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Direct Assignment of the Relative Configuration in 1,3,*n*-Methyl-Branched Carbon Chains by ^{1}H NMR Spectroscopy

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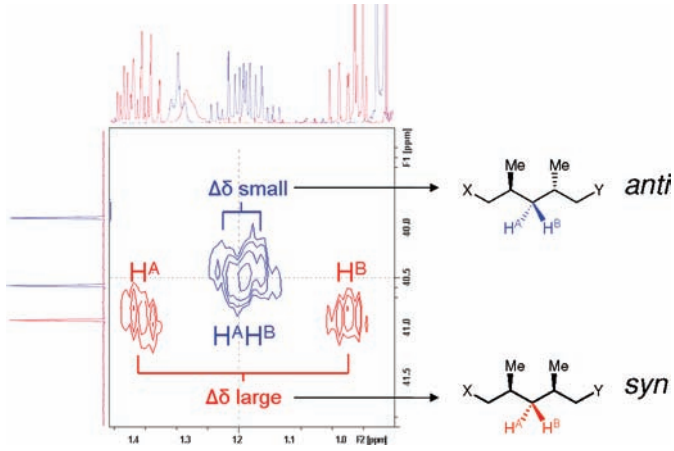
ABSTRACT



On the basis of the assignment of methylene proton signals in ^{1}H NMR and determination of the chemical shift difference ($\Delta\delta$), the relative configuration of 1,3,*n*-methyl-branched deoxypropionates can be determined directly. Comparison of the chemical shifts in the corresponding *syn*- and *anti*-configured compound pairs shows remarkable differences, while the absolute values depend on the presence and nature of adjacent functional groups. The determination of the $\Delta\delta$ values provides a reliable assessment of the relative configuration in 1,3,*n*-methyl-branched polypropionate chains and is even valid for macrocycles.

Structure elucidation of natural products is of high interest in order to find new classes of pharmaceutically active compounds. To date, the structure elucidation of highly complex molecules mainly depends on mass spectrometry and NMR-spectroscopic data, since in most cases there is not enough material for crystal structure analysis.[1] Herein, we report on an ^{1}H NMR method for assigning the relative configuration of 1,3-methyl substitutents within oligo- and monodeoxypropionate carbon chains without the need for derivatization or special NMR measurements.

For the assignment of relative configurations in polyketides, several NMR-based methods are known. For 1,3-diols, the relative stereochemistry can be assigned by synthesis of the corresponding acetonide and NOE measurements or by ^{1}H NMR measurement of OH/OD isotope shifts.[2] Relative configurations of contiguous, alcohol-containing propionate stereocenters can be assigned via Murata's method based on $^{2,3}J_{HC}$ couplings or the calculation of ^{13}C NMR-spectra and comparison with the data obtained for the natural product.[3] The latter methods require detailed conformational analyses and elaborate quantum-mechanical calculations in order to achieve exact predictions. Another approach pro-

(1) Menche, D. *Nat. Prod. Rep.* **2008**, *25*, 905–918.

(2) (a) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9–17. (b) Anderson, C. E.; Britt, D. K.; Sangji, S.; O'Leary, D. J.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 5721–5723.

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posed by Kishi, based on a universal NMR database, requires the synthesis of all diastereomers of an adequate model compound.[4]

In deoxypropionates, however, Hoffmann discusses the preferential conformation of the carbon chain, avoiding *syn*-pentane interactions (Figure 1).[3c] Both conformers **a** and **b**

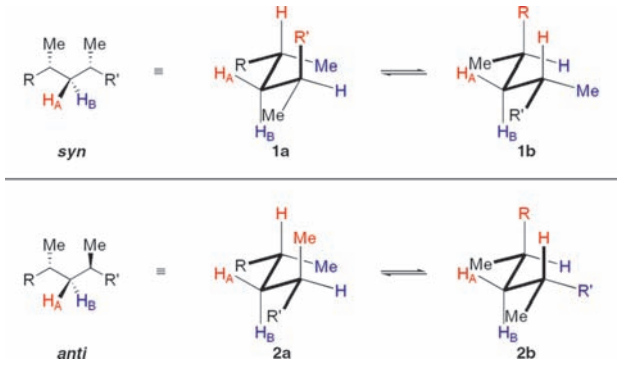

Figure 1. Conformations of *syn*- and *anti*-deoxypropionates in a denoted diamond lattice.

of the *syn*- and *anti*-isomers, respectively, represent the only populated conformations of this substructure.

