

Structural Reassignment of Obtusallenes V, VI, and VII by GIAO-Based Density Functional Prediction

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Revised structures proposed previously for obtusallenes V–VII (5–7) have been confirmed on the basis of computed GIAO-DFT ^{13}C NMR chemical shifts.

Obtusallene I (**1**) (Figure 1) was reported in 1982 after isolation from the red algae *Laurencia obtusa* collected at Gökceada in the Aegean Sea, and the structure was elucidated by NMR and by X-ray crystallographic methods.¹ Subsequently, 10-bromoobtusallene (**1a**),² obtusallenes II (**2**) and III (**3**),³ obtusallene IV (**4**),^{4,5} and obtusallenes V–IX (**5–9**) have all been reported.⁶ One of us has recently proposed an internally self-consistent hypothesis for the biosynthesis of the obtusallene family where multiple electrophilic bromination events are invoked.^{7,8} The hypothesis correctly predicts the structures of obtusallenes I–IV (**1–4**), whose identities have been solved unambiguously by X-ray crystallography. Interestingly, while the published structures of obtusallenes V–VII—as solved by NMR spectroscopy—show a bromine atom at C-7 and a chlorine atom at C-13, the hypothesis predicts that these compounds should bear the bromine atom at C-13 and the chlorine atom at C-7. Herein, we report a comparison of the predicted and observed ^{13}C NMR spectra that support our structural reassignment.

Our study was inspired by Rychnovsky's report of such a comparison for hexacyclinol⁹ in which he used the protocol first described by Bifulco et al.¹⁰ and recalibrated for "highly oxygenated systems". This involved computing geometries at the HF/3-21G level and obtaining GIAO-derived ^{13}C shifts at the mPW1PW91/6-31G(d,p) level. This procedure gave a mean average deviation for $|\Delta\delta|$ of 6.8 ppm and a maximum deviation of 22.0 ppm between ^{13}C theory and experiment for the previous structural assignment,¹¹ but this improved to 1.8/5.8 ppm (after transposition of two peaks which Rychnovsky argued were mis-assigned) for a proposed revised structure. This analysis was subsequently confirmed by a crystal structure determination, even to the extent of confirming a proposed side-chain conformation.¹² We found that the use of geometries computed at the HF/3-21G level was an unnecessary restriction given the speed of current (2007) computers. mPW1PW91/6-31G(d,p)-optimized geometries followed by mPW1PW91/6-31G(d,p) NMR calculation, with a self-consistent reaction field correction for solvation (see Experimental Section), further improved the fit to 0.9/2.4 ppm, respectively, for the revised hexacyclinol structure. A side benefit was that the empirical corrections employed by Rychnovsky were no longer needed. Further tests established that the 6-31G(d,p) basis resulted in systematic errors of about 4–5 ppm for, for example, ester carbonyl carbons, an error the aug-cc-pVDZ basis largely eliminates, while retaining a similar quality of fit for other carbons. Our obtusallene results for both basis sets are reported here.

We selected initially obtusallenes **5** and **6** for study, since these are largely free of conformational ambiguities. Three

