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Total synthesis of the proposed structure of 'brahol' and the structural revision

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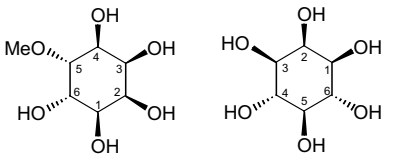
Abstract—Proposed structure of brahol, a natural product, has been disproved by total synthesis of the proposed molecule from *myo*-inositol. Readily available 1,2;4,5-di-*O*-isopropylidene-*myo*-inositol, **3** was converted to 2,5-di-*O*-acetyl-1,6;3,4-di-*O*-isopropylidene-*allo*-inositol by epimerization of the di-triflate of **3**. The acetyl group at O-5-position was selectively deprotected by aminolysis or methanolysis enabling the total synthesis of 5-*O*-methyl-*allo*-inositol, the proposed structure of brahol in six steps from *myo*-inositol. A comparison of spectral data of synthetic 5-*O*-methyl-*allo*-inositol with that reported for natural brahol revealed that the proposed structure of brahol is incorrect. A detailed structural revision revealed that brahol is nothing but quebrachitol. This study contradicts the first and only report on the natural occurrence of *allo*-inositol derivative.

A great deal of attention has been paid to the inositol chemistry since many of the family members are proved to possess interesting biological significance.[1] Of the nine possible isomers, only *myo*-inositol is naturally abundant. Until 1998, other isomeric inositols known to occur in nature are D-*chiro*, L-*chiro*, *neo, muco* and *scyllo*-inositols. In animals these inositols occur in the phosphorylated form while in plants they occur in phosphorylated, methylated or in free forms. One or more methyl ethers of each of these naturally occurring inositols are isolated from plants. Many of these methyl ethers have been synthesized[2] by different groups owing to the impractical isolation of these natural products. In 1998, Ahmad et al.[3] reported the isolation of an *allo*-inositol methyl ether, brahol, from the folklore medicinal plant *Stocksia brahuica*. This constitutes the first and only report on the natural occurrence of an *allo*-inositol derivative. Thus *allo*-inositol became the seventh isomeric inositol known to occur naturally.



Based on NMR studies, the structure was proposed to be 5-*O*-methyl-*allo*-inositol, **1**. The absolute configuration, optical rotation, mp and biological studies were not reported by these authors presumably due to the isolation being bleak and very low yielding. These facts prompted us to synthesize this molecule to provide access to sufficient quantity of the material for biological studies and characterization.

The use of cheaply available *myo*-inositol, **2**, as synthon for the synthesis of **1** is justifiable based on the close structural resemblance of **1** with *myo*-inositol. The inversion at 3, and 6 positions of *myo*-inositol and the selective methylation at 3-position are the major steps to be considered for the synthesis of **1** from **2**. Since no manipulation is required at 1, 2, 4 and 5 positions of *myo*-inositol, readily available 1,2;4,5-di-*O*-isopropylidene-*myo*-inositol, **3**,[4] was chosen as the suitably protected starting material. The selection of **3** is also advantageous for the synthesis of both D and L enantiomers of **1** since efficient resolution method is known[5] for the diketal **3**. Although we have decided to make both enantiomers of **1** starting from individual enantiomers of **3**, to standardize the synthetic conditions and route, the racemic synthesis was attempted first.

Keywords: Inositol; Cyclitol; *allo*-Inositol; Brahol; Regioselective.
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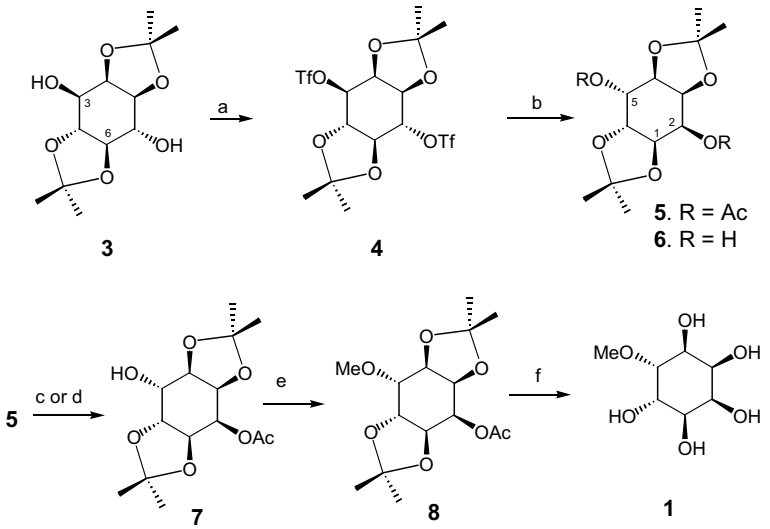


