Analysis of Two ^{13}C NMR Correlations for Determining the Stereochemistry of 1,3-Diol Acetonides

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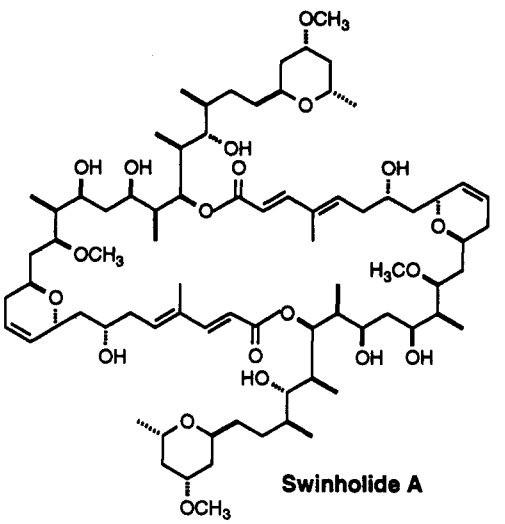
The stereochemistry of *syn*- and *anti*-1,3-diol acetonides can be assigned from the ^{13}C chemical shifts of the acetal methyl groups and from the ^{13}C chemical shifts of the acetal carbon. In general, the *syn*-1,3-diol acetonides have acetal methyl shifts at 19 and 30 ppm and acetal carbon shifts at 98.5 ppm, while the *anti*-acetonides have methyl shifts at 25 ppm and acetal shifts at 100.5 ppm. We have tested the generality and reliability of these two correlations by carrying out a complete literature search for 1,3-diol acetonides and identifying those with assignable ^{13}C spectra. The complete set of 221 1,3-diol acetonides, including several newly prepared compounds, were analyzed to test the validity of these two ^{13}C chemical shift correlations. The ^{13}C chemical shift correlation of the acetal methyl groups holds for all cases examined except those containing nitriles at the C(4) or C(6) position. The ^{13}C correlation of the acetal carbon is much less reliable; the syn and anti isomers show significant overlap with no obvious structural correlation. The acetal methyl shifts are reliable indicators of 1,3-diol acetonide stereochemistry, but the acetal carbon shift correlation is not always reliable and should be used with caution.

Determining the stereochemistry of complex polyol natural products in the absence of definitive crystallographic information is a time consuming and sometimes difficult task[2] and provides a strong impetus for the development of simple and reliable spectroscopic tools. The 1,3-diol subunit is found in many natural products such as the polyene macrolide antibiotic roflamycoin and the polypropionate swinholide A (Figure 1).[3] Several years ago we described a method for determining the relative stereochemistry of 1,3-diols by analyzing the ^{13}C NMR spectra of their acetonides.[4,5] The original report was based on the analysis of polyacetate polyols, and the method was later extended to polypropionate polyols by the Evans *et al.*[6] We subsequently demonstrated that the sensitivity of this method could be increased 100-fold by using ^{13}C-enriched acetone to prepare the acetonide, a strategy that was instrumental in the structure determination of macrolactins B and F.[7] The ^{13}C acetonide method has been widely used to assign 1,3-diol stereochemistry.[8] Our original empirical relationship between 1,3-diol acetonide stereochemistry and ^{13}C chemical shifts was based on the analysis of 31 cases.[4] In an effort to extend the method to different structural types and to analyze its reliability,



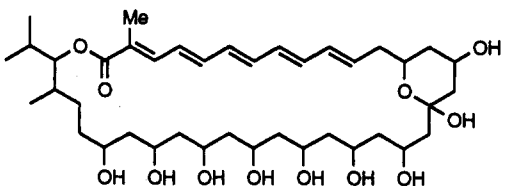


Figure 1. Structures of the polyol natural products roflamycoin and swinholide.

we have completed a thorough search of the literature and have identified over 200 cases which are analyzed below.

The ^{13}C NMR method for the stereochemical identification of 1,3-diols relies on the conformational properties of the corresponding 1,3-diol acetonides (4,6-dialkyl-2,2-dimethyl-1,3-dioxanes).[9] A *syn*-acetonide exists in a well-defined chair conformation with the C(4) and C(6) alkyl substituents in equatorial positions. An *anti*-acetonide exists in a twist-boat conformation in order to avoid the 1,3-diaxial interactions that would be present in either chair conformation (Figure 2).[10] These two conformations and thus the relative stereochemistry[11] of the diols can be

(1) Alfred P. Sloan Research Fellow 1992-1993. McKnight Land-Grant Professorship, 1990-1993.

