Natural Products Containing the Oxetane and Related Moieties Present Additional Challenge for Structure Elucidation: a *DU8+* Computational Case Study.

Andrei G. Kutateladze,* Tina Holt, and D. Sai Reddy.

Department of Chemistry and Biochemistry, University of Denver, Denver, CO 80208

ABSTRACT: Analysis of published NMR data for natural products containing the oxetane moiety, with the help of a recently developed parametric/DFT hybrid computational method *DU8+*, has revealed that oxetanes and related compounds constitute yet another significant challenge in structure elucidation and stereochemistry assignment, as more than 30 structures required revision. Most common pitfalls are discussed and revised structures are suggested for 26 natural products.

INTRODUCTION

Naturally occurring oxetanes do not constitute a statistically significant subset of oxygenated natural products (NPs). Perhaps for this reason, there are no well-established recipes for recognizing/detecting the oxetane moiety in NPs, and assigning their structure and stereochemistry. ^{13}C NMR chemical shifts of oxirane carbons generally appear in the higher fields than the corresponding acyclic ethers or alcohols which makes it easier to spot an epoxide in a natural product. In contrast, O-bonded oxetane carbons are shifted to the lower field of the spectrum. These values overlap with the chemical shift ranges of other cyclic and acyclic ethers, especially tetrahydrofurans embedded into polycyclic structures, which makes it challenging to recognize the oxetane moiety and assign molecular structure and stereochemistry.

Recent innovative developments in computational methods for prediction of NMR spectra[1] offer an increasingly more user friendly and reliable tools for facilitating structure elucidation of natural products and other complex organic molecules. This allowed for computationally-driven revisions in such high-profile cases as hexacyclinol[2] and many other NPs. We recently combined our hybrid DFT-parametric method, *rff*,[3] for computing nuclear spin-spin coupling constants with empirically-corrected DFT calculations of chemical shifts into an integrated method, *DU8+*[4] which allows for fast and accurate computations of NMR spectra of large organic molecules based on all three criteria, i.e. spin-spin coupling constants, proton, and carbon-13 chemical shifts. *DU8+* combines computations of structure and NMR properties of organic molecules at a light level of DFT theory and is implemented with the following components: (a) structure optimization: B3LYP/6-31G(d); (b) magnetic shielding: ωB97xD/6-31G(d); (c) Fermi contacts: B3LYP/DU8; (d) scaling of the computed Fermi contacts with the help of NBO hybridization parameters according to ref. 3b "*rff*" to obtain spin-spin coupling constants; (e) scaling of isotropic magnetic shielding values with empirical corrections according to ref. 4 to obtain chemical shifts.

Overall, the current training set for ^{13}C chemical shifts exceeds 7600 reliable experimental measurements calculated with the rmsd(δ_C) of 1.26 ppm. As a result, the majority of correct validated structures fall into the rmsd range of 1.0-1.6 ppm or even better. Proton spin-spin coupling constants (SSCCs) are computed with the accuracy of 0.3 Hz as determined on the training set of more than 4K reliable experimental values.

The method was used to validate or correct numerous misassigned structures, including complex marine halogenated natural products, oxygenated natural triquinanes, natural products containing the oxirane moiety, and anti-Bredt NPs.[5] Recent analysis of a large number of natural oxetanes also revealed a high rate of misassignment, addressed below.

RESULTS AND DISCUSSION

We first address the performance and accuracy of *DU8+* for the structures containing the oxetane moiety. Figure 1 shows examples where the original structures were correctly assigned (many of them are unambiguously established with the help of X-ray crystallography or total synthesis): parthoxetine (X-ray),[6] laureacetals D (X-ray) and E,[7] compositacin D,[8] dictyoxetane (X-ray),[9-10] dichrocephone B,[11] mitrephorone A[12] recently synthesized by Careira,[13] ramariolide B,[14] and wallifoliol.[15] All of them show good matches with NMR experimental data (rmsd's for ^{13}C chemical shifts are shown). *DU8+* accurately predicted spectra of oxetane-containing NPs such as holophylline O,[16] hawaiienol A (X-ray),[17] and merrilactone A (X-ray)[18] in polar solvents, where a PCM model was required.

Lipase inhibitor vibralactone,[19] diterpene rubesanolide (X-ray),[20] and neurotropic sesquiterpenoid veranisatin A[21] demonstrated that *DU8+* also accurately predicts the chemical shifts for NPs possessing the *β-lactone* moiety. These and many other examples made it abundantly clear that *DU8+* competently handles the oxetane moiety in a variety of complex natural products.

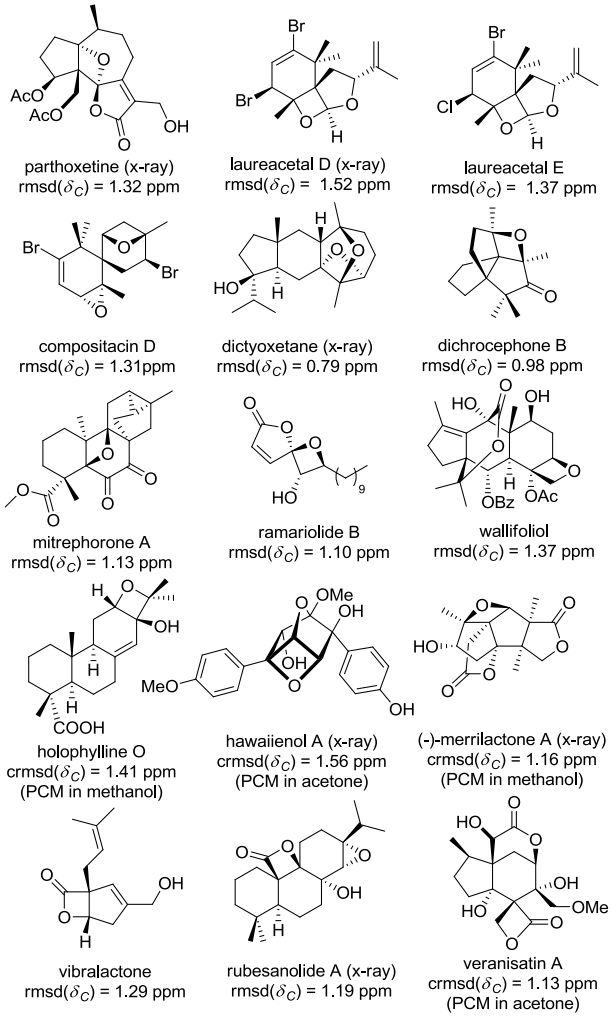


Figure 1. Oxetane-containing NPs as test cases.

As it will follow from the discussion below, complex natural products containing the oxetane moiety are often misassigned. However, it appears that even very small oxetane-containing organics present significant challenges for structure elucidation. Figure 2 illustrates this point. Two products were isolated from a Paterno-Buchi reaction of an allyl cyclopentanol:[22] the major was assigned as a *straight* oxetane, compound **47**,[23] while the minor product, compound **48**, was assigned as a *crossed* oxetane. *DU8+* computations confirmed the assignment of the major product: rmsd(δ_C) = 0.51 ppm. However, the calculated NMR chemical shifts for the minor product were in disagreement with the experimental data; rmsd(δ_C) > 7 ppm for both potential isomers, *syn* and *anti*, Figure 2A.

As ^{1}H NMR of compound **48** shows three low field protons, i.e. the oxetane potentially has the CH_2-O-CH fragment, we hypothesized that the minor compound **48** might be a product of carbonyl-olefin metathesis,[24] Figure 2C. Photolysis yielding oxetane **48** was not conducted at elevated temperatures, i.e. the most common conditions for carbonyl-olefin metathesis. However, we have demonstrated in the past that such low temperature oxametathesis could occur in strained polycyclic Paterno-Buchi products under very mild conditions.[25] This indeed turned out to be the case. *DU8+* computations for the product of oxametathesis matched the experimental NMR parameters of the minor product **48** very well, Figure 2B.[26]

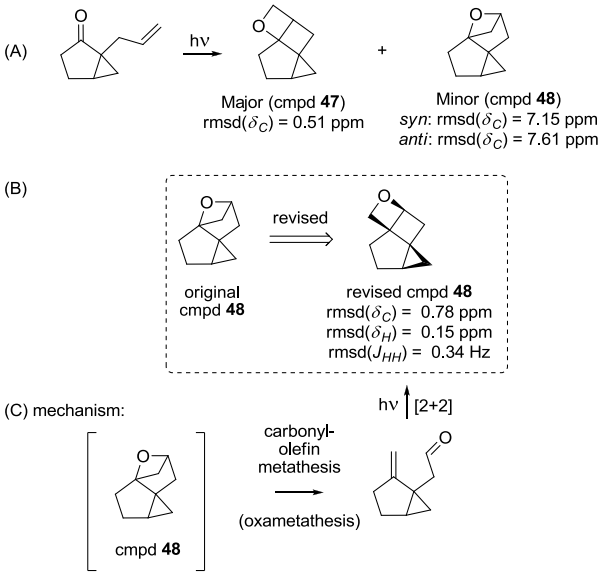


Figure 2. The Paterno-Buchi cross-product **48** is revised to the product of its oxametathesis.

