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Toward Creation of a Universal NMR Database for the Stereochemical Assignment of Acyclic Compounds: The Case of Two Contiguous Propionate Units

Yoshihisa Kobayashi, Jinhwa Lee, Kenichi Tezuka, and Yoshito Kishi*

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

kishi@chemistry.harvard.edu

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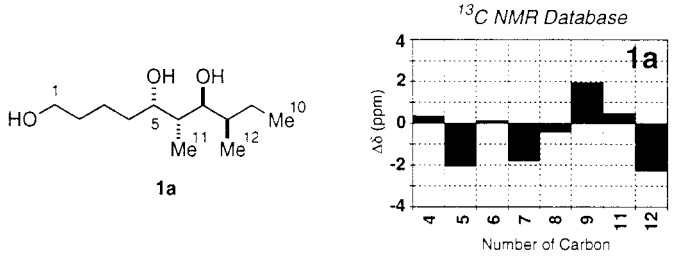
ABSTRACT



Using triol 1 as a representative example of natural products containing two contiguous propionate units, ^{13}C and ^{1}H NMR databases for the stereochemical assignment of acyclic compounds have been created. Chemical shift increments due to the presence of additional functional groups as well as solvent effects are discussed.

Work on the stereochemical assignments of palytoxin,[1] AAL toxins/fumonisins,[2] and maitotoxin[3] in our laboratory has yielded a vast volume of experimental data on the structural properties of fatty acids and related compounds. These studies have shown that the structural properties of a compound in question are (1) inherent to the specific stereochemical arrangements of (small) substituents on its carbon backbone and (2) independent from the rest of the molecule. We have therefore suggested the possibility that fatty acids and related compounds bearing (small) substituents on their backbones have the capacity to create unique structural motifs, to carry specific information, and to serve as functional materials.[3a] These experimental facts also suggest the possibility that, given a universal database(s) for various classes of functionalities, the stereochemical assign-

(1) Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; 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.

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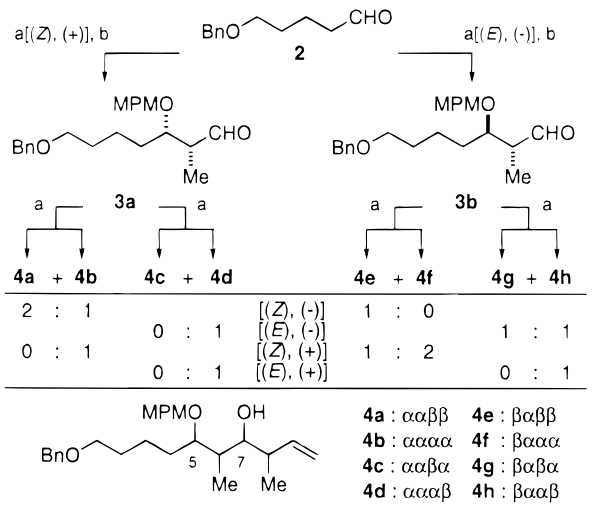
Scheme 1



(a) KO*t*-Bu, 2-butene, *n*-BuLi, $(Ipc)_2BOMe$, $BF_3{\cdot}OEt_2$, THF, -78 °C ([(Z), (+)] indicates [(Z)-butene, (+)-$(Ipc)_2BOMe$]). (b) (1) MPMCl, NaH, n-Bu_4NI, THF–DMF (4:1), rt. (2) OsO_4, NMO, acetone–H_2O, rt. (3) $Pb(OAc)_4$, benzene, rt.

ment of an unknown compound may be achieved, in contrast to our previous cases,[1−3] without synthetic efforts. In this Letter, we report our first step toward the creation of a universal NMR database through analysis of two contiguous propionate units as an example.

