

Total Synthesis of the Proposed Structure  
of Aldingenin B

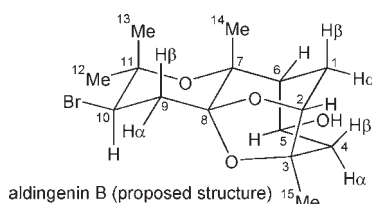
Michael T. Crimmins\* and Colin O. Hughes

Kenan, Caudill, Venable, and Murray Laboratories of Chemistry, University of North  
Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

crimmins@email.unc.edu

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## ABSTRACT



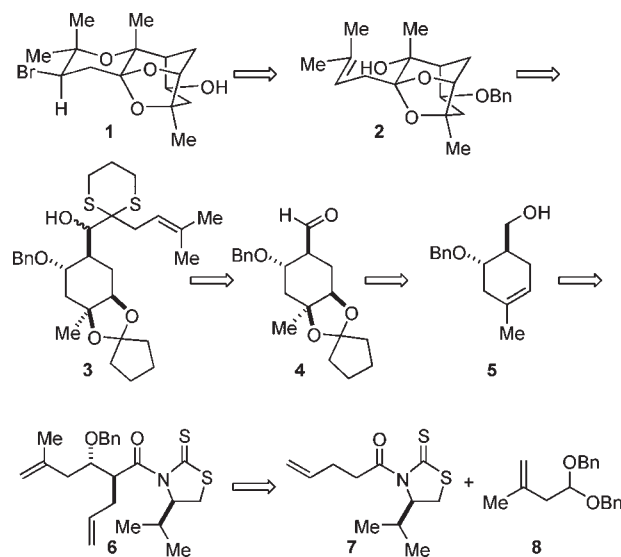
The first enantioselective total synthesis of the proposed structure of aldingenin B is reported in 16 steps from known compounds. The stereochemistry at C5 and C6 were established by an asymmetric acetal aldol. Following a ring-closing metathesis, a selective, substrate-controlled hydrogen bond-mediated dihydroxylation provided control of the C2 and C3 stereocenters. Discrepancies in the spectroscopic data of the synthetic and natural material led to the conclusion that the structure of the natural sample was misassigned.

The *Laurencia* red algae are a prolific source of halogenated secondary metabolites.<sup>1</sup> These marine natural products often serve as taxonomic markers for the determination of species within the *Laurencia* genus. It was thus of great interest when secondary metabolites of a Brazilian species identified as *Laurencia aldingensis* were characterized, as this species was previously unknown outside its native habitat off the coast of South Australia.<sup>2</sup>

Of the four novel sesquiterpene-derived natural products isolated, aldingenin B<sup>2b</sup> (**1**) was targeted for synthesis due to its compact and complex molecular architecture.<sup>3</sup> Its proposed structure, which was postulated based on extensive NMR studies, possesses a stereochemically dense tetracyclic framework, containing 7 stereocenters, 4 of which are contiguous, a brominated tetrahydropyran, and a cyclic ketal.

Our retrosynthesis is outlined in Scheme 1. It was envisioned that the proposed structure of **1** would arise

Scheme 1. Retrosynthetic Analysis of the Proposed Structure of Aldingenin B (**1**)



