Synthesis and stereochemical determination of an antifeeding bisabolanoid from Japanese cedar

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Abstract

The first enantioselective synthesis of (1S,3R,6R)-1-hydroxy-7(14),10-bisaboladien-4-one, a potent antifeedant isolated from the Japanese cedar, *Cryptomeria japonica*, was achieved starting from methyl (R)-4-hydroxy-3-methylbutanoate via a stereoselective carbonyl ene cyclization reaction as the key step. Comparison of the spectral data and specific rotation of the synthetic material with those of the natural product led to unambiguous stereochemical assignment of the antifeedant as 1S, 3R, and 6R.
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In the course of screening for bioactive products from the Japanese cedar, *Cryptomeria japonica*, Kim and co-workers isolated hydroxy bisabolatrienone **2** as a potent antifeedant against the snail, *Acusta despesta* (a well-known pest of many agricultural crops) (Fig. 1).[1] This bisabolanoid **2** had originally been reported by Nagahama et al. as a chemical constituent of *C. japonica* without the assignment of the absolute stereochemistry and with no mention of biological activity.[2] Its absolute configuration was later determined by Kim et al. as depicted in Figure 1 by converting the natural product into cryptomerione and comparing its specific rotation with those of both enantiomers of cryptomerione derived from (R)- and (S)-carvones.[3] They also discovered that sesquiterpenoid **2** exhibited repelling and antifeeding activities against the pill-bug (*Armadillidium vulgare*) and the locust (*Locusta migratoria*, a notorious pest, which often causes massive damage to agricultural crops throughout the world) when mixed with sandaracopimarinol and hydroxy bisaboladienone **1**, respectively, which were also isolated from *C.*
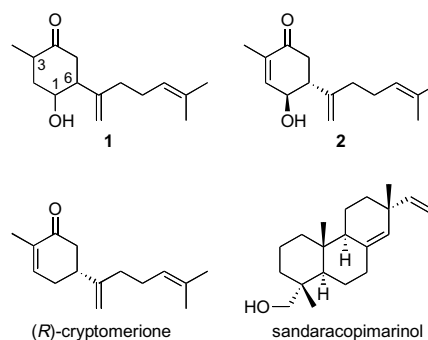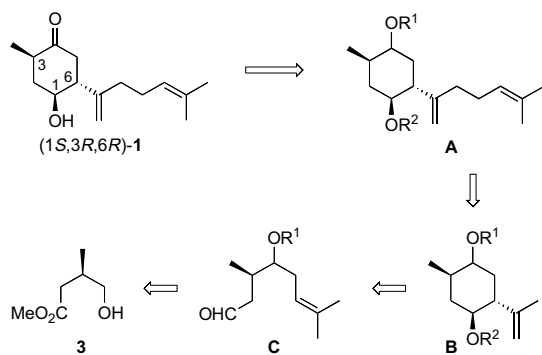

Fig. 1. Structures of antifeedants from Japanese ceder and cryptomerione.

japonica.[4,5] Based on extensive bioassays, they found that compound **1** was essential for the antifeeding activity, while compound **2** played a role to support the activity of **1**.[5] Although the gross structure of **1** was deduced from spectroscopic analyses including H–H and C–H COSY experiments, any information on the stereochemistry of **1** was not provided in their report. We describe herein the enantioselective synthesis of one of the stereoisomers of **1**, which culminated in the successful determination of the absolute stereochemistry of **1**.
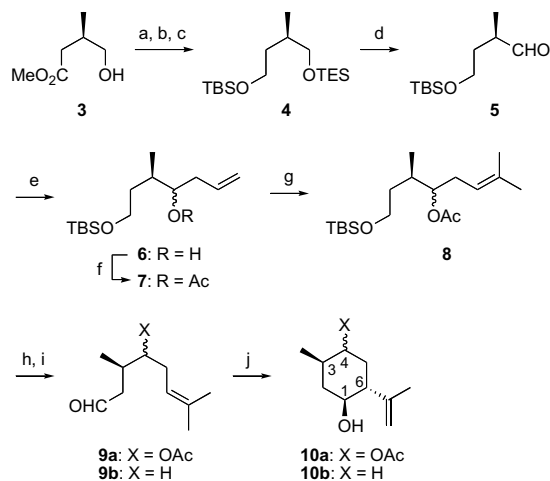
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Scheme 1. Retrosynthetic analysis of (1S,3R,6R)-1.

