Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3357–3364

O-Acetylmandelic acid as a reliable chiral anisotropy reagent for the determination of absolute configuration of alcohols

Kana M. Sureshan,* Tomomi Miyasou, Satoshi Miyamori and Yutaka Watanabe*

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Japan

Received 16 April 2004; revised 8 September 2004; accepted 9 September 2004

Abstract—NMR analyses of *O*-acetylmandelate (OAM) esters of a variety of crowded and conformationally locked cyclitol derivatives and other alcohols were carried out to examine the reliability of the use of OAM as a chiral anisotropy reagent (CAR) for the determination of the absolute configuration of an alcohol. These experiments showed that OAM can be used as a reliable CAR even in the case of sterically crowded alcohols, but the use of this method in conformationally locked alcohols should be skeptical. Although OAM is a frequently used chiral auxiliary for the resolution of cyclitol derivatives, the absolute configuration of the resolved alcohol is usually determined by converting it to a derivative of already known absolute configuration. The present study suggests that just the NMR analysis of the resolved diastereomers is sufficient enough to deduce the absolute configuration of these resolved cyclitol derivatives to determine their absolute configurations. Many literature examples where OAM is used for the resolution of different alcohols are used to generalize the fact that OAM is more reliable than other frequently used CARs such as methoxy trifluoromethyl phenyl acetic acid (MTPA), methoxy phenyl acetic acid (MPA) and mandelate.

1. Introduction

Simple, efficient and reliable methods for stereochemical assignment are of interest to a wide cross-section of the scientific community ranging from biochemists to material chemists. The classical anisotropy method introduced and developed by Dale and Mosher,[1] Trost et al.[2] and others[3] has continued to be the simplest and most reliable method for the determination of the absolute configuration of a secondary alcohol (or α-substituted primary amines). A comparison of the chemical shifts of the diastereomeric esters obtained by derivatization of an alcohol with two enantiomers of chiral anisotropy reagents (CARs) such as MTPA, MPA or similar derivatives provides information about the absolute configuration of the alcohol. Different conformational models have been proposed for different CARs to analyze the NMR and thus predict the absolute configuration. The groups facing the phenyl (aryl) ring of the CAR experience an anisotropic shielding effect and hence the protons of these groups appear at a higher field in the ^{1}H NMR spectrum. From the difference between the chemical shift values ($\Delta\delta$) of a particular proton (or group of protons) in two diastereomers obtained by the derivatization with both the enantiomers of the CAR, the absolute configuration of the alcohol can be deduced. Thus the reliability of this method obviously depends on the magnitude of $\Delta\delta$ values, a measure of anisotropic aromatic shielding effect, which in turn depends on the conformational restriction. There are many reports where these methods were inefficient in predicting the absolute configuration unambiguously[4] because of the small magnitude of $\Delta\delta$. These failures can be rationalized based on the deviation of the CAR conformation in solution from the theoretical model by any reasons. The existence of different conformers in equilibrium (conformational flexibility) for AMA (arylmethoxyacetate) derivatives has been introduced[5] to explain this small $\Delta\delta$. Such a conformational flexibility imposes significant limitations on the scope of this method for determining the absolute configuration. Consequently, the continued quest for the ideal CAR (with frozen conformation and thus higher value of $\Delta\delta$) resulted in the development of many new CARs.[6] There are a few reports[7] where comparatively less expensive *O*-acetylmandelic acid (OAM) had been used as the CAR for the determination of absolute configuration of alcohols. Despite the use of OAM as a CAR, it has not received much attention when compared to other CARs like

* Corresponding authors. Tel.: +81 899236786; fax: +81 899279944; e-mail addresses: sureshankm@yahoo.co.in; wyutaka@dpc.ehime-u.ac.jp

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.09.018

MPA and MTPA. We herein report a systematic study on the use of OAM as a CAR in alcohols of different rigidity and crowd.

2. Results and discussion

The conformational model for OAM esters is similar to that of Trost's model for MPA derivatives (Fig. 1). The OAM takes an *sp* conformation whereby the α-hydrogen, carbonyl carbon and C–OAc are coplanar. In this conformation, the phenyl group shields H_A, H_B, H_C in (*R*)-OAM ester and H_X, H_Y, H_Z in (*S*)-OAM ester. Thus $\Delta\delta^{S-R}$ for H_A, H_B, H_C protons will be positive and for H_X, H_Y, H_Z will be negative. Thus by measuring $\Delta\delta$ of the protons on both the sides of OAM plane, the absolute configuration can be determined.