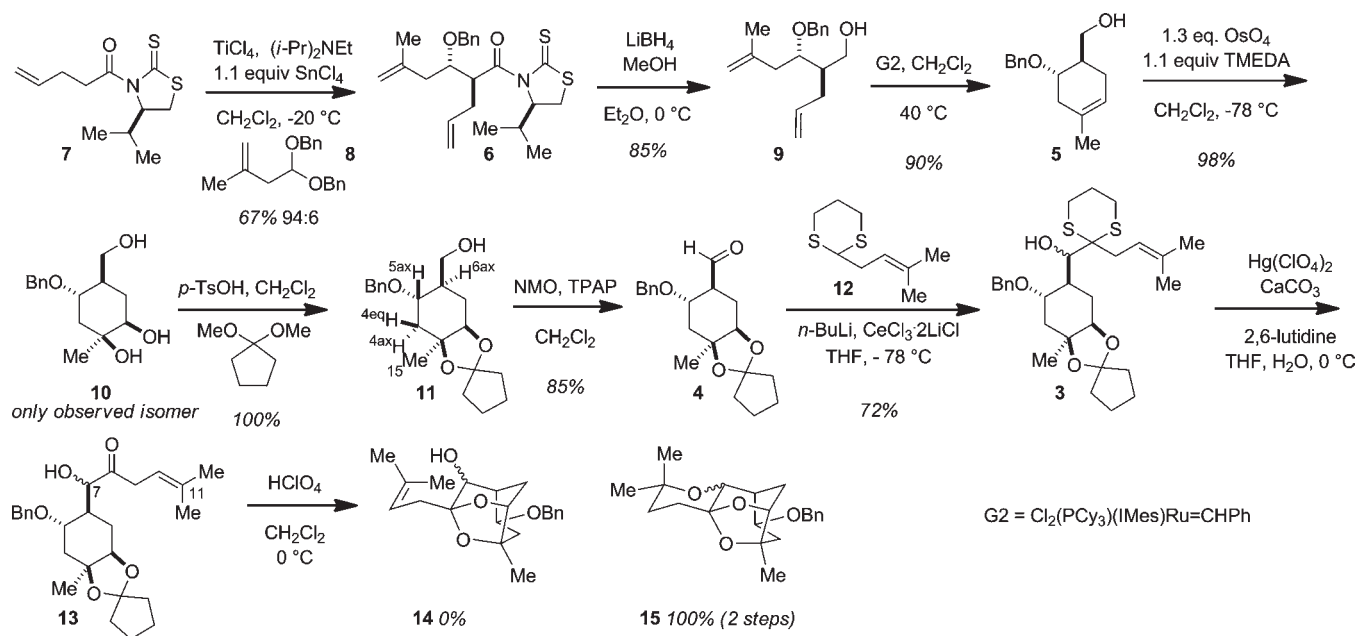
from a late stage bromoetherification of tricyclic ketal **2**. This ketal would be obtained from cycloketalization of dithiane **3** and further manipulation to install the C14 methyl. Dithiane **3** would result from a nucleophilic

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**Scheme 2.** Synthesis of the Bicyclic Ketal Precursor



addition to aldehyde **4**, the C2–C3 *syn*-diol installed via a *syn*-dihydroxylation of appended cyclohexene **5**. Cyclohexene **5** would be formed through a ring-closing metathesis of aldol adduct **6**, derived from an acetal aldol between thiazolidinethione **7** and dibenzyl acetal **8**.

The synthesis began by treating 3-methyl-3-butenal<sup>4</sup> to nonisomerizing acetalizing conditions<sup>5</sup> to provide dibenzyl acetal **8** (Scheme 2). The requisite C6–C5 stereochemistry of aldol adduct **6** was set with a chiral auxiliary mediated acetal aldol<sup>6</sup> addition of thiazolidiethione **7** and dibenzyl acetal **8**.

Reductive removal of the auxiliary upon exposure to lithium borohydride provided alcohol **9**. A ring-closing metathesis reaction<sup>7</sup> formed the cyclohexene **5**. Initial dihydroxylation of the alkene utilizing standard Upjohn conditions<sup>8</sup> led to a 3:1 inseparable mixture of isomers favoring the desired diol. Modest improvement was seen with the use of AD-mix  $\beta$ <sup>9</sup> (6:1); however the isomers could not be separated after subsequent reactions. With the focus

of harnessing the architectural features of the molecule, inspired by the work of Donohue,<sup>10</sup> an unprecedented and completely diastereoselective dihydroxylation was accomplished utilizing the H-bonding between primary alcohol **5** and the Lewis basic OsO<sub>4</sub>/TMEDA complex to direct the oxidant to the proper face of the olefin afforded triol **10**. It should be noted this fortuitous result was possible only after dihydroxylations utilizing the corresponding aldehyde led to decomposition. Since the selective oxidation of triol **10** to the corresponding aldehyde proved problematic, the *syn*-diol was initially protected as an acetonide, but later-stage removal of the protecting group proved difficult. Thus, the more acid-labile cyclopentylidene **11** was prepared. The structure of acetal **11** was confirmed by the lack of NOE signal between Me15–H5, and the coupling constants of axial H5 ( $J_{5ax-6ax} = 9.0$  Hz,  $J_{5ax-4eq} = 3.0$  Hz,  $J_{5ax-4ax} = 10.8$  Hz). The alcohol was then converted to aldehyde **4** utilizing mild TPAP/NMO oxidation conditions<sup>11</sup> to avoid decomposition experienced during Swern oxidation.

