Tetrahedron 65 (2009) 3998–4006

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total syntheses of cyclitol based natural products from *myo*-inositol: brahol and pinpollitol

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ARTICLE INFO

Article history:
Received 23 February 2009
Received in revised form 5 March 2009
Accepted 6 March 2009
Available online 19 March 2009

Keywords:
Natural product
Total synthesis
Inositol
Cyclitol
Regioselective reaction

ABSTRACT

Inositol and their derivatives are important class of biologically active natural products. Among the nine theoretically possible inositols, six are known to occur in nature. Interestingly one or more methyl ethers of these inositols have been isolated from plants and these methyl inositols are presumed to have important functions in plant biology. Brahol and pinpollitol are two naturally occurring methylated inositols reported to have *allo*-inositol and *chiro*-inositol configurations, respectively. Adopting our sulfonate inversion strategies for synthesizing protected *chiro*- and *allo*-inositols from cheaply available *myo*-inositol in combination with new methods we have achieved the total syntheses of these methylated inositols. The proposed structure of brahol has been synthesized in six steps from *myo*-inositol. We have not only disproved the proposed structure of brahol but also established its correct structure. Also, we have efficiently synthesized pinpollitol and its positional isomer from *myo*-inositol. These works involve several selective protection–deprotection strategies of inositol hydroxyl groups.

1. Introduction

Due to the involvement of various phosphorylated inositols, inositol based lipids, and glycosylated inositols in various biological processes including cellular signaling, protein anchoring, etc., a great deal of attention has been paid to the inositol chemistry.[1] Inositols, being cyclohexane hexols, have nine theoretically possible isomers. Six of these nine possible isomers, namely *myo*-, D-*chiro*-, L-*chiro*-, *neo*-, *muco*-, and *scyllo*-inositols, are known to occur naturally, *myo*-inositol being the most abundant. Phosphorylated, glycosylated, and unmodified inositols have been found in animals and plants. However, methylation is a modification of inositols found exclusively in plants.[2] Methyl ethers of all the known naturally occurring inositols have been isolated and are presumed to have important physiological functions in plants.[2] Many of these naturally occurring methyl ethers of inositols have been synthesized[3] either to validate the proposed structures or to provide easy access as the isolation from natural sources is often tedious and low-yielding.

Ahmad[4] et al. isolated a methylinositol, brahol, from the folklore medicinal plant *Stocksia brahuica* for the first time. Relying on the chemical shift values of various protons in the ^{1}H NMR spectrum, brahol was identified as 5-*O*-methyl-*allo*-inositol **1** (Chart 1), the first and only known natural *allo*-inositol derivative. A systematic investigation to assign the structure, physicochemical properties (absolute configuration, α_D, mp), and biological activities was not undertaken probably due to the insufficiency of the isolated material. In an effort to supply this material in sufficient quantity in order to study its physicochemical properties and biological profile, we have synthesized the proposed structure of brahol.[5] However, the original structural assignment of brahol was found to be wrong and hence we have revised the structural assignment. The full details of the synthesis and structural revision constitute part of this report.

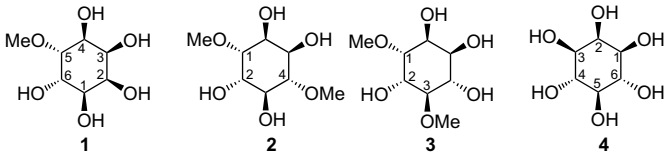

Chart 1. *myo*-Inositol and proposed structures of brahol and pinpollitol.

Gallagher isolated (+)-pinpollitol, an unsymmetrical dimethyl ether of D-*chiro*-inositol, from the pollens of the plant *Pinus radiata*.[6] The author has tentatively proposed two probable structures for pinpollitol; 1D-1,4-di-*O*-methyl-*chiro*-inositol (**2**) and 1D-1,3-di-*O*-methyl-*chiro*-inositol (**3**) based on the comparison of the chemical shifts of both pinpollitol and its tetra-*O*-acetyl derivative with structurally similar cyclitol derived compounds. In an elegant

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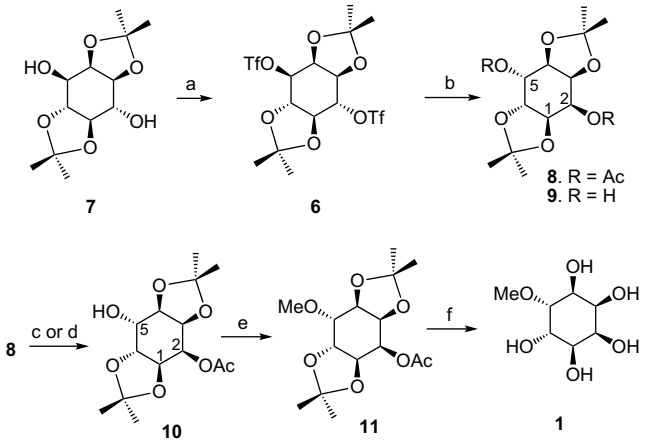
doi:10.1016/j.tet.2009.03.024

approach, Angyal et al. have synthesized **2**, one of the two proposed structures from pinitol and by comparing its NMR spectra with that of pinpollitol, it has been reported that **2** is the correct structure of pinpollitol.[7] However, dimethyl ether **3** has not been synthesized. This is important as structurally related inositol derivatives could often have similar ^{1}H NMR or the difference could be very subtle to be apparent in a spectrum recorded in a low resolution NMR spectrometer. Thus, when there are two possibilities, the practice of ruling out the alternative possibility is as important as proving one of the two possibilities for unambiguous establishment of the structure. In order to provide alternate strategy for the synthesis of **2** from cheaply available *myo*-inositol and to rule out the other proposed structure, we have synthesized both **2** and **3**.[8] This study not only established the fact that Angyal's structural assignment was correct but also provided an economical route to **2**. The full details of these studies constitute part of this report. All the unsymmetrical synthetic compounds reported here are racemic mixtures, but for brevity only one of the enantiomers is shown.



Scheme 1. (a) Tf_2O (2.2 equiv), Py, CH_2Cl_2, −20 °C; (b) KOAc, DMA, 70 °C; (c) MeOH, Et_3N, reflux; (d) MeOH, *iso*-butylamine, 60 °C; (e) MeI, NaH, DMF, rt; (f) 1 N HCl, MeOH, rt.

2. Results and discussions

myo-Inositol (**4**) being structurally related to **1**–**3** and very cheaply available, the syntheses of **1**–**3** from *myo*-inositol are justifiable. Since all the six secondary hydroxyl groups of inositol(s) are expected to have more or less similar reactivity toward methylation, other hydroxyl groups have to be protected before methylation. The selective protection–deprotection strategies for *myo*-inositol hydroxyl groups have been well explored,[9] and hence appropriately protected derivatives can easily be prepared by adopting these known methodologies. The relative stereochemistry at 1, 2, 4, and 5 positions of *myo*-inositol are preserved in compounds **1** and **2** and hence 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**7**)[10] was chosen as the suitable protected starting material. However, for the synthesis of **3**, diketal **7** cannot be an economical starting point as methylation is required at O-5. Thus we decided to synthesize **3** from *myo*-inositol 1,3,5-orthoformate. The known methods for the efficient optical resolution of orthoesters[11] and diketal **7**[12] allow the synthesis of **1**–**3** in optically pure form if required.

