Reassignments and Corroborations of Oxo-Bridged Natural Products Directed by OSE and DU8+ NMR Computation

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In memory of Paul von Ragué Schleyer and Julius Bredt

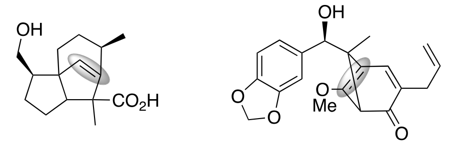
Abstract: Structural misassignments of natural products are prevalent in the literature. Developing methods and theoretical concepts to assist those undertaking structural elucidation is therefore of paramount importance, such that biologists and synthetic chemists avoid pursuing phantom chemical entities. Herein described is a strategy for predicting the isolabilities of oxygen-substituted bridgehead natural products based on calculations of olefin strain energies, NMR chemical shifts and coupling constants (DU8+). This approach provides corroborating evidence for the structures of certain bridgehead alkene natural products while leading to the reassignment of several other structures.

Determination of structure is a fundamental pillar of the discipline of chemistry.[1] However, misinterpretations of spectroscopic and/or physical data have often been known to result in structural misassignments. Such occurrences are particularly prevalent in the natural product (NP) arena, where complex atom connectivities and stereochemical complexity are abound.[2] Considering the extensive time and spectroscopic demands (e.g. NMR, IR, UV-vis, MS, CD) involved in correctly elucidating a novel natural product, the prevalence of misassignments in the literature is perhaps understandable.[3] There are now numerous *in silico* methods to help with structure elucidation by predicting spectra (e.g. NMR,[4] ECD[5]) from chemical structure input or conversely by predicting chemical structure from spectroscopic data (e.g. ACDLabs[6]). Yet in spite of these new technologies, misassignments continue to appear. X-ray crystallographic analysis in principle enables definitive structural elucidation, but in the NP arena the requisite quantities of material and suitable crystals are not always available, and furthermore misinterpretations are not unprecedented.[2a] Ultimate proof of proposed structural assignment is often provided via chemical synthesis and spectroscopic comparison of the synthesized material with the natural material,[2] although recently developed electron cryo-microscopy methodology could circumvent this requirement in the future.[7]

Given the above, there are proposed NP structures that immediately arouse suspicion by virtue of unusual molecular frameworks, bonding motifs or appended functional groups.[8] One noteworthy example is the case of anti-Bredt alkenes. In his eponymous rule, Bredt stated[9] that "the terminus of a double bond cannot exist at the bridgehead position of a caged bicyclic system".[10] Bredt developed his rule in the early 1900s while correcting erroneous monoterpene structures, but also recognized that the rule need not apply above a certain ring size (i.e. lowering double bond strain).[9d]

Since that time there have been numerous NPs isolated which have been proposed, and in certain cases confirmed, to contain a bridgehead double bond.[9g] Yet there are other NP structures which seem to be "anti-Bredt" in the sense that they appear too strained to survive under normal laboratory conditions. Distinguishing these unlikely structures from more reasonable bridgehead alkenes is a challenge.

Recently, we demonstrated that the stabilities of bridgehead alkene NPs could be predicted on the basis of olefin strain energies (OSEs).[11] Schleyer[12] had previously classified bridgehead alkenes into three categories – "isolable", "observable", and "unstable" – which have different characteristic OSE ranges. OSEs are readily calculated with molecular mechanics forcefields (the exact OSE "cutoff" values demarcating "isolable", "observable", and "unstable" alkenes depends on the forcefield used) and we previously established that all extant bridgehead alkene NPs whose structures have been verified fall into the "isolable" category.[13] Furthermore, we proposed that several putative NP structures [e.g., those for rosacedrenoic acid (**1**) and piperkadsin C (**2**)] were likely misassigned, as those alkenes fell into the "unstable" category (Figure 1).



Rosacedrenoic acid (**1**)
OSE = 38 kcal mol^{-1}
"unstable"

Piperkadsin C (**2**)
OSE = 66 kcal mol^{-1}
"unstable"

Figure 1. "Unstable" anti-Bredt natural products which are likely misassigned.

This classification scheme performed remarkably well for NPs with all-carbon skeletons, but its transferability to heteroatom-containing polycyclic frameworks was not tested. Therefore, an OSE-based classification scheme for oxo-substituted bridgehead alkenes has now been developed and, as shown herein, it can be used in tandem with NMR calculations to support or propose reassignments for a range of oxo-bridged NP structures.

