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Toward the Creation of NMR Databases in Chiral Solvents: Bidentate Chiral NMR Solvents for Assignment of the Absolute Configuration of Acyclic Secondary Alcohols

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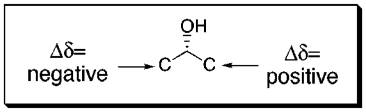
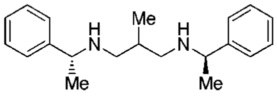
ABSTRACT





(*R*,*R*)-**1d**

The absolute configuration of acyclic secondary alcohols can be established from analysis of the chemical shift behaviors of the adjacent carbons in bidentate chiral solvents (*R*,*R*)- and (*S*,*S*)-1d as formulated in the boxed illustration.

We have recently reported the concept of a universal NMR database approach for assignments of the relative and absolute configuration of an unknown compound without degradation and/or derivatization work.[1,2] In this approach, structural motifs present in an unknown compound are treated separately from each other and the NMR profile of each structural motif is compared with the corresponding NMR databases to predict their stereochemistry. Comparison of the NMR profiles in achiral solvents such as DMSO and methanol allows establishment of the relative configuration of a given structural motif, whereas that in chiral solvents such as (*R*)- and (*S*)-*N*,α-dimethylbenzylamines (PhCH(Me)-NHMe, DMBA) allows determination of the absolute as well as relative configuration of a given structural motif.

Through the ^{13}C NMR studies on meso and optically active 1,3,5-triols in DMBA, we have suggested that a structural motif with two binding sites might play an important role for an effective recognition by the chiral NMR solvents, cf., **A** (Figure 1).[2c] In connection with the proposed recognition mode **A**, replacement of the nitrogen and oxygens in **A** for the oxygen and nitrogens, respectively, results in **B**. Although an N−H••N hydrogen bonding such as the one proposed in **B** is not observed as commonly as an N••H−O hydrogen bonding, some examples are known in the literature.[3] Assuming such a recognition mode, we noticed a possibility that a bidentate chiral NMR solvent might be useful for assignment of the absolute configuration of isolated alcohols.

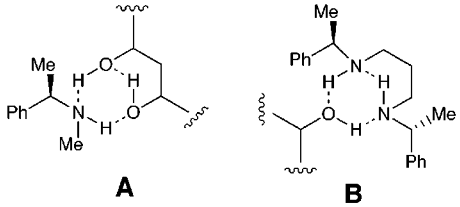


Figure 1.

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(1) For NMR databases in achiral solvents, see: (a) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177−2180. (b) Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2181−2184. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562−2571. (d) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 4279−4281. (e) Tan, C.-H.; Kobayashi, Y.; Kishi, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 4282−4284. (f) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076−2078.

(2) For NMR databases in chiral solvents, see: (a) Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2245−2248. (b) Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2249−2252. (c) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2253−2255.

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With this notion, we screened a number of bidentate chiral NMR solvents for their capacity to discriminate the enantiotopic C4/C6 carbons of *n*-nonan-5-ol (**2**).[4] Through this screening, bis-α-methylbenzylamines such as BMBA-*p* (**1a**) and BMBA-*e* (**1b**) emerged as the promising chiral NMR solvents (Figure 2).[5] The enantiotopic C4/C6 carbons of **2** were clearly discriminated in BMBA-*p* (**1a**) or BMBA-*e* (**1b**) but not in BMBA-*b* (**1c**) or DMBA. It should be noted that, because of their high viscosity, these NMR experiments were done in a 5:2 mixture of BMBA-*p* (**1a**) or BMBA-*e* (**1b**) and $CDCl_3$, DMSO-d_6, or CD_3OD, but an enantiotopic discrimination was clearly detected in all of these solvent systems.[6,7] No enantiotopic discrimination of the C4/C6 carbons was detected for the substrates with OMe, OAc, NH_2, NHMe, and Cl instead of OH in **2**. Interestingly, BMBA-*b* (**1c**) exhibited characteristics similar to those of the corresponding monomeric benzylamine *n*-BuNHCH(Me)Ph. In our view, these observations together support the proposed mode of recognition, cf., **A** and **B**.

