Neutral complexing agents with a cyclitol core. Effect of the relative orientation of the sidearms and end groups on the cation binding ability of *myo*-inositol based podands

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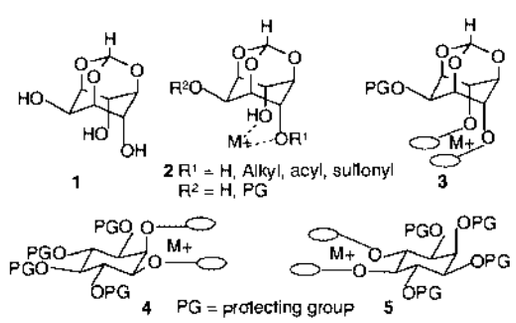
Received (in Cambridge, UK) 24th July 2001, Accepted 17th October 2001
First published as an Advance Article on the web 12th November 2001

myo-Inositol derived podands were synthesized and the extent of their binding with picrates of alkali metals, ammonia and silver was estimated. These podands bind very well with lithium and silver picrates but show moderate to poor binding toward sodium, potassium, caesium and ammonium picrates. The ion selectivity and the strength of binding are dependent on the relative orientation of the sidearms (1,3-diaxial, 1,2-diequatorial and 1,2-axial–equatorial) as well as on the nature of the end group present in the podands.

Introduction

In the last decade, there has been an upsurge of interest in the chemistry of inositols mainly due to the establishment of D-*myo*-inositol 1,4,5-trisphosphate as a second messenger in cell signaling pathways.[1] *myo*-Inositol is also involved in the anchoring of certain proteins to cell membranes.[2] The biological significance of *myo*-inositol derivatives prompted chemists to devise methods for efficient synthesis of naturally occurring phosphoinositols, glycophosphoinositol anchors as well as other derivatives of cyclitols, as potential drugs or inhibitors of enzymes involved in the *myo*-inositol cycle. We had previously reported[3] convenient methods for the preparation of several important *O*-protected *myo*-inositol derivatives *via myo*-inositol 1,3,5-orthoformate (**1**, Scheme 1). From these



Scheme 1

studies, as well as others reported[4] in the literature, it appeared that the unusual selectivities encountered during *O*-alkylation, *O*-acylation, *O*-sulfonylation and transesterification reactions of the orthoformate **1** or its derivatives, were a result of their chelation (**2**) with metal ions. We had also observed[5] that some *O*-substituted *myo*-inositol derivatives (such as racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate, racemic 2,4-di-*O*-benzoyl-6-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate, 2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate, 1,2,3,4,5,6-hexa-*O*-benzoyl-*myo*-inositol and racemic 1,2,3,4,5-penta-*O*-benzoyl-6-*O*-tosyl-*myo*-inositol) bind well with silver picrate. These results prompted us to synthesize simple polyether derivatives of *myo*-inositol and examine their metal ion complexing ability. Although inositols[6] and phosphoinositols[7] have been known to form complexes with metal ions, reports on the synthesis and study of cyclitol based neutral complexing agents began to appear only recently.[8] Six secondary hydroxy groups of *myo*-inositol allow the preparation of crown ether like compounds with varying relative configuration of two of the oxygen atoms (Scheme 1, **4**, **5**). Also, *myo*-inositol can easily be converted to its 1,3,5-orthoformate **1** which allows the preparation of neutral complexing agents that have two oxygen atoms in a 1,3-*cis* configuration (**3**). It is interesting to see if these variations result in better binding or better selectivity for complexation with metal ions.

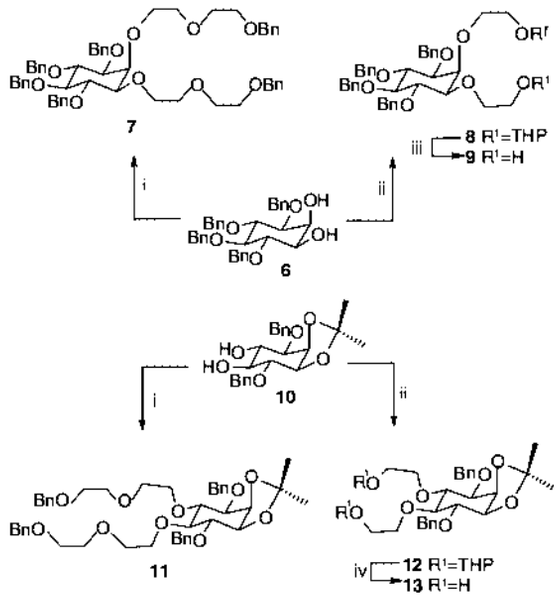
Synthesis and study of neutral complexing agents has grown into a vast area of research[9] due to their applications in various fields of chemistry, biology, medicine and industry. However the search for efficient, selective and biocompatible complexing agents for metal ions continues.[8] The present article is concerned with the results on the synthesis of *myo*-inositol based podands and an evaluation of their complexing ability with picrate salts of alkali metals, ammonia and silver.