2.1. Synthesis of 1

Methyl ether **1** can be obtained from protected *allo*-inositol **5** (Chart 2) by methylation followed by removal of the protecting groups. Protected derivative **5** can be synthesized from the ditriflate **6** by nucleophilic substitution with an appropriate oxygen nucleophile[13] and selective protection of 2-OH group. Ditriflate **6** can be synthesized from the diketal **7**, which can be prepared from *myo*-inositol.[10]

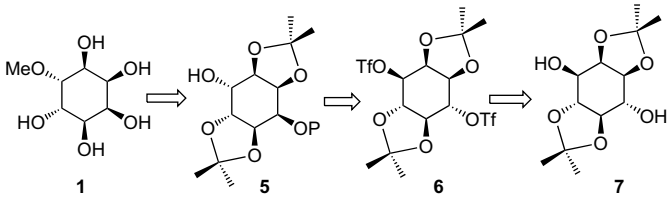


Chart 2. Retrosynthesis of **1**.

We have recently reported the synthesis of diacetate **8** during our synthesis of *allo*-inositol from *myo*-inositol.[14] The ditriflate **6** obtained by sulfonylation of diol **7** was reacted with KOAc in DMA to obtain racemic 2,5-di-*O*-acetyl-1,6:3,4-di-*O*-isopropylidene-*allo*-inositol (**8**)[5] in 87% yield (Scheme 1). Protons on C-2 and C-5 are shifted downfield as expected due to the acylation of the respective hydroxyl groups. The proton signal at 5.64 ppm appeared as a doublet of doublet (dd) with coupling constants 5.7 Hz and 2.6 Hz and the dd signal at 5.74 ppm showed coupling constants 3.3 Hz and 1.6 Hz. H-5 is expected to show one axial–equatorial (ae) and one equatorial–equatorial (ee) coupling while H-2 is expected to show two axial equatorial couplings. Since ae and ee coupling constants do not vary much, the assignment of protons was not straightforward. It is well known that the coupling constants vary with the orientation of the electronegative atoms (or groups) on the two carbons bearing coupling hydrogens.[15] Taking into consideration the orientation of oxygen atoms in **8**, H-2 is expected to show relatively larger coupling constants compared to H-5.[16] Thus the dd signal at 5.64 ppm is assigned to be due to H-2 and that at 5.74 ppm due to H-5.

Next task was to methylate the 5-OH selectively. Since the diol **9**, which can be prepared by basic hydrolysis of the diacetate **8**, has two axial hydroxyl groups (in **9**), it is not expected to show any regioselectivity toward methylation. Also, discrimination between these two axial hydroxyl groups in any reaction is difficult.[9] Since the selective protection of 2-OH or selective methylation of 5-OH is expected to be difficult, we were inclined to explore selective deacylation of one of the acetyl groups. Both the acetoxy groups at C-2 and C-5 are flanked by two protected hydroxyl groups; in the case of C-2-OAc, both the protected hydroxyls on either side (C-1-O and C-3-O) have *syn* relation to it whereas in the case of C-5-OAc, one of the adjacent protected hydroxyl groups (C-4-O) has *anti* relation with the acetoxy group. 3D model revealed that the methyl groups of isopropylidene protection make C-2-OAc more sterically protected than C-5-OAc. We were curious to know whether this through-space protection of C-2-OAc can be exploited for the selective removal of C-5-OAc and hence a regioselective de-acylation was attempted. We envisioned that a bulky nucleophile could easily attack the C-5-OAc compared to the sterically inaccessible C-2-OAc. As anticipated, aminolysis of **8** with *tert*-butylamine provided the monoacetate **10**[5] in quantitative yield. The cleavage of the acetate at C-5 was indicated by the disappearance of the signal at 5.74 ppm. Additional evidence for C-5-OAc cleavage was obtained from a comparison of the $^3J_{H-H}$ coupling constants of the most downfield shifted dd signal (5.61 ppm) in **10** (5.1, 2.5 Hz) with those of H-2 (5.7, 2.6 Hz) and H-5 (3.3, 1.6 Hz) in **8**. Furthermore, single crystal X-ray analysis of **10** (see Supplementary data) further confirmed our structural assignment.[17]

Having achieved a regioselective deacylation under mild condition, we were curious to know whether such a high degree of selectivity can be achieved under relatively harsh conditions also.

When the aminolysis with *tert*-butylamine was conducted at refluxing conditions also, C-2-OAc was found to be stable. Furthermore, aminolysis with less bulky *iso*-butylamine (yield of **10**: 93%) and even more surprisingly, methanolysis using Et_3N as the base (yield of **10**: 91%) also resulted in deacylation of the acetate group at C-5 selectively, despite methoxide ion being a less bulky nucleophile. Such a high degree of selectivity is interesting and noteworthy as the regioselective functionalization is one of the major foci in the synthetic chemistry of cyclitols.[9]

Methylation of the acetate **10** provided the methyl ether **11**[5] as the exclusive product. The $^3J_{HH}$ values (5.3, 2.7 Hz) for the downfield shifted proton signal suggest that it is due to H-2. This ruled out any possibility of acetyl migration under the alkylation condition (Williamson's condition). Also the signal due to H-5 shifted upfield as expected[18] as a result of O-5 methylation. The single crystal X-ray structure of **11** (see Supplementary data) provided additional evidence for its structure.[17] Finally, 5-*O*-methyl-*allo*-inositol (**1**) was obtained via the global deprotection by acid hydrolysis.[5]

2.2. Revision of the structure of brahol

The structural assignment of brahol by Ahmad et al. was proven to be wrong by a comparison of ^{1}H NMR spectra of our synthetic **1** with that reported for brahol.[4] While brahol is reported to have sharp signals in its ^{1}H NMR spectrum,[4] 5-*O*-methyl-*allo*-inositol (**1**) in D_2O showed very broad signals for both protons[5] and carbons. This is not surprising based on the possible slow (with respect to the NMR time scale) dynamic equilibrium between two chair conformations since *allo*-inositol possesses three axial and three equatorial hydroxyl groups. Although a substituted *allo*-inositol would prefer a conformation where the substituted hydroxyl has equatorial orientation, methyl being a very small substituent, the energy barrier between two chair conformations of monomethyl *allo*-inositol is expected to be small and hence it can be in dynamic equilibrium between two conformations. A variable temperature NMR experiment (Fig. 1) substantiated this assumption. The signals became more and more resolved as the experimental (NMR) temperature increased. Very sharp and well resolved signals were observed for different protons and carbons at 80 °C.[5] Based on the absence of any line broadening in the reported ^{1}H NMR spectrum of brahol we became skeptical about its proposed *allo*-configuration (three axial and three equatorial oxygens).

