Stereostructure Assignment of Flexible Five-Membered Rings by GIAO ^{13}C NMR Calculations: Prediction of the Stereochemistry of Elatenyne

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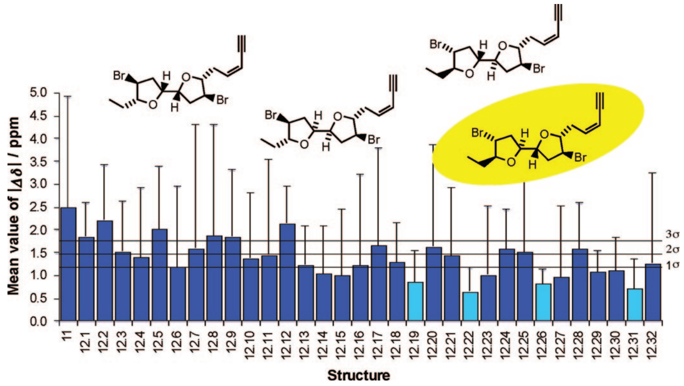

The stereochemistry of conformationally mobile five-membered rings is often hard to assign from NMR data, and [2,2′]bifuranyl systems are even more challenging. GIAO ^{13}C NMR chemical shifts have been calculated for a series of [2,2′]bifuranyl and pyranopyran species, taking into account their conformational flexibility using weighted averages of the data for all low energy conformers. We show that calculation of ^{13}C NMR chemical shifts using the geometries obtained using molecular mechanics greatly reduces the computational expense without a significant loss of accuracy, even in this demanding system. The results were sufficiently accurate to distinguish not only the pyran and furanyl isomers but also between all the diastereoisomeric forms. As a result of this validation, we predict the stereochemistry for the recently proposed revised structure of the natural product elatenyne, which contains a [2,2′]bifuranyl core.

Introduction

NMR spectroscopy is one of the most powerful and widely used techniques for establishing the structure of natural products. Nevertheless, it is not uncommon for a structural assignment to be incomplete or incorrect.[1] Establishing the stereochemistry of conformationally flexible compounds can be particularly challenging, and it may be necessary to resort to the time-consuming synthesis of all potential diastereoisomers to find which of these matches the natural product.[2]

Calculation has been used to aid the interpretation of NMR data for more than a decade.[3,4] Recently, there has been increasing interest in the use of ab initio NMR chemical shift prediction to aid structure assignment in difficult cases. The chemical shifts for all potential structures or diastereoisomers are calculated and compared to the experimental values. This technique has been pioneered by Bifulco and co-workers[5] and has since played key roles in such cases as Rychnovsky's

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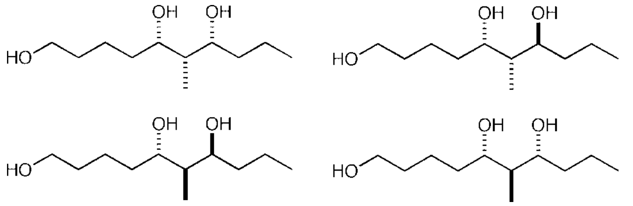

FIGURE 1. Bifulco's flexible molecules.

revision of the structure of hexacyclinol,[6] Nicolaou's investigation of the stereochemistry of maitotoxin,[7] and the stereostructural assignment of several natural products including aplidinones A−C,[8] gloriosaols A and B,[9] kadlongilactones D and F,[10] artarborol,[11] and the obtusallenes.[12] There have also been several studies investigating the effects of using different theory levels and basis sets for both the NMR shift calculation itself and for obtaining the optimized geometry on which the NMR shifts are calculated.[13–17] The area has been recently reviewed.[18]

Most of these studies have tended to focus on molecules that are conformationally rigid, so that the only important conformer is the global minimum. For more flexible systems, Bifulco has calculated the NMR chemical shift as a Boltzmann-weighted average of the chemical shifts obtained for all low energy conformers.[19] He has demonstrated the power of this approach to predict stereochemistry by applying it to the four possible diastereoisomers of a model system consisting of an open chain with three adjacent stereocenters (Figure 1).[19] Despite the flexibility of the open-chain system, Boltzmann weighting factors suggested that more than 90% of the conformational freedom was described by the lowest two or three conformations. There have been very few other investigations into the use of NMR chemical shift prediction to determine stereochemistry in conformationally flexible systems. It is noteworthy that the recent review[18] includes few examples of five-membered rings and those that are mentioned are conformationally restricted by being fused to other ring systems or through rigid functional groups.

Five-membered rings, in general, and the [2,2′]bifuranyl system **1**, in particular, are examples of highly flexible systems. Not only is there free rotation about the central bond in **1**, but each of the THF rings can adopt many envelope and twist conformations.[20] If there are substituents on the rings, as is the case with the bifuranyl acetals (**8−10**), then the number of degrees of freedom is increased further. The large number of accessible conformers separated by low energy barriers makes these molecules particularly challenging to study computationally. Despite the challenge, however, such systems play important roles in natural products, and recent studies have demonstrated how hard it is to distinguish the structures experimentally.[21]

Careful analysis of the experimentally determined ^{13}C NMR spectra has demonstrated that it is usually possible to distinguish a bifuranyl, such as **1** or **2**, from the isomeric pyranopyran, **3** or **4**, structures which have the same carbon and proton connectivity as the bifuranyls, by considering the chemical shift of central carbons (2/2′ or 4a/8a).[21] In this study, we show that it is possible to distinguish between different diastereoisomers of a bifuranyl using GIAO ^{13}C NMR chemical shift calculation.

Computational Methods

To obtain accurate geometries of all low energy conformations in as short a time as possible, accurate ab initio geometry optimization was coupled with extensive conformational searches at the molecular mechanics level. All conformational searches were performed using Macromodel[23] (Version 9.1) interfaced to the Maestro (Version 7.5.112) program.[24] In all cases, the MCMM method[25] with the standard MM2* force field[26] was used in the gas phase to identify structures for subsequent ab initio optimization. In most cases, a search of 1000 steps was sufficient to find all low energy conformers at least 5−10 times, thus giving confidence that all the important conformers had been found. In a few cases, including the diastereoisomers of the revised structure of elatenyne **12**, for which the number of conformers was larger, 3000 steps were used.

