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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 (Crimmins, *Org. Lett.* **2012**, *14*, 2168) and aldingenin C (Koshino, *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*)-acetoxycespitol. Computational evidence presented in this paper and based primarily on the computed proton spin-spin coupling constants (but also including ¹³C 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*)-hydroxycespitol **1**, and aldingenin B – hemiacetal **2** of a related 8-oxo compound.

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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, M.C.,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, H.K.,⁴ to the conclusion that aldingenins C and D are in fact known compounds, caespitol and 5-(*S*)-acetoxycespitol respectively, Figure 1. A.K. and O.M. 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 paper 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*)-hydroxycespitol **1**, and hemiacetal **2**. Also shown are previously suggested structures for aldingenins C and D (H.K.).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.

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

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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 hours and yet gives 0.2-0.5Hz 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, i.e. 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 H.K. 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 0.24Hz. Additionally, ¹³C 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 ¹³C NMR details see Supporting Information).

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. <i>J</i> 's (ref ¹) natural aldingenin A	<i>DU8</i> -calcd <i>J</i> 's 5-(<i>S</i>)-hydroxy- caespitol 1	<i>DU8</i> -calcd <i>J</i> 's aldingenin A
1	dddd 12.9, 4.2, 2.6, 1.5 q 12.9	13.3, 4.4, 2.9, 1.6 13.3, 13.2, 12.9	11.9, 9.6, 3.5 11.9
2	dd 12.9, 4.2	12.9, 4.4	3.5
4	dd 14.5, 2.7 dd 14.5, 3.1	14.3, 2.7 14.3, 3.5	12.6, 3.8 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 ddd 14.1, 13.2, 3.0	14.2, 4.1, 3.2 14.2, 13.6, 2.9	14.3, 4.2, 2.6 14.3, 13.4, 3.9
10	dd 13.2, 4.1	13.6, 4.1	13.4, 4.2

^acalculated *J*'s are listed in descending order with a cutoff value of 2Hz (unless reported experimentally); ^bsecond *J* = 2.7Hz in the triplet is possibly due to OH splitting; ^cnotice that the calculated value of *J*_{5,6} is small, (1.5Hz)

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 for a hydroxy group. Also considered were the C3 epimers of the *tert*-chloride **1** and *tert*-alcohol **6**, i.e. compounds **5** and **7**. The combination of computed SSCCs and ¹³C 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.

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 ¹³C chemical shift for carbon C8 was in agreement with an acetal or hemiacetal moiety, it was noticed by M.C.³ that 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 Dudley¹⁰ 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.

Scheme 1. Virtual transformations of aldingenin B.

However, a much better fit of computed SSCCs (Table 2) and ¹³C chemical shifts was achieved for hemiacetal **2** in which the C2–C3 diol was virtually altered into the vicinal bromo-chloride, typical of 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 B³ nicely with rmsd of 0.2Hz (mue=0.3Hz, Table 2,

last two columns). The experimental constants of the natural sample from Lago's work² matched computations for hemiacetal **2**, with one exception, the multiplet of H2 with $J_{12a}=9.6$ and $J_{12b}=6.3$ Hz, (see discussion below, Figure 4).

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

	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 dd 14.5, 4.7	14.6, 9.6 14.6, 5.2	14.1, 8.1 14.1, 7.2	13.7, 7.9 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 dd 13.5, 3.6	13.4, 12.9 13.4, 4.6	13.1, 12.8 12.8, 4.9	13.0, 12.6 12.6, 4.6
10	dd 13.5, 3.6	12.9, 4.6	13.1, 4.9	13.0, 4.6

^acalculated J 's are listed in descending order with a cutoff value of 2Hz. ^bFor consistency an experimental ¹H NMR spectrum of aldingenin B in CDCl₃ was used. ^cSecond order multiplet, simulation gives 11.2, 4.8Hz – see text below; with these simulated constants, calculated J 's for hemiacetal **2** match the experimental with rmsd = 0.46 Hz. ^dwe believe that this ddd (*pseudo*-quartet) was misreported as dd in ref.²

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

Figure 3. Alternative structures for aldingenin B.

Another complicating factor in NMR-guided structure assignments has always been the interpretation of multiplets which are not 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 6.3Hz. 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 0.006ppm for the two C1 protons, and $J_{12a} = 11.2$ Hz and $J_{12b} = 4.8$ Hz. It is reassuring that the sum of the apparent J 's, 9.6+6.3=15.9Hz, is very close to the sum of the constants obtained from the multiplet simulation, 11.2+4.8=16Hz, and that of calculated J 's for hemiacetal **2** (11.3+4.4=15.7Hz).

Figure 4. Simulation of the H2 multiplet (3.99ppm) of aldingenin B with $J_{12a}=11.2$ Hz and $J_{12b}=4.8$ Hz (reported apparent constants: 9.6 and 6.3Hz).

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*)-acetoxycasptitol **4**, which was previously proposed by H.K.⁴ as the correct structure for aldingenin D. The spectrum of 5-(*S*)-acetoxycasptitol reported in 2010 by Roussis¹² matches Lago's natural “aldingenin D” perfectly, with H2 listed as dd of 11.7, 4.9Hz in Lago's paper. Yet, six closely related derivatives of 5-(*S*)-acetoxycasptitol isolated by Roussis have this particular doublet of doublets reported with the large (*axial-axial*) constant >12.3Hz and the smaller (*axial-equatorial*) constant <4.4Hz. The calculated values for these two constants in 5-(*S*)-acetoxycasptitol are in keeping with this trend: 13.3 and 4.0Hz. The apparent constants of 11.7 and 4.9Hz 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=17.6Hz, matches the sum of the two predicted constants, 13.3+4.0=17.3Hz, very well. With these two constants excluded, our *rff* DU8 computations match the experimental constants for 5-(*S*)-acetoxycasptitol with rmsd of 0.25Hz, leaving little doubt that aldingenin D is indeed 5-(*S*)-acetoxycasptitol.

In conclusion, based on the computational evidence which includes the analysis of calculated proton spin-spin coupling constants and ¹³C 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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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.
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8. (a) for our multi-parameter *relativistic force field, DU4* see ref.⁵; (b) all computations of proton spin-spin coupling constants in this work were carried out using *relativistic force field method DU8* described in: Kutateladze, A.G.; Mukhina, O.A., "Just Accepted Manuscript" DOI: 10.1021/acs.joc.5b00619.
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11. In addition to the inferior match of computed SSCCs, the ¹H 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 vs Me-C-OH, e.g. aldingenin A: 1.93 (C₆D₆) or 1.91 (CDCl₃); aldingenin B: 1.57 (C₆D₆); aldingenin C: 1.69 (CDCl₃); aldingenin D: 1.78 ppm (CDCl₃), but for prevazol C it is 1.31ppm (Me-20, CDCl₃) and for prevazol B: 1.31 ppm (Me-20, CDCl₃) 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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