We were attracted to this field following our recent observation[8] that the crystal structure of D-1,4-di-*O*-(*O*-acetylmandeloyl)-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol, **1D** showed two different conformations for different acetylmandelate groups. One of the two OAMs was in the ideal *sp* conformation while the other was in an unusual *ap* conformation. Detailed NMR studies[8] of both **1D** and its diastereomer **1L** (Chart 1) revealed similar conformational preferences (*sp* and *ap*) of **1D** in solution also. We assumed that the reason for this conformational deviation could be the steric crowding near the OAM group, which compels its conformation to deviate from the ideal one. Conformational compromise can be either from the alcohol part or from the OAM part. Since the alcohol part is conformationally locked with two five-membered ketal rings, it is rational to think that the OAM part deviated from its ideal conformation. These results prompted us to investigate systematically the effect of steric and conformational locking (of alcohol part) factors towards OAM conformation.

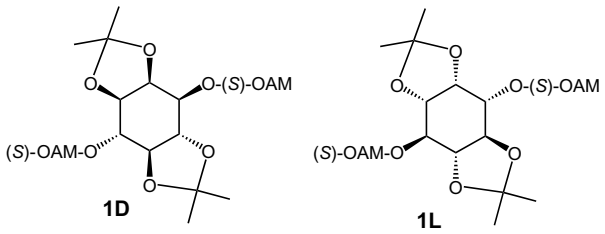

Chart 1.

Soon after the realization of the biological significance of phosphoinositols, the efforts of many research groups resulted in the development of many selective protection–deprotection strategies[9] for *myo*-inositol. Since we can access *myo*-inositol derivatives of different steric bulk and conformational flexibility by applying these known methodologies, we have chosen protected *myo*-inositol derivatives to study the reliability of OAM as a CAR. In addition, OAM has gained the attention of inositol chemists as an efficient chiral auxiliary for the resolution of *myo*-inositol derivatives.[10] However the absolute configurations of the resulting diastereomers were usually deduced by converting to a derivative of known absolute stereochemistry, at times through a number of chemical transformations, which are time consuming and costly. To the best of our knowledge, no CARs (Mosher's method) have been used on inositols (cyclitols in general) to assign the absolute configuration. Thus our selection of inositol derivatives for our study is of additional interest, in the quest for the development of an easy and efficient method for determining their absolute configuration without the need of conversion to a known derivative.

Since OAM in diketal **1D** has shown an *ap* conformation, we anticipated similar conformational preferences in the structurally similar dicyclohexylidene derivative **2D**[11] (Chart 2). Similar magnitudes of $\Delta\delta^{L-D}$ in structur-

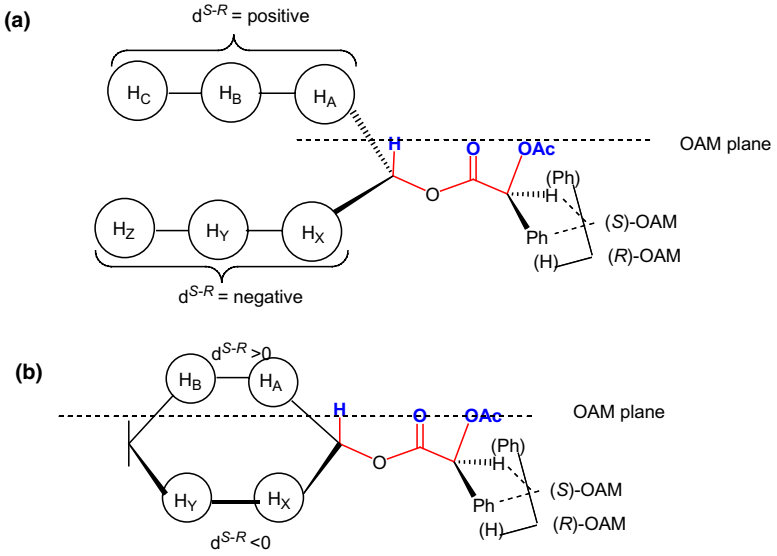

Figure 1. (a) Conformational model for (*S*)-OAM and (*R*)-OAM esters of alcohols for the determination of the absolute configuration; (b) conformational model for (*S*)-OAM and (*R*)-OAM esters of cyclic alcohols (e.g., inositols).