All quantum mechanical calculations were carried out using Jaguar[27] (version 6.5, release 112) employing the widely used DFT method B3LYP.[28] This method has been previously shown to perform well in both the geometry optimization stage and the NMR shielding tensor calculation stage of NMR chemical shift prediction,[14–16] although we note that empirically optimized functionals such as those of Cramer may perhaps have yielded even better results.[17] To check that using a different functional would not have significantly changed the results or overall conclusions, we also calculated as a test example the NMR shifts of bifuranyl **8** using the mPW1PW91 functional; this calculation employed the B3LYP-optimized geometries already found. The empirically scaled

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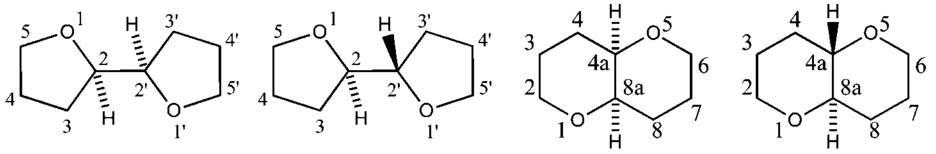
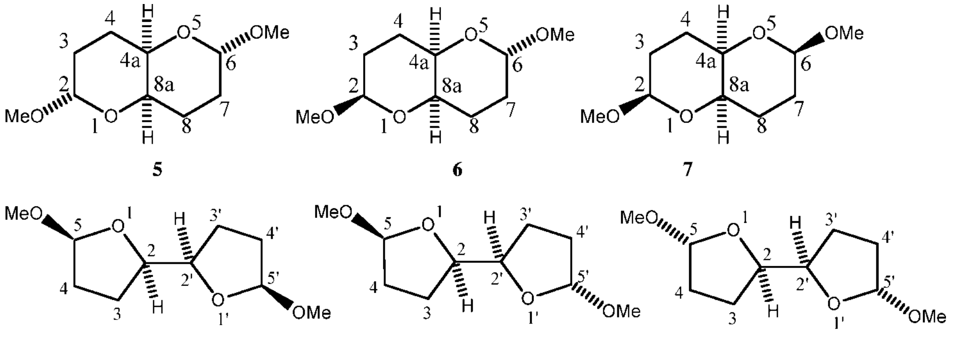


FIGURE 2. [2,2′]Bifuranyls and pyrano[3,2-*b*]pyrans.



5 **6** **7**

8 **9** **10**

FIGURE 3. Bifuranyl- and pyranopyran acetals.

calculated shifts (see eq 3) were indeed similar, with a mean absolute difference in δ_{scaled} between the two functionals of only 0.3 ppm. The 6-31G** basis set was employed on all atoms except bromine for which the LANL2DZ[30] basis set was used; 6-31G** has been recommended for NMR chemical shift calculation by Bifulco.[13] The GIAO method,[31] as implemented in Jaguar, was used for all NMR chemical shift calculations.[32]

Since the conditions under which the NMR experiment is performed will affect the conformational equilibria, the effects of solvation were described using a continuum dielectric model of $CHCl_3$ (dielectric constant = 4.81, mol wt = 119.378, density = 1.4788 g cm^{-3}).[33] Solvent energies were calculated using the Poisson−Boltzmann solver as implemented by Jaguar.[34] Test calculations (using structures **1**−**4**) showed that the gas- and solution-phase optimized geometries of all low energy conformers were essentially identical (average rmsd was only 0.0451 Å), but the ordering of the conformer energies was different in the gas and solution phase. Fortunately, the solution-phase energies (needed to calculate relative populations of each conformer) were well reproduced by a single-point solvent calculation on the gas-phase structures, thus avoiding the need for computationally expensive optimizations in solvent. For species **1**−**4**, the NMR chemical shifts calculated using the gas-phase structures with energies taken from a single-point solvent calculation differed from those calculated on the structures fully optimized in solvent by an average of only 0.2 ppm. The former approach was therefore adopted in the interests of reducing computer time. We note that, strictly speaking, relative Gibbs free energies (which include the effects of entropy) should be used for calculating the relative populations of the different conformers. However, we do not expect the different conformers of the molecules under study to have greatly different entropies and so considered the savings in computer time gained by not calculating free energies to be worth making the approximation of using relative energies instead of relative free energies.

To calculate the NMR chemical shifts for a particular species, low energy conformers identified in MCMM searches were further optimized at the B3LYP/6-31G** level (in the gas phase). Only molecular mechanics conformers within 20 kJ mol^{-1} of the global minimum were selected for ab initio optimization, since higher energy conformers have a relative population of less than 0.05% at 298 K. Even if the final ab initio energies differed from the molecular mechanics ones by several kJ mol^{-1} these structures would still have a relative population of $<$1%. For the diastereoisomers of elatenyne **12**, even this restriction resulted in a prohibitively large number of conformers, and therefore, a limit of 10 kJ mol^{-1} was used. Analysis of previous results showed that the correlation between the initial MM2* energies and the final ab initio solvent single-point energies was not particularly good. However, only a very few conformers with relative molecular mechanics energy $>$10 kJ mol^{-1} subsequently minimized to a conformer with relative ab initio energy less than 6 kJ mol^{-1} (representing a population of at most 9% at 298 K and significantly less if there were several low energy conformers besides the global minimum, as was usually the case).

Vibrational mode analysis of the ab initio structures was carried out for all identified conformers of structures **1**−**10**. The absence of imaginary frequencies confirmed that they were all true minima, and not transition structures. This gave us confidence that our conformational search methods would similarly identify only minima for the diastereoisomers of elatenyne **12**, where the large number of conformers precluded a time-consuming vibrational mode analysis for all structures.

