



Computational structure revision of a longipinane derivative meridane



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ABSTRACT

Structure revision of a recently reported longipinane derivative, meridane, was enabled by computations of its NMR spectra. This structural revision necessitates corrections in the originally proposed Wagner–Meerwein mechanism for the formation of meridane.

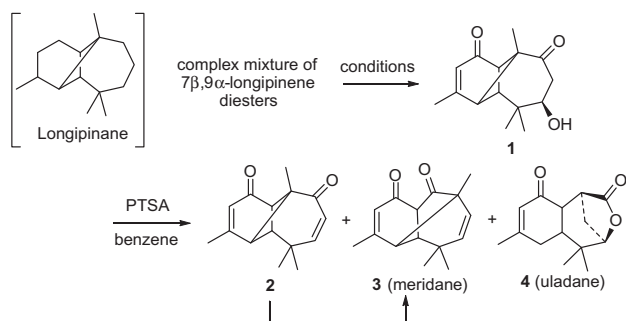
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Sesquiterpenes of the longipinane family possess a strained tricyclic skeleton containing a cyclobutane ring, and thus often serve as a starting point for accessing a diverse variety of new structures via deep carbocationic rearrangements or other straightforward transformations of the natural feedstock.¹ Recently two unprecedented sesquiterpene skeletons were obtained under the Wagner–Meerwein conditions from a longipinene derivative **1** which, in turn, was a product of a work up of a complex mixture of 7 β ,9 α -longipinene diesters isolated from dry leaves and stems of *Stevia lucida* Lagasca,² Scheme 1. Upon treatment with

p-toluenesulfonic acid in benzene, longipinene diketone **1** gave products **2–4**. New compounds **3** and **4** were named meridane and uladane, respectively. Longipin-2-en-1,9-dione **2**, is believed to be an intermediate in the formation of meridane **3**.

Analysis of ¹³C chemical shifts calculated at a mPW1PW91/6-311+G(d,p) level of DFT theory revealed excellent match with experimental data for uladane **4** and dione **2**. However, meridane **3** showed very poor correlation of calculated and experimental data. Figure 1 graphically maps largest deviations (>5 ppm) with the relative sizes of the orange circles corresponding to the magnitude of the problem. Based on this analysis we concluded that the structure of meridane is misassigned.

Meridane is believed to originate from dione **2** via a carbocationic rearrangement shown in Scheme 2 (path a). According to



Scheme 1. Formation of meridane and uladane from diketone **1**.

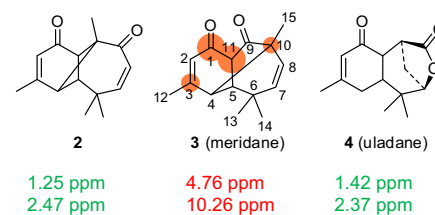
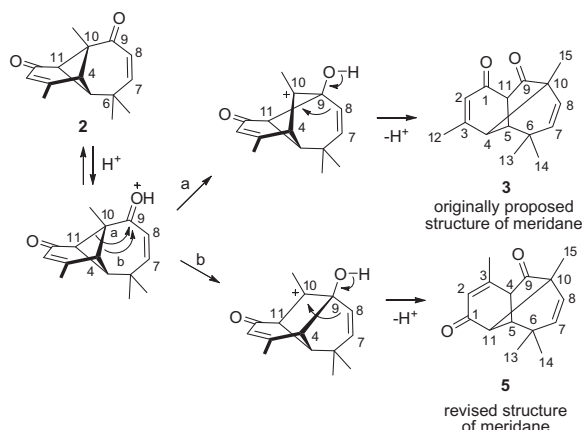


Figure 1. Analysis of DFT-calculated ¹³C chemical shifts: rmsd—root mean square deviation; mue—max. unsigned error; calcd values deviating from experimental data by more than 5 ppm are mapped proportionately as orange blobs, with the largest size corresponding to $\Delta = 10$ ppm.

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Scheme 2. Two potential pathways for carbocationic ring expansion of the cyclobutane moiety in precursor **2**.

authors,² protonation of the C9 carbonyl group triggers cyclobutane ring expansion with C10–C11 bond migrating. 1,2-Shift of the C7–C8 vinyl moiety completes the transformation restoring the C9 carbonyl and yielding meridane. As compound **2** has a pseudosymmetric structure, with the flat C6–C7–C8–C9 enone moiety dissecting the cyclobutane, we were wondering about the migratory propensity of cyclobutane's C10–C11 versus C10–C4 bond. Structurally, these two bonds have very similar overlaps with the C9 carbonyl's π orbitals. Migration of bond C10–C4 is expected to yield the alternative product **5** (path b).

To address these issues we carried out a thorough computational NMR study of structure **5**, including computations of both chemical shifts (GIAO mPW1PW91/6-311+G(d,p)), and spin–spin coupling constants with our recently developed *relativistic force field* (*rff*) parametric method for fast and accurate computations of both $J(H-H)$ and $J(C-H)$ coupling constants.³

The results of this study leave no doubt that structure **5** shown in Scheme 2 is the correct structure for meridane. One conformer adequately describes the structure of each species, as there is no conformational flexibility in all structures **2**–**5**. Figure 2A shows an excellent correlation of the computed and calculated $J(H-H)$ constants (rmsd = 0.11 Hz) for the revised meridane. Calculated $J(C-H)$ constants for **5**, Figure 2B, are instructive in evaluating whether or not this revised structure is in keeping with the reported HMBC data which, in turn, are shown in Figure 2C. One big discrepancy for the originally proposed structure is that H4 → C9 HMBC correlation was not reported for the experimental HMBC spectrum, while the computed $^3J_{C9-H4}$ is rather large, 8.8 Hz (red arrow in Fig. 2C). All *rff*-calculated $J(C-H)$ for revised structure **5** are in agreement with the reported HMBC correlations.

