Asymmetric Synthesis of Methyl (−)-13-Oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oate, Methyl Ester of a Potent Suppressor toward Carcinogenic Promotor

Takahiro KATOH, Shinsuke MIZUMOTO, Masato FUDESAKA, Tetsuya KAJIMOTO, and Manabu NODE*

Department of Pharmaceutical Manufacturing Chemistry, 21st Century COE Program, Kyoto Pharmaceutical University; 1 Shichono-cho, Misasagi, Yamashina-ku, Kyoto 607–8412, Japan.

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Asymmetric synthesis of methyl ester (4) of (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid (1), which exhibited the most potent activity for the prevention of incipient carcinogenesis among the isolated diterpenes from *Thuja standishii* and its related plants, was achieved by using methyl (−)-1,4a-dimethyl-5-oxodecahydronaphthalene-1-carboxylate (5) as a strating material, which was easily prepared on gram scale by baker's yeast-catalyzed asymmetric reduction.

Key words (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid; *Thuja standishii*; synthesis; (−)-1,4a-dimethyl-5-oxodecahydronaphthalene-1-carboxylate

A labdane-type diterpenoid, (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid (**1**) has been reported by Tanaka to have potent cancer chemopreventive activity toward papilloma-bearing mice.[1,2] The acid (**1**) isolated from the stem bark of *Thuja standishii* (GORD.) CARR. as a minor component had the most potent activity for the prevention of incipient carcinogenesis among the diterpenoids from the same plant source. Although two other plants, *Platycladus orientaris*[3] and *Juniperus chinensis*,[4,5] were reported as a natural source of **1**, its scarce supply from nature required efficient synthetic routes for further estimation as a cancer chemopreventive agent. Recently we published a chemical conversion from *trans*-communic acid (**2**), a major component of *T. standishii*, to **1** *via* allyl alcohol **3** (Fig. 1).[6] Herein, as a part of our studies on chemoenzymatic synthesis of bioactive diterpenes, we would like to report an asymmetric total synthesis of methyl ester (**4**) of **1** *via* (−)-1,4a-dimethyl-5-oxodecahydronaphthalene (**5**),[7] which can be provided on gram scale from σ-symmetric 1,3-diketone **6** by using baker's yeast-catalyzed asymmetric reduction as a key step (Chart 1).

A synthetic approach was considered on the basis of the plausibility that decahydronaphthalene-1-carboxylate (**5**) was an excellent precursor for the synthesis of **4**, and two routes (Routes A and B) were adopted as attainable strategies (Chart 1). The first strategy (Chart 1, Route A) was started with linking vinyl methyl ketone to the carbonyl carbon of **5**, followed by introduction of the terminal methylene to an intermediate **7**. The second strategy (Chart 1, Route B) passed through aldehyde **8** (X=O), of which the two carbonyl groups would be utilized to successively introduce a terminal methylene and a propane unit by Wittig-type of reactions.

In order to achieve the former strategy (Route A), the precursor **5** was first derived to enol triflate (**9**) with *N*-phenylbis(trifluoromethanesulfonimide) in the presence of potassium *tert*-butoxide in good yield (84%) (Chart 2). The successive Heck reaction of **9** with methyl vinyl ketone catalyzed by palladium acetate (2 mol%) and triphenylphosphine resulted in a low yield (15%) (Table 1, entry 1). When the reaction was run at higher temperature (Table 1, entries 2, 3) or in the presence of a larger amount of the catalyst (Table 1, entry 4), higher chemical yields (up to 78%) were obtained. Moreover, the reaction employing bis(triphenylphosphine)palladium(II) chloride as a catalyst[8] and running at 100 °C gave the best result (86%) (Table 1, entry 5).

Since we were able to obtain the coupled product **10** in good yield by using the Heck reaction, many efforts to introduce a terminal methylene were made. For example, direct conjugate addition of carbanion such as methoxymethyl cuprous magnesium bromide to the C-8 position of methyl ketone **10** was attempted in the beginning; however, all the trials resulted in failure. Thus, the conjugated methyl ketone

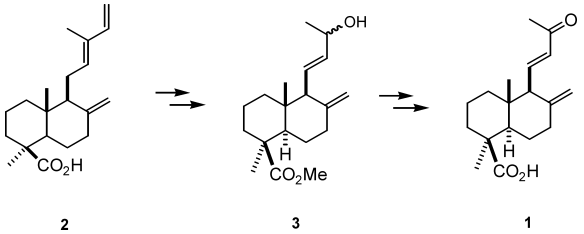


Fig. 1. Structures of Diterpenoids Related to **1** and *trans*-Communic Acid (**2**)

