ORGANIC LETTERS

2006
Vol. 8, No. 13
2895−2898

Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol

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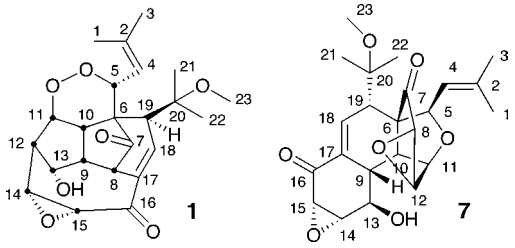
Received May 9, 2006

ABSTRACT



The structure of the natural product hexacyclinol was reassigned from endoperoxide 1 to the diepoxide 7 on the basis of calculated ^{13}C chemical shift data using HF/3-21G geometries and mPW1PW91/6-31G(d,p) GIAO NMR predictions. These predictions correlate very well with experimental data for three other highly oxygenated natural products, elisapterosin B, maoecrystal V, and elisabethin A. Hexacyclinol is proposed to arise from acid-catalyzed rearrangement of panepophenanthrin in the presence of methanol.

The structural assignment of new natural products, even with all of the 2D and 3D spectroscopic methods available today, is still a significant challenge. One underutilized tool is the prediction of NMR chemical shifts by modern computational methods.[1] In particular, ^{13}C chemical shifts are spread over a wide spectral range, are relatively insensitive to solvent shifts, and are sensitive to steric and electronic influences in the structure. Matching ^{13}C spectra is a good criterion for identity between two compounds, and the accurate prediction of ^{13}C chemical shifts could be a good test of compatibility between a proposed structure and the observed NMR data. A new structure is proposed for the natural product hexacyclinol on the basis of a predicted ^{13}C NMR shift.

Hexacyclinol was isolated in 2002 from *Panus rudis* strain HKI 0254.[2] The complex polycyclic structure **1** in Figure 1 was proposed on the basis of extensive 1D and 2D NMR data analysis. The proposed structure is a complex and highly strained endoperoxide that has attracted the attention of synthetic chemists. Recently, a provocative synthesis of hexacyclinol was reported,[3] and interest in the paper triggered my reexamination of the original structure assignment.

The accurate prediction of NMR chemical shifts and coupling constants has been a long-standing goal for chemists. As powerful computers have become widely available,

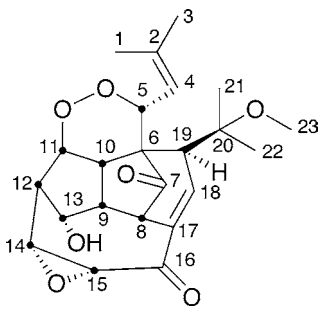


Figure 1. Proposed structure **1** of hexacyclinol.

(1) (a) Bagno, A. *Chem.−Eur. J.* **2001**, *7*, 1652−1661. (b) Meiler, J.; Sanli, E.; Junker, J.; Meusinger, R.; Lindel, T.; Will, M.; Maier, W.; Koeck, M. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 241−248.

(2) Schlegel, B.; Härtl, A.; Dahse, H.-M.; Gollmick, F. A.; Gräfe, U.; Dörfelt, H.; Kappes, B. *J. Antibiot.* **2002**, *55*, 814−817.

10.1021/ol0611346 CCC: $33.50 © 2006 American Chemical Society
Published on Web 06/01/2006

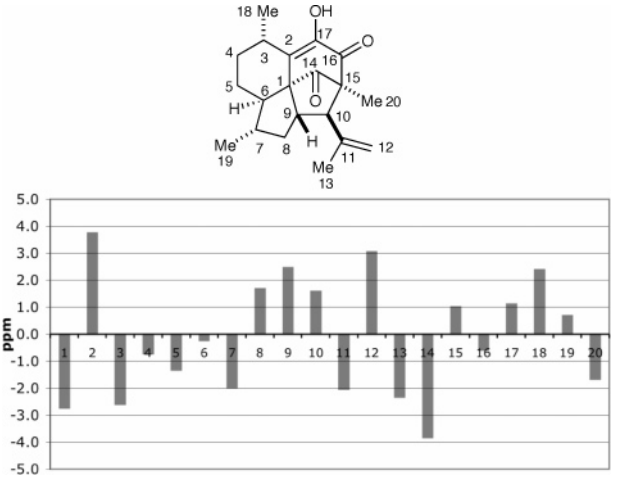


Figure 2. Structure and parts per million difference between calculated and experimental ^{13}C NMR shifts for elisapterosin B. The average $|\Delta\delta|$ was 1.9 ppm, and the maximum was 3.8 ppm.

