DU8+ Computations Reveal a Common Challenge in Structure Assignment of Natural Products Containing a Carboxylic Anhydride Moiety.

Ivan M. Novitskiy and Andrei G. Kutateladze*

Department of Chemistry and Biochemistry, University of Denver, Denver, Colorado 80210

Abstract. DU8+ computations of NMR spectra revealed a relatively common error in the structure assignment of carboxylic anhydride-containing Natural Products. Computationally driven revisions of ten of these structures are reported in this Note. Majority of the misassigned structures featured a hydroxy group proximal to the proposed anhydride moiety and capable of lactone formation.

The wealth and utility of the chemical information provided by structures of Natural Products (NPs) is hard to underestimate.[1] It is self-evident that ascribing and mapping any such information onto *misassigned* structures of NPs creates all kinds of conundrums. Given this, it is critically important not only to develop effective tools for rapid detection of structural misassignments, but also offer sensible generalizations to help guide the process of structure revision.

NMR spectroscopy remains by far the most informative method for structure elucidation of non-crystalline NPs. For complex compounds, this work is greatly assisted by computational methods. Last decade saw an unprecedented renaissance in computer-aided structure elucidation (CASE)[2] methods, which involve generation of candidate structures, calculations of their NMR parameters (spin-spin coupling constants and chemical shifts)[3] and analyzing the match between the experimental and computed data with the help of probabilistic methods, such as Goodman's DP4 and DP5,[4] or Sarotti's DP4+ and JDP4.[5] *We note that these probabilistic analyses are only as good as the quality of computed NMR chemical shifts and spin-spin coupling constants is*. The challenge here is that the existing accurate methods for computing NMR spectra are prohibitively expensive for large molecules. Our main contribution to this thriving field is in augmenting light and fast DFT computations of NMR chemical shifts and spin-spin coupling constants with parametric corrections, either NBO-driven[6] or empirical, to surpass the accuracy of existing methods substantially, at a small fraction of computational costs. We employ elements of machine learning to recognize structural fragments that are poorly described by such light DFT methods, and parametrically correct for the associated errors. This allows for the validation or revision of NPs' structures in a high-throughput manner, be it a natural product containing an oxirane[7] or oxetane[8] moieties, or complex triquinanes,[9] or natural marine products containing heavy halogens,[10] etc.[11]

This *Note* deals with NPs purported to contain a chemically reactive carboxylic anhydride moiety. Many of such anhydride-containing NPs do exist and are unambiguously characterized with the aid of single crystal X-ray diffractometry. Yet, a broader question exists: in cases when an NP contains a nucleophilic group, such as hydroxy or amino capable of forming lactone or lactam, should this provide enough motivation to investigate an issue of potential misassignment? Especially given that in two examples below for the parent structures of α-hydroxyglutaric and -adipic acids, DFT calculations give significant preference for the formation of the lactone? Glutamic acid lactam showed an even greater preference over the anhydride, Figure 1.

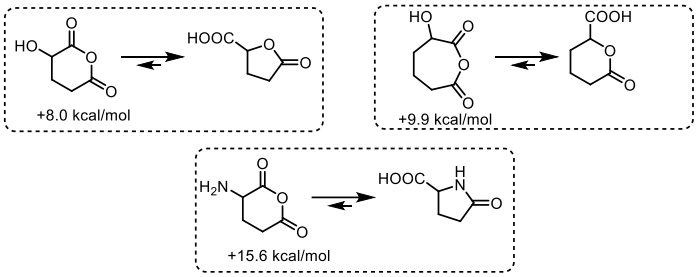


Figure 1. Calculations at the B3LYP/6-311+G(d,p) level of DFT theory for derivatives of α-hydroxyglutaric and -adipic acids or glutamic acid indicate strong preference for the lactone forms (or lactam).

A somewhat related question was addressed in our recent revision of an entire lactone subfamily of briarellins.[11a] In the case of these highly oxidized diterpenes, containing a carboxy moiety and several hydroxy groups as potential contenders for lactonization, the original structures were assigned a wrong lactone connection, i.e. the C3-C14 ester-containing bridge (highlighted in maroon), which we corrected to alternatively bridged structures: C11-C14 (highlighted in green) or C12-C14 (blue), Figure 2.