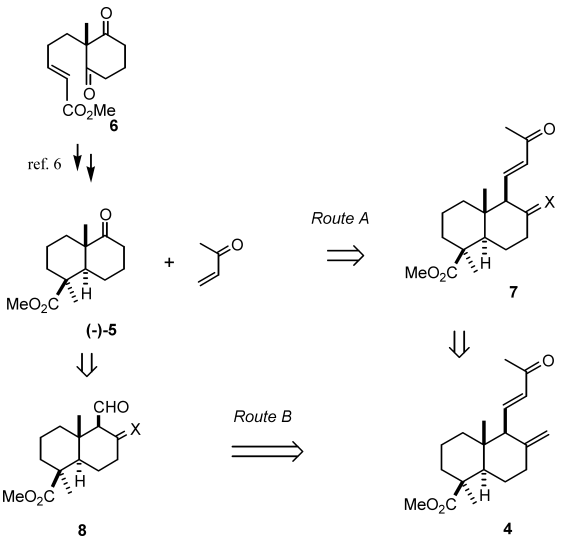


Chart 1. Synthetic Approach of **4**

* To whom correspondence should be addressed. e-mail: node@mb.kyoto-phu.ac.jp

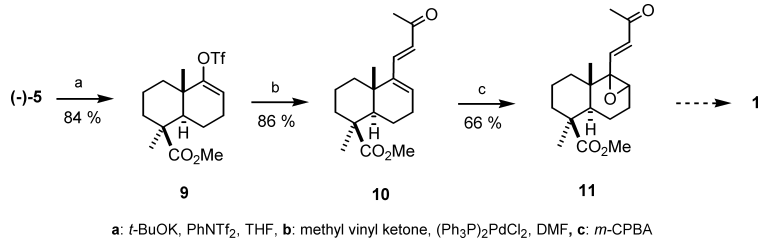
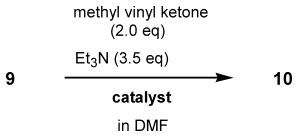


Chart 2. Synthetic Route of **1** from (−)-**5** using Heck Reaction as a Key Step

Table 1. Heck Reaction of Enol Triflate **9** with Methyl Vinyl Ketone



Entry	Catalyst (mol%)	Time (h)	Temp. (°C)	Yield (%)
1	PPh_3, $Pd(OAc)_2$ (2 mol%)	24	r.t.	15
2	PPh_3, $Pd(OAc)_2$ (2 mol%)	24	85	45
3	PPh_3, $Pd(OAc)_2$ (2 mol%)	24	100	51
4	PPh_3, $Pd(OAc)_2$ (20 mol%)	24	100	78
5	$(PPh_3)_2PdCl_2$ (10 mol%)	1.5	100	86

10 was next derived to epoxide **11**, which was attempted to transform diketone **7** (X=O) by Lewis acid-catalyzed hydride shift or was attacked by nucleophiles such as phenylthiomethyl magnesium bromide and methoxymethyl magnesium bromide. To our disappointment, none of them gave expected products (Chart 2).

After experiencing the difficulties in the Route A approach, the latter strategy (Chart 1, Route B) was attempted. In order to synthesize the key intermediate **8**, introduction of a C1 unit at the carbonyl carbon of **5** by a Wittig-type reaction using methoxymethylene phosphonium ylide was tried. Surprisingly, the reaction did not afford the methyl enolate at all while Wittig reaction with methylidene triphenylphosphorane gave **12** in almost quantitative yield (99%). Encouraged by the excellent result of the conventional Wittig reaction, the allylic methylene carbon of **12** was oxidized with selenium oxide in the presence of *tert*-butyl hydroperoxide[9] to afford allyl alcohol **13**, of which the double bond was subjected to hydroboration–oxidation to yield diol **14**. Stereochemistry of the secondary hydroxyl group of **14** was deduced on the basis of the spectral data of 2-hydroxydecahydro-5,5,8a-trimethyl-1-naphthalenemethanol (**15**) in the literature.[10] Although the oxidation of the two hydroxyl groups could formally afford the ketoaldehyde **8** (X=O), the diol **14** was oxidized stepwise to carry out regioselective Wittig reaction for the two carbonyl groups of **8** (X=O). Therefore, the primary hydroxyl group of **14** was selectively protected with *tert*-butyldimethylsilyl chloride to afford **16**. The remaining secondary hydroxyl group of **16** was then oxidized by Dess–Martin oxidation to give ketone **17**, which was successively treated with the Wittig reagent to yield exo-olefin **18**. Removal of the silyl protecting group of **18** with tetrabutylammonium fluoride led to primary alcohol **19**, of which the successive oxidation with the Dess–Martin reagent afforded the key intermediate **20**, which corresponds to **8** ($X=CH_2$) (Chart 3).

Finally, elongation of the 2-propanone side chain onto the aldehyde group of **20** was scrutinized (Table 2). Addition of an enolate prepared from acetone with lithium hexamethylsilazide did not give satisfactory results (Table 2, entries 1, 2), while a better result to lead to the target molecule **4** (45%) was obtained when aldehyde **19** was treated with triphenylphosphine ylide in refluxed toluene (Table 2, entry 4). All the spectral and physical data of our synthesized **4** completely coincided with that derived from naturally occurring **1**.

It is noteworthy that the production of conjugate aldehyde **21** decreased the chemical yield of **4**. Unfortunately, neither direct saponification of the methyl ester in **4** nor demethylation with soft nucleophiles proceeded well due to the side reactions such as Michael addition to the conjugated ketone moiety and migration of the double bond at the terminal olefin. In order to avoid these undesired reactions, the synthetic route was revised so as to follow the same route from *trans*-communic acid (**2**) to **1**. Namely, the carbonyl group of the conjugate ketone **4** was reduced to **3** under Luche's condition[11] with cerium chloride and sodium borohydride and reoxidized after cleavage of the methyl ester with *n*-dodecanthiol and *n*-butyllithium in HMPA[12,13] *via* acid **22** (Chart 4).

In conclusion, we have succeeded in the formal asymmetric synthesis of optically pure (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oate (**1**). This synthetic route was started with (−)-1,4a-dimethyl-5-oxodecahydronaphthalene (**5**), which can be provided on gram scale by using baker's yeast-catalyzed asymmetric reduction. Therefore, our strategy is applicable for the synthesis of many derivatives of **1**, which could support study on the structure–activity relationship for developing novel anti-tumor agents. Further studies are in progress.