For the *syn*- and *anti*-diastereomers, the methylene protons H_A and H_B have a different local symmetry which is apparent when considering the case where $R = R'$. For this situation, the hydrogen atoms H_A and H_B in the *anti*-diastereomers **2a** and **2b** are homotopic, and thus, ^{1}H NMR chemical shifts are per definition the same. Conversely, for the *syn*-diastereomers **1a** and **1b** these protons are diastereotopic and due to different chemical environments have different chemical shifts in the proton NMR. For $R \neq R'$, the global symmetry of the molecular objects is broken; however, this may have only a minor effect on the local symmetry situation for hydrogen atoms H_A and H_B. Hence, for the *syn*-diastereomer one expects large chemical shift differences and smaller chemical shift differences for the *anti*-diastereomer in the proton NMR resonances of hydrogen atoms H_A and H_B, respectively.

Over the past decade, our group has developed two methodologies for deoxypropionate synthesis based on copper-mediated allylic substitution employing *o*-diphenylphosphinobenzoic acid as a directing group[5] and, more recently, the zinc-catalyzed enantiospecific sp^3-sp^3 coupling.[6] Both methodologies are perfectly suited to build both *syn*- and *anti*-1,3,*n*-methyl-branched hydrocarbons in a highly enantioselective and diastereoselective manner.

In this way, we collected a multitude of NMR spectroscopic data for both *syn*- and *anti*- deoxypropionate structures. It emerged as a rule for a specific molecule that the chemical shift difference ($\Delta\delta$) for the methylene protons (H_A and H_B in Figure 1) varied significantly in the *syn*- and *anti*-compounds.

One exemplary model compound, *tert*-butyl ester **3**, is shown in Figure 2.[6] All four diastereomers are depicted with

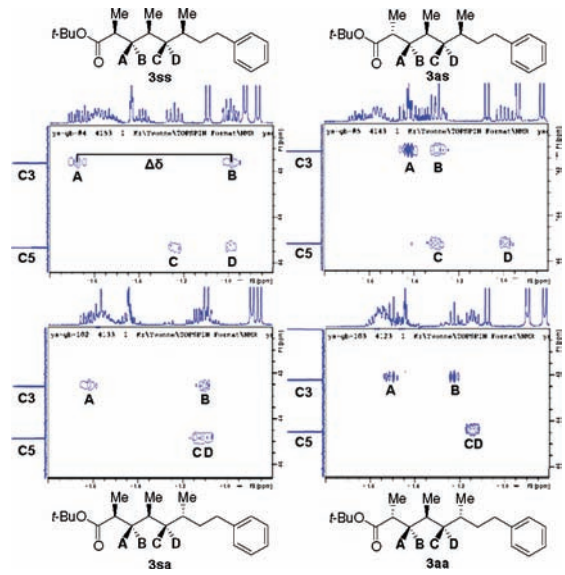

Figure 2. 2D NMR data of the four diastereomers of ester **3**.

the methylene proton section of their corresponding 2D-HSQC spectra. The hetero correlation spectrum is only necessary to correctly assign the position of the matching proton signals, especially in larger molecules.

Evidently, in between the *syn*-related stereocenters the methylene protons differ considerably in their chemical shift (e.g., A and B in **3ss**). The chemical shifts for the corresponding *anti*-relationship exhibit a convergence of the signals (for *syn*,*syn*- vs *anti*,*syn*-**3**) or the complete overlap of both signals (for *syn*,*syn*- vs *syn*,*anti*-**3**).