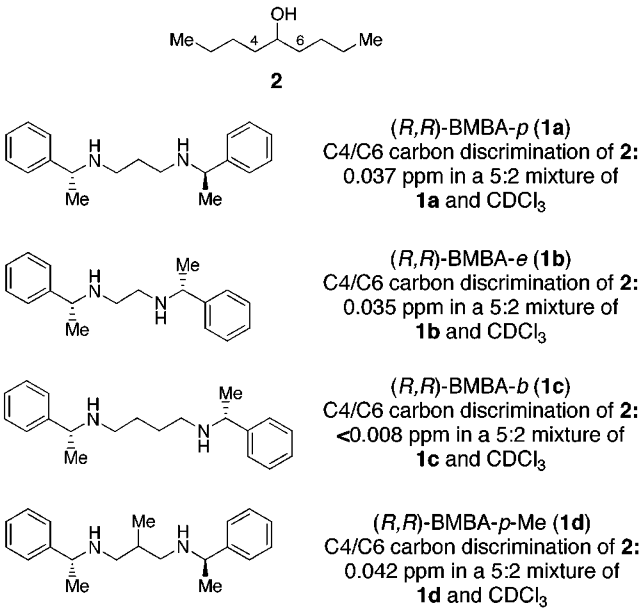

Figure 2.

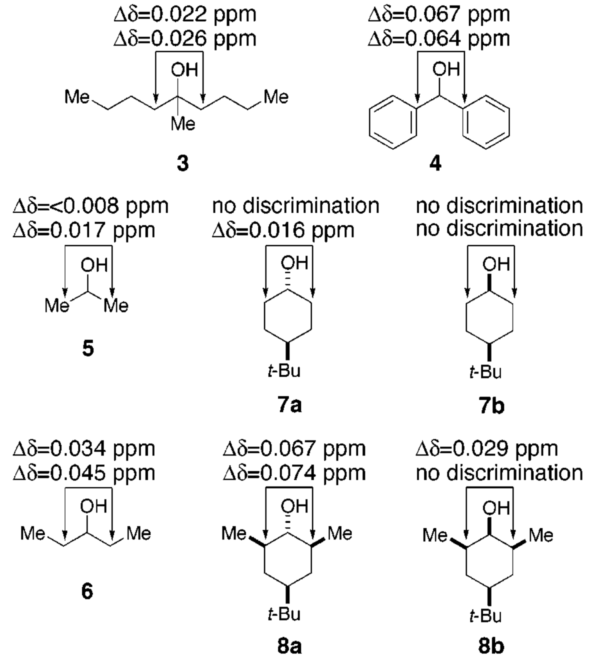

Figure 3. Chemical shift differences (ppm) observed for the indicated carbon in a 5:2 mixture of (*R*,*R*)- or (*S*,*S*)-**1a** and $CDCl_3$ (upper line) and in a 5:2 mixture of (*R*,*R*)- or (*S*,*S*)-**1d** and $CDCl_3$ (lower line).

Enantiotopic carbon discrimination by **1a** was also observed for other substrates, including **3** and **4** (Figure 3). However, the enantiotopic carbons of 2-propanol (**5**) and *cis*- and *trans*-4-*tert*-butylcyclohexanols (**7a,b**) were not clearly discriminated by **1a**. Interestingly, the enantiotopic carbons of **5** and **7a** were sharply discriminated by BMBA-*p*-Me (**1d**) (vide infra). Related to this, it is worthwhile adding that a large discrimination even in **1a** was observed for the enantiotopic carbons of *n*-pentan-3-ol (**6**) and *cis*- and *trans*-4-*tert*-butyl-2,6-dimethylcyclohexanols (**8a,b**).[8]

