Toward Creation of a Universal NMR Database for Stereochemical Assignment: Complete Structure of the Desertomycin/Oasomycin Class of Natural Products

Yoshihisa Kobayashi, Choon-Hong Tan, and Yoshito Kishi*

Department of Chemistry and Chemical Biology
Harvard University, 12 Oxford Street
Cambridge, Massachusetts 02138

Received December 4, 2000

Through the work on palytoxin,[1] AAL toxins/fumonisins,[2] and maitotoxin,[3] we have experimentally demonstrated that the structural properties of fatty acids and related compounds are inherent to the specific stereochemical arrangements of (small) substituents on their carbon backbone and are independent from the rest of the molecule. It has been shown that steric and stereoelectronic interactions between structural clusters connected either directly or with a one-methylene bridge are significant, whereas interactions between structural clusters connected with a two- or more-methylene bridge are almost negligible. On the basis of these experimental results, the concept of a universal NMR database approach for stereochemical assignment has been advanced. Using the contiguous dipropionate structural motif often found in the polyketide natural products as an example, the feasibility and reliability of this approach have been addressed.[4a] Using the case of the desertomycin/oasomycin class of natural products (Figure 1),[5,6] the applicability and usefulness of this approach have then been demonstrated. In brief, the NMR database for the two contiguous propionate units (cf., **Database 1** (Figure 2)), was used to predict the relative stereochemistry of the C.5−C.10 and C.28−C.34 portions of oasomycins.[4b,d] The second NMR database for the central carbon (and possibly the attached proton) of a 1,3,5-triol system (cf., **Database 2**), was created and used to predict the relative stereochemistry at the C.23/C.25, C.25/C.27, C.27/C.29, C.33/C.35, and C.35/C.37 positions.[4c,d] A third NMR database for the 1,2,3,5-tetraol motif (cf., **Database 3**) was created to predict the relative stereochemistry at C.22 and C.23.[4d] These efforts allowed us to determine the relative stereochemistry of the C.5−C.10 and C.21−C.38 portions of oasomycins. Through the enantioselective and stereoselective synthesis of the C.3−C.12 and C.21−C.38 degradation products of the oasomycins, the predicted relative stereochemistry was confirmed, and the absolute stereochemistry was established at the same time.[4b,e] In this communication, we report the complete structure of the desertomycin/oasomycin class of natural products for the first time.

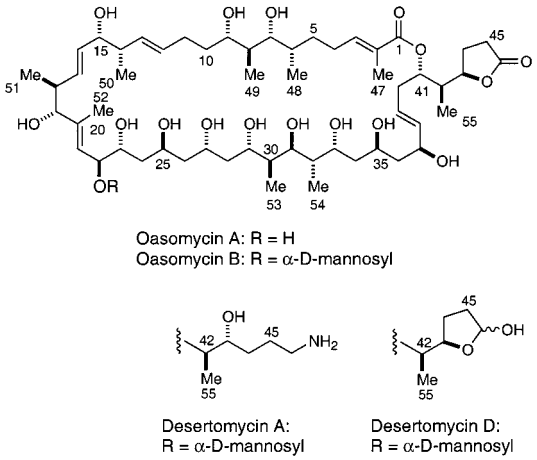


Figure 1.

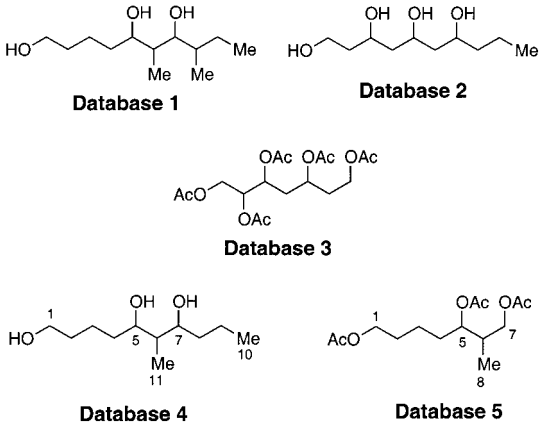


Figure 2. Structures of universal NMR databases.

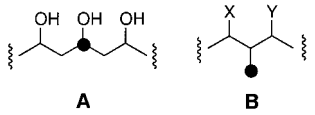


Figure 3.

The strategy for our current work originates from the previous work on the 1,3,5-triol system.[4c] The central carbon (marked with a dot) of 1,3,5-triol **A** (Figure 3) has been shown to exhibit a distinctive chemical shift that is *dependent* on the 1,3- and 3,5-relative stereochemistry, but that is *independent* of the functionality present outside of this structural motif. This demonstration suggests the possibility that the carbon (marked with a dot) of partial structure **B** may show a distinctive chemical shift that is *dependent* on the relative stereochemistry with X and Y, but that

(1) Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, Jr., W. W.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369−7371 and preceding papers.

