A New Synthesis of a Potent Cancer Chemopreventive Agent, 13-Oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic Acid from *trans*-Communic Acid

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The first synthesis of a labdane diterpenoid, (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid [(−)-1a], isolated from the stem bark of *Thuja standishii* (GORD.) CARR., from the major component *trans*-communic acid (3a) is described.

Key words *trans*-communic acid; *Thuja standishii*; chemical conversion; (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid

A labdane-type diterpenoid, (−)-13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid [(−)-**1a**], has been revealed by Tanaka *et al.* to have potent cancer chemopreventive activity, *i.e.*, the percentage of papilloma-bearing mice was reduced to 25% by the treatment of (−)-**1a**, compared with the control group (DMBA and TPA only).[1] The acid (−)-**1a**, isolated from the chopped stem bark of *Thuja standishii* (GORD.) CARR. as a minor component, along with three new and two known diterpenoids, has the most potent activity among the isolated diterpenoids for the prevention of incipient carcinogenesis. In addition to the above plant, three other sources of the labdane diterpenoid **1a** have been reported, the seeds of *Platycladus orientalis*,[2] the heartwood of *Juniperus chinensis*[3] and the pericarp of *Platycladus orientalis*.[4] Because this compound is in short supply from these natural sources, an efficient synthesis of **1a** would be highly useful in order to further evaluate the compound's potential as a cancer chemopreventive agent. A transformation of methyl *cis*-communate (**2b**) into the methyl ester **1b** has been reported,[5] however the diene isomerization required a high temperature (200 °C) in a sealed tube to proceed from the 12,14-diene to the 11,13-diene and the selective oxidative cleavage of the 13-ene in the triene *via* ozone or osmium tetroxide–sodium periodate resulted in poor yields. Among the diterpenoids in *Thuja standishii* (GORD.) CARR., the *trans*-communic acid (**3a**) was isolated as the major component (*ca.* 10 g) from the stem bark (*ca.* 5 kg), and therefore was thought to be appropriate as the starting material for the preparation of **1a**. Herein we describe the first efficient synthesis of **1a** from the major diterpenoid **3a**.

The chemical conversion of methyl *cis*-communate (**2b**) into the aldehyde **4** having been reported by Barrero *et al.*,[6] we reasoned that the aldehyde **4** would be an excellent choice as an intermediate for the synthesis of **1a** (Chart 2). Following Barrero's procedure,[6] we prepared the aldehyde **4** from *trans*-communic acid (**3a**) using the selective epoxidation with MCPBA of the 12-ene in methyl ester **3b**, which was obtained by methylation of the acid **3a** with diazomethane. Subsequent cleavage of the resultant epoxide with periodic acid gave the aldehyde **4** in high yield (3 steps, 63%).

In the transformation of the aldehyde **4** into **1a**, a two carbon elongation to the aldehyde group and appropriate functional group manipulations were required. Initially, we tried constructing the methyl vinyl ketone moiety from the aldehyde using 2-methyl-1,3-dithiane as a methyl ketone equivalent. In a model experiment, the attempted dehydration of the alcohol **5**, derived from 3-phenylpropanal and 2-methyl-1,3-dithiane, with mesyl chloride in the presence of pyridine gave the undesired 2-methylene-3-phenethyl-1,4-dithiepane (**6**), whereas in the presence of DBU as the base it afforded 2-methyl-3-phenethyl-6,7-dihydro-5*H*-1,4-dithiepine (**7**), an isomerization product of **6**, as shown in Chart 3. These results showed that the migration of sulfur to the carbocation is much faster than the desired dehydration. Attempted dehydrations from 3-hydroxy-5-phenylpenta-2-one or 1-phenyl-4,4-ethylenedioxy-3-pentanol prepared from **5** were unsuccessful.

Next, we tested the reductive detriflation of the vinyl triflate **8** derived from **5** using formic acid with the assistance