NMR shielding constants were calculated at the B3LYP/6-31G** level of theory for the ab initio optimized structures. Shielding constants were first averaged over symmetry-related positions in each conformer (for species with C_2 or C_i symmetry) and then subjected to Boltzmann averaging over all accessible conformers according to

$$\bar{\sigma}^x = \frac{\sum_{\text{confSi}} \sigma_i^x g_i \exp(-E_i/RT)}{\sum_{\text{confSi}} g_i \exp(-E_i/RT)} \qquad (1)$$

where $\bar{\sigma}^x$ is the Boltzmann-averaged calculated shielding constant for carbon x, σ_i^x is the shielding constant for carbon x in conformer

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i, and E_i is the potential energy of conformer i (relative to the global minimum) in kJ mol^{-1}, obtained from a single-point solvent calculation on the gas-phase structures as discussed previously. R is the molar gas constant (8.3145 J K^{-1} mol^{-1}), g_i is the degeneracy of conformer i, and the temperature T was taken as 298 K.

Chemical shifts were then calculated according to

$$\delta^x_{\text{calc}} = \frac{\sigma_{\text{ref}} - \bar{\sigma}^x}{1 - 10^{-6}\sigma_{\text{ref}}} \qquad (2)$$

where $\delta^x{}_{\text{calc}}$ is the calculated chemical shift for carbon x (in ppm), $\bar{\sigma}^x$ is the shielding constant for carbon x as calculated above (again in ppm) and σ_{ref} is the shielding constant for the carbons in tetramethylsilane (TMS). This last value was obtained by minimizing TMS in $CHCl_3$ solvent at the B3LYP/6-31G** level and calculating the shielding constants for this structure again at the B3LYP/6-31G** level; the value obtained was $\sigma_{\text{ref}} = 191.68929$ ppm.

In cases for which experimental data was available, empirical scaling[5] was carried out according to

$$\delta^x_{\text{scaled}} = \frac{\delta^x_{\text{calc}} - \text{intercept}}{\text{slope}} \qquad (3)$$

where slope and intercept are the slope and intercept resulting from a regression calculation on a plot of δ_{calc} against δ_{exp}.

Results and Discussion

1. Bifuranyl and Pyranopyran Acetals. Unassigned experimental NMR chemical shifts are available for five of the species **5**−**10**,[21] which equilibrate with each other in acidic methanol. This set of isomeric compounds, therefore, provides a convenient system to test the ability of the NMR chemical shift calculation method to distinguish between similar structures where a thorough treatment of conformational flexibility is vital (Table 1). The NMR chemical shifts for these structures were calculated as described in Computational Methods. Is it is possible to assign each experimental spectrum to a structure?

To quantify the agreement between a given pair of calculated and experimental shifts, Bifulco[19] has compared (i) the linear correlation coefficients r between the all pairs of calculated and experimental chemical shifts and (ii) the sum, or the average, of the absolute differences between the empirically scaled calculated chemical shifts and the experimental chemical shifts. These differences are referred to as $\Delta\delta$. The scaling process, outlined in the computational details, is used to remove systematic errors in the calculation.

(i) Correlation Coefficients. Values of the correlation coefficients for all pairs of experimental and calculated data are given in Table 2. From these data, we might assign spectra A and B to the pyranopyrans **5** and **6**, respectively, and spectra C, D, and E to the bifuranyls **10**, **9**, and **8**, respectively. We can make this assignment with some confidence because five of the six spectra are available, and we know that they correspond to five of the six structures **5**−**10**. If we had, for example, just the experimental data for D (plus all of the calculated data), an assignment to **9** would be much less convincing, although it would be possible to rule out the pyranopyran structures **5**−**7** with reasonable confidence.

(ii) Chemical Shift Differences $\Delta\delta$. The mean and maximum values of $|\Delta\delta|$ for each possible assignment are plotted in Figure 4.

TABLE 1. Illustration of the Conformational Flexibility of Bifuranyls 8−10

compd	5	6	7	8	9	10
% of the total population made up by the global minimum (at 298 K)	98.8	96.6	85.4	57.6	32.1	31.6
no. of conformers required to make up 95% of the population (at 298 K)	1	1	3	4	5	7

TABLE 2. Values of the Correlation Coefficient for All Combinations of Experimental and Calculated Data

	calculated data set					
experimental data set	5	6	7	8	9	10
A	**0.9989**	0.9946	0.9947	0.9633	0.9688	0.9740
B	0.9962	**0.9989**	0.9943	0.9692	0.9743	0.9784
C	0.9870	0.9895	0.9949	0.9968	0.9981	**0.9988**
D	0.9812	0.9855	0.9910	0.9986	**0.9991**	0.9989
E	0.9746	0.9792	0.9863	**0.9994**	0.9990	0.9980

TABLE 3. Illustration of the Conformational Flexibility of 1and 2

compd	1	2	3	4
% of the total population made up by the global minimum at 298 K	37.7	33.4	100	100
no. of conformers required to make up 95% of the population at 298 K	6	6	1	1

From Figure 4, spectra A and B can be assigned with reasonable confidence to pyranopyrans **5** and **6** respectively, using either the mean or maximum values of $|\Delta\delta|$. C−E can be assigned to the bifuranyls **8**−**10** with the best matches for the means being C with **10**, D with **9**, and E with **8**. These are the same assignments as were made using the correlation coefficients (Table 2). Use of the maximum values of $|\Delta\delta|$ gives less clear assignments. A and B can still be assigned to **5** and **6**, but the differences between **8**, **9**, and **10** are much less.

A closer examination of the data showed that most variation for the bifuranyls was at carbons C2 and C5, with values of $\Delta\delta$ for the other positions being roughly the same, regardless of which combination of experimental and calculated data was compared. The roughly constant values of $\Delta\delta$ contributed by these latter resonances to the mean of $|\Delta\delta|$ will tend to obscure the variation contributed by C2 and C5. Considering only the data for C2/C2′ and C5′C5′ therefore makes the assignment of bifuranyl C to **10**, D to **9**, and E to **8** much clearer (Figure 5). Of course, eliminating unimportant resonances from the analysis requires one to be able to assign the resonances. This can be readily achieved in most cases using two-dimensional NMR methods. In the case of bifuranyls **8**−**10** such data were not available, but identification of C2/C2′ and C5/C5′ as by far the most downfield signals was straightforward.

