. It was interesting to see whether such a simple approach could be used to tune the binding of a particular metal ion to crown ethers derived from inositols. The continued interest in the tuning of metal ion binding ability of neutral complexing agents is mainly because of the various applications that they find in different areas of chemistry,[11] biology,[12] and medicine.[13] Various approaches[2,10,14] including crown ethers derived from cyclohexane diols and tetrols[15] for improving the complexation and transport of cations have earlier been attempted, with varying degrees of success. We herein present the synthesis and metal ion binding studies with *scyllo*-inositol

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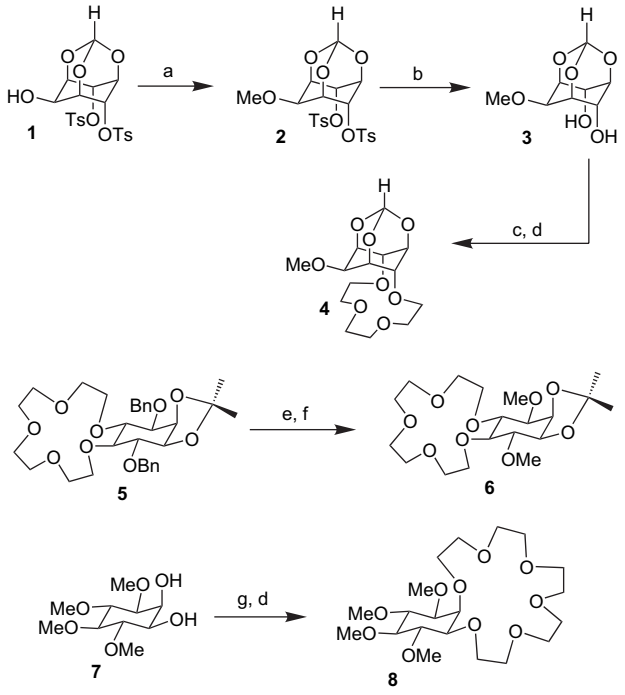
and *myo*-inositol derived crown ethers, which show that the efficiency of metal picrate binding is influenced by (i) the relative stereo-disposition of the inositol oxygen atoms involved in crown ether formation, (ii) substituents present on the oxygen atoms not involved in crown ether formation, and (iii) the relative disposition of the C2-substituent in inositol orthoester derived crown ethers.



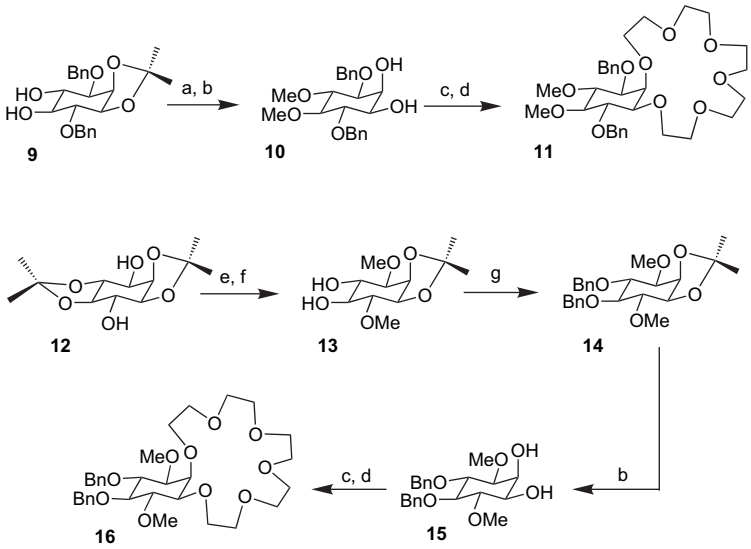
Scheme 1. Reagents and conditions: (a) DMF, NaH, MeI, rt, 10 min, 92%; (b) Mg/MeOH, rt, 3 h, 94%; (c) THF, NaH, $TsO(CH_2CH_2O)_3Ts$, reflux, 24 h; (d) MeOH, NaOMe, reflux, 12 h, 37% (over two steps); (e) MeOH, 10% Pd/C, H_2, rt, 3 h; (f) DMF, NaH, MeI, 0 °C to rt, 1 h, 52%; (g) THF, NaH, $TsO(CH_2CH_2O)_5Ts$, reflux, 24 h.

2. Results and discussion

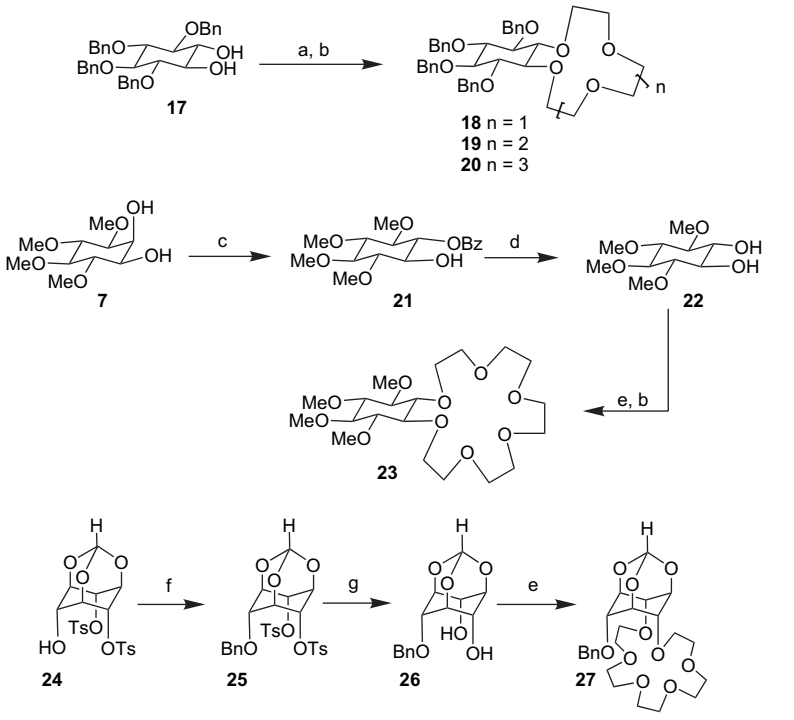
myo-Inositol derived crown ethers (**4**, **8**, **11**, and **16**)[16] having different relative orientation of the crown ether oxygen atoms and containing auxiliary methyl and benzyl ethers were prepared from suitably protected *myo*-inositol derivatives **1**, **7**, **9**, and **12**. The crown ether **6** was prepared from the previously reported *myo*-inositol derived crown ether **5**.[10b] The yield of the crown ether **6** from a reaction of the diol **13** and tetraethyleneglycol ditosylate was too low to be of practical value. Hence the di-*O*-benzyl crown ether **5** was converted to **6** by hydrogenolysis of the benzyl ethers followed by O-methylation (Scheme 1).

The crown ethers **11** and **16** (Scheme 2) were prepared from the diol **9**[17] and the diisopropylidene derivative **12**,[18] respectively. The crown ethers **11** and **16** were prepared to investigate the effect of the relative position of the benzyl groups in the binding of metal ions to *myo*-inositol derived crown ethers.

The *scyllo*-inositol derived crown ethers **18**, **19**, **20**, and **23** were prepared from the diols **17** and **7** as shown in Scheme 3. The *scyllo*-inositol orthoformate derived crown ether **27** was prepared from ditosylate **24**. During the preparation of most of the inositol derived crown ethers (Schemes 1–3) the product was contaminated with a considerable amount of the corresponding oligoethyleneglycol ditosylate used. The respective oligoethyleneglycol ditosylate could not be separated from the crown ethers by column chromatography. Hence, the crude crown ethers were refluxed with sodium methoxide in methanol to convert the unreacted oligoethyleneglycol ditosylate to the corresponding dimethyl ether, from which the crown ethers could be separated. Metal picrate extraction constants for all the crown ethers were estimated by Cram's method[19] (Tables 1 and 2).



Scheme 2. Reagents and conditions: (a) DMF, NaH, MeI, 0 °C to rt, 20 h, 87%; (b) acetic acid–water (4:1), 100 °C, 3 h, 82% (for **10**), 77% (for **15**); (c) THF, NaH, $TsO(CH_2CH_2O)_5Ts$, reflux, 24 h; (d) MeOH, NaOMe, reflux, 8–10 h, 68% (for **11**), 74% (for **16**); (e) DMF, NaH, MeI, 0 °C to rt, 30 min, 61%; (f) dichloromethane–MeOH (2:1), camphorsulphonic acid (cat), rt, 2.5 h, 87%; (g) DMF, NaH, BnBr, 0 °C to rt, 1 h, 53%.



