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Revisiting the structure of Heliannuol L: A computational approach

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Abstract

Recently, structural elucidation of natural products has undergone a revolution. The combined use of different modern spectroscopic methods has allowed obtaining a complete structural assignment of natural products using small amounts of sample. However, despite the extraordinary ongoing advances in spectroscopy, the mischaracterization of natural products has been and remains a recurrent problem, especially when the substance presents several stereogenic centers. The misinterpretation of nuclear magnetic resonance (NMR) data has resulted in frequent reports addressing structural reassignment. In this context, a great effort has been devoted to developing quantum chemical calculations that simulate NMR parameters accurately, allowing to achieve a more precise spectral interpretation. In this work, we employed a protocol for theoretical calculations of ^{1}H NMR chemical shifts and coupling constants using density functional theory (DFT), followed by the application of the DP4+ method to revisit the structure of Heliannuol L, a member of the Heliannuol class, isolated from *Helianthus annuus*. Our results indicate that the originally proposed structure of Heliannuol L needs a stereochemical reassignment, placing the hydroxyl bonded to C10 in the opposite side of the methyl and hydroxyl groups bonded to C7 and C8, respectively.

KEYWORDS

DP4+, Heliannuol, natural products, reassignment

1 | INTRODUCTION

Until the recent past, structural determination of natural products has been an arduous task, because it was based entirely on processes of total synthesis, chemical derivatization and degradation. These strategies could easily take years of effort, being usually high-cost procedures and demanding a large amount of material. Due to this, the assignment of absolute or relative configuration was, in most cases, practically out of the question.[1] In the last few decades, structural elucidation of natural products has experienced a revolution. With the combined application of complementary modern spectroscopic techniques, it became possible to achieve a complete structural assignment of natural products using few milligrams of sample.[1,2] However, concerning complex natural products, even the most advanced techniques may not be enough to undoubtedly establish the spatial connectivity

of atoms, making the mischaracterization of natural products a recurrent problem, especially for the substances presenting stereogenic centers.[1–3] The misinterpretation of nuclear magnetic resonance (NMR) data frequently results in multiples reports addressing the issue of structural reassignment in natural products chemistry.[2] In this context, a great effort has been devoted to developing quantum chemical calculations to compute NMR parameters accurately.[4,5] The computational simulations of ^{1}H and ^{13}C NMR chemical shifts and spin–spin coupling constants (J) registered a marked increase in precision, accessibility and application, leading to a more precise spectral interpretation.[4,5] Thus, in addition to aiding the structure elucidation of new natural products, computational methods have been of great utility in helping to uncover and ultimately revise the structure of previously reported compounds, leading to a considerable advance in the field of natural products.[4–11]

In our previous work, we employed a computational protocol for theoretical calculations of NMR parameters to unravel the structure of the Helianane family, an extremely rare class of sesquiterpenes isolated from the marine sponge *Haliclona fascigera*.[12] For many years, due to the remote possibility of reisolation, their structures have remained as an unsolved and controversial topic. The originally proposed structure of the Heliananes presented a benzofused macrocyclic 8-membered ether ring system. However, the NMR data of the synthesized molecules were remarkably incompatible with those obtained from the molecule isolated from nature. Our computational findings, in agreement with the comprehensive synthetic work made by Pettus group, provided reliable proof of the correct identities of the Helianane family as Curcudiol and their halogenated derivatives (Figure 1).[12,13]

Now, we turn our attention to the Heliannuol family—a larger subset of sesquiterpenes, structurally similar to Helianane, firstly isolated by Macías *et al*. in 1993 from the terrestrial plants of the *Helianthus annuus* species (sunflower).[14] The Heliannuol family comprises substances not only with the same benzofused macrocyclic 8-membered ether ring system originally proposed for the Helianane family[14–18] but also with ether rings of five to seven members, all of them with at least two stereogenic centers, as shown in Figure 2.[19,20] These secondary metabolites present a broad spectrum of biological activities, including the allelochemical activity, making them promising candidates as natural agrochemicals for pest control.[14–20] It is worth mentioning that, although there is a considerable number of articles describing the total synthesis of Heliannuols, several examples of the class do not present any synthetic proposal.[19] In many cases, the proposed structures are based on structural correlations with similar molecules already known in the literature.[19]