Are the assignments suggested above (A = **5**, B = **6**, C = **10**, D = **9**, *E* = **8**) correct? One can assign spectra A and B to pyranopyrans and C−E to bifuranyls on the basis of the diagnostic C2/C2′ or C4a/C8a chemical shift.[22] Spectra B and D can be assigned to the asymmetric species **6** and **9** on the basis of the number of distinct resonances. Further, one would expect that the pyranopyran that is not detected in the equilibrium should be **7**, since this should be the thermodynamically least stable of the three pyranopyrans. Pyranopyran **5** has a particularly low energy conformation accessible to it that benefits both from having the ring oxygens gauche to each other (the

TABLE 4. Thirty-two Diastereoisomers of Elatenyne 12[a]

structure	config	% of total population made up by the global minimum (at 298 K)	no. of conformers to make up 95% of the total population (at 298 K)	structure	config	% of total population made up by the global minimum (at 298 K)	no. of conformers to make up 95% of the total population (at 298 K)
12.1	*RRRRRR*	49.7	6	**12.17**	*RSRRRR*	20.6	20
12.2	*RRRRRS*	51.8	4	**12.18**	*RSRRRS*	41.2	5
12.3	*RRRRSR*	27.7	8	**12.19**	*RSRRSR*	26.7	12
12.4	*RRRRSS*	30.5	7	**12.20**	*RSRRSS*	25.5	10
12.5	*RRRSRR*	18.3	14	**12.21**	*RSRSRR*	20.6	28
12.6	*RRRSRS*	16.2	26	**12.22**	*RSRSRS*	12.2	43
12.7	*RRRSSR*	26.7	13	**12.23**	*RSRSSR*	22.4	21
12.8	*RRRSSS*	35.2	8	**12.24**	*RSRSSS*	17.1	29
12.9	*RRSRRR*	17.1	15	**12.25**	*RSSRRR*	25.5	23
12.10	*RRSRRS*	25.0	18	**12.26**	*RSSRRS*	17.5	23
12.11	*RRSRSR*	12.5	33	**12.27**	*RSSRSR*	9.3	37
12.12	*RRSRSS*	25.6	15	**12.28**	*RSSRSS*	21.3	20
12.13	*RRSSRR*	29.9	5	**12.29**	*RSSSRR*	26.9	7
12.14	*RRSSRS*	24.8	13	**12.30**	*RSSSRS*	42.6	15
12.15	*RRSSSR*	39.8	5	**12.31**	*RSSSSR*	42.7	7
12.16	*RRSSSS*	18.6	9	**12.32**	*RSSSSS*	15.1	17

[a] The stereochemistry is given in the form (6*R*,7*R*,9*R*,10*R*,11*R*,13*R*,14*R*).

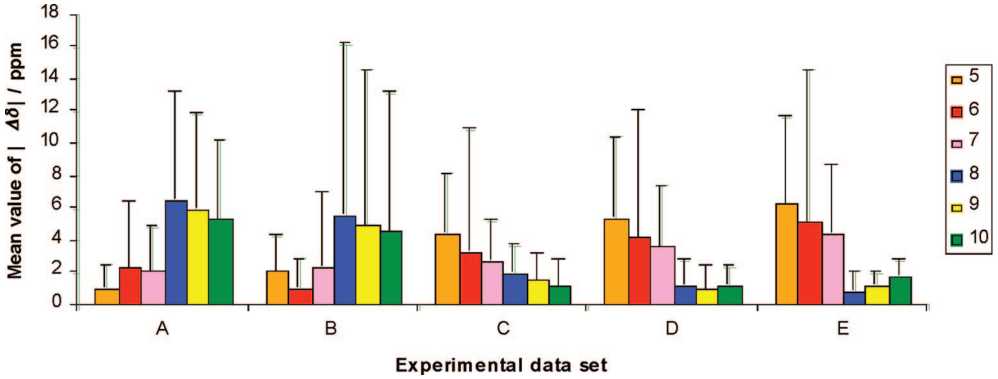

FIGURE 4. Mean and maximum values of |Δδ| for the possible assignments of each set of experimental data. Means: bars. Maxima: lines. The smallest bars are the best matches.

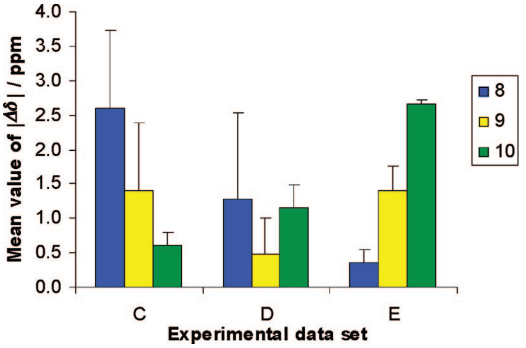

FIGURE 5. Mean and maximum values of |Δδ| for the possible assignments of the bifuranyls: carbons C2/C2′ and C5/C5′ only. Means: bars. Maxima: lines. The smallest bars are the best matches.

gauche effect[35]) and the two OMe groups axial (the anomeric effect[35]). By contrast, **7** cannot adopt such a low energy conformation, since if the ring oxygens are gauche both of the OMe groups must necessarily be equatorial (for **6** one OMe group can still give be axial to give anomeric stabilization). The calculated energies of these species (B3LYP/6-31G**) confirmed the trend in stabilities. For **5**−**7**, the most stable conformer (representing at least 85% of the population at 298 K in each case, see Table 1) had the ring oxygens gauche to each other and the order of stability was **5** (lowest energy) followed by **6** and then **7** (highest energy). Taking all of these considerations together, spectrum A should correspond to pyranopyran **5**, B to the asymmetric pyranopyran **6**, D to the asymmetric bifuranyl **9**, and C and E in some order to bifuranyls **8** and **10**.

These additional considerations confirm the assignments which were made using the NMR chemical shift calculations.

The same approach can be applied to species **1**−**4** (the ether analogues of **5**−**10**). Unfortunately, the experimental data for **4**[36] were acquired in benzene rather than chloroform as was the case for **1**−**3**.[37,38] However, we do not expect that carbon NMR shifts will be significantly different in these two solvents (both of which are nonpolar), especially as **4** is a rigid molecule with no conformational equilibria to be affected by the solvent. Hence, we felt that it was reasonable to include pyranopyran **4** in our investigation.

