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Synthesis and stereochemical determination of an antifeeding bisabolanoid from Japanese cedar

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Abstract

The first enantioselective synthesis of (1*S*,3*R*,6*R*)-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 1*S*, 3*R*, and 6*R*.

Keywords: Bisabolane; Enantioselective synthesis; Carbonyl ene reaction; Antifeedant

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. 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**.

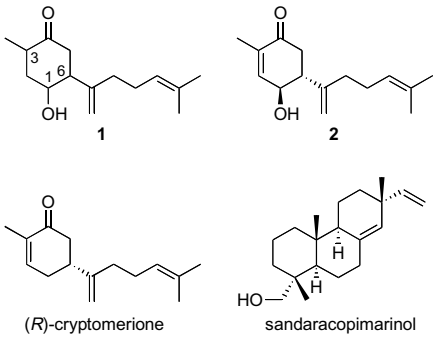

Fig. 1. Structures of antifeedants from Japanese ceder and cryptomerione.

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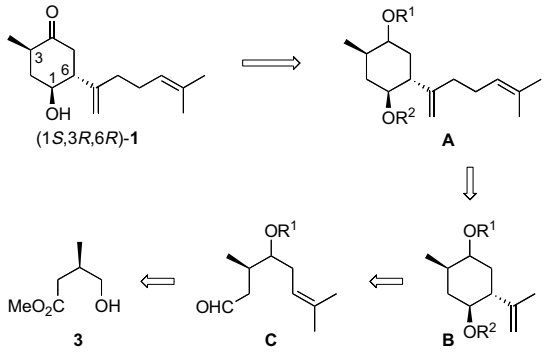
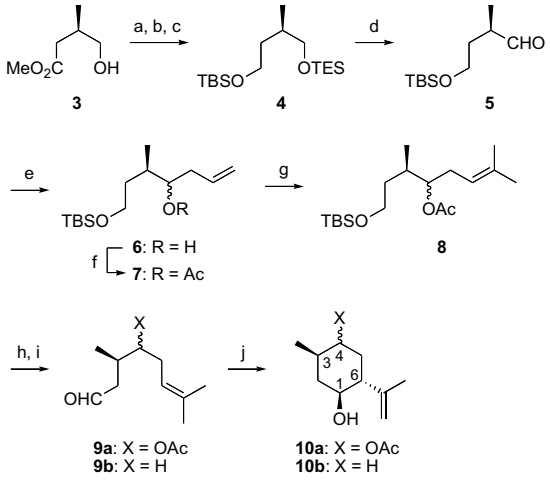


Scheme 1. Retrosynthetic analysis of (1*S*,3*R*,6*R*)-**1**.

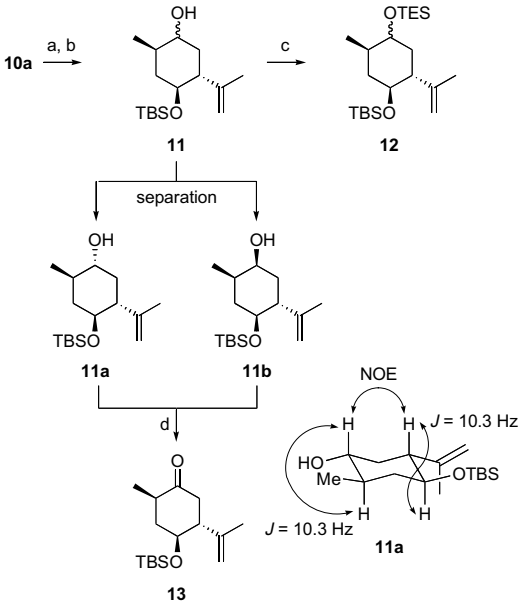
Assuming that the absolute configurations at the C1 and C6 chiral centers of **1** would be *S* and *R*, respectively, from the (1*S*,6*R*)-stereochemistry assigned to **2** by Kim et al.,[3] we decided to synthesize (1*S*,3*R*,6*R*)-**1** as a candidate for the natural stereoisomer of antifeedant **1**.[6] Our synthetic plan for (1*S*,3*R*,6*R*)-**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 (1*S*,3*R*,6*R*)-**1**.