Heliannuol L (Figure 2) is one of these examples, which was first isolated by Macías and coworkers in 2002.[17] Its structure was determined by considering the similarity with NMR data from previously isolated molecules belonging to the same class.[17] Considering that the structures of some compounds of the Heliannuol family have been reassigned previously,[21] the reexamination of the proposed structure of Heliannuol L is of interest. Following our continuous pursuit of the application and development of new tools to the structural elucidation of complex natural products by means of quantum chemical calculations of NMR parameters,[5,22–29] in this article, we discuss the first analysis of the stereoisomers of Heliannuol L and propose a revision of its relative configuration.

2 | RESULTS AND DISCUSSION

High-resolution electron ionization mass spectrometry (HREIMS) for Heliannuol L shows the molecular ion peak at m/z 266.1525, consistent with the proposed molecular formula, $C_{15}H_{22}O_4$.[17] Besides, characteristic signals of the Heliannuol class were observed in the ^{1}H NMR spectrum.[17] Supported by these data, Macías and

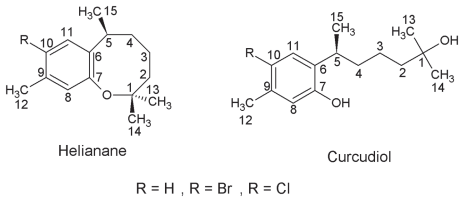


FIGURE 1 Structures of Helianane (originally proposed) and Curcudiol and their halogenated derivatives

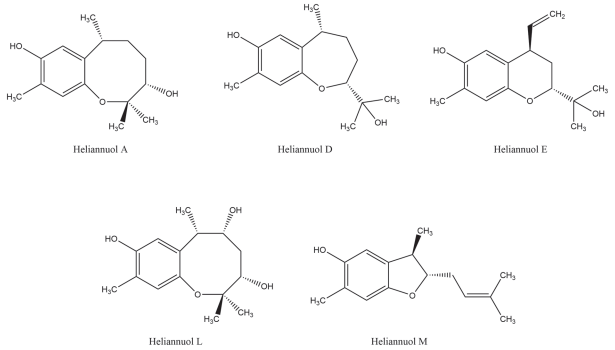


FIGURE 2 Examples of different skeletons for the Heliannuol family

coworkers proposed that the structure of Heliannuol L would be compatible with a seven or eight-membered ether ring, leading to four possible candidates for Heliannuol L (Figure 3).[17] Nuclear Overhauser effect (NOE) indicated a correlation between the signals for H7 and H8, suggesting the relative configuration of the stereogenic centers C7 and C8 to be 7S* and 8R* (Figure 3).[17] To establish the configuration at C10, the authors conducted a series of NOE experiments. However, after a nonconclusive result, a conformational study for each candidate was carried out with the GMMX conformer search methodology, followed by geometry refinement with the PM3 semiempirical method. The dihedral angles obtained for the most stable optimized conformer of each candidate were compared with the experimental *J* values for the isolated compound. With this approach, a clear correspondence with candidate D, the originally proposed structure for Heliannuol L (Figure 3), was found. This conclusion was based on ^{1}H NMR chemical shifts, NOE experiments, and coupling constant analysis, because ^{13}C NMR chemical shifts were not provided in that original work.

Aiming to confirm the structure attributed to the isolated compound using a more confident method, we compared the ^{1}H NMR chemical shift calculations using a quantum chemical approach (density functional theory, DFT) and compared them with the ^{1}H NMR experimental data of the isolated compound (Table 1).