Experimental

General Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^{1}H-NMR spectra were obtained on a JEOL JNM-AL300, or a Varian GEMINI 2000/200, or a Varian Unity INOVA-400 spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained on a Varian GEMINI 2000/200, or a Varian Unity INOVA-400 spectrometer with $CDCl_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 (silica gel) (100—200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support of the immobile phase. Kieselgel 60 F-254 plates (Merck) were used for thin-layer chromatography (TLC). Unless purification with silica gel gave a pure enough compound, the compounds were further treated with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H). In the case it is possible, diastereomeric mix-

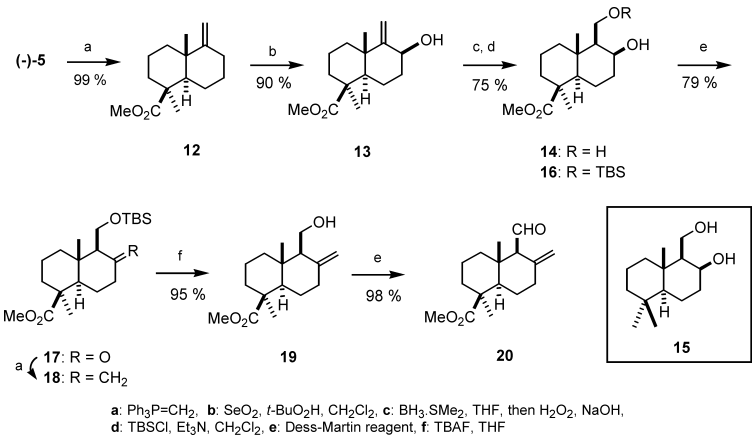
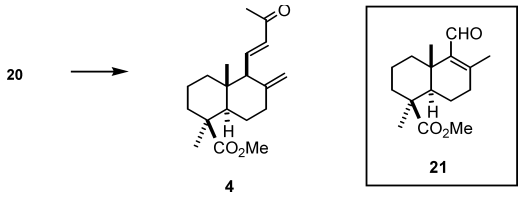


Chart 3. Synthesis of the Key Intermediate (**20**) from (−)-**5**

Table 2. Introduction of a Propane Unit to the Aldehyde **20**



Entry	C3 unit	Base	Solvent	Temp.	Time (h)	Yield (%)
1	Acetone	LHMDS	THF	−78 °C—r.t.	18	14
2	Acetone	LHMDS	THF	−78 °C—r.t.	24	29
3	$(EtO)_2P(O)CH_2COCH_3$	*n*-BuLi	THF	0 °C—r.t.	3.5	31
4	$Ph_3P{=}CHCOCH_3$		Toluene	Reflux	18	45
5	$Ph_3P{=}CHCOCH_3$		DMF	130 °C	48	—

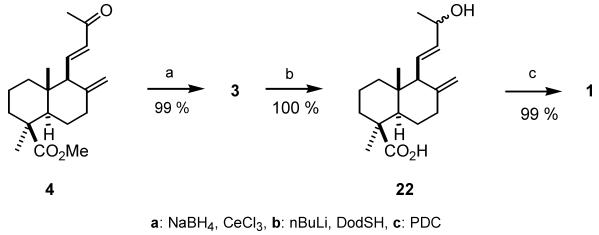


Chart 4. Synthesis of **1** from **4**

tures were also separated by a recycle HPLC (JAI LC-908) on silica gel column (Kusano Si-10) after the purification mentioned above.

Methyl 1,4a-Dimethyl-5-trifluoromethanesulfonyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (9) Potassium *tert*-butoxide (74 mg, 0.66 mmol) was added to a solution of (−)-**5** (79 mg, 0.33 mmol) in tetrahydrofuran (3 ml) at −78 °C and the mixture was stirred for 20 min. *N*-Phenylbis(trifluoromethanesulfonimide) (249 mg, 0.66 mmol) was added to the reaction mixture, which was stirred for another 20 min with keeping the temperature. After the reaction, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=5 : 1) to afford **9** (103 mg, 84%) as colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92—1.13 (1H, m), 0.96 (3H, s), 1.18—1.38 (2H, m), 1.23 (3H, s), 1.46 (2H, m), 1.75—1.87 (2H, m), 2.00—2.28 (4H, m), 3.66 (3H, s), 5.62—5.64 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.0, 18.7, 19.7, 24.9, 28.2, 34.6, 37.4, 39.6, 43.4, 51.4, 52.6, 115.5, 128.0, 156.1, 177.1. IR ($CHCl_3$) cm^{-1}: 2951, 2361, 2341, 1720, 1408, 1238, 1207, 1142. EI-MS *m/z* 370.1051 (Calcd for $C_{15}H_{21}F_3O_5S$: 370.1061). MS (70 eV) *m/z*: 370 (M^+, 2), 295 (15), 237 (28), 205 (18), 177 (30), 161 (100), 145 (38), 105 (46), 91 (31), 67 (23), 55 (42).

Methyl 1,4a-Dimethyl-5-(3-oxobutenyl)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-1-carboxylate (10) Methyl vinyl ketone (199 μl, 2.45 mmol), bis(triphenylphosphine)palladium(II) chloride (17 mg, 0.024 mmol), and triethylamine (569 μl, 4.07 mmol) were added to a solution of **9** (431 mg, 1.16 mmol) in *N*,*N*-dimethylformamide (5 ml) and the mixture was stirred for 3 h at 75 °C. After the reaction, the organic solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (hexane : ethyl acetate=6 : 1) to afford **10** (277 mg, 82%) as colorless amorphous. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (3H, s), 1.00—1.40 (4H, m), 1.23 (3H, s), 1.52—1.58 (2H, m), 1.74—2.34 (5H, m), 2.25 (3H, s), 3.66 (3H, s), 6.04—6.06 (1H, m), 6.28 (1H, d, J=15.8 Hz), 7.17 (1H, d, J=15.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.4, 19.3, 20.0, 27.4, 28.1, 28.4, 37.3, 37.6, 38.2, 43.8, 51.3, 52.8, 127.5, 128.9, 143.6, 144.5, 177.7, 198.5. IR ($CHCl_3$) cm^{-1}: 3009, 2951, 1720, 1666, 1593, 1465, 1362, 1258, 1238, 1177, 1153. EI-MS *m/z*: 290.1880 (Calcd for $C_{18}H_{26}O_3$: 290.1882). MS (70 eV) *m/z*: 290 (M^+, 2), 275 (9), 231 (11), 215 (23), 187 (21), 159 (22), 121 (100), 108 (82), 91 (29), 55 (21).