Results and discussion

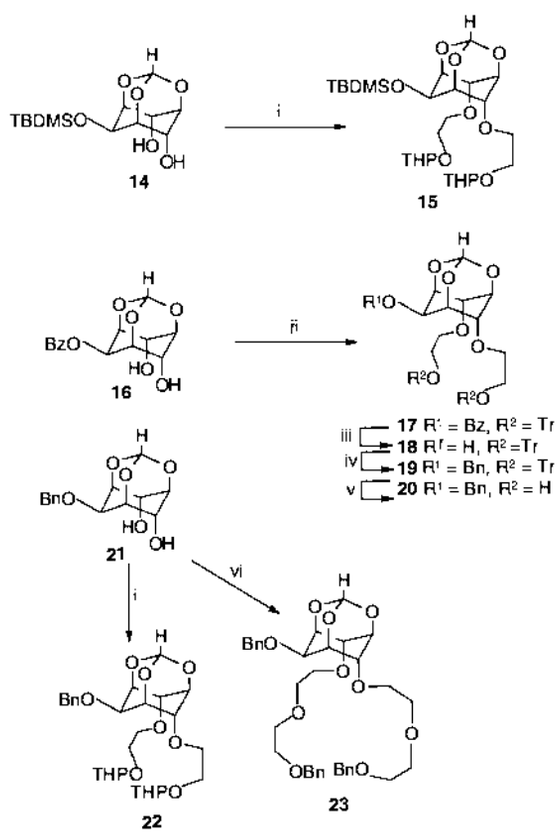
We chose the orthoformate **1**,[10] the racemic tetrabenzyl ether **6**[11] and the racemic isopropylidene derivative **10**[12] as starting materials for the synthesis of several podands with THP and benzyl ether end groups. The synthesis of podands from the diols **6** and **10** was straightforward (Scheme 2). The di(ethylene glycol) derived podands **7** and **11** with benzyl ether end groups were prepared by the alkylation of the diols **6** and **10** with the toluene-*p*-sulfonate of di(ethylene glycol) monobenzyl ether. Alkylation of **6** and **10** with THP ether derivative of 2-bromoethanol in the presence of sodium hydride provided the podands **8** and **12**. The THP ether groups were removed (in the case of **8**) by acid hydrolysis or by treatment with ethanethiol in the presence of boron trifluoride etherate (in the case of **12**) to obtain the corresponding diols **9** and **13**.

The di-THP ethers **15** and **22** (Scheme 3) were prepared by the alkylation of the diols **14** and **21** respectively, with 2-bromoethanol THP ether. For the synthesis of the diol **20**, we resorted to several protection–deprotection reactions, since no good method was available (when this work was started) for the preparation of the 2-*O*-benzyl ether **21**. The sequence

 DOI: 10.1039/b106717f



Scheme 2 *Reagents and conditions*: i) DMF, NaH, $BnOCH_2CH_2OCH_2CH_2OTs$, rt. ii) $BrCH_2CH_2OTHP$, NaH, DMF, rt. iii) Acetic acid (80%), rt, 24 h. iv) $BF_3{\cdot}Et_2O$, EtSH, CH_2Cl_2, −20 °C, 30 min.



Scheme 3 *Reagents and conditions*: i) $BrCH_2CH_2OTHP$, NaH, DMF, rt. ii) $BrCH_2CH_2OTr$ (**24**), NaH, DMF, rt. iii) Isobutylamine, methanol, rt. iv) BnBr, NaH, DMF, rt. v) H_3BO_3, benzene, reflux. vi) DMF, NaH, $BnOCH_2CH_2OCH_2CH_2OTs$, rt.

