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A convenient, reproducible two-step synthesis of 6,6-dimethylbicyclo[3.1.1]heptane-2,4-dione

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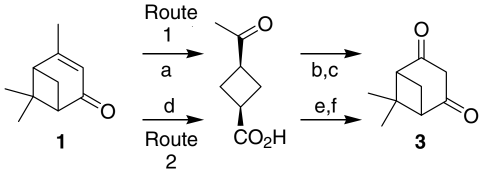
Abstract—A convenient, reproducible two-step method for preparing 6,6-dimethylbicyclo[3.1.1]heptane-2,4-dione is described. The method involves isomerizing the double bond of commercially available (−)-verbenone as previously described, followed by ozonolysis to give the desired product in good yield.

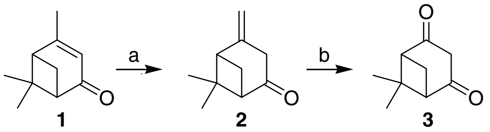
Natural products possessing the 6,6-dimethylbicyclo-[3.1.1]heptane skeleton abound in nature. Various members of the so-called pinane family have been employed as chiral building blocks for asymmetric synthesis, and a significant body of literature on the subject exists.[1] Synthetic efforts on these molecules continue today owing to their important roles in the fragrance industry and in the production of pheromones used in controlling agricultural pests.[2]

As part of a drug discovery program targeting voltage-gated potassium channels, we required ample quantities of 6,6-dimethylbicyclo[3.1.1]heptane-2,4-dione (**3**). Two routes to the synthesis of this molecule have been described in the literature. Guha and Ganapathi[3] reported obtaining the material in two steps from *cis*-pinonoic acid (Scheme 1, route 1) which was, in turn, available through the oxidation of verbenone (**1**) with potassium permanganate.[4] We attempted to repeat Guha and Ganapathi's synthesis of 6,6-dimethylbicyclo[3.1.1]heptane-2,4-dione, but were unable to obtain the product in reproducibly acceptable yield. A variation on this synthetic route was described by Welenkiwar et al. in 1970,[5] in which verbenone was converted to *cis*-pinonoic acid by ozonolysis (Scheme 1, route 2). This material was then treated with diazomethane to give the penultimate intermediate, which was condensed using the procedure described by Guha and Ganapathi to yield the final product. This variation improved the yield of the synthesis somewhat and overcame what we found to be a problem in the permanganate-catalyzed ring cleavage of verbenone (reduced yield due to partial isomerization to *trans*-pinonoic acid). However, it did not address the poor reproducibility of the last step, which was confirmed by Welenkiwar et al. in a footnote.[5]



Scheme 1. Previously published routes to compound **3**. Reagents and conditions: Route 1 (a) $KMnO_4$, 0 °C; (b) CH_3OH, KOH, reflux; (c) NaOEt, toluene. Route 2 (d) O_3, 0 °C; (e) CH_2N_2; (f) NaOEt, toluene.

We therefore devised another route to the target molecule (Scheme 2). Starting with commercially available (−)-verbenone (**1**), our route takes advantage of the ease with which the double bond of verbenone can be isomerized to the exocyclic position. Using methodology first described by Armour et al.[6] in their synthesis of the isomers of ambrinole, Ohloff and Giersch affected



Scheme 2. Reagents and conditions: (a) NaH, THF, rt, 55 h, followed by aq H_3BO_3, 90%; (b) O_3, MeOH, −78 °C, followed by Me_2S, 83%.

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the conversion of verbenone (**1**) to 6,6-dimethyl-4-methylene-bicyclo[3.1.1]heptan-2-one (**2**) by treatment with sodium hydride followed by quenching of the enolate with aqueous boric acid.[7] In contrast to the conversion of α-pinene to β-pinene,[8] the isomerization of the double bond in verbenone to the β-position proceeds smoothly. Yields as high as 91% have been reported for this transformation,[9] and our yields tended to be in the range of 90% for reactions performed on a 10 g scale. This material was then converted to **3** by ozonolysis[10] in methanol at −78 °C followed by treatment with dimethyl sulfide[11,12] to give the desired product in 83% yield, whose structure was confirmed using ^{1}H NMR and ^{13}C NMR spectroscopy (assignment of ^{1}H NMR and ^{13}C NMR resonances may be found in the Supplementary data). In the two published syntheses of **3** the six-membered ring is broken and then re-formed. Our approach avoids this difficult to reproduce manipulation. It should be noted that commercially available verbenone is supplied in varying degrees of enantiomeric purity. However, this does not affect the outcome of the synthesis since the final product is achiral.

In summary, we have developed a convenient high yield method for preparing ample quantities of 6,6-dimethylbicyclo[3.1.1]heptane-2,4-dione in two steps from commercially available (−)-verbenone. This method overcomes the poor reproducibility suffered by other synthetic routes described in the literature by circumventing the need to break and re-form the six-membered ring. The presence of the carbonyl in the 4-position does not seem to dramatically effect the ozonolysis reaction.

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Supplementary data

Assignments of the ^{1}H NMR and ^{13}C NMR resonances for compound **3** are available as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.102.

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