Similar challenges occur with the structure assignment of small molecules containing nitrogen counterparts of oxetanes, i.e. azetidines. An instructive case is presented in Figure 3, where one of the products of a photoinduced [2+2] cycloaddition, compound **8**, was assigned a structure of azetidine.[27] DU8+ analysis demonstrated that both products **7** and **8** required revision as shown, i.e. azetidine **8** is revised to the cross product **7**, while **7** is revised to its epimer at the α-carbonyl position. Because **7** was identified by the authors as an early synthon in a library synthesis, the derived downstream products potentially require revision of stereochemistry. This revision is in keeping with the recent findings from the Booker-Milburn lab: it appears that photoinduced [2+2] cycloadditions in vinyl-allylamines exclusively produce the *cross*, not the *straight* products.

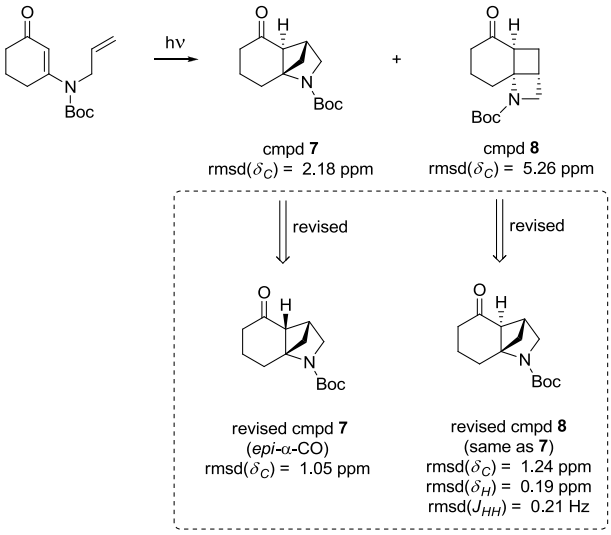


Figure 3. Revision of incorrectly assigned azetidine 8 and the *cross*-product **7**.

These challenges of oxetane structure assignment are only further compounded in complex natural products. Ascribing the oxetane fragment to what in reality is an open 1,3-diol or a chlorohydrin appears to be one of the common misassignments of the structure of natural products perceived to contain an oxetane moiety. Even for small NPs such as cleroindicin A[28] this could be an issue, Figure 4A.

The predicted chemical shifts for carbons in the oxirane ring of cleroindicin A were not in agreement with the experimental data. Both oxirane carbons deviated by more than 13 ppm. *DU8+* calculations, with PCM correction for pyridine as a solvent, matched nicely the open *syn* triol. Another piece of evidence is that the magnetically equivalent geminal protons of the "oxetane" moiety in the original structure of cleroindicin A were reported as a triplet with J = 6.6 Hz. The calculated values for the *syn*- and *anti*- vicinal ^3J constants for these protons in the original oxetane-containing structure are 9.2 and 7.1 Hz, which does not match the experiment. On the contrary, in a freely rotating primary alcohol this triplet is expected to average to approximately 7 Hz, matching the experimental observation.

Interestingly, we found one report of synthesis of the original structure of cleroindicin A.[29] As there were no details on NMR or other analytical data available in this publication, we do not have a good explanation for this report. Our calculations leave no doubt that cleroindicin A is misassigned. This is the first example that we are aware of, in which the computational revision contradicts the synthetic affirmation of the original structure.[30]

Other examples of an oxetane being confused for an open diol are shown in Figure 4B-G: 2α,6α-epoxy-3-himachalene[31] (B) is revised to the shown 2α,6α-diol; the new eudesmane derivative capitulatin B[32] (C) is revised to 1β,4α,6β-triol; its oxidized relative, 11-hydroxycapitulatin B[33] (D) is revised to a corresponding tetraol; a clerodane diterpenoid cephaloziellin B[34] (E) is revised to its open hydroxy-hemiacetal; (16R)-13,17-epoxy-16-hydroxy-*ent*-kaur-9(11)-en-19-al is revised to the shown open triol and C16-epimer (F); and 1,4-epoxy-6-deoxypseudoanisatin (cmpd **1**)[35] is revised to 1α-hydroxy-6-deoxypseudoanisatin (G).

In the last example (G), the original structure was missing the lactone oxygen, which was probably due to a typo in the drawing. However, there is no doubt that the oxetane moiety, reported for this structure should also be revised to the open diol. Search of the literature revealed that our revision is the known *seco*-prezizaane-type sesquiterpene,[36] as evidenced by a perfect match of the experimental ^{13}C chemical shifts.

The values of reported ^{13}C chemical shifts for carbons bearing oxygens in all these proposed oxetane structures are simply too low for oxetanes. *DU8+* gives a very poor match for all the original structures. Calculations for the corresponding open diols matched significantly better. Again, we have confidence in the accuracy of the method even for complex oxygenated diterpenoids such as cephaloziellin B. For example, its *correctly assigned* relative – cephaloziellin A (not shown), which is as complex as cephaloziellin B – gave an excellent rmsd(δ_C) of 1.24 ppm.

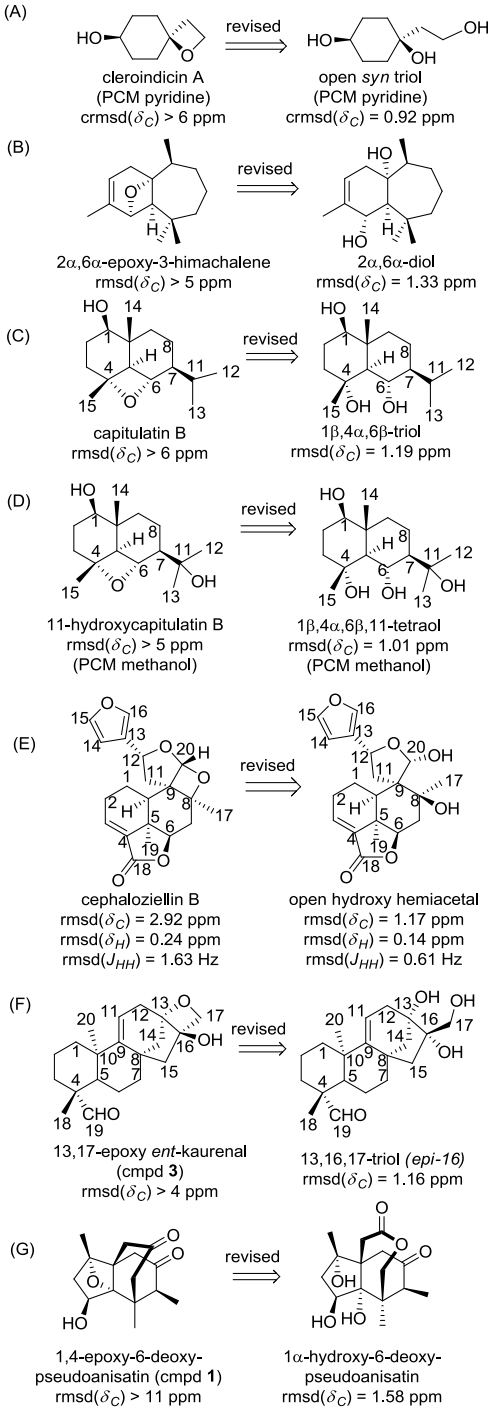


Figure 4. Mistaken diol identity in NPs.

Another common error is assigning the oxetane moiety to the structures with larger O-containing cycles, for example, tetrahydrofurans (thf's), Figure 5. A new monoterpenoid from the endophytic fungus *Periconia* sp. F-31, 8-hydroxy-1,7-expoxy-2-menthene[37] is revised to its thf isomer. A highly oxygenated abietane diterpenoid triptergulide A, isolated from the leaves of *Tripterygium wilfordii*,[38] is perhaps not as deeply rearranged as the authors hypothesized. Its revised structure also contains a thf, not oxetane moiety. Finally, the bicyclic cytotoxic β-lactone myrotheciumone B,[39] isolated from *Myrothecium roridum*, an endophytic fungus of the medicinal herb plant *Ajuga decumbens*, is in fact the shown bicyclic γ-lactone.

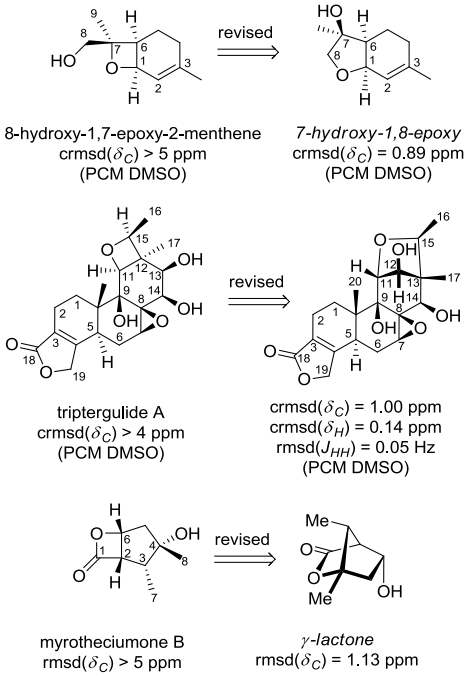


Figure 5. A tetrahydrofuran or γ-lactone moiety mistaken for oxetane or β-lactone.

In the previous report on NPs containing the oxirane moiety[5a] we also corrected stereochemistry of aromatican D; its revised structure has an oxetane ring. We now found that another member of the same family of sesquiterpene lactones, aromatican F, represents a less common misassignment – a thf moiety is assigned, but the structure, in fact, contains an oxetane moiety.

