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Toward Creation of a Universal NMR Database for the Stereochemical Assignment of Acyclic Compounds: Proof of Concept

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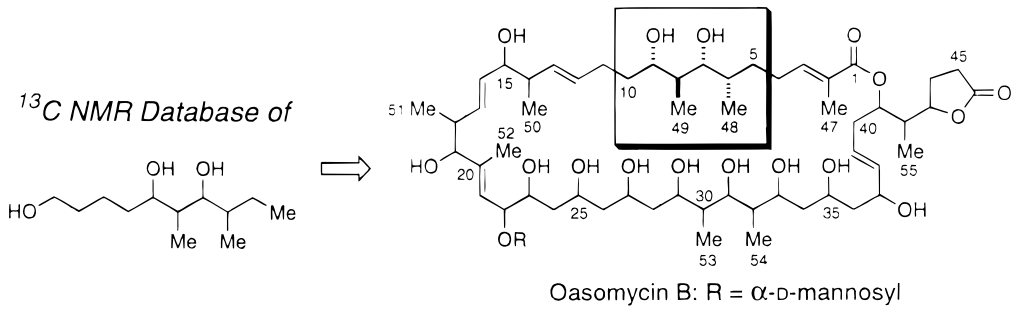
ABSTRACT



Using the C.5–C.10 portion of the oasomycin class of natural products, the reliability and usefulness of an NMR database for the stereochemical assignment of acyclic compounds has been demonstrated. The predicted relative stereochemistry based on the NMR database has unambiguously been established via synthesis.

In the preceding paper,[1] we reported our first step toward the creation of a universal NMR database through analysis of a typical structural motif often found in polypropionate natural products. In this paper, we address the reliability and usefulness of such an NMR database for the stereochemical assignment of an unknown compound. Among numerous natural products containing two contiguous propionate units, we chose the C.5−C.10 portion of the oasomycin class[2] of natural products for several reasons, including (1) the availability of detailed NMR data and (2) the fact that the stereochemistry of this class of natural products has not yet been established (Figure 1).[2]

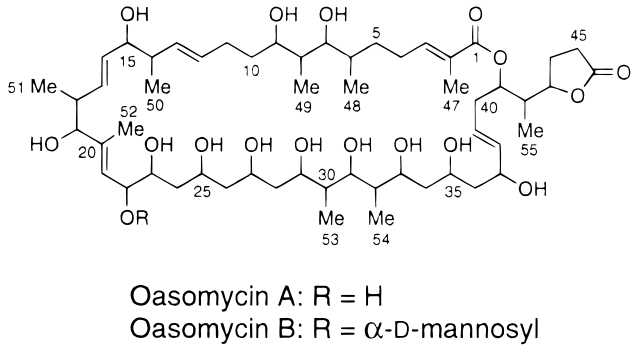


Figure 1. Structure of oasomycins A and B.

Correlation of the ^{13}C NMR characteristics of the C.5−C.10 portion of oasomycins with our ^{13}C NMR database was

(1) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177−2180.

(2) Grabley, S.; Kretzschmar, G.; Mayer, M.; Philipps, S.; Thiericke, R.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 573−579.

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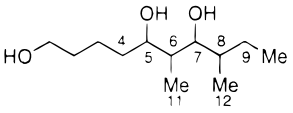
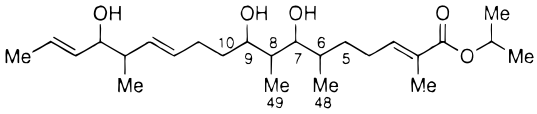
conducted via the following operations. First, using the Schaller program,[3] the chemical shifts were predicted for **2**, representing the C.1−C.16 portion of oasomycins, as well as for **1**, the structure used for the creation of the NMR database (Figure 2). Second, the chemical shift difference



1 (δ: C.4 = 35.7, C.5 = 70.6, C.6 = 40.1, C.7 = 74.6, C.8 = 37.3, C.9 = 24.1, C.11 = 8.0, C.12 =13.9)



