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Toward the Creation of NMR Databases in Chiral Solvents for Assignments of Relative and Absolute Stereochemistry: Proof of Concept

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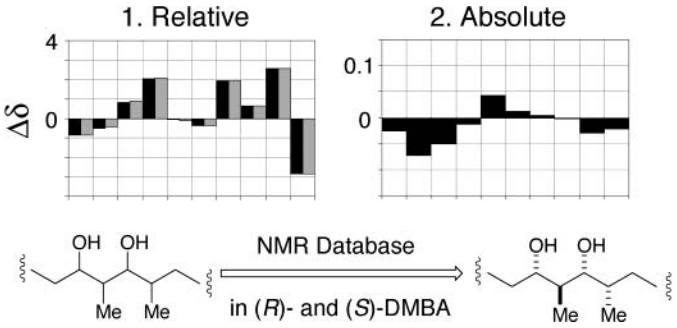
ABSTRACT



An NMR database approach in a chiral solvent allows us to predict both relative and absolute stereochemistry of an unknown compound without degradation and/or derivatization. *N*,α-Dimethylbenzylamine (DMBA) is a suitable solvent for this purpose. Using the C.5–C.10 portion of oasomycin A, the feasibility and reliability of this approach is demonstrated.

Our recent endeavors toward creation of universal NMR databases for stereochemical assignments have culminated in the establishment of the complete structure of the desertomycin/oasomycin class of natural products.[1] In this work, we treated structural motifs present in the antibiotics separately from each other and compared their NMR profiles with the corresponding NMR databases to predict their relative stereochemistry and then confirmed the predicted relative stereochemistry by enantioselective synthesis of each segment. In our view, since the reliability of this approach has been well demonstrated, confirmation of the predicted relative stereochemistry by chemical synthesis is no longer required. However, an enantioselective synthesis has provided us with information about the absolute configuration of each segment, which was essential for us to correlate the relative stereochemistry of one structural motif with the others. In this context, we recognized the possibility that the absolute, as well as relative, stereochemistry of a given structural motif could be established through an NMR database approach in a chiral solvent.[2−4] In this and the

(1) (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) Various methods have been used to establish the absolute configuration of an unknown compound. In connection with the current work, however, there is no known method to determine the absolute configuration of an intact molecule by NMR spectroscopy. Among the methods combining derivatization and NMR spectroscopy, the Kusumi−Kakisawa NMR analysis of Mosher esters is perhaps most widely used: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(3) Four chiral solvents were reported for NMR discrimination of enantiomers: see, (a) Pirkle, W. H. *J. Am. Chem. Soc.* **1966**, *88*, 1837. (b) Pirkle, W. H.; Hoekstra, M. S. *J. Magn. Reson.* **1975**, *18*, 396−400 and references therein.

(4) For reviews on subjects related to the current work, see: (a) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263−331. (b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457.

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following Letters, we would like to report the realization of this concept.

The first step of our efforts was to identify a suitable chiral NMR solvent that must meet several criteria, including, in our view, the following: (1) a high capacity to discriminate enantiomers, (2) a good capacity to dissolve organic compounds, (3) a characteristic ideally similar to that of DMSO or MeOH (vide infra), (4) chemical inertness, (5) a viscosity, boiling point, and freezing point suitable for NMR experiments, and (6) an easy access to its deuterated form. Using the arbitrarily chosen substrate **1e** (Figure 1), we conducted

