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First Total Synthesis of (±)Hedaol B

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ABSTRACT

Hedaol B, a new bisnorditerpene isolated from the Japanese brown alga *Sargassum. sp.*, was first synthesized starting from geranyl acetone, alkylation of silyl cyanide as the key step.

Key Words: Hedaol B; Alkylation; Total synthesis.

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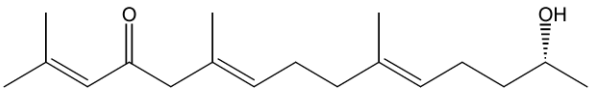
In the course of investigations on the Japanese brown alga *Sargassum. sp*., many marine natural products bearing terpenic skeletons have been found.[1–3] Takada et al.[3] recently isolated a new class of bisnorditerpenes, named hedaol A, B, C. Numerous biological activities such as antitumor, cytotoxic properties have been found among these compounds. For example, hedaol B (**1**) showed a toxicity against P_{388} cells, with IC_{50} value of 2.2 (50 μg/mL).



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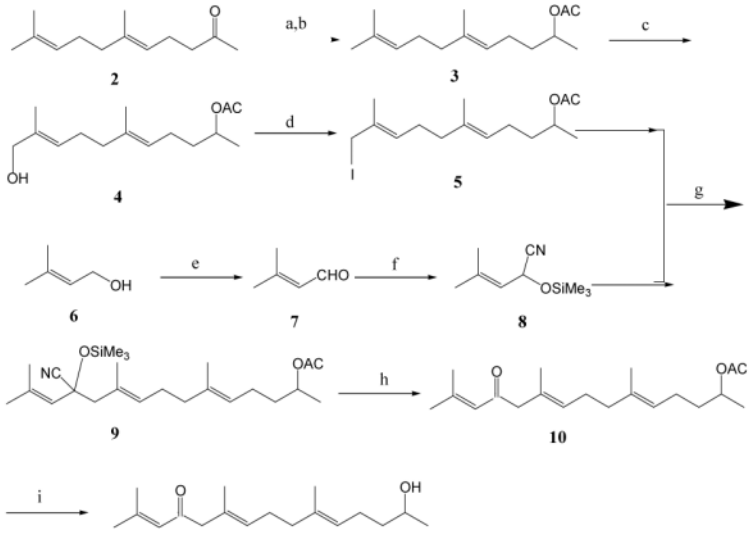
In this communication, we report the first synthesis of (±)hedaol B (**1**) involving the alkylation key-step reaction of silyl cyanide with allylic iodide, starting from geranyl acetone via six steps, successively, with high overall yield. Since the reaction of TMSCN with a variety of aldehydes and ketones was first shown by Evans et al.[4] and Lidy and Sundermeyer[5] and alkylation of silyl cyanide was reported by Deuchert et al.,[6] the reaction has been so favorable in organic synthesis.[7] We wish to apply it to the facile synthesis of (±)hedaol B (**1**) and herein provide details of this work.

Geranyl acetone **2** was reducted with $NaBH_4$ to give the corresponding alcohol, which can be transformed acetate **3** by treatment with Ac_2O, followed by regoselectively oxidized the E methyl group using $SeO_2/^tBuOOH$[8] at 0°C gave the terminal alcohol **4**, which can be transformed into iodide **5**. The key step was the alkylation of allylic iodide[9] with silyl cyanide **8**, which was conveniently prepared from 3-methyl-2-buten-1-ol **6** through two steps (oxidation with PCC and cyanosilation with Me_3SiCN in the presence of a catalytic amount of KCN/18-*crown*-6), deprotection of silyl cyanide **9** with a catalytic amount of TBAF afforded the ketone **10**, which was hydrolyzed to obtain (±)hedaol B (**1**), with spectroscopic data identical to those of literature. Our synthetic route is shown in Sch. 1.

EXPERIMENTAL

IR spectra were recorded on a Nicolet 170 FT-IR spectrophotometer in KBr dics. ^1H NMR spectra were measured on AM-200 spectrometer



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, 0°C, 30 min, 98%. (b) AC_2O, Py, DMAP, 0°C, 30 min, 100%. (c) SeO_2, ^tBuOOH, 0°C, 2 h, 50%. (d) Ph_3P, imidazole, I_2, Et_2O/CH_3CN, 0°C, 100%. (e) PCC, CH_2Cl_2, r.t., 80%. (f) Me_3SiCN, 18-*crown*-6/KCN, CH_2Cl_2, 0°C, 100%. (g) $(Me_3Si)_2NLi$, **5**, −78°C, 1 h, then **8**, −78°C, 2 h, 63%. (h) a catalytic amount of TBAF, 10% aqueous THF, r.t., 15 h, 63%. (i) K_2CO_3, MeOH, r.t. 4 h, 80%.

with TMS as internal standard in a solution of $CDCl_3$. Mass spectra were determined on a MAT-44S spectrophotometer (EI, 70 eV). All used reagents are of commercial origin and used without further purification. Unless otherwise indicated all reaction products were purified by flash chromatography on silica gel (200–300 mesh), purchased from Qing Dao Marine Chemical Co. (Qingdao, China) and eluting with a solvent mixture (v/v) of petroleum ether (60–90°C) and ethyl acetate.