Our laboratory's favored protocol for classifying a given bridgehead alkene as "isolable", "observable", or "unstable" was based on OSEs calculated with the OPLS_2005 forcefield.[14] To adapt this protocol to oxo-bridged bicyclic alkenes (i.e. structures with an oxygen atom directly connected to the double bond within the bicyclic framework), fifteen bicyclic oxo-bridged alkenes were chosen as shown in Figure 2. Each example within this calibration set is either a known isolable bridgehead olefin,[10,15] or the parent structure of a known isolable bridgehead olefin. The molecules span a broad range of OSEs (i.e. from –3.9 to 24.7 kcal mol^{-1}). Five structures (**5**, **8**, **10**, **13**, **17**) are analogues of molecules contained in the original hydrocarbon calibration set. For these molecules, the oxo-bridged and all-carbon structures differ in their OSEs by 1.2–4.5 kcal mol^{-1}, with no systematic variation evident. The most strained isolable oxo-bridged alkene, **17**, had an OSE of 24.7 kcal mol^{-1}, about 3 kcal mol^{-1} higher than its parent hydrocarbon **18**. Experimentally, Wiseman reported[16] that the C=C stretching frequency of **17** was 20 cm^{-1} higher that of **18**, and **17** underwent addition of acetic acid more slowly than **18**, both results suggesting that the C=C bond in **17** is less strained than that in **18**. In general, OSEs are not expected to capture all of the fine details of relative stabilities, but they do appear to be useful

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as a diagnostic of isolability. The OSEs correctly predict that both **17** and **18** are isolable.

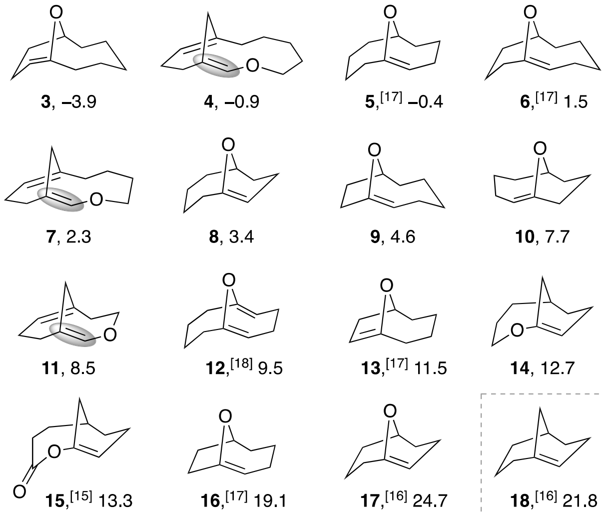
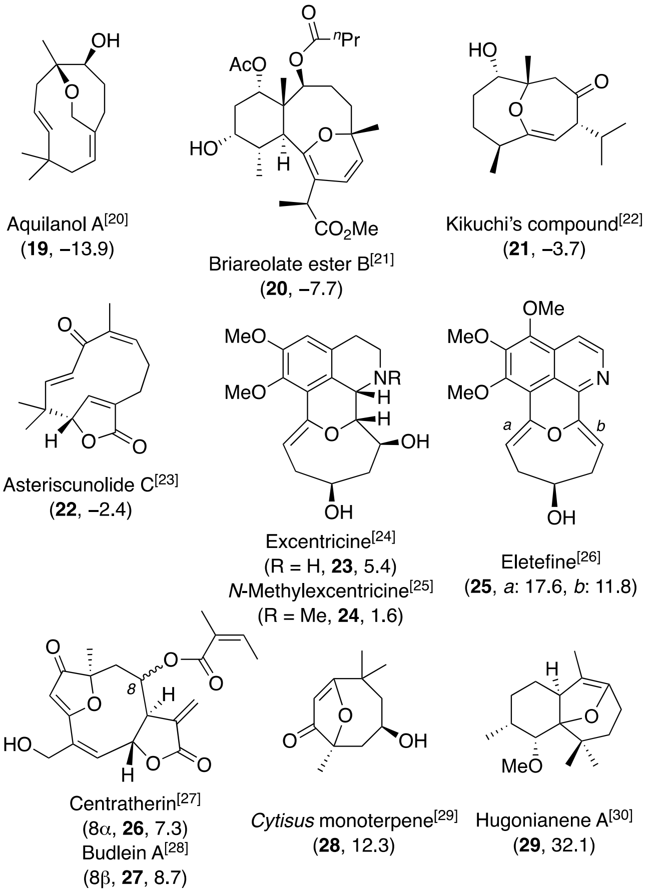