The results (Table 3, Figure 6) were not quite as encouraging as for the acetals **5**−**10**. The method could readily identify pyranopyran **3** and (with somewhat less confidence) pyranopyran

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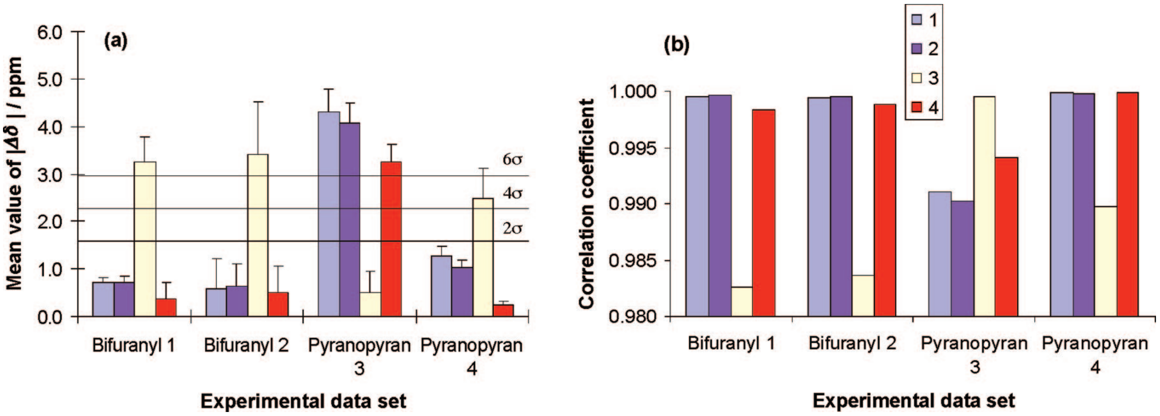

FIGURE 6. (a) Mean and maximum values of |Δ*δ*|. Mean (bars) and maximum (lines) values of |Δ*δ*|. (b) Correlation coefficients for the possible assignments of experimental data for species **1**−**4**. The highest bars are the best matches.

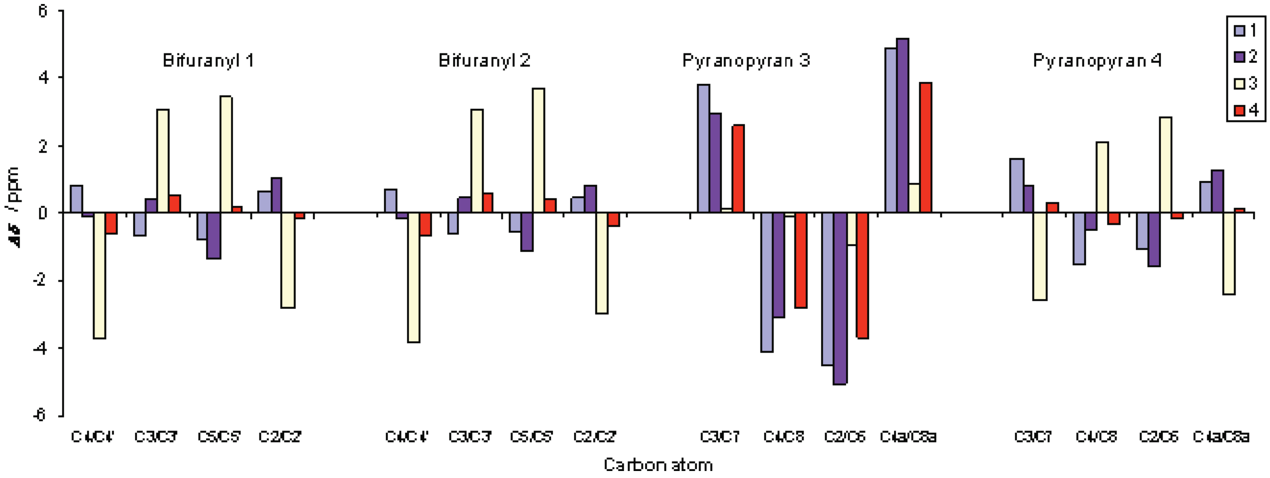

FIGURE 7. Values of Δ*δ* for the possible assignments of experimental data for species **1**−**4**.

4, but neither the correlation coefficients nor the mean or maximum values of |Δ*δ*| allow the assignment of the bifuranyl experimental data to a particular structure. Consideration of the individual values of |Δ*δ*| did not help in this case either (Figure 7).

Why was NMR chemical shift calculation successful for the bifuranyl acetals **8**−**10** but not for the bifuranyls **1** and **2**? The fundamental problem with distinguishing **1** and **2** arises because their experimental NMR chemical shifts are very similar. No resonance differs by more than 0.7 ppm between the two diastereoisomers, and such tiny differences cannot be reproduced by the computational method. By contrast, the spectra of bifuranyl acetals **8**−**10** contain resonances differing by up to 4.6 ppm.[21]

How large a difference is needed for there to be a good chance of distinguishing between structures? To answer this question we investigated values of |Δ*δ*| that are typically obtained (using our methodology) for a correct structure. Examination of the results from calculations on a range of species for which experimental data are available (i.e., **1**−**6**, **8**−**10** and also the originally proposed pyranopyran structures for elatenyne **11**[21,39] and a similar enyne from *Laurencia majuscula*[21,40]) showed that, for a correct structure, a given value of |Δ*δ*| has an expectation value of 0.91 ppm. Clearly, we have little chance of distinguishing between structures such as **1** and **2** that differ by less than 0.7 ppm if the accuracy of our calculations is only 0.9 ppm.

In this example, we had all the experimental data, and so we knew that this was a tough problem before starting the calculation. Had we had a spectrum for just one of the structures, we would still have generated calculated spectra for all the competing systems, and this calculation would also demonstrate that the spectra were all very similar. However, we would like to be able to say whether or not they are too similar for us to draw firm conclusions. From the aforementioned analysis of |Δ*δ*| values we obtained not only the expectation value of |Δ*δ*| (0.91 ppm) but also the standard deviation of |Δ*δ*| (0.68 ppm). This is the standard deviation in a single value of |Δ*δ*|; if we are considering the mean value of |Δ*δ*| for a structure with n carbons the value we should use for the standard deviation is $0.68/\sqrt{n}$ ppm. Hence, if we are comparing a particular set of calculated data with a set of experimental data and find that the mean value of |Δ*δ*| deviates from the 0.91 ppm expected for a correct structure by several times the standard deviation $0.68/\sqrt{n}$ ppm, this would suggest that the structure in question is not correct.

