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Total Synthesis of (±)-2-*O*-Methylneovibsanin H

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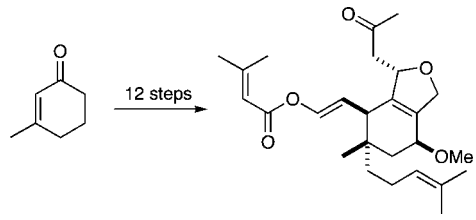
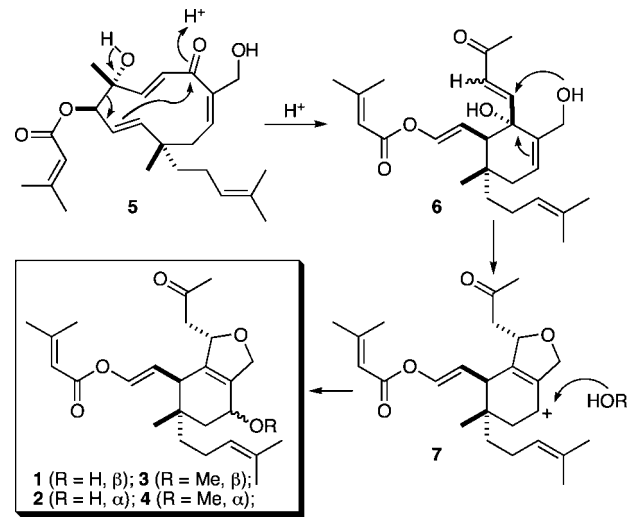
ABSTRACT



The total synthesis of (±)-2-*O*-methylneovibsanin H was achieved in 12 steps. An acid-catalyzed, one-pot, four-step cascade reaction was key to the concise total synthesis, lending support to the proposed biosynthesis.

Viburnum awabuki has yielded a plethora of rare and unusual vibsane-type diterpenes as reported by Fukuyama[1] and others.[2] Neovibsanin H (**1**),[3] neovibsanin I (**2**),[3] 2-*O*-methylneovibsanin H (**3**),[4] and 2-*O*-methylneovibsanin I (**4**)[4] (Scheme 1) constitute part of the highly functionalized six-membered ring group of this intriguing family of natural products. Fukuyama has proposed an acid-catalyzed biosynthetic pathway for the formation of neovibsanins **1**−**4** starting from vibsanin B (**5**), via plausable intermediates **6** and **7** (Scheme 1).[4] With this consideration, **6** (or masked equivalent), seems a suitable target to probe the biosynthetic postulate and total synthesis of **1**−**4**. In fact, Fukuyama has made synthetic attempts in the neovibsanin area,[5] targeting molecules of type **6** as an advanced intermediate. However,

Scheme 1. Neovibsanin H (**1**), Neovibsanin I (**2**), 2-*O*-Methylneovibsanin H (**3**), and 2-*O*-Methylneovibsanin I (**4**) Proposed Biosynthetic Pathway



no total syntheses of **1**−**4** or related family members have been reported. Therefore, considering the attraction we have

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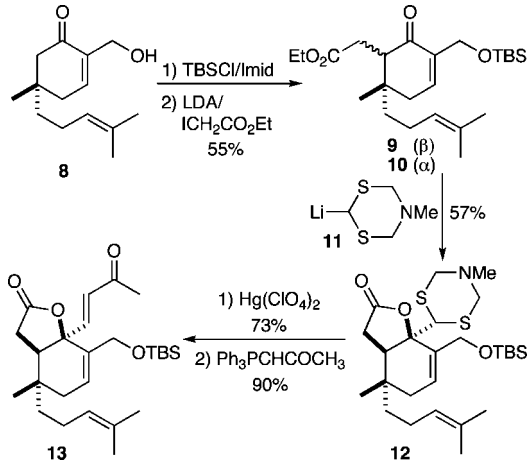
to this family of natural products,[6–11] we extended our study in this area, the results of which are now disclosed herein.

TBS protection of alcohol **8**[6–8,12] followed by alkylation with ethyl iodoacetate afforded, with poor stereocontrol, **9** and **10** in 37% and 24% yield, respectively. Attempts to react **9** with a range of metalated acetylides (including cerium), to install a masked enone function, all failed to undergo 1,2-addition, affording only recovered starting material **9** or epimerized starting material **10**. To circumvent the problematic two-carbon unit incorporation, reversion to a one-carbon unit was investigated, and in this vein, only lithium dithiazide[13] was found to add successfully to give **12**, albeit in moderate yield. Mercury-mediated deprotection revealed the aldehyde function, which was easily converted into the desired enone function, affording the key intermediate **13** in 66% yield over two steps (Scheme 2).

