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Cyclitol-Based Metal-Complexing Agents. Effect of the Relative Orientation of Oxygen Atoms in the Ionophoric Ring on the Cation-Binding Ability of *myo*-Inositol-Based Crown Ethers

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Received April 1, 2002

myo-Inositol-derived crown ethers having varying relative orientations (1,3-diaxial, 1,2-diequatorial, and 1,2-axial−equatorial) of the oxygen atoms in the ionophoric ring were synthesized and the extent of their binding with picrates of alkali metals, ammonia, and silver were estimated. These crown ethers bind very well with potassium and silver picrates and show good to moderate binding toward lithium, sodium, cesium, and ammonium picrates. These *myo*-inositol-derived crown ethers exhibit very strong binding for silver, even though they do not have sulfur or nitrogen coordinating sites in them, which are known to have high affinity for silver. The ratio of binding constants for silver to other ions tested varies from 10^2 to 10^5. The ion selectivity and the strength of binding are dependent on the relative orientation of the oxygen atoms in the ionophoric ring as well as on the size of the macrocyclic ring.

Introduction

Synthesis and study of neutral complexing agents have grown into a vast area of research[1] due to their applications in various fields of chemistry, biology, medicine, and industry. Crown ethers are a class of metal-complexing agents that have been investigated most extensively. Various modifications in the structure of crown ethers have been examined with a view to achieving improvement in the ability as well as selectivity in their binding to metal ions. Knowledge in this area is sufficiently advanced to allow qualitative prediction of the binding preferences of crown ethers to metal ions, based on their molecular structure. However, effort toward achieving better ion selectivity to suit a given application, by fine-tuning the structure of crown ethers, continues. For example, such efforts include introduction of side chains (lariat ethers),[2] introduction of heteroatoms other than oxygen atom in the ionophoric ring,[3] and restriction in the degrees of freedom of the metal ion ligating sites in the ionophoric ring.[4] Attempts to achieve variation in the metal ion binding preferences of crown ethers have also been examined by constructing them on carbohydrate derivatives,[5] biphenyls,[6] bipyridyls,[7] and rigid molecules such as calixarenes,[8] camphor,[9] cage compounds,[10] stilbenes,[11] and paddalanes.[12] These variations influenced the binding of metal ions either by restricting the stereochemical disposition of the metal ion binding sites in the ionophoric ring or by providing additional metal ion binding sites (other than those present in the ionophoric ring) or both.

We thought that the six secondary hydroxyl groups of *myo*-inositol could allow the preparation of crown ethers with varying relative configuration of two of the oxygen atoms (Scheme 1, **1**−**3**). It was interesting to see if these variations result in better binding or better selectivity for complexation with metal ions. The remaining hy-

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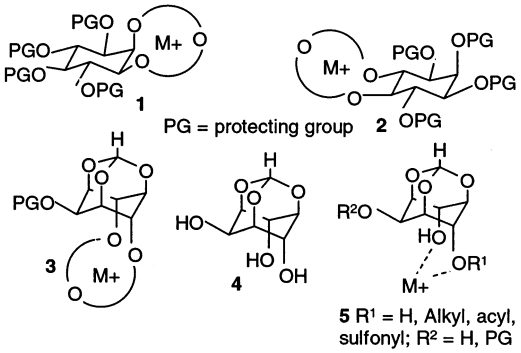
10.1021/jo025783g CCC: $22.00
Published on Web 09/05/2002

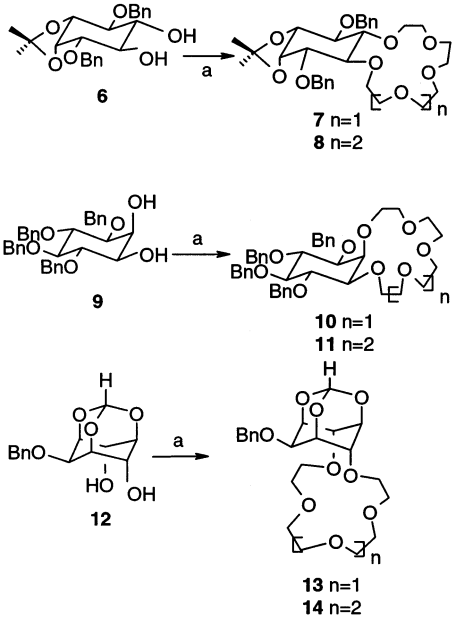
SCHEME 1



droxyl groups of inositol could be useful in introduction of functional groups that could aid to improve metal ion binding or selectivity (including the construction of bis and tris crown ethers) or could be used for further functionalization to prepare polymeric or polymer-supported crown ethers. Although inositols[13] and phosphoinositols[14] have been known to form complexes with metal ions, reports on the synthesis and study of cyclitol-based complexing agents began to appear only recently.[15] One of these[15b] attempted to use *myo*-inositol-based ligands for applications in magnetic resonance imaging studies.