The enantiotopic discrimination discussed means that NMR experiments in these chiral solvents should allow us to assign the absolute configuration of isolated secondary alcohols. The optically active alcohols **9**−**14**[9] with the indicated absolute configuration were prepared and subjected to the NMR experiments (Figure 4). As expected, the carbons adjacent to the alcohol showed significant chemical shift differences in (*R*,*R*)- and (*S*,*S*)-**1a**. On the basis of these results, the relationship between the absolute configuration of an isolated secondary alcohol and the signs of $\Delta\delta$ [$\delta_{(R,R)-\mathbf{1a}} - \delta_{(S,S)-\mathbf{1a}}$] for the adjacent carbons is formulated as summarized in the box in Figure 4. This relationship is maintained for all the isolated acyclic secondary alcohols studied and is independent from the steric bulk of substituents.[10] Thus, this NMR profile should be useful for assigning the absolute configuration of isolated acyclic secondary alcohols.[11]

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(3) For examples, see: (a) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391−3394. (b) Alvaro, G.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, *62*, 4180−4182. (c) Grepioni, F.; Grilli, S.; Martelli, G.; Savoia, D. *J. Org. Chem.* **1999**, *64*, 3679−3683.

(4) Some attempted bidentate ligands are listed in footnote 8 of ref 2c.

(5) The experimental details for the synthesis of **1a**−**d** are included in Supporting Information.

(6) A Varian Mercury 400 spectrometer (100 MHz) was used to collect all data on alcohols (10 mg) in chiral solvent (350 mg)/$CDCl_3$ (140 mg) (5:2 w/w), with acetone-d_6 in the coaxial inserts as an external reference (δ 29.800) and a lock-signal and with readout of NMR spectra being adjusted to 0.001 ppm/point (sw = 23980.8, fn = 524288). Half-bandwidth is 0.008 ppm.

(7) The $\Delta\delta$ in a 10:1 mixture of **1a** and DMSO-d_6 and CD_3OD was found to be 0.026 and 0.025 ppm, respectively, whereas that in a 5:2 mixture of **1a** and benzene-d_6 and pyridine-d_5 was found to be 0.042 and 0.020 ppm, respectively.

(8) Compound **8a** and **8b** was prepared by $NaBH_4$ reduction of 4-*tert*-butyl-*cis*-2-*cis*-6-dimethylcyclohexanone (Kenar, J. A.; Nickon, A. *Tetrahedron* **1997**, *53*, 14871−14894) and separation by SiO_2 column chromatography.

(9) The experimental details for the synthesis and stereochemistry assignment of **9**−**10** and **13**−**14** are included in Supporting Information.

(10) According to the Cahn−Ingold−Prelog convention, **9** and **11** belong to the (*S*)-series, whereas **10** belongs to the (*R*)-series.

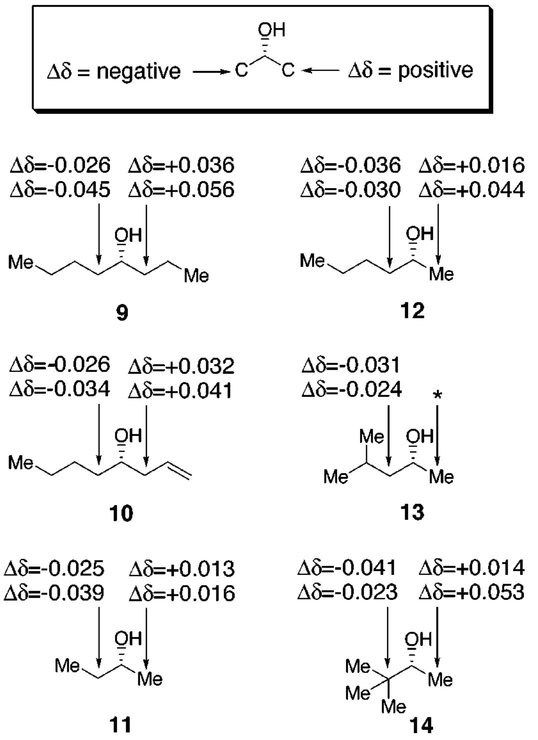

Figure 4. Chemical shift differences ($\Delta\delta = \delta(R,R) - \delta(S,S)$) observed for the indicated carbon in a 5:2 mixture of (R,R)- or (S,S)-**1a** and $CDCl_3$ (upper line) and in a 5:2 mixture of (R,R)- or (S,S)-**1d** and $CDCl_3$ (lower line). The carbon signal indicated by an asterisk is hidden under the solvent signal.

