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Structure revision of *ent*-kaurane diterpenoids, isoserrins A, B, and D, enabled by DU8+ computation of their NMR spectral data

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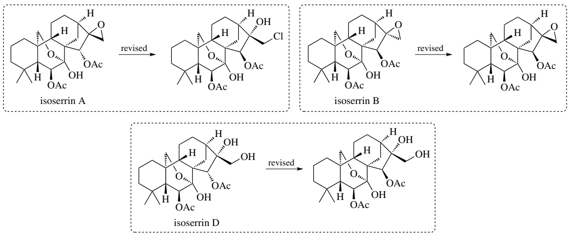
DU8+ calculations of ^{13}C NMR chemical shifts suggested that the structures of isoserrins A, B, and D – which were recently isolated from medicinal plant *Isodon serra* – are misassigned. Computationally driven structure revisions are presented in this communication.



Keywords: natural products, isoserrins, structure revision, NMR calculations, DU8+.

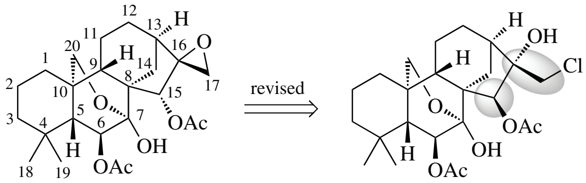
This work is dedicated to Nikolay S. Zefirov, an extraordinary chemist and mentor.

Modern computational chemistry offers a number of reliable tools to estimate nuclear magnetic resonance (NMR) spectral data of organic molecules.[1–6] However, accurate computations of NMR spectra remain challenging and require considerable resources, especially for large and conformationally flexible structures.

Recently, we have developed a fast and accurate method, DU8+, that utilizes a light level of density functional theory (DFT) augmented with empirical corrections.[7] Expedited computations of NMR spectral data with DU8+ enabled structure corroboration or revision of many large complex organic molecules, including important natural products.[7–10] Emerging fast computational predictions of NMR spectra provides a better option to validate or revise natural product structures as compared with venerable but effort-heavy revision methods based on total synthesis.[10]

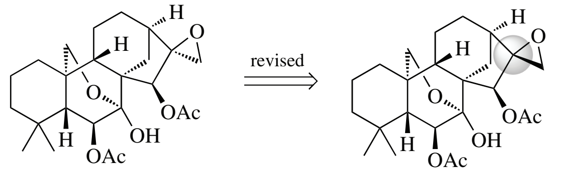
In recent work, a number of *ent*-kaurane diterpenoids were isolated from *Isodon serra*.[11] Structures containing tetrahydropyran and oxirane moieties were assigned based on extensive spectroscopic studies, including a wide array of 1D and 2D NMR techniques such as ^{1}H, ^{13}C{^{1}H}, COSY, HMBC, NOESY. However, four highly oxidized compounds, namely isoserrins A, B, D, and E, drew our attention due to the frequent misinterpretation of current experimental NMR data of oxygenated natural products.[8,9]

Our hunch was justified: DU8+ calculations revealed structure misassignment of three originally proposed isoserrins A, B, and D (**1**–**3**, Figure 1). For their structures, computed values of carbon-13 chemical shifts do not match experimental data with the root-mean-square deviations, rmsd(δ_C) > 2.44 ppm. Importantly, the accuracy of our DU8+ calculations was verified on thousands of reliable experimental chemical shifts: the training set, containing > 10 000 entries gave high accuracy with rmsd < 1.04 ppm. Generally, correct structures give a match with rmsd(δ_C) values in the range of 1.0–1.8 ppm or better.[8] Of the four isoserrins that we subjected



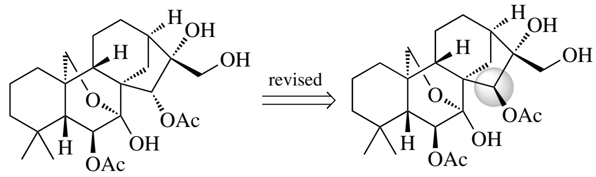
1
isoserrin A
rmsd(δ_C) = 3.93 ppm

5
16,17-chlorohydrin, *epi*-15,16
rmsd(δ_C) = 1.35 ppm



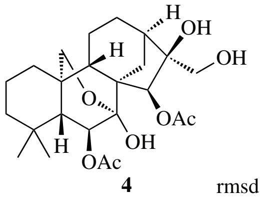
2
isoserrin B
rmsd(δ_C) = 2.44 ppm

6
epi-16
rmsd(δ_C) = 1.35 ppm



3
isoserrin D
rmsd(δ_C) = 2.92 ppm

7
epi-15
rmsd(δ_C) = 1.31 ppm



4
isoserrin E

rmsd(δ_C) = 1.30 ppm
correct

Figure 1 Structures of oxygenated isoserrins: originally proposed **1**–**4** and revised by DU8+ calculations **5**–**7**.

to DU8+ analysis, only the original structure of isoserrin E (**4**) gave a good match between the experimental and computed data, rmsd(δ_C) = 1.30 ppm, and did not require revision.

