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Computationally driven reassignment of the structures of aldingenins A and B

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ABSTRACT

Earlier four brominated sesquiterpenes, aldingenins A–D, were isolated from the red algae *Laurencia aldingensis*, and their structure elucidated by spectroscopic methods including NMR. Total syntheses of the proposed structures of aldingenin B (*Org. Lett.* **2012**, *14*, 2168) and aldingenin C (*J. Org. Chem.* **2014**, *79*, 9373) have demonstrated that the structures are misassigned. Koshino has proposed aldingenins C and D to be caespitol and 5-(*S*)-acetoxycaespitol. Computational evidence presented in this Letter and based primarily on the computed proton spin–spin coupling constants (but also including ^{13}C NMR chemical shifts) leads to the conclusion that the remaining two aldingenins A and B are also halogenated sesquiterpenes of the same caespitol family. Aldingenin A is assigned the structure of 5-(*S*)-hydroxycaespitol **1**, and aldingenin B—hemiacetal **2** of a related 8-oxo compound.

Four brominated sesquiterpenes, aldingenins A–D, were first isolated in 2003 (aldingenin A)[1] and 2006 (aldingenins B–D)[2] from the red algae *Laurencia aldingensis*, and their structure elucidated by spectroscopic methods including NMR. Total synthesis of the proposed structure of aldingenin B by one of us, Crimmins,[3] has demonstrated that aldingenin B is misassigned. Subsequent total synthesis of the proposed structure of aldingenin C and the analysis of NMR data for aldingenin D lead another one of us, Koshino,[4] to the conclusion that aldingenins C and D are in fact known compounds, caespitol and 5-(*S*)-acetoxycaespitol respectively, Figure 1. Kutateladze and Mukhina analyzed the spectrum of aldingenin A computationally and suggested that there is no oxabicyclo[2.2.1]heptane moiety in the natural compound.[5] However, it was not immediately clear what the actual structures of aldingenins A and B might be.

In this Letter we present computational evidence that aldingenins A and B are two new halogenated sesquiterpenes, which belong to the caespitol family, with their most likely structures shown in Figure 1: 5-(*S*)-hydroxycaespitol **1**, and hemiacetal **2**. Also shown are previously suggested structures for aldingenins C and D (Koshino).[4]

Computational predictions of NMR spectra have evolved over the years and reached a point when they could play a critical role in structural assignments, both due to the accuracy of the computed chemical shifts and spin–spin coupling constants (SSCC), and due to the fact that the computations can be accomplished in a reasonably short time.

Fast and accurate computations of proton spin–spin coupling constants are particularly appealing as SSCCs carry a wealth of structural information helping to inform and guide the process of structural assignment in complex organic molecules.

With recent improvements in parametric scaling of DFT-computed Fermi contacts to obtain accurate SSCCs,[7,8] the total (wall) time for running a complete set of the necessary calculations for a molecule of aldingenin size on a garden variety Linux cluster does not exceed 1–2 h and yet gives 0.2–0.5 Hz rmsd, which is normally sufficient for unambiguous structural assignment.

Aldingenin A was originally assigned a structure containing an oxabicyclo[2.2.1] moiety, *endo*-2,5-cross linked with a three atom tether. The last column in Table 1 shows that while the computed spin system in the ring B, that is, protons H8, H9, and H10, resembles the experimental data for aldingenin A, ring A (H1 through H6) shows irreconcilable discrepancies with this originally proposed structure. Based on comparative analysis of NMR data for known derivatives of caespitol and similar compounds,[9] Koshino hypothesized that aldingenin A could be 5-(*S*)-hydroxycaespitol, a new compound. As shown in Table 1, our *DU8*-computed coupling constants for 5-(*S*)-hydroxycaespitol matched the experimental data for aldingenin A with an excellent rmsd of 0.24 Hz. Additionally,

