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

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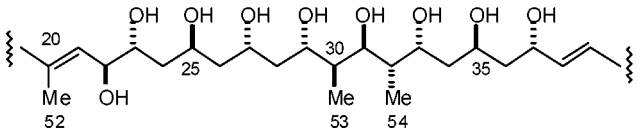
ABSTRACT



C.21-C.38 portion of oasomycin A

Three additional NMR databases, 1–3, in a chiral solvent are presented. The C.21–C.38 portion of oasomycin A is used to demonstrate the scope and limitation of the universal NMR database approach in a chiral solvent for assignment of relative and absolute stereochemistry without degradation and/or derivatization.

Encouraged by the successful demonstration of the feasibility and reliability of the NMR database approach in a chiral solvent,[1] we created three additional databases, **1**−**3**, in (*R*)- and (*S*)-DMBA (*N*,α-dimethylbenzylamine). As seen in the contiguous dipropionate database, two important phenomena are recognized for all three databases. First, each diastereomer within a database exhibits an NMR profile distinct and differing from the other diastereomers, demonstrating that these databases can be used for prediction of the relative stereochemistry of structural motifs in an intact form. Second, the ^{13}C chemical shift differences observed in (*R*)- and (*S*)-DMBA are well beyond the limit of measurement[1] for every diastereomer in all three databases, demonstrating that these databases can be used for prediction of the absolute configuration of structural motifs in an intact form.

Figure 1a gives the ^{13}C NMR database **1a**,**b** in (*R*)- and (*S*)-DMBA as a chemical shift deviation from the average for each carbon, whereas Figure 1b shows the ^{13}C chemical shift differences between (*R*)- and (*S*)-DMBA.[2] As is the case in the preceding Letter,[1] the NMR profiles (graphs 1a,b) are distinct enough to allow the relative and absolute stereochemistry of a given 1,3-diol to be predicted in an intact form. Notably, the sign of the chemical shift differences ($\delta_R - \delta_S$) of the central carbon (C.6 of **1b**) is most diagnostic in assigning the absolute configuration of *anti*-1,3-diols.

We recently demonstrated that the central carbon of 1,3,5-triols exhibits a distinctive chemical shift that is dependent on the 1,3- and 3,5-relative stereochemistry but is independent of the functionalities present outside of the structural motif.[3] This trend is recognized also in (*R*)- and (*S*)-DMBA, with the observed chemical shift of the C.5 carbon being 65 for **2a** (C.3−C.5/C.5−C.7 = anti/anti), 68 for **2b** (syn/anti) and **2c** (anti/syn), and 71 ppm of **2d** (syn/syn). This NMR

(1) Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Org. Lett.* **2001**, *3*, 0000−0000.

(2) A Varian Mercury 400 spectrometer (100 MHz) was used to collect all the NMR database data 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). 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).

(3) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562−2571.

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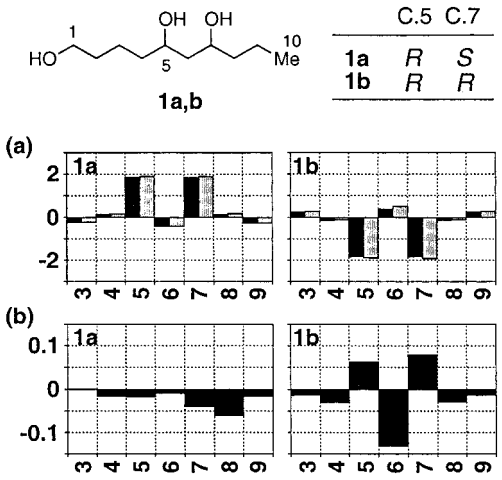


Figure 1. (a) Difference in carbon chemical shifts between the average and the values of **1a** and **1b** (100 MHz): solid bar, (*R*)-DMBA; shaded bar, (*S*)-DMBA. (b) Carbon chemical shift differences between (*R*)- and (*S*)-DMBA. The *x*- and *y*-axes represent carbon number and $\delta_R - \delta_S$ in ppm, respectively.

characteristic is diagnostic for assigning the relative stereochemistry of a given 1,3,5-triol. Figure 2 summarizes the ^{13}C chemical shift differences ($\delta_R - \delta_S$) for each diastereomer **2a**−**d**. All of the diastereomers have differences large enough to predict the absolute configuration for a given 1,3,5-triol in an intact form.