We revise aromaticane F to the oxetane shown in Figure 6 (here and everywhere in this paper relative stereochemistry is implied). Two other candidate structures **A** and **B** are also shown. The *8-epimer* B gave the worst match of the three and was discarded. The *8,9-epimer* candidate **A** gave an acceptable match. However, **A** does not satisfy the observed NOE enhancement for H1-H9, while the proposed revised structure does.

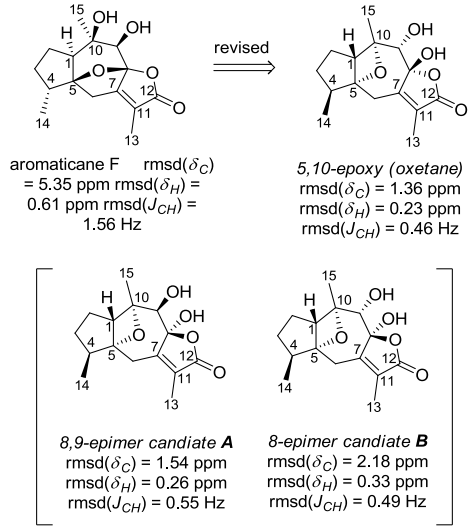


Figure 6. Aromaticane F: a rare case of an oxetane confused for a tetrahydrofuran.

Less typical error: oxetane is assigned where the actual structure contains an oxirane moiety. These are rare because oxiranes are easier to identify due to their low field C(O) resonances. However, three sesquiterpene lactones, moroccolide A and saharanolides A and B represent this very error in assignment, Figure 7.[40]

DU8+ calculations for all three originally proposed oxetanes gave very poor match with the experimental NMR data, Figure 7. Based on the higher field resonances ascribed incorrectly to the oxetane moiety of moroccolide A, its structure is now revised to the shown 3,4-epoxy-2-hydroxy sesquiterpene lactone. Analysis of other sesquiterpene lactones, isolated in this study from *Warionia saharae* leaves, namely epoxides **3** and **4** shown in Figure 7 for comparison, gave useful clues to the structure revision saharanolides A and B. Additionally, we noted that the hydroxy proton for saharanolide A is listed at 8.05 ppm, which is indicative of a peroxide,[41] not a hydroxy group. Thus we revised saharanolide A to the hydroperoxy counterpart of 8-desoxy-3α,4α-epoxyrupiculin A (i.e. 1-hydroperoxide of compound **3**) and revised saharanolide B to the hydroperoxy counterpart of 8-desoxy-3α,4α-epoxyrupiculin B (i.e. 1-hydroperoxide of compound **4**). As this revision obviously contradicts the reported HRMS data, we revise saharanolides A and B tentatively.

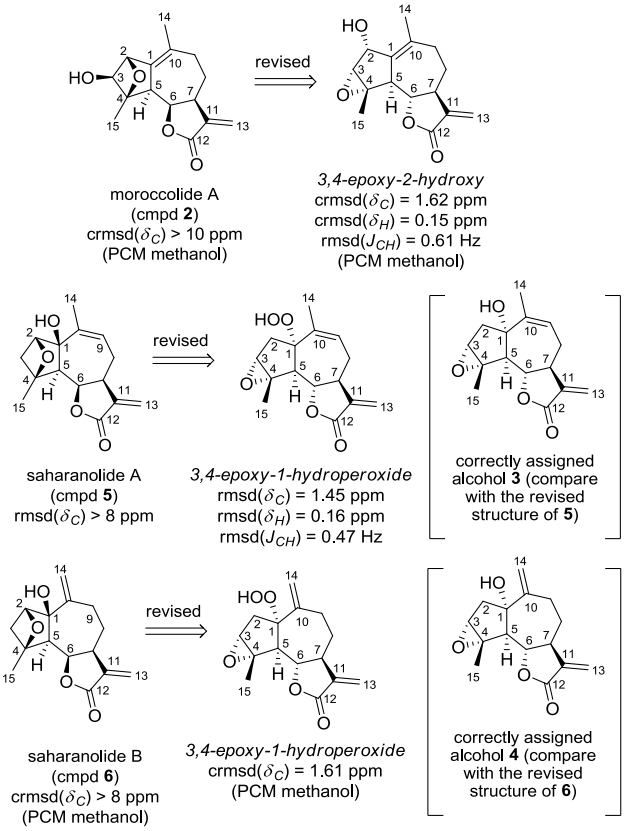


Figure 7. Oxiranes confused for oxetanes

The oxetane moiety introduces considerable distortion of idealized sp^3 geometry, which results in increased stereochemical misassignments even in the cases when the oxetane moiety is actually present in the structure of a natural product. Instructive examples for it are 6,11-epoxy-eudesmane[42] and okamuragenin,[43] Figure 8. The Me15 group of 6,11-epoxy-eudesmane is assigned the α-orientation

based on a NOE enhancement with H6. However, the analysis of the 4-epimer (i.e. β-Me15) shows that the C15-H6 distance is 3.01 Å, which places this methyl's hydrogen within a very short distance, < 2.5 Å, from H6. The originally proposed structure gave poor rmsd(δ_C) = 2.91 ppm, whereas the revised 4-epimer gave an excellent match, rmsd(δ_C) = 1.25 ppm.

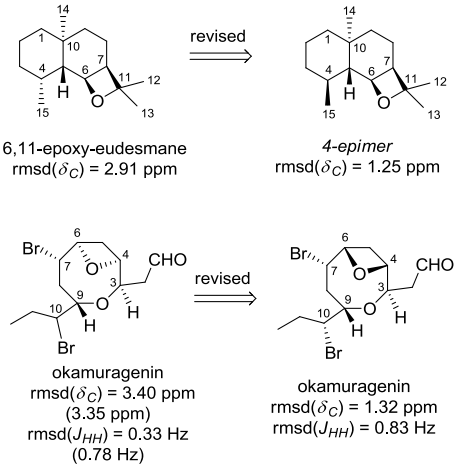


Figure 8. 6,11-epoxy-eudesmane

New C_{12}-acetogenin, okamuragenin, was isolated from the marine red alga *Laurencia okamurai*.[43] Its stereochemical configuration at C10 was not defined; we clarified it as shown in Figure 8. More importantly, the stereochemistry of the 4,6-epoxy bridge needed revision as shown.

Considerable challenges appear to complicate structure elucidation of the unsaturated oxetane relatives, oxetes. Oxetes are known and isolable, although very few of them have been fully characterized with ^{13}C NMR.[44] Figure 9A shows the examples of three small organic molecules containing the oxete moiety for which ^{13}C data is available. The first two[45] are correctly assigned, but the third compound obtained from an allenic precursor via a gold-catalyzed reaction[46] definitely required correction.

Similar challenges occur with natural products. An unusual structure of fusariumin D[47] isolated from a symbiotic strain *Fusarium oxysporum* ZZP-R1 derived from the plant *Rumex madaio* Makino called for closer investigation, Figure 9B. DU8+ analysis revealed irreconcilable differences between the computed and the experimental data, rmsd(δ_C) > 7. Closer look at the NMR data led us to consider 4-pyranones; we now revise fusariumin D to 2-methoxy-6-(1,3,5-trimethyl-1-heptenyl)-4-pyranone as shown in Figure 9B. The match between computed and experimental ^{13}C chemical shifts for a conjugated push-pull π-system like this was improved to 1.14 ppm by PCM calculations, the fact that the solvent being only weakly polar (chloroform) notwithstanding. This improvement underscores our past assertions that ^{13}C chemical shifts for sp^2-rich molecules with extended π-conjugation are more sensitive to solvent effects because their sp^2 carbons are exposed to solvent. In contrast, ^{13}C chemical shifts for the mostly saturated, sp^3-rich natural products are less sensitive to solvent effects. This is why DU8+ allows for gas phase computations and generally does not require PCM corrections for chloroform and solvents of low polarity.

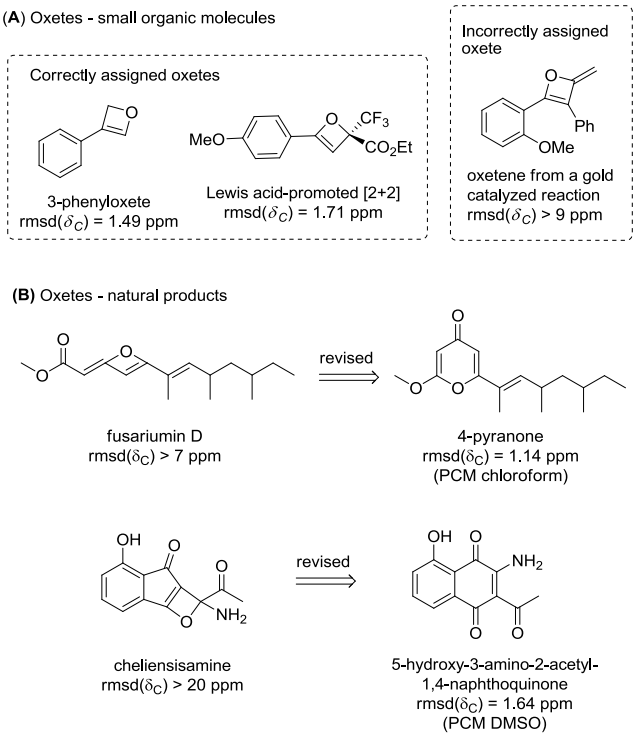


Figure 9. Oxete-containing small organic molecules (**A**), and natural products (**B**).

