Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 3–7

Is *O*-acetylmandelic acid a reliable chiral anisotropy reagent?

Kana M. Sureshan, Tomomi Miyasou, Minoru Hayashi and Yutaka Watanabe*

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577 Japan

Received 24 July 2003; revised 15 October 2003; accepted 15 October 2003

Abstract—The X-ray crystal structure of D-1,4-di-*O*-(*O*-acetylmandeloyl)-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol showed two different conformations for different acetylmandelate groups. A comparison of its conformation in solution with that in the solid is made by the use of ^{1}H NMR. The observed anisotropic shielding effect is rationalized based on these conformational studies. This study cautions the use of *O*-acetylmandelate as CAR for sterically crowded and conformationally locked alcohols.

The classical anisotropy method introduced and developed by Mosher,[1] Trost,[2] and others is continuing to be the most simple and 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 agents (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 data and thus to predict the absolute configuration. In the model, the group facing the phenyl (aryl) ring of the CAR experiences 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 have been many reports where these methods were inefficient in predicting the absolute configuration unambiguously[3] because of the small magnitude of $\Delta\delta$. These failures can be rationalized as due to the deviation of the CAR conformation in solution from the theoretical model. The existence of different conformers in equilibrium (conformational flexibility) for aryl methoxy acetate (AMA) derivatives has been introduced[4] to explain this small $\Delta\delta$. Such a conformational flexibility imposes significant limitations on the scope of this method for determining absolute configuration. Consequently, the continued search for the ideal CAR (with frozen conformation and thus higher value of $\Delta\delta$) resulted in the development of many new ones.[5]

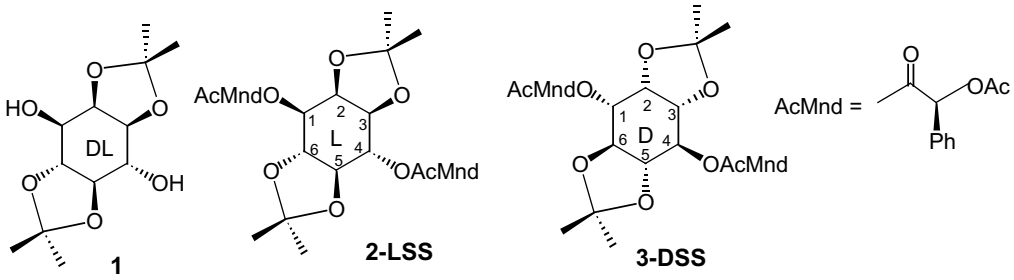
Emphasis is given to the CARs, which are both cost effective and give good enantioresolution and allow the determination of the absolute configuration. The comparatively less expensive and easy to manipulate *O*-acetylmandelic acid[6] is a preferred candidate in this context. Smith et al.[7] reported the crystal structure of an (*S*)-*O*-acetylmandelate [(*S*)-OAM] derivative of an intermediate during their synthesis of (−)-quadron. This structure showed a conformation in which the carbonyl and the *O*-acetyl are eclipsed (*syn periplanar*, *sp* like). Lee et al.[8] applied this conformational model to confirm the absolute configuration of an (*S*)-OAM derivative of 1,5-heptadien-4-ol. Recently it has been reported that the $\Delta\delta$ of diastereotopic hydrogens in isopentenyl alcohol is largest for *O*-acetylmandelate out of OAM, MPA, and MTPA esters. This has been used to determine the configuration at the 2-position of deuterium labeled isopentenyl alcohols.[9] Also there are other reports[10] where *O*-acetylmandelates (OAM) were used for the determination of the absolute configuration of alcohols. Recently Chataigner et al.[11a] compared MPA and OAM derivatives and illustrated that OAM derivative gives larger $\Delta\delta$ and hence more reliability than MPA derivatives. This study revealed that Trost's conformational model for MPA derivative could also be applied to the OAM derivative. These examples suggest that

* Corresponding author. Tel.: +81-89-927-9921; fax: +81-89-927-9944; e-mail: wyutaka@dpc.ehime-u.ac.jp

0957-4166/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2003.10.012

O-acetylmandelate derivatives have a comparatively rigid conformation (increase in $\Delta\delta$) when compared to MPA derivatives. The added advantage is that the mandelate derivatives, which can be prepared by selective deacetylation of the corresponding *O*-acetylmandelates,[11] give more reliable data (higher $\Delta\delta$ upto 0.4 ppm) due to conformational freezing (in *sp* conformation) arising from the hydrogen bonding between the carbonyl and the hydroxyl group.