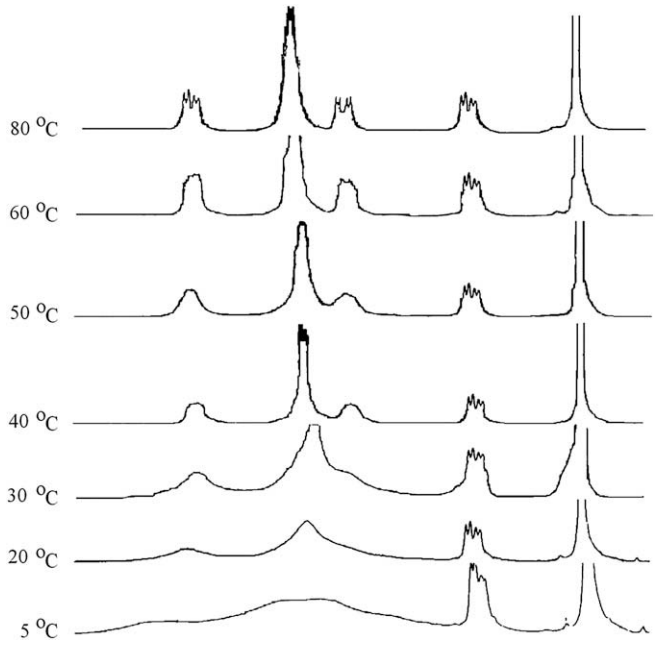


Figure 1. Variable temperature ^{1}H NMR of 5-*O*-methyl-*allo*-inositol (**1**) in D_2O.

Angyal et al. have studied and generalized[18] the effect of O-methylation in chemical shifts of protons in cyclitols. Ahmad et al. used these generalizations for the structural assignment of brahol. The axial orientation of methoxy substituent was assumed based on the chemical shift of the carbon atom bearing the OMe and the relative stereochemistry of other carbon atoms was proposed by correlating with the stereochemistry of the carbon bearing the OMe. As the O–CH_3 resonance in the ^{1}H NMR spectra of methyl ethers of inositols appear in the range 3.45–3.65 ppm in general,[18] an unusual chemical shift of 3.25 ppm for O–CH_3 resonance in brahol points that the spectrum is up-field shifted. Thus the reliance on the chemical shift values of a shifted spectrum for the stereochemical assignment resulted in wrong assignment of the structure.

As we have proved that the structure of brahol is wrong, we attempted to assign the structure of brahol using the reported NMR data. But the reported data are insufficient to predict the structure unambiguously in a straightforward manner. Thus a logistic method was applied. There are 20 theoretically possible isomeric monomethyl ethers for 8 inositols (Chart 3). Since comparison of all these structures with brahol is tedious, we have short-listed the number of possible structures based on symmetry. The reported ^{1}H NMR data of brahol are of an unsymmetrical methyl ether of inositol. Of the possible 20 monomethyl ethers (**1**, **12**–**30**, Chart 3), 8 (**12**–**19**) are having a plane of symmetry in them and are expected to give a symmetrical NMR spectrum. Based on the lack of symmetry in the reported ^{1}H NMR spectrum of brahol, the number of plausible structures was reduced to 12 (**1**, **20**–**30**). Methyl ethers of *muco*- and *allo*-inositols, having three axial and three equatorial dispositions of oxygen, are expected to give broad peaks in the ^{1}H NMR spectrum due to conformational exchange. Thus four of the methyl ethers of *allo*- and *muco*-inositols (**1**, **20**–**22**) were also set aside based on the sharp signals in the reported ^{1}H NMR spectrum of brahol. Of the remaining eight structures, two *myo*-inositol methyl ethers (**23** and **24**) were ruled out by comparing the reported data of brahol with that of bornesitol (1-*O*-methyl-*myo*-inositol)[19] and ononitol (4-*O*-methyl-*myo*-inositol).[3e] Thus by using this analysis based on symmetry and conformation, we could reduce the possible number of structures to six. All these six structures (Chart 4) are of methyl ethers of inositols having two axial and four equatorial hydroxyl groups (*epi*, *chiro*, and *neo*).

The six possible structures along with the reported structure of brahol are shown in Chart 4. The numbering and orientation (with respect to O–Me group) of the chair form of all the six methyl ethers have been adjusted to the reported structure for easy comparison. The coupling $^3J_{HH}$ constants of H-4 (dd, 3.8, 3.3 Hz) and H-3 (dd, 3.8, 3.4 Hz) of brahol have been reported in the original paper. In the case of **25**, H-3′ is expected to show a dd with one large coupling constant (and small coupling constant) due to the diaxial orientation of H-2′ and H-3′. Based on the lack of a large coupling constant for $^3J_{H\text{-}2',H\text{-}3'}$ the structure **25** has been ruled out. The methoxy protons of brahol are reported to show NOE interaction with its neighboring methyne proton (H-4). However, such NOE interaction is not possible in **26** because of their diaxial orientation. Also H-3′ and H-4′ in **26**–**28** should have at least one larger coupling constant (in **26** and **28**, H-3′ is expected to have two large coupling constants and H-4′ one large and one small coupling constants and in **27**, H-4′ is expected to have two large coupling constants and H-3′ one large and one small coupling constants) due to diaxial disposition of hydrogens. Based on the reported smaller coupling constants for both H-3 and H-4 in brahol, structures **26**–**28** were ruled out. The reported chemical shifts of axial proton, H-3 and the equatorial proton H-2 of brahol are 3.85 ppm and 3.54 ppm, respectively. But

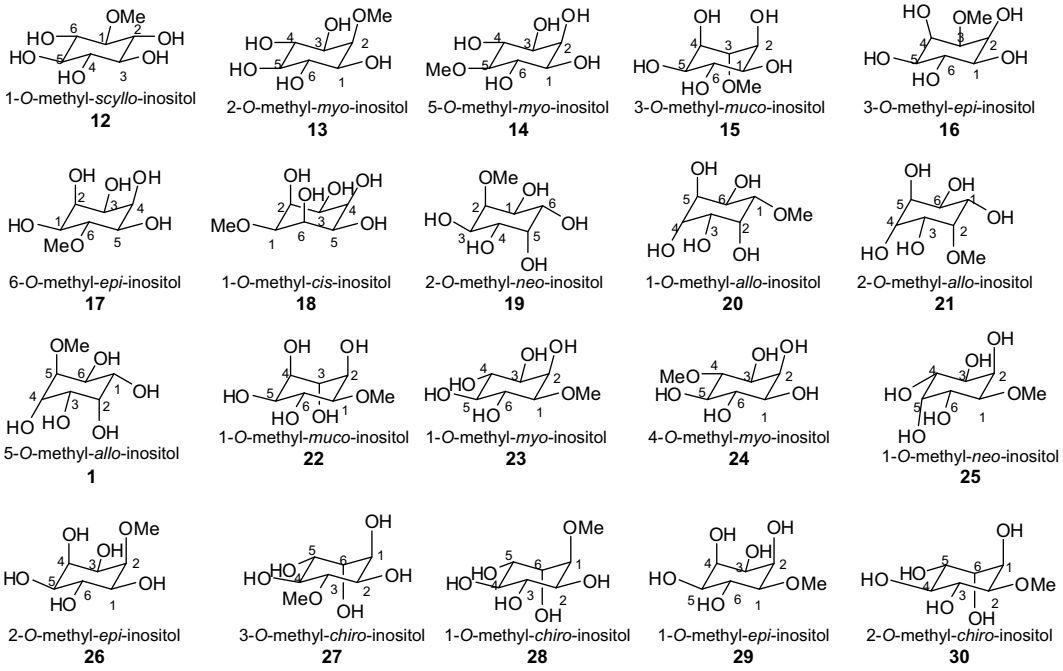


Chart 3. All theoretically possible structures for monomethyl ethers of inositols.

