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Synthesis of the Tricyclic Core of Aldingenin B by Oxidative Cyclo-Ketalization of an Alkyne-Diol

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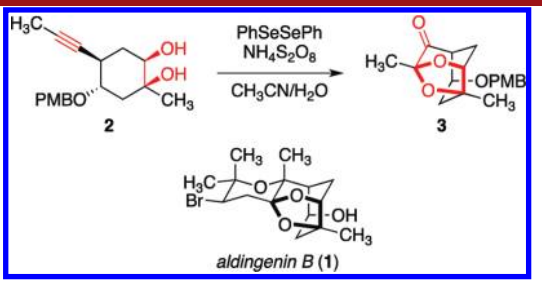
ABSTRACT



The preparation and selenium-mediated cyclo-ketalization of an alkyne-diol is described as a model study for the synthesis of aldingenin B. The oxidative cyclization is a simplifying transformation for aldingenin B, as it provides a convenient method for generating the tricylic core of the natural product from a functionalized cyclohexane.

The aldingenin family[1] of bisabolene sesquiterpenes is a collection of brominated marine natural products[2] isolated from a Brazilian strain of the red alga *Laurencia aldingensis*. Red algae of the *Laurencia* genus produce myriad halogenated secondary metabolites, many of which are useful as taxonomic markers for species identification.[3] It was in this vein that the aldingenins were isolated and characterized, as part of a taxonomic investigation of the Brazilian species of *Laurencia*.[1]

Aldingenin B[1b] (Figure 1) caught our attention due to its compact and highly oxygenated tetracyclic structure. As a target for stereoselective synthesis, it presents challenges with respect to the controlled oxidation and installation of complex functionality, especially at C5, into a relatively simple (bisabolene) carbon framework.

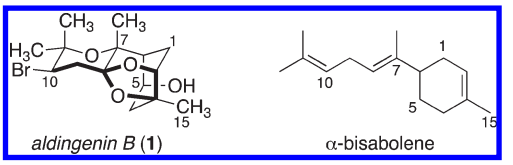


Figure 1. Aldingenin B and α-bisabolene.

Our retrosynthetic analysis of aldingenin B is presented in Scheme 1. A late stage bromoetherication is planned for installation of the C7−C11 oxane ring, leading to the identification of tricyclic keto-ketal **4** as the core target.

It was tempting retrosynthetically to unravel the keto-ketal to α-diketone **5**, but strategic analysis of **5** prompted concerns. α-Diketones easily undergo tautomerization to enols; in the case of α-diketone **5**, enolization to give **5′** would both compromise C6 stereochemistry and threaten to promote elimination of the protected C5 alcohol. Note that keto-ketal **4** cannot tautomerize (Bredt's rule). Therefore, we prioritized the goal of installing the C7−C8 keto-ketal of **4** without producing an intermediate C7−C8 diketone, and our synthetic efforts focused on alkyne **2**.

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(3) Fenical, W. *J. Phycol.* **1975**, *11*, 245–259.

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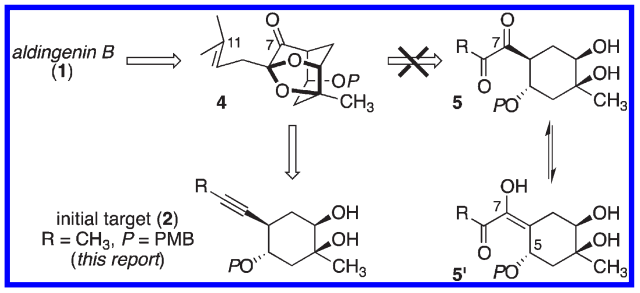
Scheme 1. Retrosynthetic Analysis



The generation[4] and synthetic application[5] of complex alkynes is an ongoing area of interest in the Dudley Lab. Herein we report the synthesis and cyclo-ketalization of alkyne-diol **2** as a model study for the synthesis of aldingenin B.