Scheme 3. Reagents and conditions: (a) THF, NaH, $TsOCH_2CH_2OCH_2(CH_2OCH_2)_nCH_2OTs$, reflux, 24 h; (b) MeOH, NaOMe, reflux, 12 h, 14% (for **18**), 57% (for **19**), 75% (for **20**), 66% (for **23**) (over two steps); (c) benzene, PPh_3, C_6H_5COOH, DIAD, 3 Å molecular sieves, 80 °C, 16 h, 69%; (d) MeOH, NaOH, reflux, 2 h, 77%; (e) THF, NaH, $TsO(CH_2CH_2O)_5Ts$, reflux, 24 h, 53% (for **27**); (f) DMF, BnBr, NaH, rt, 10 min, 97%; (g) MeOH, NaOMe, reflux, 24 h, 97%.

Table 1
Association constants ($K_a\times10^{-4}$ dm^3 mol^{-1}) of *myo*-inositol derived crown ethers with metal picrates in $CDCl_3$ at 27 °C

Picrate	Crown				
	4	**6**	**8**	**11**	**16**
Li	16	290	1.8	9.7	8
Na	2.4	2.9	6.5	22	28
K	0.7	2.2	48	550	460
Cs	0.3	0.8	1.3	11	37
NH_4^+	0.1	0.6	22	139	933
Ag	0.2	4.6	63	286	348

Table 2
Association constants ($K_a\times10^{-4}$ dm^3 mol^{-1}) of *scyllo*-inositol derived crown ethers with metal picrates in $CDCl_3$ at 27 °C

Picrate	Crown				
	18	**19**	**20**	**23**	**27**
Li	33	13	6.3	5.4	17
Na	1.5	2.3	2.1	1.7	58
K	0.7	1.5	8.5	6.8	722
Cs	0.7	3.2	8.8	2	22
NH_4^+	0.8	1.6	86	1.6	193
Ag	10	12	1900	21	245

2.1. *myo*-Inositol derived crown ethers

The crown-6-ethers **8** and **11** showed better binding to potassium and silver picrate as expected, while crown ether **16** exhibited the highest binding with ammonium picrate. The dimethyl crown-5-ether **6** exhibited the highest binding constant for lithium picrate among the newly synthesized crown ethers. Calculation of the ratio of association constants (which reveals the magnitude of the preference of a crown ether for the binding of a particular metal ion) between different metal picrates, for binding to the same crown ether showed that highest selectivity is exhibited by crown ether **6** for the binding of lithium picrate ($K_{a(Li)}/K_{a(NH_4^+)}\approx490$, see Supplementary data) and the lowest selectivity was exhibited by crown ether **16** for the binding of potassium ($K_{a(K)}/K_{a(Ag)}\approx1$) and ammonium ($K_{a(NH_4^+)}/K_{a(K)}\approx2$) picrates. The lower range of selectivity exhibited by the crown ethers **11** and **16** (for the binding of metal picrates tested) as compared to crown ether **6** (most selective for lithium) could be due to the presence of benzyl ether groups in the former two crown ethers. The presence of aromatic rings in crown ethers is known to influence their selectivity toward the binding of metal picrates (*picrate effect*:[20] preferential extraction of metal picrates due to the presence of aromatic rings in crown ethers; however, see below).

A comparison of the metal picrate extraction constants of the tetramethyl crown ether **8** to the corresponding dibenzyl crown ethers **11** and **16** shows that the latter two crown ethers exhibit better binding of potassium, ammonium, and silver picrates. The extent of selectivity for these picrates is in general better in the case of dibenzyl crown ethers **11** and **16** than the selectivity exhibited by the tetramethyl crown ether **8**. However, selectivity between any two of potassium, ammonium, and silver picrates, exhibited by **11** and **16** is marginal. Furthermore, it is interesting to note that picrates of silver,

potassium, and ammonia bind better to the crown ethers **8**, **11**, and **16**, respectively (compared to other picrates tested for a given crown ether). If benzyl ethers were merely contributing to the binding of picrates due to *picrate effect*,[20] the dibenzyl ethers **11** and **16** should have exhibited worse selectivity for potassium and silver picrates as compared to the corresponding tetramethyl crown ether **8**. Hence these results clearly show that selective binding of metal picrates can be tuned by changing the protecting groups (methyl to benzyl) on the inositol hydroxyl groups.

The results discussed above prompted us to compare the metal picrate extraction characteristics of the crown ethers reported in the present study with those containing only benzyl groups (**28**, **29**, **32**) on the *myo*-inositol ring (Fig. 1).[10b,c] We had earlier determined the association constants for the binding of crown ethers **28**,[10c] **29**,[10b] and **32**[10b] to metal picrates (**28**: $K_{a(Li)}=2.72\times10^5$; $K_{a(K)}=6.9\times10^3$; $K_{a(NH_4^+)}=2.1\times10^3$; $K_{a(Ag)}=9\times10^3$; **29**: $K_{a(Li)}=9.57\times10^4$; $K_{a(K)}=2.59\times10^4$; $K_{a(NH_4^+)}=8.1\times10^3$; $K_{a(Ag)}=3.42\times10^5$; **32**: $K_{a(K)}=3.52\times10^8$; $K_{a(Cs)}=1.18\times10^5$; $K_{a(Ag)}=4.95\times10^{10}$ dm^3 mol^{-1}). A comparison of the ratios (see Supplementary data) of picrate extraction constants between crown ethers with methyl groups (**4**, **6**, **8**) and the corresponding crown ether with benzyl groups (**28**, **29**, **32**) showed that benzyl ethers contribute significantly to the binding of potassium and silver picrates, especially in the crown-6-ether **32**. It is known that olefinic[14u,21] and aromatic[14e] π-electron systems contribute significantly to the formation of silver complexes and, binding of potassium to calixarene[14h] derived crown ethers is enhanced by aromatic groups, near the crown ether moiety. Although all the *myo*-inositol derived crown ethers containing benzyl groups bind metal picrates better than the corresponding crown ethers containing methyl ethers, an unusually high ratio of association constants is exhibited for the binding of silver picrate ($K_{a(\mathbf{32})}/K_{a(\mathbf{8})}\approx78{,}500$), followed by potassium picrate ($K_{a(\mathbf{32})}/K_{a(\mathbf{8})}\approx730$). If the contribution of benzyl ethers to the binding of metal picrates was only due to *picrate effect*,[20] then the ratio of binding constants for silver picrate between the crown ethers (as above) should have been comparable to that of other picrates.

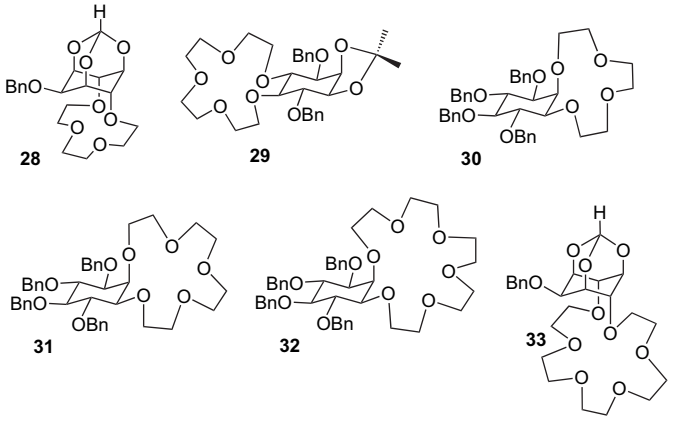


Figure 1. *myo*-Inositol derived crown ethers containing auxiliary benzyl ethers.[10b,c]

We also calculated the ratio of extraction constants between lithium picrate and other picrates for crown-4 and crown-5-ethers and similar ratios for the extraction of potassium and silver picrates for crown-6-ethers, since these ethers exhibited the highest binding constants for lithium, potassium, and silver picrates. A comparison of these values for a given crown ether containing methyl/benzyl protecting groups was interesting (also see Supplementary data). The extent of the picrate effect was revealed by the selectivity of metal picrate binding exhibited by methyl crown ethers as compared to benzyl crown ethers. For example, the selectivity for the binding of lithium picrate to the methyl crown-4-ether **4** was $K_{a(Li)}/K_{a(NH_4^+)}=160$, while the corresponding value for the benzyl crown **28** was $K_{a(Li)}/K_{a(NH_4^+)}=130$. Similarly, the highest selectivity for the binding of lithium picrate to the methyl crown-5-ether **6** observed was $K_{a(Li)}/K_{a(NH_4^+)}=490$, while the corresponding value for the benzyl crown **29** was $K_{a(Li)}/K_{a(NH_4^+)}=12$. In contrast, the selectivity for the binding of potassium and silver picrates to the methyl crown-6-ether **8** were $K_{a(K)}/K_{a(Cs)}=37$ and $K_{a(Ag)}/K_{a(Cs)}=48$, respectively, while the corresponding values for the benzyl crown **32** were $K_{a(K)}/K_{a(Cs)}=2980$ and $K_{a(Ag)}/K_{a(Cs)}=4.2\times10^5$. In the former crown ethers (**4** vs **28** and **6** vs **29**) this result is in accordance with the *picrate effect*[20] (reduction in selectivity due to the presence of aromatic groups in crown ethers) reducing the selectivity among metal picrates. However, for the crown-6-ethers (**8** vs **32**) the selectivity pattern is the opposite to that expected for the *picrate effect*.[20] Hence these results also reveal that the selectivity for the binding of metal ions to *myo*-inositol derived crown ethers could be tuned by varying the auxiliary groups on the inositol ring. These results clearly show that the benzyl groups in *myo*-inositol derived crown-6-ether **32** are indeed necessary for the better binding of K^+ and Ag^+ ions.