Although the extensive NOE analysis carried out by the authors who performed the isolation of Heliannuol L suggested the relative configuration of C7 and C8, to increase the reliability in our analysis of the relative configuration of the three stereogenic centers of Heliannuol L, we decided to simulate all possible stereoisomers. Originally, there are eight possible stereoisomers for each proposed skeleton (seven and eight members); however, for each skeleton, the possible stereoisomers comprise four pairs of enantiomers. As each pair of

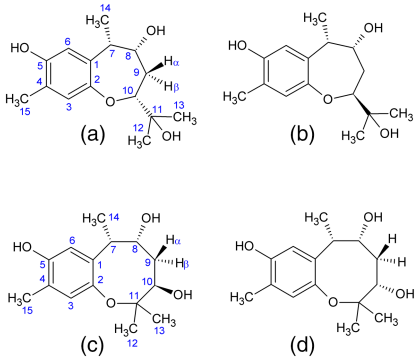


FIGURE 3 Originally proposed candidates for Heliannuol L. The structure D is the originally attributed to Heliannuol L [Color figure can be viewed at wileyonlinelibrary.com]

enantiomers displays exactly the same NMR chemical shifts in isotropic media, it suffices to compute only one enantiomer of each of the four relative configurations. Thus, we simulated four possible stereoisomers for each proposed skeleton: four candidates initially proposed by Macías and collaborators (A–D) and four candidates that were not cited in the original publication (A′–D′) (Figure 4).

From Table 1, the mean absolute deviation (MAD) and root mean square deviation (RMSD) values for the ^{1}H NMR chemical shifts are slightly smaller for Candidates A–D than for the remaining candidates, indicating that the original suggestion of the relative configuration of C7 and C8 by NOE is correct. Besides, it is remarkable that only Candidate C presented H9α and H9β values compatible with the respective experimental data, resulting in the smaller MAD and RMSD values when compared with the other candidates, including the originally proposed structure of Candidate D (MAD of 0.15 against 0.18, respectively). Furthermore, when considering just these two candidates (C and D), a clear and distinguishing point arises. Figure 5 shows the individual differences between the computed ^{1}H NMR chemical shifts for C and D and the values measured for the natural product. As diastereomers C and D are epimers differing only in the absolute configuration of C10, it is interesting to note that only Candidate C shows a calculated chemical shift for H9α compatible with the experimental data for the isolated sample (Figure 5). Similar results were found when using alternative functionals (Tables S1 and S2).

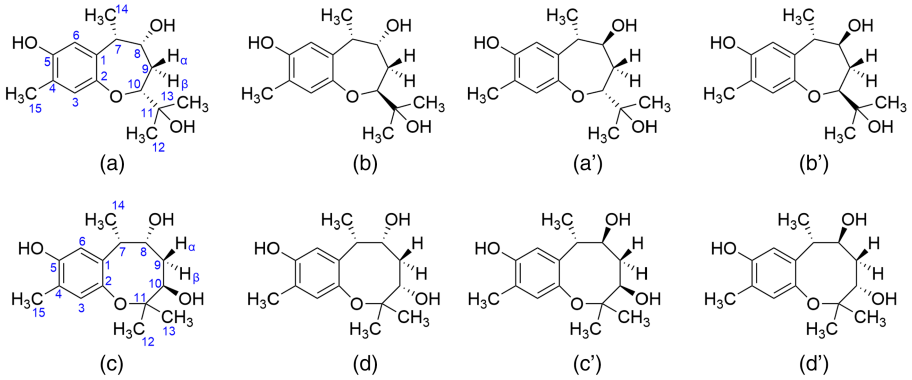
Therefore, the smaller magnitudes of MAD and RMSD in association with the remarkably smaller value of $\Delta\delta$ for H9α for Candidate C, suggests that the structure of Heliannuol L requires a deeper stereochemical assessment. To test the hypothesis that Candidate C is indeed the best representative for the structure of Heliannuol L, we employed the DP4+ procedure proposed by Sarotti and coworkers.[30] This procedure compares the simulated ^{1}H NMR chemical shifts with experimental values for each proposed structure and ranks them by a statistical treatment supported by the Student *t* test.[30] This method has been established to provide a more reliable assignment procedure compared to statistical parameters like MAD and RMSD.[30–32] However, to correctly apply the DP4+ procedure, the choice of the theoretical level is crucial. The use of other levels for which DP4+ was not parameterized can lead to a decrease in the accuracy of predictions.[33] Thus, as suggested by Sarotti's group,[33] in this work, the GIAO-mPW1PW91/6-31G(d)//B3LYP/6-31 + G(d) theoretical level was used in the DP4+ analysis (see Table S2). DP4+ (H data) results obtained for all possible candidates showed Candidate C