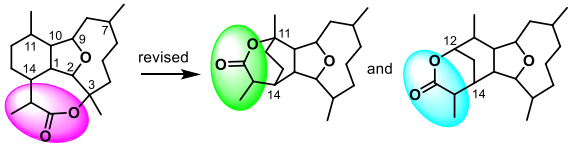


Figure 2. Prior work: reassignment of briarellins [ref.2]

In the briarellins case, the outcome of intramolecular competition of additional hydroxy groups for the lone electrophile, an ester, is presumably predicated on the relative stability of respective lactones. If such an electrophile is more reactive – as an example of carboxylic anhydrides – this begs a question: is it reasonable for it to survive in a situation when a lactone formation is plausible due to the presence of a nearby hydroxy group? One observes that a number of NPs are proposed to contain a cyclic anhydride moiety, and some of them do possess a nucleophilic functionality in the immediate vicinity of these reactive electrophiles. Using DU8+ we re-examined structures of such NPs and found that many of these structures indeed require revision.

DU8+ is based on a light level of DFT theory augmented with parametric corrections of the computed NMR properties and is capable of high-throughput analysis of reported structures and 1D proton and carbon NMR data. The training set for ^{13}C NMR chemical shifts, which contains more than 11,500 entries of reliable experimental chemical shifts, gave high accuracy with the overall root-mean-square deviation (rmsd) under 1.04 ppm. In general, the correct structures give a match with rmsd(δC) values in the range of 1.0-1.6 ppm or better. The method is parameterized for chloroform solutions, for which no additional linear corrections are applied. For other NMR solvents, we apply additional linear correction designed to better match experimental datasets, which is an accepted practice. In these cases, the results are reported as crmsd, i.e. *corrected* rmsd.

To demonstrate the method performance and verify the accuracy of computations for compounds containing the carboxylic anhydride moiety, we first tested DU8+ on several synthetic and semisynthetic anhydrides as well as isolated natural products with structures unambiguously confirmed by x-ray

diffraction analysis. Two diastereomeric propellanes **1a**,**b** obtained by Little[12] via a trimethylene methane diradical cycloaddition reaction presented a Natural Product-like scaffold containing the anhydride moiety, Figure 3. ^{13}C NMR chemical shifts calculated with DU8+ were matching the experimental data very well, with respective rmsd(δ_C) of 0.93 and 1.17 ppm. Importantly, DU8+ calculations were able to differentiate the diastereomers with high confidence, i.e. the attempt to match experimental data for one diastereomer to the chemical shifts calculated for the other gave poor rmsd's in excess of 2ppm.

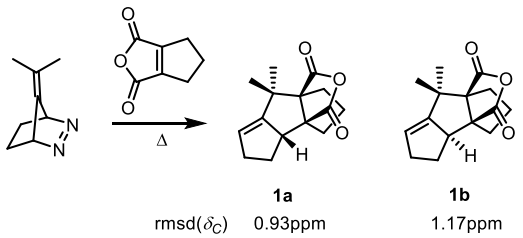


Figure 3. Synthetic NP-mimics **1a** and **1b**

Much more complex molecules, for example, *seco*-lupane derivatives **2** and **3** were also subjected to DU8+ calculations, Figure 4. Featuring a six-membered anhydride in the E-ring, compound **2** was synthesized by oxidation of a 21,22-diketone that was available from natural betulin in several steps.[13] The seven-membered ring of cyclic anhydride in compound **3** was accessed by dehydration of a A-*seco* diacid available from betulinic acid.[14] The structures of the triterpenes **2** and **3** were confirmed computationally with rmsd(δ_C) of 1.13 ppm and 1.07ppm. This result imparts confidence that complex anhydride-containing triterpenes can be adequately investigated with DU8+ method.