The realization of the existence of phosphoinositol-based cellular signal transduction mechanisms in eukaryotic systems[16] and the role played by *myo*-inositol in the anchoring of certain proteins to the cell membranes[17] drove chemists to devise novel methods for the efficient synthesis of cyclitol derivatives.[16,18] We had previously reported[19] convenient methods for the preparation of several important *O*-protected *myo*-inositol derivatives via *myo*-inositol 1,3,5-orthoformate (**4**, Scheme 1). From these studies, as well as others reported[20] in the literature, it appeared that the unusual selectivities encountered during *O*-alkylation,[19b] *O*-acylation,[19d] *O*-sulfonylation,[19e] and transesterification[21] reactions of the orthoformate **4** and its derivatives were a result of their chelation (**5**) with metal ions. We had also observed[21] that some *O*-substituted *myo*-inositol derivatives bind well with silver picrate. These results prompted us to synthesize simple polyether derivatives[15j] as well as crown ethers derived from *myo*-inositol that could serve as neutral complexing agents, and to investigate their complexing abilities with metal ions. We were particularly interested in seeing the metal ion binding ability of *myo*-inositol-derived neutral complexing agents with heavy metals such as silver. Design of complexing agents for silver often involves introduction of sulfur or nitrogen binding sites in ligands, but none of the simple *myo*-inositol derivatives that could extract silver picrate,[15j,21] contained either sulfur or nitrogen atoms. To the best of our knowledge, there are no reports on the use of cyclitols as core molecules for the construction of crown ethers. The present paper is concerned with the synthesis of *myo*-inositol-based crown ethers and an evaluation of their complexing ability with picrate salts of alkali metals, ammonia, and silver.

SCHEME 2



Results and discussion

We chose the racemic isopropylidene derivative **6**[22] (Scheme 2), the tetrabenzyl ether **9**,[23] and the orthoformate **12**[19e] as starting materials for the synthesis of

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TABLE 1. Association Constants ($K_a \times 10^{-5}$ dm^3 mol^{-1}) of Crown Ethers with Different Picrates in $CDCl_3$ at 27 °C

	7	8	10	11	13	14
Li	0.957	0.487	1.29	1.63	1.20	0.971
Na	0.443	0.466	6.47	4.55	3.86	0.628
K	0.259	3.26	0.67	3.52×10^3	0.247	75.7
Cs	0.131	0.193	0.133	1.18	0.049	0.111
NH_4	0.081	0.787	0.183	58.6	0.102	17.1
Ag	3.42	18.6	2.76×10^3	4.95×10^5	59	8.91

crown ethers (Scheme 2).[24] The *myo*-inositol-derived crown ethers were synthesized by the reaction of diols (**6**, **9**, or **12**) with an appropriate oligoethyleneglycol ditosylate, in the presence of sodium hydride. In the newly synthesized crown ethers, two of the oxygen atoms in the ionophoric ring have varying relative orientations (1,2-diequatorial in **7**, **8**; 1,2-axial−equatorial in **10**, **11**; 1,3-diaxial in **13**, **14**), as they are part of the *myo*-inositol ring. The association constants of these crown ethers with alkali metal ions as well as ammonium and silver ions, evaluated by Cram's picrate method,[25] are listed in Table 1.