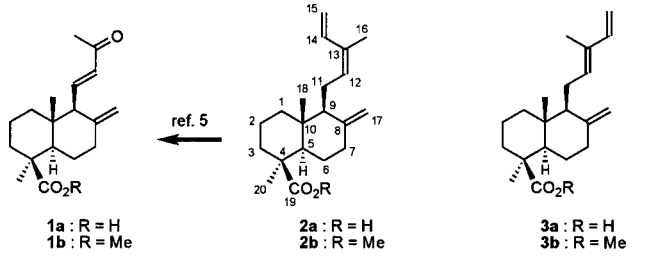

Chart 1

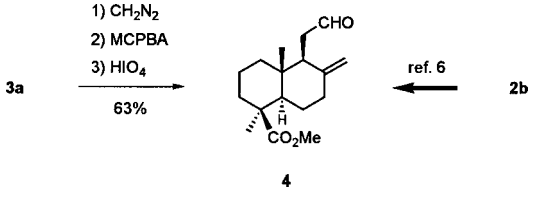

Chart 2

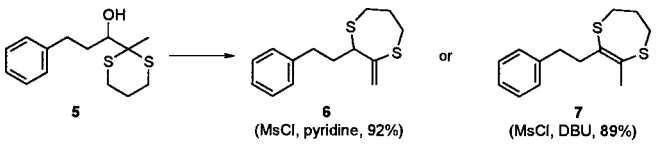

Chart 3

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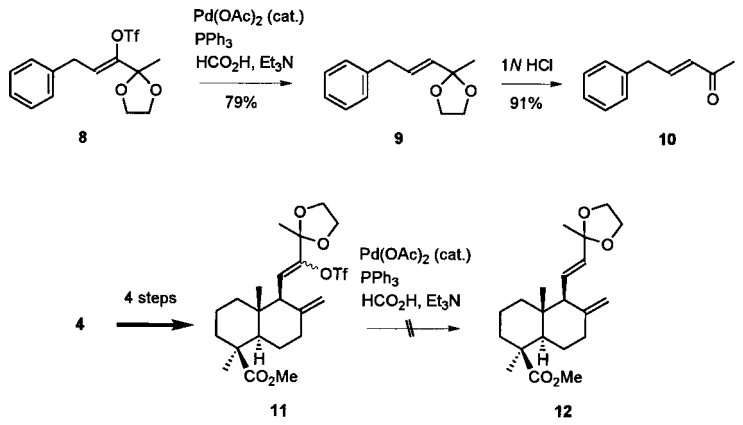

Chart 4

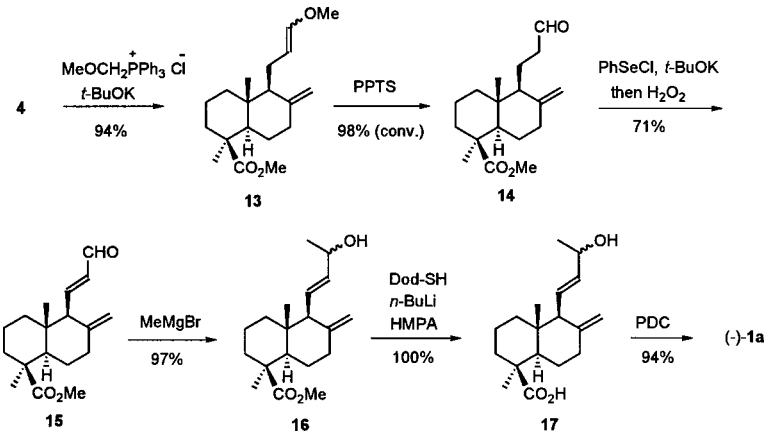

Chart 5

of a catalytic palladium(0) species,[7] as shown in Chart 4. The reaction gave the *trans*-olefin **9** in good yield. Subsequent hydrolysis afforded the methyl vinyl ketone **10**. The vinyl triflate **11** derived from **4** was subjected to the above conditions of reductive detriflation, unfortunately, no formation of the desired **12** was observed. It seems most likely that an *exo* carbon–carbon double bond at the 8,17-positions in the 13-oxo-15,16-dinorlabdane skeleton must interfere with the oxidative addition of the palladium(0) species to the carbon–oxygen bond of the vinyl triflate **11**. Therefore, we decided to undertake a stepwise synthesis of **1** through a one carbon elongation instead of a two carbon elongation, as shown in Chart 5.