3, −3.9
4, −0.9
5,[17] −0.4
6,[17] 1.5
7, 2.3
8, 3.4
9, 4.6
10, 7.7
11, 8.5
12,[18] 9.5
13,[17] 11.5
14, 12.7
15,[15] 13.3
16,[17] 19.1
17,[16] 24.7
18,[16] 21.8

Figure 2. Calculated OSEs (OPLS_2005, kcal mol^{-1}) of parent oxo-bridged alkenes corresponding to known isolable skeletons.[15-18]

While it was straightforward to determine the OSE range typical of known isolable oxo-bridged alkenes, the task of determining the OSE ranges corresponding to “observable” or “unstable” was less clear. The difficultly arises in that efforts to determine the experimental properties of the more reactive oxo-bridged alkenes have received only little systematic attention in the literature and the structural features associated with the transition from “observable” to “unstable” are not well known. This task was therefore approached indirectly by calculating the oxygen-substituted analogues of the “observable” and “unstable” hydrocarbons within the original hydrocarbon set, taking account of the observation (above) that the presence of an oxygen atom influences the OSE by a few kcal mol^{-1}. OSE values ranging from 19 to 30 kcal mol^{-1} (see the Supporting Information) were found for these presumably less-stable alkenes,[19] suggesting that the transition from isolable to observable to unstable occurs between 20 and 30 kcal mol^{-1}, i.e. over a similar OSE range in both oxo-bridged and all-carbon bicyclic alkenes. Therefore, an OSE value greater than about 30 kcal mol^{-1} (as calculated with OPLS_2005) would be considered a predictor of instability.

Having explored the effect of oxygen substitution on OSEs, twelve oxo-bridged natural products that have been proposed in the literature were evaluated (i.e. **19**–**29**, Figure 3).[20-30] The calculated OSEs were observed to range from –13.9 to 32.1 kcal mol^{-1}. Only hugonianene A (**29**) had an OSE value greater than 30 kcal mol^{-1} i.e. diagnostic for “unstable”. For the remaining NPs, the OSE analysis raised no red flags for suspect structural assignments. This was not unexpected, given that the bridgehead alkene NPs **19**-**28** have larger rings containing eight or more atoms. In the case of briareolate ester B (**20**, OSE – 7.7 kcal mol^{-1}) and asteriscunolide C (**22**, OSE –2.4 kcal mol^{-1}), the bridgehead alkene structures have been verified by X-ray crystallography.[21,23]

Given the high OSE of hugonianene A (**29**, 32.1 kcal mol^{-1}) suggested the structure may have been misassigned. To explore this notion further a comparison of the theoretical and experimental NMR chemical shifts and coupling constants were undertaken using the DU8+ method. DU8+ combines computations of structure and NMR properties of organic molecules at a lighter level of DFT theory (i.e. to accelerate computations on relatively large organic molecules including triterpenes), and is implemented with the following components: (a) structure optimizations carried out with B3LYP/6-31G(d); (b) the isotropic magnetic shielding values computed with ωB97xD/6-31G(d) and corrected;[4d] (c) Fermi contacts evaluated with B3LYP/DU8 and scaled with the help of NBO-based corrections,[4c] to obtain spin-spin coupling constants (SSCC). The predicted spectra of **29** did not match the reported NMR data (see the Supporting Information): calculated ^{13}C chemical shift values gave a very poor match, rmsd(δ_C) > 11ppm.



Aquilanol A[20]
(**19**, −13.9)

Briareolate ester B[21]
(**20**, −7.7)

Kikuchi’s compound[22]
(**21**, −3.7)

Asteriscunolide C[23]
(**22**, −2.4)

Excentricine[24]
(R = H, **23**, 5.4)
N-Methylexcentricine[25]
(R = Me, **24**, 1.6)

Eletefine[26]
(**25**, *a*: 17.6, *b*: 11.8)

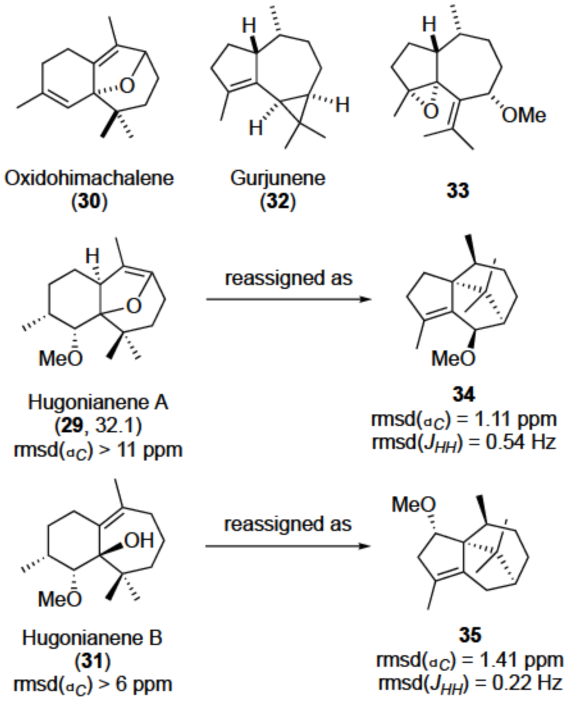
Centratherin[27]
(8α, **26**, 7.3)
Budlein A[28]
(8β, **27**, 8.7)