During our ongoing research to provide easy access to many inositol phosphates and their lipid analogues, whose chemistry and biology have undergone a remarkable advance in recent years due to their important biological roles,[12] we have resolved[13] the diketal **1** via sequential crystallizations of its di-(*S*)-OAM derivatives **2-LSS** and **3-DSS**. The absolute configurations of the individual diastereomers were determined by converting them back to the known enantiomers of diol **1**. In addition, we have confirmed the absolute configuration by solving the crystal structure of **3-DSS**.[14] Surprisingly each OAM group in **3-DSS** is found to be in a different conformation with respect to the other in the crystalline state. One of the OAM conformations (attached to C4-*O*) is in agreement (*sp*) and the other (attached to C1-*O*) is different (*anti periplanar*; *ap*) to the previously proposed conformational model (*sp*) for the determination of the absolute configuration. In the ideal conformation both phenyl rings are expected to be in parallel arrangement (both in *sp*) however both are in an anti-parallel (*sp* and *ap*) relationship (Fig. 1). Similar to the crystal structures of CAR derivatives that substantiated the conformational model for MTPA,[15] MPA,[2] and MPPA,[5f] the known crystal structures of OAM[7,16] derivatives have also shown a conformation similar to the proposed conformational model. Ours is probably the first exception where a CAR shows two distinct conformations in its crystal structure.[17]



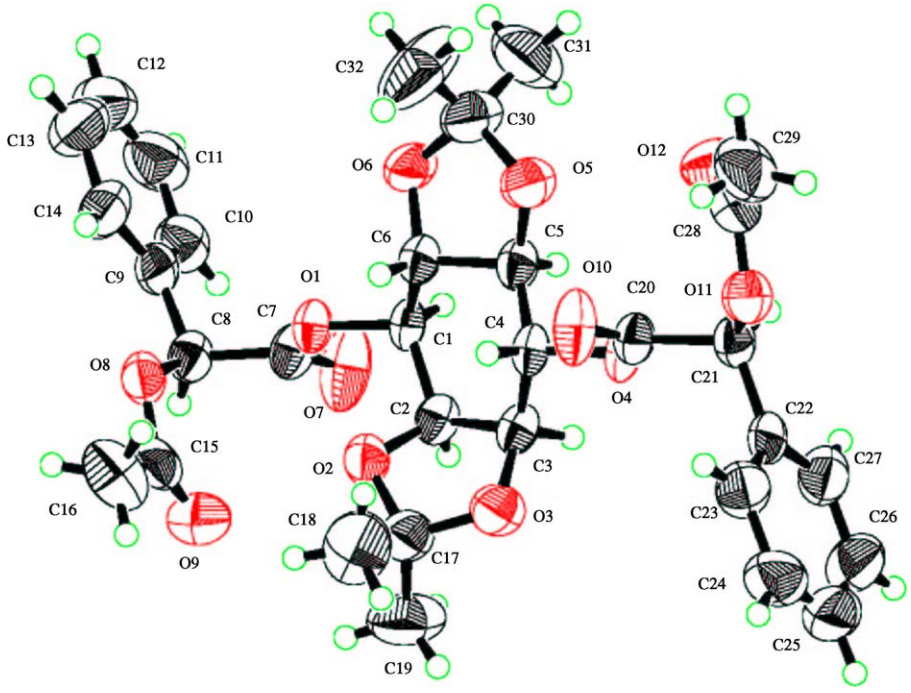


Figure 1. ORTEP diagram of **3-DSS** showing the anti-parallel relationship of two phenyl ring (*sp* and *ap* conformation).