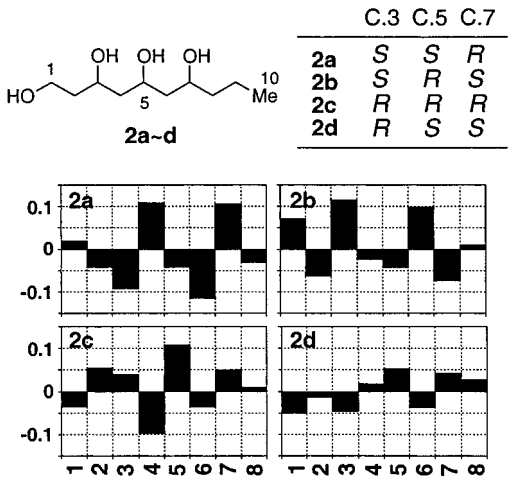
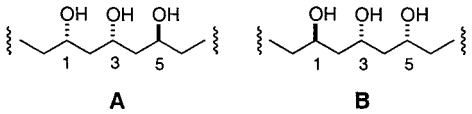


Figure 2. Carbon chemical shift difference of **2a**−**d** between (*R*)- and (*S*)-DMBA (100 MHz). The *x*- and *y*-axes represent carbon number and $\delta_R - \delta_S$ in ppm, respectively.

Interestingly, the relationship of the absolute configuration with the sign of chemical shift differences ($\delta_R - \delta_S$) observed for the central (C.6) carbon of *anti*-1,3-diol **1b** is carried over to all the *anti*-1,3-diols present in database **2**, i.e., the sign of ($\delta_R - \delta_S$) for the C.4 and C.6 carbons in **2a**, the C.6 carbon in **2b**, and the C.4 carbon in **2c**. This characteristic is a valuable means to differentiate a *syn*,*anti*-1,3,5-triol **A** from the corresponding *anti*,*syn*-1,3,5-triol **B** (Figure 3). Although the unique chemical shift at C.3 alone cannot discriminate **A** from **B**,[3] the chemical shift behaviors expected for the C.2 and C.4 carbons in (*R*)- and (*S*)-DMBA should allow us to differentiate **A** from **B**.



Expected:	δ for C.3	$\Delta\delta_{R\text{-}S}$ for C.2	$\Delta\delta_{R\text{-}S}$ for C.4
for A	ca. 68	ca. -0.02	ca. +0.1
for B	ca. 68	ca. -0.1	ca. -0.02

Figure 3. Carbon chemical shift behaviors (ppm) expected of **A** and **B** in (*R*)- and (*S*)-DMBA.

Figure 4a shows the ^{13}C NMR database **3a**−**d**[4] in (*R*)-DMBA and (*S*)-DMBA as a chemical shift deviation from

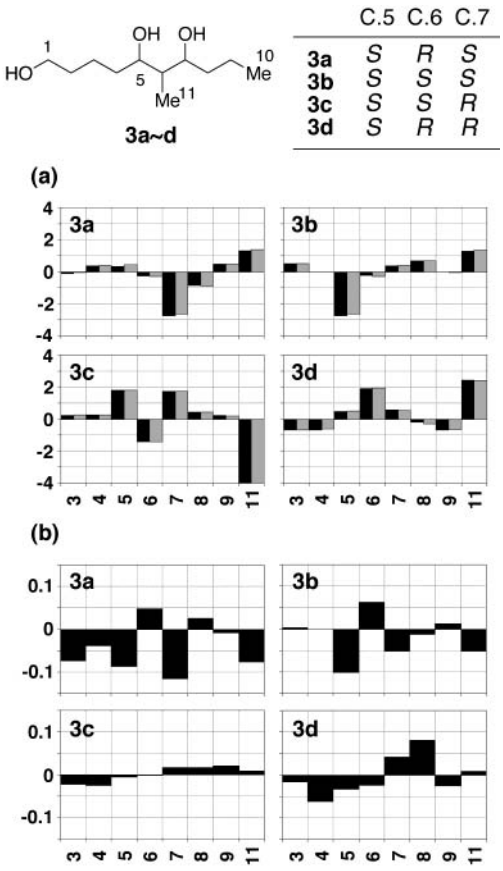


Figure 4. (a) Difference in carbon chemical shifts between the average and the values of **3a**−**d** (100 MHz): solid bar, (*R*)-DMBA; shaded bar, (*S*)-DMBA. (b) Carbon chemical shift differences between (*R*)- and (*S*)-DMBA. The *x*- and *y*-axes represents carbon number and $\delta_R - \delta_S$ in ppm, respectively.