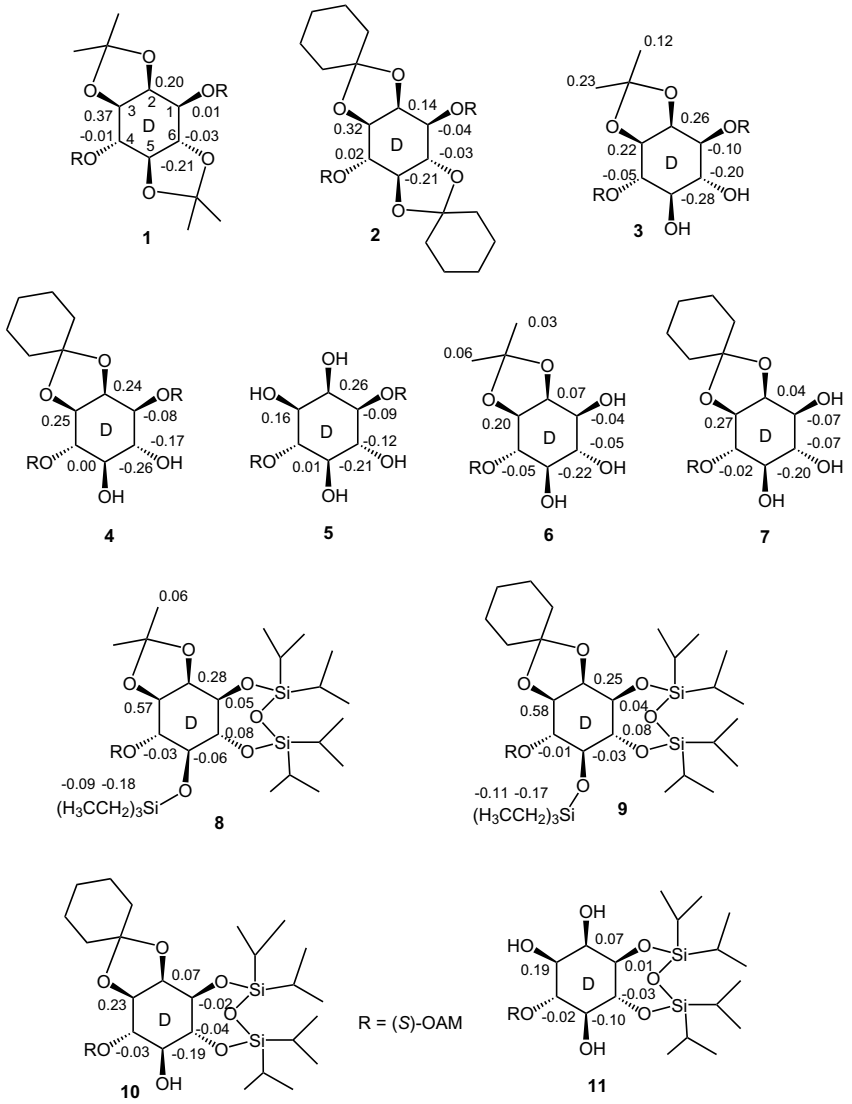

Chart 2. $\Delta\delta^{L-D}$ for different protons is marked near the carbon bearing the respective proton(s). Only one of the diastereomers (D) is shown in this chart.

ally similar isopropylidene **1** and cyclohexylidene derivatives **2** suggest that cyclohexylidene derivatives **2D** and **2L** also take conformation as in the case of isopropylidene derivatives **1D** and **1L**. It is rational to anticipate an ideal conformation for the OAM when the conformational mobility of inositol ring is improved. As expected $\Delta\delta^{L-D}$ values for different inositol ring protons of diols[12] **3D** and **3L** are in agreement with the ideal *sp* conformation of the OAM. Structurally but not sterically similar cyclohexylidene derivatives **4D** and **4L** also showed similar $\Delta\delta^{L-D}$ values as in the case of **3**. This supports our assumption that the OAM part takes an ideal (*sp*) conformation provided there is enough flexibility for the alcohol part for a small change of conformation, to compensate for the increase in energy arising from the attachment of bulky CAR (OAM). As diketals **1** and **2** have similar $\Delta\delta^{L-D}$ values, diols **3** and **4** also showed similar $\Delta\delta^{L-D}$ values for inositol protons, suggesting that changing the isopropylidene group to a bulkier cyclohexylidene group has a negligible effect on the conformation of OAM and thus on the reliability of OAM as a CAR for the determination of the absolute configuration. Tetrol **5**, where no ketal ring exists, did not show any further improvement in the magnitude of $\Delta\delta^{L-D}$ compared to monoketals **3** and **4**. Since derivatives **1**–**5** contained two OAMs at 1,4-positions in a cyclohexane ring, each of the intermediate protons (protons on C2, C3, C5 and C6) experience two types of anisotropic shielding; one from the closer OAM and one from the further OAM. Thus the observed $\Delta\delta$ values for these protons are the result of a combination of shielding effects from these two OAMs. Accordingly, to estimate the contribution from one OAM, compound **6**, which has only one OAM, was chosen. NMR analysis of **6** (**6D** and **6L**) revealed that anisotropic shielding contribution (in $\Delta\delta$) for a proton from the closer OAM is around 0.22 ppm while that from the further OAM is about 0.05–0.07 ppm. An exactly similar magnitude of $\Delta\delta$ for the cyclohexylidene derivative **7** is again in agreement with our assumption that a change in bulkiness at the locking group does not contribute much in determining the conformation of OAM.