Cytisus monoterpene[29]
(**28**, 12.3)

Hugonianene A[30]
(**29**, 32.1)

Figure 3. Calculated OS energies for reported NPs containing oxo-bridgehead alkenes.

Embarking on the structural reassignment of **29** (Figure 4) proved particularly challenging. An initial hypothesis was made that **29** could be an oxidation product of oxidohimachalene (**30**).[31] This idea would be in line with the reported structure for hugonianene B (**31**)[32] (i.e. same skeleton), but compounds matching the experimental SSCC of **29** proved difficult to identify. Many variations on structure were explored, albeit with no success. These included alternative ring systems, for example, the oxidation product (**33**) of gurjunene (**32**),[33]a well known ring system that shares the gem-dimethyl group and seven-membered ring in common with hugonianene A. Considering that the original report for **29** only provided a nominal mass along with inconclusive accurate mass data (i.e. 41 ppm mass difference) for the related structure hugonianene B (**31**), the molecular formula could perhaps be incorrect. Given that a number of carbon signals reported for **29** did not support multiple oxygenation (i.e. insufficient number of downfield resonances), the molecular formula was revised to $C_{16}H_{26}O$ (a decrease from two oxygens to one). Taking this aspect into account, along with leads provided by gurjunene, DU8+ analysis suggested that the methyl ether (**34**) of 4-patchoulene-6α-ol was a likely candidate (see the Supporting Information) as the calculated SSCCs and ^{13}C chemical shifts matched well with the experimental values for hugonianene A: rmsd(J_{HH}) = 0.54 Hz, rmsd(δ_C) = 1.11 ppm. An additional search of the literature revealed that this compound was known.[34] Thus, on comparison with the reported NMR spectra, hugonianene A (**29**) is revised to **34**. However, on comparison of the optical rotation data provided for **29** ($[\alpha]_D^{20}$ -15°) with that of **34**, isolated from *Croton muscicarpa* ($[\alpha]_D^{20}$ +24°),[34] the absolute stereochemistry of **34** is assigned as the opposite enantiomer (i.e. as shown in figure 4). Furthermore, hugonianene B (**31**) is then tentatively reassigned as **35** based on the comparison of experimental and calculated NMR data (see the Supporting Information) (Figure 4). The original structure gave a poor rmsd rmsd(δ_C) > 6 ppm, while calculations for the revised structure were in very good agreement with the experimental data, rmsd(J_{HH}) = 0.22 Hz, rmsd(δ_C) = 1.41 ppm.



Oxidohimachalene (**30**)

Gurjunene (**32**)

33

Hugonianene A (**29**, 32.1) rmsd(d_C) > 11 ppm

34 rmsd(d_C) = 1.11 ppm rmsd(J_{HH}) = 0.54 Hz

Hugonianene B (**31**) rmsd(d_C) > 6 ppm

35 rmsd(d_C) = 1.41 ppm rmsd(J_{HH}) = 0.22 Hz

Figure 4. Reassignment of hugonianenes A (**29**) and B (**31**).

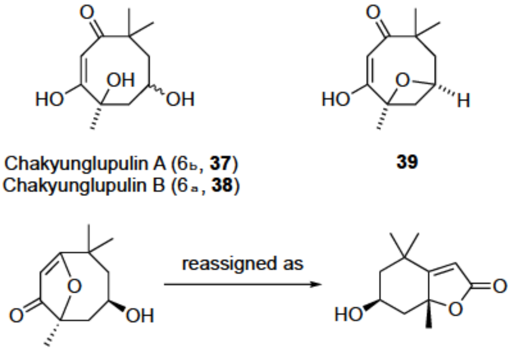
Returning to the NPs that had been classified as isolable in the OSE analysis (Figure 2), DU8+ was then deployed to check the structural assignments (except for **20** and **22**, which have already been confirmed by X-ray crystallography). DU8+ analysis revealed mismatches between the experimental and calculated NMR data for both Kikuchi's compound **21** and the *Cytisus* monoterpene **28** (see the Supporting Information). For **21**, DU8+ predicted a ^1H-^1H coupling for the 7α-hydroxy group that was not present in the experimental spectrum. However, closer agreement was observed if C7 was inverted to 7β (**36**). The predicted ^{13}C chemical shifts were also in much better agreement with the experimental data, rmsd(δ_C) = 1.37 ppm. Thus **21** was reassign as the epimer **36** (Figure 5), which is further supported by biosynthetic considerations i.e. enol attack of an *E*-alkene derived epoxide.