it is well known that the chemical shift values (δ) of equatorial protons are usually higher (lower field) than that of axial protons. So we suspected a reversal of configuration at these positions is reasonable. More clearly, the chemical shift of H-2 (3.54 ppm) is closer to that of other two axial hydrogens (H-1 and H-6, 3.40 ppm) while the chemical shift of H-3 (3.85 ppm) is closer to the value for other equatorial hydrogen (H-4, 4.06 ppm). The lower chemical shift value for H-5 is as expected since O-methylation brings about an up-field shift of α-hydrogens irrespective of their orientation (axial or equatorial).[18] These facts suggest that **30** is the more plausible structure of brahol.

A comparison of the spectra of **30** (L-2-*O*-methyl-*chiro*-inositol: L-quebrachitol) and brahol established that they are same (Fig. 2). When the ^{13}C NMR spectrum of quebrachitol was standardized by assigning its most downfield carbon signal with the chemical shift value of the most downfield carbon signal reported for brahol, the whole spectrum literally reproduced the reported spectrum of brahol (Fig. 2c). Thus our study challenges the first and only report of the natural occurrence of an *allo*-inositol (derivative). The reported spectrum of brahol has found to be shifted up-field as we have suspected. The structural assignment of brahol was done by comparing the chemical shift values of various protons and carbons following Angyal's generalization on the effect of methylation on chemical shifts of cyclitols.[18] A chemical shift of 3.25 ppm for the $O-CH_3$ misled the authors to assume that it is having an axial orientation in the chair form of cyclitol and the relative

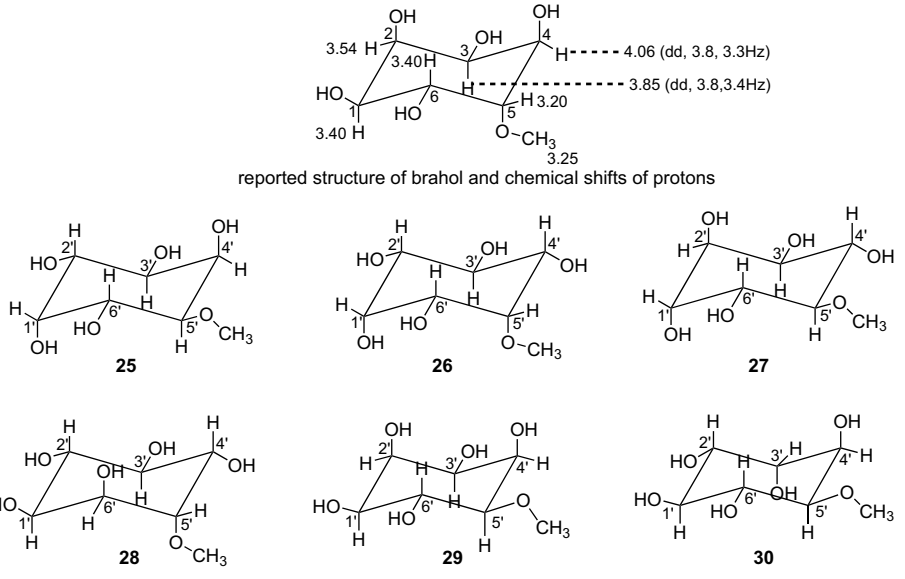


Chart 4. Structural comparison of brahol with **25**–**30**. The numbering similar to brahol has been followed for **25**–**30** and the orientation has been fixed as in brahol by taking the carbon bearing OMe as the reference point.

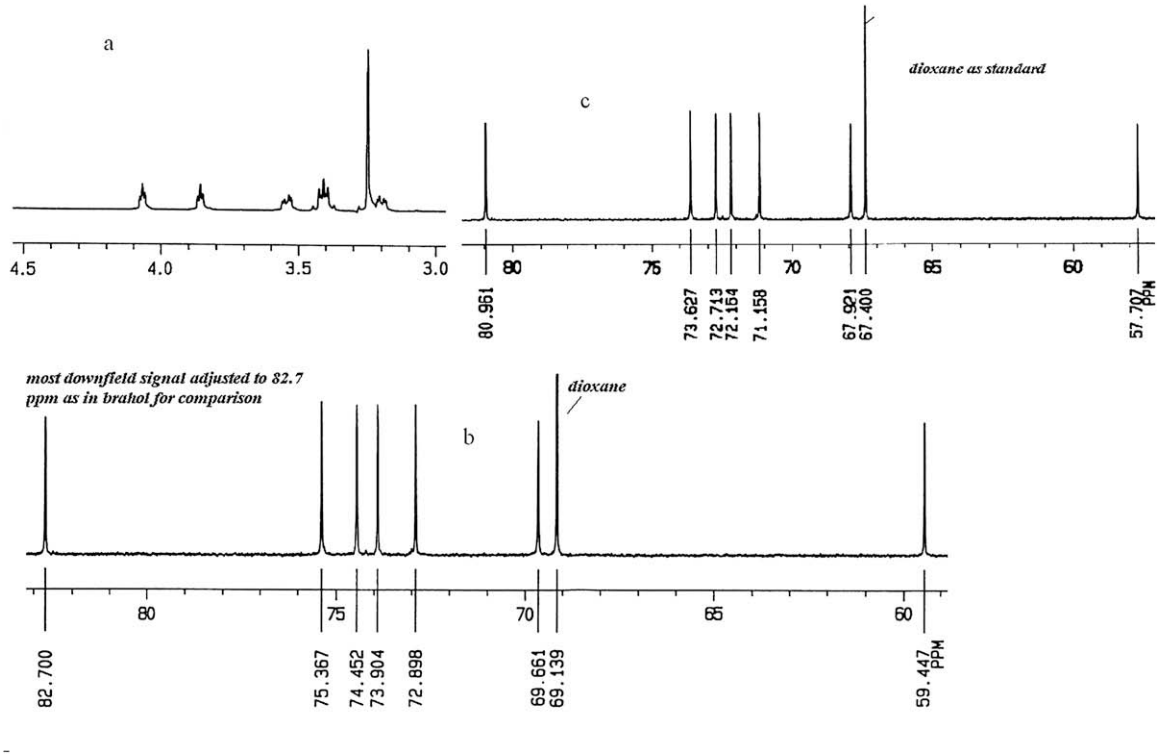


Figure 2. (a) ^{1}H NMR of quebrachitol standardized with respect to the OMe signal reported brahol. (b) ^{13}C NMR spectrum of quebrachitol standardized with respect to the most downfield signal reported brahol. (c) ^{13}C NMR spectra of quebrachitol standardized with dioxane as the internal standard.

stereochemistries of other carbons were determined by correlating (NOE, $^{3}J_{HH}$ values) with this. However, due to the reliance on a shifted spectrum, the assignment of axial orientation for the OMe was wrong. Since the relative stereochemistry of the reference center was incorrect, the relative stereochemistries of all other carbons also were wrong and this culminated in a wrong structural assignment for brahol. Although Angyal's generalizations are extremely useful for the structural assignment, care must be taken to standardize the NMR chemical shifts with a known standard peak other than HOD as the chemical shift of HOD varies with concentration, temperature, and pH.[20]

2.3. Synthesis of 2

Methylation of diol **31** followed by the deprotection of the isopropylidene groups is expected to provide dimethyl ether **2**. Diol **31** can be obtained from the triflate **32**, which can be obtained from diketal **7** (Chart 5).