2 (δ: C.10 = 35.7, C.9 = 70.7, C.8 = 40.2, C.7 = 75.0, C.6 = 35.2, C.5 = 31.3, C.49 = 8.0, C.48 = 14.3)

Figure 2. Predicted ^{13}C NMR chemical shift (ppm).

between a given carbon in **2** and the corresponding carbon in **1** was assumed to represent the chemical shift increment for the given carbon of oasomycins. Third, these increments were then subtracted from the ^{13}C NMR chemical shifts reported for oasomycin B to create a comparative chemical shift profile.[2,4] Fourth, differences between the comparative ^{13}C chemical shifts of oasomycin B and the ^{13}C chemical shifts of each synthetic diastereomer were used to compare the structural properties of the C.5−C.10 portion of the antibiotic with the structural properties of each of **1a**−**h** (Figure 3).

The pattern of chemical shift difference between the C.5−C.10 portion of oasomycin B and each diastereomer was distinct and differed from one another. Importantly, the ^{13}C NMR characteristics of the C.5−C.10 portion of oasomycin B match only with those of **1e**,[5] indicating that the relative stereochemistry at C.6, C.7, C.8, and C.9 of oasomycin B corresponds to that of this diastereomer.

The graphs shown in Figure 3 convincingly demonstrate that the relative stereochemistry of the C.5−C.10 portion of oasomycins is represented by diastereomer **1e**. Nonetheless, the reliability and usefulness of this new approach for the stereochemical assignment of an acyclic compound have not yet been tested rigorously, and we felt it important to prove unambiguously the suggested stereochemistry. Therefore, we

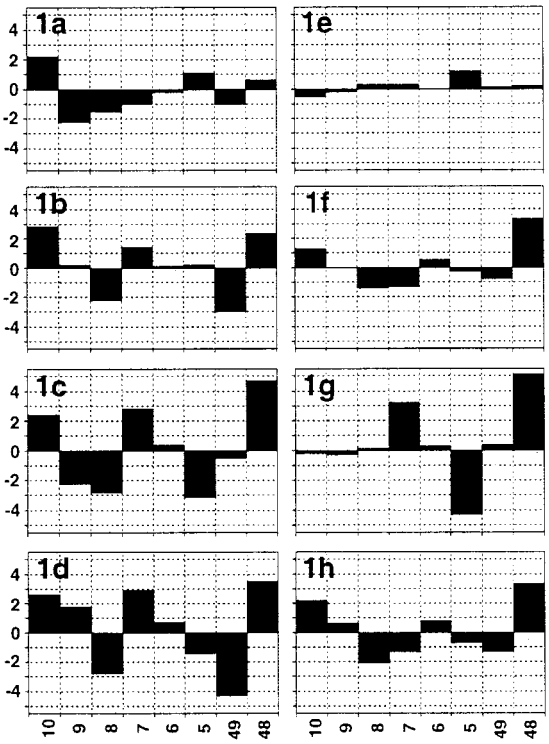
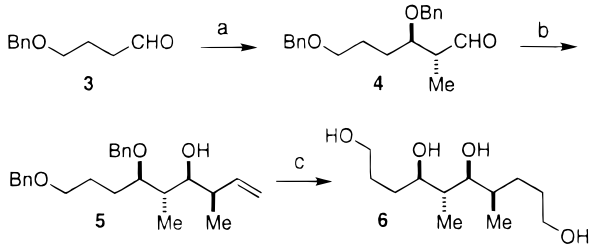


Figure 3. Difference between adjusted carbon chemical shifts of oasomycin B and those of each of **1a**−**h** (100 MHz, ppm, $(CD_3)_2SO$).

synthesized tetraol **6** with the indicated absolute configuration (Scheme 1)[6] and established that **6** has a ^{1}H NMR spectrum