All initial efforts toward the nucleophilic C8–C7 bond forming event between prenyl-dithiane **12** and aldehyde **4** resulted in decomposition of the starting material, presumably via an undesired enolization.<sup>12</sup> Cerium trichloride was explored as an additive to decrease the effective basicity while maintaining the nucleophilicity of the metalated dithiane; however, results proved inconsistent. Numerous known methods of preparing cerium trichloride<sup>13</sup> for nucleophilic additions were attempted; however all were found to be inadequate for the substrate. Following extensive

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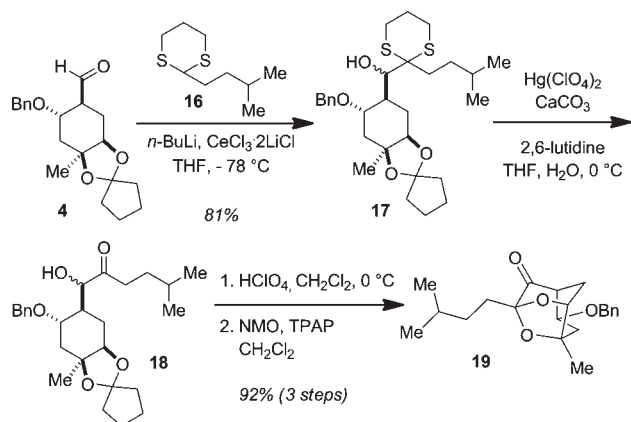
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**Scheme 3.** Control for the Formation of the Tricyclic Ketal



investigation, a new procedure was developed for purifying and solubilizing cerium trichloride,<sup>14</sup> allowing for the consistent formation of an inconsequential diastereomeric mixture of alcohol **3** in good yields.

Following numerous unsuccessful attempts at converting dithiane **3** into the tricyclic ketal core of **1** (e.g., through formation of the diol and then treatment of the dithiane to various oxidants), conditions were developed to convert the dithiane into carbonyl **13** without conjugation of the olefin. Unfortunately, upon exposure to perchloric acid, the desired tricyclic intermediate **14** was not formed, but rather tetrahydropyran **15** was formed, presumably resulting from acid-promoted tertiary carbocation formation at C11, followed by intramolecular trapping with the C7 alcohol.

Cyclization attempts utilizing milder acids led to no reaction, and efforts to avoid alcohol-carbocation trapping by mitigating the nucleophilicity of the C7 oxygen through protecting groups or oxidation to the ketone were met with no reaction and decomposition, respectively.

As a control experiment, saturated dithiane **16** was coupled with aldehyde **4**, followed by dithiane removal, whereupon exposure to perchloric acid cleanly afforded tricycle **19** after oxidation of the secondary alcohol (Scheme 3). It is notable that the <sup>1</sup>H NMR spectrum of tricycle **19** is analogous to that of similar compounds prepared by Dudley during studies toward the synthesis of aldingenin B.<sup>15</sup> The knowledge gained from this experiment indicated that the C10–11 olefin in **13** was responsible for failure to elaborate dithiane **3** into alcohol **14**. Therefore, efforts were focused toward the synthesis of an analogue of prenyl-dithiane **3** containing a masked olefin as a way to circumvent these problems.

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(14) See Supporting Information for details.

(15) Compound **3** in ref 3 above as well as two additional similar compounds provided in personal communications.