6,10-Dimethyl-5(*E*),9-undecadien-2-ol Acetyl Acetate (3)

To a clear solution of geranyl acetone **2** (1.94 g, 10 mmol) in anhydrous MeOH (20 mL) was added sodium borohydride (380 mg, 10 mmol) portionwise at 0°C with stirring. The reaction completed after 0.5 h, then, was quenched with H_2O. The reaction mixture was extracted with Et_2O (100 mL), and washed sequentially with H_2O and brine, then dried and concentrated. The residue was purified on silica gel to afford a pale yellow

oil (1.92 g, 98%), which was dissolved in pyridine (3 mL) and added to a catalytic amount of DMAP and Ac_2O (2 mL) at 0°C. After being stirred vigorously for 0.5 h at that temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3×30 mL), the combined organic layer was washed 10% aqueous HCl, H_2O, brine, then dried and concentrated, purified by chromatography to give acetate **3** (2.28 g, 100%) as a colorless oil. IR ν_{max}: 2927, 2925, 1773, 1447, 1375, 1249, 912, 734; δ_H (200 MHz, $CDCl_3$): 5.08 (2H, m, 2HC=), 4.89 (1H, m, CHOAc), 2.04 (3H, s, CH_3CO–), 2.03–2.00 (6H, m, $3CH_2$), 1.68 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.56 (2H, m, CH_2), 1.22 (3H, d, $J = 6.4$ Hz). *m/z*: 238 (1), 195 (3), 178 (8), 163 (6), 135 (17), 109 (84), 69 (100), 43 (92).

6,10-Dimethyl-11-hydroxy-5(*E*), 9(*E*)-undecadien-2-ol Acetyl Acetate (4)

To a clear solution of SeO_2 (111 mg, 1 mmol) and ^tBuOOH (70%, 1.71 mL, 12.5 mmol) in CH_2Cl_2 (30 mL) at 0°C was added compound **3** (1.19 g, 5 mmol) in CH_2Cl_2 (100 mL). After being stirred at 0°C for 2 h, the reaction mixture was diluted with Et_2O (100 mL) and washed sequentially with 10% aqueous KOH, H_2O, and brine, then dried and concentrated. The resulting oil was purified by flash column chromatography on silica gel to yield the terminal alcohol **4** (0.64 g, 50%) as a colorless oil. IR ν_{max}: 3412, 3385, 2927, 1734, 1247, 1023. δ_H (200 MHz, $CDCl_3$): 5.40 (1H, t, HC=), 5.12 (1H, t, HC=), 4.89 (1H, m, CHOAc), 4.00 (2H, s, CH_2O), 2.04 (3H, s, CH_3CO–), 2.00–2.08 (6H, m, $3CH_2$), 1.70 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.56 (2H, m, CH_2), 1.22 (3H, d, $J = 6.4$ Hz). *m/z*: 236 (M − 18) (1), 194 (1), 161 (18), 109 (77), 67 (62), 43 (100).

3-Methyl-2-butenal (7)

To the suspension of PCC (646.5 mg, 3 mmol) in CH_2Cl_2 (15 mL) was added 3-methyl-2-buten-1-ol **6** (172 mg, 2 mmol) in CH_2Cl_2 (5 mL) with stirring at room temperature for 3 h, the reaction mixture was Et_2O (100 mL) diluted and filtered through a short column on silica gel to remove the black solid, then the resulting filtrate was concentrated and purified to give enal **7** (135 mg, 80%) as a clear oil.

δ_H (200 MHz, $CDCl_3$): 9.89 (1H, d, $J = 5.6$ Hz, CHO), 5.93 (1H, d, $J = 8.2$ Hz, HC=), 2.25 (3H, s, CH_3), 2.05 (3H, s, CH_3).

6,10,14-Trimethyl-12-cyano-12-trimethylsiloxy-5(*E*), 9(*E*),13-tetradecatrien-2-ol Acetyl Acetate (9)

A catalytic amount of KCN and 18-*crown*-6 complex was first added to aldehyde **7** (168 mg, 2 mmol) in CH_2Cl_2 (2 mL), with stirring, then Me_3SiCN (0.36 mL, 2.4 mmol) was added dropwise to the suspention at 0°C under argon atmosphere. The reaction was complete within 1 h and gave silyl cyanide **8**, which was used in situ without further purification.