Based on this idea, horizontal lines at two, four, and six standard deviations above the expectation value have been drawn in Figure 6a. If, for example, we had just the experimental structure for bifuranyl **1**, we could just generate the first four bars in Figure 6a. We could use the horizontal lines to conclude that the pyranopyran **3** may be safely ruled out as a potential

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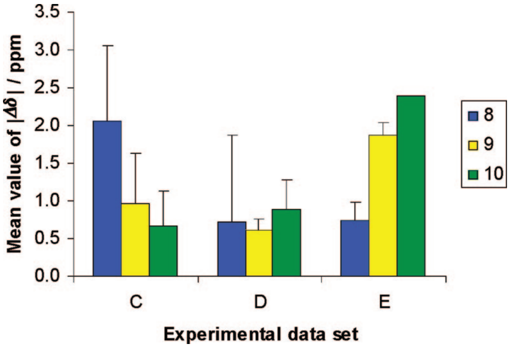

FIGURE 8. Using MMFF-optimized geometries for assigning the bifuranyl acetals: mean and maximum values of $|\Delta\delta|$ using just C2/C2′ and C5/C5′. Means: bars. Maxima: lines. The smallest bars are the best matches.

structure, but that all of the other three candidates are reasonable possibilities. Therefore, the assignment is uncertain.

2. NMR Chemical Shift Calculation Is Robust to Computationally Inexpensive Geometry Optimization. The calculation of NMR chemical shifts for a large number of potential diastereoisomers of a molecule such as the revised structure for elatenyne **12** can involve a significant amount of computer time. We therefore investigated whether NMR properties could be calculated in single-point ab initio calculations on the molecular mechanics geometries, eliminating the lengthy ab initio optimization step. This was done for species **1**−**6**, **8**−**10**, and also the originally proposed pyranopyran structures for elatenyne[21,39] and the similar *L. majuscula* enyne[21,40] (all species for which experimental data are available) using (in separate experiments) MM2*- and MMFF[44]-optimized geometries. The relative energies of the conformers (required for calculating the Boltzmann factors) were taken from single point ab initio solvent calculations on the molecular mechanics structures, since the relative molecular mechanics energies did not match those from the ab initio calculations particularly well.

The calculated chemical shifts using this method were slightly less accurate: mean $|\Delta\delta|$ was 1.40 ppm for the MMFF geometries and 2.98 ppm using MM2* compared to 0.91 ppm with ab initio optimization. However, it was still possible to distinguish between the pyranopyran- and bifuranyl acetals with similar confidence to that achieved previously Figures 5 and 8). The computer time saved was considerable. As a typical example, only a total of 0.5 h was required to calculate the chemical shifts for bifuranyl **8** (using the MMFF geometries) compared to 3.4 h when ab initio optimization was included, i.e., an 85% reduction.

3. Predicting the Stereochemistry of a Natural Product. We then applied the method to prediction of the stereochemistry of the marine natural product elatenyne. This was originally believed to have the pyranopyran structure **11**[39] (Figure 9) but, following synthetic studies, is now proposed to have the gross structure **12**,[21] which has as its core a [2,2′]bifuranyl system. Our hope was that such a prediction would avoid the need to synthesize all 32 possible diastereoisomers of **12** in order to confirm the structure of the natural product; instead, only those identified by the calculation as being most likely would need to be made.

We have shown that NMR chemical shift calculation on conformationally flexible molecules can permit assignment of stereochemistry to a bifuranyl system, and give an indication of the reliability of the assignment. We now use the technique to predict the stereochemistry of elatenyne. NMR chemical shifts were calculated for all 32 possible diastereoisomers of **12** (Figure 9), as well as for the pyranopyran structure **11** originally proposed.

The errors in the calculated shifts of the bromine substituted carbons 7 and 12 were substantially greater than those for the other carbons. The shifts were overestimated by about 20 ppm (prior to any scaling) for structure **11** compared to the experimental data for this structure, and by between 17 and 29 ppm for structures **12.1**−**12.32** compared to the experimental data for elatenyne. This is due to the spin−orbit coupling effect in heavy atoms;[41] errors of similar magnitude (though varying in the exact value) have been reported by Kaupp,[42] Bagno,[43] and Rzepa.[12] Although Kaupp has shown that it is possible to account for spin−orbit effects using significantly higher levels of theory,[42] this would have involved a prohibitive amount of computer time in our case.

The large errors in the calculated shifts of the bromine-substituted carbons (compared to the other carbons) will tend to give them a disproportionately large influence on the mean (and particularly the maximum) values of $|\Delta\delta|$, and so the carbons with least accurately estimated shifts have the largest role in determining which calculated data set fits the experimental data best. To deal with this problem, we applied Rzepa's approach[12] of systematically correcting the shifts to account for the spin−orbit effects. Assuming it is reasonable to use the same correction across all diastereoisomers, despite possible through-space effects on the spin−orbit correction, we must decide what correction to apply. If, for example, we subtract 22.8 ppm (the average value of $\Delta\delta$ for C7) from all δ_{calc} values for C7 we will simply be favoring those diastereoisomers for which the shift for C7 is closest to the average. We therefore took our corrections (all of which were applied prior to the scaling process) from comparison of the calculated and experimental data for the pyranopyran **11**, on the assumption that the spin−orbit corrections for the pyranopyran system will be similar to those for the bifuranyls. The resulting values (δ_{calc} - δ_{exp}) were 19.8 ppm for C7 and 20.6 ppm for C12. These are slightly larger than the 12 ppm or 14 ppm (depending on the basis set used) reported by Rzepa,[12] but this could be due to our use of the B3LYP functional rather than mPW1PW91 as well as the differences in the structures of the molecules involved. We also applied a correction of −10.1 ppm (again taken from the data for **11**) to the quaternary alkyne carbon C2, since the errors in the calculated shifts for this carbon were also significantly greater than for the other carbons. However, the correction here is less critical as C2 is not close to any of the stereocenters being assigned and, in contrast to C7/C12, did not show a large variation in calculated shift across the diastereoisomers.