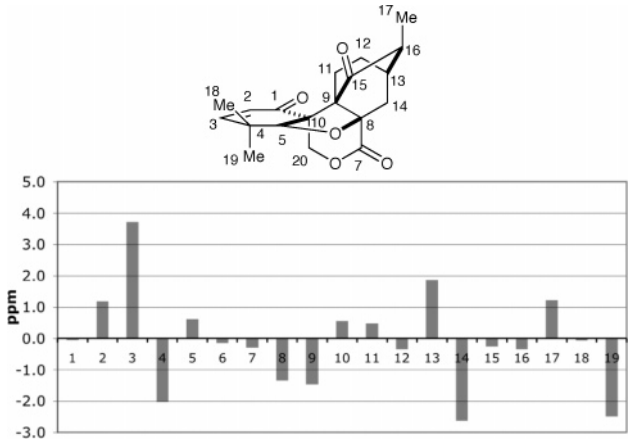


Figure 3. Structure and parts per million difference between calculated and experimental ^{13}C NMR shifts for maoecrystal V. (Note that there is no C6 in the structure; "6" is C7 and so forth.) The average $|\Delta\delta|$ was 1.2 ppm, and the maximum was 3.7 ppm.

the idea that such methods could be applied to complex structural problems of real interest to organic chemists has gained appeal.[1] Forsyth demonstrated that an inexpensive computational method could be applied to a diverse group of small organic molecules with excellent predictive power.[4] Forsyth used an MM3 geometry and evaluated the NMR shifts using GIAO with the B3LYP method and a specialized basis set. Using an empirical linear correlation, Forsyth was able to achieve an average ^{13}C chemical shift deviation of only 2.3 ppm across his data set. Bifulco refined this approach and applied it to more complex, nonpolar organic molecules.[5] He found that the HF/6-31G(d) method gave very good results with nonpolar compounds. Bifulco used an empirical linear correlation to optimize the match between experimental and predicted ^{13}C chemical shifts for each compound. The HF method returned good correlations for carbons with chemical shifts from 10 to 70 ppm but was less effective with carbon chemical shifts above 90 ppm. He extended the method to flexible molecules using a Boltzmann weighted average of the low-energy conformers.[5b] Bifulco later compared a very wide range of computational methods to identify those most effective for predicting ^{13}C chemical shifts using the GIAO method.[6]

Bifulco has advocated the use of predictive NMR ^{13}C shifts to differentiate between structural hypotheses. However, his approach had not been validated with highly oxygenated compounds, and the original HF method did not perform well with unsaturated structures. Hexacyclinol both is highly oxygenated and has enough unsaturation to be a poor candidate for the HF analysis. I decided to evaluate DFT methods with highly oxygenated terpenes to determine if they would be applicable to the hexacyclinol problem. Three diterpene natural products were selected for evaluation: elisapterosin B,[7] elisabethin A,[8] and maoecrystal V.[9] Each molecule is conformationally rigid, and its structural assignment was confirmed by X-ray analysis.

A method was selected to minimize computational cost and to maximize performance. I used a three-step analysis. First, the best minimum was identified using a Monte Carlo conformational search with the MMFF force field. This was the most critical step, as the best computed minimum did not always correspond to the experimentally observed minimum. Fortunately, the three rigid test cases presented no difficulties. Second, the minimum was calculated using the HF/3-21G method. This method leads to accurate structures with moderate computational costs. Third, the NMR chemical shifts were calculated with the GIAO option using the mPW1PW91/6-31G(d,p) DFT method. Bifulco found that this combination of DFT method and basis set performed well for predicting ^{13}C shifts.[6] The first step was carried out using Spartan 04,[10] and the next two steps were carried out using Gaussian 03.[11] The total CPU time for each molecule discussed in this paper was approximately 12 h using an inexpensive Linux computer.[12]

Each compound was analyzed separately. The calculated NMR shifts were analyzed first by subtracting the isotopic

