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Syntheses of Bioactive Bisabolane-Type *Cryptomeria japonica* Sesquiterpenes

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The first diastereoselective synthesis of (1*S*,6*R*)-1-hydroxy-2,7(14),10-bisabolatrien-4-one, an antifeedant against *Acusta despesta* and *Locusta migratoria*, was produced from *Cryptomeria japonica* (commonly known as Japanese cedar), starting from (*R*)-(−)-carvone *via* (*R*)-(−)-cryptomerione. The enantiomer was transformed into (1*S*,3*R*,6*R*)-1-hydroxy-7(14),10-bisabola-dien-4-one, a novel antifeedant against *L. migratoria* from the same tree, by 1,4-selective reduction of the enone moiety.

Key words: bisabolane-type sesquiterpene; cryptomerione; antifeedant; diastereoselective synthesis

In 1993, Nagahama and Tazaki isolated and identified, from *Cryptomeria japonica*, (+)-1-hydroxy-2,7(14),10-bisabolatrien-4-one **1** as a novel bisabolane-type sesquiterpene.[1] This compound has various potential biological uses; for example, as an antifeedant against *Acusta despesta*, a species of snail; as a repellent against *Armadillidium vulgare*, a pill-bug; and as a germination inhibitor against Dicotyledoneae and Monocotyledoneae.[2–4] The absolute configuration of **1** was determined by converting natural **1** into (*R*)-(−)-cryptomerione and comparing its specific rotation with those of both enantiomers of cryptomerione prepared from (*R*)-(−)- and (*S*)-(+)-carvone.[5] In addition to this, (+)-1-hydroxy-7(14),10-bisaboladien-4-one **2** was isolated and identified as a new compound in the same tree by Nagahama *et al.*,[6,7] and its antifeeding activity against *L. migratoria* was reported by Kim *et al.*[8] Interestingly, the combination of compounds **1** and **2** resulted in antifeeding activity against *L. migratoria*, although each of these compounds alone showed no antifeeding activity. Therefore, the hypothesis was proposed that compound **2**, with the active site, might bind directly to the receptors on chemosensory cells of *L. migratoria* and that compound **1** might support the binding by hydrophobic interaction on the surface of cellulose. The stereochemistry of **2** has recently been determined by Nakahata *et al.* through synthesis.[9] We report in this paper a diastereoselective synthesis of natural enantiomer **1** and the transformation of enone **1** to an another antifeedant **2**. Furthermore, we investigated an effective way to obtain (*R*)-(−)-cryptomerione, since the reported syntheses were of multistep and relatively low yield.[5,10]

Results and Discussion

The synthetic route to **1** and **2** is summarized in Scheme 1. Bromide **3** was obtained from (*R*)-(−)-carvone by following the reported conditions.[5] First, the carbonyl group of **3** was protected as a dimethyl ketal or 1,3-dioxolane. Unfortunately, the resulting ketals did not react with prenylmagnesium bromide in the presence of a catalytic amount of CuBr. Although both ketals were deprotected by increasing the dose of CuBr, the desired (*R*)-(−)-cryptomerione could only be obtained in a low yield. Using 3 equivalents of CuBr and unprotected bromide **3** as the substrate gave (*R*)-(−)-cryptomerione in a better 58% yield. The two routes previously reported to prepare (*R*)-(−)-cryptomerione needed 5 steps and the yield of each was 29.8%[5] and *ca.* 5%.[10]