Methyl 4,7a-Dimethyl-7b-(3-oxobutenyl)-decahydro-1-oxa-cyclopropa[*a*]naphthalene-4-carboxylate (11) A saturated aqueous solution of sodium bicarbonate (1.5 ml) was added to a solution of **10** (28 mg, 0.096 mmol) and *m*-chloroperbenzoic acid (80%) (25 mg, 0.12 mmol) in dichloromethane (2 ml) and the biphasic mixture was stirred vigorously for 2 h at 0 °C. After the reaction, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=8 : 1) to afford two diastereomers of **11** (**11a**, **b**) (19 mg, 66%) as colorless crystals, which were separated by HPLC on silica gel column.

11a: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, s), 1.00—1.14 (2H, m), 1.17 (3H, s), 1.47 (6H, m), 1.84—1.97 (1H, m), 2.17—2.28 (2H, m), 2.24 (3H, s), 2.97 (1H, s), 3.63 (3H, s), 6.28 (1H, d, J=15.4 Hz), 7.12 (1H, d, J=15.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.8, 17.7, 19.9, 28.3, 28.4, 28.7, 37.9, 38.2, 39.0, 44.0, 51.6, 53.6, 64.8, 66.4, 129.3, 144.4, 177.7,

198.3. IR ($CHCl_3$) cm^{-1}: 3036, 3009, 2980, 2949, 2853, 1719, 1676, 1624, 1468, 1437, 1360, 1290, 1238, 1155. EI-MS *m/z*: 306.1826 (Calcd for $C_{18}H_{26}O_4$: 306.1831). MS (70 eV) *m/z*: 306 (M^+, 2), 288 (2), 263 (3), 213 (2), 181 (4), 175 (8), 148 (100), 135 (60), 121(60), 109 (27), 105 (30), 91 (35), 67 (27), 55 (51).

11b: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00—1.10 (1H, m), 1.04 (3H, s), 1.17 (3H, s), 1.37—1.56 (3H, m), 1.60—1.96 (5H, m), 2.02—2.11 (1H, m), 2.13—2.21 (1H, m), 2.24 (3H, s), 2.93 (1H, d, J=4.8 Hz), 3.66 (3H, s), 6.29 (1H, d, J=15.4 Hz), 7.12 (1H, d, J=15.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.2, 18.2, 24.1, 28.3, 28.8, 35.9, 36.9, 37.5, 43.4, 45.6, 51.3, 63.8, 67.2, 130.0, 143.2, 177.8, 197.9. IR ($CHCl_3$) cm^{-1}: 3036, 3007, 2980, 2951, 2880, 1719, 1674, 1626, 1565, 1435, 1360, 1263, 1240, 1150. EI-MS *m/z*: 306.1828 (Calcd for $C_{18}H_{26}O_4$: 306.1831). MS (70 eV) *m/z*: 306 (M^+, 2), 288 (2), 263 (3), 213 (3), 175 (8), 148 (100), 135 (57), 121(47), 109 (25), 105 (31), 91 (34), 55 (39).

(−)-Methyl 1,4a-Dimethyl-5-methylenedecahydronaphthalene-1-carboxylate (12) Potassium *tert*-butoxide (814 mg, 7.25 mmol) was added to a suspension of methyltriphenylphosphonium bromide (2.59 g, 7.25 mmol) in terahydrofuran (25 ml) and the mixture was stirred for 5 min at room temperature. And then, (−)-**5** (576 mg, 2.42 mmol) was added to the mixture, which was stirred for 30 min at 60 °C. After the reaction, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was successively washed with a saturated aqueous solution of sodium chloride and distilled water, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=8 : 1) to afford **12** (564 mg, 99%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, s), 1.04 (1H, dt, J=13.5, 4.0 Hz), 1.15—1.27 (2H, m), 1.16 (3H, s), 1.46—1.60 (2H, m), 1.66—1.71 (1H, m), 1.85—1.96 (4H, m), 2.09—2.21 (2H, m), 2.26—2.34 (1H, m), 3.66 (3H, s), 4.57 (1H, m), 4.58 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.5, 19.6, 23.9, 28.8, 29.1, 33.5, 37.5, 38.3, 40.2, 44.4, 51.2, 55.2, 104.3, 159.2, 177.9. IR ($CHCl_3$) cm^{-1}: 2939, 2854, 1717, 1632, 1447, 1337. EI-MS *m/z*: 238.1776 (Calcd for $C_{15}H_{24}O_2$: 236.1775). MS (70 eV) *m/z*: 236 (M^+, 99), 204 (37), 176 (95), 161 (55), 121 (100), 107 (97), 95 (96), 81 (53), 67 (53), 55 (52). $[\alpha]_D^{25}=-51.5°$ (c=0.56, $CHCl_3$). *Anal*. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.96; H, 10.27.