(2) For example, see Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120-8122.

(3) (a) Roflamycoin: Schlegel, R.; Thrum, H.; Zielinski, J.; Borowski, E. *J. Antibiotics* **1981**, *34*, 122-123. (b) Swinholide A: Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629-3632.

(4) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948.

(5) Buchanan *et al.* have reported that the ^{13}C chemical shifts of acetal carbons are useful in distinguishing among 5-, 6-, and 7-membered acetonide rings. They discussed the conformation of several fused bicyclic acetonides derived from carbohydrates in relation to their ^{13}C chemical shifts. Although we were unaware of this work at the time of our initial publication, their analysis is consistent with the chemical shift correlations which we observed in acetonides derived from alternating polyol chains. Buchanan, J. G.; Edgar, A. R.; Rawson, D. I.; Shahidi, P.; Wightman, R. H. *Carbohydrate Res.*, **1982**, *100*, 75-86.

(6) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100.

(7) Rychnovsky, S. D.; Skalitzky, D. J.; Pathirana, C.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671-677.

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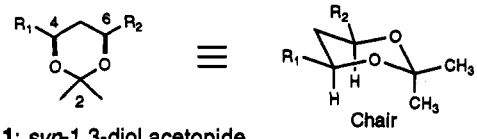
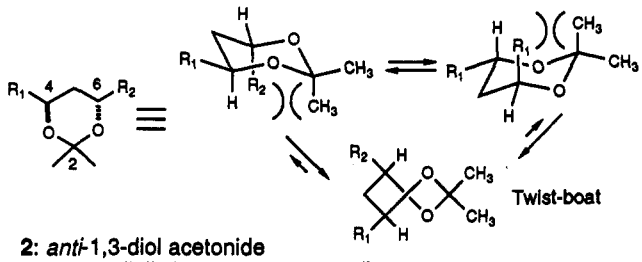


1: *syn*-1,3-diol acetonide
cis-4,6-dialkyl-2,2-dimethyl-1,3-dioxane



2: *anti*-1,3-diol acetonide
trans-4,6-dialkyl-2,2-dimethyl-1,3-dioxane

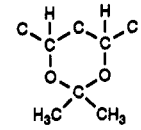
Figure 2. Conformations of *syn*-1,3-diol acetonides 1 and *anti*-1,3-diol acetonide 2.[9]

distinguished by the ^{13}C chemical shifts of the acetonide C(2)-methyl groups.[12] The ^{13}C NMR spectrum of a typical *syn*-acetonide shows an axial methyl group at ca. 19 ppm and an equatorial methyl group at ca. 30 ppm, whereas the ^{13}C NMR spectrum of a typical *anti*-acetonide shows both methyl groups at ca. 25 ppm. The C(2)-acetal ^{13}C chemical shift is also indicative of the change in conformation, where typical *syn*- and *anti*-acetonides have ^{13}C chemical shifts of 98.5 and 100.4 ppm, respectively. The methyl and acetal chemical shift correlations allow the relative stereochemistry of a typical 1,3-diol acetonide to be assigned by inspection of its ^{13}C NMR spectrum.

The stereochemical correlation is only reliable where the *syn*- and *anti*-1,3-diol acetonides adopt different conformations. Virtually any *syn*-acetonide 1 will adopt a chair conformation,[10a] but the *anti*-acetonide 2 will only adopt the twist-boat conformation when the chair conformation is strongly destabilized. When R_1 and R_2 are large (e.g. $R_1, R_2 = CH_2R$) the 1,3-diaxial interaction with the appropriate C(2)-methyl destabilizes both of the possible chair conformations and forces the acetonide to adopt a twist-boat conformation. When R_1 is small (e.g. R_1 = H), then the 1,3-diaxial interaction with the C(2)-methyl will be reduced and the acetonide will adopt a chair conformation with R_1 in the axial position. The conformational preference of an *anti*-1,3-diol acetonide 2 should correlate with the steric bulk of R_1 (or R_2), and the transition from a twist-boat to a chair conformation will fall somewhere between the steric bulk of methyl and hydrogen. A thorough conformational analysis of 1,3-diol acetonides is presented elsewhere.[13] The ^{13}C NMR stereochemical correlation is valid as long as R_1 and R_2 are large enough to force the *anti*-acetonide 2 to adopt a twist-boat conformation.