The stereoselective introduction of a hydroxyl group at the C(5) position of (*R*)-(−)-carvone has been reported by Miyashita *et al.*[11] We presumed that the methodology would also be efficient for our syntheses of bisabolane-type sesquiterpenes **1** and **2**. Therefore, the Michael addition of PhSeH to (*R*)-(−)-cryptomerione occurred preferentially from the β-axial face at C(6),[12] and subsequent protonation at C(1) occurred from the α-axial face followed by reduction by $LiAlH_4$, which resulted in β-alcohol **4** (70%) and α-alcohol **5** (19%). Two dienols, **4** and **5**, were easily separated by chromatography on silica gel. The THP ether of **4** was oxidized with H_2O_2 to the corresponding selenoxide, and benzeneselenenic acid was removed by refluxing in carbon tetrachloride to give homoallyl alcohol **6**, after deprotecting the THP group with *p*-TsOH. Minor alcohol **5** was transformed into epimeric homoallyl alcohol **8** by the same procedure as that just described. Furthermore, **8** was effectively converted into desired alcohol **6** *via* the Mitsunobu reaction and subsequent basic hydrolysis with NaOH in a 94% yield. Epoxidation of **6** with *tert*-butylhydroperoxide (TBHP) in the presence of a catalytic amount of $VO(acac)_2$ in benzene exclusively gave enantiomeric epoxide **7**.[13] Finally, oxidation of **7** with Dess-Martin periodinane (DMP) in CH_2Cl_2 and subsequent treatment of the resulting ketone with neutral Al_2O_3 produced target enone **1** ($[\alpha]_D^{27}$ +133.4 (*c* 0.8, MeOH), lit. $[\alpha]_D^{20}$ +130 (*c* 1.0, MeOH)[8]) in a 79% yield. The spectral data were in agreement with those already reported.[8]

In order to establish the conditions to transform **1** into **2**, we studied the regioselective hydrogenation of **1** by

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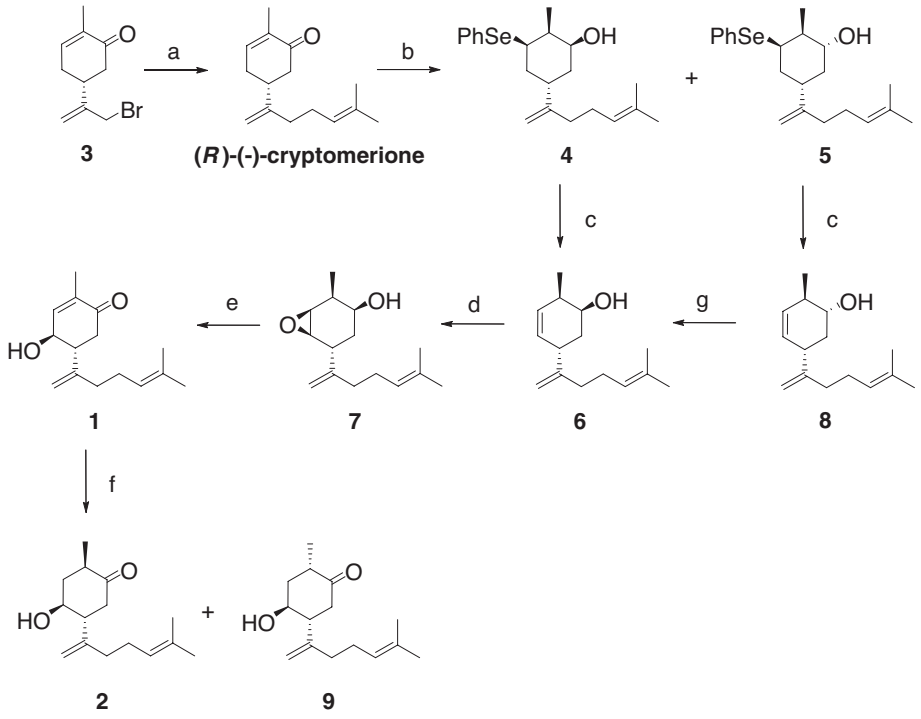

Scheme 1.

Reagents and conditions: (a) $(CH_3)_2C{=}CHCH_2MgBr$, CuBr, THF, 58%; (b) (i) Ph_2Se_2, $NaBH_4$, AcOH, EtOH; (ii) $LiAlH_4$, Et_2O, 89% (2 steps); (c) (i) DHP, PPTS, CH_2CH_2; (ii) 30% H_2O_2, pyridine, CH_2Cl_2; (iii) CCl_4, reflux; (iv) *p*-TsOH, MeOH, 56% from **4** and 54% from **5** (4 steps); (d) TBHP, cat. $VO(acac)_2$, benzene, 94%; (e) (i) DMP, CH_2Cl_2; (ii) Al_2O_3, CH_2Cl_2, 79% (2 steps); (f) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, H_2O, 77%; (g) (i) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, benzene; (ii) 1 M NaOH, MeOH, 94% (2 steps).