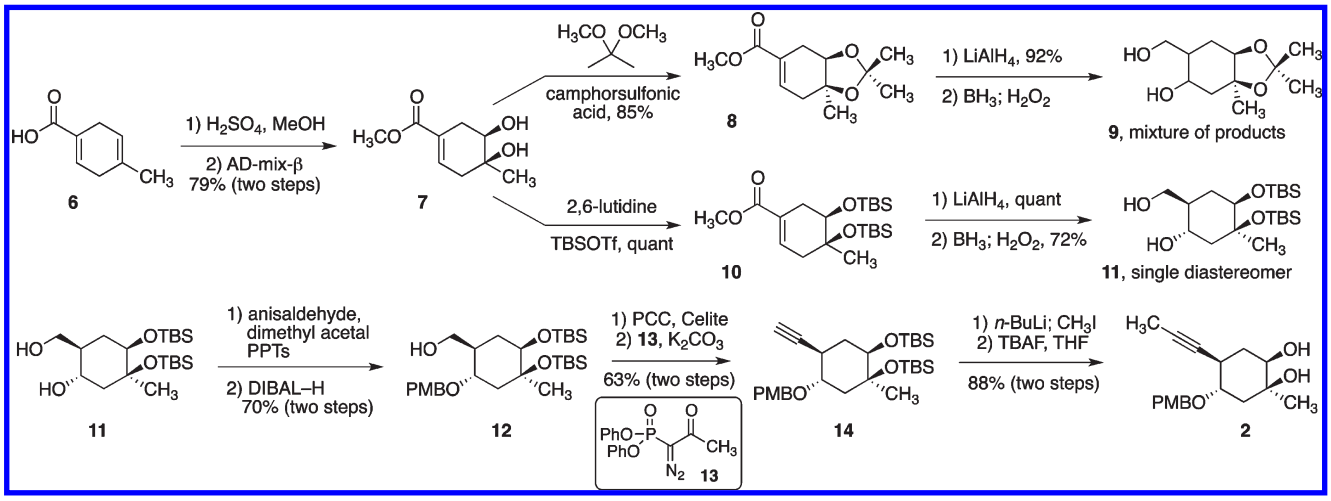
The synthesis of alkyne-diol **2** began with the known Diels–Alder reaction between propiolic acid and isoprene, which provides cyclohexadienyl acid **6** (Scheme 2).[6] After conversion to the methyl ester, regioselective dihydroxylation of the more electron-rich alkene gave diol **7**. Diol **7** was initially protected as an acetonide (**8**), but downstream in the synthetic sequence is a hydroboration that proved not to be satisfactory with the acetonide in place (cf. **8** → **9**). Therefore, the protection strategy was altered to feature TBS ethers (**10**) in lieu of the acetonide. Reduction of the methyl ester of **10** and hydroboration/oxidation gave diol **11** as a single diastereomer, in contrast to nonselective hydroboration leading to acetal **9**.

The secondary alcohol of diol **11** was converted to a PMB ether using a standard two-step sequence (**11** → **12**).[7] Primary alcohol **12** was oxidized to the aldehyde with PCC and then converted to terminal alkyne **14** using the Ohira–Bestmann reagent (**13**).[8] Finally, methylation of alkyne **14** (*n*-BuLi; MeI) and desilylation with TBAF completed the synthesis of alkyne-diol **2**.

Oxidative keto-ketalization of alkynes (Scheme 3) would be useful in the continued progression of our synthetic strategy, but such tools are not well developed in organic synthesis. Oxidation of alkynes to α-*diketones* (as opposed to α-keto ketals) can be accomplished with reagents including permanganate ion, ozone, and osmium tetroxide, as well as several transition-metal-catalyzed processes.[9] We were interested in potentially coupling one of these methods with ketal formation, such that cyclization to the ketal occurs in concert with the alkyne oxidation. However, these methods generally involve harsh oxidants with poor functional group tolerance and are best suited for use on simple alkynes with aryl and/or *tert*-alkyl substituents. Specifically, we required a method suitable for oxidation of dialkylalkynes to α-keto ketals in the presence of alcohols (Scheme 3).

A thorough scan of the literature revealed a single example of the type of keto-ketalization envisioned for the synthesis of aldingenin B. As part of a larger study on

Scheme 2. Synthesis of Alkyne-Diol **2**[a]



[a] See Supporting Information for details.

(4) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028–5029. (b) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175–177. (c) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499–6507. (d) Tummatorn, J.; Dudley, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 5050–5051. (e) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 158–160. (f) Jones, D. M.; Lisboa, M. P.; Kamijo, S.; Dudley, G. B. *J. Org. Chem.* **2010**, *75*, 3260–3267.