Another unusual 2-aminooxet, cheliensisamine (Figure 9B), was isolated from the bark of *Goniothalamus cheliensis* Hu, a tree from Yunnan Province in China.[48] Attempts to computationally optimize this structure failed. The hemi-aminal is not a minimum on the potential energy surface; the initial geometry undergoes *in silico* 4π electrocyclic ring opening into substituted indanedione. It is not clear from the NMR data for cheliensisamine what prompted the authors to propose this unusual structure. Three years after the initial discovery, the list of compounds isolated from the same plant was considerably extended by the authors.[48b] Alone with cheliensisamine there were several natural products possessing the quinone moiety. We believe that one of these compounds, 5-hydroxy-3-amino-2-acetyl-1,4-naphthoquinone is cheliensisamine. This 3-aminonaphthoquinone was earlier isolated from the stem bark of a related species *Goniothalamus marcanii* and characterized by NMR in chloroform,[49] making it somewhat challenging to compare with the ^{13}C data of cheliensisamine, which is recorded in DMSO-d$_6$. However, there is enough similarity for us to revise cheliensisamine into 5-hydroxy-3-amino-2-acetyl-1,4-naphthoquinone.

Oxetes fused to aromatic rings constitute an even smaller subset of four-membered oxygen heterocycles. Adam and co-workers demonstrated that benzoxetes are isolable and can be obtained photochemically at low temperature, see the example of 2-acetyl-2-methyl-6-methoxy-benzoxetene (top right inset in Figure 10).[50] This is the only example of correctly assigned benzoxete that has ^{13}C NMR data matching well the DU8+ calculated values, rmsd(δ_C) = 1.47 ppm. The caveat is that even at -25°C this benzoxete undergoes spontaneous ring-opening and reverts to its quinomethide photoprecuror within 24 hrs, which begs the question whether a natural product could ever possess this thermally labile moiety. Dictionary

of Natural Products[51] gives only four benzoxete-containing compounds: amentotoxin,[52] phomopsidone A,[53] roseanone,[54] and zizyberanone.[55] The last compound, zizyberanone, is the same as amentotoxin, which leaves three unique structures to analyze.

DU8+ calculations for the proposed structure of phomopsidone A poorly matched the experimental ^{13}C values, rmsd(δ_C) >7 ppm, which necessitated the revision. Given a relatively low value of ^{13}C chemical shift for the oxetane's CH_2 carbon, a logical place to start was to virtually "hydrolyze" the oxetane ring into the shown bis-hydroxy compound, which significantly improved the match. Additional search in the literature revealed that it is a known compound, excelsione,[56] for which X-ray structure is available. Its NMR was recorded in a different solvent, DMSO-d_6, as opposed to pyridine-d_5 for phomopsidone A. However, the two experimental data sets correlated well with correlation coefficient of 0.9998. Using the constant offset of 1.9 ppm for the chemical shifts of phomopsidone A allowed for the direct estimation of rmsd between the two experimental sets in different solvents, producing rmsd($\delta_{Cexp\text{-}Cexp}$) = 0.99 ppm, which leaves little doubt that phomopsidone A is in fact exelsione.

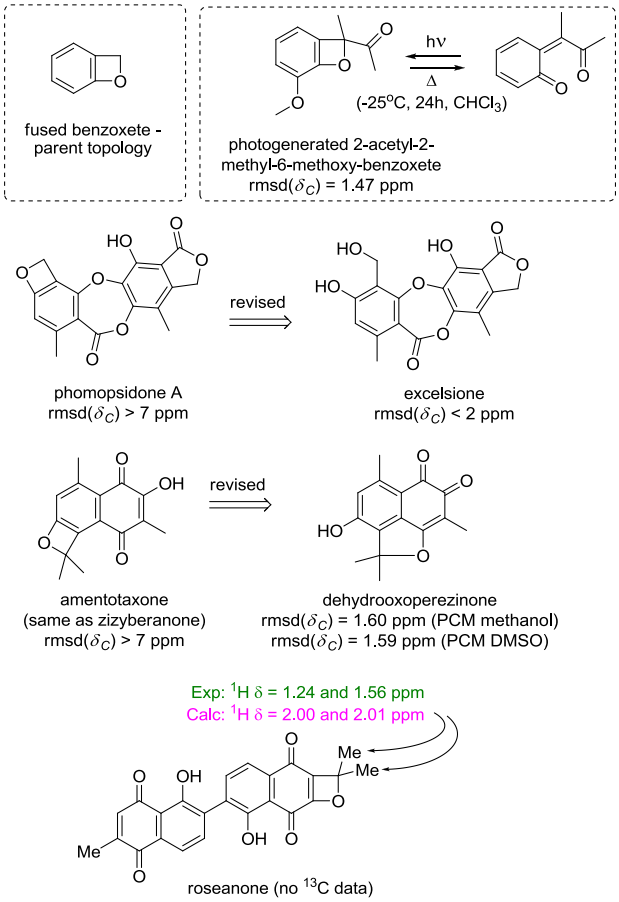


Figure 10. Benzoxetes.

Experimental chemical shifts for amentotaxone (same as zizyberanone) did not match the values calculated for its oxete-containing structure either. After careful analysis of its NMR data we arrived at a revised structure shown in Figure 10, which contains a 1,4- not 1,3-epoxy bridge. The revised structure matched the experimental ^{13}C chemical shifts for zizyberanone with crmsd(δ_C) = 1.6 ppm (PCM methanol) and for amentotaxone – with crmsd(δ_C) = 1.59 ppm (PCM DMSO). Literature search revealed that this is a known compound, dehydrooxoperezinone.[57] As the NMR spectra for dehydrooxoperezinone and zizyberanone were acquired in the same solvent, methanol, two experimental sets of ^{13}C chemical shifts were compared and shown to match nearly perfectly, rmsd($\delta_{Cexp\text{-}Cexp}$) = 0.03 ppm. Thus amentotaxone/zizyberanone is revised to dehydrooxoperezinone.

The third compound, roseanone, did not have ^{13}C data listed and therefore we were limited to the analysis of its ^1H NMR spectrum in $CDCl_3$, which is not very informative in this case. Oxete's *gem*-dimethyls were reported at 1.24 and 1.56 ppm. However, in the calculated spectrum they are nearly magnetically equivalent and predicted to have ^1H chemical shifts at 2.00 and 2.01 ppm. We are therefore very confident that roseanone is also misassigned and does not have the shown oxete moiety. However, without ^{13}C NMR data it would be impossible to suggest the revision.

Based on Adam's results indicating low stability of benzoxetes and the fact that we did not find a single confirmed example of a natural product containing the benzoxete moiety, our conclusion is that such natural products are unlikely to exist.

Similarly, benzodioxete moiety is very much questionable in NPs. The search of the Dictionary of Natural Products for benzodioxete results in only one structure, buxifoliadine,[58] which is filed under the systematic name of 5,6-epidioxy-2-hydroxy-1,7-dimethoxy-10-methylacridon. We noticed an unorthodox depiction of the structure of buxifoliadine in the original isolation paper (reproduced in Supporting Information). Based on our analysis of the NMR data, we generated several candidate structures of which the shown acridine-1,4,9-trione gave the best match, crmsd=1.50 ppm (PCM DMSO). All observed crosspeaks in the experimental HMBC spectrum of revised buxifoliadine correspond to large values of calculated J_{CH} carbon-proton spin-coupling constants, see Figure 11. The only potential discrepancy was that the crosspeak from overlapped methyl groups in the original structure to the carbon at 148.9 ppm was ascribed to the second methoxy group. In the revised structure this crosspeak is ascribed to coupling between N-Me and C-4a, J_{CH} = 2.6 Hz.

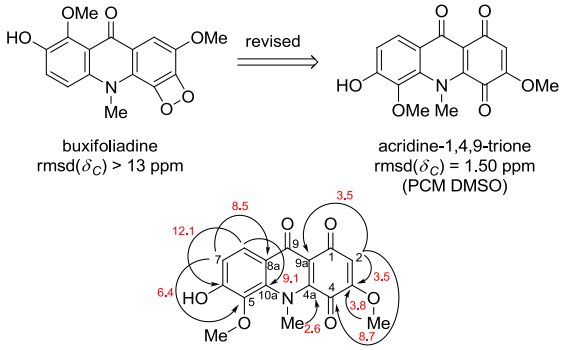


Figure 11. Revision of buxifoliadine. Observed HMBC crosspeaks (H → C arrows) are annotated with computed J_{CH} coupling constants (red numbers).

Small organic dioxetanes do exist and are isolable, but they are relatively unstable. For example, in a detailed study by Ando and co-

workers a series of dioxetanes based on adamantylideneadamantanes are described.[59] For some of them X-ray structures are obtained. However, ^{13}C NMR data for the symmetric dioxetane based on the parent unsubstituted adamantylideneadamantane has a peak listed at 47 ppm (*d*), which does not belong to the dioxetane, but rather belongs to adamantanone, indicating significant contamination of the dioxetane sample with this main product of its degradation via the retro-[2+2] reaction.

Given their instability, we were curious if any of the reported dioxetane-containing natural products are actual dioxetanes. For example, Figure 12 shows originally proposed structures for dendronophenols A and B,[60] and mansoxetane,[61] postulated to have dioxetane moieties. Computed NMR data did not agree with the experimental spectra. ^{13}C chemical shifts for the dioxetane moiety deviated the most.