Isoserrin A exhibited the highest deviation between experimental and computed spectra, rmsd(δ_C) = 3.93 ppm. The 'oxirane carbon', C(16), was predicted to be at δ_C = 70.27 ppm, which is 13.93 ppm up-field compared to the experimental value. This deviation clearly indicates the absence of 16,17-epoxide in the isolated natural product. After some trial and error, we found that the revision of the oxirane to the shown chlorohydrin moiety provides a better fit to the experimental $^{13}C\{^1H\}$ NMR spectrum of isoserrin A. But this is not all: the structure also required inversion at the C(15) center, giving the final revised structure **5** with an rmsd(δ_C) of 1.35 ppm and mean absolute error (MAE) of 0.97 ppm.

Obviously, this revision contradicts the original mass spectroscopy data, but we could suggest a possible misinterpretation of the [M–HCl] peak in the original work as the molecular ion. Another piece of evidence that isoserrin A is unlikely to be an oxirane is that its reported retention time, t_R = 38 min, differs significantly from that of oxirane **6**, t_R = 29 min, and is more in keeping with the values for diols **4**, **7** (t_R = 39 and 35 min, respectively).

The relative configuration of carbons C(15) and C(16) in isoserrin A was originally proposed to be *rel*-15*R*,16*R*-**1** based on the NOESY interactions: H(15) with H(5) (δ_H = 1.45 ppm) and H(9) (2.00 ppm); and H(17α/β) with H(15), H(9), and H(12β). The latter correlations of methylene protons as well as their strong interactions H(17α/β)···OAc-15 are in accordance with the revised structure **5**. Unfortunately, interpretation of the NOE data for H(15) is challenging due to the overlapping signals. But after close examination of the reported data, a strong interaction 'H(15)···H(9)' (δ_H = 2.00 ppm) must be revised to H(15)···OAc-6 (δ_H = 2.01 ppm). A cross-peak attributed to 'H(15)···H(5)' contact is dispersed and dubious; however, significant NOE enhancement is observed for H(15)···H(14β) contact. Altogether, the reported NOESY spectrum fits well with our revised epimer *rel*-(15*S*,16*S*)-**5**.[†]

Two other misassigned isoserrins B and D show somewhat lower but still significant discrepancies between the computed and experimental data, with an rmsd(δ_C) of 2.44 and 2.92 ppm, respectively. The proposed structure of isoserrin B (**2**) has the most offending carbons C(16) and C(17) with $\Delta\delta_C$ = 7–8 ppm, pointing to the potential locus of the erroneous assignment. Thus, its C(16)-epimer **6** gives an excellent match with the reported NMR data with an rmsd(δ_C) of 1.35 ppm and MAE of 1.00 ppm. It is instructive that even when oxirane moieties are recognized correctly, its distorted geometry deviating from the ideal sp^3-geometry makes it difficult to correctly assign the stereoconfiguration based solely on the NMR experimental data.

In the case of isoserrin D, its carbon C(9) deviated the most with its calculated δ_C shifted 9 ppm downfield. This deviation could be explained by the shielding effect of an acetyl group. Indeed, inversion at C(15) brings C(9) and OAc-15 in proximity and leads to the corrected structure **7** with an rmsd(δ_C) of 1.31 ppm and MAE of 0.97 ppm. Regrettably, the Supporting Information for the original paper only contained a NOESY spectrum of isoserrin A. We are unable to independently confirm the reassigned stereochemistry for the other two compounds, isoserrins B and D. Once again, this example points out to the value of raw NMR data availability for structure elucidation and stereochemistry assignment in natural product research.[12]

In conclusion, the structures and stereochemistry of isoserrins – highly-oxygenated *ent*-kaurane diterpenoids – were reexamined by means of DU8+ calculations. The reported NMR data of isoserrin A were irreconcilable with the originally proposed structure and suggested the presence of the chlorohydrin group instead of the oxirane. It is not clear whether the original natural product was an oxirane modified in the course of isolation and purification or, alternatively, the chlorohydrin matching the reported experimental data for isoserrin A was the actual natural product in the first place. The chemical formulae and the atomic connectivity of isoserrins B and D were validated, but their structures needed stereochemical corrections. The structure and stereochemistry of isoserrin E were proved to be accurate.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.007.

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[†] Note the change in atom priorities around C(16) for chlorohydrin and oxirane.