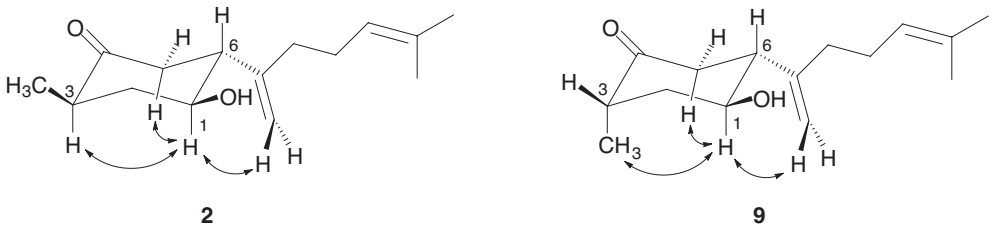

Fig. 1. Key NOESY Correlations Observed in **2** and **9**.

using a variety of reducing agents. Only the product of 1,2-reduction was obtained when L-Selectride,[14,15] DIBAL-$Co(acac)_2$,[16] and Te–$NaBH_4$[17] were employed. On the other hand, $CuF(PPh_3)_3{\cdot}2EtOH$[18] and Zn–KOH[19] did not produce any products. Only with the use of $NiCl_2{\cdot}6H_2O$–$NaBH_4$,[20] a fair yield of desired α,β-saturated ketone **2** (43%, $[\alpha]_D^{25}$ +39.3 (*c* 0.14, MeOH)) and epimer **9** (34%) could be obtained. The GC/MS, ^{1}H- and ^{13}C-NMR spectra of **2** purified by a silica gel column were identical with those of the natural product.[8] The absolute configuration at the C(3) position of **2** and **9** was deduced by analyses of the NOESY data (Fig. 1). The specific rotation of **2** was considerably different from that of the natural compound reported by Kim *et al.* ($[\alpha]_D^{20}$ +15.0 (*c* 0.1, MeOH)),[8] but matched that reported for the synthetic compound by Nakahata *et al.* ($[\alpha]_D^{22}$ +37.1 (*c* 0.29, MeOH)).[9]

In summary, antifeedant **1** was diastereoselectively synthesized from brominated (*R*)-(−)-carvone **3** in a 21% overall yield. A one-step synthesis of (*R*)-(−)-cryptomerione, an appropriate building block for the synthesis of **1** and **2**, was accomplished in a 58% yield from **3**. Although the yield of an another antifeedant **2** from **1** was only 43%, the development of a straightforward, easy and high yielding synthesis for antifeedants **1** and **2** is essential to advance biological studies. The efficient synthesis of **2** from **1** or other intermediates in this manner is in progress.

Experimental

All moisture-sensitive reactions were carried out under a nitrogen atmosphere. Solvents were dried and purified by conventional methods prior to use. Dichloromethane was freshly distilled from CaH_2, and tetrahydrofuran and diethyl ether from sodium benzophenone kethyl under a nitrogen atmosphere. All chemicals used were of reagent grade. Optical rotation data were taken by a SEPA-300 high-sensitive polarimeter (Horiba), and column chromatography was performed on silica gel (Wakosil C-200). High-resolution mass spectra were measured by a JMS SX-102 (Jeol) instrument. ^{1}H-, ^{13}C-NMR and NOESY spectra were obtained on a Bruker Biospin AC400M NMR spectrometer with TMS as an internal standard. GC/MS analysis was carried out with an Agilent Technologies 6890N Network GC System coupled with a 5975 Inert XL Mass Selective Detector, using an HP-5MS capillary column (0.25 mm i.d. × 30 m, 0.25 μm film thickness, Agilent Technologies Santa Clara, CA, USA). Helium was used as the carrier gas at a flow rate of 1.00 ml/min in the splitless mode, at 60 °C for 2 min and increasing to 290 °C at a rate of 10 °C/min, and then held for 5 min. Signals were acquired with a Chemstation (Hewlett-Packard, Palo Alto, CA, USA) coupled with an MS database (Wiley 275 library, Hewlett-Packard).