The Wittig reaction of the aldehyde **4** with (methoxymethyl)triphenylphosphonium chloride gave the enol methyl ether **13** in 94% yield. The palladium(II)-promoted oxidation[8] of **13** to **15** resulted in a complex mixture, probably due to the coordination of the palladium(II) to the *exo* carbon–carbon double bond at the 8,17-positions in the 13-oxo-15,16-dinorlabdane skeleton. Hydrolysis of **13** with 1 N-hydrochloric acid or trifluoroacetic acid was likewise unsuccessful because of contamination of the by-product.[9] Hydrolysis with the milder acid pyridinium *p*-toluenesulfonate (PPTS) proved successful and furnished the aldehyde **14** in 61% yield (with 38% of the recovered **13**). α-Phenylselenylation of the aldehyde **14** followed by oxidation with hydrogen peroxide afforded the α,β-unsaturated aldehyde **15** in an acceptable yield (71%). The chemoselective attack of the Grignard reagent on the aldehyde **15** possessing a methyl ester functionality led to the allyl alcohol **16** (1 : 1 mixture) in excellent yield (97%). Nucleophilic demethylation of the methyl ester **16** to **17** was performed in quantitative yield under odorless conditions by the use of dodecanethiol (Dod-SH),[10] a technique recently developed in our laboratory as an odorless substitute for malodorous alkanethiols such as ethanethiol. Oxidation of the allyl alcohol **17** with pyridinium dichromate (PDC) furnished the desired 13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid (**1a**) in 38% overall yield from the *trans*-communic acid (**3a**). Spectroscopic data and the specific rotation of the synthesized (−)-**1a** from *trans*-communic acid (**3a**) which was isolated from *Thuja standishii* (Gord.) Carr. by Tanaka, were identical with those of the isolated authentic sample of (−)-**1a**. However, the specific rotation of **1a** isolated from the heartwood of *Juniperus chinensis* by Cheng[3] had the opposite sign. In addition, the forms of both our synthesized and isolated authentic samples of (−)-**1a** were crystalline, while those reported in the literature were oily.[2,3] Although the absolute configuration of **1a** has not been definitively elucidated, we were able to provide the first synthetic route to (−)-**1a** from the major diterpenoid *trans*-communic acid (**3a**) isolated from *Thuja standishii* (Gord.) Carr. The synthetic route to **1a** described herein is a contribution that should be useful in further evaluating the physiological activities of the com-

pound.

Experimental

General Melting points were taken with a micro hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded with a Shimadzu FT-IR 8300. ^{1}H-NMR spectra were obtained with a JEOL JNM-AL 300 and Varian Unity INOVA 400 NMR spectrometer. Signals are given in ppm using tetramethylsilane as an internal standard. MS spectra were determined on a JEOL JMS SX-102A QQ and JEOL JMS-GCmate mass spectrometer. Combustion analyses were performed by a Yanaco CHN-corder MT-3. Silica Gel 60N (KANTO CHEMICAL CO., INC.) was used for flash column chromatography. Kieselgel 60 F_{254} plates (Merck) were used for thin layer chromatography (TLC). If necessary, the compounds were purified by a recycle HPLC (LC-908, Japan Analytical Industry Co., Ltd.) on GPC columns (JAIGEL 1H and 2H) after purification on silica gel.

Materials Diethyl ether, 1,2-dimethoxyethane and tetrahydrofuran were distilled from sodium benzophenone ketyl under a nitrogen atmosphere before use. *N*,*N*-Dimethylformamide, dichloromethane, pyridine and triethylamine were distilled from calcium hydride under a nitrogen atmosphere before use.

1-Phenyl-4,4-propylenedithio-3-pentanol (5) To a tetrahydrofuran (150 ml) solution of 2-methyl-1,3-dithiane (2.32 ml, 19.4 mmol) was added *n*-butyllithium (2.46 M solution in hexane, 7.28 ml, 17.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min under a nitrogen atmosphere. 3-Phenylpropanal (1.96 ml, 14.9 mmol) was added at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, poured into water (100 ml), then extracted with ethyl acetate (200 ml×3). The combined organic layer was washed with brine (100 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=20 : 1) to give **5** (3.8 g, 95%).

5: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.37 (3H, s), 1.68—1.80 (2H, m), 1.97—2.02 (1H, m), 2.3—2.35 (1H, m), 2.43—2.77 (5H, m), 2.83—2.92 (1H, m), 2.95—3.01 (1H, m), 3.90—3.93 (1H, m), 7.17—7.32 (5H, m). IR ($CHCl_3$) cm^{-1}: 3487, 3009, 2931, 1450, 1296, 1277, 1056. Electron ionization (EI)-MS *m*/*z*: 268.0958 (Calcd for $C_{14}H_{20}OS_2$: 268.0956). MS (70 eV) *m*/*z*: 268 (M^+, 2), 250 (1), 159 (3), 146 (4), 133 (100), 91 (3), 59 (27).

2-Methylene-3-phenethyl-1,4-dithiepane (6) To a pyridine (15 ml) solution of **5** (428 mg, 1.59 mmol) was added methanesulfonyl chloride (0.35 ml, 4.78 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h under a nitrogen atmosphere, then poured into water (30 ml), and extracted with ethyl acetate (50 ml×3). The combined organic layer was washed with brine (30 ml), dried over anhydrous magnesium sulfate, filtered, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane to hexane : ethyl acetate=10 : 1) to give **6** (368 mg, 92%).