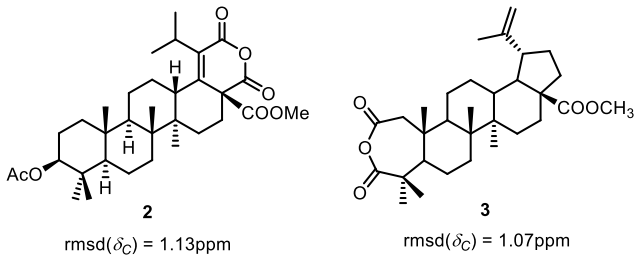
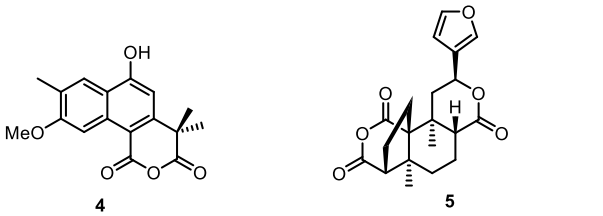


Figure 4. Anhydride of 3β-acetoxy-17β-methoxycarbonyl-28-nor-21,22-secolup-18-ene-21,22-dioic acid (**2**) and 2,3-anhydride of 28-methyl ester of 2,3-secolup-20(29)-en-2,3,28-trioic acid (**3**)

Two NPs, fimbricalyxanhydride A, **4**,[15] and a neoclerodane diterpene **5**[16] with molecular structures unambiguously confirmed by single-crystal XRD, were selected to further demonstrate the applicability of DU8+ method to handle diverse cyclic anhydrides, Figure 5. The calculated ^{13}C chemical shifts of fimbricalyxanhydride A, **4**, matched the experimental spectrum recorded in acetone-d_6 with crmsd(δ_C) of 1.31 ppm. Calculated and experimental spectral data of neoclerodane diterpene **5**, acquired in DMSO-d_6, also matched nearly perfectly, crmsd(δ_C) = 1.19 ppm, after linear correction. These two examples indicated that with additional scaling, DU8+ can accurately predict spectra of anhydride-containing NPs in polar solvents.

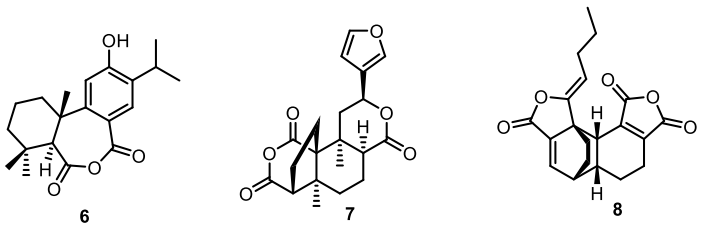


fimbricalyxanhydride A (x-ray)
crmsd(δ_C) = 1.31ppm
in acetone-d_6

a neoclerodane diterpene (x-ray)
crmsd(δ_C) = 1.22ppm
in DMSO-d_6

Figure 5. Anhydride-containing NPs with structures confirmed by x-ray analysis

Additionally, we validated the reported structures of NP anhydrides: obtuanhydride **6**,[17] rmsd(δ_C) = 1.32 ppm; neoclerodane-diterpene **7**,[16] rmsd(δ_C) = 0.98 ppm (which is a 8-epimer of **5** above); and chuanxiongnolide L3 **8**,[18] rmsd(δ_C) = 1.23 ppm, Figure 6.



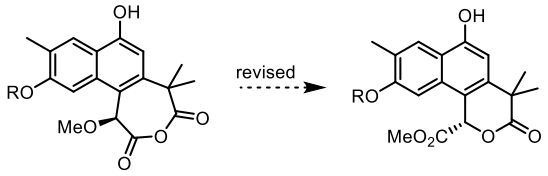
obtuanhydride
rmsd(δ_C) = 1.32ppm

neoclerodane diterpene
rmsd(δ_C) = 0.94ppm

chuanxiongnolide L3
rmsd(δ_C) = 1.23ppm

Figure 6. Obtuanhydride **6**, neoclerodane diterpene **7**, and chuanxiongnolide L3, **8**

However, a significant number of reported structures was proved incorrect. As carboxylic acid derivatives share a relatively narrow range of chemical shifts, it is not unexpected that lactones could be mistaken for cyclic anhydrides. Indeed, the predicted carbon chemical shifts of thrigonosomone A[19] and fimbricalyxanhydride B[15] were not in agreement with the experimental data, rmsd(δ_C) > 3 ppm. They were revised to lactones **10a**, crmsd(δ_C) = 1.09 ppm, and **10b**, rmsd(δ_C) = 1.10 ppm, Figure 7.



