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Configurational analysis of the natural product passifloricin A by quantum mechanical ^{13}C NMR GIAO chemical shift calculations

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Abstract—Quantum chemical calculations at mPW1PW91 level, with full geometry optimization, using the 6-31g(d) basis set, and GIAO (gauge including atomic orbitals) ^{13}C NMR chemical shifts using the 6-31g(d,p) basis set, are here utilized as a support to define the configurational features of the natural product passifloricin A, whose previously proposed relative configuration has been recently shown, by synthetic studies, to be incorrect. This study suggests that the relative stereostructure for passifloricin A corresponds to the δ-lactone of the (5*R*,7*R*,9*S*,11*R*)-tetrahydroxyhexacos-2-enoic acid.

Passifloricin A is a natural product that has been isolated from *Passiflora foetida* resin.[1] This compound belongs to an interesting class of naturally occurring lactones that, being Michael acceptors by means of their α,β-unsaturated lactone moiety, may display cytotoxic or tumor-promoting activity. Though its relative configuration has been proposed as **1** (Fig. 1), recent stereoselective synthetic studies,[2,3] aimed at establishing the absolute configuration of the natural product, have shown, through comparison of ^{1}H and ^{13}C NMR data between the natural and synthetic product, that the reported relative configuration **1** is incorrect. Moreover, NMR as well as optical rotation data of the natural passifloricin A, are not in accordance with compound **2** either, the C-5 epimer of **1**, which was also synthesized because it appeared as another plausible candidate. In the frame of our current interest in the stereochemical analysis of flexible carbon chains by NMR spectroscopy and computational methods,[4] we decided to apply our recent methodology,[5] based on the determination of the relative configuration of flexible compounds by quantum mechanical GIAO[6,7] ^{13}C chemical shift (c.s.) calculations, with the aim of suggesting the correct relative stereochemical features of this molecule and of directing the efforts toward the synthesis of passifloricin A, possibly avoiding the need of synthesizing all the remaining stereoisomers. Our approach consists of: (a) the building of all the possible relative stereoisomers of the molecule under investigation; (b) a conformational search and a preliminary geometry optimization of all the significant conformers of each stereoisomers (as defined below); (c) a final geometry optimization of all the species at Hartree–Fock or post-HF level; (d) the GIAO ^{13}C NMR calculations of all the so-obtained structures at Hartree–Fock or post-HF level; (e) the comparison of the ^{13}C c.s. calculated for each stereoisomer, obtained considering the Boltzmann distribution of all the conformers, with those reported for the natural product. Following this procedure, we considered all the possible relative stereoisomers of passifloricin A (**1**–**8**, Fig. 1), and their simplified versions (**1a**–**8a**), in which we shortened the long hydrocarbon side chain, clearly irrelevant in the frame of this study. A preliminary conformational search, performed by empirical force field molecular dynamics in the CVFF force field (InsightII, version 2000.2, Accelrys, San Diego) suggested five major conformers for compounds **1a**, **2a** and **4a**, four for **3a**, six for **5a** and **6a**, seven for **7a**, and ten for **8a**. A cut-off value of 25 kJ/mol was used to exclude the less relevant conformers.[5]

Density functional theory (DFT) thermochemical calculations, using the mPW1PW91[8] method and the 6-31g(d) basis set in the harmonic approximation of the vibration modes, allowed the evaluation of the standard Gibbs free energy of the conformers at 298.15 K. Subsequently, GIAO ^{13}C c.s. calculations were performed at the mPW1PW91/6-31g(d,p) level on each set of conformers relative to compounds **1a**–**8a**. All the calculations were carried out using the Gaussian 98W

Keywords: GIAO; ^{13}C NMR; DFT calculations; natural products; passifloricin; configurational analysis.