The picrate extraction data show that all the crown ethers bind to metal picrates well and that they are able to extract silver picrate better than other picrates (except **14**, which extracts potassium picrate better). For the calculation of the association constants in Table 1, we have assumed the formation of 1:1 complexes. But it is possible that the actual binding of metal picrates (especially that of silver) to crown ethers is a result of aggregation of metal ions and crown ethers (cooperative binding) due to the presence of several benzyl ether protecting groups.[26] The crown ether **11** shows the highest binding constant for silver picrate. Among the alkali metal and ammonium picrates, the highest binding constant is exhibited for the complexation of potassium picrate again with the crown ether **11**. This is perhaps because of the similar ionic size of potassium and silver ions.[27] However, the preference exhibited by all the crown ethers for binding with silver suggests that the cause for the binding affinities of the newly synthesized crown ethers for cations is not based only on the ionic size. It is interesting to see that these crown ethers bind better with silver picrate than with alkali metal picrates, even though these crown ethers do not contain any soft ligating sites such as thioether or amine, which are known to increase the affinity of crown ethers for binding with silver.[3a] The ability of these *myo*-inositol-derived crown ethers to extract silver picrate is comparable to crown ethers that contain one or more sulfur atoms as ligating sites in them.[2a,3a] These results show that suitably designed ligands that have only oxygen ligating sites in a constrained conformation have the ability to form complexes with silver. We had observed earlier[21] that *myo*-inositol derivatives containing aromatic rings and ether or carbonyl oxygen atoms bind reasonably well to silver picrate and that the value of the association constant for this binding is comparable to those exhibited by simple crown ethers. It is known that olefinic[11,28] and aromatic[8b] π-electron systems are suitable ligands for forming silver complexes.

The magnitude of the preference of individual crown ethers for binding to metal ions can be estimated by the ratio of association constants between different metal picrates, for binding to the same crown ether. The crown-6-ether **11** shows the highest preference for binding to silver as compared to other ions by a factor of 5, except in comparison with potassium ($K_{a(Ag)}/K_{a(K)} = 141$). The crown ether **11** also shows preference for binding to potassium as compared to other alkali metal ions by about 100−1000 times. The crown-5-ether **10** binds 3−4 orders of magnitude better to silver as compared to potassium and ammonium ions, even though they all have similar ionic radii.[27] This clearly indicates that preferential binding of silver to these crown ethers is a result of many factors, other than their ionic size. The preferences of inositol-derived crown ethers for binding to alkali metal ions (other than potassium) and ammonium ions varies; the maximum ratios observed were 24 ($K_{a(Li)}/K_{a(Cs)}$ for **13**), 79 ($K_{a(Na)}/K_{a(Cs)}$ for **13**), and 154 ($K_{a(NH4)}/K_{a(Cs)}$ for **14**).

A comparison of the ratio of association constants between crown ethers of the same size, but having different relative orientations of the two of the oxygen atoms (attached to the inositol ring), reveals that this difference matters most for the binding of silver and potassium ions. The appreciation in the association constants is by 4 and 3 orders of magnitude, respectively, for silver ($K_{a(11)}/K_{a(8)} = 2.7 \times 10^4$; $K_{a(11)}/K_{a(14)} = 5.6 \times 10^4$; $K_{a(8)}/K_{a(14)} = 2.1$) and potassium ($K_{a(11)}/K_{a(8)} = 1.1 \times 10^3$), but for the binding of sodium ($K_{a(10)}/K_{a(7)} = 15$), cesium ($K_{a(11)}/K_{a(14)} = 11$), and ammonium ($K_{a(11)}/K_{a(8)} = 74$) picrates, the increase in association constants due to this difference is not very high. The binding of lithium is insensitive to the variation in stereochemistry. This is not unexpected, since all the inositol-derived crown ethers tested have more than four oxygen atoms in the ionophoric ring and lithium is known to bind best with crown-4-ethers. It is pertinent to note that although all the crown ethers have five or six oxygen atoms in the ionophoric ring, in the diequatorial (**7**, **8**) and axial−equatorial (**10**, **11**) crown ethers, all the oxygen atoms are separated by two carbon atoms. Whereas, in the diaxial crown ethers (**13**, **14**), oxygen atoms attached to the inositol ring (at C-4 and C-6) are separated by three carbon atoms, but they are closer to each other due to their diaxial disposition. Interestingly, these differences lead to different selectivity patterns for binding to metal picrates.

A comparison of the binding of metal picrates to crown ethers of different sizes but having the same stereochemical orientation of the oxygen atoms reveals that, as expected, potassium, ammonium and silver bind better

(24) 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 the inositol ring carbons may be clockwise or anticlockwise.