9a, R = H, thrigonosomone A
crmsd(δ_C) = 3.18ppm

9b, R = Me, fimbricalyxanhydride B
rmsd(δ_C) = 5.33ppm

10a, R = H
crmsd(δ_C) = 1.06ppm

10b, R = Me
rmsd(δ_C) = 1.10ppm

Figure 7. Revision of thrigonosomone A and fimbricalyxanhydride B

More common indication of the possible misassignment is the presence of a free hydroxy group that could trigger spontaneous lactonization of the putative anhydride (provided it ever forms in the first place). For example, the reported ^{13}C NMR spectrum of lannefuran B[20] belongs to lactone **12**, crmsd(δ_C) = 1.34 ppm, rather than the originally proposed succinic anhydride **11**, crmsd(δ_C) = 3.31 ppm, Figure 8. Instructively, the lactone is also more stable than the anhydride: by 11 kcal/mol as estimated at the B3LYP/6-31G(d) level of theory.

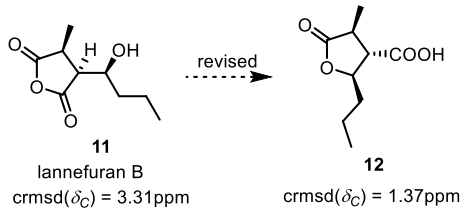


Figure 8. Revision of lannefuran

Three abietane diterpenoids, caryopterons B, C, and D (**15**-**17**) were mischaracterized to have a seven-membered cyclic anhydride in the C-ring, with a proximal free OH group at C-14.[21] DU8+ calculations revealed irreconcilable discrepancies with the experimental carbon-13 NMR data, rmsd(δ_C) > 5 ppm, and suggested that caryopterons B-D are in fact γ-lactones, **18**-**20** (which are also over 20 kcal/mol more stable than the originally proposed anhydrides). Chemical shifts of the carbonyl carbons in free carboxylic groups of **18**-**20** were difficult to predict accurately due to possible intermolecular carboxylate dimerization, or intramolecular hydrogen bonds. Omission of this carboxylate carbon from the analysis of the candidate lactone structures **18**-**20** gave a good match with experimental data, rmsd(δ_C) < 1. 3 ppm, Figure 9.

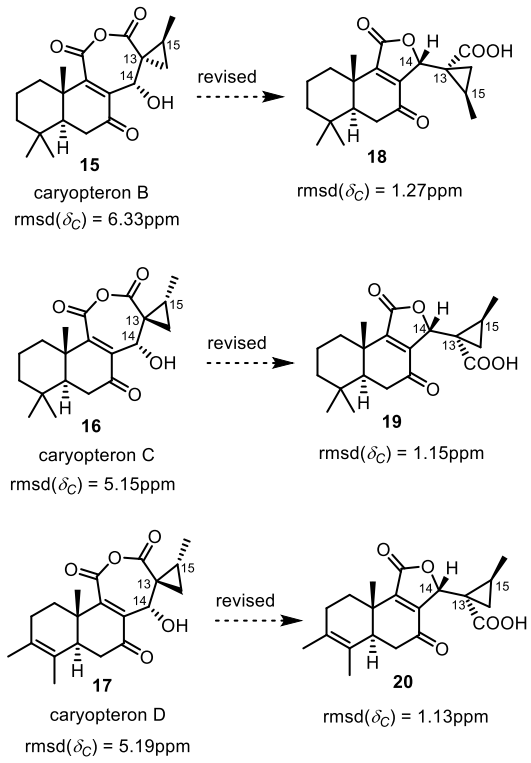


Figure 9. Structure revision of caryopterons B-D.