(2) For the stereochemical assignment of AAL toxins and fumonisins from this laboratory, see: (a) Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995−4996. (b) Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 5695−5698 and references therein. For the work from other laboratories, see: (c) Oikawa, H.; Matsuda, I.; Kagawa, T.; Ichihara, A.; Kohmoto, K. *Tetrahedron* **1994**, *50*, 13347−13368. (d) Hoye, T. R.; Jiménez, J. I.; Shier, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 9409−9410. (e) ApSimon, J. W.; Blackwell, B. A.; Edwards, O. E.; Fruchier, A. *Tetrahedron Lett.* **1994**, *35*, 7703−7706. (f) Poch, G. K.; Powell, R. G.; Plattner, R. D.; Weisleder, D. *Tetrahedron Lett.* **1994**, *35*, 7707−7710. (g) Blackwell, B. A.; Edwards, O. E.; ApSimon, J. W.; Fruchier, A. *Tetrahedron Lett.* **1995**, *36*, 1973−1976.

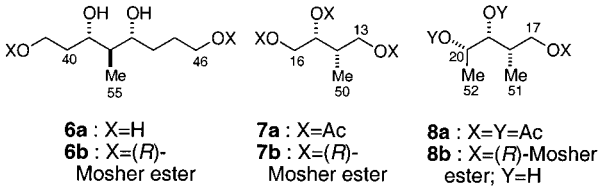
(3) For the work from this laboratory, see: (a) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946−7968. (b) Cook, L. R.; Oinuma, H.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 7928−7937. For the work from the laboratories at Tokyo and Tohoku Universities, see: (c) Sasaki, M.; Matsumori, N.; Maruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1672−1675. (d) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675−1678.

(4) (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.

(5) At least seven members, A−F and I, were identified in the desertomycin class. (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. For detailed NMR analysis, see ref 5a.

(6) At least six members, A−F, were identified in the oasomycin class. (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. For detailed NMR analysis, see ref 6a.

10.1021/ja004154q CCC: $20.00 © 2001 American Chemical Society
Published on Web 02/10/2001



6a : X=H
6b : X=(*R*)-Mosher ester

7a : X=Ac
7b : X=(*R*)-Mosher ester

8a : X=Y=Ac
8b : X=(*R*)-Mosher ester; Y=H

Figure 4. Structure of degradation products of the oasomycins.

is *independent* of the functionality present outside of this structural motif.[7] Interestingly, the methyl group of three degradation products **6a**, **7a**, and **8a** (Figure 4)[8] corresponds to the marked carbon in **B**. Of significance to the present work, all of the remaining unknown stereogenic centers reside within these degradation products.

We first focused on the C.39−46 degradation product **6a**.[9] To test the possibility discussed, we selected the structure shown in **Database 4**, synthesized the four possible diastereomers,[10] and measured the ^{13}C NMR chemical shifts. The chemical shift (ppm, CD_3OD) for the central methyl group was found to be 7.1 ppm for the syn/syn diastereomer, 10.7 for the syn (5/6)/anti (6/7), 10.7 for the anti (5/6)/syn (6/7), and 11.6 for the anti/anti, respectively. In reference to these data, the chemical shift (11.5 ppm, CD_3OD) observed for the methyl group of the degradation product **6a** predicted the relative stereochemistry at C.41, C.42, and C.43 to be anti/anti.

In the present work, **Database 4** was used to deduce the stereochemistry of the degradation product **6a**. However, it should be noted that numerous polyketide natural products contain this structural motif in its intact form, and therefore **Database 4** should be applicable for these cases. For example, monazomycin[11] contains this structural motif at C.6−C.10, and the chemical shift of the central methyl group (7.5 ppm, CD_3OD)[12] predicts the relative stereochemistry at C.7, C.8, and C.9 of this antibiotic to be syn/syn.

It is interesting to assess the reliability of this approach in reference to the strategy originally used for the contiguous dipropionate cases. Following the procedure described previously,[4b] the C.41-, C.42-, C.43-, and C.55-carbon chemical shifts of **6a** were compared with those of each diastereomer shown in **Database 4** (Figure 5).[13] Clearly, this comparison also predicts the same relative stereochemistry as the one concluded from the unique chemical shift of the central methyl group.[14]

The predicted relative stereochemistry at C.41, C.42, and C.43 was confirmed through the stereoselective synthesis of **6a** with

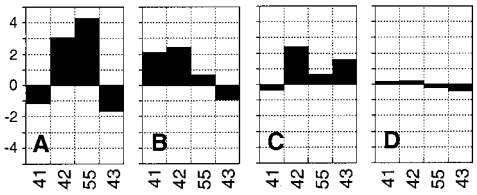


Figure 5. Difference between normalized carbon chemical shifts of **6a** and carbon chemical shifts of each diasetereomer of **Database 4**, with **A**, **B**, **C**, and **D** representing α/(C.5),α/(C.6),α/(C.7)-, α,α,*β*-, α,*β*,*β*-, and α,*β*,α-diastereomers, respectively. The *x*- and *y*-axes represent carbon numbers of **6a** and $\Delta\delta$ ($\Delta\delta = \delta_{\text{Database 4}} - \delta_{\text{6a}}$ in ppm).