TABLE 1 Comparison of ^{1}H nuclear magnetic resonance (NMR) chemical shifts (δ_{scal}) simulated for all candidates of Heliannuol L (GIAO-PBE0/PCM ($CHCl_3$)/6-311 + G(2d,p)//B3LYP/6-31 + G(d)) with the experimental values (δ_{exp}, 400 MHz, $CDCl_3$) of the isolated natural product

Atom number	A (δ_{scal} ^{1}H, ppm)	B (δ_{scal} ^{1}H, ppm)	C (δ_{scal} ^{1}H, ppm)	D (δ_{scal} ^{1}H, ppm)	A′ (δ_{scal} ^{1}H, ppm)	B′ (δ_{scal} ^{1}H, ppm)	C′ (δ_{scal} ^{1}H, ppm)	D′ (δ_{scal} ^{1}H, ppm)	Isolated compound[a] (δ_{exp} ^{1}H, ppm)
H3	6.54	6.63	6.69	6.61	6.62	6.57	6.56	6.57	6.77
H6	6.31	6.34	6.29	6.26	6.30	6.33	6.32	6.18	6.56
H7	2.67	3.21	3.35	3.25	2.80	2.97	2.95	2.56	3.49
H8	3.76	3.75	3.72	3.66	3.79	3.22	3.65	3.93	4.32
H9α	1.76	1.93	2.28	1.55	1.84	1.82	2.13	1.57	2.35
H9β	2.00	1.93	1.58	1.54	2.04	1.91	1.91	2.32	1.62
H10	3.18	3.32	3.34	3.49	3.37	3.31	3.48	3.39	3.70
H12 (CH_3)[b]	1.19	1.08	1.34	1.35	1.15	1.18	1.30	1.27	1.15
H13 (CH_3)[b]	1.14	1.20	1.25	1.15	1.14	1.13	1.26	1.23	1.13
H14 (CH_3)[b]	1.17	1.31	1.22	1.24	1.19	1.26	1.26	1.25	1.21
H15 (CH_3)[b]	2.04	2.06	2.10	2.08	2.04	2.05	2.07	2.06	2.18
MAD	0.21	0.18	0.15	0.18	0.18	0.21	0.20	0.25	
RMSD	0.32	0.23	0.20	0.28	0.28	0.34	0.25	0.36	

Abbreviations: MAD, mean absolute deviation; RMSD, root mean square deviation.
[a]Data extracted from Macías *et al.*[17]
[b]Obtained with the arithmetic average of the three methyl hydrogens.

FIGURE 4 All possible candidates for Heliannuol L [Color figure can be viewed at wileyonlinelibrary.com]



as the most likely structure in overall confidence over 99% (Figure 6). The DP4+ results, combined with the MAD and RMSD values obtained with all the employed functionals, indicated the necessity to amend the relative configuration of Heliannuol L.

In 2005, Lecornué and collaborators succeeded in the total asymmetric synthesis of Candidate D (Figure 3), the supposed structure of Heliannuol L.[34] However, in that work, only ^{13}C NMR data were provided, in contrast to the original work, in which only ^{1}H NMR data were given.[17] Thus, no direct comparison between the structure of the isolated natural product and that of the synthetic compound was possible. Even so, we compared the experimental ^{13}C NMR chemical shifts available for the synthetic Heliannuol L with our simulated values for the four candidates proposed by Macías and coworkers, shown in Figure 3.[17] As expected, our results indicate a better agreement between the synthetic molecule and the originally proposed structure for Heliannuol L (Candidate D, see Table S3). However, it is worth mentioning that the four candidates proposed by Macías and coworkers yielded a considerably large error in the ^{13}C NMR chemical shifts calculated for C2 when compared with the experimental data of the synthetic molecule (see Table S3).[17] This suggests that either there is an inconsistency in the reporting of the spectroscopic data of the