Method. To test the limits of the ^{13}C NMR method we conducted a literature search for appropriate examples and prepared several new compounds.[14] Only ^{13}C NMR data collected in $CDCl_3$ was considered in this analysis.[15] The Chemical Abstracts Service database was searched for the 1,3-diol acetonide substructure shown below, and a total of 1799 structures were found in 372 references.[16]

substructure for CAS search



The majority of compounds were eliminated due to the absence of any ^{13}C NMR data, and a small number of others were eliminated because stereochemical information was absent or the acetonide methyl groups could not be unambiguously assigned from the published ^{13}C NMR data. The result was 211 1,3-diol acetonide rings with a variety of substituents. Several common functional groups were poorly represented among the literature examples, and so several new compounds were prepared to add diversity to the final set of 221 acetonide rings.[14] The complete list of acetonide structures with the appropriate ^{13}C NMR chemical shifts and literature reference are given in the supplementary material.

Results and Discussion

Methyl ^{13}C Chemical Shifts and Stereochemistry. The ^{13}C NMR data for the *syn*- and *anti*-acetonides are plotted in Figures 3 and 4, and an overview is presented in Table I. Both the ^{13}C chemical shift and the difference between the ^{13}C NMR chemical shifts of the two C(2)-methyl groups are plotted in Figure 3. The chemical shift difference plots clearly illustrate the degree of nonequivalence between the two C(2)-methyl groups. Essentially all of the *syn*-acetonides show the expected chemical shifts for the C(2)-methyl groups. The average values are 19.6 ppm for the axial carbon and 30.0 ppm for the equatorial carbon with mean standard deviations of <0.35 ppm. The anti-acetonides show significantly more variation, with C(2) methyl signals as low as 21 ppm to as high as 30 ppm, but the vast majority have chemical shifts that fall between 23 and 26 ppm. The C(2)-methyl NMR difference plots very clearly show the homogeneity of the *syn*-acetonide

(8) (a) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550–5551. (b) Dondoni, A.; Perrone, D.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1313. (c) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260–6268. (d) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129–6132. (e) Guanti, G.; Banfi, L.; Narisano, E.; Thea, S. *Synlett* **1992**, 6943. (f) Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1990**, *55*, 6246–6248. (g) Marshall, J. A.; Crute, T. D. I.; Hsi, J. D. *J. Org. Chem.* **1992**, *57*, 115–123. (h) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797–800. (i) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161–5169. (j) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563. (k) Shao, L.; Seki, T.; Kawano, H.; Saburi, M. *Tetrahedron Lett* **1991**, *32*, 7699–7702. (l) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090–1091. (m) Mead, K. T.; Park, M. *J. Org. Chem.* **1992**, *57*, 2511–2514. (n) Trost, B. M.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1924–1925.

(9) As a matter of convenience, the term "*syn*-acetonides" will be used to describe *cis*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes and the term "*anti*-acetonides" will be used to describe *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes throughout this paper. The "acetonides" will be numbered as 1,3-dioxanes as illustrated in Figure 1.

(10) (a) Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293–371. (b) Pihlaja, K.; Nurmi, T. *Isr. J. Chem.* **1980**, *20*, 160–167.

(11) These two ring conformations can be distinguished by analysis of the appropriate ^1H coupling constants, and this procedure has been used to assign the stereochemistry of 1,3-diols. For example, see Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E.; *J. Org. Chem.* **1987**, *52*, 2896–2901.

(12) A similar procedure can be used to determine the stereochemistry of 1,2-diol acetonides: Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr. II* **1980**, 395–399.

(13) Rychnovsky, S. D.; Yang, G.; Powers, J., submitted for publication.

(14) Preparation and characterization of these new acetonides are described elsewhere; see ref 13.

(15) Two spectra collected in C_6D_6 and one spectrum collected in CD_3OD were included in the data. These three cases have typical *syn*-acetonide shifts and are identified in the supplementary material.