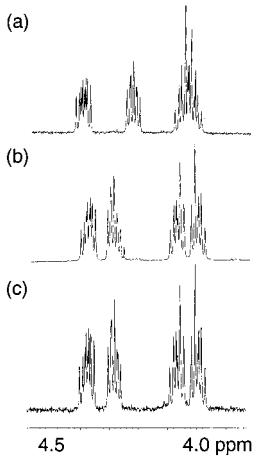


Figure 6. The H.39 and H.46 region of ^{1}H NMR (500 MHz, C_6D_6) of di-Mosher esters **6b**. (a) (*R*,*R*)-di-Mosher ester **6b** derived from the synthetic **6a**. (b) (*S*,*S*)-di-Mosher ester **6b** derived from the synthetic **6a**. (c) (*R*,*R*)-di-Mosher ester **6b** derived from **6a** derived from natural oasomycin B.

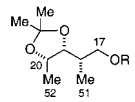
(41*R*,42*S*,43*S*)-configuration.[10] The absolute stereochemistry of **6a** was then determined through ^{1}H NMR comparison of the di-Mosher ester of **6a**. The ^{1}H NMR spectra of the (*R*,*R*)- and (*S*,*S*)-di-Mosher esters, prepared from the synthetic **6a**, were distinctively different (Figure 6). The ^{1}H NMR spectrum of the (*R*,*R*)-di-Mosher ester obtained from the degradation product **6a** was found to be superimposable on the ^{1}H NMR spectrum of the (*S*,*S*)-di-Mosher ester prepared from the synthetic **6a**, thereby establishing the absolute configuration as 41*S*, 42*R*, 43*R* (cf. **6a** in Figure 4).[15]

To address the stereochemistry of degradation products **7a** and **8a**,[9] we selected the structure shown in **Database 5**,[10] synthesized both syn- and anti-diastereomers, and measured the ^{13}C NMR chemical shift. The chemical shift (ppm, $CDCl_3$) for the methyl group of syn- and anti-diastereomers was found to be 11.3 and 13.6, respectively.[16] In reference to these data, the chemical shift (11.8 ppm, $CDCl_3$) observed for the methyl group of **7a** predicted syn-relative stereochemistry at C.14 and C.15. The predicted relative stereochemistry was confirmed through the stereoselective synthesis of the degradation products **7a** with (14*R*,15*S*)-configuration.[10] As before, the absolute stereochemistry was then established as 14*S*, 15*R* (cf. **7a** in Figure 4) through ^{1}H NMR comparison of the (*R*,*R*,*R*)-tri-Mosher ester **7b** derived from the degradation product with the (*R*,*R*,*R*)- and (*S*,*S*,*S*)-tri-Mosher esters prepared from the synthetic **7a**.[17]

Database 5 was also applied to predict the C.18/C.19-relative stereochemistry of degradation product **8a**. The chemical shift

(7) A phenomenon somewhat relevant to this case is known. For example, see: Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3980−3992.

(8) The degradation products **6a**, **7a**, and **8a** were obtained from oasomycin B in three steps, i.e.: (1) O_3/MeOH/−78 °C; (2) $NaBH_4$/MeOH/rt; (3) Ac_2O/Py/DMAP. Degradation product **8a** was isolated as a single diastereomer at C.20, the stereochemistry of which was assigned based on an NOE experiment of the corresponding acetonide **i**. We thank Dr. Gerhard Kretzschmar for a sample of oasomycins A, B, and C.



i : R=(*R*)-Mosher ester

(9) The numbering used for **6a**, **7a**, and **8a** corresponds to the desertomycins/oasomycins numbering, cf., Figure 1.

(10) The details are included in the Supporting Information.

(11) Nakayama, H.; Furihata, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1981**, *22*, 5217−5220 and references therein.

(12) The complete NMR assignment of monazomycin was carried out by Dr. Kenichi Tezuka in our laboratory. We thank Professors Y. Hayakawa, H. Seto, and K. Furihata at the Univeristy of Tokyo for a sample of monazomycin.