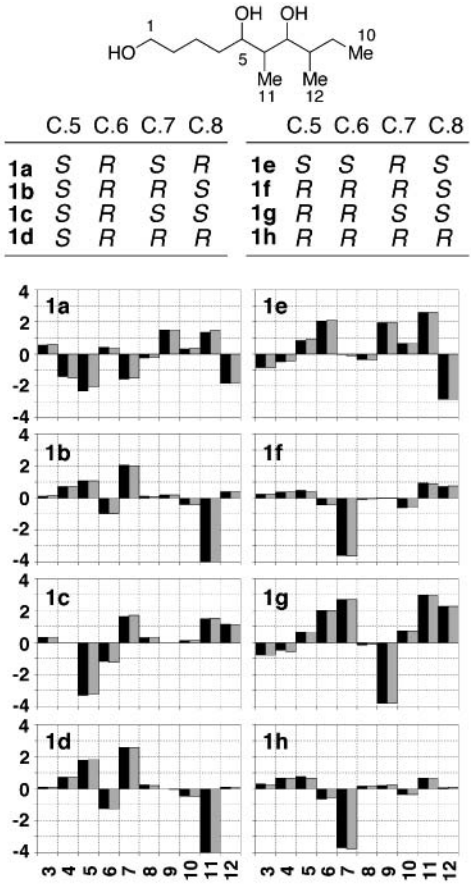

Figure 1. Difference in carbon chemical shifts between the average and the values for **1a**−**h** (100 MHz): solid bar, (*R*)-DMBA; shaded bar, (*S*)-DMBA. The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\delta_{\mathbf{1a-h}} - \delta_{ave}$ in ppm), respectively.

preliminary screenings of solvents, from which (*R*)- and (*S*)-*N*,α-dimethylbenzylamines (PhCH(Me)NHMe, DMBA) emerged as the chiral solvent of choice for the current work.[5] The second step was to measure the ^{13}C NMR spectra of all diastereomers of a given NMR database, and we chose to use the contiguous dipropionate NMR database to demonstrate the feasibility and reliability of this approach. Thus, the ^{13}C NMR spectra were recorded for the diastereomers **1a**−**h** (optically active)[1a] of both (*R*)- and (*S*)-DMBA to create the NMR database for the contiguous dipropionate motif.[6,7]

Figure 1 shows the ^{13}C NMR database in (*R*)- and (*S*)-DMBA as a deviation in chemical shift for each carbon of a given diastereomer from the average chemical shift of the carbon in question. Each diastereomer exhibits an almost identical NMR profile for (*R*)- and (*S*)-DMBA but shows an NMR profile distinct and differing from the other diastereomers, demonstrating that the database in (*R*)- and/or (*S*)-DMBA can be used for prediction of the relative stereochemistry of structural motifs in an intact form. However, we should comment on the solvent-effect studies conducted in the achiral solvent series; the overall NMR profile for each diastereomer of **1a**−**h** in DMSO was virtually identical to that in methanol, whereas the overall NMR profile in DMSO or methanol was significantly different from that in chloroform.[1a] On the basis of this observation, we concluded that DMSO or methanol is the solvent of choice for the NMR database approach. Interestingly, DMBA gives an overall NMR profile between DMSO (or methanol) and chloroform, suggesting that DMSO and methanol are superior to DMBA for the purpose of relative stereochemistry assignment. On comparison of the graphs in Figures 1 and 2, this situation becomes clearer; each diastereomer **1a**−**h** shows an NMR profile more distinct and differing from the other diastereomers in DMSO than in DMBA.[8] Nonetheless, we should emphasize that DMBA is still a viable solvent for the relative stereochemistry assignment work.

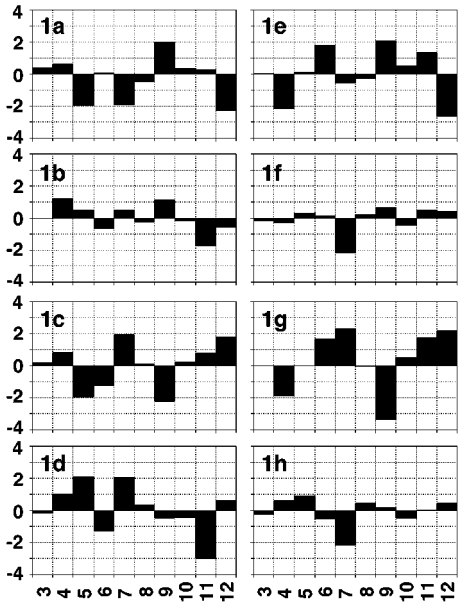

Figure 2. Difference in carbon chemical shifts between the average and the values for **1a**−**h** (100 MHz, DMSO-d_6). The *x*- and *y*-axes represent carbon number and $\Delta\delta$ ($\delta_{\mathbf{1a-h}} - \delta_{ave}$ in ppm), respectively.