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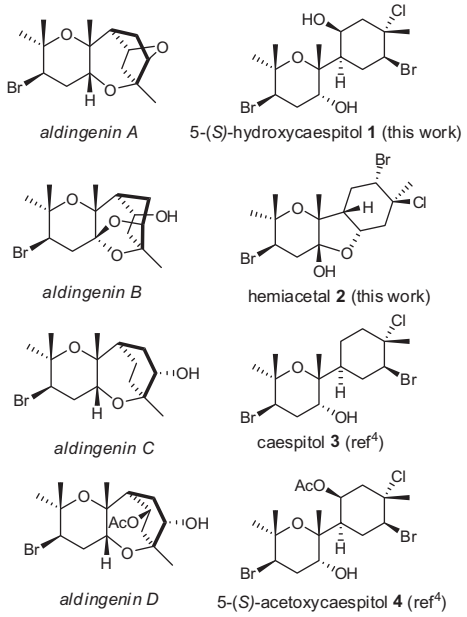
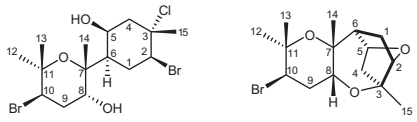


Figure 1. Originally proposed (left)[6] and revised structures of aldingenins A–D.

^{13}C NMR chemical shifts calculated at mPW1PW91/6-311+G(d,p) level of theory gave rmsd of 0.8 ppm after a linear correction for experimental chemical shifts (for ^{13}C NMR details see Supporting information).

In an attempt to partially reconcile the original HRMS data we have considered tertiary alcohol 6, Figure 2, in which the chlorine atom at C3 is replaced with a hydroxy group. Also considered were the C3 epimers of the *tert*-chloride **1** and *tert*-alcohol **6**, that is, compounds **5** and **7**. The combination of computed SSCCs and ^{13}C NMR chemical shifts indicates that 5-(*S*)-hydroxycaespitol **1** is the most likely structure for aldingenin A, although the C3 alcohol **6** cannot be completely ruled out without accurate mass spectrometric data.

Table 1
Comparison of experimental *J*'s for aldingenin A with *J*'s computed for two candidate structures: the originally proposed and 5-(*S*)-hydroxycaespitol[a]



	Exp. *J*'s (Ref. 1) natural aldingenin A	*DU8*-calcd *J*'s 5-(*S*)-hydroxy-caespitol **1**	*DU8*-calcd *J*'s aldingenin A
1	dddd 12.9, 4.2, 2.6, 1.5	13.3, 4.4, 2.9, 1.6	11.9, 9.6, 3.5
	q 12.9	13.3, 13.2, 12.9	11.9
2	dd 12.9, 4.2	12.9, 4.4	3.5
4	dd 14.5, 2.7	14.3, 2.7	12.6, 3.8
	dd 14.5, 3.1	14.3, 3.5	12.6
5	m	3.5, 2.7[c]	5.5, 3.8
6	dt 12.9, 2.7[b]	13.2, 2.9[c]	9.6, 5.5
8	t 3.0	3.2, 2.9	3.9, 2.6
9	dt 14.1, 3.0	14.2, 4.1, 3.2	14.3, 4.2, 2.6
	ddd 14.1, 13.2, 3.0	14.2, 13.6, 2.9	14.3, 13.4, 3.9
10	dd 13.2, 4.1	13.6, 4.1	13.4, 4.2

[a] Calculated *J*'s are listed in descending order with a cutoff value of 2 Hz (unless reported experimentally).
[b] Second *J* = 2.7 Hz in the triplet is possibly due to OH splitting.
[c] Notice that the calculated value of J_{5-6} is small, (1.5 Hz).

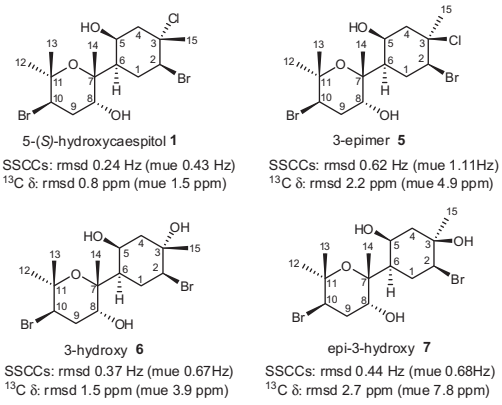


Figure 2. The C3 epimers and alcohols considered as alternatives for the structure of aldingenin A (mue = maximum unsigned error).