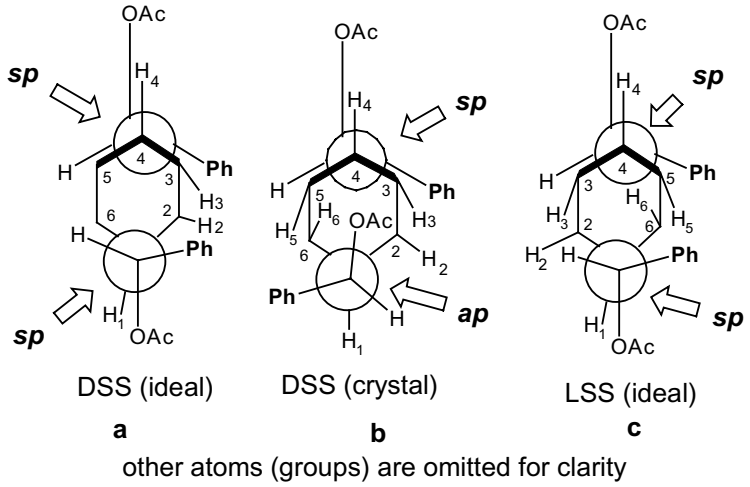


Figure 2. Conformational models.

This remarkable conformational variance prompted us to examine the conformation of these acetylmandeloyl groups in solution by comparing the ^{1}H NMR spectra of **2-LSS** and **3-DSS** based on the anisotropic shielding effect. For this purpose different conformational models were drawn (Fig. 2). Figure 2a shows the ideal conformation for **3-DSS** in which both the OAM are in *sp* conformation (ideal) and Figure 2b is exactly the extrapolation of the crystal structure conformation; one OAM in *sp* and the other in *ap* conformation. Figure 2c represents the ideal conformation for the **2-LSS**. The experimental chemical shift values of both **2-LSS** and **3-DSS** and their difference, $\Delta\delta$, are tabulated in Table 1.

According to the ideal conformation, H2 and H3 in **3-DSS** (Fig. 2a) and H5 and H6 in **2-LSS** (Fig. 2c) are shielded by two phenyl rings and hence each of these pairs of protons is expected to show an up-field shift compared to the other diastereomer. Since all of these four protons are flanked by two OAMs (one closer and one further), they are expected to suffer equal amounts of anisotropic shielding effect. But the smaller $\Delta\delta^{L-D}$ value for H2 (0.22 ppm) compared to H3 (0.37 ppm) suggests that the OAM near H2 (the one attached to C1-*O*) in **3-DSS** is in a different conformation and hence the shielding experienced by H2 is solely due to the further OAM (attached to C4-*O*). As the OAM attached to C1-*O* is not shielding H2 and H3, it must be shielding H6 and H5, the protons on the other side of the OAM plane, through a change of conformation. Let us assume that the OAM attached to C1-*O* in **3-DSS** takes an *ap* conformation in $CDCl_3$ solution as in the crystalline state (Fig. 2b) and hence shields H6 and H5. This argument was substantiated by NOESY spectroscopy of **3-DSS**, which showed cross peaks of aromatic protons with H6 and H3 but not with H2 (as in Fig. 2b) while a NOESY spectrum of **2-LSS** is in agreement with the ideal *sp* conformation (as in Fig. 2c) of both the OAM groups. However the smaller $\Delta\delta^{L-D}$ values for H5 and H6 is a direct reflection of the shielding experienced by these protons (H6 and H5) in **3-DSS**. The very small $\Delta\delta^{L-D}$ for H6 compared to H5 is due to the fact that anisotropic shielding experienced by H6 in **3-DSS** is more, as the phenyl ring (of OAM at C1-*O*) is closer to H6. The small values of $\Delta\delta$ for H1 and H4 are as expected since these protons are least affected by the aromatic shielding.