In the universal NMR database approach, steric and/or stereoelectronic interactions between structural clusters connected with a two- or more-methylene bridge have been shown to be almost negligible.[12] Therefore, such a structural cluster is treated independently from the others, and its NMR profile in achiral or chiral solvents is compared with the corresponding NMR databases to predict their relative and absolute configuration. The validity of this treatment has been shown in NMR solvents including DMSO,[1a] methanol,[1a] and monodentate chiral solvents[2a] but has not yet been tested in bidentate NMR solvents. Using *meso*-diols **16**−**19**, we studied the behaviors of their two hydroxyl groups toward **1a** (Figure 5). If the two hydroxyl groups present in **16**−**19** interact independently with the bidentate chiral solvent **1a**, we would expect their $\Delta\delta$ profile to be similar to that observed for an isolated secondary alcohol such as **9**. To the contrary, if the two hydroxyl groups interact dependently with **1a**, we would expect the $\Delta\delta$ profile to be similar to that observed for *meso*-1,3-diol **15**.[2c]

The $\Delta\delta$ profile of *meso*-1,7-diol **19** was found to be very similar to that of **9**, thereby indicating that the absolute configuration of 1,7- and higher-diols can be deduced from independent analyses of the $\Delta\delta$ for the adjacent carbons of each alcoholic center. Both *meso*-1,4- and 1,5-diols **16** and **17** gave a $\Delta\delta$ profile similar to that observed for *meso*-1,3-diol **15**, i.e., only the C3 carbon gives a significant $\Delta\delta$, showing that the 1,4- and 1,5-diol system functions as one structural cluster rather than two independent alcohols. Interestingly, the *meso*-1,6-diol **18** exhibits a large $\Delta\delta$ for the C4, instead of C3, carbon, which appears to represent a transition from one structural cluster of diol into two independent monool clusters. A similar, although less clear, overall $\Delta\delta$ trend was recognized for the optically active 1,4-