The correlation coefficients between the experimental data for elatenyne and each set of calculated data (with the above corrections) are plotted in Figure 10. On the basis of this graph,

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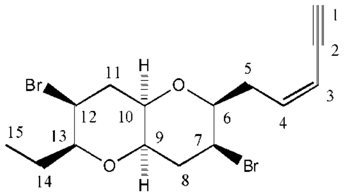
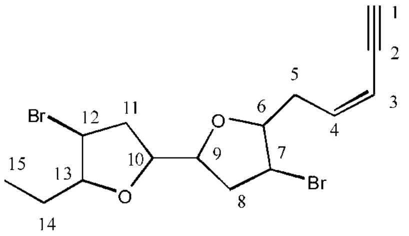
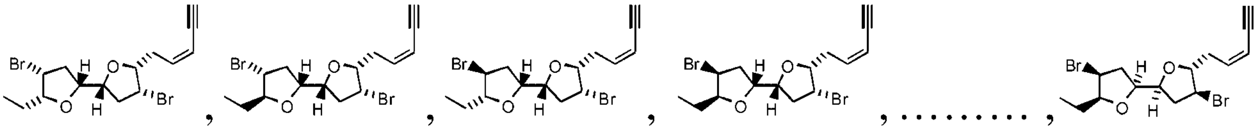


11 Originally proposed structure for elatenyne



12 Revised gross structure for elatenyne



12.1, **12.2**, **12.3**, **12.4**, ..., **12.32**

FIGURE 9. Structures proposed for elatenyne.

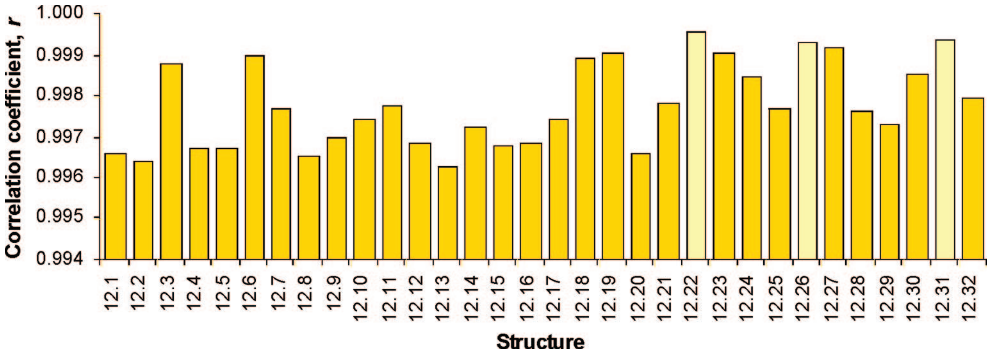


FIGURE 10. Correlation coefficient *r* between calculated and experimental data for the possible structures of elatenyne, having applied the corrections to C2, C7, and C12 described in the text. The higher bars represent the best matches. The top three matches are highlighted.

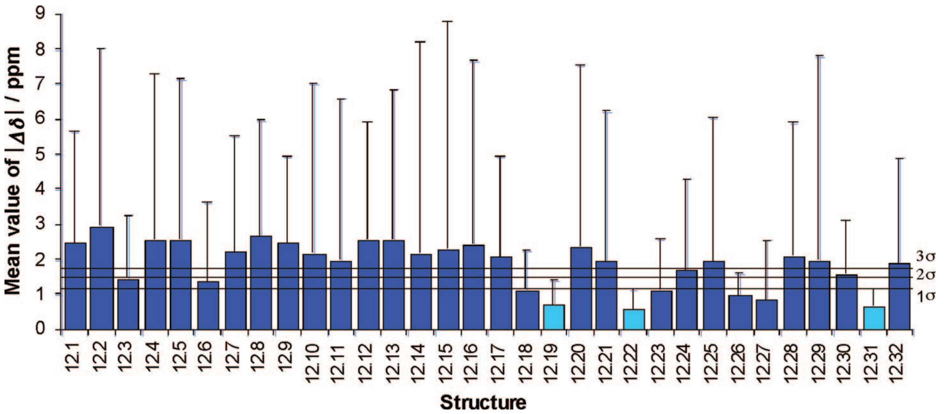


FIGURE 11. Mean and maximum values of |Δ*δ*| for carbons C6−C13 only, having applied the corrections described in the text. Means: bars. Maxima: lines. The horizontal lines represent the values of the mean of |Δ*δ*| that are one, two, and three standard deviations above the expectation value of the mean of |Δ*δ*| for a correct structure. The smaller bars represent the best matches. The top three matches are highlighted.

the calculated data for diastereoisomers **12.22**, **12.31**, and **12.26** give the best match to the experimental data.

The mean and maximum values of |Δ*δ*| for all diastereoisomers are plotted in Figures 11 and 12. Following the approach taken for the acetals **8−10**, only the ring carbon atoms (C6−C13) were included in this analysis, since these carbons showed the most variation in values of Δ*δ*. Not surprisingly, given that they are further from the stereocenters that distinguish the different diastereoisomers, carbon atoms in the side chains showed less variation in Δ*δ*, often being systematically over- or underestimated. In fact, including the side-chain carbons gave a plot quite similar to Figure 11 (with the same structures giving the best matches) except that the variations in the heights of the bars for different diastereoisomers were less marked.

To give some indication as to how significant the variations in the mean of |Δ*δ*| are, we have taken the same approach as we did in Figure 6 and have drawn horizontal lines in Figure 11 at one, two, and three standard deviations above the expectation value. From these it may be seen that several of the bifuranyl structures (such as **12.2**) may be ruled out with reasonable confidence. The best matches are **12.22**, **12.31**, and **12.19**, two of which were among the top three matches in Figure 10.