(16) Search conducted November 12, 1992.

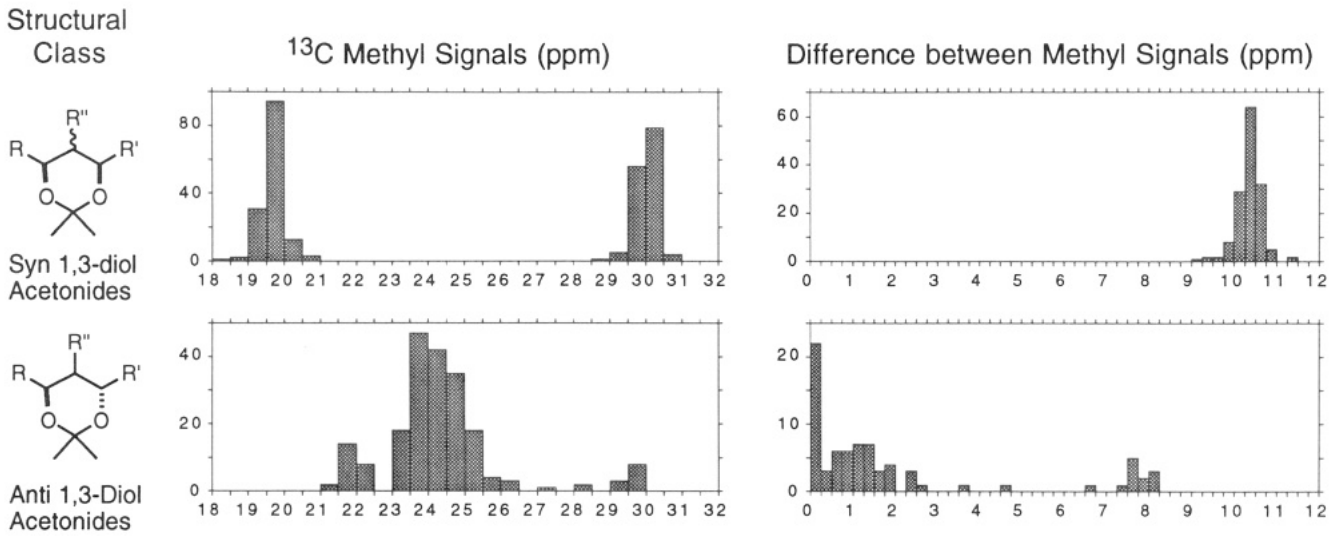


Figure 3. The C(2)-methyl ^{13}C chemical shift and difference histograms for *syn*- and *anti*-1,3-diol acetonides.

Table I. ^{13}C Stereochemical Correlation of 1,3-Diol Acetonides[a]

structural class	no.[b]	low methyl	high methyl	methyl difference	acetal
syn	145	19.66 ± 0.35	30.00 ± 0.30	10.34 ± 0.30	98.93 ± 0.67
anti	76	23.65 ± 0.93	25.64 ± 1.79	1.98 ± 2.60	100.64 ± 0.82
anti class 1	23	24.49 ± 0.26	24.69 ± 0.25	0.20 ± 0.20	100.31 ± 0.49
anti class 2	4	24.22 ± 0.66	26.14 ± 0.84	1.91 ± 1.43	100.39 ± 0.35
anti class 3	10	21.97 ± 0.66	29.41 ± 0.48	7.44 ± 1.05	100.87 ± 0.56
anti class 4	26	23.59 ± 0.32	24.92 ± 0.54	1.33 ± 0.56	100.59 ± 1.15
anti class 5	6	23.80 ± 0.26	25.12 ± 0.23	1.31 ± 0.35	100.78 ± 0.25
anti class 6	3	21.93 ± 0.11	29.10 ± 0.62	7.17 ± 0.51	101.33 ± 0.21

[a] The ^{13}C chemical shifts are reported in ppm as the mean ± std deviation. [b] The combined anti statistics include several examples that do not fall into class 1–6.

data and the heterogeneity of the *anti*-acetonide data. Even with the heterogeneity of the *anti*-acetonide data, it is important to note that when C(2)-methyl shift differences are considered, there is no overlap between the syn stereoisomers with a difference of >9 ppm and the anti stereoisomers with a difference of <9 ppm.

