A SHORT SYNTHESIS OF ENANTIOMERICALLY PURE (+)-ELDANOLIDE AND (-)-*cis*-WHISKY LACTONE BY SAMARIUM DIIODIDE PROMOTED FRAGMENTATION OF γ-HALO ESTERS

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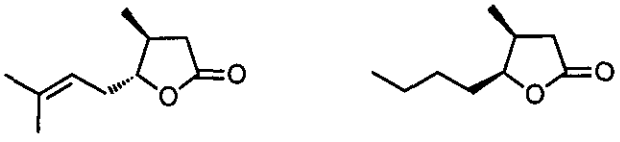
Abstract — A stereoselective synthesis of (+)-eldanolide and (-)-*cis*-whisky lactone in optically pure forms has been achieved by employing a regioselective fragmentation reaction of the γ-halo esters as a key step.

Recently we have established a novel regioselective fragmentation reaction of γ-halo esters, accessible readily from a monoterpene, carvone, and its application to the synthesis of (-)-oudemancin A.[1] As an extension of this work, we became interested in the synthesis of (+)-eldanolide (**1**),[2,3] isolated from the male wing glands of the African sugar cane borer *Eldana sacharina* (Wlk.) as a sex pheromone, and also in the synthesis of (-)-*cis*-whisky lactone (**2**),[4,5] one of the important flavors of alcoholic beverages such as whisky, wine, and brandy. It has also been known that *cis*-whisky lactone has superior scent to the *trans* isomer[6] and a mixture of *cis*- and *trans*-whisky lactones exhibits a repellent activity against mosquitos and flies.[7]

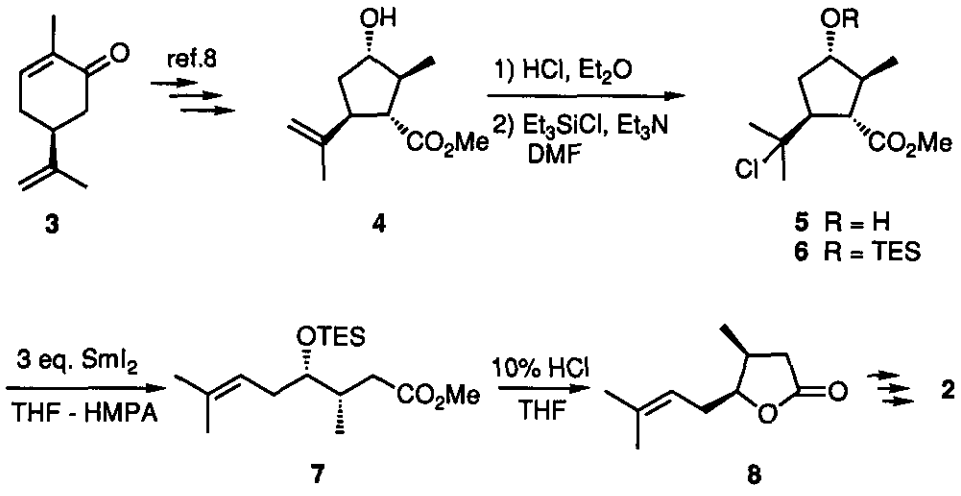


1 **2**

Figure 1

(+)-Eldanolide (**1**) and (-)-*cis*-whisky lactone (**2**) have a 3,4-disubstituted γ-lactone structure with the same configuration at the 3-position. We sought that this configuration can be transfered from (+)-carvone (**3**) by exploiting its stereochemical feature, based on our earlier work.[8] Thus (+)-carvone (**3**) was converted into the cyclopentane derivative (**4**) according to the procedure previously developed by us.[8]
Addition of hydrogen chloride to **4** in ether, and subsequent protection of the hydroxy group of the chloride (**5**) with triethylsilyl chloride afforded the silyl ether (**6**) in 99% yield from **4**. A regioselective bond cleavage reaction of the chloride (**6**) by treatment with samarium diiodide in tetrahydrofuran-HMPA (20:1, v/v)