(5) Over 20 chiral solvents were tested, including sulfoxides (CF_3SOCD_3, $PhSOCD_3$, etc.), alcohols (MeCH(OH)Et, $PhCH(CF_3)(OH)$, etc.), amide (PHCH(Me)N(Me)CHO), and others.

Figure 3 shows the ^{13}C chemical shift differences between the spectra of **1a**−**h** in (*R*)- and (*S*)-DMBA. Under the

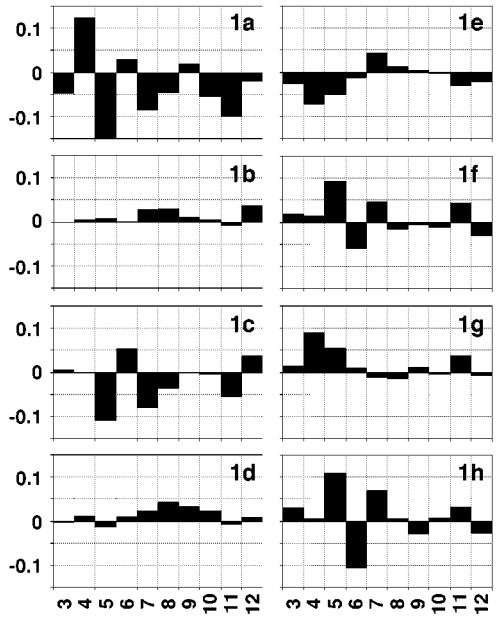

Figure 3. Difference in carbon chemical shifts of **1a**−**h** (100 MHz) between (*R*)- and (*S*)-DMBA. The *x*- and *y*-axes represent carbon number and $\delta_R - \delta_S$ in ppm, respectively.

conditions of measurement, a chemical shift difference of 0.010 ppm is reliably detected.[9] The ^{13}C chemical shift differences observed in (*R*)- and (*S*)-DMBA are well beyond this limit for **1a**−**h**. Thus, the absolute configuration of a given dipropionate motif can be deduced through comparison of the ^{13}C NMR profile in (*R*)-DMBA with that in (*S*)-DMBA, in reference to the corresponding diastereomer among **1a**−**h**.

To assess the feasibility and reliability of the NMR database approach in a chiral solvent, we chose first to use the C.5−C.10 portion of the desertomycin/oasomycin class of natural products.[10,11] For this purpose, we needed to develop a practical and scalable synthesis of perdeuterated (*R*)- and (*S*)-DMBA,[12] and the preparation included in the Supporting Information meets with our needs. We were pleased to observe that (*R*)- and (*S*)-DMBA-d_{13} could easily dissolve oasomycin A[13] (>10 mg/0.5 mL) but disappointed to see that the NMR signals were very broad in DMBA. Since aggregation appeared to be the probable cause for the observed signal broadening, we tested (*R*)- and (*S*)-DMBA-d_{13} containing 9.1% DMSO-d_6 (DMBA/DMSO = 10:1) and were delighted to observe sharp, well-resolved signals.[14,15] We then examined the capacity to discriminate enantiomers and found that although the degree of chemical shift differences decreases with an increase in DMSO content, (*R*)- and (*S*)-DMBA-d_{13} containing 9.1% DMSO-d_6 satisfactorily met with our needs (Figure 4).

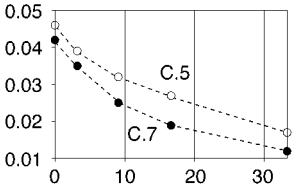

Figure 4. Difference in carbon chemical shifts for C.5 and C.7 of **1e** (100 MHz) in DMBA containing DMSO-d_6. The *x*- and *y*-axes represent DMSO-d_6 content (v/v %) in (*R*)- or (*S*)-DMBA and $|\Delta\delta_{R-S}|$ in ppm, respectively.