Scheme 2. Reagents and conditions: (a) TESCl, Et₃N, DMAP, CH₂Cl₂, rt; (b) DIBAL, CH₂Cl₂, −78 to −40 °C; (c) TBSCl, Imid, DMF, rt (95%, three steps); (d) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, −78 °C; (e) allylmagnesium bromide, ether, −78 °C (66%, two steps); (f) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt; (g) 2-methyl-2-butene (as solvent), Grubbs cat. (2nd generation), rt (95%, two steps); (h) TBAF, THF, 0 °C; (i) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, −78 °C (83%, two steps); (j) ZnBr₂, toluene, −78 to 0 °C (82%).

Assuming that the absolute configurations at the C1 and C6 chiral centers of **1** would be *S* and *R*, respectively, from the (1S,6R)-stereochemistry assigned to **2** by Kim et al.,[3] we decided to synthesize (1S,3R,6R)-**1** as a candidate for the natural stereoisomer of antifeedant **1**.[6] Our synthetic plan for (1S,3R,6R)-**1** featuring stereoselective installation of the chiral centers on its cyclohexane ring via an intramolecular carbonyl ene reaction (**C**→**B**) is shown in Scheme 1. Enal **C** was considered to be obtained from the known hydroxy ester **3** through protections and adjustment of the oxidation levels of the two oxygen functionalities of **3** followed by nucleophilic introduction of a prenyl group. On the other hand, the chain-elongation of **B** into **A** utilizing the double bond of the isopropenyl substituent and subsequent deprotections and oxidation of **A** would furnish the target molecule (1S,3R,6R)-**1**.

The known hydroxy ester **3**, obtained by the reduction of commercially available (R)-(+)-2-methylsuccinic acid 4-methyl ester with BH₃·SMe₂,[7] was protected as its TES-ether, and the ester group was reduced and then protected to give **4** (Scheme 2). Direct oxidation of the TES-oxy group under the Swern oxidation conditions proceeded smoothly to afford **5**.[8] The introduction of a prenyl group to aldehyde **5** to form **8** was performed by a three-step sequence of reactions: (1) nonstereoselective addition of allylmagnesium bromide to give **6** (diastereomeric ratio = ca. 1:1); (2) protection of the resulting alcohol **6** to acetate **7**; and (3) cross-metathesis reaction of the terminal olefin **7** with 2-methyl-2-butene.[9] The metathesis step to furnish **8** proceeded quite efficiently (ca. 95% yield), although trace amounts of olefinic byproducts (<5%) were also produced, as judged by ¹H NMR analysis.[10] Deprotection of the TBS group of **8** and the Swern oxidation of the resulting alcoholic intermediate afforded enal **9a**, which set the stage for the stereoselective construction of cyclic intermediate **10a**. It is well established that the treatment of **9b** (deacetoxy analog of **9a**) with ZnBr₂ or ZnI₂ induces a highly stereoselective cyclization via intramolecular carbonyl ene reaction, giving **10b** with 1,3-*cis*-1,6-*trans* relative stereochemistry.[11] According to this protocol, we treated enal **9a** with ZnBr₂ in toluene and found that the cyclization reaction proceeded stereoselectively to afford a mixture consisting mainly of the desired 1,3-*cis*-1,6-*trans*-dia-

stereomers (**10a**) accompanied by only a small quantity of the undesired diastereomers (<10%). The ratio of the two major diastereomers (4-α-**10a** and 4-β-**10a**) was ca. 1:1, reflecting the diastereomeric ratio of the starting enal **9a**, which means that the stereochemistry of the C4 position of **9a** bearing an acetoxy substituent had little influence on the stereochemical course of the cyclization. The stereochemical assignment of the two diastereomers was
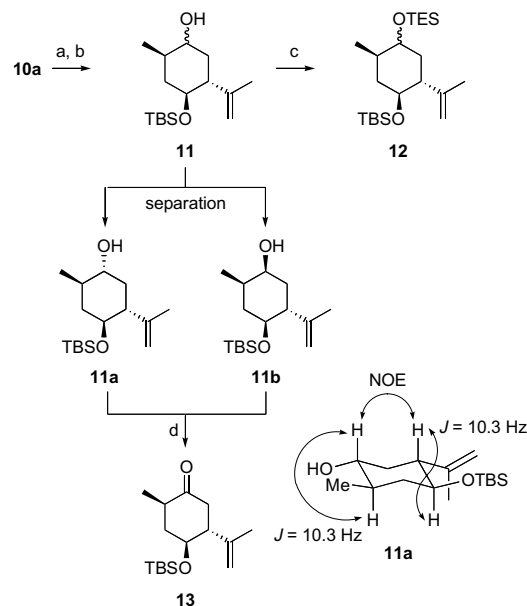
Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C; (b) DIBAL, CH₂Cl₂, −78 °C (85%, two steps); (c) TESOTf, 2,6-lutidine, CH₂Cl₂, −78 °C (quant); (d) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, −78 °C (ca. 90%).