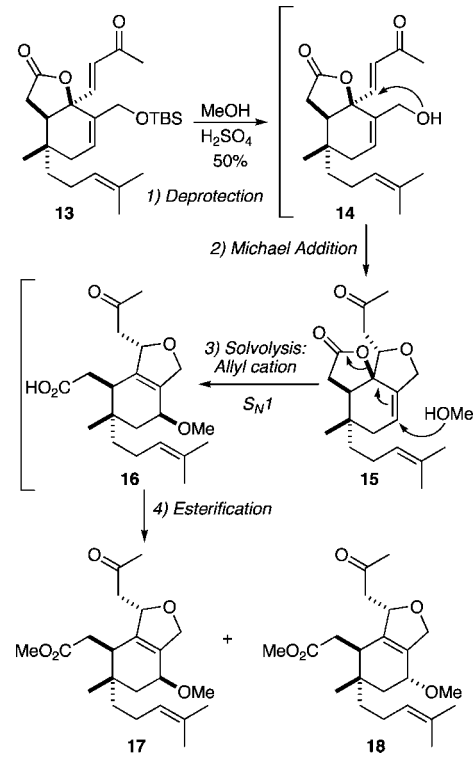
Scheme 2. Preparation of Intermediate **13**



After some initial investigation of reaction conditions, it was discovered that treatment of **13** with a gross excess of concentrated sulfuric acid in anhydrous methanol afforded methyl ester **17** and the corresponding position 2 epimer **18** (85:15, respectively)[14] in 50% yield (Scheme 3).

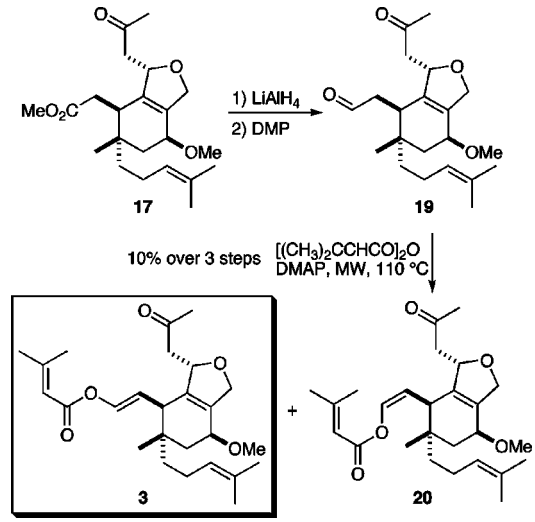
To arrive at methyl ester **17** in one synthetic manipulation required **13** to negotiate four cascading steps: (1) TBS deprotection giving primary alcohol **14**, (2) Michael addition of the primary alcohol function to the enone (i.e., **15**), (3) stepwise or concomitant solvolysis (i.e., allyl cation) and nucleophilic attack by the solvent, and (4) Fischer esterification. In addition to the succinct cascade is the remarkable stereocontrol obtained at positions 2 and 5, most likely inherent in the preexisting well-defined stereochemical congestion in the starting material (i.e., **13**).

Scheme 3. Preparation of Advanced Intermediate **17** via a Four-Step, Acid-Induced Cascade



Global reduction of **17** with lithium aluminum hydride was easily accomplished. However, gobal oxidation to access **19**

Scheme 4. Final Sequence Leading to the Total Synthesis of 2-*O*-Methylneovibsanin H (**3**)



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(14) Compound **18** is tentatively assigned.

required some effort, and Dess−Martin periodinane performed best. The remaining task to complete the synthesis was installation of the 3,3-dimethylacroyl enol ester side chain. In this instance the Davies[15] protocol, which has been slightly improved using microwave radiation,[10] was utilized. The one-pot side chain installation protocol we developed[11] is not applicable in this case. The microwave reaction, however, was found to be much more sluggish than previously observed with other substrates.[10] Optimized conditions required 15 h at 110 °C to obtain the target **3** and the *cis*-isomer **20** [10% over three steps, *E*/*Z* ratio 3:2] (Scheme 4).

In conclusion, the total synthesis of (±)-2-*O*-methylneovibsanin H (**3**) is a further demonstration of the pivotal role that cascade reactions, often based on biomimetic rationale,[16] play in the rapid construction of natural products.[17] Furthermore, this body of work lends support to Fukuyama's proposed biosynthesis, opening the opportunity to target closely related family members.

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Supporting Information Available: Experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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