To correlate the NMR profile of the C.5−C.10 segment of oasomycin A (Figure 5) with that of **1a**−**h**, it was

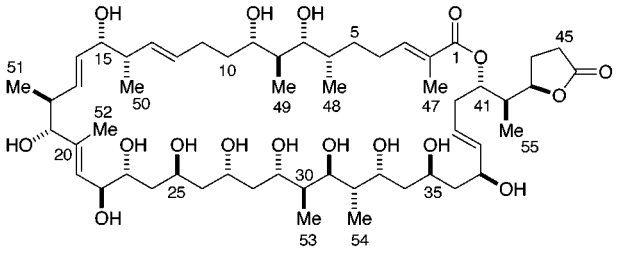

Figure 5. Structure of oasomycin A.

necessary to establish the ^{13}C chemical shift assignment for the antibiotic in (*R*)- or (*S*)-DMBA-d_{13} containing 9.1% DMSO-d_6. Given the complete chemical shift assignment

(6) A Varian Mercury 400 spectrometer (100 MHz) was used to collect all data for **1a**−**h** in DMBA, with acetone-d_6 as an external reference (δ 29.8) and a lock-signal and with readout of NMR spectra being adjusted to 0.001 ppm/point (sw = 23980.8, fn = 524288).

(7) The chemical shift assignments were established via the same procedure as the one used for oasomycin A. The details are included in the Supporting Information.

(8) In DMBA, the overall profile of **1b** and **1f** is similar to that of **1d** and **1h**, respectively. In DMSO, however, the overall profile of **1b** is notably different from that of **1d**. In addition, the difference between **1f** and **1h** is more visible in DMSO than in DMBA.

(9) Half-bandwidth was 0.008 ppm in nondeuterated DMBA.

(10) Desertomycins: (a) Bax, A.; Aszalos, A.; Dinya, Z.; Sudo, K. *J. Am. Chem. Soc.* **1986**, *108*, 8056−8063. (b) Dinya, Z.; Sztaricskai, F.; Horvath, E.; Schaag, J. B. *Rapid Commun. Mass Spectrom.* **1996**, *10*, 1439−1448 and references therein.

(11) Oasomycins: (a) Grabley, S.; Kretzschmar, G.; Mayer, M.; Philipps, S.; Thiericke, R.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 573−579. (b) Mayer, M.; Thiericke, R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2525−2531.

(12) Although perdeuterated phenethylamine is known (Ohhara, T.; Harada, J.; Ohashi, Y.; Tanaka, I.; Kumazawa, S.; Niimura, N. *Acta Crystallogr.* **2000**, *B56*, 245−253.), we prefer the method included in the Supporting Information in terms of scalability, practicability, and cost.

(13) We thank Dr. Gerhard Kretzschmar for a sample of oasomycin A.

(14) A Varian INOVA 500 spectrometer (125 MHz) at Eisai Research Institute of Boston was used to record all NMR spectra of oasomycin A in (*R*)- and (*S*)-DMBA-d_{13}, with DMSO-d_6 as an internal reference (δ 39.5). Eight out of 55 carbon signals of oasomycin A are hidden under the solvent peaks (see the spectrum included in the Supporting Information).

(15) Enantiomeric discrimination of **1e** was observed in DMBA containing 9.1% of the following cosolvents: CD_3OD, $CDCl_3$, CD_3CN, C_5D_5N, $(CD_3)_2CO$, and C_6D_6.

for this class of natural products in DMSO-d_6,[10a,11a] we made the chemical shift assignment through recording the NMR spectrum in (*R*)-DMBA-d_{13} containing 9.1% (DMBA/DMSO = 10:1), 33.3% (2:1), and 50% (1:1) DMSO-d_6 and correlating each signal in DMBA-d_{13}/DMSO-d_6 (9.1% v/v) with that in DMSO-d_6 (100%). Figure 6 shows the methyl group region for illustration of this procedure.