Table 1. Chemical shifts and $\Delta\delta^{L-D}$ of inositol ring protons

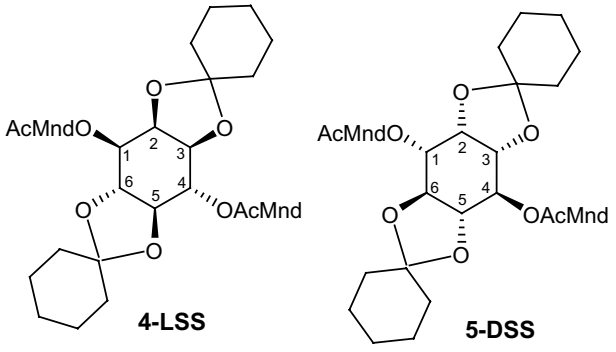
H	**2-LSS** (δ)	**3-DSS** (δ)	$\Delta\delta^{L-D}$
H1	5.09	5.07	0.02
H2	4.55	4.33	0.22
H3	4.16	3.79	0.37
H4	5.30	5.22	0.08
H5	3.23	3.45	−0.22
H6	4.04	4.06	−0.02

In the crystal structure of **3-DSS**, the average distance between the phenyl ring of the OAM attached to C4-*O* to H3 is 6.037 Å and that to H2 is 7.535 Å. The observed magnitudes of anisotropic shielding (in $\Delta\delta$) for these protons (0.37 ppm for H3 and 0.21 ppm for H2) are inversely proportional to their distances from the phenyl ring. The phenyl ring of the other OAM (attached to the C1-*O*) is 5.456 Å from H6 and 7.502 Å from H5. Hence we can expect, by analogy, a similar magnitude of shielding for these protons; that is the expected up-field shift in **3-DSS** for H6 ≅ 0.37 ppm and for H5 ≅ 0.22 ppm. In **2-LSS** both H5 and H6 are shielded by the phenyl rings. In other words, H5 and H6 are shielded in both **2-LSS** and **3-DSS**. Hence the difference in chemical shift for these protons between **2-LSS** and **3-DSS**, $\Delta\delta^{L-D}$, becomes small. This is in agreement with the observed $\Delta\delta^{L-D}$ (−0.02 for H6 and −0.21 for H5). The unreliably small value for H6 suggests that the shielding experienced by this proton in both **2-LSS** and **3-DSS** is almost similar. The relatively larger magnitude of $\Delta\delta^{L-D}$ for H5 is due to the fact that the shielding experienced by this proton in **2-LSS** (due to one closer and one further phenyl ring; see Fig. 2c) is more than that in **3-DSS** (due to one further phenyl ring; Fig. 2b). Taking these into consideration the real anisotropic shift exerted for all the protons near to OAM is around 0.37–0.40 ppm. This implies that the observed anisotropic effect of OAM is

Table 2. Comparison of $\Delta\delta^{2LSS-3DSS}$ and $\Delta\delta^{4LSS-5DSS}$

	H1	H2	H3	H4	H5	H6
$\Delta\delta^{2LSS-3DSS}$	0.02	0.22	0.37	0.08	−0.22	−0.02
$\Delta\delta^{4LSS-5DSS}$	−0.04	0.14	0.32	0.02	−0.21	−0.03

better or comparable to the best known CARs. The existence of different conformers in a dynamic equilibrium can also be ruled out. Although we found two conformers for OAM, based on the forgoing discussions, we cannot question the reliability of OAM as a CAR.



The reason for this conformational deviation could be due to 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 or 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.[18] We anticipated similar conformational preferences in structurally similar dicyclohexylidene derivatives **4-LSS** and **5-DSS**. A comparison of ^{1}H NMR of both the diastereomers revealed very similar $\Delta\delta^{L-D}$ (Table 2) as in the case of **2-LSS** and **3-DSS**. The very small value of $\Delta\delta^{L-D}$ for H6 suggests that H6 is shielded (almost equally) by the phenyl ring of the OAM in both **4-LSS** and **5-DSS** as in the case of **2-LSS** and **3-DSS**. In addition, the $\Delta\delta^{L-D}$ values for all the inositol protons in both the isopropylidene (**2-LSS** and **3-DSS**) and cyclohexylidene (**4-LSS** and **5-DSS**) derivatives are very similar. This suggests that **4-LSS** and **5-DSS** have analogous conformations to **2-LSS** and **3-DSS**, respectively. This supports the fact that the observed conformational change is due to the conformationally locked and sterically crowded nature of the alcohol (inositol). The present results caution the application of OAM as a CAR for determining the absolute stereochemistry of conformationally locked and crowded alcohols.