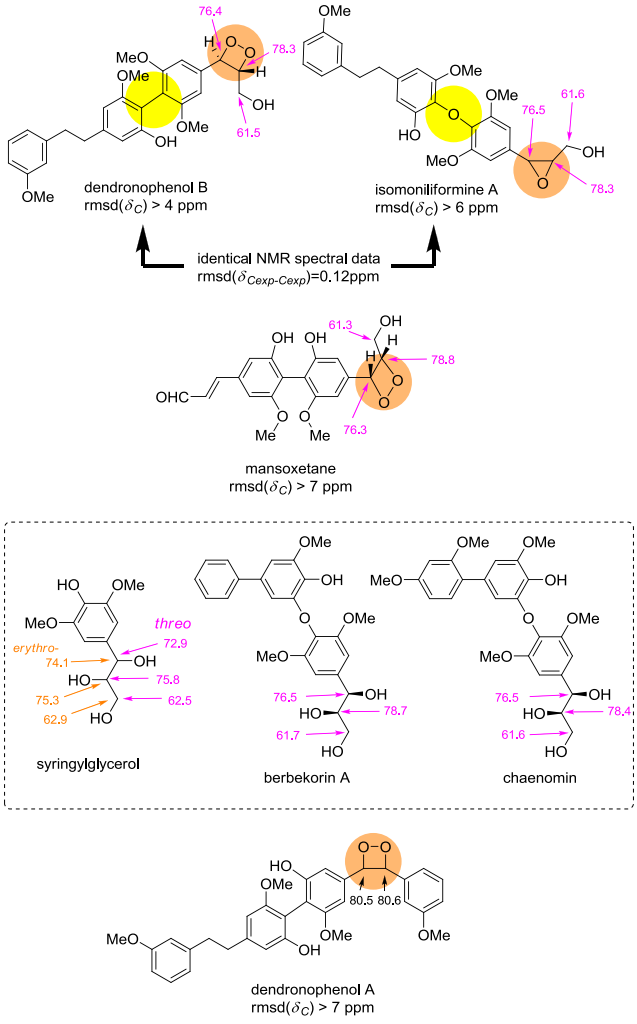


Figure 12. Dendronophenols A and B, and mansoxetane. The reported experimental ^{13}C NMR shifts are shown in colors.

The experimental chemical shift values for the purported dioxetane's carbons in the 76-79 ppm range were indicative of alcohols, not dioxetanes. Further investigation revealed that isomoniliformine A,[62] isolated from dried stem of similar species as dendronophenols, has NMR spectra identical to dendronophenol B: the match between the two experimental ^{13}C spectra is rmsd($\delta_{Cexp-Cexp}$) = 0.12 ppm. Unlike dendronophenol B, isomoniliformine A is proposed to have an oxirane moiety in place of the dioxetane moiety. However, calculated data for isomoniliformine A expectedly did not match the experimental values either, as the oxirane carbons were predicted approximately 20 ppm upfield (~56-58 ppm).

We hypothesized that dendronophenol B and isomoniliformine A are, in fact, triols. Conveniently, NMR data for several NPs possessing a similar arylpropanetriol moiety are reported: e.g. syringylglycerol,[63] berbekorin A,[64] and chaenomin,[65] shown in the insert. This near perfect match for the propanetriol moiety leaves no doubt that our hypothesis is correct, i.e. dendronophenol B and mansoxetane are not dioxetanes/oxiranes, but rather triols.

The same applies to dendronophenol A. The purported dioxetane carbons in it have experimental chemical shifts 80.5 and 80.6 ppm. The calculated values for a parent dioxetane based on stilbene are 88.2 ppm for the *cis*-isomer and 94.6 ppm for the *trans*, which is not matching the experiment, and confirming that there is no dioxetane moiety in dendronophenol A.

Complicating matters is the mismatched experimental and computational data for the aromatic moieties in all these NPs. Notice that dendronophenols A and B, and mansoxetane are proposed to have a *biphenyl* core, whereas the rest of the structures in Figure 12 possess *diphenyl ether* moiety. Our analysis of other similar phenolic NPs reported in the literature shows that there are a lot of misassignments pertaining to their aromatic cores. We will address this issue with natural polyphenols computationally elsewhere.

Just like dendronophenols, a new pseudoguaianolide neohupehenolide B, isolated from the aerial parts of *Inula hupehensis*, is not a dioxetane, but rather diol shown in Figure 13.[66] Its revision also required inversion of configuration at C11.

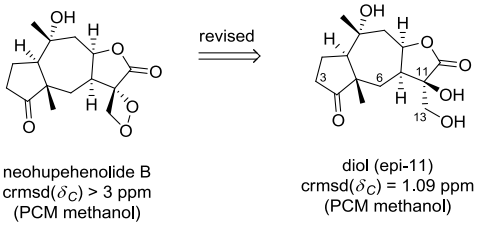


Figure 13. Revision of neohupehenolide B.

Not all dioxetane revisions required virtual reduction of the O-O bond. For example, two isoflavones **3** and **4** isolated from the *Hedysarum* plants, Figure 14,[67] were reported to contain the dioxetane moiety. Both original structures produced a poor match with computed data and needed revision. Instead of the trioxabicyclo[4.2.0]octane moiety we tested a much less strained trioxabicyclo[3.3.0]octane, which offered a much better match with experimental NMR data. We therefore revise these two isoflavone peroxides into the shown bicyclo[3.3.0] isomers. While the revised structure is not described in the literature, the rare trioxabicyclo[3.3.0] moiety is precedented in prenylated coumarins (mammea A/AB dioxalanocyclo F, cmpd **6** – see Figure 14).[68]

While we are not making a claim that NPs containing the dioxetane moiety do not exist, we are yet to encounter a confirmed case of a naturally occurring dioxetane.

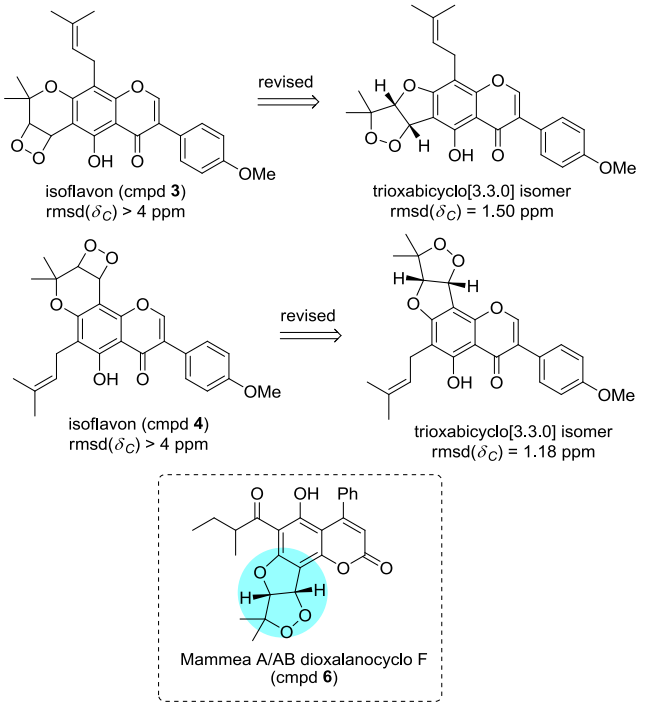


Figure 14. Revision of two isoflavon dioxetanes.

Finally, we examined the existence of oxetane-based hemiacetals, i.e. β-lactols, and related compounds. For example, a complex guaiane dimer, isolated from the bark of the plant *xylopia aromatica*, Figure 15, featured prominently a β-lactol moiety fused at C7'-C8'. While DU8+ computations did not agree with the proposed structure, we note that the purported β-lactol's C(O) carbons were significantly shifted into the low field. We then hypothesized that these high chemical shift values may be due to the presence of a peroxide moiety, i.e. 1,2-dioxolane, which could also offer a strain relief.

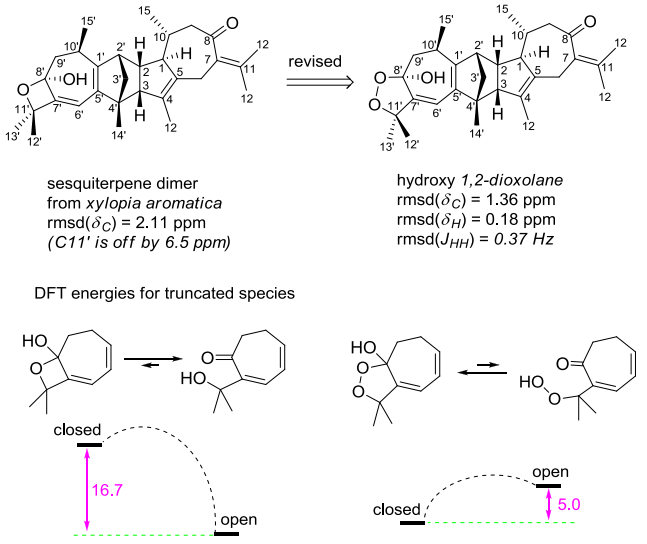


Figure 15. Revision of sesquiterpene dimer from the bark of the plant *xylopia aromatica*. ZPE corrected relative energies are obtained at the B3LYP/6-311+G(d,p) level of DFT theory for the open and closed forms of truncated substructures.