(3) La Clair, J. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2769−2773.
(4) Forsyth, D. A.; Sebag, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 9483−9494.
(5) (a) Barone, G.; Gomez-Paloma, L.; Duca, D.; Silvestri, A.; Riccio, R.; Bifulco, G. *Chem.−Eur. J.* **2002**, *8*, 3233−3239. (b) Barone, G.; Duca, D.; Silvestri, A.; Gomez-Paloma, L.; Riccio, R.; Bifulco, G. *Chem.−Eur. J.* **2002**, *8*, 3240−3245. (c) Bifulco, G.; Bassarello, C.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2004**, *6*, 1025−1028.
(6) Cimino, P.; Gomez-Paloma, L.; Duca, D.; Riccio, R.; Bifulco, G. *Magn. Reson. Chem.* **2004**, *42*, S26−S33.
(7) Rodriguez, A. D.; Gonzalez, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083−7091.
(8) Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390−1398.
(9) Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M.-L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327−4330.
(10) *Spartan 04 for Macintosh*; Wavefunction Inc.: Irvine, CA.
(11) The Gaussian 03 reference is included in the Supporting Information.
(12) The linux computer incorporated a 3.06 GHz Pentium 4 processor.

shift for each carbon atom from the corresponding shift for TMS calculated using the same method (196.62 ppm). The experimental shifts were plotted against the calculated shift, and a least-squares fit line was determined.[13] The calculated shifts for each compound were corrected using the slope and intercept to give corrected ^{13}C shifts. The difference plots were determined by subtracting the corrected shifts from the experimental chemical shifts.

The results for elisapterosin B, maoecrystal V, and elisabethin A are shown in Figures 2−4. The chemical shift

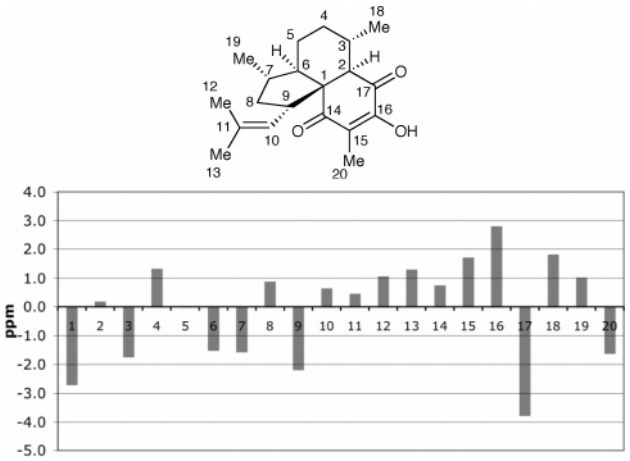


Figure 4. Structure and parts per million difference between calculated and experimental ^{13}C NMR shifts for elisabethin A. The average $|\Delta\delta|$ was 1.4 ppm, and the maximum was 3.8 ppm.

predictions are remarkably good. The average chemical shift differences for each compound are all under 2 ppm, and the maximum deviations are less than 5 ppm. The accuracy of these ^{13}C chemical shift predictions with highly oxygenated terpenes supports the use of this analysis to evaluate proposed natural product structures.

The reported structure of hexacyclinol was evaluated using the same predictive ^{13}C chemical shift analysis, and the results are shown in Figure 5. The correlation is very poor, with an average deviation of 6.8 ppm and with atoms 2, 5, 9, 11, and 19 showing differences of more than 10 ppm. Considering the excellent performance of the predictive model on similar natural products in Figures 2−4, I conclude that the proposed structure **1** of hexacyclinol is incorrect.

I set out to answer the obvious question, what is the correct structure of hexacyclinol? The key clue came with the realization that another natural product was isolated in the same year from a different strain of *Panus rudis*, panepophenanthrin (**2**).[14,15] The ring system bears no relationship with that proposed for hexacyclinol, but inspection reveals that it has almost the same set of functional groups and is of