*(*R*)-10-Bromo-1(6),8-*p*-methadien-2-one (**3**).* According to the procedure previously reported,[5] (*R*)-(−)-carvone (7.5 g, 50 mmol) was converted to bromide **3** in a 44% yield.

*(*R*)-(−)-Cryptomerione.* Magnesium turnings (8.0 g, 328 mmol) were covered with THF (40 ml), and 1,2-dibromoethane (400 µl, 4.64 mmol) was added in one portion. After stirring the mixture for 1 min at rt, a solution of prenyl bromide (9.30 ml, 80.0 mmol) in THF (120 ml) was added dropwise for 2 h at −15 °C. The mixture was stirred additionally for 2 h at 0 °C, and the resulting solution (0.4–0.45 M) was ready to use. To the cuprous bromide (5.16 g, 36.0 mmol) were successively added a freshly prepared Grignard solution (160 ml) and bromide **3** (2.75 g, 12.0 mmol) in THF (20 ml) at −15 °C. After being stirred for 30 min, the reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave an oil which was chromatographed in a silica gel column [17:1 hexane/EtOAc] to afford (*R*)-(−)-cryptomerione as a colorless oil (1.52 g, 58%). $[\alpha]_D^{25}$ −17.0 (*c* 1.0 $CHCl_3$). GC-MS *m/z* (%): 218 (M^+, 11), 203 (4), 175 (24), 148 (54), 135 (41), 121 (23), 109 (63), 69 (100), 41 (54). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.61 (s, 3H, CH_3), 1.65–1.74 (m, 1H, CH_AH$_B$CH$_2$), 1.69 (d, *J* = 1.2 Hz, 3H, CH_3), 1.79 (dt, *J* = 2.4 and 1.2 Hz, 3H, CH_3), 2.04–2.13 (m, 3H, CH$_A$$H_BCH_2$), 2.28 (m, 1H, C$H_CH_D$CO), 2.35 (dd, *J* = 16.0 and 13.2 Hz, 1H, CH_EH$_F$CH=), 2.46 (m, 1H, CH$_C$$H_D$CO), 2.59 (ddd, *J* = 16.0, 4.4 and 1.2 Hz, 1H, CH$_E$$H_F$CH=), 2.68 (m, 1H, C$HCH_2$CO), 4.82 (s, 1H, C$H_GH_H$=), 4.85 (s, 1H, CH$_G$$H_H$=), 5.09 (tt, *J* = 6.8 and 1.2 Hz, 1H, CH=C(CH$_3$)$_2$), 6.75 (ddd, *J* = 5.6, 2.4 and 1.2 Hz, 1H, CH$_2$CH=C). ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 199.9, 150.8, 144.7, 135.4, 132.0, 123.7, 109.2, 43.5, 41.2, 34.3, 31.7, 26.6, 25.7, 17.7, 15.7.

*(1*S*,2*S*,3*R*,5*S*)-3-(Phenylseleno)-7(14),10-bisaboladien-1-ol (**4**) and its C(1) epimer (**5**).* Sodium borohydride (760 mg, 20.0 mmol) was added in portions to a mixture of diphenyl diselenide (3.14 g, 10.0 mmol) in ethanol (25 ml) while stirring at rt. The colorless (or faint yellow) solution of sodium benzeneselenolate obtained was cooled to 0 °C, and then acetic acid (1.30 ml, 23.0 mmol) was added. A solution of (*R*)-(−)-cryptomerione (1.50 g, 10.0 mmol) in ethanol (5 ml) was next added and the resulting mixture was stirred at 0 °C for 2 h. The mixture was poured into water and extracted with EtOAc, and the organic layer was successively washed with water and brine. After drying over anhydrous Na_2SO_4, evaporation of the solvent *in vacuo* gave an oil which was submitted to subsequent reduction without purification. $LiAlH_4$ (380 mg, 10.0 mmol) was added to a solution of the crude selenenyl ketone (3.76 g, 10.0 mmol) in Et_2O (70 ml) at −10 °C, and the mixture was stirred for 30 min. Excess hydride was decomposed by adding wet ether, and the mixture was filtered. Evaporation of the solvent *in vacuo* gave an oil which was purified in a silica gel column [10:1–5:1 hexane/EtOAc] to afford **4** (2.65 g, 70%) and **5** (718 mg, 19%).

