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Note

Concise Synthesis of Valerena-4,7(11)-diene, a Highly Active Sedative, from Valerenic Acid

Takashi KITAYAMA,[1,†] Genki KAWABATA,[1] and Michiho ITO[2]

[1]*Department of Advanced Bioscience, Graduate School of Agriculture, Kinki University, Nara 631-8505, Japan*
[2]*Department of Pharmacognosy, Graduate School of Pharmaceutical Science, Kyoto University, Kyoto 606-8501, Japan*

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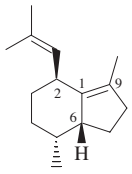
A concise synthesis of valerena-4,7(11)-diene with potent sedative activity was achieved in three steps involving, reduction of carboxylic acid, bromination of the resulting alcohol, and reduction of the bromide from valerenic acid in a 63% total yield. This synthetic method makes it possible to provide further materials for biological testing to realize comprehensive SAR studies.

Key words: valerena-4,7(11)-diene; valerenic acid; sedative activity; sesquiterpene

Valerena-4,7(11)-diene ((2*S*,5*R*,6*R*)-5,9-dimethyl-2-(2-methyl-1-propenyl)bicyclo[4.3.0]non-1(9)-ene, **1**) as shown in Fig. 1, has been isolated in a small quantity from the roots of *Nardostachys chinensis*[1,2] and *Valeriana officinalis* L.,[3,4] and is a bicyclic sesquiterpene that has recently been shown to dose-dependently reduce the locomotor activity of mice with a particularly profound effect, the strongest sedative activity being observed at a dose of 0.06%.[1]



1

Fig. 1. Valerena-4,7(11)-diene **1**.

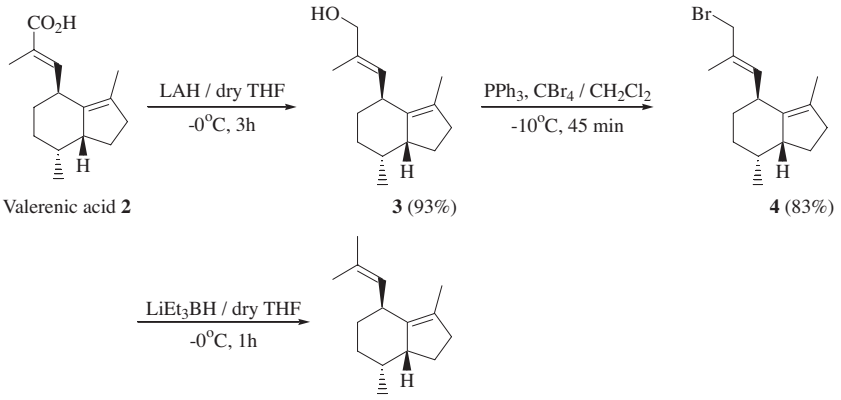
The unique aspect for the pharmacological activity of this compound is that it can be administered *via* inhalation; the compound is naturally volatile at room temperature and bears a pleasant smell.[1] It may hopefully be developed as a less-harmful remedy for attention deficit hyperactivity disorder (ADHD) and for the confused elderly. An efficient total synthesis of **1** therefore appears to be of importance, as more extensive and elaborate structural variations are envisaged. Structure-activity relationship (SAR) studies of this natural product would not only be able to elucidate the intrinsic mechanism of action, but would also open a new avenue for exploring the possible mode of action of this compound. However, an efficient method for synthesizing **1** is required before comprehensive SAR studies can become a reality.

Valerenic acid **2**, which has been isolated as the main component of *Valeriana officinalis* and previously synthesized by Mulzer *et al.*[5] and Altmann *et al.*,[6] was purchased from EXTRASYNTHÈSE (France) as an optically active compound ($[\alpha]_D$ -115° (*c* 0.13, $CHCl_3$). **2** has tranquilizing and/or sedative activity from animal experiments,[7] and the activation of adenosine receptors has been implicated in the action of valerian ingredients.[8] We present here the first concise synthesis of valerena-4,7(11)-diene **1** from valerenic acid **2** as the starting material *via* the reduction of α,β-unsaturated carboxylic acid to allylic alcohol with $LiAlH_4$, bromination of the resulting primary alcohol with CBr_4/PPh_3, and reduction of the bromide with super hydride.

Scheme 1 shows how the concise synthesis of target compound **1** was achieved in three steps from valerenic acid **2**.