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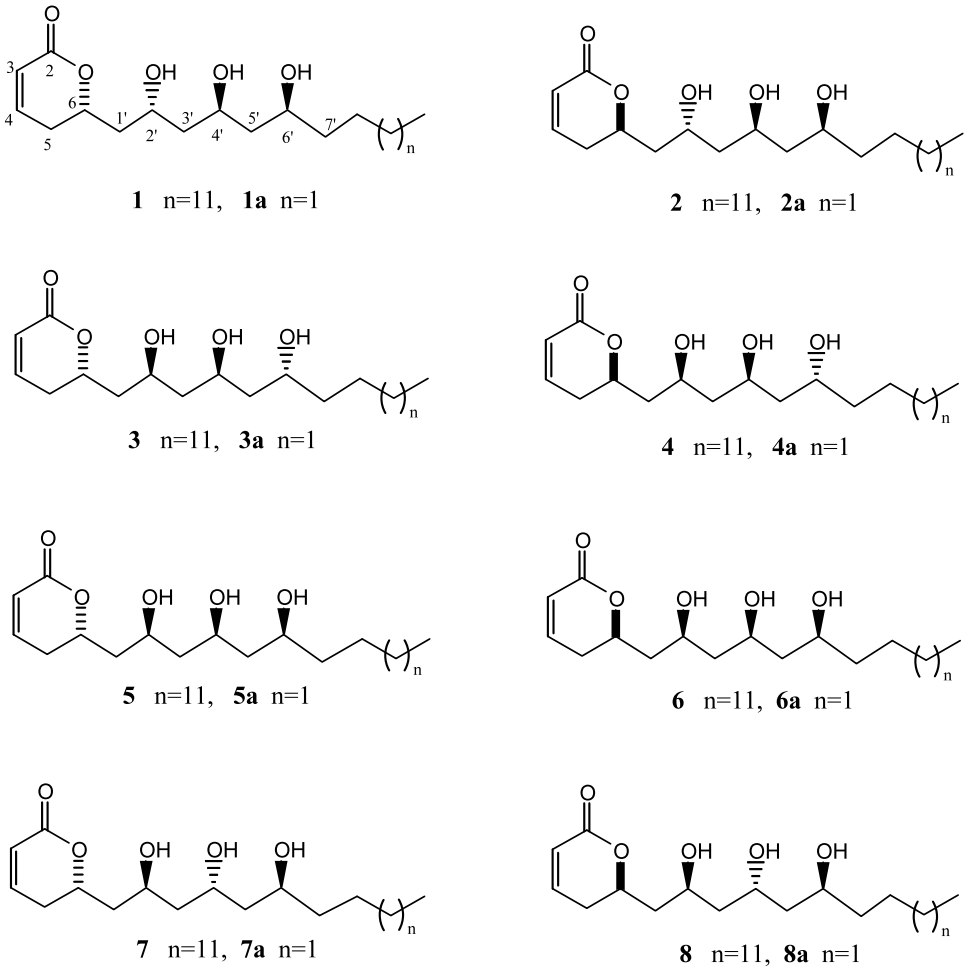

Figure 1. Structures of all the possible relative stereoisomers of passifloricin A (**1**–**8**), and their simplified versions (**1a**–**8a**).

program package.[9] For each stereoisomer, the ^{13}C NMR chemical shift of a given carbon atom was obtained as the weighted average chemical shift value of the same atom in all the conformers sampled by the initial conformational search. The c.s. averages of stereoisomers **1a**–**8a**, obtained by applying a Boltzmann distribution using the relative standard free energies as weighting factors, are listed in Table 1, along with the corresponding ^{13}C NMR data reported for passifloricin A.[1] A close inspection of this data reveals that a systematic error relative to the sp^2 carbons, particularly evident in the case of the C-2 carbonyl carbon, can be found in all the stereoisomers, suggesting their exclusion from the following analysis, especially in view of their negligible value in the context of this configurational analysis. In order to be able to appreciate which of the eight stereoisomers best fit the experimental data of passifloricin A, we have preliminarily analyzed the

Table 1. Values of Boltzmann-averaged GIAO ^{13}C c.s./ppm relative to TMS for the diastereomers **1a**–**8a** and ^{13}C experimental data reported for passifloricin A[1]