A comparison of the binding constants for the isomeric crown ethers **11** and **16** with metal picrates reveals that the relative positions of the benzyl groups in crown-6-ethers does not have much bearing on their metal picrate binding abilities. However, the ratio of metal picrate binding constants for dibenzyl crowns (**11**, **16**) and tetramethyl crown ether **8** shows that the presence of two benzyl groups in the former increases their binding to metal picrates. Similarly, the ratio of the binding constants for tetrabenzyl crown-6-ether **32** to the corresponding dibenzyl crowns (**11**, **16**) shows that the binding of potassium and silver picrates increases dramatically due to the presence of two additional benzyl groups ($K_{a(\mathbf{32})}/K_{a(\mathbf{11})}\approx17{,}000$ and $K_{a(\mathbf{32})}/K_{a(\mathbf{16})}\approx14{,}100$ for the binding of silver picrate). These results suggest that benzyl protecting groups in *myo*-inositol derived crown ethers interact with cations[14e,v,21] rather than enhancing the binding of metal picrates by merely interacting with picrate ions. It is likely that the unusually large binding of tetrabenzyl crown-6-ether **32** with silver picrate observed could be due to co-operative binding between silver picrate and crown ethers rather than the formation of 1:1 complexes. This is schematically represented in Figure 2. The results presented so far clearly suggest that the binding and selectivity of *myo*-inositol derived crown ethers to metal picrates depend on the auxiliary groups present on the *myo*-inositol ring.

Figure 2. Co-operative binding between silver picrate and *myo*-inositol derived crown ethers containing benzyl groups.

2.2. *scyllo*-Inositol derived crown ethers

Among the newly synthesized crown ethers, crown-4-ether **18** showed the highest binding to lithium picrate, while the crown-6-ether **20** showed the highest binding to silver picrate and the crown-6-ether **27** showed the highest binding to potassium picrate. The ratio of association constants for the binding of picrates to a given crown ether, revealed the selectivity exhibited by that crown ether. The crown-4-ether **18** was more selective for lithium picrate as expected ($K_{a(Li)}/K_{a(K)} \approx 47$; $K_{a(Li)}/K_{a(Na)} \approx 22$); the crown-5-ether **19** was also selective for lithium picrate, but the extent was much less ($K_{a(Li)}/K_{a(K)} \approx 9$; $K_{a(Li)}/K_{a(Na)} \approx 6$); the crown-6-ether **20** was selective for silver picrate ($K_{a(Ag)}/K_{a(Li)} \approx 300$; $K_{a(Ag)}/K_{a(Na)} \approx 900$; $K_{a(Ag)}/K_{a(K)} \approx 220$). On the other hand the crown-6-ether **23** was marginally selective for silver ($K_{a(Ag)}/K_{a(K)} \approx 3$; $K_{a(Ag)}/K_{a(Na)} \approx 12$). The crown-6-ether **23** exhibited almost no selectivity for potassium ($K_{a(K)}/K_{a(Li)} \approx 1$; $K_{a(K)}/K_{a(Na)} \approx 4$; $K_{a(K)}/K_{a(Cs)} \approx 3$) whereas the diaxial crown-6-ether **27** showed better selectivity for potassium ($K_{a(K)}/K_{a(Li)} \approx 42$; $K_{a(K)}/K_{a(Na)} \approx 12$; $K_{a(K)}/K_{a(Cs)} \approx 33$).

A comparison of the ratio of association constants between the crown-6 ethers **20** and **23** showed that the presence of benzyl groups in *scyllo*-inositol derived crown-6 ether aides the binding of ammonium and silver picrates ($K_{a(\mathbf{20})}/K_{a(\mathbf{23})} \approx 54$ and 90 for the extraction of ammonium picrate and silver picrate, respectively). A comparison of the selectivities exhibited by these crown ethers shows that the presence of methyl groups in *scyllo*-1,2-crown ethers makes the crown ether marginally selective for potassium picrate, while the presence of benzyl groups enhances the selectivity for the binding of silver picrate. In particular, for selectivity between Ag^+ and K^+, which have more or less same ionic radii, the benzyl crown-6-ether **20** is much more selective for silver ($K_{a(Ag)}/K_{a(K)} \approx 220$) as compared to the methyl crown-6-ether **23** ($K_{a(Ag)}/K_{a(K)} \approx 3$).

2.3. *scyllo*-Inositol derived crown ethers versus *myo*-inositol derived crown ethers

It is of interest to compare the picrate extraction constants of *scyllo*-crown ethers with the corresponding *myo*-crown ethers as this gives an indication of the effect of the relative stereochemical disposition of the two of the oxygen atoms in the inositol derived crown ethers or the effect of an auxiliary C2-oxygen atom in the inositol orthoester derived crown ethers. The *scyllo*-crown ethers **18**, **19**, **20**, **23** and the *myo*-crown ethers **30**, **31**, **32**, **8** only differ in the disposition of the C2-oxygen, which is axial in *myo*-inositol derived crown ethers and equatorial in *scyllo*-inositol derived crown ethers. In orthoesters **33** and **27** although the *myo*-crown ethers as well as the *scyllo*-crown ethers have two axial oxygen atoms that form the crown ether, the C2-oxygen in the former is *anti*- with respect to the crown ether moiety but *syn*- in the latter. These differences appear to considerably influence the metal picrate extraction ability of these molecules. A comparison of the metal picrate extraction constants shows that by and large *myo*-inositol derived crown ethers extract metal picrates better than the corresponding *scyllo*-inositol derived crown ethers. But, in orthoester based crown ethers, the *scyllo*-crown ether appears to be slightly better for the extraction of metal picrates (except for potassium picrate). This variation in the stereochemical disposition of one oxygen atom in the inositol ring has a very large effect for the extraction of potassium ($K_{a(\mathbf{32})}/K_{a(\mathbf{20})} \approx 4100$) and silver picrate ($K_{a(\mathbf{31})}/K_{a(\mathbf{19})} \approx 2300$; $K_{a(\mathbf{32})}/K_{a(\mathbf{20})} \approx 2600$). It is interesting to note that although the *myo*-crown-6-ether **32** exhibits a very high binding constant with silver picrate, the extent to which the picrate binding is affected due to change in stereochemistry from *myo*- to *scyllo*-configuration matters more for the binding of potassium than silver. For other cations tested, the change in stereochemistry does not have as big an influence on their binding to crown ethers.

A comparison of the picrate binding constants of the *myo*- and the corresponding *scyllo*-crown ethers also reveals that the enhanced binding observed for picrates of sodium, potassium, and silver, to *myo*-crown ethers **31** and **32**, is mainly due to the change in the disposition of one of the oxygen atoms of the inositol ring. If the enhanced picrate extraction was mainly due to the presence of aromatic rings in the crown ether (*picrate effect*[20]), *scyllo*-crown ethers should have exhibited comparable binding constants to those of *myo*-inositol crown ethers, since all the crown ethers possess four benzyl groups. This is further supported by a comparison of the picrate extraction constants of **8** and **23**; the *myo*-crown ether **8** shows better binding for sodium, potassium, ammonium, and silver picrates as compared to the *scyllo*-crown ether **23**. As mentioned earlier, binding of *myo*-inositol crown ethers (such as **8**) to metal picrates could be enhanced by replacing the methyl groups with benzyl groups. Although this effect is seen for *scyllo*-derived crown-6-ether also, the extent of increase is much smaller (*scyllo* $K_{a(\mathbf{20})}/K_{a(\mathbf{23})} \approx 1$ and *myo* $K_{a(\mathbf{32})}/K_{a(\mathbf{8})} \approx 730$ for potassium picrate; *scyllo* $K_{a(\mathbf{20})}/K_{a(\mathbf{23})} \approx 90$ and *myo* $K_{a(\mathbf{32})}/K_{a(\mathbf{8})} \approx 78{,}500$ for silver picrate).