(−)-Methyl 6-Hydroxy-1,4a-dimethyl-5-methylenedecahydronaphthalene-1-carboxylate (13) Selenium oxide (139 mg, 1.26 mmol) and *tert*-butyl hydroperoxide (70 wt% in water, 700 μl, 5.03 mmol) were added to a solution of **12** (634 mg, 2.51 mmol) in dichloromethane (15 ml) and the mixture was stirred for 24 h at room temperature. After the reaction, the reaction mixture was poured into a saturated aqueous solution of sodium thiosulfate and extracted with chloroform. The organic layer was dried over magnesium sulfate and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=10 : 1→2 : 1) to afford **12** (259 mg, 44% rec.) and **13** [326 mg, 51% (conversion yield: 91%)] as colorless needles. mp. 103—104 °C (hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02 (1H, dt, J=13.5, 4.1 Hz), 1.08 (3H, s), 1.16—1.21 (1H, m), 1.19 (3H, s), 1.40—1.58 (4H, m), 1.76—1.82 (2H, m), 1.88—2.06 (2H, m), 2.18—2.28 (2H, m), 3.67 (3H, s), 4.35 (1H, t, J=2.9 Hz), 4.86 (1H, d, J=1.1 Hz), 4.91 (1H, d, J=1.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.3, 19.1, 20.5, 28.7, 34.8, 38.1, 38.2, 39.8, 44.2, 51.3, 55.0, 74.8, 111.1, 159.3, 177.9. IR ($CHCl_3$) cm^{-1}: 3009, 2991, 2939, 2856, 1717, 1466, 1437, 1236. EI-MS *m/z*: 252.1725 (Calcd for $C_{15}H_{24}O_3$: 252.1726). MS (70 eV) *m/z*: 252 (M^+, 6), 237 (12), 192 (13), 175 (95), 159 (27), 145 (19), 123 (100), 109 (48), 105 (63), 91 (54), 67 (46), 55 (74). $[\alpha]_D^{25}=-1.30°$ (c=0.61, $CHCl_3$). *Anal*. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.27; H, 9.79.

(+)-Methyl 6-Hydroxy-5-hydroxymethyl-1,4a-dimethyldecahydronaphthalene-1-carboxylate (14) A borane dimethyl sulfide complex (2.0 M solution in tetrahydrofuran, 436 μl, 0.87 mmol) was added to a solution of **13** (220 mg, 0.87 mmol) in tetrahydrofuran (5 ml) and the mixture was stirred for 2 h at room temperature. And then, hydrogen peroxide (30 wt% solution in water, 1 ml) and an aqueous solution of sodium hydroxide (1.0 M, 1 ml) were added to the reaction mixture, which was stirred for 15 min. After the reaction, the mixture was poured into saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=1 : 1) to afford **13** (16 mg, 7% rec.) and **14** [199 mg, 85% (conversion yield: 91%)] as colorless crystals. mp. 116—118 °C (hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, s), 1.03 (1H, dt, J=13.4, 4.0 Hz), 1.11—1.20 (2H, m), 1.20 (3H, s), 1.41—1.57 (2H, m), 1.75—2.13 (7H, m), 2.16—2.20 (1H, m), 3.65 (3H, s), 3.83—3.87 (1H, m), 3.95—4.00 (1H, m), 4.27 (1H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.3, 19.1, 20.5, 28.7, 34.8, 38.1, 38.2, 39.8, 44.2, 51.3, 55.0, 74.8, 111.1, 159.3, 177.9. IR ($CHCl_3$) cm^{-1}: 3618, 3487, 3435, 3028, 2999, 2951, 2937, 1717, 1468, 1450, 1435. EI-MS *m/z*: 270.1831 (Calcd for $C_{15}H_{26}O_4$: 270.1829). MS (70 eV) *m/z*: 270 (M^+, 1), 252 (5), 238 (18), 222 (14), 193 (20), 175 (37), 161 (24), 147 (20), 121 (100), 109 (58), 93 (55), 81 (76), 67 (57), 55 (83). $[\alpha]_D^{25}=+35.6°$ (c=2.15, $CHCl_3$). *Anal*. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.61; H, 9.60.

(+)-Methyl 5-(*tert*-Butyldimethylsilyloxymethyl)-6-hydroxy-1,4a-dimethyldecahydronaphthalene-1-carboxylate (16) *tert*-Butyldimethylsilyl chloride (100 mg, 0.64 mmol) and triethylamine (167 ml, 1.20 mmol) were added to a solution of **14** (108 mg, 0.40 mmol) in dichloromethane (5 ml) and the mixture was stirred for 18 h at room temperature. After the reaction, the mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=5 : 1) to afford **16** (135 mg, 88%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.076 (3H, s), 0.079 (3H, s), 0.89 (9H, s), 0.94—1.12 (3H, m), 0.99 (3H, s), 1.19 (3H, s), 1.23—1.35 (2H, m), 1.40—1.48 (2H, m), 1.73—2.00 (4H, m), 2.06—2.20 (2H, m), 3.64 (3H, s), 3.80 (1H, dd, J=10.4, 4.2 Hz), 4.03 (1H, dd, J=10.4, 4.9 Hz), 4.22—4.23 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −5.7, −5.6, 15.6, 18.0, 18.6, 18.8, 25.8 (3), 28.7, 34.8, 37.8, 38.2, 40.0, 43.6, 51.2, 54.1, 56.7, 62.8, 69.8, 178.0. IR ($CHCl_3$) cm^{-1}: 3672, 3468, 3024, 3001, 2953, 2932, 1715, 1472, 1450, 1436. CI-MS *m/z*: 385.2774 (Calcd for $C_{21}H_{41}O_4Si$: 385.2775). MS *m/z*: 385 (M^++H, 3), 367 (8), 327 (3), 251 (4), 235 (100), 175 (85), 119 (8), 105 (11), 75 (17), 57 (72). $[\alpha]_D^{25}=+43.1°$ (c=0.74, $CHCl_3$).