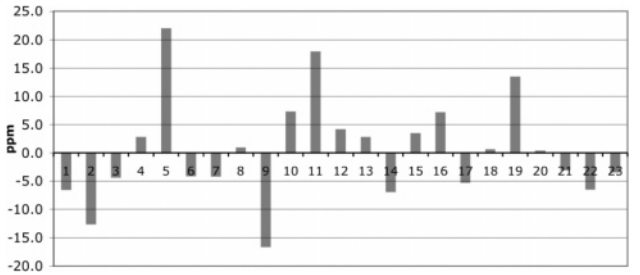
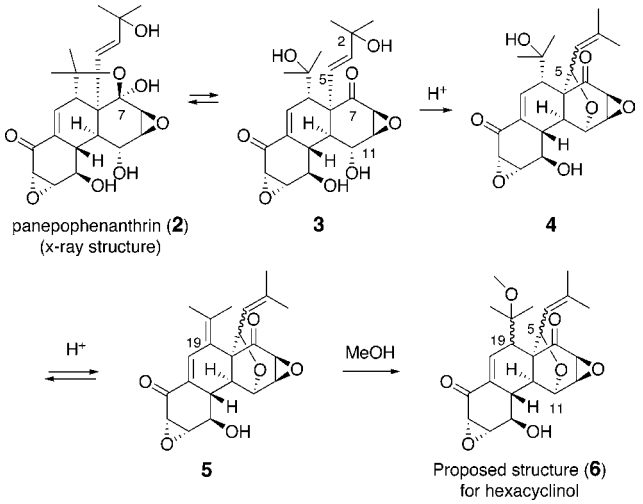


Figure 5. The plotted parts per million difference between calculated and experimental ^{13}C NMR shifts for the proposed structure of hexacyclinol (Figure 1). The average $|\Delta\delta|$ was 6.8 ppm, and the maximum was 22.0 ppm.

a similar molecular weight. Hexacyclinol incorporates an additional molecule of methanol. Both natural products were isolated by chromatography on silica gel with methanol, but if the Jena group used more acidic silica gel, one can envision a sequence from panepophenanthrin to produce an isolation artifact of the correct molecular weight for hexacyclinol. One possible pathway is illustrated in Scheme 1. Reversible

Scheme 1. Formation of Hexacyclinol **6** from Panepophenanthrin **2**



opening of the hemiacetal would generate **3**, which could cyclize onto the C11 alcohol by solvolysis of the tertiary allylic alcohol at C2.[16] Elimination of the C20 alcohol and addition of methanol to the dienone **5** could generate **6**. Both the C5 and C19 side chains could be introduced with either configuration, so four possible stereoisomers might result.

(13) The slopes (0.9540, 0.9604, 0.9681) and intercepts (2.11, 2.06, 1.84) for elisapterosin B, maoecrystal V, and elisabethin A, respectively, are all very similar. Full details can be found in the Supporting Information.

(14) Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, *65*, 1491−1493.

(15) Syntheses of panepophenanthrin: (a) Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987−2988. (b) Lei, X.; Johnson, R. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 3913−3917. (c) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 7683−7687. (d) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2004**, *45*, 1985−1987.

(16) The carbon numbers for structures **6** and **7** correspond to the carbon numbers reported for hexacyclinol, which simplifies comparison with the experimental NMR data.

In the characterization of hexacyclinol, the authors noted a strong NOE between C5 and C10 but no NOE between C19 and C5, which strongly suggests that the side chain at C5 is up and the side chain at C19 is down. Thus, isomer **7** (Figure 6) is the most probable structure of hexacyclinol.[17]