6: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.99—2.08 (2H, m), 2.14—2.26 (2H, m), 2.66—2.75 (3H, m), 2.89—3.07 (3H, m), 3.73 (1H, t, J=7.2 Hz), 5.22 (1H, s), 5.46 (1H, s), 7.16—7.31 (5H, m). IR ($CHCl_3$) cm^{-1}: 3001, 2928, 1600, 1497, 1454, 1423, 1308, 1238, 921. EI-MS *m*/*z*: 250.8450 (Calcd for $C_{14}H_{18}S_2$: 250.0850). MS (70 eV) *m*/*z*: 250 (M^+, 25), 175 (15), 159 (34), 146 (100), 106 (54), 91 (60), 85 (15), 73 (27), 65 (24), 59 (11).

2-Methyl-3-phenethyl-6,7-dihydro-5*H*-1,4-dithiepine (7) To a toluene (3 ml) solution of **5** (60 mg, 0.22 mmol) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.16 ml, 1.12 mmol) and methanesulfonyl chloride (0.05 ml, 0.67 mmol) at 0 °C. The reaction mixture was refluxed for 18 h under a nitrogen atmosphere, poured into water (10 ml), and finally extracted with ethyl acetate (20 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=5 : 1) to give **7** (50 mg, 89%).

7: Pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.77 (3H, s), 2.06—2.10 (2H, m), 2.45 (2H, t, J=6.6 Hz), 2.82 (2H, t, J=6.6 Hz), 3.19—3.23 (4H, m), 7.18—7.30 (5H, m). IR ($CHCl_3$) cm^{-1}: 2928, 1215. EI-MS *m*/*z*: 250.0855 (Calcd for $C_{14}H_{18}S_2$: 250.0850). MS (70 eV) *m*/*z*: 250 (M^+, 35), 159 (100), 125 (11), 113 (10), 91 (27), 59 (13).

1-Phenyl-4,4-ethylenedioxy-2-penten-3-yl Trifluoromethanesulfonate (8) To an ethylene glycol (150 ml) solution of **5** (3.5 g, 13.0 mmol) was added methyl iodide (40.6 ml, excess). The reaction mixture was stirred at room temperature for 3 d under a nitrogen atmosphere, poured into water (100 ml), and extracted with ethyl acetate (300 ml×3). The combined organic layer was washed with brine (100 ml), dried over anhydrous magnesium sulfate, filtered, then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=4 : 1) to give 1-phenyl-4,4-ethylenedioxy-3-pentanol (2.16 g, 75%).

1-Phenyl-4,4-ethylenedioxy-3-pentanol: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (3H, s), 1.71—1.95 (2H, m), 2.20—2.21 (1H, m), 2.62—2.73 (1H, m), 2.88—2.98 (1H, m), 3.51 (1H, dt, J=9.9, 2.9 Hz), 3.94—4.00 (4H, m), 7.15—7.30 (5H, m). IR ($CHCl_3$) cm^{-1}: 3584, 3009, 2889, 2360, 1381, 1242, 1176, 1049. EI-MS *m*/*z*: 222.1259 (Calcd for $C_{13}H_{18}O_3$: 222.1256). MS (70 eV) *m*/*z*: 222 (M^+, 1), 204 (1), 91 (16), 87 (100), 65 (5).

To a chloroform (35 ml) suspension of pyridinium chlorochromate (PCC) (2.3 g, 10.6 mmol) and Celite® (2.3 g) was added a chloroform (5 ml) solution of 1-phenyl-4,4-ethylenedioxy-3-pentanol (784 mg, 3.57 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. PCC (1.1 g, 5.3 mmol) and Celite® (1.1 g) were added and the reaction mixture was stirred at room temperature for 8 h. Again, PCC (0.8 g, 3.5 mmol) and Celite® (0.8 g) were added, the reaction mixture was stirred at room temperature for an additional 3 h, and PCC and Celite® were filtered off with silica gel (eluent; ethyl acetate). The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=5 : 1) to give 1-phenyl-4,4-ethylenedioxy-3-pentanone (669 mg, 86%).

1-Phenyl-4,4-ethylenedioxy-3-pentanone: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.42 (3H, s), 2.90 (4H, s), 3.86—4.01 (4H, m), 7.18—7.27 (5H, m). IR ($CHCl_3$) cm^{-1}: 3008, 2893, 1728, 1454, 1373, 1195, 1037. EI-MS *m*/*z*: 220.1099 (Calcd for $C_{13}H_{16}O_3$: 220.1079). MS (20 eV) *m*/*z*: 220 (M^+, 1), 87 (100), 58 (8).