Recently isolated triterpenoid applanhydrides A and B – as their name implies – were purported to contain an anhydride moiety in the C-ring based on extensive NMR experimental and theoretical studies.[22] Nonetheless, DU8+ calculations did not agree with the original assignment, crmsd(δ_C) > 4ppm. Again, even if such anhydride structure existed, the C-15 hydroxy group is likely to account for the spontaneous lactonization leading to δ-lactones **22** and **24**, which are calculated to be >20kcal/mol lower in energy than the anhydrides. Revised structure **22** is in an excellent agreement with the experimental ^{13}C NMR spectrum for applanhydride B, crmsd(δ_C) = 1.20 ppm. Applanhydride A, which has the same core and differs only in the C-17 substituent, is revised to δ-lactone core by analogy, without full conformational search of the carboxyheptanone tail (R), Figure 10.

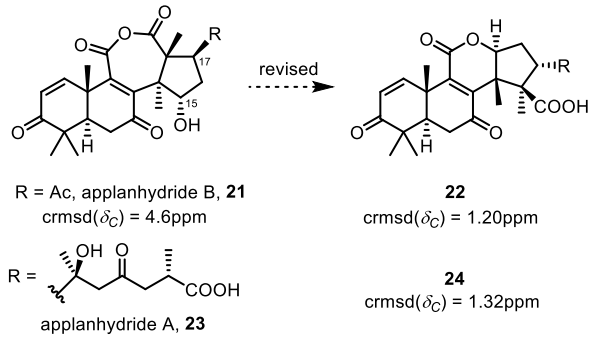


Figure 10. Structure revision of applanhydride B.

Several new friedelane triterpenes were isolated from *Crossopetalum lobatum*.[23] Among them, lobatanhydride was assigned an anhydride-containing structure **25** bearing a hydroxymethyl group in its proximity. DU8+ driven calculations clearly indicated the misassignment. While the originally proposed structure was inconsistent with the reported ^{13}C NMR spectrum, rmsd = 4.76 ppm, more thermodynamically stable (Δ*E* = -17 kcal/mol) lactone **26** nearly perfectly matched the experimental data, rmsd = 1.17 ppm, Figure 11.

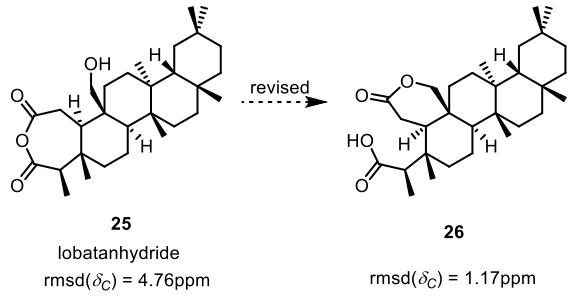


Figure 11. Structure revision of lobatanhydride.

Another instructive example of DU8+'s capabilities is offered by the revision of 11α,30-dihydroxy-2,3-seco-olean-12-en-2,3-dioic anhydride.[24] Originally suggested *seco*-oleanene anhydride **27** exhibited a moderate mismatch with the experimental data, crmsd = 2.26 ppm. However, DU8+ calculations for lactone **28** matched the experimental NMR data substantially better. The lactone structure is calculated

11 kcal/mol downhill from the original anhydride structure. Considering the poor performance of DFT to account for the specific interactions of a basic solvent (pyridine) and the free carboxylic acid, we omitted the carboxylate carbon from the analysis and obtained an excellent match with the experimental spectrum, crmsd = 0.88 ppm, for the remaining 29 carbons, Figure 12.

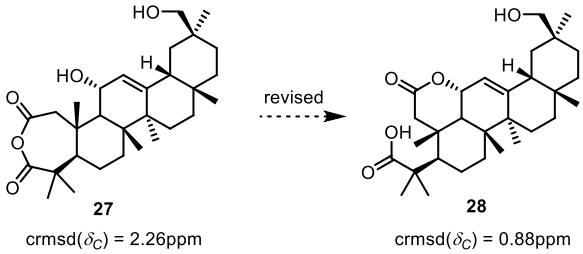


Figure 12. Structure revision of 11α,30-dihydroxy-2,3-*seco*-olean-12-en-2,3-dioic anhydride **27**.