The known hydroxy ester **3**, obtained by the reduction of commercially available (*R*)-(+)-2-methylsuccinic acid 4-methyl ester with $BH_3{\cdot}SMe_2$,[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 ^{1}H 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 $ZnBr_2$ or ZnI_2 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 $ZnBr_2$ 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-



Scheme 2. Reagents and conditions: (a) TESCl, Et_3N, DMAP, CH_2Cl_2, rt; (b) DIBAL, CH_2Cl_2, −78 to −40 °C; (c) TBSCl, Imid, DMF, rt (95%, three steps); (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (e) allylmagnesium bromide, ether, −78 °C (66%, two steps); (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (g) 2-methyl-2-butene (as solvent), Grubbs cat. (2nd generation), rt (95%, two steps); (h) TBAF, THF, 0 °C; (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C (83%, two steps); (j) $ZnBr_2$, toluene, −78 to 0 °C (82%).

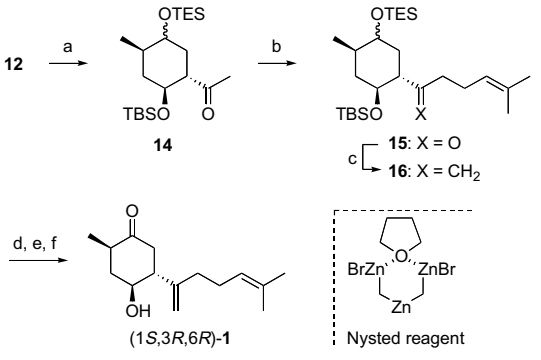
stereomers (**10a**) accompanied by only a small quantity of the undesired diastereomers (<10%). The ratio of the two major diastereomers (4-α-**10a** and 4-β-**10a**) was ca. 1:1, reflecting the diastereomeric ratio of the starting enal **9a**, which means that the stereochemistry of the C4 position 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, CH_2Cl_2, −78 °C; (b) DIBAL, CH_2Cl_2, −78 °C (85%, two steps); (c) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (quant); (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C (ca. 90%).

conducted after converting the diastereomeric mixture **10a** into **11** through protection (TBSOTf, 2,6-lutidine) and reduction (DIBAL) (Scheme 3). The diastereomeric mixture of alcohols (**11**) could readily be separated by SiO_2 column chromatography to provide pure samples of **11a** and **11b**, which were subjected to ^1H NMR analysis (500 MHz, $CDCl_3$). In the α-alcohol **11a**, the coupling constants between 1-H and 6-H, and 3-H and 4-H were both 10.3 Hz, and a NOE correlation was observed between 4-H and 6-H, supporting the stereochemistry as shown in Scheme 3.[12] On the other hand, the signals for 1-H and 4-H of **11b** were observed as a double triplet ($J_{1,6} = 10.3$ Hz) and seemingly as a broad singlet with a narrow half-width of 8.5 Hz, respectively.[12] Furthermore, both **11a** and **11b** converged into the same ketone **13** when exposed to the Swern oxidation conditions. These results confirmed our stereochemical assignments for **11a** and **11b**, and thereby for the ene cyclization products **10a** as well. In our actual synthesis, the mixture of alcohols **11** was treated, without separation, with TESOTf and 2,6-lutidine to give **12**, and the resulting epimeric mixture was subjected to the next step.

The final stage of our synthesis required the installation of a prenyl group at the allylic methyl position of **12** (Scheme 4). For this purpose, the olefinic compound **12** was first exposed to ozonolysis conditions to afford ketone **14**, which was then prenylated by a conventional method (LDA, prenyl bromide, THF/HMPA) to furnish **15**. Treatment of ketone **15** with the Nysted reagent gave methylenated product **16**,[13] and subsequent selective deprotection of its TES group (TBAF, AcOH, DMF)[14] followed by oxidation (Dess–Martin's periodinane) and removal of the TBS protecting group (aq HF, CH_3CN)[15] gave (1*S*,3*R*,6*R*)-**1** as a white crystalline solid (mp 79.5–80 °C, lit.[6] 75.5–76 °C). The ^1H and ^{13}C NMR spectra of (1*S*,3*R*,6*R*)-**1** recorded in $CDCl_3$ at 500 MHz and 125 MHz, respectively, were identical with those of the natural product,[5] and, furthermore, the specific rotation of (1*S*,3*R*,6*R*)-**1** ($[\alpha]_D^{22}$ +41 (*c* 0.29, $CHCl_3$)) matched that reported for the natural product by Nagahama et al. ($[\alpha]_D^{31.3}$ +38 (*c* 0.087, $CHCl_3$)).[6,16] On the basis of these results, the stereochemistry of antifeedant **1** was unambiguously determined to be 1*S*, 3*R*, and 6*R*.