Kikuchi's compound (**21**) rmsd(d_C) = 4.13 ppm rmsd(d_H) = 0.37 ppm rmsd(J_{HH}) = 1.91 Hz

36 (OSE = -3.4) rmsd(d_C) = 1.37 ppm rmsd(d_H) = 0.21 ppm rmsd(J_{HH}) = 0.47 Hz

Figure 5. Reassignment of Kikuchi's compound (**21**).

For the *Cytisus* monoterpene **28**, a biosynthetic analysis[35] suggested a possible origin in chakyunglupulin A (**37**) or B (**38**),[36] via a cyclodehydration step (Figure 6). Therefore oxetane **39** was postulated as an alternative structure, however, the predicted NMR did not match with experiment. A clue was gained from the chemical shift (δ_c 183.5ppm[29]) of the ketone seen in **28**, which had the hallmarks of an α,β-unsaturated lactone. This led to common NP lactone ring systems being explored, which after considerable trial and error (i.e. DU8+ calculations) arrived at the known fused γ-lactone of loliolide (**40**) (see the Supporting Information). On this basis, the *Cytisus* monoterpene **28** should be reassigned as loliolide (**40**)[37a] (Figure 6). Furthermore, on comparison of the optical rotation data provided for **28** ($[\alpha]_D^{20}$ -88°)[37a] with that of **40** ($[\alpha]_D^{15}$ -97°),[37b] the absolute stereochemistry of **40** is assigned as the enantiomer shown in figure 6.



Chakyunglupulin A (6_b, **37**)
Chakyunglupulin B (6_a, **38**)

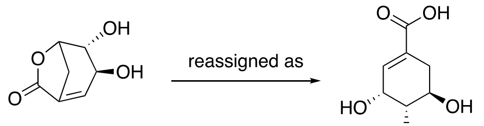
39

Cytisus monoterpene (**28**) rmsd(d_C) > 11ppm

Loliolide (**40**) rmsd(d_C) = 0.95 ppm rmsd(d_H) = 0.22 ppm rmsd(J_{HH}) = 0.41 Hz

Figure 6. Reassignment of *Cytisus* monoterpene (**28**).

Having demonstrated the utility of the OSE/DU8+ approach, the study was extended to consider one further example: folenolide[38] (**41**, Figure 7). Folenolide is not an oxo-bridged alkene, but its [3.2.1]-bicyclic skeleton raised suspicion as it appeared likely to be an anti-Bredt alkene. The OSE of **41** (39.6 kcal mol^{-1}) is well above the typical lower bound for an "unstable" bridgehead alkene. Reassignment was therefore pursued. It was noted that the plant species from which folenolide was isolated had previously been reported[39] to contain shikimic acid (**42**). The molecular formula of folenolide differs from that of shikimic acid by the loss of H_2O. In the mass spectrum of shikimic acid, the molecular ion is reported to occur with very low intensity, and the main fragment ion arises from loss of water, i.e. coincident with the reported mass of the folenolide molecular ion.[40] Therefore it was hypothesized that folenolide in fact represented a misassignment of shikimic acid. Comparison of the NMR data of folenolide and shikimic acid[41] provided a good match and thus supported reassignment of folenolide to shikimic acid (Figure 7).



Folenolide
(**41**, OSE = 39.6)

Shikimic acid (**42**)

Figure 7. Reassignment of folenolide (**41**).

In conclusion, reported herein is the application of olefin strain energy (OSE) calculations in conjunction with DU8+ NMR calculations to natural product structure elucidation. These techniques have been used to reassign the structures of several oxo-bridged NPs. This combination represents a valuable approach to interrogate the ever increasing number of natural products being reported by chemists and those working in aligned areas. It is also a timely reminder that having access to raw NMR spectroscopic data,[42,43] potentially in the form of an open access database, is paramount for accurate structure elucidation lest phantom targets be adopted by chemists, and biologists alike, for further study.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anti-Bredt • bridgehead double bond • natural product• reassignment • Bredt

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