In conclusion, we examined nineteen anhydride-containing structures of NPs with the aid of the hybrid DFT-parametric method DU8+ and revised ten of them. Most of the incorrect structures contained a hydroxy group accessible for intramolecular lactonization. The proximity of these two reactive functional groups in the considered candidate structures should serve as a red flag in the process of their structure elucidation.

Supporting Information. Computational details, cartesian coordinates of conformers, computed chemical shifts and spin-spin coupling constants is available free of charge at https://pubs.acs.org/doi/...

AUTHOR INFORMATION

Corresponding Author

Andrei G. Kutateladze – Department of Chemistry and Biochemistry, University of Denver, F.W. Olin Hall 202, 2190 E. Iliff Ave., Denver, Colorado, 80210, USA

http://orcid.org/0000-0003-3066-517X

Author

Ivan M. Novitskiy – Department of Chemistry and Biochemistry, University of Denver, F.W. Olin Hall 202, 2190 E. Iliff Ave., Denver, Colorado, 80210, USA

https://orcid.org/0000-0002-2675-3348

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is supported by the National Science Foundation, CHE-1955892

REFERENCES

(1) Romo, D.; Vanderwal, C. D. Synthetic Strategies for Mining the Information-Rich Content of Natural Products for Biology and Medicine. *Nat. Prod. Rep.* **2020**, *37* (11), 1393–1394. DOI: 10.1039/D0NP90042G.

(2) (a) Elyashberg, M. E.; Argyropoulos, D. Computer Assisted Structure Elucidation (CASE): Current and Future Perspectives. *Magn. Reson. Chem.* **2021**, *59* (7), 669–690. DOI: 10.1002/mrc.5115. (b) Costa, F. L. P.; Albuquerque, A. C. F. de; Fiorot, R. G.; Lião, L. M.; Martorano, L. H.; Mota, G. V. S.; Valverde, A. L.; Carneiro, J. W. M.; Junior, F. M. dos S. Structural Characterisation of Natural Products by Means of Quantum Chemical Calculations of NMR Parameters: New Insights. *Org. Chem. Front.* **2021**, *8* (9), 2019–2058. DOI: 10.1039/D1QO00034A. (c) Buevich, A. V.; Elyashberg, M. E. Enhancing computer-assisted structure elucidation with DFT analysis of J-couplings. *Magn. Res. Chem.* **2020**, *58* (6), 594–606. DOI: 10.1002/mrc.4996. (d) Koos, M. R. M.; Navarro-Vazquez, A.; Anklin, C.; Gil, R. R. Computer-Assisted 3D Structure Elucidation (CASE-3D): The Structural Value of $^{2}J_{CH}$ in Addition to $^{3}J_{CH}$ Coupling Constants. *Angew. Chem. Int. Ed*. **2020**, *59* (10), 3938–3941. DOI: 10.1002/anie.201915103.

(3) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. Computational prediction of ^{1}H and ^{13}C chemical shifts: a useful tool for natural product, mechanistic, and synthetic organic chemistry. *Chem. Rev.* **2012**, *112*, 1839; see also Tantillo's compilation of various NMR computational approaches at http://cheshirenmr.info.

(4) (a) Smith, S. G.; Goodman, J. M. Assigning stereochemistry to single diastereoisomers by GIAO NMR calculation: the DP4 probability. *J. Am. Chem. Soc.* **2010**, *132*, 12946; (b) Howarth, A; Goodman, J. M. The DP5 Probability, Quantification and Visualisation of Structural Uncertainty in Single Molecules. *ChemRxiv*, **2021**. DOI: 10.17863/CAM.65145

(5) (a) Grimblat, N.; Zanardi, M. M.; Sarotti, A. M. Beyond DP4: An Improved Probability for the Stereochemical Assignment of Isomeric Compounds Using Quantum Chemical Calculations of NMR Shifts. *J. Org. Chem.* **2015**, *80* (24), 12526–12534. DOI: 10.1021/acs.joc.5b02396; (b) Marcarino, M. O.; Cicetti, S.; Zanardi, M. M.; Sarotti, A. M. A Critical Review on the Use of DP4+ in the Structural Elucidation of Natural Products: The Good, the Bad and the Ugly. A Practical Guide. *Nat. Prod. Rep.* **2021**. DOI: 10.1039/D1NP00030F.