The analogue **21** was synthesized by the nucleophilic addition of dithiane **20**<sup>16</sup> to aldehyde **4** (Scheme 4). Dithiane **21** was converted to ketone **22**, which when exposed to perchloric acid, serendipitously cleaved the silyl ether in addition to the cyclopentylidene resulting in cyclization to ketal **23**. The structure of the major diol isomer was confirmed by <sup>1</sup>H, <sup>13</sup>C NMR, a NOE crosspeak between H7–H5, and a COSY signal between H6–H7. Unfortunately, on larger scale reactions (> 20 mg) these conditions proved very inconsistent, a result attributed to the immiscibility of the dichloromethane with aqueous perchloric acid. It was found that ultrasonic irradiation was necessary to ensure proper mixing of the biphasic system on larger scales.<sup>17</sup>

Allaying concerns of lactonization, bis-oxidation under Swern conditions<sup>18</sup> provided keto-aldehyde **24**. Exploiting the hindered steric environment of the ketone, exposure of aldehyde **24** to isopropylidene triphenylphosphorane formed the desired trisubstituted olefin **25**. Axial methyl lithium addition provided the necessary stereochemistry at C7 (as confirmed by NOESY correlation between Me14–H1β), forming tertiary alcohol **2** in low yield (17%) as well as C9 elimination products. Again, the use of cerium trichloride proved important in suppressing elimination, as its inclusion in the axial methyl lithium addition formed only tertiary alcohol **2** without any side products.

Formation of prenyl **25** with isopropylidene triphenylphosphorane proved very inconsistent, necessitating the development of an alternative strategy to forge trisubstituted olefin **25**. Both “salt-free” methylene Wittig conditions<sup>19</sup> and Tebbe olefination<sup>20</sup> provided terminal olefin **26**, however in low yields (< 22%). It was discovered that addition of keto-aldehyde **24** to a solution of Nysted reagent<sup>21</sup> reliably produced terminal olefin **26**, which when exposed to cross-metathesis conditions in neat 2-methyl-2-butene<sup>22</sup> provided trisubstituted olefin **25**. Bromoetherification of alcohol **2** using 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO)<sup>23,24</sup> afforded bromo-tetrahydropyran **27** along with a mixture of bromo-tetrahydrofurans. The stereochemistry of **27** was identified by the characteristic axial H10 *J*-values of 13.2 and 4.2 Hz and NOE signals between H9β–Me13, H9β–Me14, and Me13–Me14. Removal of the benzyl group via standard palladium hydroxide promoted hydrogenation afforded the proposed structure of aldingenin B (**1**).

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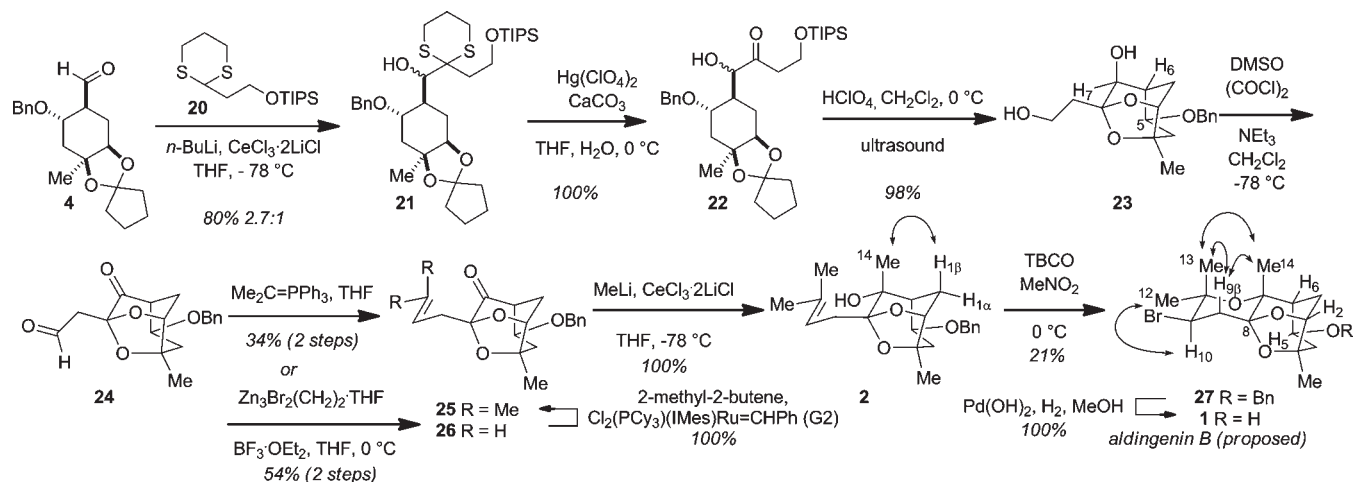
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**Scheme 4.** Completion of the Synthesis of the Proposed Structure of Aldingenin B