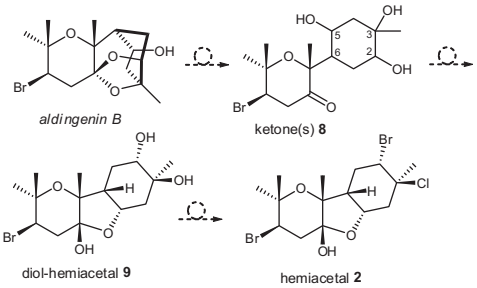
For aldingenin B we propose the structure of hemiacetal **2**. While the ^{13}C chemical shift for carbon C8 was in agreement with an acetal or hemiacetal moiety, it was noticed by Crimmins[3] that the HMBC spectrum of the natural sample does not display a H2–C8 crosspeak. Several additional NMR spectra discrepancies between the C1–C6 moiety of the natural product and the bicyclic acetal moiety synthesized by Dudley[10] were noted.

Virtual 'hydrolysis' of the acetal moiety in aldingenin B gives ketone **8**, Scheme 1. Subsequent formation of hemiacetal moiety via the C5-OH group produced stereoisomeric diol-hemiacetals, of which stereoisomer **9** had a computed NMR spectrum closely resembling that of aldingenin B.

However, a much better fit of computed SSCCs (Table 2) and ^{13}C chemical shifts was achieved for hemiacetal **2** in which the C2–C3 diol was virtually altered into the vicinal bromo-chloride, typical of the caespitol family of halogenated sesquiterpenes. The published mass spectrometry data for aldingenin B do not support structure **2**, but this could potentially be ascribed to a partial hydrolysis and dehydrohalogenation of **2**.

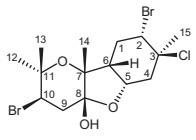
Table 2 shows side-by-side comparison of the experimental SSCCs for the natural aldingenin B,[2] synthetic aldingenin B,[3] and the *DU8*-computed SSCCs for the originally proposed structure as well as that of hemiacetal **2**. The constants computed for the original structure matched the experimental data for synthetic aldingenin B[3] nicely with rmsd of 0.2 Hz (mue = 0.3 Hz, Table 2, last two columns). The experimental constants of the natural sample from Lago's work[2] matched computations for hemiacetal **2**, with one exception, the multiplet of H2 with J_{1a2} = 9.6 and J_{1b2} = 6.3 Hz, (see discussion below, Fig. 4).

As with the computed spectra of hydroxycaespitol, it is challenging to differentiate between C–Cl and C–OH without accurate mass-spectrometry data, especially when the respective carbons are not carrying any protons. However, based on our

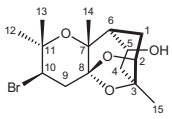


Scheme 1. Virtual transformations of aldingenin B.

Table 2
Comparison of experimental *J*'s for aldingenin B with *J*'s computed for two candidate structures: the originally proposed and hemiacetal **2**[a]



hemiacetal **2**



aldingenin B

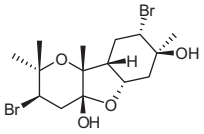
	Exp. *J*'s (Ref. 2), natural aldingenin B	*DU8*-calcd *J*'s hemiacetal 2	*DU8*-calcd *J*'s aldingenin B	Exp. *J*'s[b] synthetic aldingenin B
	← match →		← match →	
1	m (overlap)	14.8, 8.8, 4.4 14.8, 11.3, 8.5	14.2, 2.5, 2.4 14.2, 3.7, 2.0	14.5, 2.4, 2.2 14.5, 3.8, 2.1
2	dd (9.6, 6.3)[c]			
	11.2, 4.8	11.3, 4.4	2.5, 2.0	2.5, 2.0
4	dd 14.5, 9.6	14.6, 9.6	14.1, 8.1	13.7, 7.9
	dd 14.5, 4.7	14.6, 5.2	14.1, 7.2	13.7, 7.5
5	ddd 9.6, 8.4, 4.7	9.6, 9.0, 5.2	8.1, 7.2	8.1, 7.5
6	dd 9.0, 8.4[d]	9.0, 8.8, 8.5	3.7, 2.4	br s
9	t 13.5	13.4, 12.9	13.1, 12.8	13.0, 12.6
	dd 13.5, 3.6	13.4, 4.6	12.8, 4.9	12.6, 4.6
10	dd 13.5, 3.6	12.9, 4.6	13.1, 4.9	13.0, 4.6