To a 1,2-dimethoxyethane (30 ml) solution of 1-phenyl-4,4-ethylenedioxy-3-pentanone (684 mg, 3.11 mmol) was added potassium *tert*-butoxide (697 mg, 6.21 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 20 min under a nitrogen atmosphere. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (2.33 g, 6.21 mmol) was added at −78 °C, and the reaction mixture was stirred at −78 °C for 20 min. The reaction mixture was poured into a saturated ammonium chloride solution (20 ml), then extracted with diethyl ether (40 ml×3). The combined organic layer was washed with brine (30 ml), dried over anhydrous magnesium sulfate, filtered, and finally concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : chloroform=2 : 1) to give **8** (1.04 g, 95%).

8: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54 (3H, s), 3.53 (2H, d, J=7.7 Hz), 3.99—4.03 (4H, m), 5.96 (1H, t, J=7.7 Hz), 7.18—7.34 (5H, m). IR ($CHCl_3$) cm^{-1}: 3001, 2901, 1412, 1238, 1196, 1137, 1042, 1007, 945, 907. EI-MS *m*/*z*: 352.0599 (Calcd for $C_{14}H_{15}O_5F_3S$: 352.0592). MS (20 eV) *m*/*z*: 352 (M^+, 7), 337 (10), 219 (17), 157 (6), 115 (4), 87 (100), 73 (7).

2-Methyl-2-(3-phenylpropenyl)-1,3-dioxolane (9) To a *N*,*N*-dimethylformamide (7 ml) solution of **8** (247 mg, 0.70 mmol) was added palladium(II) acetate (3.1 mg, 0.014 mmol), triphenylphosphine (7.4 mg, 0.028 mmol), triethylamine (0.29 ml, 2.10 mmol) and formic acid (60 μl, 1.40 mmol). The resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was poured into water (10 ml), then extracted with diethyl ether (30 ml×3). The organic layer was washed with water (10 ml) and brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent; hexane : ethyl acetate=10 : 1) gave **9** (112 mg, 79%).

9: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.47 (3H, s), 3.38 (2H, d, J=6.6 Hz), 3.85—3.98 (4H, m), 5.51 (1H, d, J=15.4 Hz), 5.98 (1H, dt, J=15.4, 6.6 Hz), 7.15—7.31 (5H, m). IR ($CHCl_3$) cm^{-1}: 3009, 2990, 2889, 1497, 1450, 1337, 1196, 1042, 976, 860. EI-MS *m*/*z*: 204.1144 (Calcd for $C_{13}H_{16}O_2$: 204.1150). MS (20 eV) *m*/*z*: 204 (M^+, 1), 189 (100), 117 (13), 87 (47), 58 (17).

5-Phenylpent-3-en-2-one (10) To a tetrahydrofuran (6 ml) solution of **9** (112 mg, 0.55 mmol) was added 1 N hydrochloric acid (3 ml), which was stirred at room temperature for 9 h. The reaction mixture was poured into a saturated sodium hydrogencarbonate solution (5 ml), then extracted with diethyl ether (10 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent; hexane : ethyl acetate=8 : 1) gave **10** (88 mg, 91%).

10: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.24 (3H, s), 3.55 (2H, dd, J=7.0, 1.3 Hz), 6.09 (1H, dt, J=16.0, 1.3 Hz), 6.92 (1H, dt, J=16.0, 7.0 Hz), 7.16—7.35 (5H, m). IR ($CHCl_3$) cm^{-1}: 3009, 1670, 1362, 1258, 980. EI-MS *m*/*z*: 160.0896 (Calcd for $C_{11}H_{12}O$: 160.0888). MS (20 eV) *m*/*z*: 160 (M^+, 42), 145 (19), 127 (10), 117 (100), 58 (24).

Methyl 12-Trifluoromethanesulfonyloxy-13,13-ethylenedioxy-15,16-di-

norlabda-8(17),11-dien-19-oate (11) To a tetrahydrofuran (40 ml) solution of 2-methyl-1,3-dithiane (0.64 ml, 5.3 mmol) was added *n*-butyllithium (2.46 M solution in hexane, 1.7 ml, 4.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min under a nitrogen atmosphere. A tetrahydrofuran (3 ml) solution of **4** (1.14 g, 4.1 mmol) was added at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h., poured into water (100 ml), and then extracted with ethyl acetate (200 ml×3). The combined organic layer was washed with brine (100 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=10 : 1) to give methyl 12-hydroxy-13,13-propylenedithio-15,16-dinorlabda-8(17)-en-19-oate (1.25 g, 74%).