Scheme 4. Reagents and conditions: (a) O_3, Py, MeOH, CH_2Cl_2, then Me_2S, −78 °C to rt (99%); (b) LDA, prenyl bromide, HMPA, THF, −78 °C to rt (90%); (c) Nysted reagent, $TiCl_4$, THF, −78 °C to rt (65%); (d) TBAF, AcOH, DMF, rt; (e) DMP, Py, CH_2Cl_2 (95%, two steps); (f) aq HF, CH_3CN, rt (80%).

In conclusion, the enatioselective synthesis of (1*S*,3*R*,6*R*)-1-hydroxy-7(14),10-bisaboladien-4-one (**1**) was accomplished in 15% overall yield from the known hydroxy ester **3** by a 19-step sequence involving the stereoselective intramolecular carbonyl ene reaction of **9a** into **10a** as the key step. Good agreement between the synthetic and natural products in spectral data and specific rotation enabled us to unambiguously determine the absolute stereochemistry of the antifeedant as 1*S*, 3*R*, and 6*R*. The synthesis of the other antifeedant component **2** and related natural products is currently in progress.

Acknowledgments

We are grateful to Professor Kim (Kochi University) for providing the copies of the NMR spectra of the natural antifeedant (**1**). We also thank Ms. Yamada (Tohoku University) for measuring NMR and MS spectra. This work was supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 19380065).

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6. Compound **1** had previously been isolated from *C. japonica* by Nagahama et al., and its absolute stereochemistry had been proposed to be 1*S*, 3*R*, and 6*R*. However, their stereochemical assignment was based only on the chemical shift of its 3-Me (δ_C 14.2 ppm) and the sign of its specific rotation (+), and therefore seemed to lack definite proofs. Nagahama, S.; Iwaoka, T.; Ashitani, T. *Mokuzai Gakkaishi* **2000**, *46*, 225–230.
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10. It is known that the cross-metathesis reactions of 2-methyl-2-butene with terminal olefins give, in some cases, small amounts of 1,2-disubstituted olefins bearing a terminal ethylidene group as well as desired trisubstituted olefins with a terminal isopropylidene group such as **8**.[9] By analogy with those facts, coupled with an additional experimental result obtained in a cross-metathesis reaction between the pivaloyl-protected analog of **7** and 2-methyl-2-butene, which gave considerable amounts (ca. 25%) of byproducts enough for their structural analysis by NMR (Kuwahara, S., unpublished work), we consider that the olefinic byproducts produced in the conversion of **7** into **8** would also be 1,2-disubstituted olefins (epimers due to the

acetoxy-bearing chiral center and, probably, geometrical isomers as well). Detailed discussions on the structures of the olefinic byproducts will soon be reported elsewhere.

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12. ^{1}H NMR data for **11a** and **11b** (500 MHz, $CDCl_3$). **11a**: δ –0.01 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.02 (3H, d, $J = 6.3$ Hz), 1.15 (1H, dt, $J = 10.3$, 12.7 Hz), 1.37–1.46 (1H, m), 1.39 (1H, dt, $J = 10.3$, 12.7 Hz), 1.53 (1H, br s, OH), 1.68 (3H, s), 1.80–1.87 (2H, m), 2.08 (1H, ddd, $J = 12.7$, 10.3, 3.4 Hz), 3.21 (1H, dt, $J = 3.9$, 10.3 Hz), 3.51 (1H, dt, $J = 4.4$, 10.3 Hz), 4.74 (1H, br s), 4.77 (1H, br s). **11b**: δ –0.01 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 0.98 (3H, d, $J = 6.8$ Hz), 1.36 (1H, d, $J = 2.9$ Hz, OH), 1.45 (1H, dt, $J = 10.3$, 12.7 Hz), 1.51 (1H, dt, $J = 2.9$, 13.5 Hz), 1.56–1.64 (2H, m), 1.68 (3H, s), 1.77 (1H, dt, $J = 14.2$, 3.4 Hz), 2.34 (1H, ddd, $J = 13.5$, 10.3, 3.9 Hz), 3.49 (1H, dt, $J = 4.4$, 10.3 Hz), 3.76 (1H, br s), 4.76 (1H, br s), 4.76–4.78 (1H, m).
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15. Treatment of the TBS ether with TBAF/THF brought about a substantial degree of epimerization at the C3 stereogenic center.
16. The specific rotation of (1*S*,3*R*,6*R*)-**1** measured in MeOH ($[\alpha]_D^{22}$ +37.1 (*c* 0.29, MeOH)) was considerably different in magnitude from that reported for the natural product by Kim et al. ($[\alpha]_D^{20}$ +15.0 (*c* 0.1, MeOH)).[5] We consider that this discrepancy would be ascribable to impurities contained in the natural sample of **1**, judging from its ^{1}H NMR spectrum provided to us by Professor Kim.