Analysis of $\Delta\delta$ values of above seven pairs of diastereomers revealed that OAM can endure steric bulk, to some extent, without conformational change. This is interesting since other usually used CARs cannot endure steric bulk.[4] To what extent can OAM endure bulkiness without much deviation from its ideal (*sp*) conformation? To answer this question, we compared the ^{1}H NMR of the diastereomers of bulky silylated derivatives **8** (**8D** and **8L**) and **9** (**9D** and **9L**). The $\Delta\delta$ values for **8** are interesting in that a $\Delta\delta$ of about 0.6 ppm was observed for a proton in the less crowded side (H3) of OAM plane while a $\Delta\delta$ for the ring proton in the more crowded side (H5) was very small (-0.06) in magnitude. However the $\Delta\delta$ values for the ethyl protons of TES attached to O-5 suggest that phenyl group of OAM shields TES group. This suggests that there is a little conformational deviation either for the inositol ring or for the OAM. However a comparison of $^3J_{HH}$ coupling constants (Table 1) of inositol ring protons of **8D** and **8L** with that of other derivatives having a conformational lock (ketal)[13] suggested that the inositol ring deviated considerably in **8D** and **8L**. However this does not rule out the possibility of conformational deviation of both OAM and inositol ring. To resolve this issue, we relied on molecular model analysis. The approximate torsion angles between vicinal protons were calculated by using Haasnoot–Altona equation[14] from observed $^3J_{HH}$ values. Such an analysis suggests that the conformation of **8D** is a flattened chair while that of **8L** is a flattened half chair. In **8L** C2–C3–C4–C5–C6 tend to be coplanar and constitutes the seat of the half chair and C6–C1–C2 forms the backrest of the half chair. Now assuming an *sp* conformation for the OAM, the observed $\Delta\delta$ can be rationalized. In the flattened chair conformation of **8D**, the H3 comes closer to the phenyl group of OAM (in an *sp* conformation) and hence the effective shielding as expected. In the half-chair conformation of **8L**, the TES group is very near to the phenyl ring of OAM (assuming an *sp* conformation for OAM); this TES also masks the H5. This is in agreement with the small magnitude of observed $\Delta\delta$ for H5 and high $\Delta\delta$ for ethyl protons of TES. Thus the conformation of OAM has not deviated from its ideal *sp* conformation. As anticipated, exactly similar $\Delta\delta^{L-D}$ values for the cyclohexylidene derivatives **9** (**9D** and **9L**) also supports this line of thought. A comparison of $\Delta\delta^{L-D}$ values of triols **6** and **7** with that of the corresponding silylated bulky derivatives **8** and **9** suggests that when bulkiness increases, the inositol ring deviates slightly such that H3 comes directly under the shielding zone of OAM in the diastereomer D. The observed $^3J_{HH}$ values for other inositol ring protons also support this argument. The exceptionally higher magnitude of $\Delta\delta$ for H3 in **8** and **9** suggests that when aligned properly, the anisotropic shielding effect of OAM can bring about a $\Delta\delta$ of 0.6 ppm.

It is interesting to note that the removal of TES from ketal **9**, resulted in an increase in magnitude of $\Delta\delta$ for H5 to -0.19 ppm (in **10**) and a decrease for H3 to 0.23 ppm, both in the normal $\Delta\delta$ range for a non-deviated inositol derivative such as **6**. This suggests that the conformational deviation of the inositol ring in **9** (and in **8**) was due to the presence of the TES group rather than TIPDS. This was further established by the fact that triol **7** and TIPDS derivative **10** have similar $\Delta\delta$ values for the inositol ring protons, the only structural difference being the presence of TIPDS in **10**. This similar $\Delta\delta$ values for **7** and **10** suggests that they have similar conformations. This is also evident from the $^3J_{HH}$ values of both **7** and **10**. Despite **10** being very bulky, it did not affect the conformation of OAM.

Compound **10**, allows the selective deprotection of either the TIPDS group or the ketal group to provide triol **7** or triol **11** (Chart 3). A comparison of the $\Delta\delta$ between either of these triols with that of **10** provides

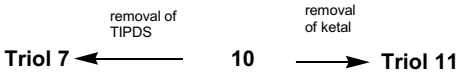

Chart 3.

Table 1. $^3J_{HH}$ coupling constants of different ring protons of ketal locked inositol derivatives

Entry	Compound	H1–H2	H2–H3	H3–H4	H4–H5	H5–H6	H6–H1
1	**1D**	4.4	4.4	6.8	11.2	10.3	10.5
2	**1L**	4.4	4.9	6.8	11	9.3	10.5
3	**2D**	4.9	4.9	6.8	11.2	10.3	10.3
4	**2L**	4.9	4.9	6.8	11.2	9.8	9.8
5	**3D**	4.4	4.4	7.3	9.8	9.8	9.8
6	**3L**	4.4	4.4	7.3	9.8	9.8	9.8
7	**4D**	4.9	4.9	7.8	9.8	9.8	9.8
8	**4L**	4.4	4.4	7.8	9.8	9.8	9.8
9	**6D**	4.4	4.4	7.3	9.8	9.8	9.8
10	**6L**	4.4	4.4	7.3	9.3	9.3	9.3
11	**7D**	4.8	4.8	7.8	10.3	10.3	10.3
12	**7L**	4.9	4.9	7.8	10.7	8.8	—
13	**8D**	**4.4**	**5.4**	**6.3**	**7.8**	**7.8**	**9.8**
14	**8L**	**3.4**	**5.9**	**4.4**	**4.4**	**5.4**	**9.8**
15	**9D**	**4.4**	**4.4**	**6.8**	**8.3**	**8.3**	**9.3**
16	**9L**	**3.4**	**5.9**	**5.9**	**6.4**	**6.4**	**9.8**
17	**10D**	4.4	4.4	7.8	10.8	8.8	8.8
18	**10L**	3.9	4.4	7.8	10.3	8.8	8.8

