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A short and efficient synthesis of (±)-*trans*-sabinene hydrate

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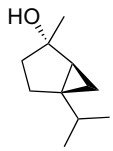
Abstract—A short synthesis of sabinene hydrate is reported. It uses cheap starting materials and affordable reagents. The main product of the synthesis is *trans*-sabinene hydrate. © 2001 Elsevier Science Ltd. All rights reserved.

trans-Sabinene hydrate **1** is an important flavor chemical found in a variety of essential oils from mint[1] and herbs.[2] Its flavor has been described as cooling, minty, eucalyptol and green with a sweet spicy terpineol-like character. Although *trans*-sabinene hydrate is commercially available from a few flavor ingredient suppliers, its current market price ($1200–1800/kg) limits its use in flavors.



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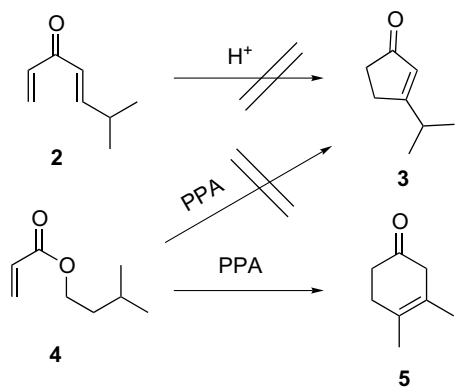
Several syntheses of *trans*-sabinene hydrate have been published. However partial syntheses start with expensive materials such as 3-thujone[3] or sabinene,[4] while total syntheses either use impractical reactions such as ozonolysis[5] or diazoalkane coupling,[6] or require too many steps.[7] There is a need for a simple, straightforward total synthesis of sabinene hydrate that can be upscaled for large production. We wish to present a practical synthesis of sabinene hydrate that is short, efficient and cost effective.

The challenge in the synthesis of sabinene hydrate is building the 5+3 bicyclic skeleton. It appeared to us[8] that the best way of building this skeleton was to use 3-isopropyl-2-cyclopentenone **3** as an intermediate since it has a double bond that can be functionalized into a cyclopropane ring, and a ketone that could be transformed into the tertiary alcohol of sabinene hydrate **1**. Our initial objective was to build this structure by using the Nazarov cyclization of 6-methyl-1,4-heptadien-3-one **2** (Scheme 1).[9] However, like many mono-substituted dienones of this kind, this compound failed to cyclize under a variety of conditions. A variation[10] of the Nazarov cyclization, treating isopentyl acrylate **4** with polyphosphoric acid (PPA), gave a cyclized product, but not the desired cyclopentenone **3**. Instead, we obtained an isomer to which structure **5** was tentatively assigned.[11]

These experiments convinced us that the best way of making cyclopentenone **3** might be the intramolecular aldol condensation of dione **8** as described by Fanta and Erman.[5] In order to avoid ozonolysis of α-terpinene or oxidative hydroboration of 6-methyl-5-hepten-2-one,[5] we thought of making the dione **8** by using the Stetter addition of isovaleraldehyde **7** to methylvinylketone **6** (Scheme 2).[12] We first repeated the original procedure from Stetter using 10 mol% catalyst to give the desired product in 64% yield. We found out



Scheme 1. Attempts at a one-step synthesis of **3**.

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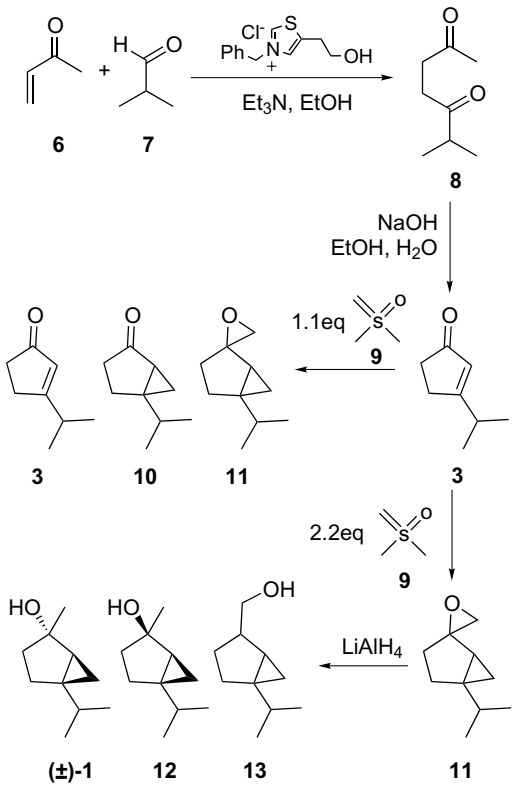

Scheme 2. Total synthesis of (±)-**1**.

that decreasing the amount of catalyst to 5 or even 1 mol% increased the yield of the reaction up to 82% but reaction times of up to 2 days had to be used. Cyclization was done in 70% as described by Fanta and Erman.[5] Attempts at changing the reaction conditions of the cyclization only returned lower yields.

The cyclopentenone was then cyclopropanated using the Corey–Chaykovsky reagent **9** made by deprotonation of trimethylsulfoxonium iodide with sodium hydride.[13] To our surprise this reaction resulted in a mixture of starting material **3**, desired product (sabina ketone, **10**) and overreacted product (epoxysabinene, **11**) in a 4:3:1 ratio (Scheme 2). Modification of reaction temperature and mode of addition resulted in the same type of mixture suggesting that the attack on the very electrophilic cyclopentanone **10** is faster than the attack on the unreactive, polysubstituted enone **3**.

Since the reduction of epoxysabinene **11** to sabinene hydrate is known,[4] cyclopentenone **3** was reacted with 2.2 equiv. of Corey–Chaykovsky reagent at room temperature in DMSO overnight to be converted completely to epoxysabinene **11** in 71% yield (Scheme 2). The epoxide was reduced with $LiAlH_4$ to give a mixture of (±)-*trans*-sabinene hydrate (±)-**1**, (±)-*cis*-sabinene hydrate **12** and (±)-sabinane alcohol **13** in a surprising 10:1.6:2.8 ratio.[14]

The high *trans*/*cis* ratio shows that both attacks of the Corey–Chaykovsky reagent have taken place on the same side of the molecule. This would suggest that the second attack was directed by the steric hindrance of the isopropyl group on the β-carbon.

This is in contradiction with the attack of MeLi on sabina ketone **10**, which was shown[5] to be directed by the steric hindrance of the cyclopropane group and yield the *cis*-sabinene hydrate **12** as the major product.

This difference may be explained by the size of the nucleophile. The small MeLi may only interact unfavorably with substituents at the α-carbon whereas the bigger $CH_2{=}S(=O)Me_2$ can interact with substituents both α- and β- to the ketone. Therefore MeLi will attack on the less hindered face of the α-carbon (which is *anti* to the cyclopropane ring) whereas the sulfoxide will attack on the less hindered face of the β-carbon (which is *syn* to the cyclopropane).

In conclusion, we have developed a short and efficient (28% overall yield) synthesis of *trans*-sabinene hydrate by using common reagents. There are only two expensive reagents in this route: Stetter's thiazolium ion and the Corey–Chaykovsky reagent precursor, trimethylsulfoxonium iodide. However, the former is only used in catalytic amounts while the latter can easily be made in the laboratory.[15]

Acknowledgements

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