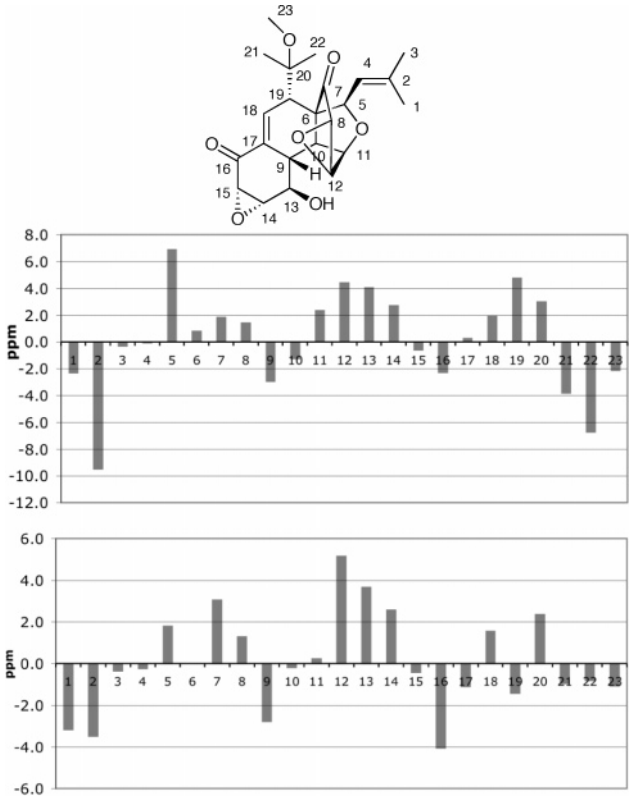


Figure 6. Structure and parts per million difference between calculated and experimental ^{13}C NMR shifts for two conformations of hexacyclinol **7**. The lowest-energy conformation (top) shows a H4−H5 dihedral angle of 65°, incompatible with the observed 10.1 Hz coupling constant. The conformation (bottom) shows a plausible 159° dihedral angle between H4 and H5. The average $|\Delta\delta|$ was 1.8 ppm, and the maximum was 5.8 ppm for the second conformation.

A problem immediately became apparent in the correlation of ^{13}C chemical shift data. The shift for C9 at 54.5 was almost 20 ppm too high compared with the predictions, and the C12 shift was low by a similar amount. The corresponding protons were close (reported as multiplets at 3.64 and 3.55 ppm),[18] and confusion in the HMQC assignments might have resulted in a misassignment. I have assumed this was the case and have exchanged the two carbon peaks for the analysis. The new analysis with compound **7** resulted in the chemical shift difference plot at the top of Figure 6. The correlation is very good with the exception of C2 and C5. The MMFF conformational search identified a minimum with the C4 alkene twisted out of the plane of the C5 hydrogen. The experimental data for hexacyclinol show a J_{4-5} coupling constant of 10.1 Hz, suggesting that the observed conformation should have a H4−H5 dihedral angle near 180°. A second conformation for compound **7** was located about 1.6 kcal/mol higher than the ground state (MMFF), and it was used to predict the ^{13}C chemical shift differences plotted in the lower graph in Figure 6. Now the correlation is very good. One atom shows a deviation of greater than 5 ppm, but the average deviation is less than 2 ppm, in keeping with the results from the models in Figures 2−4. Most likely, several conformations are populated in this molecule, and a Boltzmann average might provide an even better correlation. Unfortunately, MMFF calculations do not rank the different conformers accurately, so a Boltzmann analysis would not be useful. The ^{13}C chemical shifts predicted for structure **7** (Figure 6) correlate very well for those reported for hexacyclinol.

Structure **7** corresponds well with the experimental data for hexacyclinol. The IR bands at 1698 and 1700 cm^{-1} match the two six-membered ring ketones in **7** much better than the five-membered ring ketone in structure **1**. The ^{1}H and ^{13}C NMR data for 8 and 15 and for 12 and 14 are very similar, as one would expect from such similar environments. The coupling constants of J_{9-13} (9.5 Hz), J_{9-10} (7.8 Hz), and J_{10-11} (5.2 Hz) correspond well to the modeled dihedral angles (178°, 160°, and 52°, respectively). The HMBC and COSY data are consistent, with the proviso that several cross-peaks with very close ^{1}H NMR shifts (8 and 15, 12 and 14) may be incorrectly assigned. The NMR data for hexacyclinol are consistent with the proposed diepoxide structure **7**.[19]

I propose that the correct structure of hexacyclinol is diepoxide **7**, which may be an isolation artifact derived from exposure of panepophenanthrin to acid and methanol. The prediction of ^{13}C chemical shifts by calculation at HF/3-21G minima using DFT mPW1PW91/6-31G(d,p) is a very powerful tool for screening proposed structures and should be used more widely.

Acknowledgment. This work was supported by the National Institute of General Medical Sciences (GM-43854). I thank Christopher Anderson for helpful advice.

Supporting Information Available: Calculated geometries and predicted NMR shifts are presented for the compounds discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The ^{13}C chemical shift analysis was performed on the other three stereoisomers of **6**, but the correlations were inferior to that of compound **7**. Details are provided in the Supporting Information.

(18) These two peaks were reported at 3.65 and 3.62 ppm in the German patent: Schlegel, B.; Härtle, A.; Dahse, H.-M.; Gollmick, F. A.; Gräfe, U.; Dörfelt, H. DE 10213481 A1.

(19) Porco prepared a closely related structure (diketone **24** in ref 15b) as part of his elegant synthetic approach to panepophenanthrin. The spectra of Porco's compound **24** and hexacyclinol show the expected similarities. The C18 proton shows a 2.4 Hz allylic coupling with C9, as was observed for hexacyclinol.