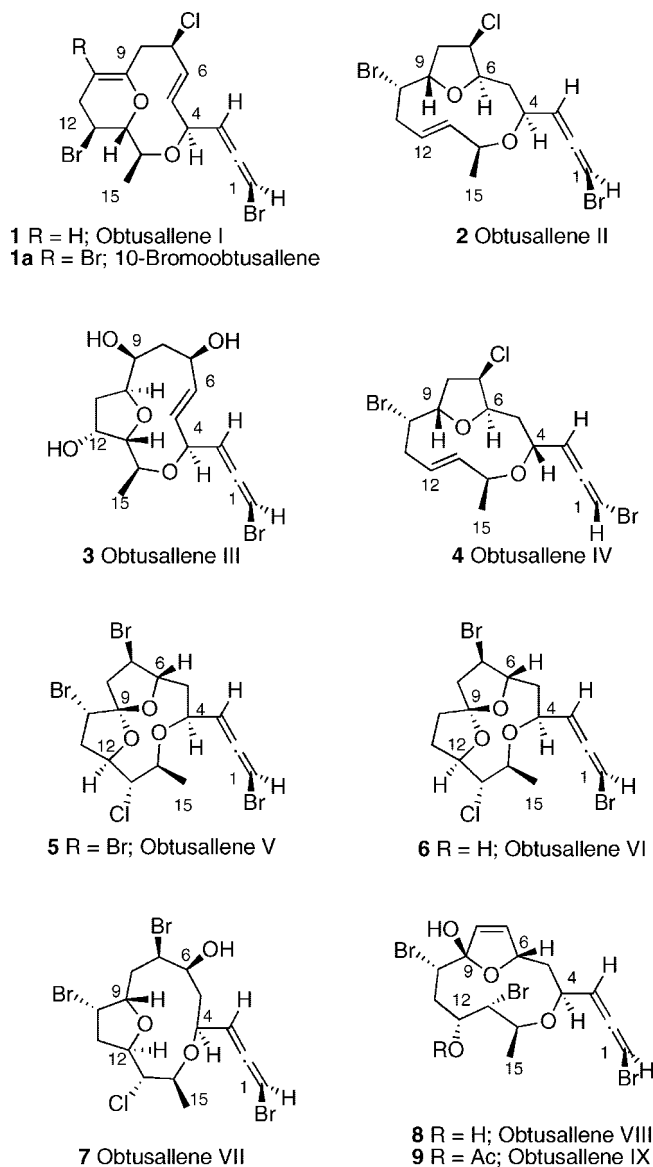


Figure 1. The obtusallene family.

possibilities were considered: (a) the original structures **5** and **6**; (b) the revised structures involving transposition of the halides on C-7 and C-13; and (c) transposition of both the halide and the ^{13}C NMR assigned shifts of the carbons. Another effect became immediately apparent; the predicted ^{13}C NMR shifts for

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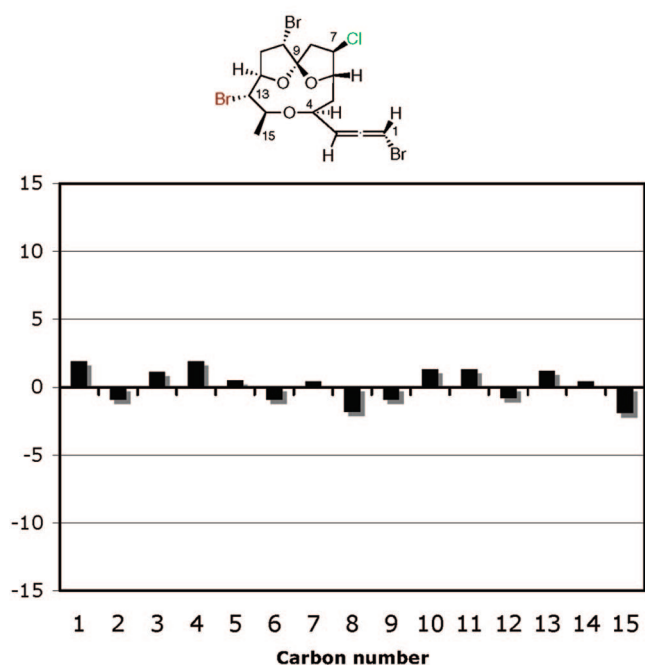
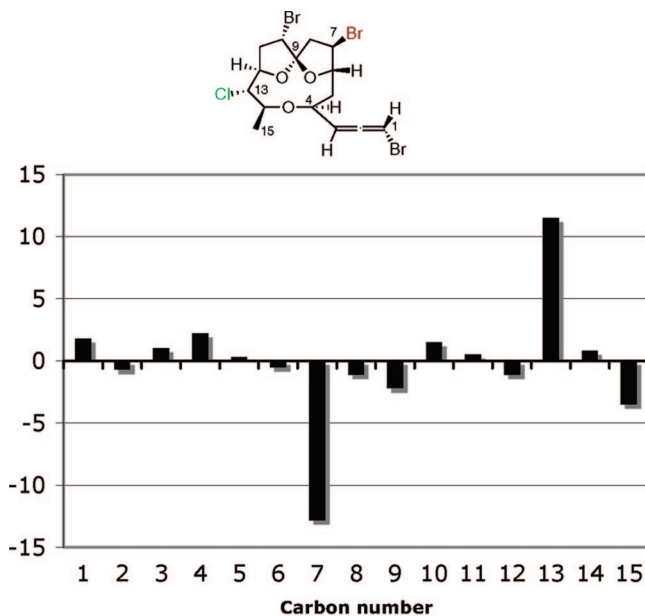


Figure 2. Deviation from calculated and observed ^{13}C NMR shifts for **5** (aug-cc-pVDZ basis set) for case (a) [top] and case (c) [bottom] (mean absolute, maximum, and standard deviations for cases (a)–(c): 2.77, 12.8 and 3.91; 1.43, 3.7, 0.83; 1.15, 1.9, 0.53 ppm, respectively).