To test the feasibility and reliability of this approach, we selected a partial structure typically found in the polypropionate class of natural products. Specifically, we chose triol **1** as a representative example of natural products containing two contiguous propionate units. Our strategy was then to synthesize the eight possible diastereomers **1a**−**h** to create universal ^{1}H and ^{13}C NMR databases for this structural motif. Several comments on this plan are in order. First, any compound accommodating two contiguous propionate units could be used for the present data collection, but we prefer that the system meet the following criteria: (1) the two side chains should be different, thereby enabling the ^{13}C and ^{1}H chemical shifts to be precisely measured and (2) the two side chains should not bear a substituent(s) which may influence the propionate units via unusual electronic and/or steric effects. Second, in the previous cases,[1−3] we compared the chemical shifts of synthetic diastereomers with the chemical shifts of the natural product and used a degree of chemical shift deviation as the indicator for match/mismatch judgments. For the current purpose, we will use a deviation of chemical shift from the average value of the eight synthetic diastereomers as the reference point. Third, to correlate the NMR data of an unknown compound with a universal database, we need to estimate the effects on chemical shifts due to an additional functional group or groups present in an unknown compound. The left side chain of **1** should allow us to install representative functional groups on the backbone and to determine their effects on the database. Degrees of such effects could also be estimated via use of an empirical formula for predicting ^{13}C chemical shifts. Comparison of

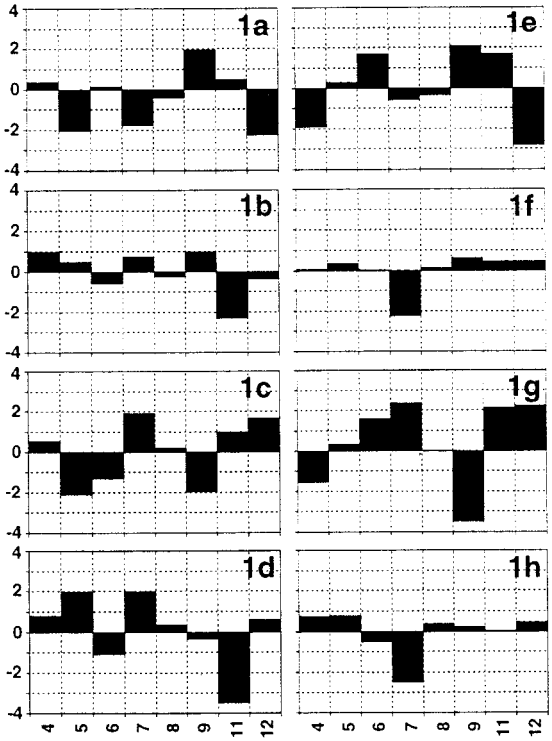
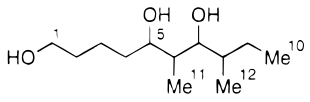


Figure 1. Difference in carbon chemical shifts between the average and the values of **1a**−**h** (100 MHz, CD_3OD). The *x* and *y* axes represent carbon number and $\Delta\delta$ ($\delta_{\mathbf{1a-h}} - \delta_{ave}$) in ppm, respectively, for all the graphs in this paper.

experimental values with predicted values should form a basis to estimate the chemical shift increments due to additional functional groups present in an unknown compound.



1

	C.5	C.6	C.7	C.8		C.5	C.6	C.7	C.8
1a	α	α	β	β	**1e**	β	α	β	β
1b	α	α	α	α	**1f**	β	α	α	α
1c	α	α	β	α	**1g**	β	α	β	α
1d	α	α	α	β	**1h**	β	α	α	β

Among numerous synthetic methods available for the iterative construction of polypropionates, we elected to adopt the Brown crotylboration protocol[4] for the preparation of the eight diasteromers possible for **1**. In the first chain elongation (Scheme 1), both the expected syn and anti products were obtained in approximately 93% and 75% enantiomeric

(4) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919−5923. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576.

(5) The enantiomeric excess was estimated from the ^{19}F NMR of its (*R*)-Mosher ester. It is worthwhile adding that 4 diastereomers **4b**, **4d**, **4e**, and **4h** obtained stereospecifically in the second crotylboration were found to be optically pure.