Methyl 12-Hydroxy-13,13-propylenedithio-15,16-dinorlabda-8(17)-en-19-oate: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.53 (3H, s), 1.19 (3H, s), 1.29—1.65 (3H, m), 1.45 (3H, s), 1.73—1.88 (4H, m), 1.94—2.10 (4H, m), 2.39—2.52 (1H, m), 2.40—2.67 (3H, m), 2.86—3.02 (2H, m), 3.62 (3H, s), 3.89—3.96 (1H, m), 4.82 (1H, s), 4.91 (1H, s).

To an ethylene glycol (5.2 ml) solution of the methyl 12-hydroxy-13,13-propylenedithio-15,16-dinorlabda-8(17)-en-19-oate (340 mg, 0.82 mmol) was added methyl iodide (2.6 ml, excess). The reaction mixture was stirred at room temperature for 6 d under nitrogen atmosphere, poured into water (20 ml), then extracted with ethyl acetate (30 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=3 : 1) to give methyl 12-hydroxy-13,13-ethylenedioxy-15,16-dinorlabda-8(17)-en-19-oate (154 mg, 51%).

Methyl 12-Hydroxy-13,13-ethylenedioxy-15,16-dinorlabda-8(17)-en-19-oate: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.51 (2H, s), 0.69 (1H, s), 1.02—2.46 (14H, m), 1.19 (2H, s), 1.29 (1H, s), 1.32 (2H, s), 1.33 (1H, s), 3.63 (2H, s), 3.65 (1H, s), 3.93—3.99 (4H, m), 4.55 (0.6H, s), 4.72 (0.3H, s), 4.857 (0.6H, s), 4.86 (0.3H, s).

To a dichloromethane (5 ml) solution of methyl 12-hydroxy-13,13-ethylenedioxy-15,16-dinorlabda-8(17)-en-19-oate (104 mg, 0.28 mmol) was added pyridinium chlorochromate (PCC) (184 mg, 0.85 mmol) and Celite® (184 mg). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 3 d. PCC and Celite® were then filtered off with silica gel (eluent; ethyl acetate). The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=5 : 1) to give the methyl 12-oxo-13,13-ethylenedioxy-15,16-dinorlabda-8(17)-en-19-oate (71 mg, 69%).

Methyl 12-Oxo-13,13-ethylenedioxy-15,16-dinorlabda-8(17)-en-19-oate: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.56 (3H, s), 1.20 (3H, s), 1.42—1.63 (3H, m), 1.46 (3H, s), 1.73—1.89 (2H, m), 1.96—2.22 (4H, m), 2.35—2.58 (3H, m), 2.81—2.95 (1H, m), 3.62 (3H, s), 3.95—4.06 (4H, m), 4.40 (1H, s). 4.73 (1H, s).

To a 1,2-dimethoxyethane (1.5 ml) solution of the ketone (45 mg, 0.12 mmol) was added potassium *tert*-butoxide (28 mg, 0.25 mmol) at −50 °C. The resulting mixture was stirred at −50 °C under a nitrogen atmosphere for 30 min. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (94 mg, 0.25 mmol) was added at −50 °C. The reaction mixture was stirred at −50 °C for 1 h, poured into a saturated ammonium chloride solution (10 ml), then extracted with ethyl acetate (20 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=8 : 1) to give **11** (58 mg, 95%).

11: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.65 (3H, s), 1.21 (3H, s), 1.28—1.61 (3H, m), 1.59 (3H, s), 1.95—2.06 (3H, m), 1.70—1.87 (3H, m), 2.18—2.22 (1H, m), 2.41—2.48 (1H, m), 2.76—2.85 (1H, m), 3.64 (3H, s), 3.99—4.05 (4H, m), 4.38 (1H, d, J=1.2 Hz), 4.78 (1H, d, J=1.5 Hz), 5.87 (1H, d, J=10.5 Hz).

Methyl 13-Oxo-14,15,16-trinorlabda-8(17)-en-19-oate [(+)-14] To a diethyl ether (20 ml) suspension of (methoxymethyl)triphenylphosphonium chloride (2.32 g, 6.78 mmol) was added potassium *tert*-butoxide (761 mg, 6.78 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 30 min under a nitrogen atmosphere. A diethyl ether (3 ml) solution of **4** (629 mg, 2.26 mmol) was added, and the reaction mixture was stirred at room temperature for 7 h. The mixture was poured into a saturated ammonium chloride solution (10 ml), then extracted with diethyl ether (20 ml×3). The combined organic layer was washed with water (20 ml) and brine (20 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=20 : 1) to give methyl 13-methoxy-14,15,16-trinorlabda-8(17),12-dien-19-oate (**13**) (652 mg, 94%) as a mixture of isomers.