of reactions involved (a) alkylation of the diol **16** with 2-bromoethanol trityl ether (**24**), (b) aminolysis of the benzoate **17** to the corresponding alcohol **18**, (c) benzylation of **18** to the corresponding benzyl ether **19** and (d) cleavage of the trityl ethers in **19** to obtain the corresponding diol **20**. Trityl ethers were used in this sequence of reactions since the THP ethers (in **22**) are rather difficult to cleave in the presence of the orthoformate moiety. We later developed[3e] a convenient and high yielding method for the synthesis of **21** using sulfonate protection for the axial hydroxy groups in **1**, which was adopted for the preparation of the podands **22** and **23**. We then proceeded to estimate the cation binding abilities of the newly synthesized podands with alkali metal, ammonium and silver picrates using literature procedures.[13]

Results on the solvent extraction (into $CDCl_3$) of picrates from their aqueous solution, by the newly synthesized podands are shown in Table 1. The association constants (K_a) clearly show that the podands have a high preference for binding to lithium ions, the highest affinity being exhibited by **23**. Most of the synthetic ligands show poor binding to alkali metal ions and the ammonium ion. Some of the inositol based ligands also show moderate to very good affinity for silver and the highest binding to silver is shown by **7**. The ratio of association constants for different metal picrates varies from 158 (K_{Li}/K_{Cs} for **15**) to 7 (K_{Li}/K_{Na} for **7**). A comparison of K_a for the THP ethers (**8**, **12**, **22**) and the corresponding diols (**9**, **13**, **20**) indicates the role of THP ether moieties of the ligands in binding to metal picrates. It is interesting to note that despite having similar ionic size[14] silver (0.252 nm) binds much better than potassium (0.266 nm) with the newly synthesized podands. A comparison of K_a for **15** and **22** reveals that the protecting group at the 2-*O* position does not contribute towards the binding of the picrates to ligand. A comparison of binding characteristics of all the ligands reveals that the strongest binding to lithium and silver is exhibited by podands with benzyl ether end groups, **23** and **7** respectively.

A comparison of the binding constants of the ligands with the same relative orientation indicates that among the diaxial ligands (**15**, **22** and **23**), **23** binds Li, Na and Ag ions better. Among the diequatorial ligands (**11** and **12**), the di-THP ether **12** binds more strongly with Li and Na ions while both **11** and **12** bind well to silver. In the case of axial–equatorial ligands (**7** and **8**), the di-THP ether **8** shows preference for Li while **7** shows preference for Na and Ag ions. It is known that the nature of the end groups[9] and the relative configuration[15] of the donor functional groups in a ligand play a vital role in deciding the complexing ability of the host with cations. The fact that tetrahydropyranyl moieties are known to contribute significantly towards complexation with metal ions[9,16] and are also present in many biologically active compounds such as antibiotics, led us to choose THP ethers as the end group for some of the *myo*-inositol based podands.

To see the effect of relative orientation of the sidearms of the ligands on binding to metal picrates, we compared the binding constants of isomeric ligands having different relative orientations. Such a comparison for THP ethers (**8**, **12**, **22**) reveals that lithium and silver ions bind better with ligand **8** having axial–equatorial orientation while sodium prefers to bind with THP ethers having diequatorial orientation (**12**). However in the case of di(ethylene glycol) derived podands with benzyl ether end groups (**7**, **11**, **23**) lithium and sodium ions bind better to **23** (having diaxial orientation) while silver ions prefer to bind to **7** (having axial–equatorial orientation). It is interesting to note that although all the synthetic ligands have six oxygen atoms in their side arms, in the podands **7** and **11** all the oxygen atoms are separated by two carbon atoms (as in poly(ethylene glycols)). Whereas, in the THP ethers **8** and **12** the two oxygen atoms present in the THP ether moiety are separated by one carbon atom and the other oxygen atoms are separated by two carbon atoms. In the case of podands derived from orthoformate **1**, in addition to this difference, oxygen atoms attached to the inositol ring (at C-4 and C-6) are separated by three carbon atoms, but are closer to each other due to their diaxial disposition. Interestingly, these differences lead to different selectivity patterns for binding to lithium and silver picrates.

