Syntheses of Bioactive Bisabolane-Type Cryptomeria japonica Sesquiterpenes

Nobuhiro SHIMIZU* and Yasumasa KUWAHARA

Department of Bioscience and Biotechnology, Faculty of Bioenvironmental Science, Kyoto Gakuen University, 1-1 Nanjo, Sagabe, Kameoka 621-8555, Japan

Received September 24, 2008; Accepted October 20, 2008; Online Publication, March 7, 2009


The first diastereoselective synthesis of (1S,6R)-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 (1S,3R,6R)-1-hydroxy-7(14),10-bisaboladien-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 Dicotyledonae 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 through synthesis.5-7 We 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 LiAlH4, 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 H2O2 to the corresponding selenoxide, and benzeneselenenic acid was removed by refluxing in carbon tetrachloride to give homoallyl alcohol 6, after deprotection of 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 CH2Cl2 and subsequent treatment of the resulting ketone with neutral Al2O3 produced target enone 1 ([α]D27 +133.4 (c 0.8, MeOH), lit. [α]D25 +130 (c 1.0, MeOH)9)) in a 79% yield. The spectral data were in agreement with those already reported.5)

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

---

* To whom correspondence should be addressed. Tel: +81-771-29-3588; Fax: +81-771-29-3429; E-mail: shimizu@kyotogakuen.ac.jp
using a variety of reducing agents. Only the product of 1,2-reduction was obtained when L-Selectride, DIBAL-Co(acac)1,2-reduction was obtained when L-Selectride, 14,15) and Te–NaBH417) were employed. On the other hand, CuF(PPh3)2,2EtOH10) and Zn–KOH19) did not produce any products. Only with the use of NiCl2,6H2O–NaBH4,20) a fair yield of desired α,β-saturated ketone 2 (43%), [α]D25 +39.3 (c 0.14, MeOH) and epimer 9 (34%) could be obtained. 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. ([α]D20 +15.0 (c 0.1, MeOH)),5) but matched that reported for the synthetic compound by Nakahata et al. ([α]D25 +37.1 (c 0.29, MeOH)).5)

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 CaH2, and tetrahydrofuran and diethyl ether from sodium benzophenone ketyl 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. 1H- and 13C-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).
were covered with THF (40 ml), and 1,2-dibromoethane (400 \mu l, 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 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 (0.45 M) was ready to use. To the cuprous bromide (5.16 g, 36.0 mmol) in saturated NH₄Cl and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na₂SO₄, and evaporated to dryness. The obtained oil was chromatographed in a silica gel column [7:1 hexane/EtOAc] to afford (R)-(-)-cryptomerene (79.3 g, 15% yield).

(R)-(-)-Cryptomerene. Magnesium turnings (8.0 g, 328 mmol) were covered with THF (40 ml), and 1,2-dibromoethane (400 \mu l, 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 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 (0.45 M) was ready to use. To the cuprous bromide (5.16 g, 36.0 mmol) in saturated NH₄Cl and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na₂SO₄, and evaporated to dryness. The obtained oil was chromatographed in a silica gel column [7:1 hexane/EtOAc] to afford (R)-(-)-cryptomerene as a colorless oil (1.52 g, 58%).

\[ \text{H-NMR (400 MHz, CDCl}_3\text{:} \] 1.10 (d, \( J = 6.7 \) Hz, 3H, CH₃), 1.65-1.74 (m, 1H, CH₃CH₃), 1.69 (d, \( J = 1.2 \) Hz, 3H, CH₃), 1.79 (dt, \( J = 2.4 \) and 1.2 Hz, 3H, CH₃), 2.04-2.13 (m, 3H, CH₃CH₂), 2.46 (m, 1H, CH₂CH₃), 2.89 (dd, \( J = 16.0 \), 4.4 and 1.2 Hz, 1H, CH₂CH₃), 2.60 (m, 1H, CH₂CH₂), 4.02 (s, 1H, CH₂), 4.59 (s, 1H, CH₂), 5.09 (t, \( J = 6.8 \) and 1.2 Hz, 1H, CH=CH₂), 6.75 (dd, \( J = 5.6 \), 2.4 and 1.2 Hz, 1H, CH₂=CH=), 10.79 (s, 1H, CH₂), 11.09 (s, 1H, CH₂), 12.73, 12.97, 13.75, 13.76, 31.6, 25.7, 17.7, 15.7.

\[^{(1S,2S,3S)}\text{-3-Phenylseleno}-7(14),10-bisaboladien-1-ol (4) and its C(1) epimer (5).\]

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)-(-)-cryptomerene (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 Na₂SO₄, evaporation of the solvent in vacuo gave an oil which was chromatographed in a silica gel column [17:1 hexane/EtOAc] to afford (R)-(-)-cryptomerene as a colorless oil (1.52 g, 58%).

\[^{(1H,4R,7S)}\text{-10-Bromo-1(6),8-D25-benzoselenol as a colorless oil (1.52 g, 58%).}]

were covered with THF (40 ml), and 1,2-dibromoethane (400 \mu l, 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 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 (0.45 M) was ready to use. To the cuprous bromide (5.16 g, 36.0 mmol) in saturated NH₄Cl and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous Na₂SO₄, and evaporated to dryness. The obtained oil was chromatographed in a silica gel column [7:1 hexane/EtOAc] to afford (R)-(-)-cryptomerene as a colorless oil (1.52 g, 58%).

(1S,2R,3S)-3,7(14),10-Bisaboladien-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 dihydropyrane (336 mg, 4.0 mmol) in CH₂Cl₂ (10 ml) was stirred for 3 h. The mixture was diluted with EtOAc and successively washed with water and brine. After drying over anhydrous Na₂SO₄, removal of the solvent gave a residual oil, a crude THF ether, which was dissolved in CH₂Cl₂ (20 ml) containing pyridine (320 \mu l, 4.0 mmol). Then, 30% H₂O₂ (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 water and brine, and, after drying over anhydrous Na₂SO₄, the solvent was removed in vacuo, leaving an oil which was dissolved in CCl₄ (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 Na₂SO₄, 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.

(1S,2R,3S)-3,7(14),10-Bisaboladien-1-ol (6) from 8. A 40% solution of DEAD in toluene (540 \mu l, 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-N0₂C₆H₄CH₂OH (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 NaHCO₃ and brine, the organic layer was dried over anhydrous Na₂SO₄. 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 2N HCl and extracted with EtOAc. The organic layer was successively washed with water, saturated NaHCO₃ and brine, and after drying (anhydrous Na₂SO₄), 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%).
[CH3]2CO, 2.74 (q, J = 6.8 Hz, 3H, C-17), 3.08 (dd, J = 6.8 Hz, 1H, C-18), 3.39 (d, J = 6.8 Hz, 1H, C-19), 3.57 (d, J = 6.8 Hz, 1H, C-20), 3.80 (d, J = 6.8 Hz, 1H, C-21). The residual oil was chromatographed on a silica gel column (3:1 hexane/EtOAc) to afford a colorless oil (155 mg, 79%).

References


16) Ikeno, T., Kimura, T., Ohtsuka, Y., and Yamada, T., Selective 1,4-reduction of α,β-unsaturated carbonyl compounds by combined use of bis(1,3-diketono)cobalt(II) complex and disobutyldiammonium hydride. Synlett, 96–98 (1999).


Acknowledgments

This work was supported in part, by grant-aid for young scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan (no. 20780086).