The ^{13}C NMR data suggests that the *anti*-acetonides exist in different conformations depending on their substituents. The importance of substitution on conformation was confirmed by dividing the *anti*-acetonides into six different structural classes and plotting the C(2)-methyl chemical shift and difference values for each class (Figure 4). The first three classes of *anti*-acetonides are derived from polyacetates with the C(5) carbon unsubstituted. The second three classes of *anti*-acetonides are derived primarily from polypropionates where the C(5) carbon bears a methyl group. The C(6) alkyl substituent in each class is an sp^3 carbon atom, while the C(4) alkyl substituent is an sp^3 carbon in classes 1 and 4, an sp^2 carbon in classes 2 and 5, and an sp carbon in classes 3 and 6. These classes were chosen to be easily assignable, to cover the most common structural types, and to logically divide the substituents into classes with comparable steric bulk.

All of the C(2)-methyl ^{13}C shifts in class 1 (sp^3) compounds are very similar, and the difference between the two chemical shifts averages only 0.2 ppm (Figure 4). When the two alkyl substituents in a class 1 acetonides are equivalent, then the molecule has C_2 symmetry: thus the two C(2)-methyl groups are homotopic and must have identical chemical shifts. Even when the two sp^3 alkyl substituents on a class 1 acetonide are slightly different the two C(2)-methyl groups are in very similar environments and have very similar chemical shifts. The class 2 (sp^2) compounds show dissimilar C(2)-methyl ^{13}C NMR shifts, presumably due to the presence of both twist-boat and chair conformations. The chemical shift difference of 1–4 ppm is easily distinguished from that of the syn isomer (>9 ppm) and presents no problem with stereochemical assignment. The class 3 (sp) compounds are more problematic. The two sp functional groups represented are an alkyne with a chemical shift difference of 4.5 ppm and several nitriles with chemical shift differences of ca. 8 ppm. The nitrile-substituted acetonides exist predominantly in chair conformations, whereas the alkyne is present as a mixture of chair and twist-boat conformations.[13] The class 3 anti isomers can be distinguished from the syn isomers by chemical shift difference, but this is more useful with alkynes where the chemical shift difference is more significant. With the exception of nitriles, the methyl ^{13}C chemical shift differences for each compounds in class 1–3 can be used to assign the relative stereochemistry as syn (>9 ppm) or anti (<5 ppm).

The compounds in class 4 (sp^3) differ from those in class 1 (sp^3) in that the difference between the two C(2)-methyl NMR shifts is significantly larger, 1.3 ppm verses 0.2 ppm. Where class 1 (sp^3) molecules are nearly C_2 symmetric, the additional C(5) substituent in class 4 molecules removes the possibility of C_2 symmetry. We believe that the class 4 (sp^3) molecules adopt a slightly distorted twist-boat conformation rather than significantly populating the chair conformations, and that this distortion accounts for the nonequivalence of the two C(2)-methyl chemical shifts.[13] The class 5 (sp^2) acetonides show similar C(2)-methyl chemical shifts as both class 2 (sp^2) and class 4 (sp^3). Finally, all of the examples in class 6 (sp) are nitriles and they