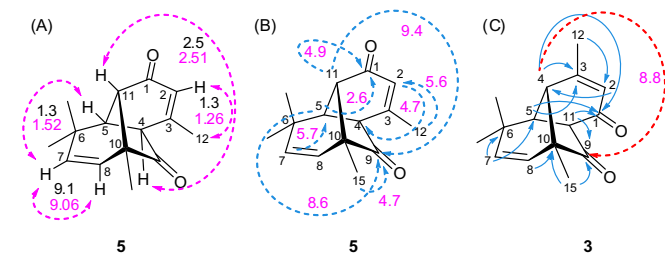


Figure 2. (A) Comparison of the experimental (black) and *rff*-calculated (magenta) $J(H-H)$, Hz for revised meridian **5**. (B) Selected *rff*-computed $J(C-H)$ for revised meridian **5**. (C) Originally reported HMBC correlations for structure **3**. Large calculated $^3J_{C9-H4}$ = 8.8 Hz is shown with the red arrow; H4 → C9 HMBC correlation is not reported in Ref. 2 but should be detectable for the original structure **3**.

Table 1
rff-calculated NMR data for the revised meridane structure (**5**)

	Exp	Calcd	Δ
$J(H-H)$, Hz			
J_{4-11}	2.5	2.51	–0.01
J_{7-8}	9.1	9.06	0.04
J_{5-7}	1.3	1.52	–0.22
J_{2-12}	1.3	1.26	0.04
		rmsd = 0.11 Hz	
δ_H , ppm			
H2	5.83	5.82	0.01
H7	5.53	5.50	0.03
H8	5.42	5.49	–0.07
H4	3.28	3.16	0.12
H11	2.89	2.75	0.14
H5	2.39	2.12	0.27
H12	2.12	2.19	–0.07
H15	1.18	1.25	–0.07
H13	1.11	1.17	–0.06
H14	1.08	1.08	0.00
		rmsd = 0.11 ppm	
δ_C , ppm			
C9	202.2	201.1	1.10
C1	200.1	197.6	2.50
C3	163.3	165.58	–2.28
C7	139.5	141.02	–1.52
C8	129.7	134.26	–4.56
C2	125.5	127.18	–1.68
C11	57.8	58.16	–0.36
C4	57	57.98	–0.98
C5	54.8	54.49	0.31
C10	45.8	48.23	–2.43
C6	37.2	39.11	–1.91
C13	28.8	27.01	1.79
C12	24.5	23.39	1.11
C14	24	22.29	1.71
C15	16.4	15.81	0.59
		rmsd = 1.95 ppm	

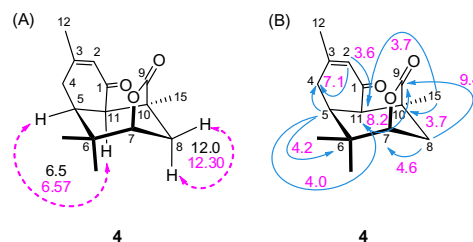


Figure 3. (A) Comparison of the experimental (black) and *rff*-calculated (magenta) $J(H-H)$, Hz for uladane **4**. (B) Reported HMBC correlations in uladane (blue arrows) are annotated with *rff*-computed $J(C-H)$ values, Hz, for uladane **4**.

Table 1 summarizes the results of GIAO B3LYP/6-311+G(d,p) calculations of 1H and ^{13}C chemical shifts and the *rff*-calculations of $J(H-H)$ coupling constants for revised structure **5**.

Uladane: our NMR computational analysis indicate that the originally proposed structure of uladane is correct. While only two $J(H-H)$ coupling constants are reported for uladane, they match very well the *rff*-computed values, Figure 3A. Experimental HMBC correlations for **4** are also in agreement with the *rff*-computed $J(C-H)$ values, Figure 3B. Table 2 shows excellent correlation between the experimental and GIAO-computed values for ^{13}C chemical shifts.

The mechanism for the acid-catalyzed formation of uladane from longipinene diketone **1**, as proposed by the authors,² is initiated by the cyclobutane ring expansion involving the C4–C10 bond, i.e., ‘path b’ in our terminology, Scheme 2. The fact that in both reactions, **1** → uladane and **2** → meridane, it is the bond

Table 2
¹³C chemical shifts data for uladane **4**

	Exp	Calcd	Δ
C1	197	194.76	2.24
C9	179.6	178.16	1.44
C3	162.7	163.78	-1.08
C2	125.6	127.27	-1.67
C7	85.6	83.23	2.37
C11	49.8	49.96	-0.16
C10	42.4	43.56	-1.16
C5	41.8	42.35	-0.55
C8	40.9	42.21	-1.31
C6	35.4	36.77	-1.37
C4	31.2	30.71	0.49
C12	24.4	24.05	0.35
C13	26.3	24.09	2.21
C14	24.9	23.09	1.81
C15	18.2	18.26	-0.06
rmsd = 1.42 ppm			

C4–C10 which migrates, provides additional mechanistic support for the formation of the revised structure **5**, not **4**, in the Wagner–Meerwein rearrangement of **2**.

In conclusion, *rff* computations of C–H and H–H nuclear spin coupling constants, and GIAO computations of NMR chemical shifts provide clear evidence that the originally proposed structure of meridane **4** is incorrect. The correct structure of meridane is structure **5**.

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Supplementary data

Supplementary data (computational details, atomic coordinates) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2016.09.030>.

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