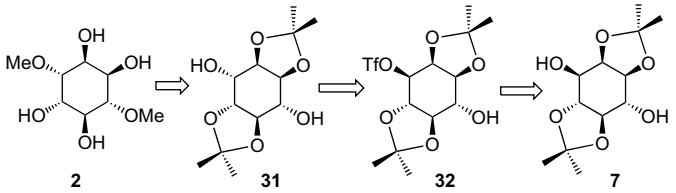
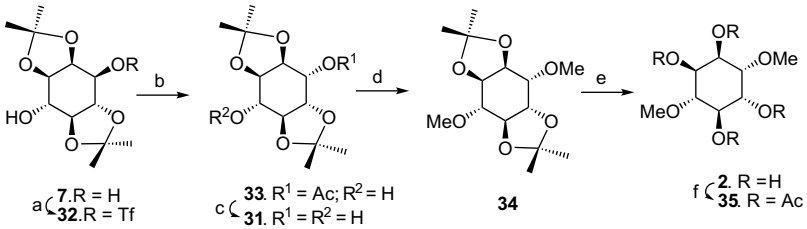


Chart 5. Retrosynthesis of **2**.

The diol **31**, the precursor for the synthesis of **2**, was synthesized from *myo*-inositol diketal **7**.[21] Regioselective sulfonylation of racemic diol **7** with triflic anhydride provided the monotriflate **32**, which on nucleophilic substitution with KOAc in *N*,*N*-dimethylacetamide (DMA) gave the racemic 1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (**33**) in quantitative yield. Single crystal X-ray structure of (−)-**33**[22]confirmed its structure (see Supplementary data). Methanolysis of the acetate **33** provided diol (±)-**31** (85% from **7**), which on methylation provided (±)-1,2:4,5-di-*O*-isopropylidene-3,6-di-*O*-methyl-*chiro*-inositol (**34**) in good (99%) yield. Hydrolytic removal of the isopropylidene groups under acidic conditions provided (±)-1,4-di-*O*-methyl-*chiro*-inositol (**2**, 73%), which on acetylation provided the tetraacetate **35** (93%) (Scheme 2).

2.4. Synthesis of 3

Dimethyl ether **3** can be synthesized from the protected diol **36** by methylation followed by deprotection of the hydroxyl groups. The diol **36** can be synthesized by nucleophilic substitution of the differentially protected *myo*-inositol derived triflate **37** with an appropriate oxygen nucleophile (acetate), followed by the removal of protecting group P2. Acetyl and benzyl were chosen as the protecting group P2 and P1, respectively, so that both the acetyl groups (newly introduced acetate at the inversion site and P2) can be cleaved simultaneously to provide the diol **36**. It has been known that 1-OH and 3-OH are more nucleophilic than 5-OH in *myo*-inositol toward various electrophilic reagents.[9] Thus the triflate **37** can be obtained from triol **38** by sequential protection of 1-OH with protecting group P1 (Bn), triflylation of 3-OH, and protection of the 5-OH with protecting group P2 (Ac). Triol **38** can be prepared from orthoformate **39** by protection of its three hydroxyl groups with P1 (Bn) followed by acid hydrolysis of the orthoester cage. Orthoformate **39** can be obtained from *myo*-inositol in good yield (Chart 6).[23]



Scheme 2. (a) Tf_2O (1.1 equiv), py, CH_2Cl_2, −20 °C; (b) KOAc, DMA, 70 °C; (c) NaOMe, MeOH, reflux; (d) MeI, NaH, DMF, rt; (e) TFA, H_2O, rt; (f) Ac_2O, py, rt.

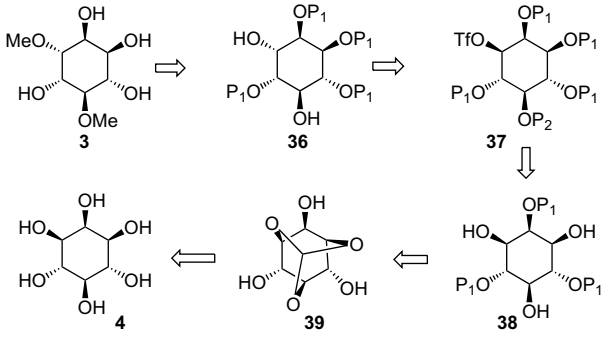
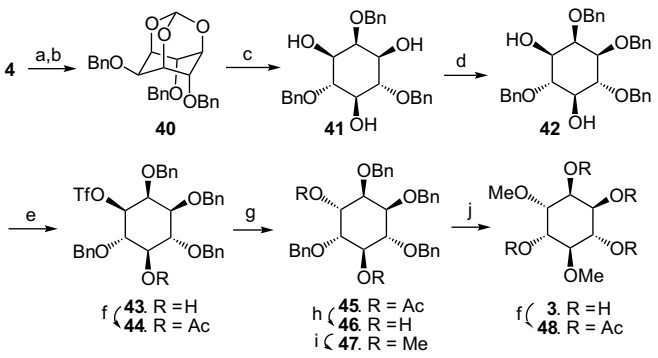


Chart 6. Retrosynthesis of **3**.

2,4,6-Tri-*O*-benzyl-*myo*-inositol **41**[24] was prepared from *myo*-inositol 1,3,5-orthoformate (**39**)[23] via benzylation to tribenzyl ether **40**[24a,25] followed by acid hydrolysis. Benzylation of triol **41** with one equivalent of NaH and benzyl bromide provided the known[26] tetrabenzyl ether **42** selectively. Triol **41** being a *meso* compound, 1-OH and 3-OH are chemically equivalent. The lack of symmetry in the NMR spectrum of **42** is indicative of benzylation at 1(3)-position (benzylation at 5-OH give a *meso* compound). Sulfonylation of the diol **42** gave the triflate **43** (81%) as anticipated based on the enhanced reactivity of 3-OH over 5-OH.[9] A deshielded dd signal with $^3J_{HH}$ coupling constants 7.6 Hz and 2.0 Hz, the typical *J* values for H-3 of inositol, confirm the sulfonylation at O-3. In addition, coupling of H-5 with OH (J=2.4 Hz) further supports the fact that 5-OH is unaffected during sulfonylation. The hydroxyl group in triflate **43** was protected as acetate (98%). Nucleophilic substitution of triflate **44** with KOAc provided racemic 1,2,3,5-tetra-*O*-benzyl-4,6-di-*O*-acetyl-*chiro*-inositol (**45**, 30%) and a mixture of unidentified products. This could be either due to the partial hydrolysis of the diacetate **45** or due to the action of other pathways like S_N1 or elimination reactions. However, a detailed study was not undertaken to separate and identify these byproducts. The hydroxyl groups at 3- and 5-position were exposed by methanolytic removal of the acetate protecting groups. Methylation of diol **46** provided the dimethyl ether **47** (63%), which on hydrogenolysis provided 1,3-di-*O*-methyl-*chiro*-inositol (**3**, 89%). Tetrol **3** on acetylation afforded the tetraacetate **48** in 93% yield (Scheme 3).