According to our computations this is definitely the case, i.e. the revised structure, shown in Figure 15, contains the hydroxy 1,2-dioxolane moiety. While this exact revised structure is not known, somewhat similar dimeric peroxy-hemiacetals, xylopidimers C and E, [69] and vielopsides A-C[70] were recently isolated from a related species *xylopia vielana*. To better understand the energetics of the open and closed forms in these species, we subjected the truncated β-lactol and its peroxy counterpart to DFT calculations shown in Figure 15. It is clear that the closed β-lactol is unfavorable species at the equilibrium with its open form, i.e. β-hydroxyketone. Contrary to that, the open form of a β-hydroperoxyketone has a significant driving force to cyclize. Given that ring-opening of β-lactol in this model system is such an exergonic process, it is unlikely that β-lactols (i.e. oxetanes with free 2-hydroxy group) exist in any detectable concentration. For example, small organic molecules and sugars, postulated to exist in a β-lactol form[71] based on the absence of the carbonyl peak in ^{13}C NMR, could be dimeric 2,5-dihydroxy-1,4-dioxanes. Fluorinated β-lactols[72] could be the dimeric 1,4-dioxanes or simply carbonyl hydrates, i.e. *gem*-diols. While we may not know for certain in all cases what these NPs are, we know what they are not – they are not β-lactols.

The case of biphenyl **1** isolated from a shrub *Caesalpinia decapetala*, Figure 16A,[73] further supports this point: DU8+ computations disagree with the experimental data, rmsd(δ_C) > 13 ppm. Based on the limited experimental data we could not propose the revision, but we can confidently state that this compound is not a β-lactol. At the same time, we do have evidence that DU8+ handles confidently this structural type: Figure 16B shows that the NMR data for methyl ether of β-lactol – i.e. 2-methoxyoxetane, accessible via a photoinduced [2+2] cycloaddition – is accurately calculated by DU8+, rmsd(δ_C) = 0.89 ppm.

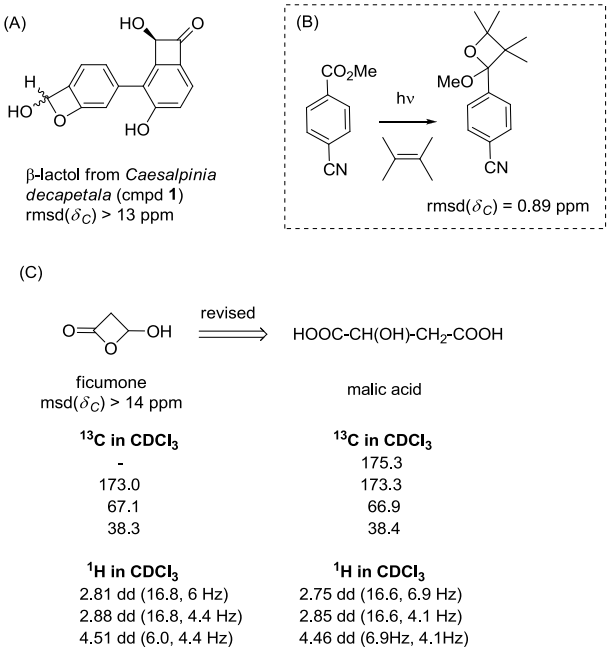


Figure 16. (A) Incorrect structure of a β-lactol from *Caesalpinia decapetala* (cmpd **1**); (B) an example of a photogenerated 2-methoxyoxetane demonstrates the accuracy of DU8+ computations for this structural type. (C) Revision of ficumone to malic acid based on comparison of experimental NMR data in $CDCl_3$.

A related question is whether 2-oxo-4-hydroxydioxetanes exist, i.e. β-lactols formed from 3-*oxo*-carboxylic acids. The purported parent compound in the series, ficumone, was isolated from an evergreen shrub *Synsepalum dulcificum* Daniell (Sapotaceae).[74] Its reported NMR spectra did not agree with the results of DU8+ computations, rmsd(δ_C) > 14 ppm. The lactol carbon, predicted at 89.7 ppm deviated the most. Its reported experimental value of 67.1 ppm was more commensurate with an alcohol moiety. After testing several candidate structures we arrived at malic acid as most likely candidate. Its experimental NMR spectrum in chloroform-*d* matches that of ficumone nearly perfectly, provided the authors overlooked the peak from the second carboxy-group.[75]

Peroxy-counterparts of β-lactols, i.e. 3-hydroxydioxetanes do not exist either. It is highly unlikely that ligulariaphytin A[76] or bidenphytin B,[77] Figure 18, possess the proposed 3-hydroxydioxetane moiety, as the hemiacetal carbon is expected to have a chemical shift of 107 ppm or more (observed ~100-102 ppm) and the second carbon in the truncated model dioxetane, Figure 18, is expected at ~ 90 ppm.

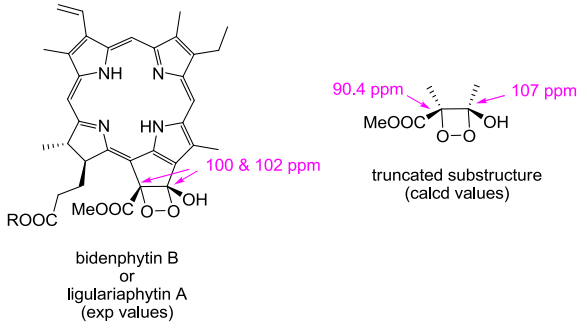


Figure 18. Bidenphytin B and ligulariaphytin A. Mismatch in the experimental and calculated ^{13}C shift values in the hydroxydioxetane moiety.

We identified a number of additional oxetane-containing natural products requiring revision, for which we could not generate a revised structure. Yet we are confident that they are misassigned. Figure 19 gives two representative examples. Sphaeroxetane[78] from the red alga *Sphaerococcus coronopifolius* was isolated with two other diterpenes. Two NPs of these three – sphaerococcenol A and bromosphaerol – gave a nice match with the experimental NMR data, rmsd(δ_C) = 0.99 ppm and 1.30 ppm respectively. However, sphaeroxetane itself is definitely misassigned. Based on the analysis of its congeners, we could propose its potential revision shown in Figure 19, but this would require ignoring the reported carbon multiplicities and, obviously, the mass-spectrometry data. Stereumone A,[79] Figure 19, is another representative misassigned oxetane for which we did not find any acceptable candidate structure yet.

In challenging cases like these, it would be beneficial to have careful reporting of chemical shifts and *J*-coupling constants with sufficiently high accuracy, which potentially could be achieved with approaches such as HiFSA (^{1}H iterative Full Spin Analysis).[80] Another additional difficulty of structure validation/revision is a high rate of typos in the reported NMR data. This underscores the importance of dissemination of the original NMR data (i.e., FID data deposited in a digital format suitable for subsequent analysis).[81]

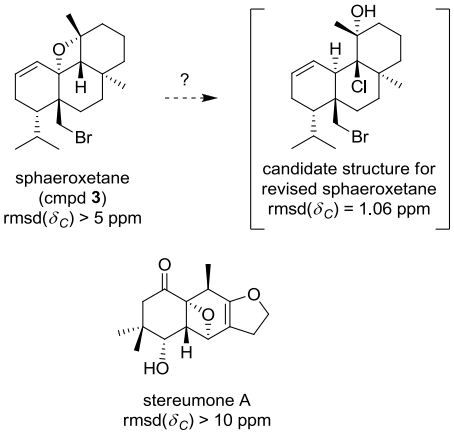


Figure 19. Additional examples of misassigned NPs containing the oxetane moiety: sphaeroxetane and stereumone A.

CONCLUSIONS

Natural products and small organic molecules possessing the oxetane or related four-membered heterocyclic moiety present a challenge of structural assignment. The hybrid DFT-parametric method DU8+ performs well for these structural types, and offers a fast and accurate computational path to structure validation or revision based primarily on the ubiquitous 1D NMR data.

ASSOCIATED CONTENT

Supporting Information. Computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: akutatel@du.edu
ORCID: 0000-0003-3066-517X

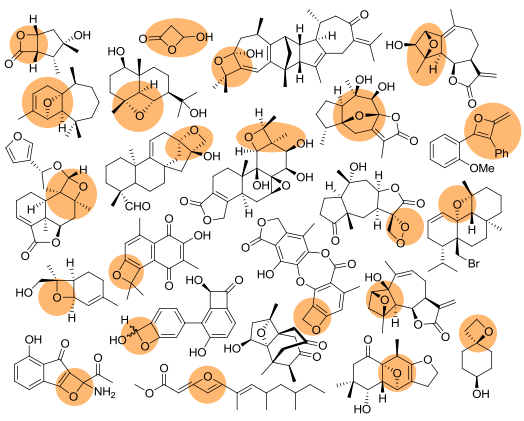
Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research is supported by the NSF, CHE-1665342

TOC GRAPHICS:



REFERENCES

(1) (a) for review see Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839. (b) see also Tantillo's compilation of various computational approaches at http://cheshirenmr.info (c) Smith, S. G.; Goodman, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12946. (d) Grimblat, N.; Zanardi, M. M.; Sarotti, A. M. *J. Org. Chem.* **2015**, *80*, 12526. (e) Elyashberg, M. E.; Williams, A. J. *Nat. Prod. Rep.* **2010**, *27*, 1296. (f) Elyashberg, M. E.; Williams, A. J. Computer-Based Structure Elucidation from Spectral Data. The Art of Solving Problems; Springer: Heidelberg, **2015**. (g) Buevich, A. V.; Elyashberg, M. E. *J. Nat. Prod.* **2016**, *79*, 3105. (h) Bally, T.; Rablen, P. R. *J. Org. Chem*. **2011**, *76*, 4818.