the site of bromine attachment (e.g., C-10, C-13) were $\sim 12/14$ ppm too high (6-31G(d,p)/aug-cc-pVDZ bases, respectively). This is a well-known effect due to spin-orbit (SO) coupling and is exhibited increasingly by “heavy elements”.¹⁴ While calculation of the SO effect is possible using third-order perturbation theory,¹⁵ the corrections appear reasonably transferable for our purpose and are furthermore internally consistent with the bromine positioned at C-10 in **5**. We also chose a correction of ca. -3 ppm for chlorine attached to a sp^3 carbon.¹⁵

With these standard values applied, the results summarized in Web-enhanced-object (WEO) 1 were obtained and plotted in Figures 2 and 3 for cases (a) and (c). Case (c) reveals the best fits (mean deviations 1.15, 1.15; standard deviations 0.53, 0.94 ppm for **5** and **6**, respectively), in line with the errors obtained for hexacyclinol itself. Case (b) is only slightly inferior to (c) (mean

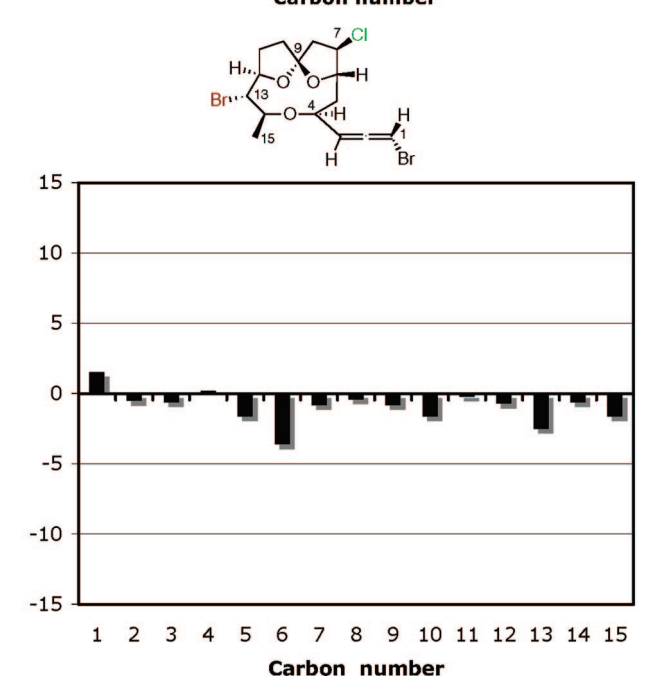
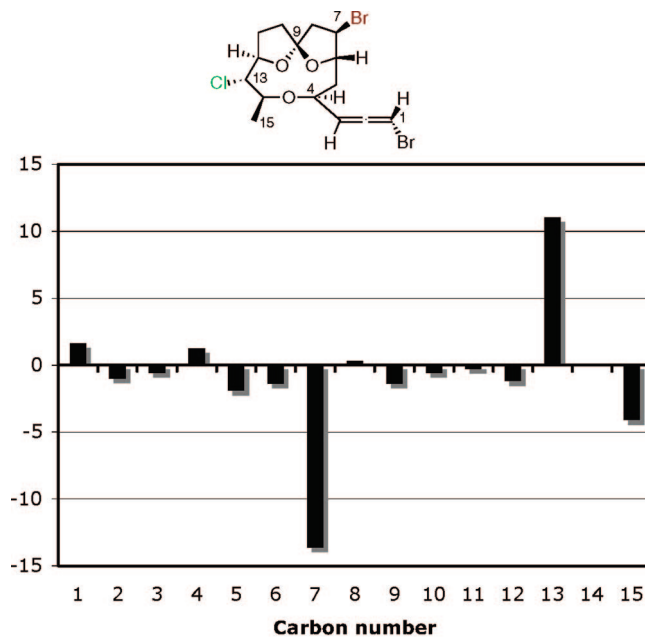


Figure 3. Deviation from calculated and observed ^{13}C NMR shifts for **6** (aug-cc-pVDZ basis set) for case (a) [top] and case (c) [bottom] (mean absolute, maximum, and rms deviations 2.68, 13.6, and 4.05; 1.15, 3.6, 0.94 ppm, respectively).

deviation 1.42, standard deviation 0.83 ppm) for **5** in particular, but more so for **6** (mean deviation 1.67, standard deviation 1.90 ppm). Case (a) shows a distinctly worse fit for the halogen-bearing centers for both **5** and **6**, reflected in larger mean deviations (2.77, 2.68 ppm) and particularly for the standard deviations (3.91, 4.05 ppm). We note in passing that the two possible configurations for the terminal $\text{C}=\text{C}-\text{Br}$ center give very similar fits and that this approach at its current level of accuracy cannot be used to distinguish stereochemistry at such centers.