To a stirred clear solution of **4** (508 mg, 2 mmol), Ph_3P (786 mg, 3 mmol), and imidazole (204 mg, 3 mmol) in a mixed solvent of CH_3CN (4 mL) and Et_2O (6 mL) was added iodine crystals (762 mg, 3 mmol) portionwise at 0°C, until the reaction was complete with TLC monitoring. The reaction mixture was diluted with Et_2O (60 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution, H_2O, and brine, then dried. The solvent was removed in vacuo below 40°C, the crude oil was purified by chromatography to afford ioide **5**, which was dissolved in anhydrous THF (2 mL) and used for the followed procedure.

To a clear solution of $HN(SiMe_3)_2$ (3 mmol) in anhydrous THF (5 mL) was added BuLi (1 mL, 3 N) at 0°C under argon atmosphere. After the reaction mixture was stirred 0.5 h, silyl cyanide **8** (2 mmol) in the anhydrous THF (2 mL) was added dropwise at −78°C and stirring was continued for 1 h at that temperature, then, the above solution of allylic ioide **5** (2 mmol) in THF (2 mL) was added by syringe and the reaction mixture was stirred at −78°C for a further 2 h before the reaction was quenched by the addition of saturated aqueous NH_4Cl and Et_2O (50 mL). The organic phase was washed H_2O and brine, then, dried and concentrated. The residue was purified on silica gel to afford silyl cyanide **9** as a colorless 503 mg (60%). IR ν_{max}: 2964, 1740, 1251, 1089, 848; δ_H (200 MHz, $CDCl_3$): 5.32 (1H, t, HC=), 5.24 (1H, s, HC=), 5.12 (1H, t, HC=), 4.89 (1H, m, CHOAc), 2.49 (2H, d, CH_2), 2.03 (3H, s, CH_3CO–), 2.14–1.48 (8H, m, $4CH_2$), 1.89 (3H, s, CH_3), 1.76 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.22 (3H, d, $J = 6.4$ Hz), 0.21 (6H, s, $2CH_3$), 0.08 (3H, s, CH_3); *m*/*z*: 419 (1), 310 (1), 260 (1), 182 (39), 83 (100).

6,10,14-Trimethyl-12-oxo-5(*E*),9(*E*),13-tetradecatrien-2-ol Acetyl Acetate (10)

Silyl cyanide **9** (210 mg, 0.5 mmol) was dissolved in 10% aqueous THF (5 mL) and a catalytic amount of n-$Bu_4N^+F^-$ was added. After being stirred at room temperature for 15 h, the reaction mixture was extracted with Et_2O (30 mL) and the combined organic phase was

washed with H_2O and brine, then dried and concentrated, purified by chromatography to afford ketone **10** 100 mg as a colorless oil (63%). IR ν_{max}: 3409, 2925, 1735, 1621, 1446, 1245, 1065; δ_H (200 MHz, $CDCl_3$): 6.13 (s, 1H, CH=), 5.24 (1H, t, HC=), 5.10 (1H, t, HC=), 4.89 (1H, m, CHOAc), 3.05 (2H, s, CH_2), 2.15 (3H, s, CH_3), 2.04 (3H, s, CH_3), 2.16–1.48 (8H, m, $4CH_2$), 1.89 (3H, s, CH_3), 1.60 (6H, s, $2CH_3$), 1.22 (3H, d, $J = 6.4$ Hz); *m/z*: 320 (1), 260 (1), 205 (1), 109 (37), 83 (100).

(±)Hedaol B (1)

To a solution of ketone **10** (50 mg, 0.16 mmol) in dry MeOH (3 mL) was added anhydrous K_2CO_3 (18 mg, 0.16 mmol). The mixture was stirred at room temperature for 4–5 h, then extracted with Et_2O (15 mL). The ether layer was washed with H_2O and brine, then dried and concentrated, purified by chromatography to afford (±)hedaol B **(1)** 35 mg as a colorless oil (80%). IR ν_{max}: 3420, 2921, 2965, 1682, 1619, 1443, 1112; δ_H (200 MHz, $CDCl_3$): 6.12 (s, 1H, CH=), 5.23 (1H, t, HC=), 5.15 (1H, t, HC=), 3.82 (1H, m, CHOH), 3.05 (2H, s, CH_2), 2.15 (3H, s, CH_3), 2.17–1.50 (8H, m, $4CH_2$), 1.89 (3H, s, CH_3), 1.63 (6H, s, $2CH_3$), 1.20 (3H, d, $J = 6.4$ Hz); *m/z*: 278 (1), 260 (1), 209 (1), 180 (1), 83 (100).

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