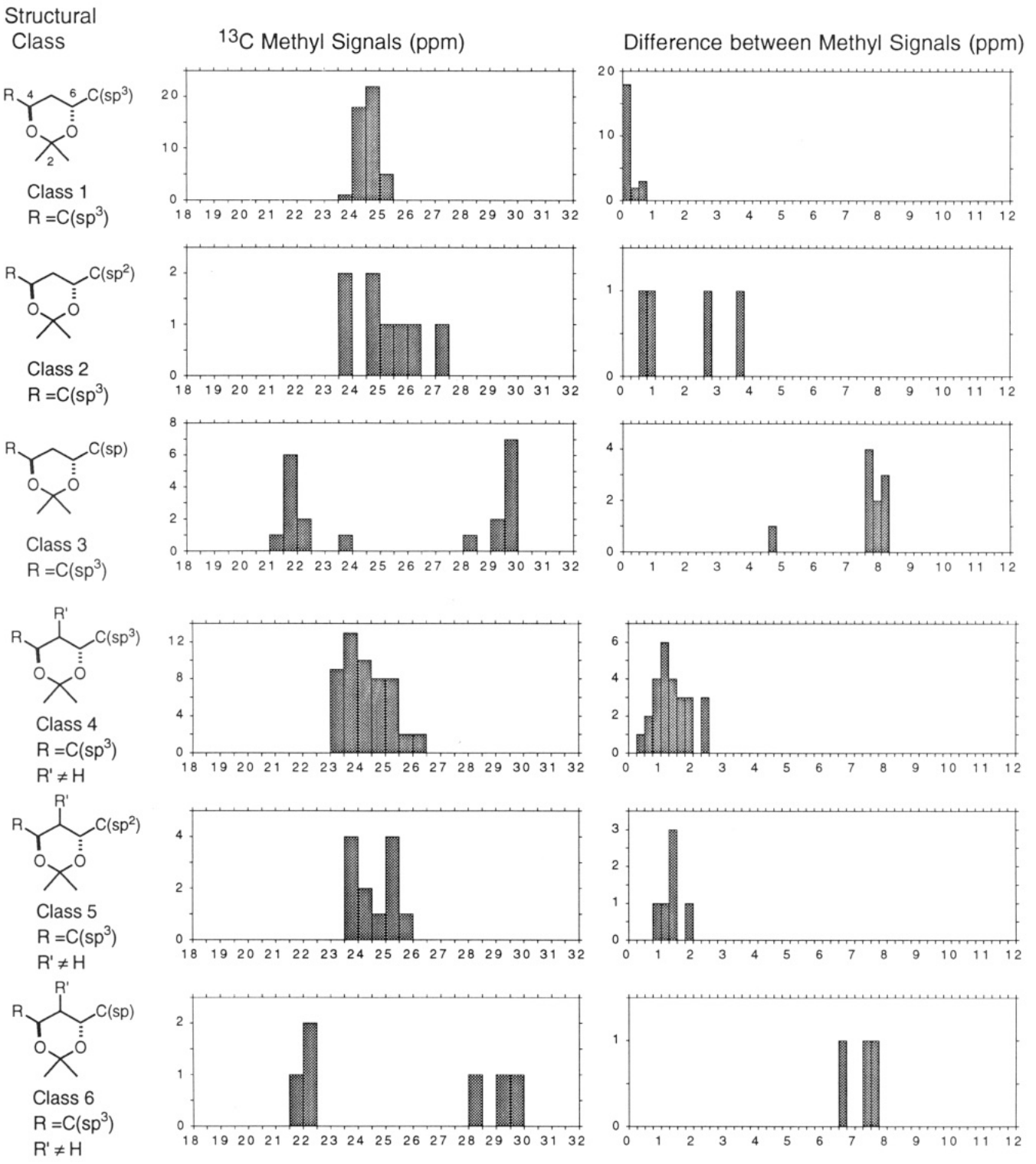


Figure 4. The C(2)-methyl ^{13}C chemical shift and difference histograms for classes 1–6 of *anti*-1,3-diol acetonides.

show the ^{13}C-methyl shift differences typical of the class 3 (sp) acetonides. One would expect an alkyne substituent to give a C(2)-methyl shift difference of ca. 5 ppm based on the single class 3 acetonides, but no examples were found. With the exception of nitriles, the C(2)-methyl ^{13}C chemical shift differences for each compound in class 4–6 can be used to assign the relative stereochemistry as syn (>9 ppm) or anti (<5 ppm).

Acetal Correlation with Stereochemistry. The correlation of C(2)-acetal ^{13}C chemical shift with stereochemistry is shown in Figure 5 and Table I. In our initial report we observed that the ^{13}C-acetal chemical shifts for *syn*-acetonides averages 98.5 ppm while the corresponding chemical shift in the *anti*-acetonides average 100.4 ppm. Evans pointed out that the ^{13}C-acetal chemical shift is much easier to identify than the acetonides C(2)-methyl signals, particularly in polypropionate-derived acetonides where the 20–30 ppm region of the ^{13}C spectrum is crowded with other methyl signals. The syn and anti ^{13}C acetal signals plotted in Figure 5 immediately demonstrate the limits of this strategy. The average values for syn (98.9 ppm) and anti (100.6 ppm) acetal ^{13}C peaks are different, but there is significant overlap between the two sets. For instance, if one assumed that any acetonide with an acetal