Scheme 1. Reagents and conditions: (a) Tf_2O (2.2 equiv), Pyr, CH_2Cl_2, −20 °C; (b) KOAc, DMA, 70 °C; (c) MeOH, Et_3N, reflux; (d) MeOH, isobutylamine, 60 °C; (e) MeI, NaH, DMF, rt; (f) 1 N HCl, MeOH, rt.

Racemic 1,2;4,5-di-*O*-isopropylidene-*myo*-inositol, **3** was sulfonylated with 2.2 equiv of triflic anhydride in pyridine to get the ditriflate **4** (Scheme 1) in excellent yield. After usual work up, the crude reaction mixture was treated with KOAc in *N*,*N*-dimethylacetamide (DMA) followed by work up provided racemic 2,5-di-*O*-acetyl-1,6;3,4-di-*O*-isopropylidene-*allo*-inositol, **5**[6] in quantitative yield.[7] Compound **5** can be crystallized from chloroform–hexane to get hair like silky crystals (mp 140 °C). Although diol, **6**, can be prepared by basic hydrolysis of the diacetate **5**, the resulting two axial hydroxyl groups (in **6**) are not expected to show any regioselectivity towards alkylation or similar reaction with an electrophilic reagent.[8] Molecular model analysis revealed that C-2-OAc is masked by two isopropylidene groups due to their *cis* orientation with respect to the C-2-OAc whereas the other C-5-OAc is not hindered and it is fully exposed to the less bulkier side of the carbocyclic ring. Hence a regioselective de-acylation was attempted under milder conditions. It was anticipated that a bulky nucleophile could easily attack the C-5-OAc compared to the sterically hindered C-2-OAc. Thus treatment of **5** with *tert*-butylamine (excess) in methanol at room temperature yielded the monoacetate **7**[9] in quantitative yield. The disappearance of the signal at 5.74 ppm is indicative of the C-5-OAc cleavage. Also the comparison of coupling constants of the remaining downfield signal at 5.61 ppm (dd, 5.1, 2.5 Hz) with that in the parent diacetate, **5**, suggests that C-2-OAc is intact in **7**. This structural assignment was further substantiated by solving the single crystal X-ray structure of **7**. To check the stability of the acetate functionality at C-2, the aminolysis reaction was carried out at reflux. Surprisingly the C-2-OAc was stable under this condition also. Later experiments with relatively less bulkier nucleophiles such as isobutylamine in methanol (aminolysis) or triethylamine in methanol (methanolysis) also yielded the monoacetate **7** as the sole product in excellent yields. Despite methoxide anion being smaller, high selectivity in methanolysis is observed. Such a high degree of selectivity is interesting since regioselective protection or deprotection is one of the major concerns in the chemistry of inositols.[8]

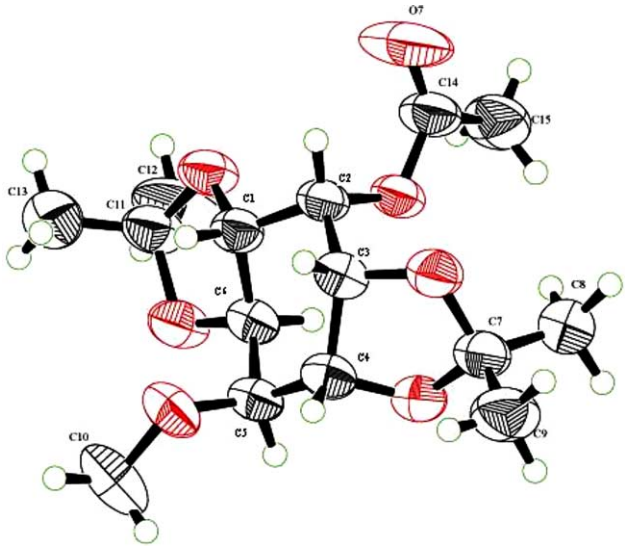


Figure 1. ORTEP diagram of **8**.