the average for each carbon, whereas Figure 4b shows the carbon chemical shift differences between (*R*)- and (*S*)-DMBA. Since the NMR profiles observed for **3a**−**d** are significantly different from each other, the relative and absolute stereochemistry of the structural motif of acetate/propionate can be predicted in an intact form, in reference to this NMR database. Interestingly, the relationship of the absolute configuration with the sign of chemical shift differences ($\delta_R - \delta_S$) observed for the central (C.6) carbon of *anti*-1,3-diol **1b** is once again recognized in the *anti*-1,3-diols **3a** and **3b**. Not surprisingly, due to the pseudo-meso nature of the structure, the chemical shift differences were found to be small for the *syn*-1,3-diol **3c**.[5] However, as the chemical shift differences ($\delta_R - \delta_S$) of the C.4 and C.5 carbons and C.7 and C.8 carbons are well beyond the limit of detection, the signs of the chemical shift differences can be used for prediction of the absolute configuration. It is worthwhile noting that the introduction of a methyl group at the central (C.6) carbon with an *anti*-orientation significantly amplifies the chemical shift differences, cf., **3d** vs **3c** in Figure 4b. Interestingly, this trend was also recognized in the contiguous dipropionate database reported in the preceding Letter.[1]

To demonstrate the scope and limitation of our approach for determining the relative and absolute stereochemistry in an intact molecule, we used the C.21−C.38 portion of oasomycin A (Figure 5). Following the stepwise procedure

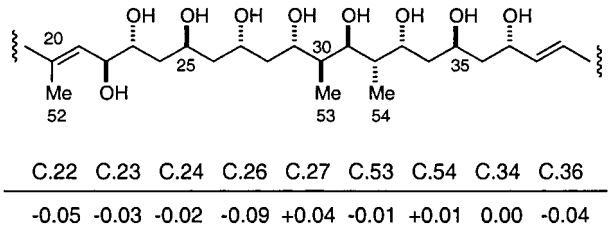


Figure 5. Carbon chemical shift differences ($\delta_R - \delta_S$; ppm) observed for the C.21−C.38 portion of oasomycin A in DMBA-d_{13}/DMSO-d_6 (10:1).

demonstrated in the achiral solvent system,[6] we compared the appropriate NMR databases with the NMR profiles obtained from the ^{13}C NMR data of intact oasomycin A,[1] predicting the relative stereochemistry for all of the stereogenic centers except the C.22 position. In the achiral solvent series, the C.22 relative stereochemistry was deduced from a comparison of the peracetate of the C.21−C.38 degradation product with the NMR database of 1,2,3,5-tetraol peracetate. In this connection, we should quote the work by Tanaka,[7] which clearly points to the possibility that the C.22 absolute stereochemistry can be predicted from the NMR profile obtained on the intact natural product.

The C.21−C.38 segment contains four *anti*-1,3-diols, the absolute configuration of which could be deduced in reference to the NMR profile found for *anti*-1,3-diol **1a** in (*R*)- and (*S*)-DMBA. Supported by a vast volume of experimental data, we concluded that steric and/or stereoelectronic interactions between the structural motifs connected either directly or with a one-methylene bridge are significant, whereas interactions between the structural motifs connected with a bridge of two or more methylenes are almost negligible.[3] Thus, the C.23/C.25 and C.33/C.35 *anti*-1,3-diols were excluded from this analysis, because these diols bear a hydroxyl or methyl group at the adjacent carbon. The ^{13}C chemical shift differences ($\delta_R - \delta_S$) observed for the C.26 and C.36 carbons of the C.25/C.27 and C.35/C.37 *anti*-1,3-diols were −0.09 and −0.04 ppm, respectively, predicting the absolute configuration as 25*S*, 27*S*, 35*S*, and 37*S*.[8] This prediction agrees with the conclusion derived from the enantioselective synthesis of the C.21−C.38 degradation product.[9]