13: Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.52 (1H, s), 0.53 (2H, s), 1.04—1.18 (2H, m), 1.18 (3H, s), 1.29—1.34 (1H, m), 1.52—1.56 (1H, m), 1.70—2.41 (7H, m), 3.46 (2H, s), 3.58 (1H, s), 3.61 (3H, s), 4.57 (1H, d, J=7.3 Hz), 4.85 (1H, m), 5.81—5.83 (1H, m), 6.24—6.29 (1H, m).

To an acetone (16 ml) solution of **13** (478 mg, 1.56 mmol) was added pyridinium *p*-toluenesulfonate (392 mg, 1.56 mmol). The resultant mixture was stirred at room temperature for 3 h, poured into a saturated sodium hydrogencarbonate solution (5 ml), then concentrated *in vacuo*. The aqueous layer was extracted with ethyl acetate (20 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent; hexane : ethyl acetate=10 : 1) gave **13** (181 mg, 38%) and (+)-**14** [276 mg, 61% (conversion: 98%)].

(+)-**14**: Colorless needles; mp 75—78 °C (ether); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.53 (3H, s), 1.01—1.70 (2H, m), 1.18 (3H, s), 1.29—1.33 (1H, m), 1.51—1.60 (3H, m), 1.77—2.02 (6H, m), 2.16—2.20 (1H, m), 2.31—2.43 (2H, m), 2.56—2.64 (1H, m), 3.62 (3H, s), 4.45 (1H, s), 4.87 (1H, d, J=0.9 Hz), 9.76 (1H, dd, J=1.6, 1.1 Hz). IR ($CHCl_3$) cm^{-1}: 2947, 2847, 2361, 1717, 1450, 1161, 798, 675. EI-MS *m/z*: 292.2034 (Calcd for $C_{18}H_{28}O_3$: 292.2038). MS (70 eV) *m/z* 292 (M^+, 5), 274 (28), 259 (8), 232 (14), 214 (100), 199 (70), 143 (46), 121 (74), 106 (32), 91 (55), 55 (27). $[\alpha]_D^{24}$ +58.0° (*c*=1.2, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.66; H, 9.38.

Methyl 13-Oxo-14,15,16-trinorlabda-8(17),11*E*-dien-19-oate [(+)-15] To a tetrahydrofuran (1.5 ml) solution of (+)-**14** (35 mg, 0.12 mmol) was added phenylselenyl chloride (30 mg, 0.16 mmol) and potassium *tert*-butoxide (20 mg, 0.18 mmol) at −78 °C. The resulting mixture was stirred at −78 °C under a nitrogen atmosphere for 1 h. Potassium *tert*-butoxide (20 mg, 0.18 mmol) was added at −78 °C, and the reaction mixture was stirred at −78 °C for 2 h. Additional potassium *tert*-butoxide (40 mg, 0.36 mmol) was added at −78 °C, and the mixture was stirred again at −78 °C for 2 more h. The reaction mixture was poured into a saturated ammonium chloride solution (5 ml), and extracted with ethyl acetate (10 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=10 : 1) to give a selenylated compound as a colorless oil. To a dichloromethane (1 ml) solution of the above selenylated compound was added a hydrogen peroxide solution (30% solution in water, 18 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for 20 min. The mixture was filtered off (eluent; chloroform) to remove the phenylselenenic acid. The eluate was washed with a saturated sodium hydrogencarbonate solution (5 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent; hexane : ethyl acetate=10 : 1) gave (+)-**15** (18.6 mg, 71%).

(+)-**15**: Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.73 (3H, s), 1.03—1.12 (2H, m), 1.22 (3H, s), 1.33—1.36 (1H, m), 1.43—1.50 (2H, m), 1.79—1.87 (2H, m), 1.99—2.04 (2H, m), 2.18—2.22 (1H, m), 2.46—2.51 (1H, m), 2.63 (1H, d, J=10.4 Hz), 3.65 (3H, s), 4.43 (1H, d, J=1.5 Hz), 4.84 (1H, d, J=1.5 Hz), 6.12 (1H, ddd, J=15.7, 7.9, 0.4 Hz), 6.89 (1H, dd, J=15.7, 10.4 Hz), 9.57 (1H, d, J=7.9 Hz). IR ($CHCl_3$) cm^{-1}: 2951, 2847, 1717, 1690, 1465, 729. EI-MS *m/z*: 290.1897 (Calcd for $C_{18}H_{26}O_3$ (M^+) 290.1882). MS (70 eV) *m/z*: 290 (M^+, 13), 230 (24), 213 (13), 181 (18), 161 (18), 121 (100), 107 (88), 95 (79), 81 (61), 55 (37). $[\alpha]_D^{24}$ +2.42° (*c*=0.6, $CHCl_3$).