In conclusion, we have observed for the first time in the crystal structure of an OAM derivative two distinct conformations for the CAR. A comparison of its conformation in solid and solution states revealed that similar conformations are retained in solution also. A structurally analogous molecule also showed similar conformational preferences suggesting that the observed anomaly is inherent with the diketal systems due to conformational locking and steric factors. To answer the question, '*Is O-acetylmandelic acid a reliable CAR?*' authoritatively, additional results with structurally diverse alcohols and amines are necessary and such studies are underway in our laboratory, the detailed results of which will be reported in due course.

Acknowledgements

We thank JSPS for a postdoctoral fellowship (K.M.S.) and Grant-in-aid (No. 02170) and Naito foundation for the financial support. We are grateful to Prof. Hidemitsu Uno for the timely help in crystal data collection. Yamakawa Chemical Industry Co. Ltd is hereby acknowledged for a gift of mandelic acid. Also we thank Venture Business Laboratory and Advanced Instrumentation Center for Chemical Analysis, Ehime University for NMR and elemental analysis, respectively.

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. (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.
4. (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.
5. (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) Harada, N.; Watanabe, M.; Kuwahara, S.; Sugio, A.; Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249; (f) Ichikawa, A.; Ono, H.; Harada, N. *Tetrahedron: Asymmetry* **2003**, *14*, 1593.
6. Breitholle, E. G.; Stammer, C. H. *J. Org. Chem.* **1974**, *39*, 1311.

7. Smith, A. B., III; Konopelski, J. P.; Wexler, B. A.; Sprengeler, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 3533.
8. Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444.
9. Giner, J.-L.; Kiemle, D.; Zuniga, D. J. *Tetrahedron Lett.* **2002**, *43*, 1175.
10. (a) Spino, C.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 731; (b) Drouin, J.; Costante, J. *J. Chem. Edu.* **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.
11. (a) Chataigner, I.; Lebreton, J.; Durand, D.; Guingant, A.; Villieras, J. *Tetrahedron Lett.* **1998**, *39*, 1759; (b) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548; (c) Panek, J. S.; Sparks, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 801.
12. (a) Hinchliffe, K.; Irvine, R. *Nature* **1997**, *390*, 123; (b) *Phosphoinositides: Chemistry, Biochemistry and Biomedical Applications*; Bruzik, K. S., Ed., ACS Symposium Series 718, 1999; (c) Ferguson, M. A. J.; Williams, A. F. *Annu. Rev. Biochem.* **1988**, *57*, 285; (d) Berridge, M. J. *Nature* **1993**, *361*, 315.
13. Sureshan, K. M.; Yamasaki, T.; Hayashi, M.; Watanabe, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 1771.
14. Crystallographic data is deposited as CCDC 215964. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.
15. (a) Oh, S. S.; Butler, W. M.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 4499; (b) Doesburg, H. M.; Petit, G. H.; Merckx, E. M. *Acta. Crystallogr. B* **1982**, *38*, 1181; (c) Balani, S. K.; Boyd, D. R.; Cassidy, E. S.; Devine, G. I.; Malone, J. F.; McCombe, K. M.; Sharma, N. D.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2751.
16. (a) Kirihara, M.; Kawasaki, M.; Takuwa, T.; Kakuda, H.; Wakikawa, T.; Takeuchi, Y.; Kirk, K. L. *Tetrahedron: Asymmetry* **2003**, *14*, 1753; (b) Kirihara, M.; Kawasaki, M.; Katsumata, H.; Kakuda, H.; Shiro, M.; Kawabata, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2283.
17. But different conformers with 0.5:0.5 occupancy for a mono-MTPA derivative have been reported: Inouye, Y.; Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *Chem. Lett.* **1990**, 2073.
18. In the crystal structure there is a short CH···O contact (3.2 Å, 124°), which may be one of the stabilizing interactions in the distorted state.