4: $[\alpha]_D^{25}$ −172 (*c* 0.1 $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.24 (d, *J* = 7.2 Hz, 3H, CH_3), 1.49 (td, *J* = 13.6 and 2.8 Hz, 1H, H-6$_A$), 1.61 (s, 3H, CH_3), 1.63 (td, *J* = 13.6 and 3.6 Hz, 1H, H-6$_B$), 1.69 (d, *J* = 0.8 Hz, 3H, CH_3), 1.84–2.16 (m, 7H, CHCH$_3$, H-4, C(CH_2)$_2$CH), 2.82 (tt, *J* = 12.0 and 2.8 Hz, 1H, CH$_2$CHCH$_2$), 3.54 (q, *J* = 3.6 Hz, 1H, CHSePh), 3.95 (br.s, 1H, CHOH), 4.74 (s, 1H, CH_CH$_D$=), 4.76 (d, *J* = 1.2 Hz, 1H, CH$_C$$H_D$=), 5.10 (tt, *J* = 5.2 and 1.2 Hz, 1H, CH=C(CH$_3$)$_2$), 7.25 (m, 3H, aromatic of PhSe), 7.55 (m, 2H, aromatic of PhSe). ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 153.2, 134.0, 132.1, 131.6, 129.0, 127.1, 124.2, 107.9, 71.6, 49.4, 39.7, 38.6, 38.5, 35.2, 32.2, 26.8, 25.7, 18.0, 17.8.

5: $[\alpha]_D^{25}$ −208 (*c* 0.2 $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.23 (d, *J* = 6.8 Hz, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.58–1.71 (m, 2H, H-6), 1.69 (d, *J* = 1.2 Hz, 3H, CH_3), 2.00–2.15 (m, 7H, CHCH$_3$, H-4, C(CH_2)$_2$CH), 2.60 (tt, *J* = 12.2 and 3.0 Hz, 1H, CH$_2$CHCH$_2$), 3.55 (td, *J* = 10.4 and 4.0 Hz, 1H, CHOH), 3.65 (q, *J* = 3.2 Hz, 1H, CHSePh), 4.76 (s, 2H, CH_2=), 5.09 (tt, *J* = 8.8 and 1.6 Hz, 1H, CH=C(CH$_3$)$_2$), 7.25 (m, 3H, aromatic of PhSe), 7.56 (m, 2H, aromatic of PhSe). ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 152.6, 134.4, 131.7, 130.7, 129.0, 127.3, 124.1, 108.0, 72.9, 52.7, 44.3, 40.9, 38.5, 38.1, 35.0, 26.8, 25.7, 17.8, 17.5.

*(1*S*,2*R*,5*S*)-3,7(14),10-Bisabolatrien-1-ol (**6**) and its C(1) epimer (**8**).* A mixture of **4** (756 mg, 2.0 mmol), PPTS (51 mg, 0.20 mmol) and dihydropyran (336 mg, 4.0 mmol) in CH_2Cl_2 (10 ml) was stirred at rt for 3 h. The mixture was diluted with EtOAc and successively washed with water and brine. After drying over anhydrous Na_2SO_4, removal of the solvent gave a residual oil, a crude THP ether, which was dissolved in CH_2Cl_2 (20 ml) containing pyridine (320 µl, 4.0 mmol). Then, 30% H_2O_2 (2.0 ml, 20 mmol) was added at 0 °C, and the resulting solution was stirred at rt for 1.5 h. To the solution was added water, and the solution was extracted with EtOAc. The organic layer was washed with brine and, after drying over anhydrous Na_2SO_4, the solvent was removed *in vacuo*, leaving an oil which was dissolved in CCl_4 (20 ml). The mixture was refluxed for 30 min, and the solvent was removed *in vacuo*. The resulting oil was dissolved in MeOH (5 ml) containing a catalytic amount of *p*-TsOH. After stirring at rt for 1 h, the mixture was diluted with EtOAc and successively washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and, after removing the solvent *in vacuo*, an oil was left that, upon purification in a silica gel column [7:1 hexane/EtOAc] afforded **6** as a colorless oil (246 mg, 56%). According to the same procedure, C(1) epimer **8** was prepared in a 54% yield.