a direct comparison of the effect of steric bulkiness (TIPDS) and conformational locking (cyclohexylidene) on the reliability of OAM as a CAR for the determination of absolute configuration. Thus a comparison of δ^{L-D} of **7** and **10** suggests that even though TIPDS is a very bulky group, and hence offers crowding to the inositol ring, the OAM has no conformational deviation either on addition or removal of this group. In contrast, a comparison of $\Delta\delta^{L-D}$ of **10** and **11** reveals that the ketal, a conformational lock, has a decisive role in the magnitude of $\Delta\delta$. This suggests that OAM can endure steric crowding at the alcohol part while a conformational lock at the alcohol (which restricts the alcohol part from conformational compromising to reduce the energy) part may give rise to a conformational deviation of OAM from its ideal *sp* conformation.

At this stage, we turned our attention to diastereomeric OAM esters where no ketal rings are present. Fortunately, a survey of the recent literature revealed that during the syntheses of phosphoinositols or other natural products, different groups have resolved racemic inositol derivatives as their OAM esters.[10] In all of these cases, the absolute configurations of these resolved diastereomers were determined by converting them to a known derivative. For our study, we analyzed the reported NMR data of these diastereomers. The $\Delta\delta$ values of different protons of different derivatives are shown in Chart 4.

During the synthesis of methyl uronates, Chida et al.[10e] resolved 3,4,5,6-tetra-*O*-benzyl-*myo*-inositol as its (*S*)-OAM diastereomers **12D** and **12L**. The $\Delta\delta^{L-D}$ for H2 was 0.25 ppm while that for H6 was only −0.04 ppm. Although OAM is not shielding H6 in **12L** effectively, careful analysis of the reported NMR data revealed that it is shielding the protons in the protecting group attached to O-6. While all four pairs of benzylic protons in **12D** appeared in the range 4.65–4.87 ppm, only three pairs in **12L** appeared in this range. The other pair of benzylic protons appeared as an AB quartet at 4.12 and 4.47 ppm. This suggests that OAM is shielding the benzylic protons, probably the one attached to O-6. This is in agreement with the *sp* conformation of OAM, even though the alcohol is sterically bulky. A similar trend was observed for the structurally identical derivative **13**.[10k] Mills and Potter has used OAM, as a chiral auxiliary, extensively for the resolution of various inositol derivatives during their elegant syntheses of various phosphoinositols. The observed chemical shifts of these various derivatives (**14**,[10g] **15**,[10d] **16**,[10j]) are in agreement with the *sp* conformation of OAM. In all these derivatives (**12**–**16**), the $\Delta\delta$ value for the proton on one side of OAM is very low compared to the other side, presumably due to minor conformational changes in these derivatives. Much earlier Mills and Potter[10i] resolved DL-1,4-di-*O*-allyl-5-*O*-benzyl-6-*O*-(4-methoxybenzyl)-*myo*-inositol via chromatographic separation of their diastereomeric (*S*)-OAM derivatives **17D** and **17L**. Analysis of the reported NMR data for both **17D** and **17L** revealed that the ring protons at either sides of OAM experience similar shielding from the phenyl group of OAM. The remarkably high $\Delta\delta$ value for H6 in **17** compared to that in other derivatives **12**–**16** suggests that the allyl group at 6-position does not affect the conformation.

During the synthetic efforts for the preparation of mannostatin A, Ogawa et al.[15] synthesized various optically active aminocyclopentane tetrols via the diastereomeric resolution of the corresponding racemic derivatives with (*S*)- or (*R*)-OAM. The $\Delta\delta$ values of various protons of these compounds (**18**–**20**, Chart 5) are in agreement with the *sp* conformation of OAM. These analyses further suggest that OAM can also be used reliably to deduce the absolute configuration of heavily protected cyclopentitol derivatives too.

From the $\Delta\delta$ values of all 20 pairs of diastereomers of cyclitol derivatives discussed above, the reliability of the use of OAM as a CAR even in sterically crowded cyclitol derivatives is ratified, where no CAR has been used to date to determine the absolute configuration. Thus with OAM being a frequently used chiral auxiliary for the diastereomeric resolution, especially in inositol chemistry, the present results suggest that the use of OAM in inositol has the advantages of determining the absolute configuration without the need for laborious practice of conversion to a derivative of known absolute configuration.