3. Conclusion

The metal picrate binding ability of inositol derived crown ethers varies depending on the relative orientation of crown ether oxygen atoms. The extent of metal ion binding to the inositol derived crown ethers can be tuned by changing the auxiliary protecting groups on the hydroxyl groups not involved in crown ether formation. Further, the results suggest that the efficiency of metal picrate binding is a result of a concerted effect of all these factors rather than primarily due to one factor, which enhances metal picrate binding. Binding of inositol-based crown ethers to silver can be enhanced without

the introduction of any soft ligating sites such as sulfur or nitrogen. Due to the presence of six hydroxyl groups in inositols, the hydroxyl groups unutilized for the construction of crown ethers can be derivatized to modulate the binding efficiency of cations to crown ethers. We are currently investigating the possibility of such fine tuning of cyclitol derived crown ethers for the selective binding of other metal ions.

4. Experimental section

4.1. General methods

All the solvents used were purified according to literature procedures.[22] Sodium hydride used in experiments was 60% suspension in mineral oil and it was washed with dry petroleum ether prior to use. All air or moisture sensitive reactions were conducted under argon or nitrogen atmosphere. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} aluminum plates and the spots were rendered visible either by shining UV light or by charring the plates with chromic acid. Flash column chromatography was carried out on silica gel (230–400 mesh). Compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with the reported data. IR spectra were recorded in $CHCl_3$ solution or in Nujol or as thin film (neat) on a Shimadzu FTIR-8400 spectrophotometer. NMR spectra were recorded in $CDCl_3$ solutions on Bruker AV200 spectrometer unless otherwise mentioned and chemical shifts (δ) reported are referred to TMS as an internal standard. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Büchi B-540 electro-thermal melting point apparatus and are uncorrected. Yields refer to chromatographically and spectroscopically pure compounds. Procedures for the preparation of crown ethers and estimation of their binding constants (with metal picrates) were as reported earlier.[10b,c]

4.1.1. 2-O-Methyl-4,6-di-O-tosyl-myo-inositol 1,3,5-orthoformate (2)

A mixture of ditosylate **1**,[23] (3.05 g, 6.11 mmol), sodium hydride (0.488 g, 12.20 mmol), in dry DMF (10 mL) was stirred for 5 min and methyl iodide (1.14 mL, 18.31 mmol) was added and stirring continued for another 5 min. The reaction was quenched by the addition of ice and the solvents were evaporated under reduced pressure. Usual workup of the residue with dichloromethane, followed by column chromatography (eluent: 20% ethyl acetate in light petroleum) gave the methyl ether **2** (2.88 g, 92%) as a white solid. R_f=0.2 (25% ethyl acetate in light petroleum); mp 138–140 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ=2.46 (s, 6H; $ArCH_3$), 3.40 (s, 3H; OCH_3), 3.57–3.65 (m, 1H; Ins-H), 4.12–4.22 (m, 1H; Ins-H), 4.25–4.35 (m, 2H; Ins-H), 5.09 (t, J=3.9 Hz, 2H; Ins-H), 5.42 (d, J=1.0 Hz, 1H; HCO_3), 7.37 (d, J=8.3 Hz, 4H; Ar-H), 7.83 (d, J=8.8 Hz, 4H; Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=21.5 ($ArCH_3$), 56.8 (OCH_3), 67.1 (Ins-C), 67.4 (Ins-C), 68.5 (Ins-C), 71.6 (Ins-C), 102.5 (HCO_3), 127.8 (Ar-C), 130.0 (Ar-C), 132.4 (Ar-C), 145.7 (Ar-C). Anal. Calcd for $C_{22}H_{24}O_{10}S_2$: C, 51.55; H, 4.72; S, 12.51. Found: C, 51.76; H, 4.95; S, 12.14%.

4.1.2. 2-O-Methyl-myo-inositol 1,3,5-orthoformate (3)

The ditosylate **2** (4.8 g, 9.35 mmol) was dissolved in a mixture of dry methanol (90 mL) and dry THF (30 mL). Magnesium turnings (3.40 g) were added and the mixture was stirred at room temperature for 3 h. Silica gel was added to the reaction mixture and the solvent was evaporated under reduced pressure. The diol **3** (1.80 g, 94%) was isolated by flash column chromatography of this residue (eluent: 30% light petroleum in ethyl acetate) as a white solid. R_f=0.6 (70% light petroleum in ethyl acetate); mp 173–175 °C; ^{1}H NMR (200 MHz; DMSO-d_6): δ=3.35 (s, 3H; OCH_3), 3.65–3.70 (m, 1H; Ins-H), 4.00–4.10 (m, 1H; Ins-H), 4.10–4.20 (m, 2H; Ins-H), 4.25–4.40 (m, 2H; Ins-H), 5.44 (s, 1H; HCO_3), 5.50 (d, J=6 Hz, 2H; OH, D_2O Exchangeable); ^{13}C NMR (50.3 MHz, DMSO-d_6): δ=56.0 (OCH_3), 67.5 (Ins-C), 68.4 (Ins-C), 69.7 (Ins-C), 71.3 (Ins-C), 102.1 (HCO_3); IR (Nujol): ν_{max}=3323, 3523 cm^{-1}. Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 46.91; H, 5.90%.

4.1.3. 2-O-Methyl-4,6-(13-crown-4)-myo-inositol 1,3,5-orthoformate (4)

The diol **3** (0.204 g, 1.00 mmol), sodium hydride (0.16 g, 4.00 mmol), triethyleneglycol ditosylate (0.596 g, 1.30 mmol), and dry THF (100 mL) were used to prepare the crown ether **4** as reported earlier[10b,c] and was isolated as a pale yellow gum (0.108 g, 37%) by column chromatography (eluent: 35% ethyl acetate in light petroleum). R_f=0.1 (35% ethyl acetate in light petroleum); ^{1}H NMR (200 MHz; $CDCl_3$): δ=3.53 (s, 3H; OCH_3), 3.58–3.81 (m, 12H; OCH_2CH_2O), 3.85 (dd, J_1=7 Hz, J_2=2 Hz, 1H; Ins-H), 4.25 (t, J=4 Hz, 2H; Ins-H), 4.31–4.41 (m, 2H; Ins-H), 4.49–4.60 (m, 1H; Ins-H), 5.52 (s, 1H; HCO_3); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=56.4 (OCH_3), 67.4 (Ins-C), 69.1 (Ins-C), 69.5 (CH_2), 69.6 (Ins-C), 70.2 (CH_2), 70.7 (CH_2), 74.4 (Ins-C), 103 (HCO_3); IR (Neat): ν_{max}=3390–3640 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_8\cdot 2H_2O$: C, 47.45; H, 7.39. Found: C, 47.85; H, 7.13%.

4.1.4. Racemic 1,2-O-isopropylidene-3,6-di-O-methyl-4,5-(15-crown-5)-myo-inositol (6)

A mixture of racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-4,5-(15-crown-5)-*myo*-inositol[10b] (**5**, 0.136 g, 0.24 mmol) and 10% Pd/C (0.040 g) in methanol (7 mL) was stirred at room temperature, under hydrogen atmosphere for 3 h. The reaction mixture was filtered and the filtrate was concentrated on rotary evaporator to get the corresponding crude diol as a gum (0.087 g, 95%). This experiment was repeated to get more of the crude diol, which was further methylated. A mixture of the diol (0.188 g, 0.49 mmol) obtained above, sodium hydride (0.080 g, 2.00 mmol), and DMF (4 mL) was stirred for 10 min at 0–5 °C and then a solution of methyl iodide (0.31 mL, 5.00 mmol) in DMF (1 mL) was added dropwise. The reaction mixture was allowed to come to room temperature and stirred for further 1 h. Excess sodium hydride was destroyed by the

addition of methanol (1 mL) and the reaction mixture was concentrated under reduced pressure to a semi-solid. This was dissolved in chloroform (80 mL), washed with water (20 mL×3) followed by brine, and the organic layer was dried over anhyd sodium sulfate and the solvent was removed under reduced pressure to get a gum. This was purified by flash column chromatography (eluent: 35% ethyl acetate in light petroleum) to get the crown ether **6** as a gum (0.105 g, 52%), which turned to a colorless solid on storing in a refrigerator. R_f=0.2 (35% ethyl acetate in light petroleum); mp 57 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ=1.36 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 3.10 (t, J=9 Hz, 1H; Ins-H), 3.33–3.43 (m, 2H; Ins-H), 3.54 (s, 3H; OCH_3), 3.57 (s, 3H; OCH_3), 3.60–4.03 (m, 18H; 2 Ins-H and OCH_2CH_2O), 4.39 (dd, J_1=5 Hz, J_2=4 Hz, 1H; Ins-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=25.8 (CH_3), 27.7 (CH_3), 59.0 (OCH_3), 60.1 (OCH_3), 70.3 (CH_2), 70.4 (CH_2), 70.6 (CH_2), 71.09 (CH_2), 71.11 (CH_2), 72.2 (CH_2), 72.3 (CH_2), 73.6 (Ins-C), 78.6 (Ins-C), 79.5 (Ins-C), 80.8 (Ins-C), 82.5 (Ins-C), 84.4 (Ins-C), 109.7 (CMe_2); IR (Neat): ν_{max}=3400–3600 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_9\cdot 0.75H_2O$: C, 54.33; H, 8.52. Found: C, 54.39; H, 8.27%. A small amount (0.07 g, 38%) of 1,4-di-*O*-methyl-5,6-(15-crown-5)-*myo*-inositol was also obtained (as revealed by ^{1}H NMR spectrum) but it was not characterized completely.