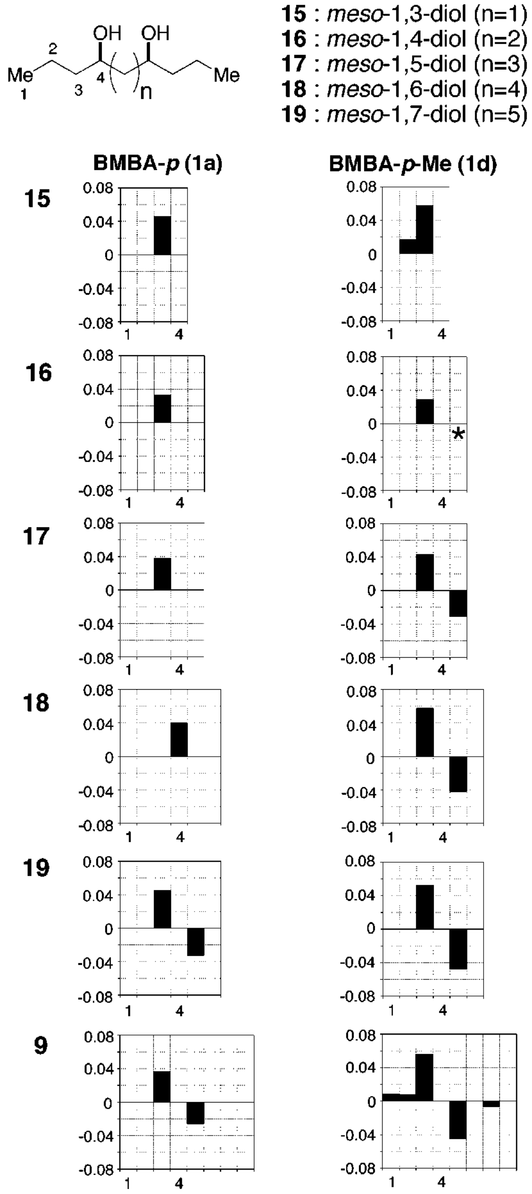

Figure 5. Difference in carbon chemical shifts of diols **15**−**19** (100 MHz) between (R,R)- and (S,S)-chiral solvent (**1a** and **1d**). The x- and y-axes represent carbon number and $\delta(R,R) - \delta(S,S)$ in ppm, respectively. Only one-half of the $\Delta\delta$ graphs is shown for **15**−**19**. The entire $\Delta\delta$ graphs for **15**−**19** are included in Supporting Information. Because of the meso nature, the sign of $\Delta\delta$ cannot be assigned for **15**−**19** but, on the basis of the profile of **9**, the sign of $\Delta\delta$ is given for them.

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(11) The relationship between the $\Delta\delta$ signs and the absolute configuration of other types of alcohols, including acyclic tertiary, cyclic secondary, and diaryl alcohols, will be reported in a separate account.

(12) For a case of the structural cluster spaced with a two-methylene bridge, see: Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946−7968.

through 1,7-diols corresponding to the *meso*-1,4- through 1,7-diols **16**−**19**; these data are included in Supporting Information.

The Δδ profiles identified for diols **16**−**18** are useful for assigning the absolute configuration of an unknown compound. Nonetheless, for application of this approach to an unknown case, it would be *operationally* simpler to have a chiral NMR solvent that allows us to treat independently the two alcohols present in a substrate, cf., the two alcohols in **16**−**18**. For this reason, we have made further structural modifications of BMBA-*p* (**1a**), with the assumption that **1a** may recognize **16**−**18** through a cyclic hydrogen-bonded network such as **C** and that destabilization of **C**, relative to **D**, might result in a chiral NMR solvent with an improved property in this respect (Figure 6). From this line of analysis, BMBA-*p*-Me (**1d**, Figure 2) emerged as the second generation of bidentate chiral NMR solvents.

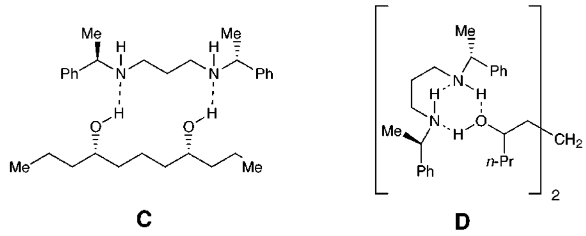

Figure 6.

The Δδ profiles in **1d** observed for *meso*-diols **15**−**19** as well as the isolated, optically active secondary alcohol **9** are summarized in Figure 5. With a sharp contrast in **1a**, *meso*-1,5- and 1,6-diols **17** and **18**, and most likely *meso*-1,4-diol **16**,[13] gave a Δδ profile similar to that of **9** in **1d**. This experiment shows that, as long as the alcohols are spaced with a three- (most likely two-)[13] or more-methylene bridge, one can deduce their absolute configuration via a simple analysis of the Δδ of the carbons adjacent to the alcoholic center independently from the rest of a molecule. In contrast, for the case where the alcoholic carbon is connected to the next alcoholic carbon directly or through a one-methylene bridge, one needs to treat this system as one structural cluster. It is equally important to note that the relationship observed in **1a** between the absolute configuration of alcohol and the signs of Δδ for the adjacent carbons is maintained in **1d**, except that Δδ in **1d** is significantly larger than Δδ in **1a** (Figure 4). Interestingly, this is a general trend for the substrates listed in Figures 2−5.