(13) In the study of **Database 2**, the effect of the primary alcohol in HO-$(CH_2)_2$CH(OH)CH_2CH(OH)− was recognized to be equal to that of an anti-1,3-diol.[4c] Therefore, additional +1.5 ppm was added to the increment obtained in the procedure reported in ref 4a.

(14) It is worthwhile noting that application of **Database 4** for the C.49, C.53, and C.54 methyl groups of the oasomycins resulted in the C.7/C.8/C.9-, C.29/C.30/C.31-, and C.31/C.32/C.33-relative stereochemistry same as the one predicted, and proved, via **Database 1**.

(15) **6b** was prepared by treatment of **6a** with (*R*)-Mosher acid, EDCI and DMAP. The details are included in the Supporting Information.

(16) It should be added that the methyl group of the syn- and anti-triols corresponding to **Database 5** gave unique and useful chemical shifts (ppm, CD_3OD) at 11.0 and 13.8, respectively.

(17) **7b** was prepared by treatment of **7a** with KOH in methanol followed by (*S*)-Mosher acid chloride, NEt_3, and DMAP. The details are included in the Supporting Information.

of the relevant methyl group in **8a** was found at 11.6 ppm ($CDCl_3$), predicting syn-relative stereochemistry at C.18 and C.19. The predicted relative stereochemistry was then confirmed through the stereoselective synthesis of the degradation product **8a** with (18*S*,19*R*,20*S*)-configuration.[10] Once again, the absolute stereochemistry was determined as 18*S*,19*R*,20*S* (cf. **8a** in Figure 4),through ^{1}H NMR comparison of the (*R*)-mono-Mosher ester **8b** derived from the degradation product with the (*R*)- and (*S*)-mono-Mosher esters prepared from the synthetic **8a**.[18]

The degradation product **8a** contains one additional stereogenic center just outside the structural motif in question. Using this system,[19] the effect on the chemical shift from an additional functional group present *outside* the structural motif was assessed. Interestingly, the chemical shift difference between the C.19/C.20-syn ($\delta_{C.51}$: 11.4 ppm, $CDCl_3$) and C.19/C.20-anti ($\delta_{C.51}$: 11.8 ppm, $CDCl_3$) was found to be small, supporting the previously presented hypothesis.

The structural motif represented by **Database 5** is found in a number of degradation products of polyketide natural products. For example, this database predicts the relative stereochemistry at C.4/C.5, C.25/C.26, and C.30/C.31 of copiamycin[20] to be anti, syn, and anti, respectively. Related to **Database 5**, it should be noted that the ^{13}C- and ^{1}H chemical shift differences between syn- and anti-diastereomers of *trans*-$Me(CH_2)_2CH{=}CHCH(OH)$-$CH(Me)CH{=}CH_2$ were found to be negligibly small, suggesting that an additional device may be required to apply this type of database to an intact molecule.

Combined with previous results on the C.5−C.10 and C.21−C.38 portions, the present work allows us to establish the complete stereochemical assignment of the oasomycins. Comparison of their NMR data clearly demonstrates that the desertomycins share the same stereochemistry with the oasomycins.[5a,6a] Thus, the complete structure of the desertomycin/oasomycin class of natural products is described as shown in Figure 1. In the present work, we treated several structural motifs of the oasomycins independently from each other, applied five simple NMR databases (Figure 2) to predict the relative stereochemistry, and confirmed the predicted stereochemistry by chemical synthesis. In our view, the reliability of this approach has been well demonstrated, and confirmation of the predicted stereochemistry by chemical synthesis is no longer necessary. However, to correlate the relative stereochemistry of one segment with that of others, we need information regarding the absolute stereochemistry of each segment, which has been provided through chemical synthesis at present. In this context, we recognize the possibility that the absolute configuration of a given structural motif can be determined through an NMR database approach in chiral environments.[21] Finally, it is our belief that we are sufficiently prepared to initiate a computer-assisted, universal database approach for the stereochemical assignment of unknown compounds.

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support (NS 12108).

Supporting Information Available: Complete experimental details for the synthesis of **6a,b**−**8a,b**, including their independent stereochemical assignments and spectroscopic data, as well as NMR **Databases 4** and **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA004154Q

(18) **8b** was prepared by treatment of **8a** with KOH in methanol followed by with (*R*)-Mosher acid, EDCI, and DMAP. The details are included in the Supporting Information.

(19) The C.20 diastereomer of **8a** was prepared prepared by a reduction of the corresponding hydroxyl ketone with $NaBH_4$.

(20) Fukushima, K.; Arai, T.; Iwasaki, S.; Namikoshi, M.; Okuda, S. *J. Antibiot.* **1982**, *35*, 1480−1494 and references therein.

(21) For a similar purpose, a chiral shift-reagent was used.[2a] For related examples, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457 and references therein.