In agreement with Angyal's report, the structural identity of pinpollitol as 1,4-di-*O*-methyl-*chiro*-inositol has been proven based on comparison of ^{1}H NMR of pinpollitol and its tetraacetate with that of dimethyl ethers (**2** and **3**) and their tetraacetates (**35** and **48**).



Scheme 3. (a) $CH(OEt)_3$, *p*-TSA, DMF, 100 °C, 2 h; (b) BnBr, NaH, DMF, rt; (c) 1 M HCl, MeOH, reflux, 1 h; (d) BnBr, NaH, DMF, rt, 10 min; (e) Tf_2O, py, 0 °C; (f) Ac_2O, py, 0 °C; (g) KOAc, DMA, 70 °C; (h) Et_3N, MeOH, reflux, 1 h; (i) MeI, NaH, DMF, 0 °C; (j) Pd/C, H_2, MeOH, EtOAc, rt.

3. Conclusions

In conclusion, we have reported the efficient syntheses of three methyl inositols from *myo*-inositol via sulfonate inversion strategy. The synthesis of the reported structure of brahol, 5-*O*-methyl-*allo*-inositol, and a comparison of its spectral data with that of the natural product revealed that the structural assignment of brahol was wrong. We have reassigned the structure of brahol to be 2-*O*-methyl-*chiro*-inositol based on the spectral data and logistical approach. Also, we have synthesized both the proposed plausible structures of pinpollitol; 1,3-di-*O*-methyl-*chiro*-inositol and 1,4-di-*O*-methyl-*chiro*-inositol. Agreeing with previous report, a comparison of the spectral data of the natural product with the synthetic compounds unambiguously established that the correct structure is 1,4-di-*O*-methyl-*chiro*-inostol. In addition to achieving the total synthesis of these methyl inositols and establishing the structures of these natural compounds, our syntheses involved several regioselective protection–deprotection of inositol hydroxyl groups and several useful synthetic transformations, which will be of interest to a broad cross-section of organic chemists as inositol and other cyclitols are increasingly being recognized as synthons for many natural products,[27] metal complexing agents,[28] gelators,[29] catalysts,[30] supramolecular assemblies,[31] chiral auxiliary,[32] etc.

4. Experimental

4.1. General

All chemicals were purchased from Aldrich chemical company. All experiments were conducted under nitrogen atmosphere. Melting points were determined with a Yanaco Micro Melting Point Apparatus and are uncorrected. Flash column chromatography was performed using silica gel (Fuji Silysia, Silica gel BW-300). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-DPX-400 instrument. Chemical shifts (δ_H values relative to tetramethylsilane and δ_C values relative to $CDCl_3$) and coupling constants (*J* values) are given in parts per million and hertz, respectively. Elemental analyses were carried out on a YANACO MT-5 elemental analyzer. Usual work-up refers to evaporation of the reaction solvent followed by dissolution of the residue in ethyl acetate and washing successively with water, dil HCl, satd $NaHCO_3$ solution, and brine followed by drying over anhydrous $MgSO_4$ and concentration under reduced pressure.

4.2. 3-*O*-Acetyl-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (10)

4.2.1. Method A

The diacetate **8**[14] (344 mg, 1 mmol) was stirred with *tert*-butylamine (1 mL, 9.5 mmol) in methanol (9 mL) at rt for 2 h, when the TLC showed disappearance of starting material. The solvents were evaporated and the residue was chromatographed using ethyl acetate and hexane as eluent to get pure monoacetate **10**[5] (299 mg, 99%). Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C, 55.46; H, 7.46.

4.2.2. Method B

The diacetate **8** (172 mg, 0.5 mmol) was stirred with *iso*-butylamine (0.5 mL, 4.55 mmol) in methanol (5 mL) at rt for 1 h. The solvents were evaporated and the residue was chromatographed using ethyl acetate and hexane as eluent to get pure monoacetate **10** (140 mg, 93%).

4.2.3. Method C

The diacetate **8** (172 mg, 0.5 mmol) was refluxed with triethylamine (0.5 mL) in methanol (5 mL) at rt for 1 h. The solvents were evaporated and the residue was chromatographed using ethyl acetate and hexane as eluent to get pure monoacetate **10** (138 mg, 91%).

4.3. 2-*O*-Acetyl-1,6:3,4-di-*O*-isopropylidene-5-*O*-methyl-*allo*-inositol (11)

To a solution of acetate **10** (302 mg, 1 mmol) in DMF (6 mL) at 0 °C, sodium hydride (29 mg, 1.2 mmol) was added and the solution was stirred for 5 min. Then, methyl iodide (125 μL, 2 mmol) was added and the mixture was stirred at rt for 3 h, when the TLC showed complete disappearance of the starting material. The mixture was diluted with ethyl acetate, washed with water, dil HCl, and satd $NaHCO_3$ solution, and brine. The organic layer was dried and evaporated under reduced pressure to provide pure methyl ether **11**[5] (310 mg, 98%). Further purification was done by crystallization from a mixture of ethyl acetate and hexane. Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 56.79; H, 7.78.

4.4. 5-*O*-Methyl-*allo*-inositol (1)

The acetate **11** (280 mg, 0.88 mmol) was stirred in a mixture of 1 N HCl (1 mL) and methanol (4 mL) at rt overnight. Evaporation of the solvents followed by co-evaporation with toluene provided pure methyl ether **1**[5] (171 mg, 100%). Anal. Calcd for $C_7H_{14}O_6$: C, 43.30; H, 7.27. Found: C, 43.09; H, 7.41.

4.5. (±)-1-*O*-Acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (33)

The monotriflate **32**[14] (542 mg, 1.38 mmol) was stirred with potassium acetate (677 mg, 6.9 mmol) in DMA (12 mL) at 70 °C for 12 h. The reaction mixture was diluted with ethyl acetate, washed successively with water, dil HCl, satd $NaHCO_3$, and brine. The organic layer was dried and evaporated under reduced pressure. The crude residue was chromatographed to get the known monoacetate **33**[14] (380 mg, 91%).

4.6. (±)-1,2:4,5-Di-*O*-isopropylidene-*chiro*-inositol (31)

The acetate **33** (358 mg, 1.18 mmol) was refluxed with sodium methoxide (6 mg, 0.11 mmol) in methanol (10 mL) for 2 h. Methanol was evaporated and the residue was chromatographed to get pure diol **31**[14] (290 mg, 94%).