We also determined the bathochromic shifts[17] (Table 2) induced by some of the synthetic *myo*-inositol derivatives for

Table 1 Association constants ($K_a/10^3$ dm^3 mol^{-1}) for the complexation of univalent cations (M) with synthetic *myo*-inositol derivatives (25 °C)

M	7	8	9	11	12	13	15	20	22	23
Li[a]	156.83	221.4	52.75	42	208.87	23.37	201.89	23.31	205.5	331.82
Na	23.11	5.01	3.24	3.14	17.09	—[b]	14.11	0.70	14.88	30.38
K	5.20	6.27	4.36	3.33	4.85	3.11	5.77	—[b]	5.68	3.34
Cs	7.14	5.62	1.52	4.11	2.6	0.54	1.28	—[b]	1.52	6.75
NH_4	1.76	1.68	1.82	1.63	5.76	1.52	2.56	0.08	2.87	2.14
Ag	348.12	114	112.81	74.1	73.55	40.4	12.07	12.62	14.23	57.9

[a] Association constants (log (K_a/dm^3 mol^{-1})) of 4.25 (in acetonitrile), 1.62 (in acetone) and 0.7 (in pyridine) are reported[19c] for the lithium ion–12-crown-4 system. [b] No detectable amount of picrate was extracted.

Table 2 Optical spectroscopic results on the complexation[a] of alkali metal picrates (M^+Pi^-) with synthetic *myo*-inositol derivatives in THF (25 °C)

	Bathochromic shift ($\Delta\lambda_{max}$/nm)[b]						
M^+ (λ_{max}[c]/nm)	**8**	**9**	**12**	**13**	**15**	**20**	DBC[d]
Li^+ (332)	7	5	6	4	13	9	3
Na^+ (351)	11	5	9	4	1	0	24
K^+ (357)	0	0	7	0	0	0	22

[a] Ratio of [M^+Pi^-]–[*myo*-inositol derivative] was 1 : 20. [b] No shift in λ_{max} was observed on mixing **6**, **10** or **14** with M^+Pi^- except in the case of **14** + Li^+Pi^- where $\Delta\lambda_{max}$ = 4 nm. [c] λ_{max} for alkali metal picrates in THF. [d] Dibenzo-crown-6.

alkali metal picrates in THF, in order to gain an insight into the nature of the metal ion–inositol derivative complexes involved. The λ_{max} (345 nm) observed for the complexation of **15** with lithium picrate is close to the value reported[18] for the complexation of lithium picrate with tetra(ethylene glycol) dimethyl ether, indicating the existence of similar complexes in both the cases. Potassium picrate in THF is known to exist as a tight ion pair (λ_{max} 357 nm). A crown ether which shifts the λ_{max} of potassium picrate in THF to 361 nm is indicative[17] of a crown-complexed tight ion pair, while a shift to 380 nm (λ_{max} of free picrate anion) would indicate a crown-separated ion pair (as in the case of DBC, λ_{max} = 379 nm). We obtained a λ_{max} of 364 nm for the binding of potassium picrate to **12** (and λ_{max} of 352–362 nm for the binding of sodium picrate to other ligands under study), which suggests the presence of podand-complexed tight ion pairs.

Conclusions

We have reported novel *myo*-inositol based neutral complexing agents, which show good selectivity for binding to lithium and silver ions. The association constants for these podands are much higher than those observed for glyme and some crown ethers.[19] It is known[20] that complexing agents that bind lithium ions strongly have applications in lithium ion selective electrodes, while the relatively weakly binding compounds are useful in lithium batteries. Since these ligands show affinity for lithium ion, which is known to inhibit the catalytic activity of *myo*-inositol-1-phosphatase, the results presented here could aid in the development of cyclitol derivatives, which are useful in biology and medicine related to the *myo*-inositol cycle.

Experimental

General

Di(ethylene glycol) and 2-bromoethanol were obtained from Fluka, UK. Dihydropyran, sodium hydride, *myo*-inositol, benzyl bromide, trityl chloride and toluene-*p*-sulfonyl chloride were obtained from Aldrich, USA. All the solvents and picric acid were obtained from SD Fine Chemicals, India. Silica gel for column chromatography was obtained from Spectrochem Co., India. Compounds **6**,[11] **10**,[12] **14**,[10] **16**,[3d] **21**,[3e] *O*-benzyl-di(ethylene glycol) toluene-*p*-sulfonate,[21] THP ether derivative of 2-bromoethanol,[22] alkali metal and ammonium picrates[13] and silver picrate[19] were prepared as reported in the literature. Compounds **6**–**13** are racemic, but only one of the enantiomers is shown in Scheme 2 for brevity. All the solvents were purified according to literature procedures, before use.[23] All the NMR spectra (200 MHz for ^{1}H on Bruker AC 200 instrument) were recorded in $CDCl_3$ solution unless otherwise noted. Infrared spectra were recorded as neat or as Nujol mull on a Shimadzu FT-IR instrument. Elemental analyses were performed on a Carlo Erba CHNS-0-EA-1108 instrument. Column chromatography was performed over silica gel (200–400 mesh) using ethyl acetate–light petroleum as the eluent (gradient elution). The picrate binding constants reported in Table 1 were estimated by literature procedures.[13]