4.1.5. Racemic 1,4,5,6-tetra-O-methyl-myo-inositol (7)

The racemic tetramethyl ether **7** was prepared as reported earlier[24] except that sodium hydride was used instead of silver(I) oxide for the O-methylation of racemic 1,2-*O*-isopropylidene-*myo*-inositol. The product was crystallized from ethyl acetate–light petroleum, to give colorless needles, mp 105–106 °C (lit[24] mp 102–104 °C); ^{1}H NMR (500 MHz; $CDCl_3$): δ=2.56 (s, 1H; OH, D_2O exchangeable), 2.68 (s, 1H; OH, D_2O exchangeable), 3.0 (t, J=9 Hz, 1H; Ins-H), 3.05 (dd, J_1=7 Hz, J_2=3 Hz, 1H; Ins-H), 3.34–3.42 (m, 2H; Ins-H), 3.45 (t, J=9 Hz, 1H; Ins-H), 3.50 (s, 3H; OCH_3), 3.61 (s, 3H; OCH_3), 3.62 (s, 3H; OCH_3), 3.65 (s, 3H; OCH_3), 4.20–4.25 (m, 1H; Ins-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=58.1 (OCH_3), 60.5 (OCH_3), 60.8 (OCH_3), 68.4 (Ins-C), 71.2 (Ins-C), 81.6 (Ins-C), 82.6 (Ins-C), 82.8 (Ins-C), 85.1 (Ins-C); IR ($CHCl_3$): ν_{max}=3210–3600 cm^{-1}.

4.1.6. Racemic 1,2-(18-crown-6)-3,4,5,6-tetra-O-methyl-myo-inositol (8)

The diol **7** (0.236 g, 1.00 mmol), sodium hydride (0.16 g, 4.00 mmol), pentaethyleneglycol ditosylate (0.710 g, 1.30 mmol), and dry THF (100 mL) were used to prepare the crown ether **8**, which was isolated as a gum (0.163 g, 37%) after flash column chromatography (eluent: 3% methanol in dichloromethane). R_f=0.4 (5% methanol in chloroform); ^{1}H NMR (200 MHz; $CDCl_3$): δ=2.85–2.98 (m, 2H; Ins-H), 3.05 (dd, J_1=10 Hz, J_2=2 Hz, 1H; Ins-H), 3.35–3.85 (m, 32H; OCH_3, OCH_2CH_2O), 3.97 (t, J=6 Hz, 2H; Ins-H), 4.07 (t, J=3 Hz, 1H; Ins-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=57.9 (OCH_3), 58.7 (OCH_3), 60.5 (OCH_3), 70.2 (CH_2), 70.6 (CH_2), 71.4 (CH_2), 71.6 (CH_2), 74.1 (Ins-C), 81.2 (Ins-C), 82.0 (Ins-C), 82.6 (Ins-C), 82.7 (Ins-C), 85.3 (Ins-C); IR (Neat): ν_{max}=3200–3650 cm^{-1}. Anal. Calcd for $C_{20}H_{38}O_{10}\cdot H_2O$: C, 52.61; H, 8.83. Found: C, 52.66; H, 8.73%.

4.1.7. Racemic 1,4-di-O-benzyl-5,6-di-O-methyl-myo-inositol (10)

Racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol[17] (**9**, 0.8 g, 2.00 mmol), sodium hydride (0.32 g, 8.00 mmol), and DMF (8 mL) were stirred at 0–5 °C under nitrogen atmosphere for a few minutes. Then methyl iodide (0.74 mL, 12.00 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature and stirred for further 20 h. The reaction was quenched by adding methanol (0.5 mL); DMF was removed under reduced pressure to get a solid. This solid was dissolved in dichloromethane (200 mL), washed with water (50 mL×3) followed by brine and the organic layer dried over anhyd sodium sulfate. The solvent was removed under reduced pressure; the residue was purified by column chromatography (eluent: 15% ethyl acetate in light petroleum) to get racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-4,5-di-*O*-methyl-*myo*-inositol as a gum (0.753 g, 87%). R_f=0.5 (25% ethyl acetate in light petroleum); ^{1}H NMR (200 MHz; $CDCl_3$): δ=1.35 (s, 3H; CH_3), 1.50 (s, 3H; CH_3), 3.01–3.14 (m, 1H; Ins-H), 3.51–3.59 (m, 2H; Ins-H), 3.59 (s, 3H; OCH_3), 3.62 (s, 3H; OCH_3), 3.68 (dd, J_1=2 Hz, J_2=1 Hz, 1H; Ins-H), 4.07 (t, J=6 Hz, 1H; Ins-H), 4.24 (dd, J_1=6 Hz, J_2=3 Hz, 1H; Ins-H), 4.70–4.90 (m, 4H; CH_2Ph), 7.30–7.50 (m, 10H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=25.4 (CH_3), 27.3 (CH_3), 60.1 (OCH_3), 72.9 (CH_2Ph), 73.4 (CH_2Ph), 74.3 (Ins-C), 76.3 (Ins-C), 78.4 (Ins-C), 81.6 (Ins-C), 82.3 (Ins-C), 83.9 (Ins-C), 109.4 (CMe_2) 127.2 (Ar-C), 127.5 (Ar-C), 127.6 (Ar-C), 128.0 (Ar-C), 128.1 (Ar-C), 138.1 (Ar-C), 138.3 (Ar-C). 1,2-*O*-Isopropylidene-3,6-di-*O*-benzyl-4,5-di-*O*-methyl-*myo*-inositol (0.720 g, 1.68 mmol) obtained above was dissolved in acetic acid–water (4:1, 10 mL) and stirred at 100 °C for 3 h. The solution obtained was cooled to ambient temperature and evaporated at reduced pressure to get a gum. Co-evaporation of the gum with dry benzene (10 mL×3) gave **10** as a white solid (0.538 g, 82%), mp 109–111 °C; crystallization from dichloromethane–light petroleum gave colorless needles, mp 111–112 °C. ^{1}H NMR (200 MHz; $CDCl_3$): δ=2.51 (br s, 2H; OH, D_2O exchangeable), 3.09 (t, J=9 Hz, 1H; Ins-H), 3.31 (dd, J_1=10 Hz, J_2=3 Hz, 1H; Ins-H), 3.41 (dd, J_1=10 Hz, J_2=3 Hz, 1H; Ins-H), 3.58 (t, J=9 Hz, 1H; Ins-H), 3.67 (s, 3H; OCH_3), 3.68 (s, 3H; OCH_3), 3.69–3.76 (m, 1H; Ins-H), 4.16 (t, J=3 Hz, 1H; Ins-H), 4.65–5.10 (m, 4H; CH_2Ph), 7.25–7.45 (m, 10H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=60.9 (OCH_3), 61.1 (OCH_3), 69.3 (Ins-C), 71.4 (Ins-C), 72.5 (CH_2Ph), 75.2 (CH_2Ph), 79.5 (Ins-C), 81.1 (Ins-C), 83.4 (Ins-C), 85.2 (Ins-C), 127.6 (Ar-C), 127.7 (Ar-C), 127.9 (Ar-C), 128.37 (Ar-C), 128.39 (Ar-C), 137.9 (Ar-C), 138.6 (Ar-C); IR ($CHCl_3$): ν_{max}=3220–3568 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 68.16; H, 7.27%.

4.1.8. Racemic 1,2-(18-crown-6)-3,6-di-O-benzyl-4,5-di-O-methyl-myo-inositol (11)

The racemic diol **10** (0.200 g, 0.51 mmol), sodium hydride (0.124 g, 3.07 mmol), pentaethyleneglycol ditosylate (0.365 g,

0.67 mmol), and dry THF (75 mL) were used to prepare the crown ether **11**, which was isolated as a gum (0.207 g, 68%) after column chromatography (eluent: 30% ethyl acetate in light petroleum). R_f=0.3 (35% ethyl acetate in light petroleum); ^{1}H NMR (200 MHz; $CDCl_3$): δ=3.04 (t, J=9 Hz, 1H; Ins-H), 3.12 (dd, J_1=10 Hz, J_2=2 Hz, 1H; Ins-H), 3.19 (dd, J_1=10 Hz, J_2=2 Hz, 1H; Ins-H), 3.50–3.85 (m, 26H; OCH_3, OCH_2CH_2O), 3.92 (t, J=5 Hz, 1H; Ins-H), 4.00 (dd, J_1=5 Hz, J_2=4 Hz, 1H; Ins-H), 4.06 (t, J=2 Hz, 1H; Ins-H), 4.55–4.95 (m, 4H; CH_2Ph), 7.25–7.45 (m, 10H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=60.8 (OCH_3), 60.9 (OCH_3), 70.31 (CH_2), 70.37 (CH_2), 70.38 (CH_2), 70.42 (CH_2), 70.43 (CH_2), 70.55 (CH_2), 70.61 (CH_2), 70.63 (CH_2), 70.66 (CH_2), 71.8 (CH_2), 72.4 (CH_2), 75.28 (Ins-C), 75.3 (CH_2), 80.2 (Ins-C), 81.2 (Ins-C), 83.2 (Ins-C), 85.4 (Ins-C), 127.2 (Ar-C), 127.3 (Ar-C), 127.8 (Ar-C), 128.0 (Ar-C), 128.1 (Ar-C), 138.4 (Ar-C), 139.0 (Ar-C); IR ($CHCl_3$): ν_{max}=3300–3500 cm^{-1}. Anal. Calcd for $C_{32}H_{46}O_{10}\cdot H_2O$: C, 63.14; H, 7.94. Found: C, 63.35; H, 8.03%.