^{13}C atom	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	Passifloricin A
C2	153.77	153.61	153.20	153.56	155.29	155.40	155.10	153.74	**164.91**
C3	119.85	119.78	119.66	119.54	120.90	120.17	120.74	119.77	**121.57**
C4	141.01	141.40	141.11	141.21	139.88	140.89	139.93	141.16	**145.96**
C5	30.85	29.40	31.40	31.22	31.29	31.30	31.35	31.06	**32.29**
C6	76.59	74.57	73.85	77.53	70.77	72.67	71.29	77.08	**76.64**
C1′	40.27	37.92	40.10	42.23	44.43	42.32	42.87	41.46	**42.68**
C2′	69.98	66.84	71.90	72.82	66.08	66.46	63.47	67.84	**72.60**
C3′	41.8	41.48	39.94	43.34	43.49	41.39	38.98	40.36	**42.95**
C4′	70.58	69.89	70.71	69.86	74.05	74.23	67.05	67.16	**69.71**
C5′	43.64	43.79	42.54	42.43	42.90	39.81	39.53	40.65	**34.35**
C6′	71.7	70.96	69.60	69.77	75.00	73.43	70.82	66.99	**72.10**
C7′	40.14	40.12	37.07	36.90	39.09	39.54	39.08	39.83	**37.73**

R^2 correlation factors coming from a linear regression analysis of the calculated versus experimental ^{13}C c.s. reported for passifloricin A, and eventually the mean absolute error (MAE) relative to each stereoisomer, in accordance to our protocol. A careful analysis of the data reported in Table 2 shows that the highest correlation coefficient R^2 would suggest compound **4a** as the best candidate for fitting passifloricin A experimental data. In Figure 2, expressed in $\Delta\delta$ units, are the mean absolute errors (MAE) displayed by the calculated chemical shifts of **1a**–**8a** versus passifloricin A. The lowest value of 1.60 ppm for compound **4a** is in accordance with what has already been suggested by the linear regression analysis, and it strongly puts in evidence a better agreement between the calculated chemical shifts of the relative stereoisomer **4a** with respect to the natural compound. Figure 3 shows the absolute errors, for compounds **1a**–**8a**, relative to each of the carbon atoms considered in our analysis. It is straightforward how all the carbon resonances of **4a** are in a very good agreement with the experimental ones, except for C-5′. Indeed, the calculated ^{13}C c.s. values of this carbon atom are suspiciously far from the experimental value for all of the stereoisomers considered, thus indicating a possible error in the original assignment. We wish to point out that relatively high absolute errors of ca. 5–10 ppm (still acceptable, though, in a relative sense) can be expected in the prediction of c.s. of low-field carbons, such as sp^2 carbons resonating in the 140–200 ppm range, because of a current, intrinsic limit of the methodology. The same consideration does not apply for high field sp^3 carbons, which display mean absolute errors of ca. 1.5–3.0 ppm.[10] Therefore, the absolute error and the MAE of calculated **1a**–**8a** versus experimental c.s. of passifloricin A were re-evaluated, this time discarding C-5′ c.s. as an anomalous datum. The new sets of data supports even more clearly, the relative configuration of **4a** for passifloricin A (Figs. 4 and 5).

Table 2. Linear regression analysis: correlation coefficients (R^2) of least-squares linear fits of the theoretical versus experimental ^{13}C chemical shifts reported for passifloricin A

	R^2
1a	0.9940
2a	0.9915
3a	0.9941
4a	0.9954
5a	0.9914
6a	0.9942
7a	0.9938
8a	0.9949

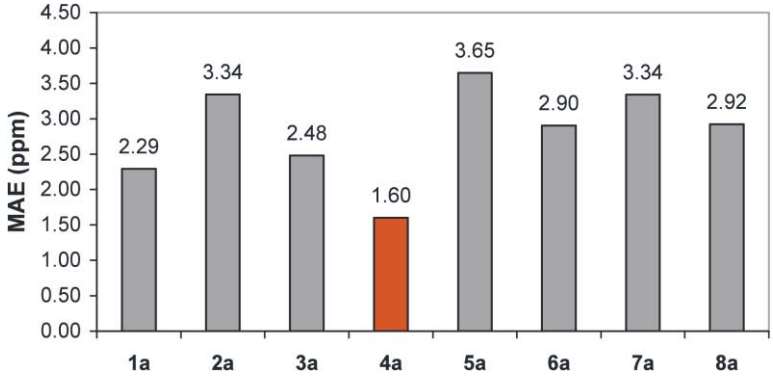

Figure 2. Mean absolute error (MAE) found for the ^{13}C NMR calculated chemical shifts of compounds **1a**–**8a** versus the experimental values of passifloricin A for C5–C6, C1′–C7′. MAE $=\Sigma[|(\delta_{exp}-\delta_{calcd})|]/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and calculated ^{13}C chemical shifts), normalized to the number of the carbon atoms considered.