(−)-Methyl 5-(*tert*-Butyldimethylsilyloxymethyl)-6-oxo-1,4a-dimethyldecahydronaphthalene-1-carboxylate (17) Dess–Martin periodinane (1.69 g, 3.97 mmol) was added to a solution of **16** (953 mg, 2.48 mmol) in dichloromethane (35 ml) at 0 °C and the mixture was stirred for 5 h at room temperature. After the reaction, the reaction mixture was poured into a saturated aqueous solution of sodium thiosulfate and extracted with diethyl ether. The organic layer was successively washed with a saturated aqueous solution of sodium bicarbonate and sodium chloride, dried over magnesium sulfate and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=5 : 1) to afford **17** (915 mg, 97%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.034 (3H, s), 0.054 (3H, s), 0.55 (3H, s), 0.86 (9H, s), 1.12 (1H, dt, J=13.2, 3.9 Hz), 1.27 (3H, s), 1.34—1.56 (2H, m), 1.67—1.90 (3H, m), 2.09—2.42 (6H, m), 3.58 (1H, dd, J=10.4, 4.0 Hz), 3.63 (3H, s), 4.04 (1H, dd, J=10.4, 6.6 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: −5.4, −5.2, 13.8, 18.3, 19.7, 25.8, 26.0 (3), 28.9, 38.1, 39.7, 43.0, 44.3, 51.4, 54.9, 57.1, 65.5, 177.0, 210.3. IR ($CHCl_3$) cm^{-1}: 3690, 3030, 2993, 2952, 2931, 1715, 1653, 1603, 1472, 1435. EI-MS *m/z*: 382.2539 (Calcd for $C_{21}H_{38}O_4Si$: 382.2540). MS (70 eV) *m/z*: 382 (M^+, 1), 325 (32), 293 (7), 265 (9), 233 (7), 213 (7), 181 (9), 173 (53), 157 (100), 121 (92), 105 (20), 91 (26), 75 (55), 55 (21). $[\alpha]_D^{25}=-15.8°$ (c=0.53, $CHCl_3$).

(+)-Methyl 5-(*tert*-Butyldimethylsilyloxymethyl)-6-methylene-1,4a-dimethyldecahydronaphthalene-1-carboxylate (18) *n*-Butyllitium (2.60 M solution in *n*-hexane, 1.9 ml, 4.93 mmol) was added to a suspension of methyltriphenylphosphonium bromide (2.11 g, 5.92 mmol) in tetrahydrofuran (30 ml) at 0 °C and the mixture was stirred for 30 min at room temperature. And then, a solution of **17** (755 mg, 1.97 mmol) in tetrahydrofuran (10 ml) was added to the reaction mixture, which was stirred for another 5 h. After the reaction, the mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : diethyl ether=50 : 1) to afford **18** (612 mg, 82%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.034 (6H, s), 0.57 (3H, s), 0.87 (9H, s), 1.06 (1H, dt, J=13.3, 4.2 Hz), 1.18 (3H, s), 1.21—1.34 (2H, m), 1.48—1.54 (1H, m), 1.71—1.86 (4H, m), 1.93—2.00 (2H, m), 2.14—2.20 (1H, m), 2.36—2.41 (1H, m), 3.62 (3H, s), 3.75 (1H, dd, J=10.4, 7.4 Hz), 3.84 (1H, dd, J=10.4, 3.8 Hz), 4.64 (1H, m), 4.85 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −5.4, −5.3, 13.5, 18.2, 19.9, 25.8, 25.9 (3), 28.9, 38.2, 38.4, 39.4, 39.5, 44.1, 51.2, 56.2, 57.6, 59.8, 107.2, 147.2, 177.8. IR ($CHCl_3$) cm^{-1}: 3690, 3036, 2991, 2932, 1717, 1645, 1603, 1472, 1450. EI-MS *m/z*: 380.2747 (Calcd for $C_{22}H_{40}O_3Si$: 380.2738). MS (20 eV) *m/z*: 380 (M^+, 1), 365 (1), 323 (100), 291 (7), 281 (4), 263 (7), 207 (11), 189 (48), 159 (12), 147 (10), 133 (8), 105 (7), 75 (16). $[\alpha]_D^{25}=+30.3°$

(c=0.85, $CHCl_3$).

(+)-Methyl 5-Hydroxymethyl-6-methylene-1,4a-dimethyldecahydronaphthalene-1-carboxylate (19) Tetra-*n*-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 2.3 ml, 2.26 mmol) was added to a solution of **18** (574 mg, 1.51 mmol) in tetrahydrofuran (20 ml) and the mixture was stirred for 14 h at room temperature. After the reaction, the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : diethyl ether=3 : 1) to afford **19** (382 mg, 95%) as colorless needles. mp. 93—94 °C (hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.54 (3H, s), 1.07 (1H, dt, J=13.4, 4.0 Hz), 1.19 (3H, s), 1.23—1.33 (1H, m), 1.35—1.36 (1H, m), 1.42—1.43 (1H, m), 1.50—1.56 (1H, m), 1.73—1.89 (3H, m), 1.93—2.00 (3H, m), 2.16—2.21 (1H, m), 2.43—2.48 (1H, m), 3.62 (3H, s), 3.73—3.88 (2H, m), 4.65 (1H, d, J=1.1 Hz), 4.97 (1H, dd, J=2.6, 1.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 19.8, 26.0, 28.8, 38.1, 38.3, 39.1, 39.5, 44.1, 51.2, 56.0, 58.5, 58.7, 106.3, 147.4, 177.6. IR ($CHCl_3$) cm^{-1}: 3692, 3593, 3036, 2993, 2949, 2907, 1717, 1643, 1603, 1468, 1450. EI-MS m/z: 266.1887 (Calcd for $C_{16}H_{26}O_3$: 266.1882). MS (70 eV) m/z: 266 (M^+, 5), 248 (2), 206 (4), 188 (15), 173 (8), 147 (7), 121 (100), 107 (25), 93 (21), 81 (25), 69 (22), 55 (36). $[\alpha]_D^{25}$=+40.5° (c=0.64, $CHCl_3$).