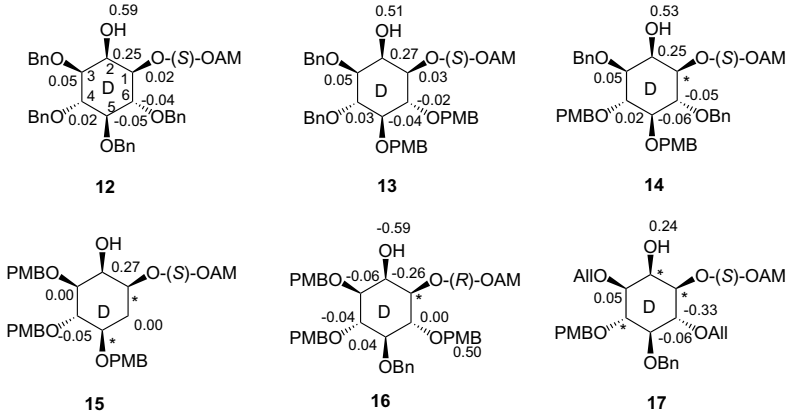

Chart 4. *Since these protons overlapped in the ^{1}H NMR, an exact $\Delta\delta$ cannot be measured. However the magnitude seems to be negligibly small as expected.

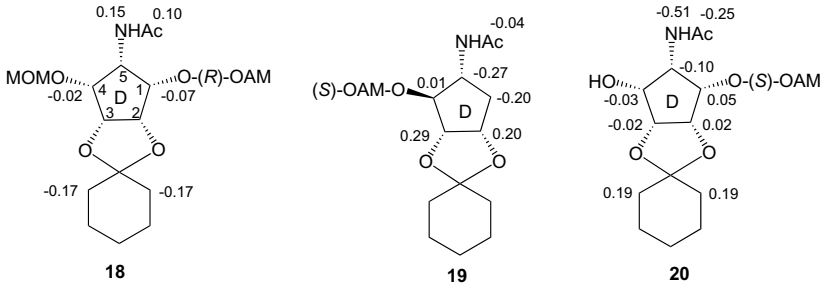

Chart 5. $\Delta\delta^{L-D}$ of cyclopentitol derivatives.

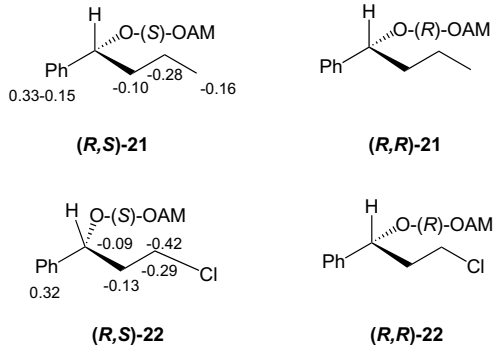

Chart 6. $\Delta\delta^{S-R}$ of open chain compounds.

The exciting results on the reliability of OAM as a CAR in cyclitols prompted us to investigate the reliability of OAM in general systems too. As a representative example, open chain alcohols, namely (*R*)-1-phenyl-1-butanol and (*R*)-3-chloro-1-phenyl-1-propanol were converted into their diastereomeric esters by treatment with both (*S*)-OAM and (*R*)-OAM acids (Chart 6). A comparison of NMR spectra revealed that open chain derivatives also gave reliably good $\Delta\delta$ values of up to 0.42 ppm. Similarly the lower δ values of the methyl protons in the (*R*,*S*)-diastereomers of the (*S*)-OAM esters of β-hydroxy sulfides[7e] **23**–**26**, when compared to the (*S*,*S*)-diastereomer are in agreement with the *sp* conformation of the OAM (Chart 7).