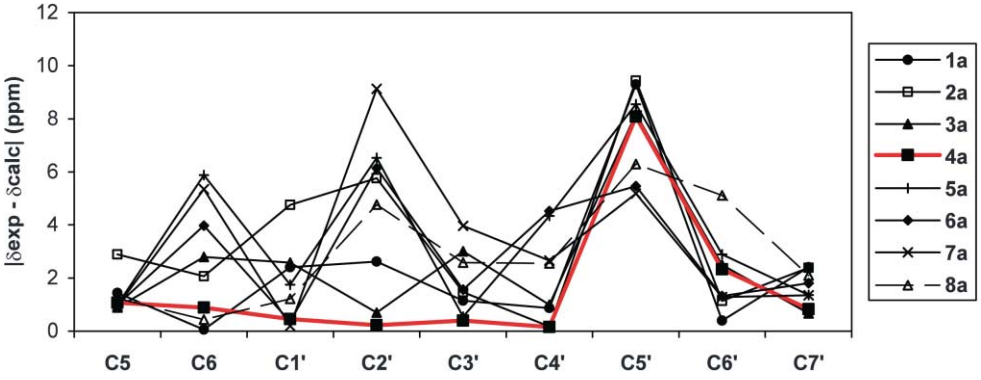

Figure 3. Differences, in absolute values, for the calculated (**1a**–**8a**) versus experimental ^{13}C NMR chemical shifts of passifloricin A.

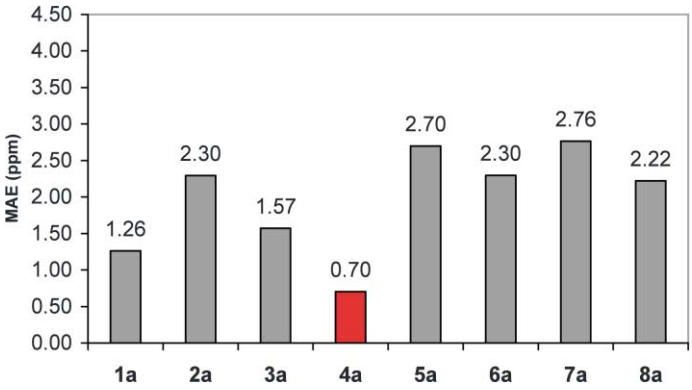

Figure 4. Mean absolute error (MAE) found for the ^{13}C NMR calculated chemical shifts of compounds **1a**–**8a** versus the experimental values of passifloricin A for C5–C6, C1′–C4′, C6′–C7′. $MAE = \Sigma[|(\delta_{exp} - \delta_{calcd})|]/n$, summation through n of the error absolute values, difference of the absolute values between corresponding experimental and calculated ^{13}C chemical shifts, normalized to the carbon atom number considered for species.

To test the efficiency of our approach, we compared the calculated ^{13}C c.s. values for **1a**–**8a** with the experimental ^{13}C c.s. values reported for the synthetic compounds **1** (Fig. 6) and **2**[2,3,11] (Fig. 7). The evaluation of the minimum absolute error (MAE) reported in Figure 7 demonstrates that the calculated ^{13}C c.s. of **2a** fit very well the experimental chemical shifts reported for **2**, thus proving accuracy and soundness of our method. On the other hand, in Figure 6 it is clear that both the sets of calculated ^{13}C c.s. of **1a** and **2a** fit the experimental data reported for **1** much better than the calculated data for stereoisomers **3a**–**8a**, but the lowest value of 1.34 ppm for the MAE of **1a** is not significantly different from the MAE of **2a** (1.35 ppm), leaving a doubt about the correct epimer. This evidence suggests that the method has some limitations whenever a couple of epimers, **1** and **2** in our case, display an intrinsic similarity of their experimental ^{13}C values.

In conclusion, the present study suggests that the correct relative stereostructure of the natural passifloricin A is **4** and that the described approach of configurational analysis, based on the ab initio calculation of ^{13}C c.s. for all the possible relative stereoisomers of the molecule under investigation, can be considered reliable and is able to provide solid indications on the relative configuration of a given compound with multiple stereogenic centers, especially when they are in a carbon chain with conformational mobility.