Scheme 1



(a) (1) KO*t*-Bu, (*E*)-2-butene, *n*-BuLi, (-)-$(Ipc)_2$BOMe, $BF_3{\cdot}OEt_2$, THF, -78 °C. (2) BnBr, NaH, *n*-Bu_4NI, THF–DMF (4:1), rt. (3) OsO_4, NMO, acetone–H_2O, rt. (4) $Pb(OAc)_4$, benzene, rt. (b) KO*t*-Bu, (*Z*)-2-butene, *n*-BuLi, (-)-$(Ipc)_2$BOMe, $BF_3{\cdot}OEt_2$, THF, -78 °C. (c) (1) BnBr, NaH, *n*-Bu_4NI, THF–DMF (4:1), rt. (2) $BH_3{\cdot}$THF; H_2O_2–NaOH. (3) *p*-TsCl, pyr. (4) KCN, DMSO, 75 °C. (5) DIBAL, CH_2Cl_2, -78 °C. (6) $NaBH_4$, EtOH, rt. (7) H_2, $Pd(OH)_2$, EtOH, rt.

identical to that of the tetraol derived[7] from natural oasomycin B[8] (Figure 4).

(3) CS ChemNMR Pro version 1.0, Renate Buergin Schaller, Development Centre, Bergstr. 114, Zurich, Switzerland, installed in CS ChemDraw Pro version 4.5, was used.

(4) The graphs shown in Figure 3 were prepared on the basis of the NMR data reported for oasomycin B. However, there is virtually no difference in the NMR data reported for oasomycins A−D, excluding the C.20−C.22 and C.39−C.46 moieties.[2]

(5) The stereochemistry of **1a**−**h** corresponds to that in the preceding paper.

(6) The structure of the synthetic tetraol **6** was established by adopting the same procedure as the one described in the preceding paper. The experimental details are included in the Supporting Information.

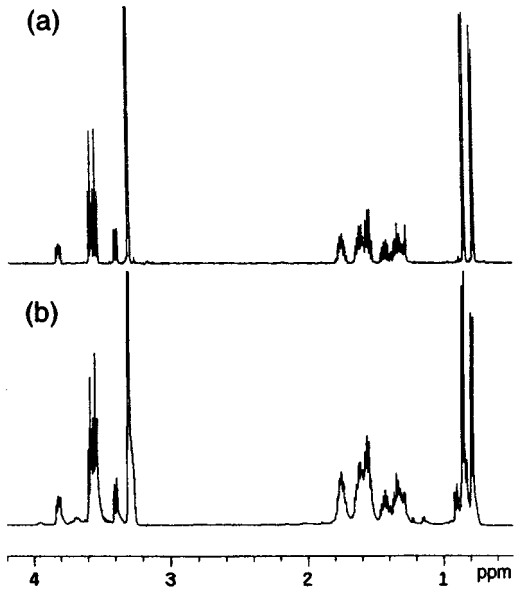
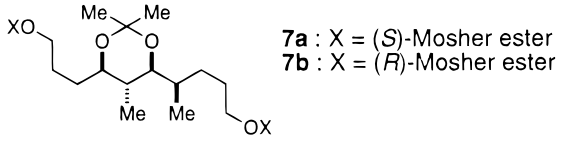


Figure 4. ^{1}H NMR spectra (500 MHz, CD_3OD). (a) Synthetic tetraol **6**. (b) Tetraol derived from oasomycin B.

The absolute configuration of the C.5−C.10 segment of oasomycins was then determined via the derivatization of **6**.[9] The C.7,C.9-acetonide C.3,C.12-di-Mosher esters **7a**,**b** were prepared from **6**.[10] Importantly, the ^{1}H NMR spectra



of **7a** and **7b** were distinctly different (Figure 5). The tetraol derived from natural oasomycin B was then converted to the corresponding C.7,C.9-acetonide C.3,C.12-di-(*S*)-Mosher ester, and its ^{1}H NMR spectrum was found to be superimposable on the ^{1}H NMR spectrum of the synthetic C.7,C.9-acetonide C.3,C.12-di-(*R*)-Mosher ester **7b**, thereby establishing the absolute configuration of the C.5−C.10 portion of oasomycin B to be the opposite of **6** (Figure 6).