6: $[\alpha]_D^{25}$ −120 (*c* 0.1 $CHCl_3$). GC-MS *m/z* (%): 220 (M^+, 6), 202 (17), 187 (23), 159 (71), 151 (46), 109 (66), 91 (61), 69 (100), 41 (76). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.05 (d, *J* = 7.6 Hz, 3H, CH_3), 1.53–1.71 (m, 2H, CHCH_2CH), 1.61 (s, 3H, CH_3), 1.68 (d, *J* = 1.2 Hz, 3H, CH_3), 2.00–2.17 (m, 4H, C(CH_2)$_2$CH), 2.38 (m, 1H, CHCH$_3$), 2.97 (m, 1H, H-5), 3.97 (br.s, 1H, CHOH), 4.81 (s, 2H, CH_2=), 5.11 (tq, *J* = 6.8 and 1.4 Hz, 1H, CH=C(CH$_3$)$_2$), 5.48 (dtd, *J* = 10.0, 2.4 and 0.8 Hz, 1H, H-4), 5.59 (ddd, *J* = 10.0, 2.4 and 0.4 Hz, 1H, H-3). ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 152.5, 131.7, 130.3, 129.3, 124.1, 109.6, 68.7, 38.5, 34.9, 34.8, 34.4, 26.7, 25.7, 17.7, 16.0.

8: $[\alpha]_D^{25}$ −30.5 (*c* 0.2 $CHCl_3$). GC-MS *m/z* (%): 220 (M^+, 4), 202 (9), 187 (14), 159 (31), 151 (37), 109 (71), 91 (49), 69 (100), 41 (66). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.11 (d, *J* = 7.2 Hz, 3H, CH_3), 1.46–1.77 (m, 2H, CHCH_2CH), 1.61 (s, 3H, CH_3), 1.69 (d, *J* = 0.8 Hz, 3H, CH_3), 1.93–2.18 (m, 5H, C(CH_2)$_2$CH, CHCH$_3$), 2.94 (m, 1H, H-5), 3.45 (ddd, *J* = 11.6, 8.4 and 3.2 Hz, 1H, CHOH), 4.78 (dd, *J* = 2.8 and 1.2 Hz, 1H, CH_AH$_B$=), 4.83 (d, *J* = 0.4 Hz, 1H, CH$_A$$H_B$=), 5.11 (tt, *J* = 7.2 and 1.4 Hz, 1H, CH=C(CH$_3$)$_2$), 5.46 (m, 2H, CH=CH). ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 152.4, 131.7, 131.5, 129.3, 124.1, 109.0, 74.5, 43.5, 39.3, 38.3, 34.0, 26.7, 25.7, 18.4, 17.7.

*(1*S*,2*R*,5*S*)-3,7(14),10-Bisabolatrien-1-ol (**6**) from (**8**).* A 40% solution of DEAD in toluene (540 µl, 1.2 mmol) was added at 0 °C to a solution of 8 (88 mg, 0.40 mmol) in benzene (5 ml) containing triphenylphosphine (524 mg, 2.0 mmol) and *p*-$NO_2C_6H_4CO_2H$ (200 mg, 1.20 mmol). The mixture was stirred at rt for 1 h and diluted with EtOAc. After successively washing the mixture with water, saturated $NaHCO_3$ and brine, the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, leaving an oil which was submitted to subsequent hydrolysis without purification. A mixture of the crude ester and 1 M NaOH (1 ml) in MeOH (5 ml) was stirred at rt for 1.5 h. The mixture was treated with 2*N* HCl and extracted with EtOAc. The organic layer was successively washed with water, saturated $NaHCO_3$ and brine, and after drying (anhydrous Na_2SO_4), the solvent was removed *in vacuo*, leaving an oil that, upon purification in a silica gel column [8:1 hexane/EtOAc], afforded **6** (83 mg, 94%).