General procedure for the *O*-alkylation of *myo*-inositol derivatives

To a solution of the required inositol derivative (0.5–2 mmol) in dry DMF (5 mL, unless otherwise noted) was added sodium hydride (2–8 mmol, 60% emulsion in mineral oil) followed by the appropriate alkyl bromide (2–6 mmol) or the glycol toluene-*p*-sulfonate (2–6 mmol). The resulting mixture was stirred at ambient temperature (24 h, unless otherwise noted) and then diluted with chloroform (50 mL) and washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to a gum under reduced pressure. The crude product so obtained was purified by column chromatography.

Racemic 1,2-di-*O*-[2-(2-benzyloxyethoxy)ethyl]-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (7). The diol **6** (0.27 g, 0.5 mmol), DMF (3 mL), sodium hydride (0.17 g, 4.25 mmol) and 2-(2-benzyloxyethoxy)ethyl toluene-*p*-sulfonate (0.39 g, 1.1 mmol) were used (reaction time 1 h) to obtain **7** (0.44 g, 98%) as a thick colorless oil. δ_H 3.30–3.50 (m, 3H), 3.50–3.85 (m, 14H), 3.85–4.10 (m, 5H), 4.55 (2s, 4H), 4.65–5.05 (m, 8H), 7.20–7.50 (m, 30H). δ_C 69.3, 69.9, 70.3, 70.7, 72.3, 72.8, 75.1, 75.3, 75.6, 77.4, 80.5, 81.3, 81.6, 83.3, 127.0, 127.2, 127.5, 128.0, 138.0, 138.2, 138.7, 138.9. Anal. calcd for $C_{56}H_{64}O_{10}$: C, 74.96; H, 7.20. Found C, 74.63; H, 7.62%.

Racemic 1,2-di-*O*-[2-(tetrahydropyran-2-yloxy)ethyl]-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (8). The diol **6** (1.08 g, 2 mmol), sodium hydride (0.32 g, 8 mmol) and tetrahydro-2-(2-bromoethoxy)-2*H*-pyran (1.01 g, 4.8 mmol) were used to obtain **8** (1.50 g, 94%) as a colorless oil. δ_H 1.3–2.00 (m, 12H), 3.2–3.6 (m, 7H), 3.60–4.20 (m, 11H), 4.60–5.00 (m, 10H), 7.10–7.50 (m, 20H). δ_C 19.2, 19.6, 25.0, 25.1, 25.3, 30.4, 61.7, 61.8, 66.6, 66.9, 67.0, 69.7, 69.8, 70.2, 71.9, 72.0, 72.3, 72.4, 72.7, 75.2, 75.4, 75.7, 75.8, 80.5, 80.6, 80.7, 80.9, 81.0, 81.4, 81.7, 83.0, 83.4, 98.4, 98.5, 98.7, 126.5, 127.0, 127.2, 127.3, 127.4, 127.45, 127.5, 127.6, 127.9, 128.0, 138.1, 138.3, 138.7, 138.8, 138.85, 138.9, 139.0. Anal. calcd for $C_{48}H_{60}O_{10}\cdot 0.6H_2O$: C, 71.35; H, 7.64. Found C, 71.63; H, 8.01%.

Racemic 1,2-di-*O*-(2-hydroxyethyl)-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (9). The di-THP ether **8** (0.40 g, 0.5 mmol) was stirred in aqueous acetic acid (80%, 10 mL) at ambient temperature for 24 h. The reaction mixture was then diluted with chloroform (50 mL), washed with water and brine, and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography to get **9** (0.25 g, 79.6%) as a white solid, mp 61 °C. ν_{max} 3100–3600 cm^{-1}. δ_H 3.20–3.40 (d of t, 2H), 3.50 (t, 2H), 3.55–3.80 (m, 8H), 3.85–4.10 (m, 4H), 4.70–4.75 (m, 2H), 4.75–4.80 (m, 1H), 4.85–5.00 (m, 5H), 7.20–7.45 (m, 20H). δ_C 61.6, 61.9, 71.9, 73.1, 75.0, 75.6, 77.0, 80.2, 81.1, 81.3, 81.5, 83.2, 127.4, 127.5, 127.6, 127.8, 128.1, 128.3, 137.7, 138.2, 138.5. Anal. calcd for $C_{38}H_{44}O_8$: C, 72.59; H, 7.05. Found C, 72.89; H, 7.40%.

Racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-4,5-di-*O*-[2-(2-benzyloxyethoxy)ethyl]-*myo*-inositol (11). The podand **11** was prepared using the diol **10** (0.20 g, 0.5 mmol), DMF (3 mL), sodium hydride (0.17 g, 4.2 mmol) and 2-(2-benzyloxyethoxy)ethyl toluene-*p*-sulfonate (0.39 g, 1.1 mmol) as described in the general procedure (reaction time 1 h). The podand **11** was obtained as colorless oil (0.34 g, 90%). δ_H 1.32 (s, 3H), 1.45 (s, 3H), 3.20 (t, 1H), 3.50–3.75 (m, 16H), 3.90–4.05 (m, 4H), 4.2 (t, 1H), 4.55 (2s, 4H), 4.70–4.95 (m, 4H), 7.20–7.50 (m, 20H). δ_C 25.4, 27.3, 61.3, 69.3, 70.2, 70.6, 71.5, 71.7, 72.1, 72.8, 73.3, 74.2, 78.6, 81.0, 81.7, 82.6, 109.2, 126.5, 127.0, 127.1, 127.2, 127.5, 127.7, 127.9, 128.3, 138.2, 138.5. Anal. calcd for $C_{45}H_{56}O_{10}$: C, 71.38; H, 7.46. Found C, 71.12; H, 7.70%.

Racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-4,5-di-*O*-[2-(tetrahydropyran-2-yloxy)ethyl]-*myo*-inositol (12). The THP ether **12** was prepared using the diol **10** (0.30 g, 0.75 mmol), DMF (3 mL), sodium hydride (0.32 g, 8 mmol) and tetrahydro-2-(2-bromoethoxy)-2*H*-pyran (0.84 g, 4 mmol) as described in the general procedure (colorless oil, 0.45 g, 91.4%). δ_H 1.32 (s, 3H), 1.45 (s, 3H), 1.4–1.9 (m, 12H), 3.2 (t, 1H), 3.35–3.75 (m, 8H), 3.8–4.00 (m, 8H), 4.2 (m, 1H), 4.55–4.7 (m, 2H), 4.7–4.95 (m, 4H), 7.1–7.5 (m, 10H). δ_C 19.0, 25.1, 25.3, 27.2, 30.2, 61.6, 66.5, 71.5, 71.6, 72.9, 73.3, 74.3, 78.6, 80.9, 81.6, 82.7, 98.4, 109.2, 126.9, 127.5, 127.8, 127.9, 138.8, 139.0. The di-THP ether **12** has the tendency to retain water (as revealed by its IR spectrum, ν_{max} 3100–3600 cm^{-1} and Anal. calcd for $C_{37}H_{52}O_{10}\cdot 3.5H_2O$: C, 61.74; H, 8.26. Found C, 61.56; H, 8.17%). The podand **12** is not very stable (even when stored in a refrigerator) and decomposes to give unidentified products. Consequently, the picrate extraction data given in Table 1 are not for an analytically pure sample of **12**.

Racemic 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-4,5-di-*O*-(2-hydroxyethyl)-*myo*-inositol (13). The di-THP ether **12** (0.33 g, 0.5 mmol) was dissolved in dry dichloromethane (3 mL) containing 5% v/v of ethanethiol and stirred with $BF_3\cdot Et_2O$ (6 μL, 0.05 mmol) at −20 °C and the resulting solution was allowed to warm up to 0 °C over a period of 30 min. The reaction mixture was poured into a saturated solution of sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product obtained was chromatographed to isolate the diol **13** as a gum (0.21 g, 86%). ν_{max} 3200–3600 cm^{-1}. δ_H 1.3 (s, 3H), 1.45 (s, 3H), 3.25 (t, 2H), 3.4–4.1 (m, 13H), 4.25 (m, 1H), 4.55–5.00 (m, 4H), 7.2–7.5 (m, 10H). δ_C 25.7, 27.7, 62.2, 62.3, 72.7, 73.4, 73.9, 74.5, 74.6, 77.3, 77.5, 79.1, 80.4, 81.9, 82.5, 109.8, 125.0, 127.0, 127.6, 127.9, 128.2, 128.4, 128.5, 128.7, 137.6, 137.9. Anal. calcd for $C_{27}H_{36}O_8$: C, 66.39; H, 7.37. Found C, 66.70; H, 7.24%.