[a] Calculated *J*'s are listed in descending order with a cutoff value of 2 Hz.
[b] For consistency an experimental ^{1}H NMR spectrum of aldingenin B *in CDCl*$_3$ was used.
[c] Second order multiplet, simulation gives 11.2, 4.8 Hz—see text below; with these simulated constants, calculated *J*'s for hemiacetal **2** match the experimental with rmsd = 0.46 Hz.
[d] We believe that this *ddd* (*pseudo*-quartet) was misreported as *dd* in Ref. 2.

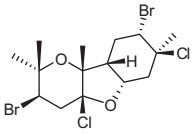
computational analysis, the alcohol **10**, Figure 3, similar to **6**, is a very unlikely candidate for aldingenin B.[11] α-Chloroether **11**, for which SSCCs are predicted with marginally acceptable rmsd of 0.57 Hz and ^{13}C chemical shifts—with rmsd of 1.8 ppm, is ruled out based on a clearly observed OH singlet at 0.7 ppm in the experimental NMR.

Another complicating factor in NMR-guided structure assignments has always been the interpretation of multiplets which are not of first-order. The spectrum of the proposed aldingenin B is an instructive case, where the two *apparent* spin–spin coupling constants of the H2 proton are listed as 9.6 and 6.3 Hz. However, the neighboring geminal protons at C1 are clearly superimposed resulting in a complex spin system, which can be simulated as shown in Figure 3 using a small $\Delta\delta$ of 0.006 ppm for the two C1 protons, and J_{1a2} = 11.2 Hz and J_{1b2} = 4.8 Hz. It is reassuring that the sum of the apparent *J*'s, 9.6 + 6.3 = 15.9 Hz, is very close to the sum of the constants obtained from the multiplet simulation, 11.2 + 4.8 = 16 Hz, and that of calculated *J*'s for hemiacetal **2** (11.3 + 4.4 = 15.7 Hz).

This problem is actually more common than it is recognized. Similar, but smaller discrepancy between the 'expected' and apparent spin–spin coupling constants is also important for 5-(*S*)-acetoxycaespitol **4**, which was previously proposed by Koshino[4] as the correct structure for aldingenin D. The spectrum of



10
SSCCs: rmsd 0.74 Hz (mue 1.42Hz)
13C δ: rmsd 2.4 ppm (mue 4.8 ppm)



11
SSCCs: rmsd 0.57 Hz (mue 0.96Hz)
13C δ: rmsd 1.8 ppm (mue 3.9 ppm)

Figure 3. Alternative structures of aldingenin B.

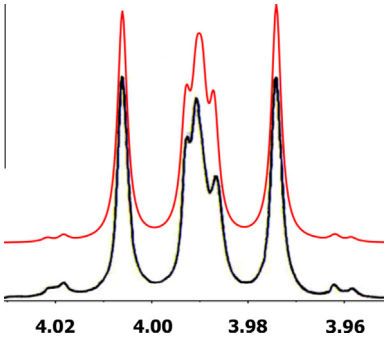


Figure 4. Simulation of the H2 multiplet (3.99 ppm) of aldingenin B with J_{1a2} = 11.2 Hz and J_{1b2} = 4.8 Hz (reported apparent constants: 9.6 and 6.3 Hz).