The C.21−C.38 segment possesses two *anti*,*anti*-triols and one *anti*,*syn*-triol. The NMR behavior of the central carbon (cf., C.5 of **2**) is most diagnostic for assigning the absolute configuration of a *syn*,*anti*- or *anti*,*syn*-1,3,5-triol. The ^{13}C chemical shift difference ($\delta_R - \delta_S$) observed for the central (C.27) carbon for the C.25−C.29 *anti*,*syn*-triol was +0.04 ppm, thereby predicting the absolute configuration shown. The two methylene carbons (cf., C.4 and C.6 of **2**) are most indicative for assigning the absolute configuration of an *anti*,*anti*-1,3,5-diol. The C.23−C.27 and C.33−C.37 triols belong to this subgroup, with the observed chemical shift difference ($\delta_R - \delta_S$) being −0.02 (C.24), −0.09 (C.26), 0.00 (C.34), and −0.04 ppm (C.36), respectively. However, only the C.26 and C.36 chemical shift differences were used for the analysis, since the C.22 hydroxyl and C.32 methyl groups should affect the NMR profile of C.24 and C.34 carbons (vide ante).[3] Overall, the NMR profiles observed for the three 1,3,5-triols allowed us to assign the relative and absolute stereochemistry as 23*R*, 25*S*, 27*S*, 29*S*, 33*R*, 35*S*, and 37*S*,[8] which is the same as the previous conclusion.[9]

The NMR database **3a**−**d** in DMBA is useful for predicting the absolute configuration at C.29−C.33. The C.53 and C.54 methyl carbons are expected to exhibit NMR behavior independent of the functional groups present outside of this structural motif.[4] Although the absolute value is very small, the observed chemical shift differences (C.53, $\delta_R - \delta_S = -0.01$; C.54, $\delta_R - \delta_S = +0.01$ ppm) predicted the absolute configuration as 29*S*, 30*S*, 31*R*, 32*S*, and 33*R*,[8] which is the same as the previous assignment.[9]

(4) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076−2078.

(5) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2001**, *3*, 2253−2256.

(6) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 4279−4281.

(7) Kasai, R.; Okihara, M.; Asakawa, J.; Mizutani, K.; Tanaka, O. *Tetrahedron* **1979**, *35*, 1427−1432.

(8) The *R*,*S*-convention is adopted to define the absolute configuration of a given stereogenic center in this work. We realize that this convention may cause some confusion. For example, for comparison of the NMR profile of oasomycin A with the NMR database **2a**, the C.27 stereogenic center of oasomycin A shares the same absolute configuration with the C.7 stereogenic center of **2a**. However, by the *R*,*S*-convention, these are defined as *S* and *R*, respectively.

(9) Tan, C.-H.; Kobayashi, Y.; Kishi, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 4282−4284.

The C.29−C.32 and C.33−C.30 moieties can be viewed as contiguous dipropionate structural motifs, and we have presented our logic for application of the dipropionate NMR database in an achiral solvent to deduce the relative stereochemistry of the C.29−C.33 segment.[9] In brief, the NMR behaviors of the C.30 and C.53 carbons as well as the C.32 and C.54 carbons are reliably used for NMR profile comparison. This logic can be applied to an analysis in the chiral solvent series. However, we found that the C.30 and C.32 carbon resonances were hidden underneath the solvent signals[10] and that the analysis relied only on the chemical shift behavior of the C.53 and C.54 methyl groups. Nonetheless, this analysis led to the same absolute configuration as previously determined.

In summary, three new NMR databases in (*R*)- and (*S*)-DMBA are reported. Using the C.21−C.38 portion of oasomycin A, we presented the scope and limitation of the NMR database approach in a chiral solvent for predicting the relative and absolute stereochemistry of a given, unknown compound without degradation and/or derivatization. There are 11 stereogenic centers present in this portion of the antibiotic. Once provided with the relative stereochemistry, the absolute configuration can be deduced by establishing the absolute configuration of any one of the 11 stereogenic centers. However, we should note that the four, including the dipropionate, NMR databases allowed us separately to treat the stereogenic centers present in this segment and therefore a prediction derived from one NMR profile comparison could be verified by a prediction from the other NMR profile comparison. In this context, we should also note that the current method relies on the overall NMR profile, instead of one physicochemical data point, to deduce the relative and absolute stereochemistry of a given, unknown compound in an intact form.

(10) Eight out of 55 carbon signals of oasomycin A are hidden under the solvent peaks: see the spectrum included in the Supporting Information of the preceding Letter.

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Supporting Information Available: Chemical shift assignments and NMR databases of **1a**,**b**, **2a**−**d**, and **3a**−**d** in the chiral solvent. This material is available free of charge via the Internet at http://pubs.acs.org.

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