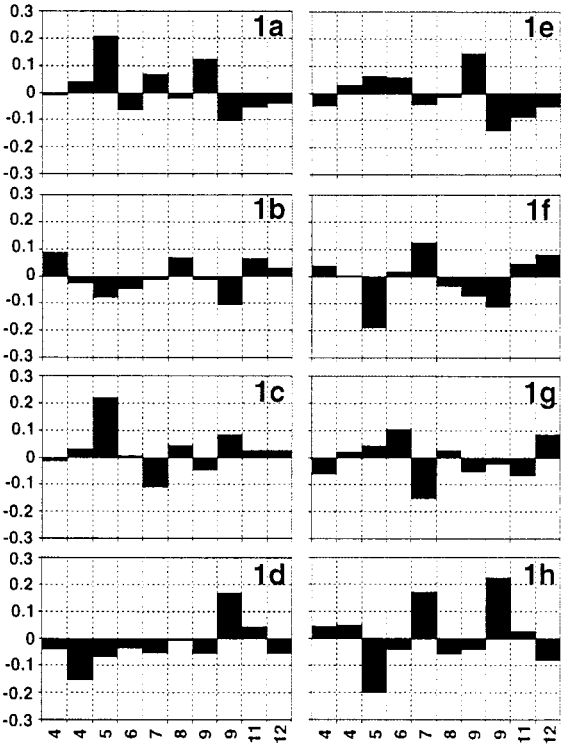


Figure 2. Difference in proton chemical shifts between the average and the values of **1a**−**h** (500 MHz, CD_3OD).

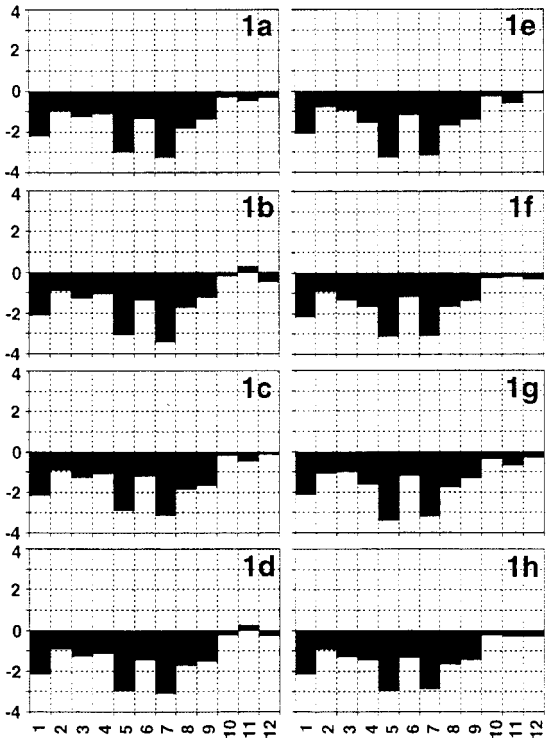


Figure 3. Difference in carbon chemical shifts of each of **1a**−**h**, $\Delta\delta = \delta_{((CD_3)_2SO)} - \delta_{(CD_3OD)}$ in ppm (100 MHz).

excess, respectively.[5] In the second chain elongation, it should be noted that (1) four diastereomers, **4b**, **4d**, **4e**, and **4h**, out of eight were obtained stereospecifically,[5] (2) three diastereomers, **4a** (stereoselectivity = 2:1), **4f** (2:1), and **4g** (1:1), were formed as a mixture of diastereomers, and (3) diastereomer **4c** could not be obtained by this method. Diastereomer **4c** was instead prepared via zinc-mediated crotylation (stereoselectivity = 5:1),[6] which was found also to be a stereoselective (5:1) means for the preparation of diastereomer **4g**. In addition, application of the tin-mediated crotylation developed by Keck[7] improved the stereoselectivity in the formation of **4a** (5:1) and **4f** (5:1).[8] Finally, hydrogenation/hydrogenolysis [H_2/$Pd(OH)_2$ on C/MeOH] of **4a**−**h** furnished **1a**−**h**, respectively.