(−)-Methyl 5-Formylmethyl-6-methylene-1,4a-dimethyldecahydronaphthalene-1-carboxylate (20) Dess–Martin periodinane (167 mg, 0.39 mmol) was added to a solution of **19** (35 mg, 0.13 mmol) in dichloromethane (5 ml) at 0 °C and the mixture was stirred for 4 h at room temperature. After the reaction, the reaction mixture was poured into a saturated aqueous solution of sodium thiosulfate and extracted with diethyl ether. The organic layer was successively washed with a saturated aqueous solution of sodium bicarbonate and sodium chloride, dried over magnesium sulfate and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=5 : 1) to afford **20** (34 mg, 98%) as colorless needles. mp. 102—104 °C (hexane/ethyl acetate). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, s), 1.08 (1H, dt, J=13.4, 4.0 Hz), 1.20 (3H, s), 1.20—1.30 (2H, m), 1.47—1.64 (2H, m), 1.80—1.94 (2H, m), 1.97—2.07 (2H, m), 2.19—2.24 (1H, m), 2.42—2.47 (2H, m), 3.66 (3H, s), 4.51 (1H, m), 4.94 (1H, m), 9.87 (1H, d, J=4.9 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.3, 19.4, 24.8, 28.7, 37.3, 38.0, 39.3, 40.0, 43.9, 51.4, 55.0, 67.1, 109.3, 144.6, 177.4, 205.1. IR ($CHCl_3$) cm^{-1}: 3690, 3035, 3008.7, 2993, 2910, 1717, 1645, 1602, 1466, 1450, 1441. EI-MS m/z: 264.1725 (Calcd for $C_{16}H_{24}O_3$: 264.1732). MS (70 eV) m/z: 264 (M^+, 25), 249 (5), 232 (9), 220 (8), 204 (37), 189 (19), 181 (10), 161 (16), 149 (20)135 (17), 121 (100), 109 (30), 95 (25), 81 (22), 67 (15), 55 (21). $[\alpha]_D^{25}$=−34.3° (c=0.50, $CHCl_3$). *Anal*. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.72; H, 9.03.

(−)-Methyl 13-Oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oate (4) 1-Triphenylphosphoranylidene-2-propanone (63 mg, 0.20 mmol) was added to a solution of **20** (17 mg, 0.065 mmol) in toluene (2 ml) and the mixture was stirred for 24 h at refluxing temperature. After the reaction, the organic solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (hexane : ethyl acetate=5 : 1) to afford **4** (9 mg, 45%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.71 (3H, s), 1.02—1.14 (2H, m), 1.21 (3H, s), 1.32 (1H, dd, J=12.5, 2.8 Hz), 1.42—1.50 (2H, m), 1.73—1.89 (2H, m), 1.97—2.07 (2H, m), 2.17—2.23 (1H, m), 2.27 (3H, s), 2.43—2.49 (2H, m), 3.65 (3H, s), 4.42 (1H, dd, J=3.0, 1.5 Hz), 4.81 (1H, dd, J=3.0, 1.5 Hz), 6.07 (1H, d, J=15.9 Hz), 6.85 (1H, dd, J=15.9, 10.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.5, 19.6, 25.0, 27.3, 28.7, 37.1, 38.2, 39.7, 40.9, 44.2, 51.3, 55.4, 60.0, 108.3, 133.7, 146.0, 148.1, 177.5, 198.0. IR ($CHCl_3$) cm^{-1}: 3690, 3038, 3001, 1719, 1670, 1645, 1624, 1603, 1545, 1533, 1466, 1434. EI-MS m/z: 304.2038 (Calcd for $C_{19}H_{28}O_3$: 304.2043). MS (70 eV) m/z: 304 (M^+, 4), 289 (2), 261 (3), 244 (6), 201 (10), 161 (13), 137 (31), 121 (100), 109 (52), 93 (39), 81 (99), 77 (28), 55 (53). $[\alpha]_D^{25}$=−1.61° (c=0.16, $CHCl_3$).