4.1.9. Racemic 1,2-O-isopropylidene-3,6-di-O-methyl-myo-inositol (*13*)

A mixture of racemic 1,2:4,5-diisopropylidene-*myo*-inositol[18] (**12**, 3.161 g, 12.15 mmol), sodium hydride (1.94 g, 48.63 mmol), and DMF (28 mL) was stirred at 0–5 °C for 10 min under nitrogen atmosphere, then methyl iodide (3 mL, 48.63 mmol) was added. The reaction mixture was allowed to come to room temperature and stirred for 30 min. Excess sodium hydride was destroyed by the addition of methanol (0.5 mL) and solvent was evaporated under reduced pressure to obtain a solid. The solid was dissolved in dichloromethane (200 mL), washed with water (50 mL×3) and brine. Organic layer was dried over anhyd sodium sulfate, and solvent was removed under reduced pressure to obtain crude 1,2:4,5-di-*O*-isopropylidene-3,6-di-*O*-methyl-*myo*-inositol. The crude dimethyl ether, on filtration through a column of silica gel (eluent: 20% ethyl acetate in light petroleum), gave the dimethyl ether as a white solid (2.136 g, 61%), mp 81–83 °C. Crystallization from dichloromethane–light petroleum, gave colorless crystals. R_f=0.4 (25% ethyl acetate in light petroleum); mp 83 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ=1.33 (s, 3H; CH_3), 1.39 (s, 3H; CH_3), 1.41 (s, 3H; CH_3), 1.52 (s, 3H; CH_3), 3.27 (dd, J_1=10 Hz, J_2=9 Hz, 1H; Ins-H), 3.40–3.50 (m, 1H; Ins-H), 3.52 (s, 6H; OCH_3), 3.59 (dd, J_1=10 Hz, J_2=4 Hz, 1H; Ins-H), 3.80–3.95 (m, 1H; Ins-H), 4.00–4.13 (m, 1H; Ins-H), 4.50 (t, J=5 Hz, 1H; Ins-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=25.3 (CH_3), 26.4 (CH_3), 27.5 (CH_3), 57.4 (OCH_3), 58.2 (OCH_3), 75.1 (Ins-C), 76.2 (Ins-C), 77.7 (Ins-C), 80.7 (Ins-C), 82.3 (Ins-C), 109.3 (CMe_2), 111.5 (CMe_2). The racemic 1,2:4,5-di-*O*-isopropylidene-3,6-di-*O*-methyl-*myo*-inositol (0.576 g, 2.00 mmol) obtained above was dissolved in dry dichloromethane–methanol (2:1, 15 mL) and was stirred in the presence of catalytic amount of camphorsulfonic acid for 2.5 h at room temperature under nitrogen atmosphere. The reaction was quenched by the addition of triethylamine (2 mL). The solvent was evaporated under reduced pressure to give a white solid. This crude product was purified by filtration through a column of silica gel (ethyl acetate–light petroleum, gradient elution) to obtain **13** as a white solid (0.435 g, 87%). Crystallization from ethyl acetate–light petroleum gave colorless crystals. R_f=0.2 (70% acetate–light petroleum); mp 143–144 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ=1.39 (s, 3H; CH_3), 1.56 (s, 3H; CH_3), 2.98 (br s, 2H; OH, D_2O exchangeable), 3.25–3.45 (m, 3H; Ins-H), 3.57 (s, 3H; OCH_3), 3.60 (s, 3H; OCH_3), 3.88 (t, J=9 Hz, 1H; Ins-H), 4.00–4.15 (m, 1H; Ins-H), 4.52 (dd, J_1=5 Hz, J_2=4 Hz, 1H; Ins-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=25.9 (CH_3), 28.0 (CH_3), 58.0 (OCH_3), 59.6 (OCH_3), 71.4 (Ins-C), 72.8 (Ins-C), 79.0 (Ins-C), 79.1 (Ins-C), 84.0 (Ins-C), 109.9 (CMe_2); IR ($CHCl_3$): ν_{max}=3400–3600 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.11. Found: C, 53.22; H, 8.35%.

4.1.10. Racemic 1,2-O-isopropylidene-3,6-di-O-methyl-4,5-di-O-benzyl-myo-inositol (*14*)

A mixture of racemic **13** (1.045 g, 4.21 mmol), sodium hydride (2.524 g, 63.12 mmol), and DMF (10 mL) was stirred at 0–5 °C under nitrogen atmosphere and then benzyl bromide (5 mL, 42.08 mmol) was added dropwise. The reaction mixture was allowed to attain room temperature and stirred for 1 h. Excess sodium hydride was destroyed by adding methanol (0.5 mL) and the mixture concentrated under reduced pressure to get a semi-solid. This was dissolved in chloroform (200 mL), washed with water (30 mL×4) followed by brine, and dried over anhyd sodium sulfate. The solvent was evaporated under reduced pressure to get crude **14** as an oily liquid. This was purified by column chromatography (eluent: 10% ethyl acetate in light petroleum) to get the dibenzyl ether **14** as a gum (0.965 g, 53%). R_f=0.2 (10% ethyl acetate in light petroleum); ^{1}H NMR (200 MHz; $CDCl_3$): δ=1.41 (s, 3H; CH_3), 1.59 (s, 3H; CH_3), 3.37 (t, J=9 Hz, 1H; Ins-H), 3.45–3.56 (m, 2H; Ins-H), 3.60 (s, 3H; OCH_3), 3.63 (s, 3H; OCH_3), 3.89 (t, J=9 Hz, 1H; Ins-H), 4.12 (dd, J_1=7 Hz, J_2=6 Hz, 1H; Ins-H), 4.48 (dd, J_1=5 Hz, J_2=4 Hz, 1H; Ins-H), 4.70–4.95 (m, 4H; CH_2Ph), 7.30–7.55 (m, 10H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=25.6 (CH_3), 27.6 (CH_3), 59.0 (OCH_3), 60.0 (OCH_3), 73.5 (Ins-C), 74.94 (CH_2Ph), 74.98 (CH_2Ph), 78.6 (Ins-C), 79.5 (Ins-C), 80.5 (Ins-C), 82.0 (Ins-C), 84.3 (Ins-C), 109.7 (CMe_2), 127.5 (Ar-C), 127.8 (Ar-C), 128.2 (Ar-C), 138.5 (Ar-C). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.52. Found: C, 69.63; H, 7.33%.

4.1.11. Racemic 1,4-di-O-methyl-5,6-di-O-benzyl-myo-inositol (*15*)

A mixture of racemic **14** (0.924 g, 2.15 mmol) and acetic acid–water (4:1, 10 mL) was stirred at 100 °C for 3 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to get a gum. Co-evaporation of the residue with dry benzene (7 mL×3) gave a white solid. This was purified by filtration through a column of silica gel (eluent: 50% ethyl acetate in light petroleum) to obtain the diol **15** as a white solid (0.647 g, 77%). R_f=0.2 (50% ethyl acetate in light petroleum); mp 112–114 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ=2.62 (br s, 1H; OH, D_2O exchangeable), 2.69 (br s, 1H; OH, D_2O exchangeable), 3.20 (dd, J_1=9 Hz, J_2=3 Hz, 1H; Ins-H), 3.39 (t, J=9 Hz, 1H; Ins-H),

3.45 (dd, J_1=10 Hz, J_2=3 Hz, 1H; Ins-H), 3.53 (s, 3H; OCH_3), 3.54–3.59 (m, 1H; Ins-H), 3.66 (s, 3H; OCH_3), 3.85 (t, J=9 Hz, 1H; Ins-H), 4.26 (t, J=3 Hz, 1H; Ins-H), 4.75–4.90 (m, 4H; CH_2Ph), 7.25–7.40 (m, 10H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=58.3 (OCH_3), 61.3 (OCH_3), 68.5 (Ins-C), 71.6 (Ins-C), 75.4 (CH_2Ph), 75.6 (CH_2Ph), 81.4 (Ins-C), 82.1 (Ins-C), 82.9 (Ins-C), 83.0 (Ins-C), 127.4 (Ar-C), 127.7 (Ar-C), 127.8 (Ar-C), 128.2 (Ar-C), 138.4 (Ar-C), 138.6 (Ar-C); IR ($CHCl_3$): ν_{max}=3270–3585 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 67.62; H, 7.31%.