2-*O*-*tert*-Butyldimethylsilyl-4,6-di-*O*-[2-(tetrahydropyran-2-yloxy)ethyl]-*myo*-inositol 1,3,5-orthoformate (15). The THP ether **15** was prepared using the diol **14** (0.61 g, 2 mmol), sodium hydride (0.24 g, 6 mmol) and tetrahydro-2-(2-bromoethoxy)-2*H*-pyran (1.25 g, 6 mmol) as described in the general procedure (gum, 0.96 g, 86%). ν_{max} 2800–3000 cm^{-1}. δ_H 0.15 (d, 6H), 0.95 (d, 9H), 1.4–1.9 (m, 12H), 3.40–3.60 (m, 4H), 3.60–4.00 (m, 7H), 4.1 (m, 2H), 4.2–4.3 (m, 3H), 4.35 (m, 1H), 4.4–4.5 (m, 1H), 4.55–4.65 (m, 2H), 5.55 (s, 1H). δ_C −5.1, 17.9, 18.7, 18.9, 19.0, 24.9, 25.1, 25.5, 29.9, 30.0, 30.2, 60.5, 61.3, 61.4, 61.6, 61.8, 65.7, 65.9, 66.2, 66.4, 66.9, 67.0, 67.6, 68.1, 68.8, 72.3, 73.0, 74.7, 74.9, 75.2, 98.2, 98.3, 98.6, 98.7, 102.2, 102.7. Anal. calcd for $C_{27}H_{48}O_{10}Si\cdot 0.5H_2O$: C, 56.90; H, 8.67. Found C, 56.92; H, 8.86%.

4,6-Di-*O*-(2-trityloxyethyl)-*myo*-inositol 1,3,5-orthoformate (18). The trityl ether **17** was prepared using the diol **16** (0.29 g, 1 mmol), sodium hydride (0.09 g, 2.25 mmol) and the trityl ether **24** (0.81 g, 2.2 mmol) as described in the general procedure (0.63 g, 72%), mp 123–126 °C. ν_{max} 1722 cm^{-1}. δ_H 3.0–3.35 (m, 4H), 3.55–3.85 (m, 4H), 4.3–4.7 (m, 5H), 5.55 (br s, 1H), 5.65 (s, 1H), 7.0–7.75 (m, 33H), 8.2 (d, 2H). δ_C 63.4, 64.5, 68.2, 69.1, 70.4, 74.7, 86.5, 103.2, 126.9, 127.1, 127.7, 128.3, 128.5, 129.8, 133.1, 143.8, 165.8. The benzoate **17** (0.63 g, 0.72 mmol) and isobutylamine (1 mL) were stirred in dry methanol (10 mL) at ambient temperature for 10 h. Methanol was evaporated under reduced pressure, and the resulting syrup was purified by column chromatography to obtain **18** (0.54 g, 98%) as a white solid, mp 67 °C. ν_{max} 3500 cm^{-1}. δ_H 3.0–3.3 (m, 5H), 3.5–3.8 (m, 4H), 4.05–4.15 (m, 1H), 4.20–4.30 (m, 2H), 4.35–4.40 (m, 2H), 4.45–4.55 (m, 1H), 5.5 (s, 1H), 7.1–7.3 (m, 17 H), 7.35–7.50 (m, 13H). δ_C 61.4, 63.4, 67.8, 69.3, 73.0, 74.7, 86.5, 103.2, 126.9, 127.7, 128.5, 143.8. Anal. calcd for $C_{49}H_{46}O_8$: C, 77.13; H, 6.08. Found C, 77.52; H, 6.32%.

2-*O*-Benzyl-4,6-di-*O*-(2-trityloxyethyl)-*myo*-inositol 1,3,5-orthoformate (19). The benzyl ether **19** was prepared using **18** (0.38 g, 0.5 mmol), DMF (2 mL), sodium hydride (0.06 g, 1.5 mmol) and benzyl bromide (0.24 mL, 2 mmol) as described (reaction time 3 h) in the general procedure (0.38 g, 90%), mp 53 °C. δ_H 3.0–3.30 (m, 4H), 3.5–3.8 (m, 4H), 4.05 (s, 1H), 4.35 (d, 4H), 4.40–4.50 (m, 1H), 4.7 (s, 2H), 5.6 (s, 1H), 7.10–7.30 (m, 21H), 7.35–7.55 (m, 14H). δ_C 63.4, 68.0, 69.2, 70.7, 71.6, 74.9, 86.5, 103.2, 126.9, 127.7, 128.3, 128.6, 137.9, 143.8. Anal. calcd for $C_{56}H_{52}O_8$: C, 78.83; H, 6.15. Found C, 78.62; H, 6.35%.