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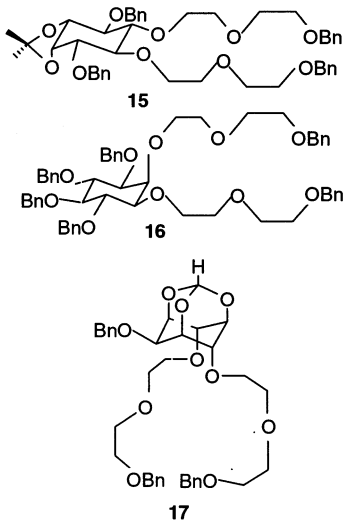
SCHEME 3



to crown-6. The maximum ratios being $K_{a(11)}/K_{a(10)} = 5 \times 10^3$, 1.8×10^2, and 320, respectively, for potassium, silver, and ammonium picrates. However, it is interesting to note that sodium and silver bind better to crown-5 ($K_{a(13)}/K_{a(14)} = 6$), in the case of diaxial crown ethers, although they have different ionic radii. This result substantiates the earlier statement that the preferences of *myo*-inositol-derived crown ethers for the binding of metal ions is a consequence of several factors in effect.

We had earlier reported[15j] the metal picrate-binding characteristics of a few *myo*-inositol-derived podands (Scheme 3), which are open chain analogues of crown-6 ethers (Scheme 2). Of all the podands tested, the ones with benzyl ether end groups exhibited good association constants for the binding of alkali metal, ammonium, and silver picrates. A comparison of the binding characteristics of the podands **15**−**17** with the analogous crown ethers could suggest the effect of ring closure as well as the contribution of benzyl ether groups on the extent of binding to metal picrates. As expected, all these crown ethers bind metal picrates (except lithium) better than the corresponding *myo*-inositol-based podand. The ratio of the association constants for a crown-6 and its open chain analogue shows that, for the binding of lithium, ring-closure does not make much difference. However, for potassium ($K_{a(11)}/K_{a(16)} = 6.7 \times 10^4$), ammonium ($K_{a(14)}/K_{a(17)} = 814$), and silver ($K_{a(11)}/K_{a(16)} = 1.4 \times 10^5$), the association constants increase by 2−5 orders of magnitude. For sodium and cesium, this increase varies from 2 to 20. Also, the increase in association constants is a maximum in the case of the crown ether in which oxygen atoms of the inositol ring are present in the axial−equatorial configuration (**11**). The increase in the value of the association constants on going from podands to crown ethers clearly shows the contribution of the ionophoric ring toward the binding of metal picrates.

It is pertinent to note that the ratio of binding constants for the extraction of silver picrate by crown-6-ethers varies from 2.1 to 5.6×10^4 (see above) and for crown-5-ethers varies from 0.06 to 810 ($K_{a(10)}/K_{a(7)} = 810$; $K_{a(10)}/K_{a(13)} = 47$; $K_{a(7)}/K_{a(13)} = 0.06$), while for the podands the corresponding range is from 1.3 to 4.7 ($K_{a(16)}/K_{a(15)} = 4.7$, $K_{a(16)}/K_{a(17)} = 6.1$, $K_{a(15)}/K_{a(17)} = 1.3$). If the difference in binding of silver picrate to crown ethers was mainly due to the change in the number of benzyl ether groups, the ratio of binding constants must have been comparable between the three groups of ionophores (i.e., crown-6-ethers, crown-5-ethers, and podands). This view is supported by the fact that crown-5-ether **13**, which has only one benzyl ether moiety, is able to extract silver picrate about 17 times better than the crown-6-ether **7**, which has two benzyl ether groups. Furthermore, if the binding of silver picrate to the ionophores under study was mainly due to the presence of benzyl ether groups in them, the range of ratio of binding constants observed must have been narrower, especially since podands **15**−**17** contain more benzyl ether groups than the corresponding crown ether. Hence it is reasonable to conclude that, although benzyl ether groups in the ionophores can contribute to the binding of metal picrates, the major differences in cation-binding abilities of *myo*-inositol-based crown ethers is due to the effect of the relative orientation of oxygen atoms in the ionophoric ring.

In conclusion, we have presented results on the synthesis of a few *myo*-inositol-derived crown ethers that have varying relative orientations of two of the oxygen atoms in the ionophoric ring. Estimation of the association constants of these crown ethers with metal picrates shows that this variation results in unusual and interesting selectivity patterns for binding to metal ions. These inositol-based crowns prefer to bind to silver, even though they do not contain any soft ligating sites such as sulfur or nitrogen. The association constants for these crown ethers are much higher than those observed for ordinary crown ethers.[29] As these crown ethers bind to silver well, these findings may be of potential use in silver-based radioimmunotherapy[8b,30] and perhaps useful in photography and recovery of silver from wastewater. Inositol-based crown ethers can also be used to prepare polymer-supported materials due to the presence of free hydroxyl groups. We are presently working to see if the protecting groups of inositol hydroxyl groups have any effect on the binding of metal ions to these neutral complexing agents. These results will be reported in due course.