4.1.12. Racemic 1,2-(18-crown-6)-3,6-di-O-methyl-4,5-di-O-benzyl-myo-inositol (**16**)

Racemic **15** (0.200 g, 0.51 mmol), sodium hydride (0.124 g, 3.10 mmol), pentaethyleneglycol ditosylate (0.365 g, 0.67 mmol), and dry THF (75 mL) were used to prepare the crown ether **16**, which was isolated as a gum (0.222 g, 74%) after column chromatography (eluent: 25% ethyl acetate in light petroleum). R_f=0.2 (25% ethyl acetate in light petroleum); ^1H NMR (200 MHz; $CDCl_3$): δ=3.00–3.19 (m, 2H; Ins-H), 3.31 (t, J=9 Hz, 1H; Ins-H), 3.50 (s, 3H; OCH_3), 3.61–3.82 (m, 23H; OCH_3, OCH_2CH_2O), 3.99 (t, J=6 Hz, 2H; Ins-H), 4.12 (t, J=2 Hz, 1H; Ins-H), 4.55–5.05 (m, 4H; CH_2Ph), 7.25–7.45 (m, 10H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=58.2 (OCH_3), 61.0 (OCH_3), 70.38 (CH_2), 70.43 (CH_2), 70.5 (CH_2), 70.7 (CH_2), 70.8 (CH_2), 70.9 (CH_2), 71.7 (CH_2), 71.8 (CH_2), 74.3 (Ins-C), 75.6 (CH_2Ph), 75.7 (CH_2Ph), 81.4 (Ins-C), 81.6 (Ins-C), 82.7 (Ins-C), 83.1 (Ins-C), 83.5 (Ins-C), 127.3 (Ar-C), 127.4 (Ar-C), 127.8 (Ar-C), 128.2 (Ar-C), 138.8 (Ar-C), 138.9 (Ar-C); IR (Neat): ν_{max}=3481–3587 cm^{-1}. Anal. Calcd for $C_{32}H_{46}O_{10}\cdot H_2O$: C, 63.14; H, 7.94. Found: C, 63.34; H, 7.81%.

4.1.13. Racemic 1,2,3,4-tetra-O-benzyl-5,6-(12-crown-4) scyllo-inositol (**18**)

The diol **17**[25] (0.300 g, 0.55 mmol), sodium hydride (0.133 g, 3.33 mmol), triethyleneglycol ditosylate (0.331 g, 0.72 mmol), and dry THF (80 mL) were used to prepare the crown ether **18** and was isolated as a white sticky solid (0.05 g, 14%) by column chromatography (ethyl acetate–light petroleum, gradient elution). R_f=0.1 (25% ethyl acetate–light petroleum); ^1H NMR (200 MHz; $CDCl_3$): δ=3.22–3.37 (m, 2H; Ins-H), 3.44–3.53 (m, 4H; Ins-H), 3.54–4.09 (m, 12H; OCH_2CH_2O), 4.43–5.00 (m, 8H; CH_2Ph), 7.23–7.35 (m, 20H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=70.6 (CH_2), 71.1 (CH_2), 72.9 (CH_2), 75.87 (CH_2), 75.93 (CH_2), 82.4 (Ins-C), 82.8 (Ins-C), 83.4 (Ins-C), 127.59 (Ar-C), 127.65 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 138.4 (Ar-C), 138.5 (Ar-C); IR (Neat): ν_{max}=3269–3517 cm^{-1}. Anal. Calcd for $C_{40}H_{46}O_8\cdot H_2O$: C, 71.40; H, 7.19. Found: C, 71.79; H, 7.21%.

4.1.14. Racemic 1,2,3,4-tetra-O-benzyl-5,6-(15-crown-5) scyllo-inositol (**19**)

The diol **17**[25] (0.200 g, 0.37 mmol), sodium hydride (0.118 g, 2.96 mmol), tetraethyleneglycol ditosylate (0.214 g, 0.48 mmol), and dry THF (65 mL) were used to prepare the crown ether **19** and was isolated as a white solid (0.147 g, 57%) by column chromatography (eluent: 25% ethyl acetate in light petroleum). R_f=0.2 (25% ethyl acetate in light petroleum); mp 119–121 °C; ^1H NMR (200 MHz; $CDCl_3$): δ=3.10–3.36 (m, 2H; Ins-H), 3.37–3.58 (m, 4H; Ins-H), 3.60–3.81 (m, 12H; OCH_2CH_2O), 3.83–3.95 (m, 2H; OCH_2CH_2O), 3.96–4.14 (m, 2H; OCH_2CH_2O), 4.43–5.00 (m, 8H; CH_2Ph), 7.25–7.40 (m, 20H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=69.3 (CH_2), 70.5 (CH_2), 70.56 (CH_2), 70.6 (CH_2), 71.1 (CH_2), 73.0 (CH_2), 73.1 (CH_2), 75.8 (CH_2), 82.7 (Ins-C), 82.9 (Ins-C), 83.0 (Ins-C), 127.5 (Ar-C), 127.53 (Ar-C), 127.57 (Ar-C), 127.6 (Ar-C), 127.78 (Ar-C), 127.82 (Ar-C), 128.3 (Ar-C), 128.33 (Ar-C), 138.39 (Ar-C), 138.42 (Ar-C). Anal. Calcd for $C_{42}H_{50}O_9$: C, 72.18; H, 7.21. Found: C, 72.24; H, 7.20%.

4.1.15. Racemic 1,2,3,4-tetra-O-benzyl-5,6-(18-crown-6) scyllo-inositol (**20**)

The diol **17**[25] (0.200 g, 0.37 mmol), sodium hydride (0.088 g, 2.22 mmol), pentaethyleneglycol ditosylate (0.263 g, 0.48 mmol), and dry THF (65 mL) were used to prepare the crown ether **20** and was isolated as a white solid (0.206 g, 75%) by column chromatography (ethyl acetate–light petroleum, gradient elution). R_f=0.2 (30% ethyl acetate–light petroleum); mp 107–109 °C; ^1H NMR (200 MHz; $CDCl_3$): δ=3.22–3.39 (m, 2H; Ins-H), 3.40–3.52 (m, 4H; Ins-H), 3.60–3.79 (m, 16H; OCH_2CH_2O), 3.82–4.00 (m, 2H; OCH_2CH_2O), 4.09–4.23 (m, 2H; OCH_2CH_2O), 4.52–4.91 (m, 8H; CH_2Ph), 7.23–7.39 (m, 20H; Ar-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=70.5 (CH_2), 70.6 (CH_2), 70.7 (CH_2), 70.9 (CH_2), 73.0 (CH_2), 75.8 (CH_2), 82.58 (Ins-C), 82.62 (Ins-C), 83.2 (Ins-C), 127.49 (Ar-C), 127.52 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.25 (Ar-C), 128.27 (Ar-C), 138.4 (Ar-C), 138.5 (Ar-C). Anal. Calcd for $C_{44}H_{54}O_{10}$: C, 71.13; H, 7.32. Found: C, 70.77; H, 7.13%.

4.1.16. Racemic 1-O-benzoyl-2,3,4,5-tetra-O-methyl scyllo-inositol (**21**)

A mixture of diol **7**[24] (0.600 g, 2.54 mmol), triphenylphosphine (0.939 g, 3.22 mmol), benzoic acid (0.389 g, 3.22 mmol), diisopropyl azidodicarboxylate (DIAD) (0.725 mL, 3.68 mmol), and 3 Å molecular sieves was stirred in dry benzene (20 mL) at 80 °C for 16 h. The reaction mixture was allowed to attain ambient temperature and filtered. The filtrate was evaporated under reduced pressure to get a gum, which was purified by column chromatography (eluent: 25% ethyl acetate in light petroleum) to get racemic **21** as a white solid (0.595 g, 69%). R_f=0.2 (35% ethyl acetate in light petroleum); mp 107–108 °C; ^1H NMR (200 MHz; $CDCl_3$): δ=2.54 (br s, 1H; OH, D_2O exchangeable), 3.05–3.32 (m, 4H; Ins-H), 3.49 (s, 3H; OCH_3), 3.53–3.61 (m, 1H; Ins-H), 3.64 (s, 6H; OCH_3), 3.65 (s, 3H; OCH_3), 5.15 (t, J=10 Hz, 1H; HCOBz), 7.35–7.65 (m, 3H; Ar-H), 8.08 (dd, J_1=8 Hz, J_2=1.5 Hz, 2H; Ar-H_{ortho}); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=60.7 (OCH_3), 60.8 (OCH_3), 60.9 (OCH_3), 61.1 (OCH_3), 72.0 (Ins-C), 74.6 (Ins-C), 82.3 (Ins-C), 83.8 (Ins-C), 84.4 (Ins-C), 128.3 (Ar-C), 129.7 (Ar-C), 129.9 (Ar-C), 133.0 (Ar-C), 166 (C=O); IR ($CHCl_3$): ν_{max}=1724, 3337–3566 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.98; H, 7.10. Found: C, 60.16; H, 7.13%.