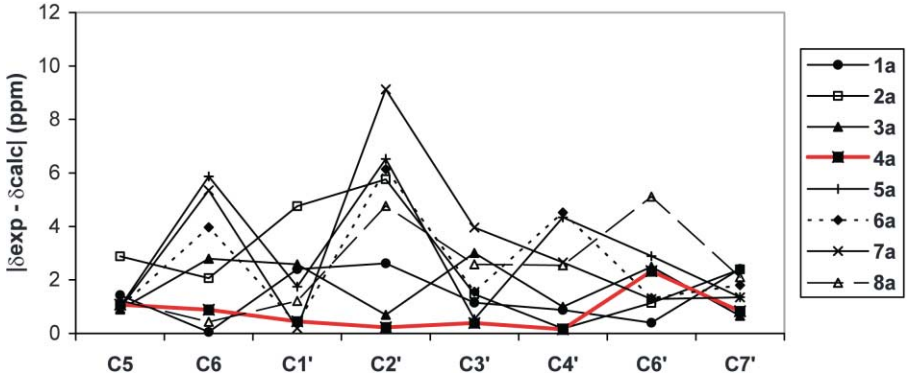

Figure 5. Differences, in absolute values, for the calculated (**1a**–**8a**) versus experimental ^{13}C NMR chemical shifts of passifloricin A, obtained discarding C5′.

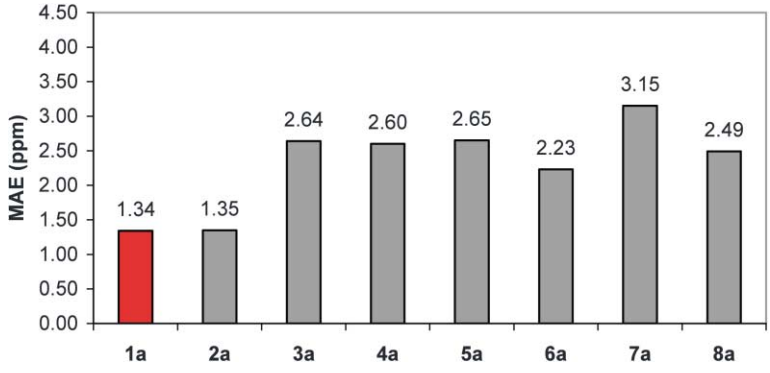

Figure 6. Mean absolute error (MAE) found for the ^{13}C NMR calculated chemical shifts of compounds **1a**–**8a** versus the experimental values of **1** for C5–C6, C1′–C7′. $MAE = \Sigma[|(\delta_{exp} - \delta_{calcd})|]/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and calculated ^{13}C chemical shifts), normalized to the number of the carbon atoms considered.

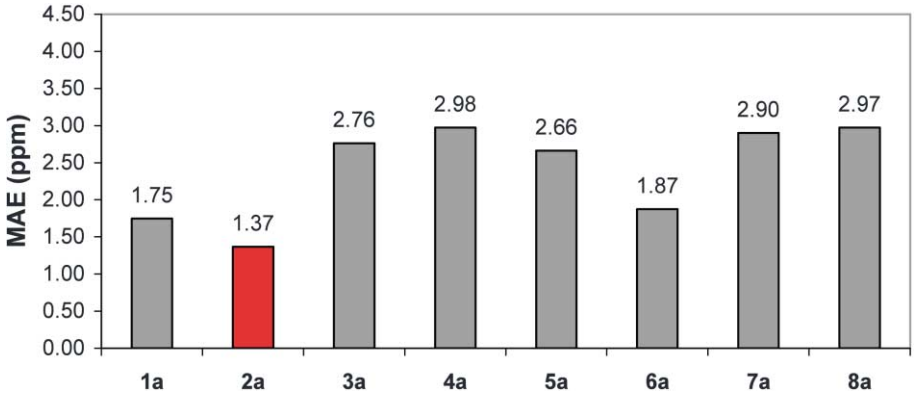

Figure 7. Mean absolute error (MAE) found for the ^{13}C NMR calculated chemical shifts of compounds **1a**–**8a** versus the experimental values of **2** for C5–C6, C1′–C7′. MAE $=\Sigma[|(\delta_{exp}-\delta_{calcd})|]/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and calculated ^{13}C chemical shifts), normalized to the number of the carbon atoms considered.

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