Experimental Section

General Methods. For details on general methods, see refs 15j and 21. *myo*-Inositol derivatives **6**,[22] **9**,[23] and **12**[19e] were prepared using literature procedures. Flash column chromatographic separations were carried out using ethyl acetate−light petroleum mixtures. Metal picrate−crown ether binding constants were estimated by the method of Cram.[25]

Synthesis of Crown Ethers. General Procedure. The diol **6**, **9**, or **12** (1 mmol) was dissolved in dry THF (100 mL). To this solution was added oil free sodium hydride (3−10 mmol) followed by a solution of the required poly(ethylene glycol) ditosylate (1.3 mmol) in dry THF (50 mL), dropwise over 2 h under reflux. The reaction mixture was heated at reflux for another 24 h. It was then cooled to ambient temperature and the solvent was evaporated under reduced pressure. The residue was diluted with chloroform and washed successively with water followed by brine. The organic layer was dried over Na_2SO_4 and the solvent evaporated under

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reduced pressure. The crude product was dissolved in dry methanol (10−20 mL) and heated at reflux with sodium methoxide (5−10 mmol) for 3−5 h (to convert unreacted oligoethyleneglycol ditosylate to the corresponding dimethyl ether, which is easily separable from crown ethers). Methanol was then evaporated, and the residue was dissolved in chloroform and worked up as above. The crown ether was isolated by chromatography over silica gel (ethyl acetate−light petroleum, gradient elution).

Racemic 1,2-*O*-Isopropylidine-3,6-di-*O*-benzyl-4,5-(15-crown-5)-*myo*-inositol (7). The diol **6** (0.44 g, 1.1 mmol), sodium hydride (0.06 g, 2.5 mmol), and tetraethyleneglycol ditosylate (0.67 g, 1.3 mmol) were used to prepare the crown ether **7** as a gum (0.40 g, 65%). ^{1}H NMR ($CDCl_3$): 1.30 (s, 3H), 1.45 (s, 3H), 3.15 (t 1H, J = 9 Hz), 3.50−4.05 (m, 20H), 4.20 (t, 1H, J = 5 Hz), 4.55−4.90 (m, 4H), 7.20−7.50 (m, 10H). ^{13}C NMR ($CDCl_3$): 25.4, 27.3, 69.2, 70.1, 70.4, 70.8, 71.5, 71.8, 72.1, 72.5, 72.7, 73.3, 74.2, 75.0, 80.7, 81.3, 82.0, 82.3, 83.2, 109.3, 127.0, 127.5, 127.8, 128.0, 138.4, 138.5. Anal. Found C 66.52, H 7.70; $C_{31}H_{42}O_9$ requires C 66.63, H 7.58.

Racemic 1,2-*O*-Isopropylidene-3,6-di-*O*-benzyl-4,5-(18-crown-6)-*myo*-inositol (8). The diol **6** (0.40 g, 1 mmol), sodium hydride (0.12 g, 5 mmol), and pentaethyleneglycol ditosylate (0.71 g, 1.3 mmol) were used to prepare the crown ether **8** as a gum (0.40 g, 67%). ^{1}H NMR ($CDCl_3$): 1.35 (s, 3H), 1.50 (s, 3H), 3.10−3.25 (t, 1H, J = 9 Hz), 3.50−3.95 (m, 21H), 3.95−4.15 (m, 3H), 4.20 (t, 1H, J = 4 Hz), 4.65−4.90 (2q, 4H), 7.20−7.50 (m, 10H). ^{13}C NMR ($CDCl_3$): 25.6, 27.5, 70.5, 70.6, 72.2, 72.4, 73.0, 73.7, 74.4, 76.7, 78.7, 80.9, 82.1, 82.4, 109.4, 127.2, 127.7, 128.0, 128.1, 138.1, 138.4. Anal. Found C 65.50, H 7.93; $C_{33}H_{46}O_{10}$ requires C 65.76, H 7.69.