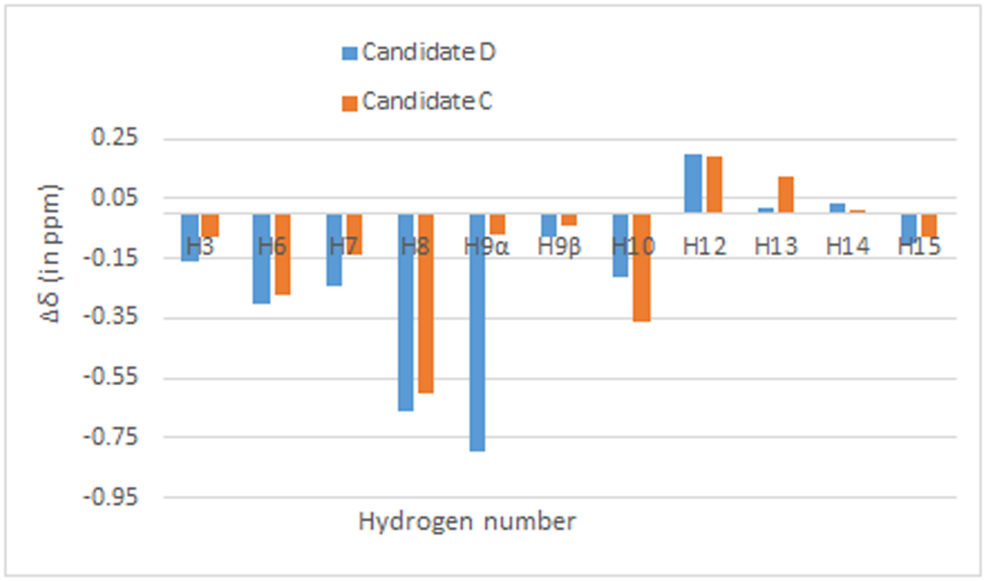


FIGURE 5 Comparison of the difference in ^{1}H nuclear magnetic resonance (NMR) chemical shifts ($\Delta\delta$, in ppm) of simulated Candidates C and D of Heliannuol L with the corresponding chemical shifts of the isolated natural product

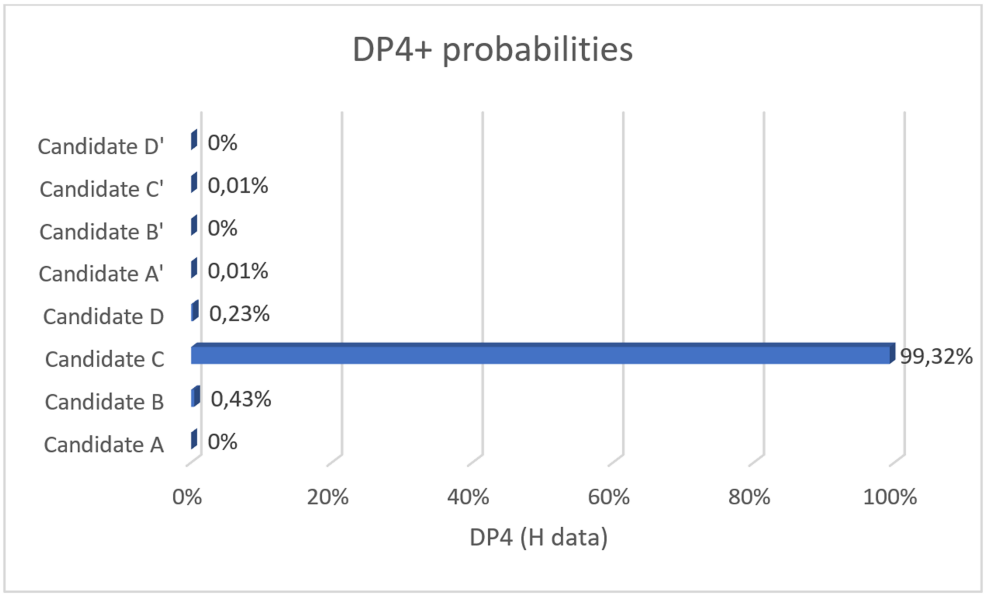


FIGURE 6 DP4+ (H data) values obtained by correlating the calculated nuclear magnetic resonance (NMR) chemical shifts of all possible candidate structures of Heliannuol L with the experimental NMR data of the isolated natural product