It is also obvious that next to a carbonyl group (signals A and B), $\Delta\delta$ is very large for the *syn*-compounds **3ss** and **3sa** and is still observable in the *anti*-compounds **3as** and **3aa**. Farther away from the functional group (signals C and D) in **3ss** and **3as**, $\Delta\delta$ is smaller than for the A/B signals but in **3as** and **3aa** $\Delta\delta$ diminishes to nearly zero.

Based on these findings, an extensive literature research was undertaken. We found more than 60 compounds, mostly natural products, with assigned ^{1}H NMR data (necessary for the $\Delta\delta$ analysis) and proven relative configuration. In this set of known compounds, we could identify six pairs of matching *syn*,*anti*-compounds.

(3) For a review on NMR-spectroscopic and computational methods, see: (a) Bifulco, G.; Dambuoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744–3779. (b) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870–871. (c) Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *J. Org. Chem.* **1996**, *61*, 8083–8088.

(4) (a) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177–2180. For a review on Kishi's work, see: (b) Kishi, Y. *Tetrahedron* **2002**, *58*, 6239–6258.

(5) (a) For a review, see: Breit, B.; Schmidt, Y. *Chem. Rev.* **2008**, *108*, 2928–2951. (b) For novel synthetic applications, see: Schmidt, Y.; Breit, B. *Org. Lett.* **2009**, *11*, 4767–4769. (c) Schmidt, Y.; Lehr, K.; Breit, B. *J. Org. Chem.*, submitted .

(6) Brand, G. J.; Studte, C.; Breit, B. *Org. Lett.* **2009**, *11*, 4668–4670.