Racemic 1,2-(15-Crown-5)-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (10). The diol **9** (0.47 g, 0.87 mmol), sodium hydride (0.12 g, 5 mmol), and tetraethyleneglycol ditosylate (0.61 g, 1.2 mmol) were used to prepare the crown ether **10** as a gum (0.38 g, 63%). ^{1}H NMR ($CDCl_3$): 3.20 (dd, 1H, J = 10 Hz, 2 Hz), 3.30−3.50 (m, 2H), 3.50−3.90 (m, 14H), 3.90−4.25 (m, 5H), 4.50−4.95 (m, 8H), 7.15−7.45 (m, 20H). ^{13}C NMR ($CDCl_3$): 68.9, 69.3, 70.4, 70.7, 71.0, 71.6, 72.4, 73.0, 75.3, 75.4, 80.9, 81.3, 81.5, 81.6, 83.5, 126.6, 127.1, 127.3, 127.4, 127.6, 128.0, 129.4, 129.5, 138.3, 138.8, 139.0. Anal. Found: C 72.01, H 6.89; $C_{42}H_{50}O_9$ requires C 72.13, H 7.21.

Racemic 1,2-(18-Crown-6)-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (11). The diol **9** (0.54 g, 1 mmol), sodium hydride (0.12 g, 5 mmol), and pentaethyleneglycol ditosylate (0.71 g, 1.3 mmol) were used. After the addition was complete (2 h), the reaction mixture was concentrated (10 mL) and stirred at room temperature for 24 h and treated as described in the general procedure to obtain the crown ether **11** as a gum (0.73 g, 98%). ^{1}H NMR ($CDCl_3$): 3.20 (dd, 1H, J = 10 Hz, 2 Hz), 3.30−3.50 (q, 2H), 3.60−3.90 (m, 18H), 3.90−4.20 (m, 5H), 4.65−5.00 (m, 8H), 7.20−7.50 (m, 20H). ^{13}C NMR ($CDCl_3$): 70.4, 70.6, 71.8, 72.4, 75.0, 75.4, 75.6, 80.5, 81.4, 83.3, 127.4, 127.6, 127.8, 128.1, 138.2, 138.6, 138.8. Anal. Found C 70.96, H 7.61; $C_{44}H_{54}O_{10}$ requires C 71.14, H 7.33.

2-*O*-Benzyl-4,6-(16-crown-5)-*myo*-inositol 1,3,5-Orthoformate (13). The diol **12** (0.14 g, 0.5 mmol), sodium hydride (0.12 g, 5 mmol), and tetraethyleneglycol ditosylate (0.35 g, 0.7 mmol in 25 mL THF) were used to prepare the crown ether **13** as a gum (0.14 g, 64%). ^{1}H NMR ($CDCl_3$): 3.50−3.75 (m, 16H), 4.10 (m, 1H), 4.15−4.25 (t, 2H, J = 4 Hz), 4.25−4.35 (m, 2H), 4.40−4.50 (m, 1H), 4.75 (s, 2H), 5.55 (s, 1H), 7.20−7.50 (m, 5H). ^{13}C NMR ($CDCl_3$): 67.3, 68.2, 69.4, 70.2, 70.6, 71.3, 71.7, 74.7, 103.0, 127.7, 128.2, 138.0. Anal. Found C 60.52, H 7.18; $C_{22}H_{30}O_9$ requires C 60.26, H 6.90.

2-*O*-Benzyl-4,6-(19-crown-6)-*myo*-inositol 1,3,5-Orthoformate (14). The diol **12** (0.14 g, 0.5 mmol) in dry THF (50 mL), sodium hydride (0.12 g, 5 mmol), and pentaethyleneglycol ditosylate (0.4 g, 0.73 mmol) in dry THF (25 mL) were used to prepare the crown ether **14** as a gum (0.21 g, 87%). ^{1}H NMR ($CDCl_3$): 3.50−3.80 (m, 20H), 3.95 (m, 1H), 4.20−4.30 (m, 2H), 4.30−4.40 (m, 2H), 4.55 (m, 1H), 4.75 (s, 2H), 5.55 (s, 1H), 7.20−7.50 (m, 5H). ^{13}C NMR ($CDCl_3$): 67.4, 68.0, 69.4, 70.4, 70.5, 70.9, 71.2, 74.8, 103.0, 127.4, 127.6, 128.1, 138.0. Anal. Found C 59.37, H 7.40; $C_{24}H_{34}O_{10}$ requires C 59.74, H 7.10.

Acknowledgment. The Department of Science and Technology, New Delhi, supported this work, (research grant No. SP/S1/G-30/94 to M.S.S. and A.J.V.). K.M.S. thanks the Council of Scientific and Industrial Research, New Delhi, for a Senior Research fellowship.

JO025783G