synthetic compound or even the synthetic molecule of Heliannuol L displayed some sort of structural disparity, because a ~20 ppm difference in these types of molecules is not suitable for the proposed structure. Therefore, it clearly demonstrates the necessity of a deeper analysis and a possible amendment in the structure of Heliannuol L. As previously mentioned, in the structural elucidation of Heliannuol L, the authors compared the different dihedral angles for the lowest energy conformers of the proposed candidates with the experimental *J* values of the isolated sample.[17] Therefore, taking this into account, in an additional effort to validate the stereochemical assignment, we also computed the *J* coupling constants for all possible candidates. Although the full calculation of *J* spin–spin coupling constants requires the simulation of four terms (diamagnetic, and paramagnetic spin–orbit, spin-dipole, and Fermi contact terms), Bally and coworkers demonstrated that the Fermi contact term represents the major contribution to the J_{HH} coupling constant in small organic molecules.[35] Hence, to reduce the computational cost, we decided to apply this protocol (using B3LYP/6-31G(d,p) u + 1 s) to compute exclusively the Fermi contact term. The results are shown in Table 2.

Table 2 clearly shows that MAD and RMSD values are lower for Candidates C and C′. However, a detailed analysis of the individual *J* values can assist in this stereochemical analysis. Although Candidates C and C′

TABLE 2 Comparison of calculated spin–spin coupling constants $J_{(H,H)}$ for the four candidates of Heliannuol L with the corresponding experimental values of the isolated natural product

$J_{(H,H)}$	A (Hz)	B (Hz)	C (Hz)	D (Hz)	A′ (Hz)	B′ (Hz)	C′ (Hz)	D′ (Hz)	Isolated compound[a] (Hz)
H7–8	3.0	0.6	1.4	2.2	4.8	8.1	5.1	5.7	3.5
H8–9α	3.9	2.3	2.9	3.8	4.4	3.6	4.7	7.0	6.0
H8–9β	11.1	3.8	5.9	6.4	2.2	3.9	3.1	1.9	9.0
H9α–10	1.3	10.7	9.2	1.8	1.3	2.3	9.1	1.5	6.1
H9β–10	11.7	1.4	0.9	8.6	11.8	5.7	1.7	9.2	2.5
MAD	3.8	3.5	2.6	3.3	4.8	3.8	2.5	4.3	
RMSD	4.9	3.8	2.7	3.7	5.6	3.9	3.1	4.9	

Abbreviations: MAD, mean absolute deviation; RMSD, root mean square deviation.
[a]Data extracted from Macías et al.[17]

yielded similar MAD values, it can be seen that Candidate C′ exhibited a higher RMSD value of 3.1 Hz, resulting from a large discrepancy associated with the *J* coupling H8–9β, directly related to the inversion of the C8 configuration. Taking into account the previously analysis based on chemical shifts (Table 1 and DP4+), we emphasize that Candidate C is the one that presented the best results. Additionally, when considering only epimers C and D, the *J* coupling H9α–10 simulated for Candidate C shows a large value of 9.2 Hz, the closest to the experimental value of 6.1 Hz for the isolated sample. On the other hand, Candidate D exhibits a discrepantly low simulated value of 1.8 Hz. The same opposite magnitudes are observed for the *J* coupling H9β–10 (low values for Candidate C and for the isolated natural product and a large value for Candidate D). Considering that these specific coupling constants are causally related to the configuration at C10, these opposite magnitudes presented for Candidates C and D clearly demonstrate that our stereochemical reassignment proposal is plausible, because Candidate C presents calculated *J* values with magnitudes compatible with experimental data for the isolated compound, unlike the calculated data obtained for Candidate D, the originally suggested structure of Heliannuol L.

3 | CONCLUSIONS

The exhaustive calculations of NMR data (^{1}H and ^{13}C chemical shifts and *J* coupling constants) followed by statistical treatments (comparison of MAD, RMSD, and DP4+ analysis) firmly suggest an inconsistency in the structural assignment of Heliannuol L. Testing all stereochemical possibilities, our results indicate that the correct Heliannuol L structure is actually one of the four possible candidates supposed by Macías and coworkers.[17] Using the experimental ^{1}H NMR data provided by them, our computational findings agreed with a structure displaying a macrocyclic eight-membered ether ring. However, our data indicate that the originally proposed structure of Heliannuol L needs a stereochemical reassignment, placing the hydroxyl bond at C10 in the opposite side of the methyl and hydroxyl groups bonded to C7 and C8, respectively. Therefore, among those proposed structures, Candidate C (Figure 3) seems to be the most suitable for Heliannuol L.