In conclusion, using a structural motif often found in the polypropionate class of natural products, we have demonstrated the reliability and usefulness of our NMR database for the stereochemical assignment of an acyclic compound. We recognize that the current approach critically depends on the availability of an NMR database properly representing a given arrangement of functional groups in question. As demonstrated in the preceding paper, such an NMR database can be created by synthesizing all of the possible diastereomers for a chosen representative system. However, this approach requires extensive synthetic effort for each case. In this connection, we recognize the possibility that an NMR database for a larger array of functional groups could be assembled from NMR databases of smaller arrays of functional groups and, given a minimum number of NMR databases, synthetic efforts could totally, or at least largely, be eliminated. We plan to test the feasibility of this approach through further studies on the oasomycins.

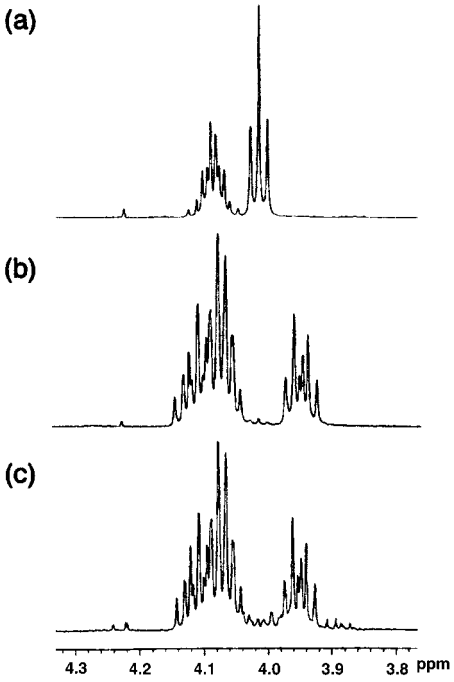


Figure 5. ^{1}H NMR (500 MHz, CD_3OD). (a) Di-(*S*)-Mosher ester **7a** derived from synthetic tetraol **6**. (b) Di-(*R*)-Mosher ester **7b** derived from synthetic tetraol **6**. (c) Di-(*S*)-Mosher ester derived from the tetraol derived from natural oasomycin B.

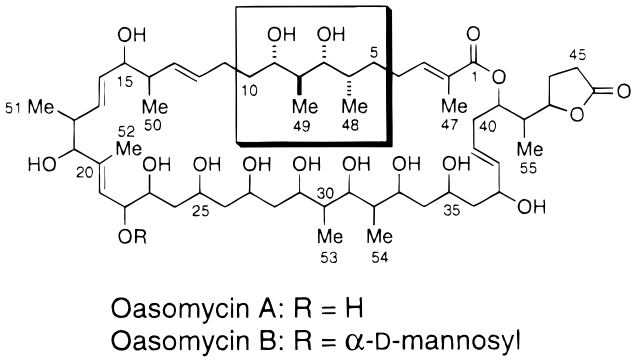


Figure 6. Absolute stereochemistry of the C.5−C.10 portion of oasomycins A and B.

(7) This degradation was achieved in 59% overall yield in two steps, i.e., (1) O_3/MeOH/−78 °C, followed by Me_2S treatment, and (2) $NaBH_4$/MeOH/0 °C.

(8) We thank Dr. Gerhard Kretzschmar for a sample of oasomycins A, B, and C.

(9) The α_D value of synthetic tetraol **6** was found approximately +5.9° (*c* 1.2, MeOH). We were concerned that this value might be too small to draw our conclusion.

(10) This transformation was carried out in two steps, i.e., (1) acetone/CSA/rt and (2) Mosher acid/EDCI/DMAP/CH_2Cl_2/rt.

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Supporting Information Available: Details for correlation of the ^{13}C NMR data of the C.5−C.10 portion ofoasomycin B with the ^{13}C NMR database, experimental procedures summarized in Scheme 1, and degradation of oasomycin B into the tetraol. This material is available free of charge via the Internet at http://pubs.acs.org.

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