The acetate **7** was methylated with methyl iodide in the presence of sodium hydride to afford the methyl ether, **8**[10] as the sole product. The structure of **8** was confirmed by detailed NMR studies and solving its single crystal X-ray structure (Fig. 1). Finally the global deprotection in acid medium provided racemic 5-*O*-methyl-*allo*-inositol, **1**[11] as a white powder. The structure of **1** was unambiguously confirmed by spectroscopic methods. By following similar reaction sequence, optically active **1** also can be accomplished starting from chiral version of **3**.

A comparison of ^{1}H NMR of **1** with that reported for brahol[12] revealed that brahol is not 5-*O*-methyl-*allo*-inositol. Thus the assigned structure of brahol is wrong. In the reported conformation of brahol, 5-OMe, 4-OH

and 2-OH are in axial disposition and other hydroxyls are in equatorial orientation. Since *allo*-inositol possesses three axial and three equatorial hydroxyl groups, ring flipping is an easy and inexpensive way of reducing energy on substitution. Hence a substituted *allo*-inositol prefer a conformation in which substituent is in an energetically more favorable equatorial orientation. Although methyl group is not a very bulky substituent, it is reasonable to expect a dynamic equilibrium between two conformers, the conformer with equatorial O–Me being more populated. Sharp signals in ^{1}H NMR spectrum are reported for brahol.[12] In contrast, our synthetic 5-*O*-methyl-*allo*-inositol showed very broad signals for both protons[11] and carbons. We reasoned that this line broadening is due to the slow (with respect to the NMR time scale) dynamic equilibrium between two conformations. To substantiate this line of thought a variable temperature NMR experiment was carried out. As the temperature increased, the signals became more and more sharp and at a temperature of 80 °C, very sharp signals were observed for different protons and carbons in the respective spectrum.[13] Lack of such broadening in the reported ^{1}H NMR spectral data of brahol suggests that brahol is not having *allo*-configuration (a 3-axial and 3-equatorial oxygens). Generally, the O–Me resonance in methyl ethers of inositols appears in the range 3.45–3.65 ppm in the ^{1}H NMR spectrum.[14] But the unusually upfield O–Me resonance (at 3.25 ppm) of brahol suggests that the whole spectrum is likely to be an upfield shifted one. The structural assignment was made based on the chemical shift values by applying Angyal's generalization[14] on the effect of O-methylation in cyclitols. This reliance on the chemical shift values of a shifted spectrum could have resulted in a wrong assignment of the structure.

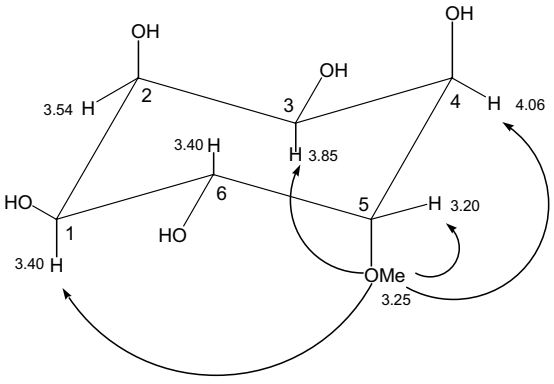
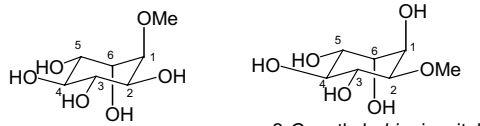


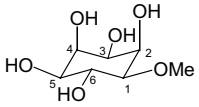
Figure 2. Reported NOE interactions for brahol.

The nonequivalence of brahol with 5-*O*-methyl-*allo*-inositol prompted us to do a rigorous analysis of the structure of brahol based on the reported data. Of the 20 possible isomeric monomethyl ethers for eight inositols, 14 structures were ruled out based on symmetry and conformations. To fish out the right structure we have relied on the NOE interactions (Fig. 2) reported for brahol along with molecular models.