The correct structure of Heliannuol L can only be unequivocally determined through reisolation of the natural product, followed by an accurate comprehensive spectroscopic study (or deeper analysis of the available NMR free induction decays [FIDs]). Nevertheless, we expect that the present computational findings will contribute to uncover the inconsistency observed in the structure of Heliannuol L and provide a helpful assistance to guide a concluding required study to identify the correct structural identity of Heliannuol L.

4 | COMPUTATIONAL METHODS

The randomized conformational searches were performed for each candidate of Heliannuol L using the Monte Carlo method and the molecular mechanic force field (MMFF) in the Spartan'10 software package.[36] For each candidate, all conformations within a 10 kcal. mol^{-1} window were reoptimized using the B3LYP/6-31 + G(d) DFT method. The resulting conformers within the energy range of 3.0 kcal. mol^{-1} above the lowest minimum energy conformer, accounting for more than 97.0% of the total Boltzmann population (see electronic supplementary information [ESI], Figures S1–S8, for detailed information), were selected

for the GIAO NMR calculations. To simulate the ^{1}H NMR chemical shifts, three different functionals were used: PBE0/6-311 + G(2d,p), WP04/aug-cc-pVDZ and mPW1PW91/6-31G(d). The ^{1}H NMR chemical shifts were obtained after scaling the absolute isotropic ^{1}H magnetic shielding constants by an appropriate scale factor obtained from the CHEmical SHIft Repository.[37] For the PBE0/6-311 + G(2d,p) functional, the scaled factor $\delta_{scal} = 31.7532 - \delta_{calc}/1.0958$ was used. For the WP04/aug-cc-pVDZ functional, the scaled factor $\delta_{scal} = 31.9173 - \delta_{calc}/1.041$ was used. As both functionals were specifically parameterized to reproduce proton chemical shifts in chloroform solvent, we employed the polarizable continuum model with the integral equation formalism (IEFPCM) to implicitly simulate chloroform as the solvent medium.[37] For the mPW1PW91/6-31G (d) functional, no scaling factor was used, and calculations were simulated in the gas phase. The theoretical approaches employed to simulate the ^{1}H NMR chemical shifts have been recommended for good performance and cost when calculating chemical shifts in the CHEmical SHIft Repository, maintained by Tantillo's group.[7,37] Concerning the simulation of ^{13}C NMR chemical shifts, each selected structure was reoptimized at the mPW1PW91/6-31G(d) method, followed by absolute isotropic ^{13}C magnetic shielding constants calculations for each structure and tetramethylsilane (TMS), used as an internal reference, at the same level of theory. The predicted ^{13}C NMR chemical shifts ($\delta_i = \sigma_0 - \sigma_i$) were then scaled by $\delta_{scal} = 1.05.\delta_{calc} - 1.22$.[38] This approach allows the cancelation of systematic errors, because scaling factors are determined via linear regression analyses between the calculated and experimental chemical shifts of a pool of adequately chosen compounds.[38] This is an alternative to avoid demanding calculations necessary to include solvent and rovibrational effects.[7,38] For the application of the DP4+ method, the ^{1}H NMR data obtained for all candidates of Heliannuol L at the GIAO-mPW1PW91/6-31G(d)//B3LYP/6-31 + G(d) level were added to the DP4+ Excel spreadsheet provided by the authors of the method.[30] For the calculation of the spin–spin *J* coupling constant, the protocol proposed by Bally and coworkers was used, computing only the Fermi contact term at the B3LYP/6-31G(d,p) u + 1 s level. As proposed by the protocol, after each Fermi contact *J* value is obtained, they are scaled by a factor of 0.9117.[35] The DFT calculations were carried out using the Gaussian 09 software.[39] When required, the temperature of 298 K was specified.

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CONFLICT OF INTEREST

There are no conflicts to declare.

PEER REVIEW

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