(6) Kutateladze, A. G.; Mukhina, O. A. Minimalist Relativistic Force Field: Prediction of Proton–Proton Coupling Constants in 1H NMR Spectra Is Perfected with NBO Hybridization Parameters. *J. Org. Chem.* **2015**, *80* (10), 5218–5225. DOI: 10.1021/acs.joc.5b00619.

(7) Kutateladze, A. G.; Kuznetsov, D. M.; Beloglazkina, A. A.; Holt, T. Addressing the Challenges of Structure Elucidation in Natural Products Possessing the Oxirane Moiety. *J. Org. Chem.* **2018**, *83* (15), 8341–8352. DOI: 10.1021/acs.joc.8b01027.

(8) Kutateladze, A. G.; Holt, T.; Reddy, D. S. Natural Products Containing the Oxetane and Related Moieties Present Additional Challenges for Structure Elucidation: A DU8+ Computational Case Study. *J. Org. Chem.* **2019**, *84* (12), 7575–7586. DOI: 10.1021/acs.joc.9b01005.

(9) Kutateladze, A. G.; Kuznetsov, D. M. Triquinanes and Related Sesquiterpenes Revisited Computationally: Structure Corrections of Hirsutanols B and D, Hirsutenol E, Cucumin B, Antrodins C–E, Chondroterpenes A and H, Chondrosterins C and E, Dichrocephone A, and Pethybrene. *J. Org. Chem.* **2017**, *82* (20), 10795–10802. DOI: 10.1021/acs.joc.7b02018.

(10) Kutateladze, A. G.; Reddy, D. S. High-Throughput in Silico Structure Validation and Revision of Halogenated Natural Products Is Enabled by Parametric Corrections to DFT-Computed 13C NMR Chemical Shifts and Spin–Spin Coupling Constants. *J. Org. Chem.* **2017**, *82* (7), 3368–3381. DOI: 10.1021/acs.joc.7b00188.

(11) (a) Holt, T. A.; Reddy, D. S.; Huple, D. B.; West, L. M.; Rodríguez, A. D.; Crimmins, M. T.; Kutateladze, A. G. The Discreet Structural Diversity of Briarellins: DU8+ Guided Multiple Structure

Revisions Yielded Two Unknown Structural Types. *J. Org. Chem.* **2020**, *85* (9), 6201–6205. DOI: 10.1021/acs.joc.0c00555; (b) Maslovskaya, L. A.; Savchenko, A. I.; Krenske, E. H.; Chow, S.; Holt, T.; Gordon, V. A.; Reddell, P. W.; Pierce, C. J.; Parsons, P. G.; Boyle, G. M.; Kutateladze, A. G.; Williams, C. M. EBC-232 and 323: A Structural Conundrum Necessitating Unification of Five In Silico Prediction and Elucidation Methods. *Chem. – Eur. J.* **2020**, *26* (51), 11862–11867. DOI: 10.1002/chem.202001884; (c) Kutateladze, A. G.; Krenske, E. H.; Williams, C. M. Reassignments and Corroborations of Oxo-Bridged Natural Products Directed by OSE and DU8+ NMR Computation. *Angew. Chem. Int. Ed.* **2019**, *58* (21), 7107–7112. DOI: 10.1002/anie.201902777.

(12) Leonetti, J. A.; Gross, T.; Little, R. D. Cycloaddition−Fragmentation as a Route to Bicyclic Ring Systems. Use of the Intermolecular Diyl Trapping Reaction. *J. Org. Chem.* **1996**, *61* (5), 1787–1793. DOI: 10.1021/jo951879h.

(13) Šarek, J.; Klinot, J.; Džubák, P.; Klinotová, E.; Nosková, V.; Křeček, V.; Kořínková, G.; Thomson, J. O.; Janošťáková, A.; Wang, S.; Parsons, S.; Fischer, P. M.; Zhelev, N. Z.; Hajdúch, M. New Lupane Derived Compounds with Pro-Apoptotic Activity in Cancer Cells: Synthesis and Structure−Activity Relationships. *J. Med. Chem.* **2003**, *46* (25), 5402–5415. DOI: 10.1021/jm020854p.