(2) hexacyclinol: (a) original report: Schlegel, B.; Härtl, A.; Dahse, H. -M.; Gollmick, F. A.; Gräfe, U.; Dörfelt, H.; Kappes, B. *J. Antibiotics*, **2002**, *55*, 814. (b) computational revision: Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2895. (c) synthetic validation of the revised structure: Porco, J. A. Jr.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5790.

(3) (a) Kutateladze, A. G.; Mukhina, O. A. *J. Org. Chem.* **2014**, *79*, 8397. (b) Kutateladze, A. G.; Mukhina, O. A. *J. Org. Chem.* **2015**, *80*, 5218. (c) Kutateladze, A. G.; Mukhina, O. A. *J. Org. Chem.* **2015**, *80*, 10838.

(4) for the full description of the components of *DU8+* method see Kutateladze, A. G.; Reddy, D. S. *J. Org. Chem.* **2017**, *82*, 3368.

(5) (a) Kutateladze A. G.; Krenske E. H.; Williams, C. M. *Angew.Chem.* **2019**, accepted (b) Kutateladze, A. G.; Kuznetsov, D. M.; Beloglazkina, A. A.; Holt, T. J. *J. Org. Chem.,* **2018**, *83*, 8341. (c) Kutateladze, A. G.; Kuznetsov, D. M. *J. Org. Chem.*, **2017**, *82*, 10795. (d) Reddy, D. S.; Kutateladze, A. G. *Org. Lett.*, **2016**, *18*, 4860. (e) Kutateladze, A. G. *J. Org. Chem.*, **2016**, *81*, 8659. (f) Reddy, D. S.; Kutateladze, A. G. *Tetrahedron Lett.*, **2016**, *57*, 4727. (g) Mukhina O. A.; Koshino, H.; Crimmins M. T.; Kutateladze, A. G. *Tetrahedron Lett.*, **2015**, *56*, 4900.

(6) Ortega, A.; Maldonado, E. *Phytochemistry*, **1986**, *25*, 699.

(7) Kurata, K.; Suzuki, T.; Suzuki, M.; Kurosawa, E.; Furusaki, A.; Matsumoto, T. *Chem. Lett.* **1983**, 557.

(8) Yu, X.-Q.; Jiang, C.-S.; Zhang, Y.; Sun, P.; Kurtan, T.; Mandi, A.; Li, X.-L.; Yao, L.-G.; Liu, A.-H.; Wang, B.; Guo, Y.-W.; Mao, S.-C. *Phytochem.* **2017**, *136*, 81.

(9) original discovery of dictyoxetane: (a) Pullaiah, K. C.; Surapaneni, R. K.; Rao, C. B.; Albizati, K. F.; Sullivan, B. W.; Faulkner, D. J.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 3665. (b) Rao, C. B.; Pullaiah, K. C.; Surapaneni, R. K.; Sullivan, B. W.; Albizati, K. F.; Faulkner, D. J.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 2736.

(10) ^{13}C NMR chemical shifts for dyctyoxetane are taken from the total synthesis paper: Hugelshofer, C. L.; Magauer, T. A. *J. Am. Chem. Soc.* **2016**, *138*, 6420. This paper also gives a nice introduction to naturally occurring oxetanes (or lack thereof).

(11) Tian, X.; Li, L.; Hu, Y.; Zhang, H.; Liu, Y.; Chen, H.; Ding, G.; Zou, Z. *RSC Adv.* **2013**, *3*, 7880.

(12) Li, C.; Lee, D.; Graf, T. N.; Phifer, S. S.; Nakanishi, Y.; Burgess, J. P.; Riswan, S.; Setyowati, F. M.; Saribi, A. M.; Soejarto, D. D.; Farnsworth, N. R.; Falkinham III, J. O.; Kroll, D. J.; Kinghorn, A. D.; Wani, M. C.; Oberlies, N. H. *Org. Lett.* **2005**, *7*, 5709.

(13) Richter, M. J. R.; Schneider, M.; Brandstätter, M.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2018**, *140*, 16704.

(14) Centko, R. M.; Ramon-Garcia, S.; Taylor, T.; Patrick, B. O.; Thompson, C. J.; Miao, V. P.; Andersen, R. J. *J. Nat. Prod.* **2012**, *75*, 2178.

(15) Vander Velde, D. G.; Georg, G. I.; Gollapudi, S. R.; Jampani, H. B.; Liang, X.-Z.; Mitscher, L. A.; Ye, Q.-M. *J. Nat. Prod.* **1994**, *57*, 862.

(16) Kim, C. S.; Oh, J.; Subedi, L.; Kim, S. Y.; Choi, S. U.; Lee, K. R. *J. Nat. Prod.* **2018**, *81*, 1795.

(17) Ren, F.; Chen, S.; Zhang, Y.; Zhu, S.; Xiao, J.; Liu, X.; Su, R.; Che, Y. *J. Nat Prod.* **2018**, *81*, 1752.

(18) Huang, J.-M.; Yokoyama, R.; Yang, C.-S.; Fukuyama, Y. *Tetrahedron Lett.* **2006**, *41*, 6111.

(19) Liu, D.-Z.; Wang, F.; Liao, T.-G.; Tang, J.-G.; Steglich, W.; Zhu, H.-J.; Liu, J.-K. *Org. Lett.* **2006**, *8*, 5749.

(20) Zou, J.; Pan, L.; Li, Q.; Zhao, J.; Pu, J.; Yao, P.; Gong, N.; Lu, Y.; Kondratyuk, T. P.; Pezzuto, J. M.; Fong, H. H. S.; Zhang, H.; Sun, H. *Org. Lett.* **2011**, *13*, 1406.

(21) Nakamura, T.; Okuyama, E.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1908.

(22) Kirschberg, T.; Mattay, J. *J. Org. Chem.* **1996**, *61*, 8885.

(23) here and later we will retain the numbering of the products as reported in the original papers, to avoid confusion.

(24) (a) Jones, G.; Schwartz, S. B.; Marton, M. T. *Chem. Commun.* **1973**, *11*, 374. (b) Jones, G.; Acquadro, M. A.; Carmody, M. A. *Chem.Commun.* **1975**, *6*, 206. (c) Perez-Ruiz, R.; Miranda, M. A.; Alle, R.; Meerholz, K.; Griesbeck, A. *Photochem. Photobiol. Sci*. **2006**, *5*, 51.

(25) (a) Valiulin, R.A.; Kutateladze, A.G. *Org. Lett.*, **2009**, *11*, 3886. (b) Valiulin, R.A.; Arisco, T.M., Kutateladze, A.G. *J. Org. Chem.*, **2011**, *76*, 1319 (c) Valiulin, R.A.; Arisco, T.M.; Kutateladze, A.G. *J. Org. Chem.*, **2013**, *78*, 2012.

(26) It is possible but unlikely that the revised minor product is derived from oxametathesis of **47**. This would involve fragmentation into cyclobutene and formaldehyde followed by bimolercular Paterno-Buchi reaction of these pieces, which is highly unlikely.

(27) Blanco-Ania, D.; Gawade, S. A.; Zwinkels, L. J. L.; Maartense, L.; Bolster, M. G.; Benningshof, J. C. J.; Rutjes, P. J. T. *Org. Proc. Res. Dev.* **2016**, *20*, 409.

(28) Tian, J.; Zhao, Q.-S.; Zhang, H.-J.; Lin, Z.-W.; Sun, H.-D. *J. Nat. Prod.* **1997**, *60*, 766.

(29) Ogasawara, K. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 957.

(30) Another curious fact is that SciFinder identifies seven suppliers of cleroindicin A with the original oxetane structure.

(31) himachalene *Chem. Pharm. Bull.* **1999**, *47*, 557.

(32) Li, N.; Chen, J.-J.; Zhou, J. *J. Asian Nat. Prod. Res.* **2005**, *7*, 279.

(33) Li, D.; Chen, Y.; Pan, Q.; Tao, M.; Zhang, W. *Rec. Nat. Prod.* **2014**, *8*, 330.

(34) (a) Li, R.-J.; Zhu, R.-X.; Li, Y.-Y.; Zhou, J.-C.; Zhang, J.-Z.; Wang, S.; Ye, J.-P.; Wang, Y.-H.; Morris-Natschke, S. L.; Lee, K.-H.; Lou, H.-X. *J. Nat. Prod.* **2013**, *76*, 1700. (b) Another complex clerodane diterpenoid, cephaloziellin A (not shown), was assigned correctly, as evidenced by a good match, rmsd(δ_C) = 1.24 ppm, see SI.

(35) Jianmei, H.; Jialin, W.; Chunshu, Y. *Phytochem.* **1997**, *46*, 777.

(36) Yokoyama, R.; Huang, J.-M.; Hosoda, A.; Kino, K.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2003**, *66*, 799.

(37) Liu, J.-M.; Zhang, D.-W.; Du, W.-Y.; Zhang, M.; Zhao, J.-L.; Chen, R.-D.; Xie, K.-B.; Dai, J.-G. *J. Asian Nat. Prod. Res.* **2017**, *19*, 541.