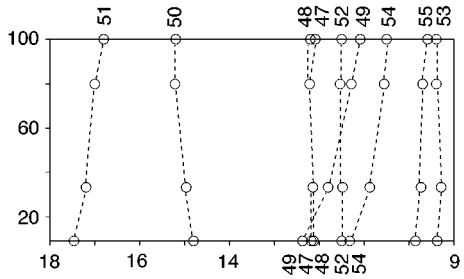

Figure 6. Correlation of carbon chemical shifts of the methyl groups of oasomycin A between DMSO-d_6 and (*R*)-DMBA-d_{13}. The *x*- and *y*-axes represent the 9−18 ppm region and DMSO-d_6 content (v/v %) in (*R*)-DMBA-d_{13}, respectively. The numbers 47−55 correspond to the numbers assigned to the methyl groups of oasomycin A, cf. Figure 5.

With the complete chemical shift assignment established, we followed the previous procedure to correlate the ^{13}C NMR profile of each of the diastereomers **1a**−**h** with that of the C.5−C.10 portion of oasomycin A.[1b] The adjusted ^{13}C NMR profiles thus obtained (Figure 7) correctly predict that the diastereomer **1e** represents the relative stereochemistry of the C.5−C.10 portion of oasomycin A.[1b]

The absolute configuration of the C.5−C.10 portion of oasomycin A was then established through comparison of its ^{13}C NMR profile in (*R*)- and (*S*)-DMBA-d_{13} with that of the diastereomer **1e** representing the stereochemistry of this portion of the antibiotic. The ^{13}C chemical shift differences ($\delta_R - \delta_S$) observed for C.7, C.9, C.10, C.48, and C.49 were +0.002, −0.110, −0.050, −0.029, and −0.030 ppm, respectively.[14] The corresponding carbons of **1e** gave $\Delta(\delta_R - \delta_S)$ = +0.034, −0.039, −0.069, −0.015, and −0.027 ppm in DMBA/DMSO-d_6 (9.1% v/v). On the basis of this experiment, the absolute configuration of the C.5−C.10 portion of oasomycin A was concluded to be the same as the absolute configuration of **1e**. This conclusion agrees with the absolute configuration previously established via the enantioselective synthesis of the C.3−C.12 degradation product.[1b]

In conclusion, using the C.5−C.10 portion of oasomycin A, we have demonstrated the feasibility and reliability of the NMR database approach in a chiral solvent. This approach allows us to predict the absolute and relative stereochemistry of a given, unknown compound without degradation and/or derivatization work. In the following Letter,[16] we will present further extension of this approach.

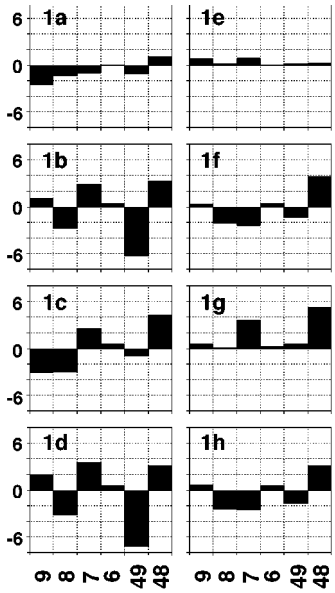

Figure 7. Difference between adjusted carbon chemical shifts of oasomycin A and those for **1a**−**h** ($\Delta\delta = \delta_{\mathbf{1a-h}} - \delta_{\text{oasomycin A}}$, 100 MHz, (*R*)-DMBA-$d_{13}$/DMSO-$d_6$ (9.1% v/v)). The *x*- and *y*-axes represent carbon number of oasomycin A and $\Delta\delta$ in ppm, respectively.

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Supporting Information Available: Chemical shift assignments and NMR databases of **1a**−**h** in the chiral solvents, NMR spectrum and chemical shift assignments of oasomycin A in the chiral solvents, procedure for correlating the NMR profile of the C.5−C.10 portion of oasomycin A with those of **1a**−**h**, and experimental procedures for the synthesis of (*R*)- and (*S*)-DMBA-d_{13}. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2249−2252.