1-*O*-methyl-*chiro*-inositol **9**

2-*O*-methyl-*chiro*-inositol **10**



1-*O*-methyl-*epi*-inositol **11**

Based on the NOE report, three of the six plausible structures were also ruled out, further narrowing to only three putative (**9**, **10** and **11**) structures for brahol. 1-*O*-Methyl-*chiro*-inositol, **9** was ruled out based on the smaller coupling constants (3.8, 3.4 Hz) for H-3 in brahol as in the structure **9**, third position proton with respect to O–Me (H-5 in **9**) is expected to give a larger coupling constant due to diaxial dispositions of H-5 and H-4. A careful analysis of the relative chemical shifts of H-3 (axial) and H-2 (equatorial) protons in brahol suggests that their orientation assignment is reversed. Thus it is reasonable to think that structure **10** is a more probable structure of brahol. To substantiate our assumption, we have compared the spectra of L-quebrachitol (L-2-*O*-methyl-*chiro*-inositol) and found that brahol is nothing but quebrachitol. As we suspected the reported spectra of brahol has shifted upfield. A comparison of chemical shifts and coupling constants (Table 1) revealed that H-1, H-2, H-3, H-4, H-5 and H-6 of 2-*O*-methyl-*chiro*-inositol (quebrachitol) were misinterpreted as H-4, H-5, H-6, H-1, H-2 and H-3 of 5-*O*-methyl-*allo*-inositol (brahol), respectively. Similar misinterpretations of carbon signals also have been verified by comparing ^{13}C NMR of brahol and quebrachitol (Table 1). Furthermore, the NOE spectra of quebrachitol is in agreement with the NOE results reported for

Table 1. Comparison of the ^{1}H and ^{13}C NMR spectra of brahol and quebrachitol

Brahol		Quebrachitol[a]	
δ_H (m, *J* Hz), δ_C	H, C	δ_H (m, *J* Hz), δ_C	H, C
3.40 (m), 75.3	H-1, C-1	3.40 (m), 75.4	H-4, C-4
3.54 (m), 72.9	H-2, C-2	3.54 (dd, 9.3, 2.9), 72.9	H-5, C-5
3.85 (dd, 3.8, 3.4), 73.9	H-3, C-3	3.86 (dd, 2.9, 3.9), 73.9	H-6, C-6
4.06 (dd, 3.8, 3.3), 69.7	H-4, C-4	4.07 (t, 3.42), 69.7	H-1, C-1
3.20 (m), 82.7	H-5, C-5	3.20 (dd, 9.3, 3.4), 82.7	H-2, C-2
3.40 (m), 74.4	H-6, C-6	3.40 (m), 74.4	H-3, C-3
3.25 (s), 59.4	O–Me	3.25 (s), 59.4	O–Me

[a] The OMe in ^{1}H NMR and the most downfield signal in ^{13}C NMR of quebrachitol are standardized to brahol's values (3.25 and 82.7 ppm, respectively) for comparison.

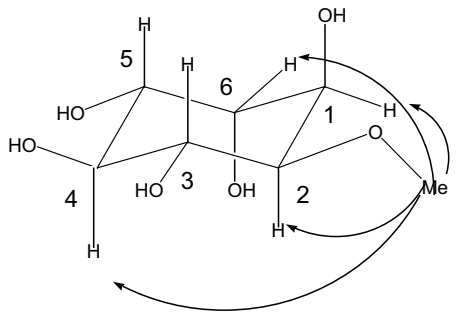


Figure 3. Observed NOE interactions of OMe in quebrachitol.

brahol (Fig. 3). Thus the structure of brahol is unambiguously established to be 2-*O*-methyl-*chiro*-inositol.

For the structural assignment of brahol, authors have relied on the chemical shifts of protons and carbons based on Angyal's generalization on the effect of methylation on chemical shifts of cyclitols.[14] For instance, the axial orientation of methoxy substituent was assumed based on the chemical shift of the carbon atom bearing the OMe. The relative stereochemistry of the remaining carbons were deduced based on NOE connectivity and coupling constants. Since the first assignment was wrong, the stereochemistry of all other carbons also changed and resulted in a wrong assignment of structure. Angyal's generalization works well with cyclitols. But in such cases the NMR need to be carefully standardized with a standard peak (other than HOD) when solvent is D_2O as HOD is known to vary its chemical shift depending on concentration, temperature and pH. Thus our study contradicts the first and only report of the natural occurrence of an *allo*-inositol (derivative). Thus to date only six inositols (*myo*, *scyllo*, *neo*, D-*chiro*, L-*chiro* and *muco*) are known to occur naturally.