5-(*S*)-acetoxycaespitol reported in 2010 by Roussis[12] matches Lago's natural 'aldingenin D' perfectly, with H2 listed as *dd* of 11.7, 4.9 Hz in Lago's Letter. Yet, six closely related derivatives of 5-(*S*)-acetoxycaespitol isolated by Roussis have this particular doublet of doublets reported with the large (*axial–axial*) constant >12.3 Hz and the smaller (*axial–equatorial*) constant <4.4 Hz. The calculated values for these two constants in 5-(*S*)-acetoxycaespitol are in keeping with this trend: 13.3 and 4.0 Hz. The apparent constants of 11.7 and 4.9 Hz are outliers here because the adjacent geminal protons are superimposed, so the H2 signal cannot be treated as a first-order multiplet. Again, the sum of the two apparent constants, 11.7 + 4.9 = 17.6 Hz, matches the sum of the two predicted constants, 13.3 + 4.0 = 17.3 Hz, very well. With these two constants excluded, our *rff DU8* computations match the experimental constants for 5-(*S*)-acetoxycaespitol with rmsd of 0.25 Hz, leaving little doubt that aldingenin D is indeed 5-(*S*)-acetoxycaespitol.

In conclusion, based on the computational evidence which includes the analysis of calculated proton spin–spin coupling constants and ^{13}C NMR chemical shifts, we suggest that the remaining two aldingenins A and B most likely belong to the same caespitol family of halogenated sesquiterpenes, with aldingenin A being 5-(*S*)-hydroxycaespitol **1**, and aldingenin B—hemiacetal **2**.

Acknowledgments

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Supplementary data

Supplementary data (computational details) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.078. These data include MOL files and InChiKeys of the most important compounds described in this article.

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6. The structures shown in the left column of the table are our interpretation of the original drawings of aldingenins B–D in Ref. 2, for details see Supporting information.
7. for Bally and Rablen's single parameter scaling of Fermi contacts see: Bally, T.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 4818.

8. For our multi-parameter *relativistic force field, DU4* see Ref. 5. All computations of proton spin-spin coupling constants in this work were carried out using *relativistic force field method DU8* described in: (a) Kutateladze, A. G.; Mukhina, O. A. *J. Org. Chem.* **2015**, *80*, 5218–5225.
9. NMR data of the following related structures were analyzed to arrive at a hypothesis of 5-(S)-hydroxycaespitol as the actual structure for aldingenin A: (a) *deodactol* Hollernbeak, K. H.; Schmitz, F. J.; Hossain, M. B.; van der Helm, D. *Tetrahedron* **1979**, *35*, 541; (b) *caespitol* González, A. G.; Martín, J. D.; Martín, V. S.; Norte, M. *Tetrahedron Lett.* **1979**, *20*, 2719; (c) esters from *Conyza canadensis* Ding, Y.; Su, Y.; Guo, H.; Yang, F.; Mao, H.; Gao, X.; Zhu, Z.; Tu, G. *J. Nat. Prod.* **2010**, *73*, 270.
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11. In addition to the inferior match of computed SSCCs, the ^{1}H NMR chemical shift of the Me group geminal to OH seems to be not in keeping with the generally observed trend for Me–C–Cl versus Me–C–OH, for example, aldingenin A: 1.93 (C_6D_6) or 1.91 ($CDCl_3$); aldingenin B: 1.57 (C_6D_6); aldingenin C: 1.69 ($CDCl_3$); aldingenin D: 1.78 ppm ($CDCl_3$), but for prevazol C it is 1.31 ppm (Me-20, $CDCl_3$) and for prevazol B: 1.31 ppm (Me-20, $CDCl_3$) with Me–C–OH. Other Me groups with Me–C–O of the original aldingenins A–D, and synthetic aldingenin B are observed in the range between 0.80 and 1.49 ppm. For the original discovery and subsequent structure revisions of prevazols see: (a) Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V. *J. Org. Chem.* **2003**, *68*, 7667; (b) Leung, A. E.; Blair, M.; Forsyth, C. M.; Tuck, K. L. *Org. Lett.* **2013**, *15*, 2198; (c) Leung, A. E.; Rubbiani, R.; Gasser, G.; Tuck, K. L. *Org. Biomol. Chem.* **2014**, *12*, 8239.
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