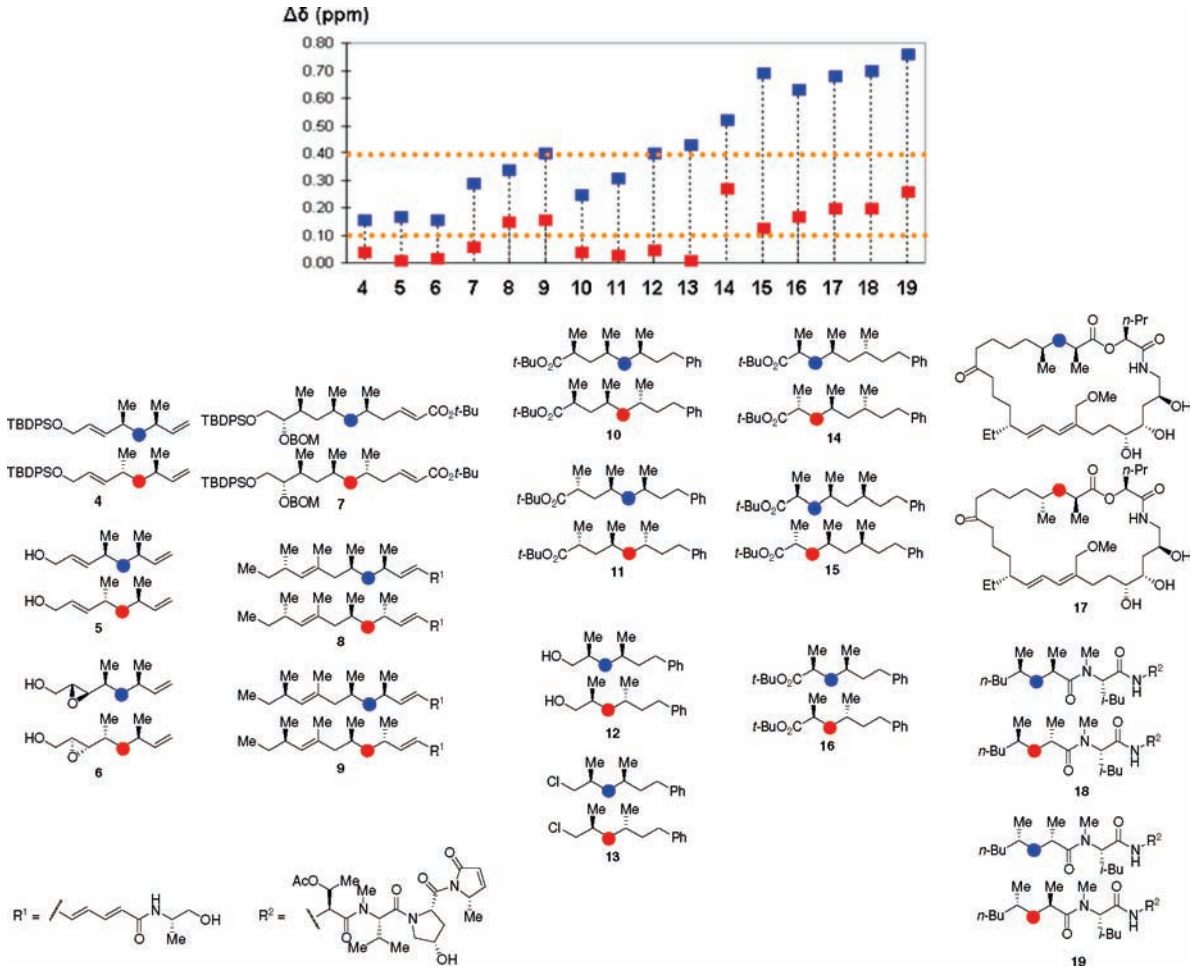

Figure 3. Direct comparison of corresponding *syn*- and *anti*-pairs.[11]

In Figure 3, the corresponding chemical shift differences for these *syn* and *anti* compounds, together with another 10 examples synthesized in our laboratory, are compared. First, the effect is lowest in substances with an (unsubstituted) double bond next to the 1,3 methyl substituents (**4**−**6**). Medium effects can be detected in alkyl-substituted chains with long distances to functional groups or in the case of hydroxy or chlorine substituents (**7**−**13**). A significant difference can be observed in proximity to carbonyl functions such as esters (**14**−**17**) or amides (**18** and **19**).

It is remarkable, that even in the macrocycle of myxovirescin (**17**) the Δ*δ*-values show the same tendency as in unstrained carbon chains. Additionally, the effect seems to be independent from neighboring stereogenic centers.

Together with the literature survey of 60 compounds and the data we collected in our group we could study the NMR data of over 80 deoxypropionate natural products and intermediates (Figure 4). Most of the *anti*-configured substances exhibit Δ*δ* values of 0.0−0.2 ppm, whereas the main part of the *syn* compounds exhibits Δ*δ* values from 0.2 to 0.5 ppm. The overlap of both histograms (region in between 0.1 and 0.4 ppm) can be explained

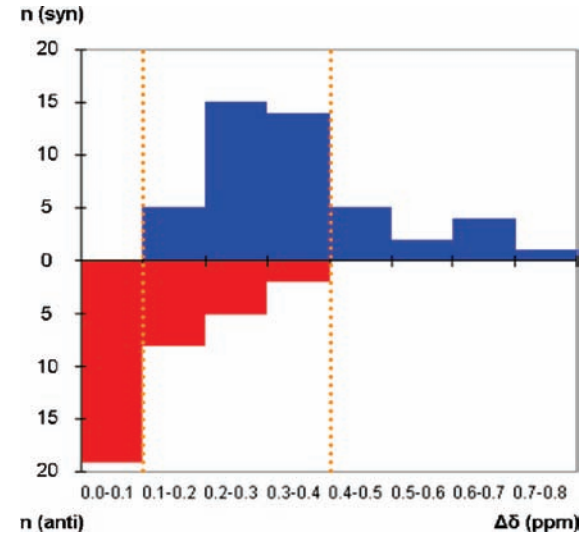

Figure 4. Δ*δ* values of known compounds.