Methyl 13-Hydroxy-15,16-dinorlabda-8(17),11*E*-dien-19-oate (3) Sodium borohydride (2 mg, 0.056 mmol) was added to a solution of cerium chloride (14 mg, 0.056 mmol) in methanol (1 ml), to which **4** (6 mg, 0.018 mmol) was added and the mixture was stirred for 1 h at 0 °C. After the reaction, the mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=3 : 1) to afford a mixture of diastereomers of **3** (6 mg, 99%) as colorless amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.60 (1.5H, s), 0.62 (1.5H, s), 1.01—1.09 (2H, m), 1.20 (3H, s), 1.27 (1.5H, d, J=6.4 Hz), 1.28 (1.5H, d, J=6.4 Hz), 1.31—1.32 (1H, m), 1.44—1.58 (3H, m), 1.74—1.85 (2H, m), 1.93—2.04 (2H, m), 2.14—2.19 (1H, m), 2.28—2.30 (1H, m), 2.41—2.46 (1H, m), 3.63 (1.5H, s), 3.63 (1.5H, s), 4.33 (1H, quint., J=6.4 Hz), 4.46 (0.5H, d, J=1.7 Hz), 4.51 (0.5H, d, J=1.1 Hz), 4.75—4.77 (1H, m), 5.51 (0.5H, dd, J=15.4, 6.5 Hz), 5.52 (0.5H, dd, J=15.4, 6.5 Hz), 5.68 (1H, dd, J=15.4, 9.7 Hz). IR ($CHCl_3$) cm^{-1}: 2947, 2850, 1717, 1450, 1381, 1246, 1157. EI-MS m/z: 306.2196 (Calcd for $C_{19}H_{30}O_3$: 306.2195). MS (70 eV) m/z: 306 (M^+, 1), 288 (6), 246 (8), 213(9), 188 (13), 159 (15), 121 (100), 105 (23), 93 (32), 79 (22), 67 (15), 55 (20).

13-Hydroxy-15,16-dinorlabda-8(17),11*E*-dien-19-oic Acid (22) *n*-Butyllithium (2.46 M solution in *n*-hexane, 104 μl, 0.28 mmol) was added to a solution of 1-dodecanethiol (66 μl, 0.28 mmol) in hexamethylphosphoramide and the mixture was stirred for 30 min at room temperature. The allyl alcohol **3** (9 mg, 0.028 mmol) was added to the reaction mixture, which was stirred for 30 min. After the reaction, the mixture was poured into a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with distilled water, dried over magnesium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=4 : 1) to afford a mixture of diastereomers of **22** (8 mg, quantitative) as colorless amorphous. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.70 (1.5H, s), 0.71 (1.5H, s), 1.02—1.10 (2H, m), 1.24—1.35 (2H, m), 1.26 (3H, s), 1.28 (1.5H, d, J=6.5 Hz), 1.28 (1.5H, d, J=6.5 Hz), 1.45—1.59 (2H, m), 1.76—2.04 (4H, m), 2.15—2.19 (1H, m), 2.29—2.31 (1H, m), 2.43—2.47 (1H, m), 4.34 (0.5H, t of quint., J=6.4, 1.1 Hz), 4.46 (0.5H, d, J=1.1 Hz), 4.51 (0.5H, d, J=1.1 Hz), 4.75—4.77 (1H, m), 5.52 (0.5H, dd, J=15.4, 6.5 Hz), 5.52 (0.5H, dd, J=15.4, 6.5 Hz), 5.68 (1H, dd, J=15.4, 9.7 Hz). IR ($CHCl_3$) cm^{-1}: 3028, 2936, 2851, 1693, 1230. FAB-MS m/z: 315.1942 (Calcd for $C_{18}H_{28}O_3Na$: 315.1936). MS (FAB) m/z: 315 ($M+Na^+$, 100).

(−)-13-Oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic Acid (1) Pyridinium dichromate (26 mg, 0.07 mmol) and Celite® (26 mg) were added to a solution of **22** (8 mg, mmol) in *N*,*N*-dimethylformamide (1 ml) and the mixture was stirred for 7 h at room temperature. After the reaction, the organic solvent was removed *in vacuo* and purified by silica gel column chromatography (hexane : ethyl acetate=3 : 1) to afford **1** (8 mg, 99%) as colorless crystals. The ^{1}H-NMR spectrum of our synthesized **1** coincided with that of naturally occurring **1**.[6)]

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References

1) Tanaka R., Ohtsu H., Iwamoto M., Minami T., Tokuda H., Nishino H., Matsunaga S., Yoshitake A., *Cancer Lett.*, **161**, 165—170 (2000).
2) Narisawa T., Fukaura Y., Hasebe M., Noura S., Ohshima S., Sakamoto H., Inakuma T., Takayasu J., Nishino H., *J. Cancer Res.*, **89**, 1003—1008 (1988).
3) Inoue M., Hasegawa S., Hirose Y., *Phytochemistry*, **24**, 1602—1604 (1985).
4) Fang J.-M., Chen W.-C., Wang B.-W., Cheng Y.-S., *Phytochemistry*, **41**, 1361—1365 (1996).
5) Kuo Y.-H., Cheng W.-C., *J. Chin. Chem. Soc.*, **46**, 819—824 (1999).
6) Katoh T., Tanaka R., Takeo M., Nishide K., Node M., *Chem. Pharm. Bull.*, **50**, 1625—1629 (2002).
7) Katoh T., Mizumoto S., Fudesaka M,, Takeo M., Kajimoto T., Node M., *Tetrahedron: Asymmetry*, **17**,1655—1662 (2006).
8) Scott W., Sward P. K., Stoessel S. J., Stille J. K., *J. Org. Chem.*, **50**, 2302—2308 (1985).
9) Umbreit M. A., Sharpless K. B., *J. Am. Chem. Soc.*, **99**, 5526—5528 (1977).
10) Toshima H., Okikawa H., Toyomatsu T., Sassa T., *Tetrahedron*, **56**, 8443—8450 (2000).
11) Gemal A., Luche J.-L., *J. Am. Chem. Soc.*, **103**, 5454—5459 (1981).
12) Node M., Kumar K., Nishide K., Ohsugi S., Miyamoto T., *Tetrahedron Lett.*, **42**, 9207—9210 (2001).
13) Nishide K., Miyamoto T., Kumar K., Ohsugi S., Node M., *Tetrahedron Lett.*, **43**, 8569—8573 (2002).