In conclusion, we have reported an efficient route for the synthesis of 5-*O*-methyl-*allo*-inositol, the proposed structure of brahol. NMR and X-ray diffraction studies were used to assign the structure unambiguously. A comparison of ^{1}H NMR of 5-*O*-methyl-*allo*-inositol with that of brahol revealed that they are not identical. A logistic approach combined with the analysis of spectral data reported for brahol revealed that brahol is not *allo*-inositol derivative but 2-*O*-methyl-*chiro*-inositol, quebrachitol. We have explored the regioselective de-acetylation in *allo*-inositol derivative as the key step, which constitutes the first exploitation of regioselectivity in *allo*-inositol. This regioselectivity will be of interest to a wider cross section of organic chemists as inositol and other cyclitols are increasingly being used as synthons for many natural products,[15] metal complexing agents,[16] gelators,[17] catalysts,[18] supramolecular assemblies,[19] chiral auxiliary[20] etc.

Acknowledgements

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References and notes

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6. ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 2.11 (s, $COCH_3$), 2.12 (s, $COCH_3$), 3.93 (dd, 1H, 10.2, 2.6 Hz, H-1), 4.24 (dd, 1H, 5.7, 1.6 Hz, H-4), 4.27 (dd, 1H, 10.2, 3.4 Hz, H-6), 4.37 (t, 1H, 5.7 Hz, H-3), 5.64 (dd, 1H, 5.7, 2.6 Hz, H-2), 5.74 (dd, 1H, 3.3, 1.6 Hz, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): 20.5, 20.9, 24.8, 25.7, 26.4, 26.43, 65.9, 66.6, 70.6, 72.0, 72.6, 76.8, 109.9, 111.3, 169.1, 169.5. Elemental analysis calcd for, $C_{16}H_{24}O_8$C 54.64, H 7.11. Found C 54.77, H 6.90.
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9. ^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 2.11 (s, $COCH_3$), 2.47 (br s, OH), 3.97 (dd, 1H, 10.1, 2.5 Hz, H-1), 4.21 (dd, 1H, 10.1, 3.1 Hz, H-6), 4.35–4.40 (m, 2H, H-3 and H-4), 4.54 (dd, 1H, 2.1, 1.0 Hz, H-5), 5.61 (dd, 1H, 5.1, 2.5 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 24.8, 25.8, 26.6, 65.3, 67.0, 71.4, 72.7, 72.72, 78.3, 109.4, 111.2, 169.6.
10. ^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 2.11 (s, $COCH_3$), 3.57 (s, 3H, OCH_3), 4.04 (dd, 1H, 10.3, 2.7 Hz, H-1), 4.10 (dd, 1H, 2.6, 1.7 Hz, H-5), 4.22 (dd, 1H, 10.3, 2.9 Hz, H-6), 4.30–4.35 (m, 2H, H-3 and H-4), 5.59 (dd, 1H, 5.3, 2.7 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 25.1, 25.9, 26.6, 26.7, 60.1, 67.2, 71.8, 72.8, 73.3, 74.4, 77.6, 109.7, 111.0, 169.7. FAB MS (+); M+H = 317.
11. ^{1}H NMR (400 MHz, D_2O): 3.45 (s, 3H, OCH_3), 3.66 (dd, 1H, 7.4, 3.2, Hz), 3.80–4.10 (br m, 4H), 4.10–4.30 (br, 1H).
12. ^{1}H NMR (400 MHz, D_2O): 3.20 (m, 1H), 3.25 (s, 3H, OCH_3), 3.40 (overlapped dd, 2H), 3.54 (m, 1H), 3.85 (dd, 1H, 3.8, 3.4 Hz), 4.06 (dd, 1H, 3.8, 3.3 Hz).
13. ^{1}H NMR (400 MHz, D_2O, 80 °C): 3.45 (s, 3H, OCH_3), 3.64 (dd, 1H, 6.84, 3.42 Hz), 3.87 (dd, 1H, 6.35, 2.44 Hz), 3.97 (m, 3H), 4.16 (dd, 1H, 6.84, 2.93 Hz). ^{13}C NMR (100 MHz, D_2O): 57.7, 67.4, 69.6, 70.4, 71.9, 79.3.

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