2-*O*-Benzyl-4,6-di-*O*-(2-hydroxyethyl)-*myo*-inositol 1,3,5-orthoformate (20). To a solution of the trityl ether **19** (0.20 g, 0.23 mmol) in benzene (25 mL) was added boric acid (0.90 g) and the mixture was refluxed for 48 h. The reaction mixture was then diluted with chloroform (50 mL), washed several times with water and finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography to get the diol **20** (0.07 g, 85.6%) as a gum. ν_{max} 3100–3600 cm^{-1}. δ_H 3.25 (br s, 2H), 3.6 (s, 8H), 3.9 (s, 1H), 4.15–4.35 (m, 4H), 4.4–4.5 (m, 1H), 4.75 (s, 2H), 5.55 (s, 1H), 7.25–7.5 (m, 5H). δ_C 61.2, 66.8, 67.4, 70.0, 71.2, 71.5, 74.7, 76.9, 77.5, 102.9, 127.7, 127.9, 128.3, 137.6. Anal. calcd for $C_{18}H_{24}O_8\cdot 0.5H_2O$: C, 57.29; H, 6.63. Found C, 57.51; H, 6.80%.

2-*O*-Benzyl-4,6-di-*O*-[2-(tetrahydropyran-2-yloxy)ethyl]-*myo*-inositol 1,3,5-orthoformate (22). The THP ether **22** was prepared using the diol **21** (0.09 g, 0.32 mmol), sodium hydride (0.06 g, 1.5 mmol) and tetrahydro-2-(2-bromoethoxy)-2*H*-pyran (0.22 g, 1.05 mmol) as described in the general procedure (gum, 0.17 g, 98.7%). δ_H 1.4–1.9 (m, 12H), 3.40–3.90 (m, 12H), 3.90–4.00 (s, 1H), 4.25–4.40 (m, 4H), 4.45–4.50 (m, 1H), 4.50–4.65 (m, 2H), 4.70 (s, 2H), 5.55 (s, 1H), 7.20–7.50 (m, 5H). δ_C 19, 25.0, 29.3, 30.2, 61.6, 66.3, 66.4, 67.4, 67.8, 68.7, 70.3, 71.1, 74.5, 98.4, 98.6, 102.8, 127.4, 128.0, 137.8. Anal. calcd for $C_{28}H_{40}O_{10}$: C, 62.65; H, 7.52. Found C, 62.55; H, 7.65%.

2-*O*-Benzyl-4,6-di-*O*-[2-(2-benzyloxyethoxy)ethyl]-*myo*-inositol 1,3,5-orthoformate (23). The podand **23** was prepared using the diol **21** (0.28 g, 1 mmol), DMF (3 mL), sodium hydride (0.2 g, 5 mmol) and *O*-benzyldi(ethylene glycol) toluene-*p*-sulfonate (0.80 g, 2.3 mmol) as described (reaction time 1 h) in the general procedure (oil, 0.58 g, 91.2%). δ_H 3.50–3.75 (m, 16H), 3.95 (m, 1H), 4.3 (t, 2H), 4.35 (m, 2H), 4.50 (m, 1H), 4.55 (s, 4H), 4.70 (s, 2H), 5.55 (s, 1H), 7.20–7.50 (m, 15H). δ_C 67.3, 67.8, 69.0, 69.3, 70.4, 71.2, 73.0, 74.7, 102.9, 127.5, 128.1, 138.0. Anal. calcd for $C_{36}H_{44}O_{10}\cdot 0.5H_2O$: C, 66.94; H, 7.03. Found C, 66.65; H, 7.23%.

1-Bromo-2-trityloxyethane (24). 2-Bromoethanol (2.4 mL, 32 mmol), trityl chloride (12 g, 43 mmol) and *N*,*N*-diisopropylethylamine (15 mL) were mixed in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 24 h. Conventional work up of the reaction mixture yielded the trityl ether **24** (10.6 g, 90%), mp 127 °C.[24]

Acknowledgements

This work was supported by the Department of Science and Technology, New Delhi (research grant No. SP/S1/G-30/94 to MSS and AJV). KMS thanks the Council of Scientific and Industrial Research, New Delhi, for a Senior Research fellowship. Technical assistance by Ms S. V. Deshpande is appreciated.

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