Treatment of valerenic acid **2** with $LiAlH_4$ (LAH) at $0\,^\circ C$ for 3 h gave valerenol **3** in a 93% yield without reduction of the conjugated olefin.[9] Alcohol **3** was reacted with triphenylphosphine and then exposed to tetrabromomethane at $-10\,^\circ C$ for 45 min to afford **4** in an 83% yield. Bromide **4** was converted to desired compound **1** as soon as possible since **4** easily decomposed. Bromide **4** was reacted with $LiBHEt_3$ at $-20\,^\circ C$ for 1 h to afford target compound **1** in an 82% yield. Compound **1** showed a minus sign for its specific rotation which is consistent with the natural product.[3] The ^{1}H-NMR spectrum of synthetic compound **1** was also completely consistent with the natural product.[3] Characteristic peaks of one olefin and two allylic protons at the C2 and C6 positions were clearly observed. The first concise synthesis of **1** was therefore achieved in three steps from valerenic acid in a 63% total yield to provide further material for biological testing. The synthetic route should be applicable to a variety of derivatives that would be suitable for SAR investigation. Various derivatives of valerena-4,7(11)-diene **1** for SAR could be synthesized by introducing nucleophilic agents including oxygen, nitrogen, and a sulfur group, and by extending the carbon chain on the allylic position by using reactive allyl bromide intermediate **4**, in addition to converting to carboxylic acid derivatives by using valerenic acid. We believe that the development of novel active sedatives might quickly become possible from the results of this study.

† To whom correspondence should be addressed. Tel: +81-742-43-7415; Fax: +81-742-43-8976; E-mail: kitayama@nara.kindai.ac.jp



Valerenic acid **2** **3** (93%) **4** (83%)

Valerena-4,7(11)-diene **1** (82%)

Scheme 1.

Experimental

Column chromatography was performed on silica gel (70–230 mesh), and TLC was performed on Merck 60 F_{254} silica gel plates. NMR spectra were recorded by a Bruker instrument at 400 MHz for protons, and at 100 MHz for ^{13}C in $CDCl_3$, with tetramethylsilane (TMS) used as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from TMS. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were obtained by direct injection. Optical rotations were measured by a Jasco DIP-140 polarimeter. All chemicals were of commercially available reagent grade and were without further purification.

*(2S,5R,6R)-5,9-Dimethyl-2-(3-hydroxy-2-methyl-1-propenyl)bicyclo[4.3.0]non-1(9)-ene (Valerenol) (**3**).* Valerenic acid **2** (36 mg, 0.15 mmol) in absolute THF (2 ml) was added dropwise to a suspension of $LiAlH_4$ (41 mg, 1.1 mmol) in absolute THF (2 ml) at 0 °C in an N_2 atmosphere, and the mixture was stirred for 3 h in an ice-salt bath. Cold water (10 ml) was added, and the mixture was extracted with AcOEt (3 × 30 ml). The combined organic solution was washed with brine (3 × 30 ml), dried over Na_2SO_4, and concentrated on a rotary evaporator. The resulting residue was subjected to silica gel column chromatography using AcOEt and hexane (1:8) as the eluent, to afford valerenol **3** as a colorless oil in a 94% (31.4 mg) yield. NMR δ_H ($CDCl_3$): 0.77 (3H, d, $J = 7.0$ Hz, *CH*$_3$ at C5), 1.27–1.40 (2H, m, 2*CH* at C3 and C4), 1.49-1.58 (1H, m, *CH* at C7), 1.64 (3H, s, *CH*$_3$ at C9), 1.72 (3H, s, CH=C(*CH*$_3$)CH_2OH), 1.76–1.89 (3H, m, 3*CH* at C3, C4, and C7), 1.94–2.00 (1H, m, *CH* at C5), 2.19 (2H, t, $J = 7.6$ Hz, *CH*$_2$ at C8), 2.89–2.95 (1H, m, *CH* at C6), 3.45 (1H, m, *CH*CH=C(CH_3)CH_2OH), 4.00 (2H, s, CH=C(CH_3)*CH*$_2$OH), 5.75 (1H, d, $J = 9.3$ Hz, *CH*=C(CH_3)CH_2OH); NMR δ_C ($CDCl_3$): 12.0, 13.4, 13.7, 24.5, 26.2, 28.7, 33.2, 33.4, 37.5, 47.4, 69.3, 127.7, 129.1, 133.1, 135.2.