depending on the nature of the neighboring functional groups (compare Figure 3).[7]

In 2005, a highly elaborate structure elucidation was published where the relative configuration of the stereotetrad in 4,6,8,10,16,18-hexamethyldocosane (**4**), a cuticular hydrocarbon of the cane beetle, was assigned by synthesis of all possible diastereomers.[8] By comparison of the ^{13}C NMR data to the natural diastereomer, Kitching et al. found an exceptional *anti*,*anti*,*anti*-relationship in the stereotetrad of the molecule. Applying our method, we would have predicted the *anti*,*anti*,*anti* and even the *syn* configuration between C16 and C18 simply from the analysis of the assigned ^{1}H NMR data reported (Figure 5).

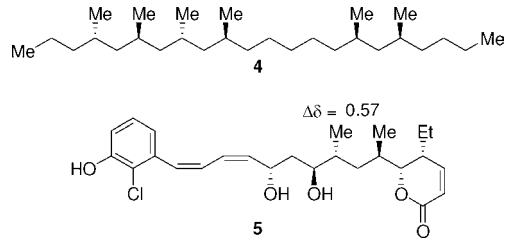

Figure 5. $\Delta\delta$ values of several natural products.

Despite the large scope of the method, which can even be applied in macrocycles,[9] we also found limitations. In the natural product bitungolide A (**5**), whose absolute configuration was unambiguously assigned by X-ray crystal structure analysis, the $\Delta\delta$ value was found to be 0.57 ppm.[10] In this structure, a chiral six-membered lactone is located directly adjacent to the 1,3-methyl branches, which of course influences the conformer stability and therefore contradicts the presumed *syn* assignment.

In summary, by correct assignment of the ^{1}H NMR signals of the geminal methylene protons of a 1,3,*n*-methyl-substituted carbon chain, the relative configuration can be assigned as follows:

$$\textit{anti}: = \Delta\delta = 0.00-0.1 \text{ ppm}$$

$$\textit{syn}: = \Delta\delta = >0.4 \text{ ppm}$$

For a chemical shift difference between 0.1 and 0.4 ppm, a comparison of the electronic and steric environment with literature data is necessary (compare list of substances in the Supporting Information). This assignment method is valid for unstrained carbon chains or macrocycles, whereas a prediction in conformationally strained molecules such as **5** is not possible.

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Supporting Information Available: Full 2D spectra of compounds **3** and a list of compounds contributing to Figure 4, with $\Delta\delta$ values and literature references. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Compounds **4**−**6**: Reiss, T.; Breit, B. *Chem.*−*Eur. J.* **2009**, *15*, 6345–6348. (b) Compounds **7**: Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784–13792. (c) Compounds **8** and **9**: Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481–1483. (d) Compounds **10**−**16**, see ref 6. (e) Compounds **17**: Trowitzsch, W.; Borgschulte, K.; Wray, Y.; Schomburg, D.; Höfle, G. *Liebigs Ann.* **1985**, 1629–1652. (f) Compounds **18** and **19**: Decicco, C. P.; Grover, P. *J. Org. Chem.* **1996**, *61*, 3534–3541.

(8) All compounds with $\Delta\delta$ values and ^{1}H chemical shifts are listed in the Supporting Information.

(9) Chow, S.; Fletcher, M. T.; Lambert, L. K.; Gallagher, O. P.; Moore, C. J.; Cribb, B. W.; Allsopp, P: G.; Kitching, W. *J. Org. Chem.* **2005**, *70*, 1808–1827.

(10) See compounds **17** and two additional examples in the Supporting Information.

(11) Sirirath, S.; Tanaka, J.; Ohtani, I. I.; Ichiba, T.; Rachmat, R.; Ueda, K.; Usui, T.; Osada, H.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1820–1823.