(5) (a) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936–938. (b) Jones, D. M.; Dudley, G. B. *Synlett* **2010**, 223–226. (c) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698–4701. (d) Jones, D. M.; Dudley, G. B. *Tetrahedron* **2010**, *60*, 4860–4866.

(6) Fráter, G.; Müller, U. *Helv. Chim. Acta* **1989**, *72*, 653–658.

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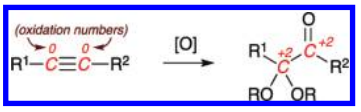
(8) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59–62.

Scheme 3. Oxidative Keto-Ketalization of Alkynes[a]



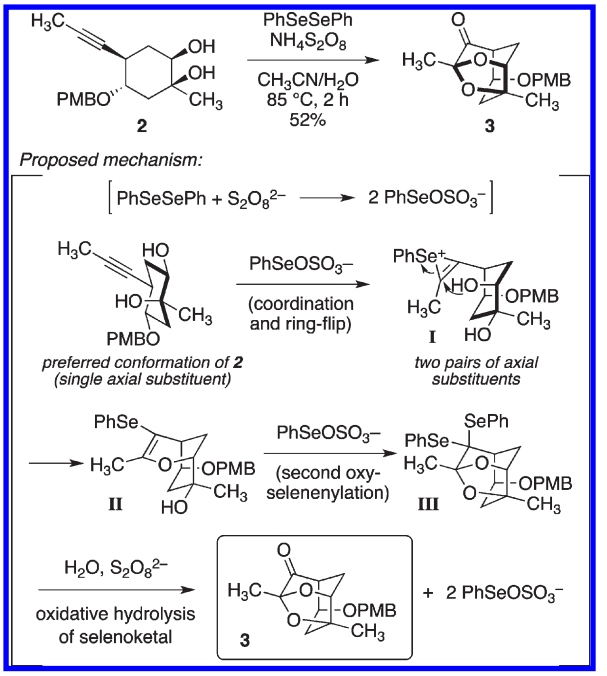
[a] R, R^1, R^2 = alkyl groups. Oxidation numbers assigned (red).

selenium-mediated oxidations,[10] Tiecco reported the oxidation of 4-octyne to 5,5-dimethoxy-4-octanone using ammonium peroxydisulfate and diphenyl diselenide in methanol[11] (cf. Scheme 3, R = methyl; R^1, R^2 = *n*-propyl, 51% yield). Two features of this reaction were especially attractive for our purposes: use of methanol as solvent suggests compatibility with alcohols, and the postulated mechanism does *not* involve an intermediate α-diketone.

The mechanism envisioned for the oxidation and diol cyclization process is outlined in Scheme 4. The first steps involve coordination of the active selenium oxidant and cyclohexane ring-flipping into a conformation (**I**) in which cyclization is possible. Cyclohexane conformations with multiple axial substituents are typically disfavored because of diaxial interactions, but in this case one diaxial interaction is believed to be favorable, leading to bond construction and formation of vinylselenide intermediate **II**. A second oxy-selenenylation would result in seleno-ketal **III**, the hydrolysis of which provides keto-ketal **3**. In the event, treatment of alkyne-diol **2** with 1 equiv of diphenyl diselenide and 2 equiv of ammonium persulfate in aqueous acetonitrile at 85 °C provided tricylic α-keto ketal **3** in 52% yield (Scheme 4).

This novel cyclo-ketalization reaction using Tiecco's conditions simplifies the synthesis of aldingenin B by building two new heterocycles into the monocyclic carbon

Scheme 4. Oxidative Alkyne-Diol Keto-Ketalization [and Proposed Mechanism] for the Synthesis of Aldingenin B[a]



[a] See Supporting Information for details.

framework. Optimization of this key step remains a work in progress, but we have concluded that water is a critical cosolvent (alongside acetonitrile) and 85 °C seems to be the optimal temperature. As we shift our attention to the natural product, what remains is to construct a more elaborate analog of alkyne **2**, with functionality in place to facilitate bromoetherification and complete the fourth and final ring of aldingenin B.

In summary, we report the first example of an alkyne-diol oxidative cyclo-ketalization as a model study for the synthesis of aldingenin B. The selenium-mediated process delivers the complex tricyclic core of aldingenin B from a modestly functionalized cyclohexane precursor. Continuing efforts toward the enantioselective synthesis of the natural product will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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