The stereochemistry of **1a**−**h** was assigned on the basis of the following facts. First, it is well established that (*E*)- and (*Z*)-crotylboronates yield anti and syn products,[4] respectively, thereby allowing assignment of the relative stereochemistry at C.5 and C.6 as well as C.7 and C.8. Second, each diastereomer was converted to the corresponding C.5,C.7-acetonide, the NMR analyses[9] of which allowed us to conclude the relative stereochemistry at C.5 and C.7. Third, the eight diastereomers were prepared in an optically active form, the absolute configuration of which was determined by the chirality of $(Ipc)_2BOMe$ used in the first crotylboration.[4]

The ^{13}C and ^1H NMR spectra of each diastereomer were recorded in three commonly used NMR solvents [CD_3OD, $(CD_3)_2SO$, and $CDCl_3$], and the chemical shift assignments were established through COSY, HMQC, and DEPT experiments. The ^{13}C and ^1H databases were created and shown as a deviation in chemical shift for each nucleus of a given diastereomer from the average chemical shift of the nucleus in question (Figures 1 and 2).

As anticipated from our previous work, each diastereomer exhibited distinct and differing NMR spectroscopic properties from each other. It should be noted that the diastereomers **1f** and **1h** exhibit relatively small differences in the ^{13}C NMR database in CD_3OD but exhibit significant differences in the ^1H NMR database. Interestingly, this trend, i.e., the complementary nature of the ^1H and ^{13}C NMR databases, was also noticed for several cases in our maitotoxin studies.[3a]

Upon comparison of the chemical shifts found for each nucleus in CD_3OD, $(CD_3)_2SO$, and $CDCl_3$, the presence of solvent effects was evident. However, it is important to note that, upon changing the solvent from CD_3OD to $(CD_3)_2SO$, each nucleus of the eight diastereomers **1a**−**h** was found to

(6) For examples similar to the present case, see ref 3a.
(7) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883−1886.
(8) For the case of **4a**, although the stereoselectivity (**4a**:**4b**) could be improved up to 5:1, a significant amount of the linear product (3:2 regioselectivity) was also formed.
(9) The ^{13}C chemical shifts of two acetonide methyl groups are known to be diagnostic in differentiating syn- and anti-1,3-diol acetonides: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948. (b) Evans, D. A.; Reiger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100. In addition, NOE studies were conducted on the acetonides to confirm the stereochemical assignment at C.5 and C.7.
(10) CS ChemNMR Pro version 1.0, Renate Buergin Schaller, Development Centre, Bergstrasse 114, Zurich, Switzerland, installed in CS ChemDraw Pro version 4.5, was used.

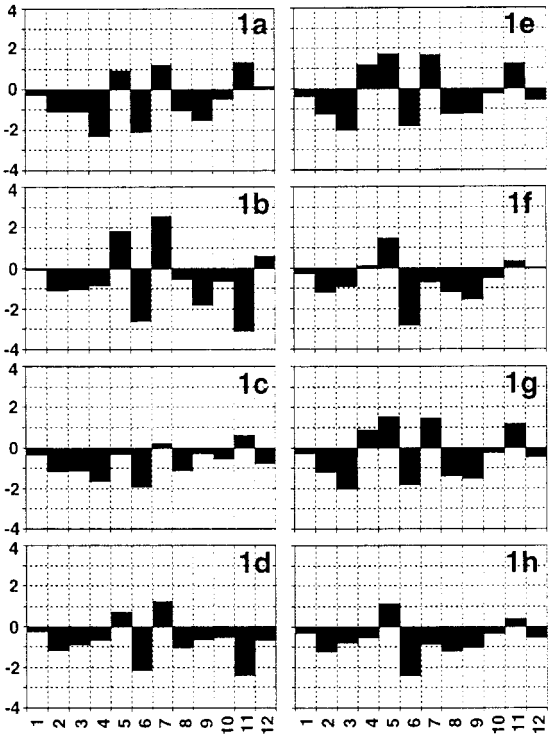
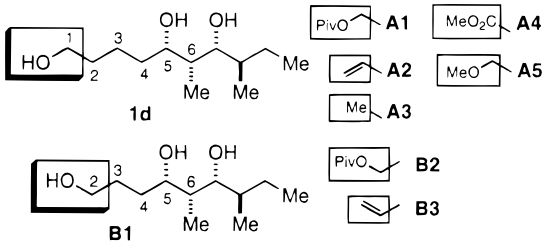


Figure 4. Difference in carbon chemical shifts of each of **1a**−**h**, $\Delta\delta = \delta_{(CDCl_3)} - \delta_{(CD_3OD)}$ in ppm (100 MHz).