As demonstrated previously, the absolute configuration of structural motifs often found in the polyketide class of natural products can be assigned through comparison of the NMR profiles in (*R*)- and (*S*)-DMBA.[2] Nonetheless, it is interesting and worthwhile adding that the Δδ trend summarized in the box in Figure 4 is recognized even for the α- or α,α′-substituted cases, as seen in the monopropionate (**20** and **21**) and dipropionate structural motifs (**22**−**25**) (Figure 7).[14]

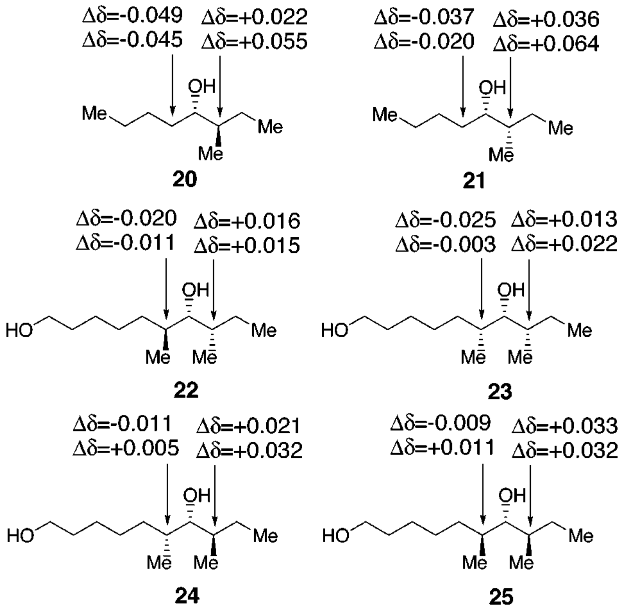

Figure 7. Chemical shift differences (Δδ = $\delta(R,R) - \delta(S,S)$) observed for the indicated carbon in a 5:2 mixture of (*R*,*R*)- or (*S*,*S*)-**1a** and $CDCl_3$ (upper line) and in a 5:2 mixture of (*R*,*R*)- or (*S*,*S*)-**1d** and $CDCl_3$ (lower line).

In conclusion, we have demonstrated that bidentate chiral NMR solvents such as BMBA-*p* (**1a**), BMBA-*e* (**1b**), and BMBA-*p*-Me (**1d**) allow us to assign the absolute configuration of acyclic secondary alcohols. Among the bidentate solvents studied, BMBA-*p*-Me (**1d**) exhibits the most ideal properties. On the basis of the relationship between the absolute configuration of alcohol and the signs of Δδ for the adjacent carbons formulated in the box in Figure 4, the absolute configuration of an acyclic secondary alcohol can be deduced. As long as the alcohols are spaced with a three- (likely two-) or more-methylene bridge, their absolute configuration can be assigned through analysis of the Δδ profile of each alcohol independently from the rest of a molecule. In contrast, for the case where the alcoholic carbon is connected to the next alcoholic carbon directly or through a one-methylene bridge, their absolute configuration can be determined through treatment of the Δδ profile as one structural cluster.

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Supporting Information Available: Experimental details for the synthesis of **1a**−**d**, **9**, **10**, **13**, and **14**, stereochemistry assignment of **9**−**10** and **13**−**14**, and entire Δδ graphs for **15**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] As noted in the text, the *meso*-1,6-diol **18** exhibited a large Δδ for the C4 carbon, instead of C3, which appeared to represent a transition from one diol-structural cluster to two independent monool-structural clusters. Assuming that this trend is held in the BMBA-*p*-Me solvent series, the Δδ profile of **16** appears to belong to the two independent monool-structural clusters, although the C5 carbon signal is hidden under the solvent peak.

[14] The sign of Δδ for the C6 carbon of **24** and **25** does not follow the prediction. However, it should be noted that the relative intensity of the C6 and C8 carbons agrees with the general trend.