Methyl 13-Hydroxy-15,16-dinorlabda-8(17),11*E*-dien-19-oate (16) To a tetrahydrofuran (4 ml) solution of (+)-**15** (108 mg, 0.37 mmol) was added methyl magnesium bromide (3.0 M solution in tetrahydrofuran, 0.15 ml, 0.44 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min under a nitrogen atmosphere, poured into a saturated ammonium chloride solution (5 ml), then extracted with ethyl acetate (10 ml×3). The combined organic layer was washed with brine (10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate=3 : 1) to gave **16** (109 mg, 97%) as a diasteremeric mixture (1 : 1).

16: Colorless oil; ^{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, q, J=1.7 Hz), 4.51 (0.5H, q, J=1.7 Hz), 4.75 (0.5H, q, J=1.7 Hz), 4.76 (0.5H, q, J=1.7 Hz), 5.51 (0.5H, dd, J=15.3, 6.4 Hz), 5.52 (0.5H, dd, J=15.3, 6.4 Hz), 5.67 (1H, d, J=15.3 Hz). IR ($CHCl_3$) cm^{-1}:

2497, 2850, 1717, 1450, 1381, 1246, 1157, 983, 895. 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 (82).

13-Hydroxy-15,16-dinorlabda-8(17),11*E*-dien-19-oic Acid (17) To a hexamethylphosphoramide (0.5 ml) solution of 1-dodecanethiol (76 μl, 0.32 mmol) was added *n*-butyllithium (2.46 M solution in hexane, 0.13 ml, 17.9 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min under nitrogen atmosphere. To a hexamethylphosphoramide (1 ml) solution of **16** (10 mg, 0.03 mmol) was added the above mercaptide solution at room temperature. The resulting mixture was stirred at room temperature for 2.5 h, then poured into 1 N hydrochloric acid (3 ml), and extracted with diethyl ether (5 ml×3). The combined organic layer was washed with water (5 ml) and brine (5 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent; hexane : ethyl acetate=5 : 1) gave **17** (10 mg, 100%) as a diastereomeric mixture (1 : 1).

17: Pale pink amorphous solid; ^{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 (1H, t of quint., *J*=6.5, 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 *m/z*: 315 (M^++Na, 100).

13-Oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic Acid [(−)-1a] To a *N*,*N*-dimethylformamide (4 ml) solution of **17** (118 mg, 0.40 mmol) was added pyridinium dichromate (PDC) (304 mg, 0.81 mmol) and Celite® (304 mg), which was stirred at room temperature for 7 h under a nitrogen atmosphere. PDC and Celite® were filtered off with silica gel (eluent; diethyl ether). The crude material was purified with silica gel column chromatography (hexane : ethyl acetate=3 : 1) to gave (−)-**1a** (110 mg, 94%).

(−)-**1a**: Colorless crystals; mp 155—161 °C (hexane/ethyl acetate); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.81 (3H, s), 1.04—1.14 (2H, m), 1.27 (3H, s), 1.34—1.37 (1H, m), 1.43—1.50 (2H, m), 1.77—2.07 (4H, m), 2.17—2.20 (1H, m), 2.28 (3H, s), 2.45—2.50 (2H, m), 4.43 (1H, d, *J*=1.1 Hz), 4.81 (1H, d, *J*=1.3 Hz), 6.08 (1H, d, *J*=15.8 Hz), 6.86 (1H, dd, *J*=15.8, 10.3 Hz). The proton of carboxylic acid part was not observed. ^{13}C-NMR (75 MHz, $CDCl_3$) 13.6, 19.5, 24.8, 27.3, 28.9, 37.1, 37.9, 39.9, 40.9, 44.1, 55.4, 60.0, 108.8, 133.8, 146.0, 147.9, 183.4, 198.1. IR ($CHCl_3$) cm^{-1}: 3032, 3013, 2939, 1732, 1693, 1670, 1450, 1362, 1258, 1234, 1200, 995, 895. FAB-MS *m/z*: 313.1787 (Calcd for $C_{18}H_{26}O_3Na$: 313.1780). MS (FAB) *m/z*: 313 (M^++Na, 23). $[\alpha]_D^{24}$ −10.4° (*c*=0.6, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{28}O_3$: C, 74.45; H, 9.02. Found: C, 74.64; H, 9.45.

References and Notes

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