*(1*S*,2*S*,3*S*,4*R*,5*R*)-3,4-Epoxy-7(14),10-bisaboladien-1-ol (**7**).* A mixture of **6** (236 mg, 1.07 mmol), TBHP (70% aqueous solution, 284 µl, 2.14 mmol) and a catalytic amount of $VO(acac)_2$ in benzene (10 ml) was stirred at rt for 3 h. The mixture was diluted with EtOAc and successively washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and, after removing the solvent *in vacuo*, left epoxide **7** as an oil (237 mg, 94%) which was submitted to subsequent oxidation without purification.

$[\alpha]_D^{25}$ −25.6 (*c* 0.5 $CHCl_3$). GC-MS *m/z* (%): 236 (M^+, 3), 218 (4), 203 (4), 175 (17), 147 (16), 135 (16), 121 (16), 109 (23), 93 (23), 69 (100), 41 (54). ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.22 (d, *J* = 7.2 Hz, 3H, CH_3), 1.61–1.73 (m, 2H, CHCH_2CH), 1.62 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.00–2.22 (m, 4H, C(CH_2)$_2$CH), 2.67 (d, *J* = 11.2 Hz, 1H, CHCH$_3$), 2.85 (dd, *J* = 12.0 and 6.4 Hz, 1H, H-5), 3.20 (dd, *J* = 4.8 and 0.4 Hz, 1H, H-3), 3.23 (dd, *J* = 4.8 and 1.2 Hz, 1H, H-4), 3.73 (m, 1H, CHOH), 4.90 (s, 1H, CH_AH$_B$=), 4.93 (s, 1H, CH$_A$$H_B$=), 5.11

(m, 1H, C*H*=C(CH_3)$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 150.7, 132.1, 123.6, 110.7, 69.3, 59.5, 57.7, 36.4, 35.5, 35.4, 33.8, 26.4, 25.7, 17.8, 14.8.

*(1S,6R)-1-Hydroxy-2,7(14),10-bisabolatrien-4-one (**1**).* To a solution of epoxide **7** (198 mg, 0.83 mmol) in CH_2Cl_2 (5 ml), Dess-Martin periodinane (1.06 g, 2.49 mmol) was added at 0 °C. The mixture was stirred for 30 min and then diluted with EtOAc. After adding saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ to the mixture while vigorously stirring at rt, the resulting solution was extracted with EtOAc, before the organic layer was successively washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 ml) and a moderate amount of neutral alumina was added. After stirring at rt for 1 h, the mixture was filtered, and the solvent was concentrated *in vacuo*. The residual oil was chromatographed in a silica gel column [3:1 hexane/EtOAc] to afford **1** as a colorless oil (155 mg, 79%).

$[\alpha]_D^{27}$ +133.4 (*c* 0.8 MeOH). GC-MS *m/z* (%): 234 (M^+, 2), 219 (1), 191 (10), 173 (5), 163 (6), 109 (14), 93 (11), 69 (100), 41 (44). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.62 (s, 3H, CH_3), 1.69 (d, J = 0.8 Hz, 3H, CH_3), 1.80 (t, J = 1.6 Hz, 3H, CH_3), 2.07 (dd, J = 9.2 and 5.6 Hz, 2H, CH_2C=), 2.17 (q, J = 7.0 Hz, 2H, CH_2CH=), 2.36 (dd, J = 16.4 and 14.0 Hz, 1H, CH_AH$_B$CO), 2.55 (dd, J = 16.4 and 3.6 Hz, 1H, CH$_A$$H_B$CO), 2.68 (ddd, J = 14.0, 10.0 and 4.0 Hz, 1H, H-6), 4.50 (ddt, J = 11.6, 5.6 and 2.0 Hz, 1H, C*H*OH), 5.04 (s, 2H, CH_2=), 5.10 (tt, J = 6.8 and 1.4 Hz, 1H, C*H*=C(CH_3)$_2$), 6.72 (t, J = 1.6 Hz, 1H, CHC*H*=C). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.4, 147.4, 147.2, 135.1, 132.6, 123.4, 112.7, 69.2, 52.0, 41.6, 33.3, 26.3, 25.7, 17.8, 15.3. HR-FABMS *m/z* (M + H)$^+$: calcd. 235.1699 for $C_{15}H_{23}O_2$, found 235.1692.