exhibit approximately same magnitude of solvent effects (Figure 3). Consequently, the overall profile of the NMR databases in CD_3OD and $(CD_3)_2SO$ became virtually identical. On the other hand, upon changing the solvent from CD_3OD to $CDCl_3$, each nucleus of **1a**−**h** was found to exhibit a different magnitude of the solvent effects among the eight diastereomers. However, a similarity is noticeable in the overall profile of solvent effects between **1a**/**1c**, **1b**/**1d**, **1e**/**1g**, and **1f**/**1h** (Figure 4). Interestingly, the diastereomers in these pairings share the same relative configuration at the C.5, C.6, and C.7 positions. These observations may suggest that a six-membered intramolecular hydrogen bonding array plays a major role in determining the overall structural properties of these diastereomers in $CDCl_3$, whereas it does not play a role in CD_3OD and $(CD_3)_2SO$.

To determine chemical shift increments on the ^{13}C NMR database due to the presence of additional functional groups, two series of derivatives of **1d** were prepared, i.e., **A1**−**5** and **B1**−**2**. Although chemical shift increments were obtained also for the ^1H NMR spectra, we focused only on the ^{13}C NMR spectra because such incremental values could be estimated via the empirical formula known in the literature. Using the program developed by Renate Buergin Schaller,[10] the chemical shifts were estimated for each carbon of **A1**−**5**, **B1**−**3**, and **1d**. The chemical shift difference between a given carbon in **1d** or **B1** and the corresponding carbon in **A1**−**5** or **B2**−**3** was assumed to represent the chemical shift increment, respectively. The chemical shift increments thus estimated were found to compare well with the experimentally obtained values both in the **1d** and **A1**−**5** or **B1** and **B2**−**3** series (Table 1). This exercise demonstrates that

Table 1. Experimental[a] (Upper Line) and Predicted[10] (Lower Line) Increments (ppm) of ^{13}C NMR Chemical Shifts



	1	2	3	4	5	6
$\delta_{1d} - \delta_{A1}$	-2.7 -4.3	+3.8 +3.8	-0.2 -0.2	+0.2 +0.3	+0.3 ±0.0	-0.2 ±0.0
$\delta_{1d} - \delta_{A2}$		-1.3 -0.3	-3.1 -3.7	+0.3 -0.1	+0.2 -0.1	-0.1 ±0.0
$\delta_{1d} - \delta_{A3}$	+48.4 +49.0	+9.7 +10.1	-6.0 -6.2	±0.0 +0.3	+0.1 ±0.0	±0.0 ±0.0
$\delta_{1d} - \delta_{A4}$		-1.1 -0.1	+0.8 +0.9	+0.5 +0.3	+0.6 ±0.0	-0.2 ±0.0
$\delta_{1d} - \delta_{A5}$	-10.9 -9.4	+3.0 +2.5	-0.3 -0.3	±0.0 ±0.0	+0.2 ±0.0	-0.1 ±0.0
$\delta_{B1} - \delta_{B2}$		-2.7 -4.3	+3.8 +3.3	+0.1 -0.2	+0.5 +0.3	±0.0 ±0.0
$\delta_{B1} - \delta_{B3}$			-1.1 -0.3	-2.8 -3.7	+0.6 -0.1	+0.2 -0.1

[a] CD_3OD, 100MHz

necessary adjustment(s) to the ^{13}C NMR database due to the presence of a new array of functional groups can be made using the established empirical formula.

The reliability and usefulness of our NMR database for the stereochemical assignment of acyclic compounds are discussed in the following paper using the oasomycin class of natural products as an example.

Acknowledgment. We gratefully acknowledge Dr. Laura Cook-Blumberg for her contributions at the early phase of this program. Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged.

Supporting Information Available: Experimental procedures summarized in Scheme 1, table listing the chemical shifts of acetonides derived from **1a**−**h**, database graphs in $(CD_3)_2SO$ and $CDCl_3$, and tables listing complete ^1H and ^{13}C NMR assignments of **1a**−**h** in CD_3OD, $(CD_3)_2SO$, and $CDCl_3$, and ^{13}C NMR assignments of **A1**−**5** and **B1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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