4.7. (±)-1,2:4,5-Di-*O*-isopropylidene-3,6-di-*O*-methyl-*chiro*-inositol (34)

To a solution of diketal **31** (260 mg, 1 mmol) in DMF (8 mL) at 0 °C, sodium hydride (60 mg, 2.5 mmol) was added and stirred for 5 min. Then, methyl iodide (187 μL, 3 mmol) was added and stirred for 3 h gradually warming the reaction mixture to rt. The excess NaH was destroyed by adding few drops of methanol and the mixture was diluted with ethyl acetate, washed successively with water, dil HCl, and satd $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to get the dimethyl ether **34** (285 mg, 99%). A small fraction (50 mg) of this material was passed through a small pad of silica column to get analytically pure **34**.[8] Mp 99 °C. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.14; H, 8.47.

4.8. (±)-1,4-Di-*O*-methyl-*chiro*-inositol (2)

Diketal **34** (235 mg, 0.81 mmol) was stirred in a mixture of trifluoroacetic acid (TFA) and water (2.5 mL, 4:1 v/v) at rt for 3 h. The solvents were evaporated and the residue was chromatographed using ethyl acetate as the eluent to get pure dimethyl ether **2**[8] (124 mg, 73%).

4.9. (±)-1,2,4,5-Tetra-*O*-acetyl-3,6-di-*O*-methyl-*chiro*-inositol (35)

To a solution of tetrol **2** (100 mg, 0.48 mmol) in pyridine (5 mL) at 0 °C, acetic anhydride (472 μL, 5 mmol) was added dropwise and the mixture was stirred overnight gradually warming the reaction mixture to rt. Pyridine was evaporated under reduced pressure and the residue was dissolved in ethyl acetate, washed successively with water, dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue thus obtained was chromatographed using ethyl acetate/hexane as the eluent to provide pure tetraacetate **35**[8] (168 mg, 93%).

4.10. 2,4,6-Tri-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (40)

To a solution of triol **39**[23] (760 mg, 4 mmol) in DMF (20 mL) at 0 °C, NaH (360 mg, 15 mmol) was added and the mixture was stirred under argon atmosphere for 10 min. Then, BnBr (1.8 mL, 15 mmol) was added at 0 °C and the mixture was stirred for 3 h gradually warming the reaction mixture to rt. The excess NaH and BnBr were quenched by adding methanol and the mixture was diluted with ethyl acetate and washed successively with water, cold dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness to get a gummy material, which was further purified by column chromatography using ethyl acetate and hexane as eluent to get the known tribenzyl ether **40**[24a,25] (1.638 g, 89%).

4.11. 2,4,6-Tri-*O*-benzyl-*myo*-inositol (41)

A suspension of tribenzyl ether **40** (920 mg, 2 mmol) in a mixture of methanol (15 mL) and 1 N HCl (2 mL) was refluxed for 1 h. Evaporation of the solvent provided the known triol **41**[24] (900 mg) in quantitative yield.

4.12. 1,2,4,6-Tetra-*O*-benzyl-*myo*-inositol (42)

To a solution of triol **41** (900 mg, 2 mmol) in DMF (15 mL) at 0 °C, NaH (52 mg, 2.2 mmol) was added and the mixture was stirred under argon atmosphere for 10 min. Then, BnBr (240 μL, 2 mmol) was added at 0 °C and the mixture was stirred for 3 h

gradually warming the reaction mixture to rt. The mixture was diluted with ethyl acetate and washed successively with water, cold dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness to get a gummy material, which was further purified by column chromatography using ethyl acetate and hexane (3:7 v/v) as eluent to get pure tetrabenzyl ether **42**[26] (767 mg, 71%).

4.13. 1,2,4,6-Tetra-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-*myo*-inositol (43)

To a solution of tetrabenzyl ether **42** (750 mg, 1.39 mmol) in pyridine (12 mL) at 0 °C, trifluoromethanesulfonic anhydride (252 μL, 1.5 mmol) was added dropwise and the solution was stirred at that temperature for 2 h. The mixture was then diluted with ethyl acetate and washed with cold dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude material thus obtained was further purified by column chromatography using ethyl acetate/hexane as eluent to get the 3-triflate **43** (757 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.41 (d, 2.4 Hz, OH), 3.44 (dd, 9.6, 2.4 Hz, H-1), 3.53 (dd, 9.2, 2.4 Hz, H-5), 3.90 (dd, 10.0, 8.8 Hz, H-6), 4.00 (dd, 10.0, 9.6 Hz, H-4), 4.16 (dd, 2.4, 2.0 Hz, H-2), 4.62 (dd, 7.6, 2.0 Hz, H-3), 4.64–4.96 (m, 8H, 4×PhCH_2), 7.20–7.40 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): 73.2 (Ins C), 74.7 (Ins C), 75.3 (Ins C), 75.5 (2×Ins C), 76.2 (Ins C), 78.1, 79.8, 80.3, 86.7 (Ins C-3), 117.5 (q, CF_3), 127.6, 127.9, 128.0, 128.1, 128.4, 128.48, 128.51 (Ph), 137.5, 137.6, 137.7, 138.3 (4×*ipso* C). Anal. Calcd for $C_{35}H_{35}F_3O_8S$: C, 62.49; H, 5.24. Found: C, 62.19; H, 5.30.

4.14. 5-*O*-Acetyl-1,2,4,6-tetra-*O*-benzyl-3-*O*-trifluoromethanesulfonyl-*myo*-inositol (44)

To a solution of the triflate **43** (750 mg, 1.11 mmol) in pyridine (10 mL) at 0 °C, acetic anhydride (142 μL, 1.5 mmol) was added dropwise and the mixture was stirred under argon atmosphere for 3 h gradually warming the mixture to rt. Pyridine was then evaporated and the residue was dissolved in ethyl acetate, washed successively with water, dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was further purified by column chromatography using ethyl acetate/hexane as eluent to provide pure acetate **44** (781 mg. 98%). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.76 (s, 3H, COCH_3), 3.52 (dd, 9.77, 2.44 Hz, H-1), 3.96 (t, 9.77 Hz, H-6), 4.08 (t, 9.28 Hz, H-4), 4.17 (t, 2.44 Hz, H-2), 4.48–4.96 (m, 9H, H-3, 4×PhCH_2), 5.08 (dd, 9.77, 9.28 Hz, H-5), 7.22–7.39 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): 20.7 (CH_3), 73.2 (Ins C), 73.5 (Ins C), 75.4 (Ins C), 75.5 (Ins C), 75.7 (Ins C), 76.3, 76.9, 78.4 (q, CF_3), 79.9, 86.7, 118.4 (q, CF_3), 127.68, 127.74, 127.8, 127.9, 128.0, 128.2, 128.35, 128.43, 128.6 (Ph), 137.3, 137.4, 137.6, 138.1 (4×*ipso* C), 169.6 (CO). Anal. Calcd for $C_{37}H_{37}F_3O_9S$: C, 62.18; H, 5.22. Found: C, 61.98; H, 5.25.