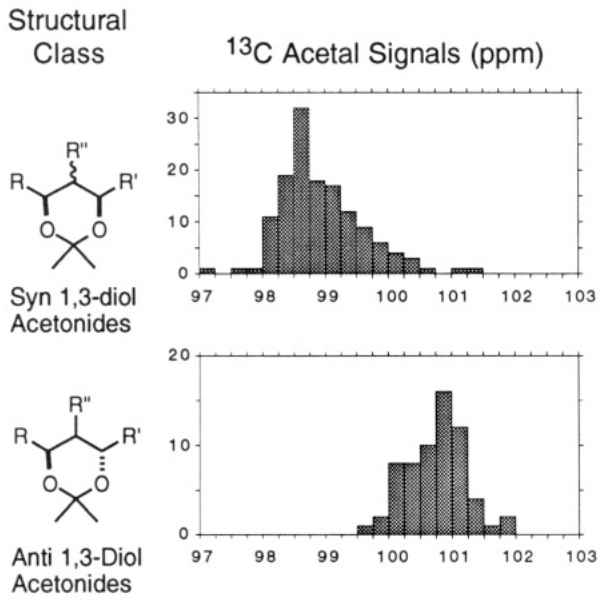


Figure 5. The C(2)-acetal ^{13}C chemical shift histograms for *syn*- and *anti*-1,3-diol acetonides.

peak below 100 ppm were syn and above 100 ppm were anti, then 10 of 145 or 6.9% of the syn acetals would be misassigned as anti and 3 of 76 or 4% of the anti isomers would be misassigned as syn. Poorly referenced ^{13}C NMR spectra may be responsible for some, but certainly not all of this overlap. For instance, the highest ppm acetal peaks for *syn*-acetonides come from a paper where a series of synthetic intermediates show normal acetal peak positions with the exception of these two acetonides, Figure 6.[17] Acetal ^{13}C chemical shifts are indicative of stereochemistry, but should be used with caution particularly in the region between 99.5 and 100.5 ppm.

Conclusions

Stereochemistry of 1,3-diol acetonides can be assigned based on the C(2)-methyl ^{13}C chemical shifts. The difference in chemical shift between the two C(2)-methyl groups is the most reliable indicator of stereochemistry, with all of the syn isomers showing a difference of >9 ppm and all of the anti isomers (except those bearing a nitrile substituent) showing a difference of <5 ppm. The chemical shift of the acetal carbon is also indicative of stereochemistry in 1,3-diol acetonides, with most acetals below 99.5 ppm having the syn stereochemistry and most acetals above 100.5 ppm having the anti stereochemistry. Assignments based on intermediate acetal values are less reliable and should be confirmed using C(2)-methyl chemical shift differences.

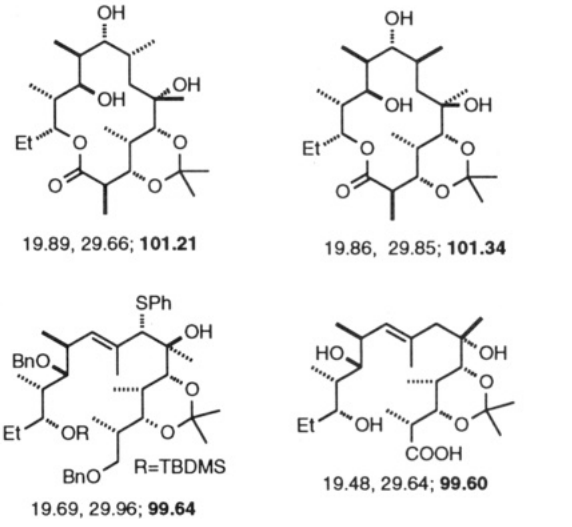


Figure 6. Two *syn*-acetonides that show anomalous C(2)-acetal chemical shifts and two closely related acetonides.[17]

Acknowledgment. Support has been provided by the Camille and Henry Dreyfus Teacher-Scholar program, the American Cyanamide Co., the Hoffmann-La Roche Co., and the National Science Foundation Presidential Young Investigator Program.

Supplementary Material Available: The structure of all acetonides along with the literature references and assigned chemical shifts (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910–23.