(38) Ni, L.; Ma, J.; Li, C.-J.; Li, L.; Guo, J.-M.; Yuan, S.-P.; Hou, Q.; Guo, Y.; Zhang, D.-M. *Tetrahedron Lett.* **2015**, *56*, 1239.
(39) Lin, T.; Wang, G.; Shan, W.; Zeng, D.; Ding, R.; Jiang, X.; Zhu, D.; Liu, X.; Yang, S.; Chen, H. *Bioorg. Med. Chem. Lett.* **2014**, *42*, 2504.
(40) Hilmi, F.; Sticher, O.; Heilmann, J. *J. Nat. Prod.* **2002**, *65*, 523.
(41) Swern, D.; Clements, A. H.; Luong, T. M. *Analytical Chem.* **1969**, *41*, 412.
(42) Adio, A. M.; Paul, C.; König, W. A.; Muhle, H. *Phytochem.***2003**, *64*, 637.
(43) Liang, Y.; Li, X.-M.; Cui, C.-M.; Li, C.-S.; Sun, H.; Wang, B.-G. *Mar. Drugs* **2012**, *10*, 2817.
(44) Aitken, R. A.; Karodia, N.; McCarron, H. B.; Rouxel, C.; Sahabo, N.; Slawin, A. M. Z. *Org. Biomol. Chem.***2016**, *14*, 1794 and references therein.
(45) (a) Friedrich, L. E.; Lam, P. Y.-S. *J. Org. Chem.* **1981**, *46*, 306. (b) Aikawa, K.; Hioki, Y.; Shimizu, N.; Mikami, K. *J. Am. Chem. Soc.* **2011**, *133*, 20092.
(46) Alcaide, B.; Almendros, P.; Martinez del Campo, T.; Fernandez, I. *Chem. Comm.* **2011**, *47*, 9054.
(47) Chen, J.; Bai, X.; Hua, Y.; Zhang, H.; Wang, H. *Fitoterapia*, **2019**, *134*, asap https://doi.org/10.1016/j.fitote.2019.01.016
(48) (a) Gu, Z.; Liang, H.; Chen, H.; Xu, Y.; Zhang, W. *Chinese Trad. Herb. Drugs* **2000**, *31*, 885. (b) Wang, Q.-Z.; He, M.-F.; Liang, J.-Y. *Chinese Trad. Herb. Drugs* **2003**, *34*, 277.
(49) Soonthornchareonnon, N.; Suwanborirux, K.; Bavovada, R.; Patarapanich, C.; Cassady, J. M. *J. Nat. Prod.* **1999**, *62*, 1390.
(50) Adam, W.; Hadjiarapoglou, L.; Peters, K.; Sauter, M. *J. Am. Chem. Soc.***1993**, *115*, 8603.
(51) http://dnp.chemnetbase.com
(52) Chen, H.-L.; Wang, L.-W.; Su, H.-J.; Wei, B.-L.; Yang, S.-Z.; Lin, C.-N. *Org. Lett.* **2006**, *8*, 753.
(53) Zhang, W.; Xu, L.; Yang, L.; Huang, Y.; Li, S.; Shen, Y. *Fitoterapia*, **2014**, *96*, 146.
(54) Dinda, B.; Das, S. K.; Hajra, A. K. *Indian J. Chem.* **1995**, *34B*, 525.
(55) Guo, S.; Tang, Y. P.; Duan, J. A.; Su, S. L.; Ding, A. W. *Chinese Chem. Lett.* **2009**, *20*, 197.
(56) Lang, G.; Cole, A. L. J.; Blunt, j. W.; Robinson, W. T.; Munro, M. H. G. *J. Nat. Prod.* **2007**, *70*, 310.
(57) Wu, P.-L.; Su, G.-C.; Wu, T.-S. *J. Nat. Prod.* **2003**, *66*, 996.
(58) Shan, F.; Yin, Y.-Q.; Huang, F.; Huang, Y.-C.; Guo, L.-B.; Wu, Y.-F. *Nat. Prod. Res.* **2013**, *27*, 1956.
(59) Kabe, Y.; Takata, T.; Ueno, K.; Ando, W. *J. Am. Chem. Soc.* **1984**, *106*, 8174.
(60) Liu,Q.-F.; Chen, W.-L.; Tang, J.; Zhao, W.-M. *Helv. Chim. Acta* **2007**, *90*, 1745.
(61) Tiew, P.; Takayama, H.; Kitajima, M.; Aimi, N.; Kokpol, U.; Chavasiri, W. *Tetrahedron Lett.* **2003**, *44*, 6759.
(62) Zhang, C.; Wang, M.; Lin, P.; Zhang, M.; Wang, Z.; Xu, L. *J. Indian Chem. Soc.***2007**, *84*, 714.
(63) Otsuka, H.; Takeuchi, M.; Inoshiri, S.; Sato, T.; Yamasaki, K. *Phytochem.* **1989**, *28*, 883.
(64) Kim, K. H.; Choi, S. U.; Ha, S. K.; Kim, S. Y.; Lee, K. R. *J. Nat. Prod.* **2009**, *72*, 2061.
(65) Kim, C.S.; Subedi, L.; Kwon, O. K.; Kim, S. Y.; Yeo, E.-J.; Choi, S. U.; Lee, K. R. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 351.
(66) the rmsd value calculated for all the reported carbons; however, two carbon peaks were "not detected" in the experimental spectrum, which makes this revision tentative.
(67) Chen, S.-G.; Chen, J.-J.; Gao, K. *Chem. Pharm. Bull.* **2007**, *55*, 1181.
(68) Guilet, D.; Seraphin, D.; Rondeau, D.; Richomme, P.; Bruneton, J. *Phytochem.* **2001**, *58*, 571.
(69) Guo, Y.-G.; Xie, Y.-G.; Wu, G.-J.; Cheng, T.-F.; Zhu, S.-L.; Yan, S.-K.; Jin, H.-Z.; Zhang, W.-D. *ACS Omega*, **2019**, *4*, 2047.
(70) Xie, Y.-G.; Wu, G.-J.; Cheng, T.-F.; Zhu, S.-L.; Yan, S.-K.; Jin, H.-Z.; Zhang, W.-D. *Fitoterapia*, **2018** *130*, 43 (there is a typo in the structures of vielopsides A-C: OH, not Me should be in the position 8).
(71) examples of β-lactols: (a) Vittimberga, B. M.; Herz, M. *J. Org. Chem.***1970**, *35*, 3974. (b) Pistara, V.; Corsaro, A.; Rescifina, A.; Catelani, G.; D'Andrea, F.; Guazzelli, L. *J. Org. Chem.* **2013**, *78*, 9444. (c) Hanessian, S.; Girard, C.; *Synlett.* **1994**, 865. (d) Soengas, R. G. *Tetrahedron Lett.* **2010**, *51*, 105.
(72) Jimenez, O.; Bosch, M.P.; Guerrero, A. *J. Org. Chem.* **2005**, *70*, 10883.
(73) Zhang, Q.; Liu, X.-T.; Liang, J.-Y.; Min, Z.-D. *Chinese J. Nat. Med.* **2008**, *6*, 168.
(74) Cheng, M.-J.; Lo, W.-L.; Huang, L.-Y.; Wang, C.-J.; Chen, C.-Y. *Nat. Prod. Res.* **2010**, *24*, 1850.
(75) Malic acid is poorly soluble in chloroform. It is conceivable that the low intensity peak from one of the carboxylates was not detected in the original work on ficumone.
(76) Li, H.; Li, L.; Zheng, Q.; Kuroda, C.; Wang, Q. *Molecules*, **2012**, *17*, 5219.
(77) Lee, T.-H.; Lu, C.-K.; Kuo, Y.-H.; Lo, J.-M.; Lee, C.-K. *Helv. Chim. Acta*, **2008**, *91*, 79.
(78) De Rosa, S.; De Stefano, S.; Scarpelli, P.; Zavodnik, N. *Phytochem.* **1988**, *27*, 1875.
(79) Li, G.-H.; Li, L.; Duan, M.; Zhang, K.-Q. *Chem. Biodiversity*, **2006**, *3*, 210.
(80) (a) Napolitano, J. G.; G decke, T.; Rodríguez-Brasco, M. F.; Jaki, B. U.; Chen, S. -N.; Lankin, D. C.; Pauli, G. F. *J. Nat. Prod.* **2012**, *75*, 238. (b) Napolitano, J. G.; Lankin, D. C.; McAlpine, J. B.; Niemitz, M.; Korhonen, S. -P.; Chen, S. -N.; Pauli, G. F. *J. Org. Chem.* **2013**, *78*, 9963. (c) Pauli, G. F.; Niemitz, M.; Bisson, J.; Lodewyk, M. W.; Soldi, C.; Shaw, J. T.; Tantillo, D. J.; Saya, J. M.; Vos, K.; Kleinnijenhuis, R. A.; Hiemstra, H.; Chen, S. -N.; McAlpine, J. B.; Lankin, D. C.; Friesen, J. B. *J. Org. Chem.* **2016**, *81*, 878. (d) Gao, W.; Napolitano, J. G.; Lankin, D. C.; Kim, J. -Y.; Jin, Y. -Y.; Lee, H.; Suh, J. -W.; Chen, S. -N.; Pauli, G. F. *Magn. Reson. Chem.* **2017**, *55*, 239.
(81) (a) Pauli, G. F.; Niemitz, M.; Bisson, J.; Lodewyk, M. W.; Soldi, C.; Shaw, J. T.; Tantillo, D. J.; Saya, J. M.; Vos, K.; Kleinnijenhuis, R. A.; Hiemstra, H.; Chen, S. -N.; McAlpine, J. B.; Lankin, D. C.; Friesen, J. B. *J. Org. Chem.* **2016**, *81*, 878. (b) Bisson, J.; Simmler, C.; Chen, S. -N.; Friesen, J. B.; Lankin, D. C.; McAlpine, J. B.; Pauli, G. F. *Nat. Prod. Rep.* **2016**, *33*, 1028.