A revised structure for obtusallene VII, also involving halide transposition, had also been previously proposed.⁷ Unfortunately, the ^{13}C NMR assigned shifts were reported for only some of the carbon atoms,⁶ and the system is also conformationally more uncertain. We investigated two conformations, differing in the H-bonding environment of the hydroxyl group (WEO 1). Again, the fit for one conformation of the revised structure (standard

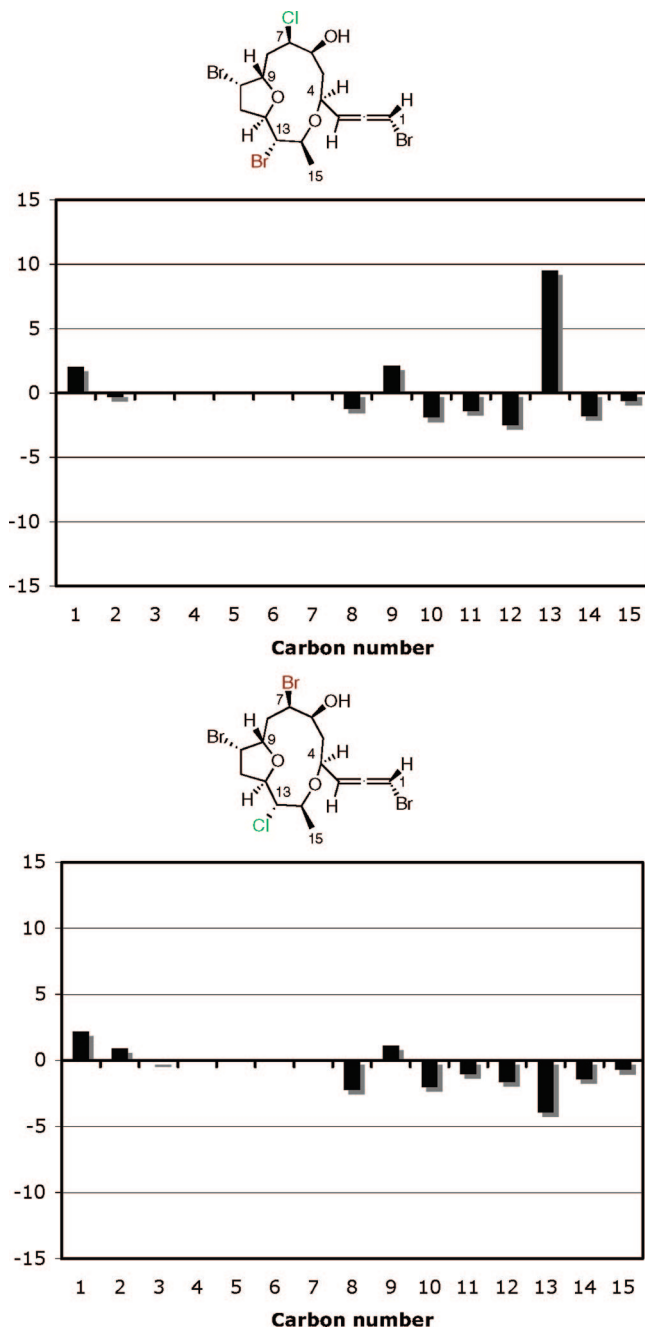


Figure 4. Deviation from calculated and observed ^{13}C NMR shifts for **7** (aug-cc-pVDZ basis set) for case (a) [top] and case (b) [bottom] (mean absolute, maximum, and standard deviations 1.55, 9.5 and 2.38; 1.55, 3.9, 1.02 ppm, respectively).

deviation 1.02 ppm) is better than for the original assignment (standard deviation 2.38 ppm) but not as conclusive (Figure 4).

In conclusion, we have provided supporting computational evidence for the original biosynthetically derived structural reassignments for obtusallenes **V** (**5**), **VI** (**6**), and **VII** (**7**), in which the halogens at C-7 and C-13 were transposed. We have additionally enhanced the original computational protocol to reduce the mean errors by around half to ~ 1.2 ppm (standard deviations < 1) and extended the protocol for dealing with systems containing “heavy elements” such as the heavier halogens.

Experimental Section

All calculations were performed using the Gaussian G03 program¹³ with the following keywords: mpw1pw91/basis opt (for geometry optimization) and mpw1pw91/basis NMR scrf(cpcm, solvent=chloroform) (for NMR calculation), where basis=6-31G(d,p) or aug-cc-pVDZ.

A Web enhanced object showing 3D coordinates for obtusallenes **V**, **VI**, and **VII** is available in the Web version of this article.

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Supporting Information Available: Excel spreadsheet for **5–7**, cases (a)–(c). This material is available free of charge via the Internet at <http://pubs.acs.org>. For entries in the institutional digital repository, see WEO 1.

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