*(2S,5R,6R)-5,9-Dimethyl-2-(3-bromo-2-methyl-1-propenyl)bicyclo[4.3.0]non-1(9)-ene (**4**).* Triphenylphosphine (52.3 mg, 0.2 mmol) was added to a solution of valerenol **3** (31.4 mg, 0.14 mmol) in absolute CH_2Cl_2 (0.7 ml) at −10 °C in an N_2 atmosphere, and the mixture was stirred for 3 min in an ice-salt bath. Carbon tetrabromide (56.7 mg, 0.17 mmol) was added to the mixture at the same temperature, and stirring was continued for 45 min. CH_2Cl_2 was removed by a rotary evaporator, pentane (2 ml) was added to the residue, and the mixture was stirred at room temperature for 5 min. The mixture was finally subjected to silica gel column chromatography using pentane as the eluent, to afford (2S,5R,6R)-5,9-dimethyl-2-(3-bromo-2-methyl-1-propenyl)bicyclo[4.3.0]non-1(9)-ene **4** as a light yellow oil in an 83% (33 mg) yield. NMR δ_H ($CDCl_3$): 0.75 (3H, d, $J = 7.0$ Hz, *CH*$_3$ at C5), 1.32–1.42 (2H, m, 2*CH* at C3 and C4), 1.49–1.58 (1H, m, *CH* at C7), 1.62 (3H, s, *CH*$_3$ at C9), 1.64–1.80 (2H, m, 2*CH* at C3 and C4), 1.80 (3H, d, $J = 1.3$ Hz, CH=C(*CH*$_3$)CH_2Br), 1.82–1.85 (1H, m, *CH* at C7), 1.94–2.00 (1H, m, *CH* at C5), 2.19 (2H, t, $J = 7.6$ Hz, *CH* at C8), 2.85–2.90 (1H, m, *CH* at C6), 3.39 (1H, m, *CH* at C2), 3.98 (2H, s, CH=C(CH_3)*CH*$_2$Br), 5.89 (1H, d, $J = 9.2$ Hz, *CH*=C(CH_3)CH_2Br); NMR δ_C ($CDCl_3$): 12.0, 13.4, 14.7, 24.6, 25.8, 28.7, 33.3, 33.9, 37.5, 42.5, 47.4, 129.8, 130.3, 132.8, 134.4. HRMS (M-Br) *m/z*: calcd. for $C_{15}H_{23}$, 203.1800; found, 203.1823.

*(2S,5R,6R)-5,9-Dimethyl-2-(2-methyl-1-propenyl)bicyclo[4.3.0]non-1(9)-ene (valerena-4,7(11)-dinene **1**).* $LiBHEt_3$ (125 µl, 12.5×10^{-2} mmol) was added dropwise to a solution of **4** (174.7 mg, 6.3×10^{-2} mmol) in absolute THF (1.0 ml) at 0 °C in an N_2 atmosphere, and the mixture was stirred for 1 h in an ice-salt bath. Water (5 ml) was added to the solution at −20 °C and the mixture was extracted with hexane (3 × 10 ml). The combined organic solution was washed with brine (3 × 20 ml), dried over Na_2SO_4, and concentrated on a rotary evaporator. The resulting residue was subjected to silica gel column chromatography, using hexane as the eluent, to afford valerena-4,7(11)-diene **1** as a colorless oil in an 82% (10.4 mg) yield. $[\alpha]^{23.5}_D$ −6.2° (*c* 0.13, $CHCl_3$); NMR δ_H ($CDCl_3$): 0.75 (3H, d, $J = 7.0$ Hz, *CH*$_3$ at C5), 1.27–1.37 (2H, m, 2*CH* at C3 and C4), 1.48–1.57 (2H, m, *CH* at C7), 1.63 (3H, s, *CH*$_3$ at C9), 1.66 (3H, s, CH=C(*CH*$_3$)$_2$), 1.69 (3H, s, CH=C(*CH*$_3$)$_2$), 1.69–1.88 (2H, m, 2*CH* at C3 and C4), 1.92–1.99 (1H, m, *CH* at C5), 2.15–2.22 (2H, m, *CH* at C8), 2.88–2.97 (1H, m, *CH* at C6), 3.4 (1H, m, *CH* at C2), 5.46 (1H, d, $J = 9.3$ Hz, *CH*=C(CH_3)$_2$); NMR δ_C ($CDCl_3$): 12.1, 13.4, 17.8, 24.6, 26.1, 26.6, 28.7, 33.6, 33.6, 37.5, 47.4, 126.2, 128.4, 129.8, 136.0.

Elemental Analysis. Found: C, 88.27; H, 11.73%. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84%.

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