*(1S,3R,6R)-1-Hydroxy-7(14),10-bisaboladien-4-one (**2**) and its C(3) epimer (**9**).* To a solution of **1** (23 mg, 98.3 µmol) in MeOH (1.2 ml) were added $NiCl_2$·$6H_2O$ (1.16 g, 4.9 mmol) and then distilled water (0.2 ml). $NaBH_4$ (74 mg, 1.97 mmol) was next added, and the reaction mixture was stirred at rt for 2 h. The mixture was treated with water and extracted with EtOAc. The organic layer was washed with brine, and after drying (anhydrous Na_2SO_4), the solvent was removed *in vacuo*, leaving an oil that, upon purification in a silica gel column [3:1 hexane/EtOAc] afforded **2** as a white crystalline solid (10 mg, 43%) and **9** as an oil (8 mg, 34%).

2: Mp 76.5–77 °C. $[\alpha]_D^{25}$ +39.3 (*c* 0.14 MeOH). GC-MS *m/z* (%): 236 (M^+, 2), 218 (16), 193 (12), 175 (14), 149 (12), 109 (31), 69 (100), 41 (50). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.06 (d, J = 6.4 Hz, 3H, CH_3), 1.09 (m, 1H, CHCH_AH$_B$CH), 1.48 (q, J = 13.0 Hz, 1H, CHCH$_A$$H_B$CH), 1.62 (s, 3H, C$H_3$), 1.69 (d, J = 0.8 Hz, 3H, CH_3), 1.98–2.10 (m, 2H, CH$_2$ CH_2C=), 2.17 (q, J = 6.8 Hz, 2H, CH_2CH=), 2.32–2.40 (m, 3H, CH_2CO, H-6), 2.53 (m, 1H, C*H*CH$_3$), 4.01 (m, 1H, C*H*OH), 5.03 (s, 1H, CH_AH$_B$=), 5.04 (t, J = 1.6 Hz, 1H, CH$_A$$H_B$=), 5.11 (tt, J = 6.8 and 1.6 Hz, 1H, C*H*=C(CH_3)$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 210.4, 148.2, 132.6, 123.4, 112.5, 69.7, 53.5, 44.1, 42.3, 41.4, 32.9, 26.2, 25.7, 17.8, 14.2. HR-FABMS *m/z* (M + H)$^+$: calcd. 237.1855 for $C_{15}H_{25}O_2$, found 237.1853.

9: $[\alpha]_D^{25}$ +13.3 (*c* 0.09 MeOH). GC-MS *m/z* (%): 236 (M^+, 3), 218 (11), 193 (17), 175 (13), 147 (6), 109 (34), 69 (100), 41 (40). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.12 (d, J = 6.8 Hz, 3H, CH_3), 1.61 (d, J = 2.0 Hz, 3H, CH_3), 1.69 (d, J = 0.8 Hz, 3H, CH_3), 1.91 (m, 2H, CHCH_2CH), 2.05 (m, 2H, CH_2C=), 2.14 (m, 2H, CH_2CH=), 2.46 (q, J = 8.4 Hz, 1H, H-6), 2.63–2.69 (m, 2H, CH_2CO), 2.74 (q, J = 7.2 Hz, 1H, C*H*CH$_3$), 4.17 (br.q, J = *ca.* 5.0 Hz, 1H, C*H*OH), 4.88 (s, 1H, CH_AH$_B$=), 4.97 (s, 1H, CH$_A$$H_B$=), 5.08 (tt, J = 6.8 and 1.4 Hz, 1H, C*H*=C(CH_3)$_2$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 213.0, 149.0, 132.3, 123.5, 112.5, 66.9, 50.7, 40.5, 37.6, 34.6, 26.5, 25.7, 17.8, 15.6. HR-FABMS *m/z* (M + H)$^+$: calcd. 237.1855 for $C_{15}H_{25}O_2$, found 237.1863.

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