4.15. 4,6-Di-*O*-acetyl-1,2,3,5-tetra-*O*-benzyl-*chiro*-inositol (45)

The triflate **44** (770 mg, 1.08 mmol) and potassium acetate (491 mg, 5 mmol) were dissolved in dimethylacetamide (6 mL) and the mixture was stirred at 70 °C for 12 h. The mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography provided the diacetate **45** (202 mg, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.93 (s, 3H, COCH_3), 2.01 (s, 3H, COCH_3), 3.71 (t, 3.9 Hz, H-1), 3.74–3.80 (2×dd, H-2 and H-5), 3.88 (t, 9.8 Hz, H-3), 4.31–4.89 (m, 8H, 4×PhCH_2), 5.31 (t, 9.8 Hz, H-4), 5.35 (t, 3.9 Hz, H-6), 7.20–7.40 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$, 100.4 MHz): 20.90 (COCH_3), 20.95 (COCH_3), 67.3, 71.9, 73.1, 73.3, 73.6, 74.6, 74.7, 75.5, 77.2, 79.4, 79.4, 127.5, 127.6, 127.7, 127.8, 127.83, 127.9, 127.90, 127.92, 128.3, 128.4, 128.43, 137.8, 137.9, 138.1, 138.6, 169.8 (OCOCH$_3$), 170.02 (OCOCH$_3$). Anal. Calcd for $C_{38}H_{40}O_8$: C, 73.06; H, 6.45. Found: C, 72.91; H, 6.69.

4.16. 1,2,3,5-Tetra-*O*-benzyl-*chiro*-inositol (46)

A mixture of diacetate **45** (190 mg, 0.3 mmol) and triethylamine (1 mL) was refluxed in methanol (8 mL) for 1 h. The solvents were evaporated and the residue was dissolved in ethyl acetate, washed with water, dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to provide the diol **46** (137 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): 2.34 (s, OH), 2.47 (s, OH), 3.69 (dd, 9.6, 4.0 Hz, H-2), 3.80–3.91 (m, 3H, H-3, H-4 and H-5), 3.94 (dd, 4.0, 2.0 Hz, H-6), 3.99 (dd, 4.4, 2.8 Hz, H-1), 4.66 (AB q, 57.2, 12.0 Hz, PhCH_2), 4.67 (AB q, 98.0, 12.0 Hz, PhCH_2), 4.67 (AB q, 24.8, 11.6 Hz, PhCH_2), 4.86 (AB q, 87.6, 10.8 Hz, PhCH_2), 7.20–7.40 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$, 100.4 MHz): 68.1, 72.98, 72.99, 73.6, 75.3, 76.0, 79.5, 79.7, 81.1, 127.56, 127.61, 127.64, 127.91, 127.95, 128.0, 128.14, 128.4, 128.6, 138.1, 138.50, 138.53, 138.9. Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.52; H, 6.88.

4.17. 4,6-Di-*O*-methyl-1,2,3,5-tetra-*O*-benzyl-*chiro*-inositol (47)

To a solution of diol **46** (130 mg, 0.24 mmol) in DMF (3 mL), NaH (24 mg, 1 mmol) was added at 0 °C and stirred for 5 min. Then, methyl iodide (63 μL, 1 mmol) was added and stirred for additional 1 h. The reaction was quenched by addition of few drops of methanol. The mixture was diluted with ethyl acetate, washed with water, dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography to yield pure dimethyl ether **47** (100 mg, 73%). ^{1}H NMR ($CDCl_3$, 270 MHz): 3.21 (s, 3H, CH_3), 3.34 (dd, 3.42, 2.93 Hz, H-6), 3.51 (t, 9.28 Hz, H-4), 3.68 (s, 3H, CH_3), 3.65–3.85 (m, 4H, 4×InsH), 4.40–4.90 (m, 8H, 4×PhCH_2), 7.20–7.40 (m, 20H, Ph); ^{13}C NMR ($CDCl_3$, 100.4 MHz): 58.8 (CH_3), 61.3 (CH_3), 73.2, 73.4, 73.5, 74.2, 75.8, 77.2, 77.7, 79.3, 79.7, 82.2, 83.8, 127.4, 127.5, 127.58, 127.61, 127.9, 128.0, 128.02, 128.26, 128.31, 138.4, 138.77, 138.8, 139.2. Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09. Found: C, 75.81; H, 7.27.

4.18. 1,3-Di-*O*-methyl-*chiro*-inositol (3)

A solution of tetrabenzyl ether **47** (90 mg, 0.16 mmol) in a mixture of methanol and ethyl acetate (5 mL, 1:1 v/v) was stirred with 10% Pd on charcoal (18 mg, 20 wt %) under atmosphere of hydrogen (H_2 balloon) at rt for 24 h. The mixture was filtered through a membrane filter by washing well with methanol and water. The combined filtrate and washings were evaporated under reduced pressure to obtain pure dimethyl ether **3** (29 mg, 89%). ^{1}H NMR (D_2O, 400 MHz): 3.28 (t, 9.4 Hz, H-3), 3.48 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.63 (t, 9.6 Hz, H-4), 3.64 (t, 3.6 Hz, H-1), 3.69 (dd, 9.6, 3.6 Hz, H-5), 3.86 (dd, 10.2, 3.6 Hz, H-2), 4.22 (t, 3.6 Hz, H-6); ^{13}C NMR (D_2O, 100.4 MHz, std dioxane 66.5 ppm): 58.5, 59.8, 67.8, 70.6, 71.9, 81.5, 83.0. Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.89; H, 7.86.

4.19. 1,2,3,5-Tetra-*O*-acetyl-4,6-di-*O*-methyl-*chiro*-inositol (48)

To a solution of dimethyl ether **3** (20 mg, 0.1 mmol) in pyridine (2 mL) at 0 °C was added acetic anhydride (95 μL, 1 mmol) and the mixture was stirred for 3 h gradually warming the mixture to rt. The excess pyridine and acetic anhydride were evaporated and the

residue was dissolved in ethyl acetate, washed with water, dil HCl, satd $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude acetate was further purified by column chromatography using ethyl acetate and hexane as eluent to get pure tetraacetate **48** (34 mg, 93%). ^1H NMR ($CDCl_3$, 400 MHz): 1.99 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.14 (s, 6H, $2\times COCH_3$), 3.47 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.68 (t, 3.4 Hz, H-1), 3.68 (t, 9.8 Hz, H-3), 5.12 (dd, 10.3, 2.9 Hz, H-2), 5.20 (10.3, 3.4 Hz, H-5), 5.34 (9.8 Hz, H-4), 5.49 (t, 3.9 Hz, H-6); ^{13}C NMR ($CDCl_3$, 100.4 MHz): 20.65 ($COCH_3$), 20.82 ($COCH_3$), 20.86 ($COCH_3$), 21.02 ($COCH_3$), 59.32 (OCH_3), 60.57 (OCH_3), 67.24, 69.23, 71.26, 72.62, 76.55, 78.66, 169.73 ($OCOCH_3$), 169.75 ($OCOCH_3$), 170.04 ($OCOCH_3$), 170.11 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{24}O_{10}$: C, 51.06; H, 6.43. Found: C, 50.98; H, 6.54.

Acknowledgements

We thank JSPS for a postdoctoral fellowship (K.M.S.) and Grant-in-aid (No. 02170). Also we thank Venture Business Laboratory and Advanced Instrumentation Center for Chemical Analysis, Ehime University for NMR and elemental analysis, respectively.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.024.

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