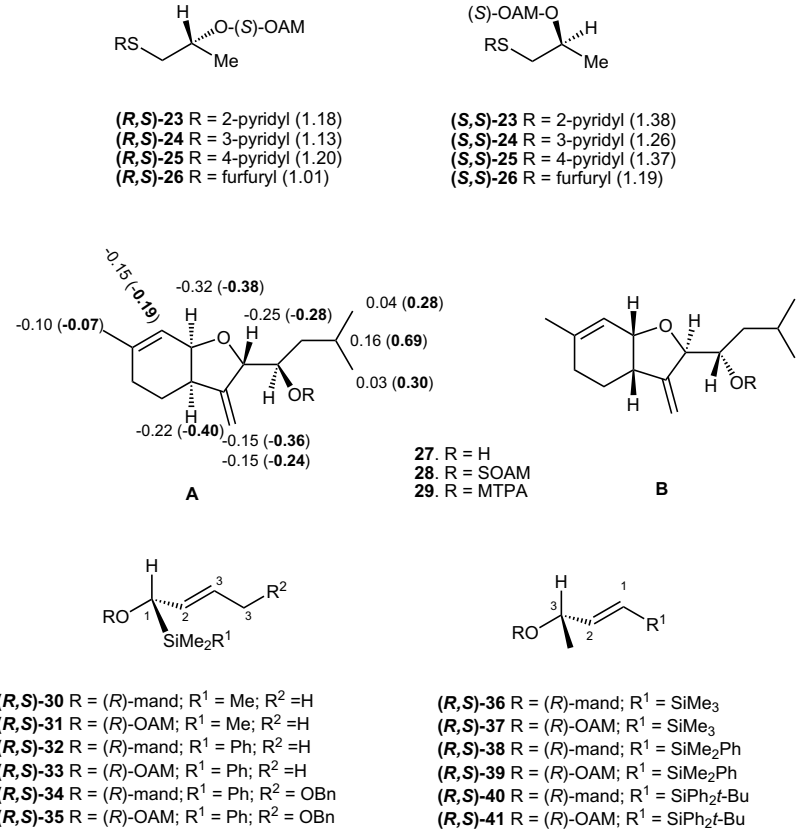

Chart 7. The values in the parenthesis of **23**–**26** are the δ values for the methyl protons. $\Delta\delta^{B-A}$ of different protons of OAM and MTPA esters are shown on structure **A**. The values in the parenthesis are $\Delta\delta^{OAM}$ values. Only the diastereomers derived from the (*S*)-alcohol were shown for **30**–**41**.

There are some reports in the literature, where OAM has been used as a resolving agent for secondary alcohols during different synthetic efforts. A comparison of the reported chemical shift values of both the diastereomers in such reports gave $\Delta\delta$ values, which can interpret the absolute configuration of both diastereomers. During the total synthesis of (+)-cheimonophyllon E, Tadano and co-workers[16] resolved the intermediate racemic alcohol **27** by converting it into diastereomers **28A** and **28B** with (*S*)-OAM followed by chromatographic separation. Analysis of the NMR spectra of (*S*)-OAM derivatives **28A** and **28B** and comparison of $\Delta\delta^{(B-A)OAM}$ with that of the Mosher esters (prepared for determination of absolute configuration) ($\Delta\delta^{MTPA}$) revealed that OAM derivatives give larger $\Delta\delta$'s than that of MTPA derivatives. This supports the fact that OAM is more reliable than MTPA. Chataigner et al.[17] compared MPA and OAM derivatives of five simple alcohols and illustrated that OAM derivatives give larger $\Delta\delta$'s meaning OAM is more reliable than MPA. Panek and Sparks[18] resolved different C1-oxygenated *E*-crotyl silanes and C3-oxygenated vinyl silanes via their (*R*)-*O*-mandelate diastereomers. The absolute configurations of these derivatives were assigned by comparing the NMR of the corresponding *O*-mandelate derivatives. A comparison of $\Delta\delta$ in both mandelate and OAM derivatives revealed that OAM is equally reliable as the corresponding mandelate derivatives.

3. Conclusion

In conclusion, our investigation on cyclitol derivatives revealed that OAM endure steric crowding and thus can be used reliably for the determination of absolute configuration of crowded alcohols too unlike other CARs. This study also revealed that the conformation of OAM deviates when the alcohol part is conformationally frozen. This supports our theory that the alcohol part compromises for minimizing energy of the system. We have also established that OAM can be reliably used as a CAR in crowded inositol and other cyclitol systems for the determination of their absolute configurations, where no CAR has been used to date. Simple derivatives were also investigated to generalize the reliability of the method. Many literature examples have been used to compare the reliability of OAM as a CAR with other frequently used CARs. Such a comparison proved that OAM is better than MTPA, MPA and even mandelate derivatives. We are currently investigating the reliability of this method for the determination of the absolute configuration of chiral amines, which will be reported in due course elsewhere.

4. Experimental

4.1. Preparation of the OAM ester by the DCC method

To a solution of the alcohol in dichloromethane, was added DCC (1.1 equiv) and *O*-acetylmandelic acid (1.1 equiv) and stirred at 0 °C for 2–3 h. The urea was filtered off and the filtrate evaporated and chromatographed to give the corresponding OAM ester.

4.2. Preparation of the OAM ester by the chloride method

To a solution of alcohol in pyridine was added a solution of *O*-acetyl mandeloyl chloride in dichloromethane dropwise at 0 °C. After being stirred for 1–2 h, the solvents were evaporated under reduced pressure and the resulting gummy material dissolved in ethyl acetate and washed successively with water, dil-HCl, satd $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Further purification was done by chromatography wherever necessary.

4.3. Typical procedure for the determination of absolute configuration of cyclitol or any other secondary alcohols

Measure the δ values of the group of protons on either side of the CH-OAM plane in two different diastereomers [derived from opposite enantiomers of the alcohol with an OAM of known absolute configuration or from a single enantiomer of the alcohol with both (*S*)- and (*R*)-OAM]. Then by using the conformational model and the sign of the $\Delta\delta$ values, the absolute configuration of the alcohol(s) can be determined.