(14) Urban, M.; Sarek, J.; Klinot, J.; Korinkova, G.; Hajduch, M. Synthesis of A-Seco Derivatives of Betulinic Acid with Cytotoxic Activity. *J. Nat. Prod.* **2004**, *67* (7), 1100–1105. DOI: 10.1021/np049938m.

(15) Seephonkai, P.; Pyne, S. G.; Willis, A. C.; Lie, W. Bioactive Compounds from the Roots of Strophioblachia Fimbricalyx. *J. Nat. Prod.* **2013**, *76* (7), 1358–1364. DOI: 10.1021/np400268d.

(16) Ma, Z.; Deng, G.; Lee, D. Y. W. Novel Neoclerodane Diterpene Derivatives from the Smoke of Salvinorin A. *Tetrahedron Lett.* **2010**, *51* (39), 5207–5209. DOI: 10.1016/j.tetlet.2010.07.144.

(17) Kuo, Y.-H.; Chen, C.-H.; Huang, S.-L. New Diterpenes from the Heartwood of Chamaecyparis Obtusa Var. Formosana. *J. Nat. Prod.* **1998**, *61* (6), 829–831. DOI: 10.1021/np970531+.

(18) Wei, W.; Wu, X.-W.; Yang, X.-W. Novel Phthalide Derivatives from the Rhizomes of Ligusticum Chuanxiong and Their Inhibitory Effect against Lipopolysaccharide-Induced Nitric Oxide Production in RAW 264.7 Macrophage Cells. *RSC Adv.* **2016**, *6* (66), 61037–61046. DOI: 10.1039/C6RA10023F.

(19) Hu, X.-J.; Wang, Y.-H.; Kong, L.-Y.; He, H.-P.; Gao, S.; Liu, H.-Y.; Ding, J.; Xie, H.; Di, Y.-T.; Hao, X.-J. New Phenanthrenes from Trigonostemon Lii Y.T. Chang. *Tetrahedron Lett.* **2009**, *50* (24), 2917–2919. DOI: 10.1016/j.tetlet.2009.03.186.

(20) Tameko, J. E. M.; Chouna, J. R.; Nkeng-Efouet-Alango, P.; Tapondjou, L. A.; Sewald, N. Furan Derivatives from Lannea Kerstingii. *Phytochem. Lett.* **2017**, *20*, 282–284. DOI: 10.1016/j.phytol.2017.04.040.

(21) Saruul, E.; Murata, T.; Selenge, E.; Sasaki, K.; Yoshizaki, F.; Batkhuu, J. An Antibacterial Ortho-Quinone Diterpenoid and Its Derivatives from Caryopteris Mongolica. *Bioorg. Med. Chem. Lett.* **2015**, *25* (12), 2555–2558. DOI: 10.1016/j.bmcl.2015.04.048.

(22) Gao, J.; Chen, Y.; Liu, W.; Liu, Y.; Li, M.; Chen, G.; Yuan, T. Applanhydrides A and B, Lanostane Triterpenoids with Unprecedented Seven-Membered Cyclo-Anhydride in Ring C from Ganoderma Applanatum. *Tetrahedron* **2021**, *79*, 131839. DOI: 10.1016/j.tet.2020.131839.

(23) Rodríguez, F. M.; Perestelo, N. R.; Jiménez, I. A.; Bazzocchi, I. L. Friedelanes from Crossopetalum Lobatum. A New Example of a Triterpene Anhydride. *Helv. Chim. Acta* **2009**, *92* (1), 188–194. DOI: 10.1002/hlca.200800252.

(24) Chen, I.-H.; Du, Y.-C.; Hwang, T.-L.; Chen, I.-F.; Lan, Y.-H.; Yen, H.-F.; Chang, F.-R.; Wu, Y.-C. Anti-Inflammatory Triterpenoids from the Stems of Microtropis Fokienensis. *Molecules* **2014**, *19* (4), 4608–4623. DOI: 10.3390/molecules19044608.