

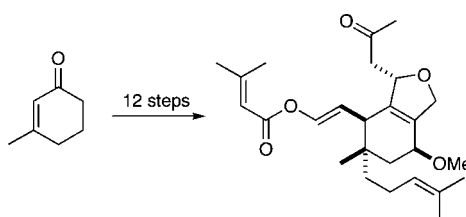
Total Synthesis of
(±)-2-*O*-Methylneovibsanin H

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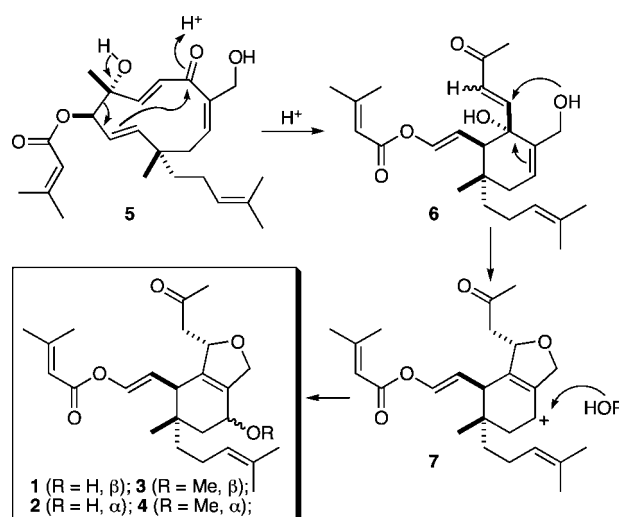
ABSTRACT



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 vibsanine-type diterpenes as reported by Fukuyama¹ 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 plausible 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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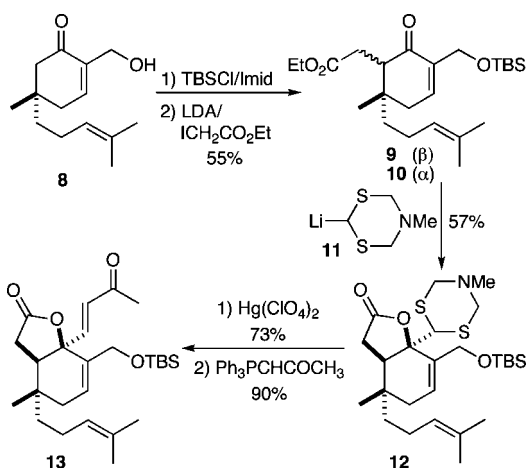
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to this family of natural products,^{6–11} we extended our study in this area, the results of which are now disclosed herein.

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 dithiazide¹³ 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).

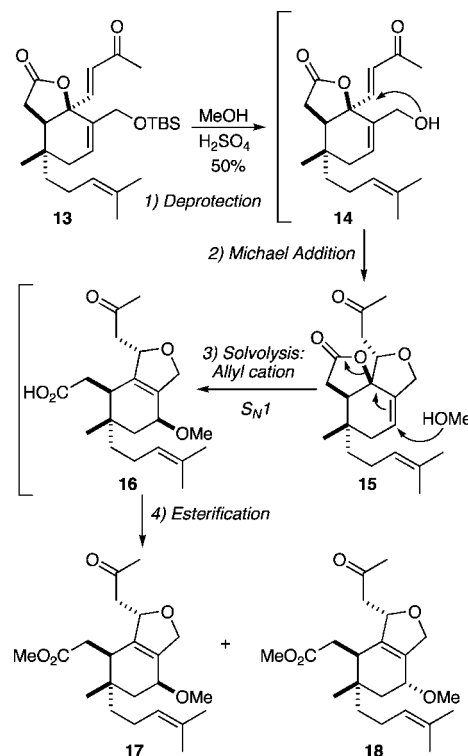
Scheme 2. Preparation of Intermediate **13**



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)

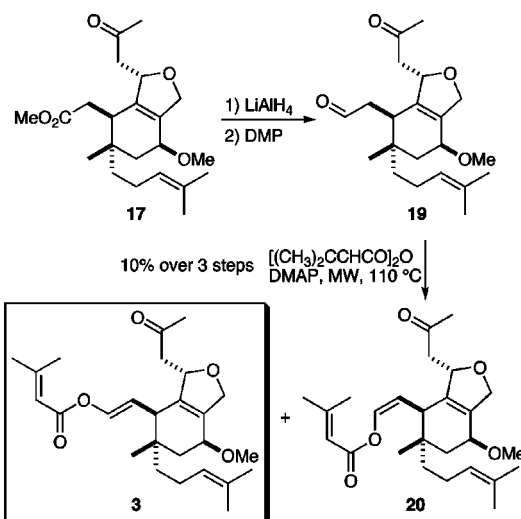
Scheme 3. Preparation of Advanced Intermediate **17** via a Four-Step, Acid-Induced Cascade



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**).

Global reduction of **17** with lithium aluminum hydride was easily accomplished. However, global 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-dimethylacryl enol ester side chain. In this instance the Davies¹⁵ protocol, which has been slightly improved using microwave radiation,¹⁰ was utilized. The one-pot side chain installation protocol we developed¹¹ 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 ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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