Acknowledgements

We thank JSPS for a postdoctoral fellowship (K.M.S.) and Grant-in-aid (No. 02170). Also we thank Venture Business Laboratory, Ehime University for NMR facility. We thank Prof. Noritaka Chida, Keio University for kindly sending us the spectra of **13D** and **13L**.

References

1. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
2. Trost, B. M.; Belletire, J. L.; Godleski, S.; Mcdougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.
3. For a recent review, see: Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.
4. (a) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781; (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092; (c) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731; (d) Ohtani, I.; Kusumi, T.; Ishitsuka, O. M.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147; (e) Kusumi, T.; Fujitha, Y.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2923; (f) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296; (g) Joshi, B. S.; Newton, M. G.; Lee, D. W.; Barber, A. D.; Pelletier, W. *Tetrahedron: Asymmetry* **1996**, *7*, 25.
5. (a) Seco, J. M.; Latypov, Sh. K.; Quinoa, E.; Riguera, R. *Tetrahedron Lett.* **1994**, *35*, 2921; (b) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504; (c) Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **1995**, *6*, 107.
6. (a) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256; (b) Harada, N.; Watanabe, M.; Kuwahara, S.; Sugio, A.;

Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249; (c) Kusumi, T.; Takahashi, H.; Xu, P.; Fukushima, T.; Asakawa, Y.; Hashimoto, T.; Kan, Y.; Inouye, Y. *Tetrahedron Lett.* **1994**, *35*, 4397; (d) Kusumi, T.; Takahashi, H.; Hashimoto, T.; Kan, Y.; Asakawa, Y. *Chem. Lett.* **1994**, 1093; (e) Ichikawa, A.; Ono, H.; Harada, N. *Tetrahedron: Asymmetry* **2003**, *14*, 1593.

7. (a) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731; (b) Drouin, J.; Costante, J. *J. Chem. Educ.* **1997**, *74*, 992; (c) Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1983**, 83; (d) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78; (e) Chimni, S. S.; Singh, S.; Kumar, S.; Mahajan, S. *Tetrahedron: Asymmetry* **2002**, *13*, 511; (f) Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444.
8. Sureshan, K. M.; Miyasou, T.; Hayashi, M.; Watanabe, Y. *Tetrahedron: Asymmetry* **2004**, *14*, 3.
9. Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477.
10. (a) Suzuki, T.; Tanaka, S.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *Org. Lett.* **2000**, *2*, 1137; (b) Suzuki, T.; Suzuki, S. T.; Koashi, Y.; Yamada, K.; Chida, N. *J. Org. Chem.* **2002**, *67*, 2874; (c) Riley, A. M.; Potter, B. V. L. *Tetrahedron Lett.* **1999**, *40*, 2213; (d) Horne, G.; Potter, B. V. L. *Chem. Eur. J.* **2001**, *7*, 80; (e) Chida, N.; Yamada, E.; Ogawa, S. *J. Carbohydr. Chem.* **1988**, *7*, 555; (f) Mills, S. J.; Liu, C.; Potter, B. V. L. *Carbohydr. Res.* **2002**, *337*, 1795; (g) Mills, S. J.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1279; (h) Garegg, P. J.; Lindberg, B.; Kvarnstrom, I.; Svensson, S. C. T. *Carbohydr. Res.* **1985**, *139*, 209; (i) Mills, S. J.; Potter, B. V. L. *J. Org. Chem.* **1996**, *61*, 8980; (j) Mills, S. J.; Backers, K.; Erneux, C.; Potter, B. V. L. *Org. Biomol. Chem.* **2003**, *1*, 3546; (k) Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 111.
11. For the reasons of space and simplicity, only one of the two diastereomers is represented in charts.
12. *trans*-Ketal is a more rigid conformational lock than the *cis*- as 1,2-*trans*-mono-ketal restricts the ring flipping and mobility of the cyclohexane skeleton while the 1,2-*cis*-mono-ketal allows ring flipping.
13. The $^{3}J_{HH}$ coupling constants of *cis*-ketalized inositol derivatives are different from derivatives where no ketal is present. This is due to the change in the dihedral angle between different vicinal protons due to a slight conformational change on ketalization.
14. Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
15. Ogawa, S.; Kimura, H.; Uchida, C.; Ohashi, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1695.
16. (a) Takao, K.; Hara, M.; Tsujita, T.; Yoshida, K.; Tadano, K. *Tetrahedron Lett.* **2001**, *42*, 4665; (b) Takao, K.; Tsujita, T.; Hara, M.; Tadano, K. *J. Org. Chem.* **2002**, *67*, 6690.
17. Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villieras, J. *Tetrahedron Lett.* **1998**, *39*, 1759.
18. Panek, J. S.; Sparks, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 801.