**Table 1.** <sup>1</sup>H NMR Assignments of Natural and Synthetic **1**

H no.	natural sample C <sub>6</sub> D <sub>6</sub> , 500 MHz	synthetic <b>1</b> C <sub>6</sub> D <sub>6</sub> , 600 MHz
1 $\alpha$	1.65 <i>m</i>	1.55 <i>ddd</i> (15.0, 3.6, 1.8)
1 $\beta$		1.65 <i>ddd</i> (15.0, 3.6, 1.8)
2	3.99 <i>dd</i> (9.6, 6.3)	3.62 <i>dd</i> (3.6, 1.8)
4 $\beta$	1.92 <i>dd</i> (14.5, 9.6)	1.10 <i>dd</i> (13.8, 7.8)
4 $\alpha$	2.16 <i>dd</i> (14.5, 4.7)	2.21 <i>dd</i> (13.8, 7.8)
5	3.86 <i>ddd</i> (9.6, 8.4, 4.7)	4.65 <i>app. t</i> (7.8)
6	1.44 <i>dd</i> (9.0, 8.4)	1.53 <i>app. s</i>
9 $\alpha$	1.72 <i>dd</i> (13.5, 3.5)	2.25 <i>dd</i> (13.2, 4.2)
9 $\beta$	2.19 <i>t</i> (13.5)	2.50 <i>t</i> (13.2)
10	4.17 <i>dd</i> (13.5, 3.5)	4.55 <i>dd</i> (13.2, 4.2)
12	1.36 <i>s</i>	1.40 <i>s</i>
13	1.49 <i>s</i>	1.39 <i>s</i>
14	1.19 <i>s</i>	1.24 <i>s</i>
15	1.57 <i>s</i>	1.00 <i>s</i>

Unfortunately, the NMR spectra of synthetic **1** differ significantly from the data for the natural sample. Inspection of the assigned spectra of the natural sample raises doubts as to the validity of its structural assignment. In particular, several discrepancies exist between the observed couplings of H5, H6, and H2 in the natural sample and the expected couplings of the assigned structure.

Inspection of models of **1** reveals the H6–H5 dihedral angle to be 90° ( $\pm 2^\circ$ ); the expected coupling of such vicinally orthogonal protons is < 2 Hz. The natural sample displays an 8.4 Hz coupling between these protons, while there is no detected coupling between H5–H6 in synthetic **1**.

Furthermore, the reported coupling constants for the “bridgehead” protons H6 and H2 in the natural sample are 9.0, 8.4 and 9.6, 6.3 Hz respectively (Table 1). The expected value of coupling constants of such bridgehead protons is < 4 Hz, as observed in the couplings of H2 ( $J = 3.6, 1.8$  Hz) and H6 (*app. s*) in the synthetic sample and examples reported by Dudley.<sup>3,15</sup>

Additionally, the HMBC spectrum of the natural sample does not display a H2–C8 crosspeak, whereas this key HMBC signal is observed in synthetic **1**. Moreover, COSY, NOESY, HMQC, HMBC, and DEPT-135 spectra indicate the structure of synthetic **1** is as shown, and spectral information of all intermediates are as expected for such structures.

In summary, the first total synthesis of the proposed structure of aldingenin B has been accomplished in 16 steps (LLS) in 2.7% overall yield. Key steps include a diastereoselective acetal aldol, a ring-closing metathesis, a substrate-controlled, hydrogen bond-mediated dihydroxylation, a cycloketalization to construct the compact tricycle, and a bromoetherification to complete the carbocycle. The development of a novel way of drying and solubilizing cerium trichloride for use in nonbasic nucleophilic additions was also achieved.

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**Note Added after ASAP Publication.** An incomplete SI file was replaced on April 6, 2012.

**Supporting Information Available.** Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.