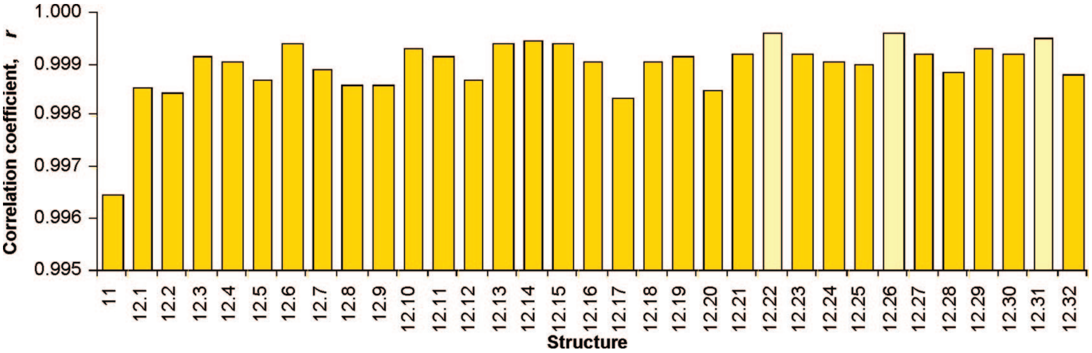


FIGURE 12. Correlation coefficient *r* between calculated and experimental data for the possible structures of elatenyne, excluding the carbons for which a correction was previously applied. The higher bars represent the best matches. The top three matches are highlighted.

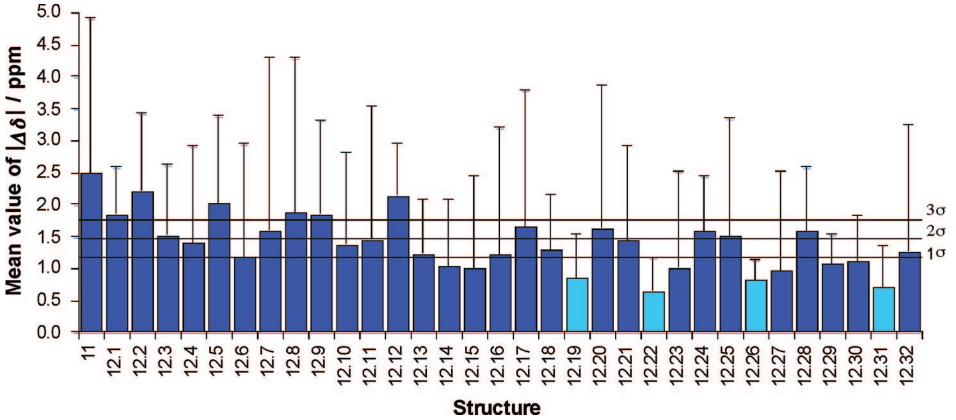
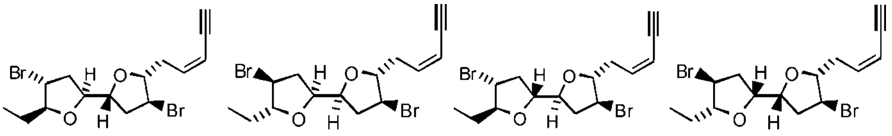


FIGURE 13. Mean and maximum values of $|\Delta\delta|$ for carbons C6, C8, C9, C10, C11, and C13 only. Means: bars. Maxima: lines. Carbons C2, C7, and C12 were excluded from all stages of analysis, including the scaling process. The horizontal lines represent the values of the mean of $|\Delta\delta|$ that are one, two, and three standard deviations above the expectation value of the mean of $|\Delta\delta|$ for a correct structure. The smaller bars represent the best matches, and the top four matches are highlighted.



12.22 **12.31** **12.26** **12.19**

FIGURE 14. Likely candidates for the structure of elatenyne, with the most likely first.

An alternative approach to the spin−orbit problem, rather than applying a systematic correction to the bromine substituted carbons, is simply to exclude these carbons from the analysis. This approach has the advantage of being simpler and also of avoiding the need to make assumptions about the transferability of the correction. It also allows us to include the pyranopyran structure **11** on a more even footing as a potential candidate for elatenyne; this was not done before since the pyranopyran data was used to derive the corrections that were applied.

Excluding from all analyses the carbons to which we previously applied corrections (C2, C7, and C12) gives the graphs in Figure 12 and Figure 13 (equivalent to Figure 10 and Figure 11). Reassuringly, the same structures as before are picked out as being the most likely candidates: the top match is **12.22** with **12.31**, **12.26**, and **12.19**also being among the best matches. Thus, the same conclusions as before are obtained using a simpler approach with fewer assumptions. The pyranopyran structure **11** gives a particularly poor match in terms of both correlation coefficient and mean $|\Delta\delta|$.

Weighing up the conclusions from Figures 10–13, the most likely candidate for the structure of elatenyne is **12.22**, although **12.31** is also a strong candidate and both **12.26** and **12.19** remain possibilities.

Conclusions

We have shown that NMR chemical shift calculation at the B3LYP/6-31G** level gives results accurate enough to distinguish between different diastereoisomers of flexible bifuranyl systems, and low precision geometry optimization using MMFF followed by a single-point calculation at the B3LYP/6-31G** level is almost as effective. We propose that this approach could be useful in situations where stereochemistry is difficult to establish from NMR experiments alone, by suggesting likely candidates from the possible diastereoisomers and so reducing the number of potential structures that must be considered. We also have suggested the most likely stereochemistries for elatenyne. It remains to be seen whether or not the actual structure of elatenyne is one of the structures proposed in Figure

14. Furthermore, the prediction of ^{13}C NMR chemical shifts for carbon atoms substituted with halogens and for substituted alkynes is still challenging. Work is ongoing both to confirm the structure of elatenyne by total synthesis and to develop the methodology of NMR chemical shift prediction.

Acknowledgment. We thank the EPSRC and St. Catharine's College, Cambridge, for a Research Fellowship (RSP), and the Royal Society (URF to J.W.B.) and Unilever for financial support. We are very grateful to Prof. R. W. Hoffmann, Philipps-Universität, Marburg, for supplying the spectra of **3** and to the late Dr. D. R. Kelly for providing the multiplicities of the carbon atoms for **1** and **2**.

Supporting Information Available: Complete details of coordinates, total energies, NMR shielding constants and calculated shifts, and experimental shifts. This material is available free of charge via the Internet at http://pubs.acs.org.

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