*4.1.17. Racemic 1,2,3,4-tetra-O-methyl scyllo-inositol (**22**)*

The racemic benzoate **21** (0.590 g, 1.73 mmol) and sodium hydroxide (0.277 g, 6.93 mmol) were refluxed in methanol (15 mL) for 2 h. The reaction mixture was cooled to ambient temperature, neutralized with 2% HCl, and the solvent was evaporated under reduced pressure. The solid residue was extracted with ethyl acetate and filtered; the filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (ethyl acetate–light petroleum, gradient elution) to get **22** as a white solid (0.315 g, 77%). R_f=0.2 (ethyl acetate); mp 129–131 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ=2.78–3.12 (m, 6H; 4 Ins-H and 2 OH, D_2O exchangeable), 3.31–3.40 (m, 2H; Ins-H), 3.62 (s, 6H; OCH_3), 3.64 (s, 6H; OCH_3); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=60.7 (OCH_3), 60.9 (OCH_3), 73.4 (Ins-C), 83.7 (Ins-C), 84.9 (Ins-C); IR (Nujol): ν_{max}=3178–3521 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 50.74; H, 8.86%.

*4.1.18. Racemic 1,2,3,4-tetra-O-methyl-5,6-(18-crown-6) scyllo-inositol (**23**)*

The diol **22** (0.150 g, 0.63 mmol), sodium hydride (0.152 g, 3.80 mmol), pentaethyleneglycol ditosylate (0.451 g, 0.82 mmol), and dry THF (100 mL) were used to prepare the crown ether **23** and was isolated as a gum (0.185 g, 66%) by column chromatography (ethyl acetate–light petroleum, gradient elution). R_f=0.1 (ethyl acetate); ^{1}H NMR (400 MHz; $CDCl_3$): δ=2.93 (dd, J_1=7 Hz, J_2=2.6 Hz, 1H; Ins-H), 2.95–3.08 (m, 2H; Ins-H), 3.10 (dd, J_1=6.7 Hz, J_2=2.6 Hz, 1H; Ins-H), 3.38 (s, 3H; OCH_3), 3.53–3.56 (m, 2H; OCH_2CH_2O), 3.60 (s, 6H; 2 OCH_3), 3.60–3.67 (m, 15H; OCH_3 and OCH_2CH_2O), 3.67–3.78 (m, 6H; OCH_2CH_2O), 3.83–3.88 (m, 1H; Ins-H), 4.02–4.09 (m, 1H; Ins-H); ^{13}C NMR (50.3 MHz; $CDCl_3$): δ=58.8 (OCH_3), 60.7 (OCH_3), 60.8 (OCH_3), 70.29 (CH_2), 70.37 (CH_2), 70.39 (CH_2), 70.53 (CH_2), 70.58 (CH_2), 70.7 (CH_2), 71.7 (CH_2), 72.6 (CH_2), 82.9 (Ins-C), 84.18 (Ins-C), 84.26 (Ins-C); IR (Nujol): ν_{max}=3440–3560 cm^{-1}. Anal. Calcd for $C_{20}H_{38}O_{10}\cdot 2H_2O$: C, 50.62; H, 8.92. Found: C, 50.30; H, 9.09%.

*4.1.19. 2-O-Benzyl-4,6-di-O-tosyl-scyllo-inositol 1,3,5-orthoformate (**25**)*

To a solution of 2,4-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate (**24**)[1f] (1.000 g, 2.00 mmol) and benzyl bromide (0.342 g, 2.00 mmol) in dry DMF (5 mL), sodium hydride (0.084 g, 2.10 mmol) was added and stirred for 5 min. The reaction was quenched by the addition of ice, and the mixture concentrated under reduced pressure. Usual workup of the residue with dichloromethane followed by crystallization of the product from a mixture of chloroform and light petroleum gave **25** as a white solid (1.150 g, 97%), mp 147–149 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=2.43 (s, 6H; Ar-CH_3), 4.21–4.33 (m, 1H; Ins-H), 4.33–4.40 (m, 1H; Ins-H), 4.41–4.48 (m, 2H; Ins-H), 4.53 (s, 2H; CH_2Ph), 5.18–5.23 (t, J=3.5 Hz, 2H; Ins-H), 5.47 (s, 1H; HCO_3), 7.12–7.30 (m, 9H; Ar-H), 7.65–7.75 (d, J=8.6 Hz, 4H; Ar-H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ=21.6 (Ar-CH_3), 67.5, 67.9, 69.4, 71.2, 102.5 (HCO_3), 127.3 (Ar-C), 127.8 (Ar-C), 128.1 (Ar-C), 129.8 (Ar-C), 132.9 (Ar-C), 137.2 (Ar-C), 145.0 (Ar-CSO_3). Anal. Calcd for $C_{28}H_{28}O_{10}S_2$: C, 57.13; H, 4.79. Found: C, 56.90; H, 4.76%.

*4.1.20. 2-O-Benzyl-scyllo-inositol 1,3,5-orthoformate (**26**)*

The ditosylate **25** (0.588 g, 1.00 mmol) and sodium methoxide (0.562 g, 10.41 mmol) were dissolved in dry methanol (10 mL) and refluxed for 24 h. The reaction mixture was cooled to ambient temperature, ice was added and solvents were evaporated under reduced pressure. Usual workup with dichloromethane followed by purification of the crude product by flash column chromatography (ethyl acetate–light petroleum, gradient elution) gave the diol **26** as a white solid (0.272 g, 97%). R_f=0.1 (20% ethyl acetate–light petroleum); mp 124–125 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ=3.31 (d, J=8 Hz, 2H; OH, D_2O exchangeable), 4.36–4.39 (m, 1H; Ins-H), 4.39–4.43 (m, 1H; Ins-H), 4.44–4.49 (m, 2H; Ins-H), 4.49–4.54 (m, 2H; Ins-H), 4.71 (s, 2H; CH_2Ph), 5.48 (s, 1H; HCO_3), 7.31–7.41 (m, 5H; Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=67.1 (Ins-C), 69.1 (Ins-C), 70.6 (Ins-C), 72.2 (CH_2Ph), 73.2 (Ins-C), 102.1 (HCO_3), 128.0 (Ar-C), 128.4 (Ar-C), 128.7 (Ar-C), 136.5 (Ar-C); IR ($CHCl_3$) ν_{max}=3153–3600 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 59.84; H, 5.58%.

*4.1.21. 2-O-Benzyl-4,6-(18-crown-6)-scyllo-inositol 1,3,5-orthoformate (**27**)*

The diol **26** (0.200 g, 0.71 mmol), sodium hydride (0.160 g, 4.00 mmol), and pentaethyleneglycol ditosylate (0.438 g, 0.80 mmol) were refluxed in dry THF (105 mL) for 15 h. Methanol (1 mL) was added to destroy excess of sodium hydride. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure to get a gum. This was dissolved in dichloromethane and washed several times with water (20×5 mL) over 24 h. Dichloromethane layer was then dried over anhyd sodium sulfate and concentrated under reduced pressure to get **27** as a gum (0.185 g, 53%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=3.40–3.96 (m, 22H; 2 Ins-H and OCH_2CH_2O), 4.20–4.30 (m, 2H; Ins-H), 4.42–4.55 (m, 2H; Ins-H), 4.60–4.69 (m, 2H; CH_2Ph), 5.49 (s, 1H; HCO_3), 7.27–7.47 (m, 5H; Ar-H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ=68.4 (Ins-C), 68.5 (Ins-C), 69.6 (CH_2), 70.5 (CH_2), 70.6 (CH_2), 70.8 (CH_2), 72.00 (Ins-C), 73.6 (Ins-C), 102.9 (HCO_3), 127.4 (Ar-C), 128.2 (Ar-C), 138.1 (Ar-C); IR ($CHCl_3$) ν_{max}=3380–3604 cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_{10}\cdot 0.25H_2O$: C, 59.18; H, 7.14. Found: C, 59.02; H, 7.29%.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.034.

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16. Compounds reported in this paper are either *racemic* or have *meso* configuration. However, for racemic compounds, one of the enantiomers is shown in schemes for brevity and simplicity. Accordingly, numbering of inositol ring carbons may be clockwise or anti-clockwise.
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