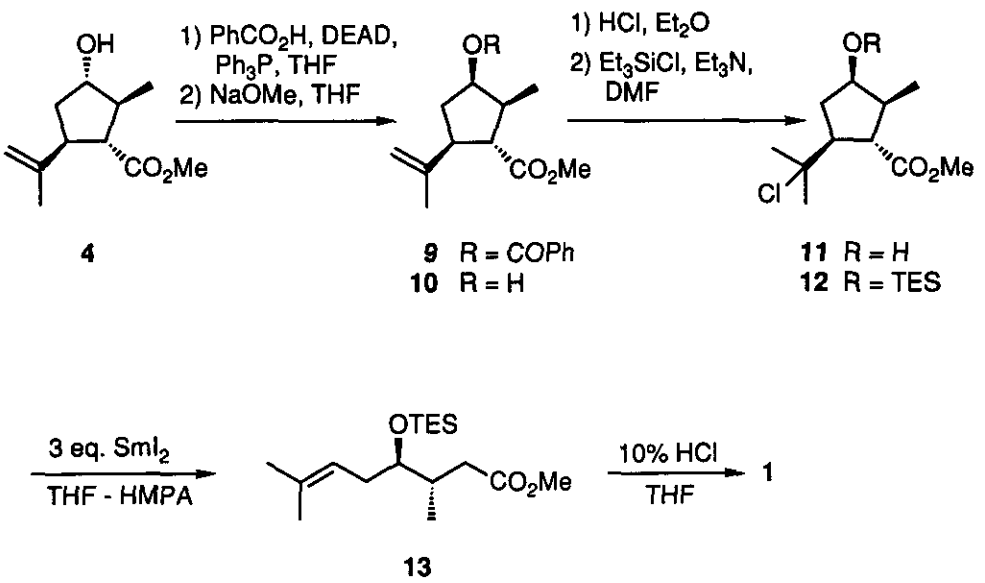
provided the acyclic ester (**7**) in 85.5% yield, which on exposure to 10% hydrochloric acid brought about deprotection of the silyl group and lactone formation simultaneously to furnish the γ-lactone (**8**) in 92% yield. The spectroscopic data including its specific optical rotation of **8**, $[\alpha]_D$ -87.5° (AcOEt), were identical with the authentic specimen.[8h] Since we have already established the conversion of **8** into (-)-*cis*-whisky lactone,[8h] this synthesis constitutes its formal synthesis.



Scheme 1

(+)-Eldanolide (**1**) is the diastereoisomer of the intermediate (**8**) for (-)-*cis*-whisky lactone with the epimeric dimethylallyl group at the 4-position, therefore inversion of the configuration of the hydroxyl group in the hydroxy ester (**4**) was required for completion of the synthesis. The Mitsunobu reaction[9] of **4** with benzoic acid in the presence of diethyl azodicarboxylate and triphenylphosphine provided the benzoate (**9**), which was hydrolyzed with sodium methoxide to give the alcohol (**10**) in quantitative yield from **4**. After addition of hydrogen chloride, followed by protection of the hydroxyl group of **11** as the triethylsilyl ether, the resulting chloride (**12**) was subjected to the regioselective fragmentation reaction with samarium diiodide providing the ester (**13**) in 66% yield. Deprotection of the silyl group of **13** with 10% hydrochloric acid afforded (+)-eldanolide (**1**) in one-step as above in 91% yield. Again the spectroscopic data including the specific optical rotation of the synthetic (+)-eldanolide, $[\alpha]_D$ +53.7° (EtOH), were identical to those of the natural material recorded in the literature.[2,8h] When this fragmentation reaction was applied to the hydroxy ester (**10**), (+)-eldanolide was also formed in one-step, although the yield (22%) was rather poor.

Thus, we developed a short synthesis of (+)-eldanolide and (-)-*cis*-whisky lactone from (+)-carvone by utilizing a regioselective fragmentation reaction as a key step, and this strategy should be applicable to the synthesis of other types of natural products.



Scheme 2

EXPERIMANTAL SECTION

Ir spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H-Nmr spectra were obtained for solution in $CDCl_3$ on a JEOL GSX-270 instrument, and chemical shifts are reported on the δ-scale from internal TMS. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

Methyl (1*S*,2*S*,3*S*,5*S*)-5-(2-Chloro-2-methylethyl)-3-hydroxy-2-methylcyclopetane-1-carboxylate (**5**) --- Hydrogen chloride gas was bubbled into a stirred solution of the ester (**4**)(200 mg, 1.0 mmol) in ether (20 ml) at 0°C for 1 h. The solution was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) afforded the chloride (**5**)(237 mg, 100%) as a colorless oil; ir ($CHCl_3$) 3300 and 1730 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (3H, d, J = 7.3 Hz, Me), 1.50 and 1.55 (each 3H, each s, 2×Me), 1.90 (1H, ddd, J = 5.5, 9.2, and 13.4 Hz, 2-H), 2.00 (1H, br s, OH), 2.05-2.15 (2H, m, 4-H_2), 2.52 (1H, t, J = 7.9 Hz, 1-H), 2.80 (1H, dt, J = 7.9 and 9.2 Hz, 5-H), 3.72 (3H, s, OMe), 3.82 (1H, q, J = 5.5 Hz, 3-H); ms *m/z* Calcd for $C_{11}H_{19}O_3Cl$ requires: 234.1021 (M^+). Found: 234.1014 (M^+). Anal. Calcd for $C_{11}H_{19}O_3Cl$: C, 56.29; H, 8.16. Found: C, 56.99; H, 8.44. $[\alpha]_D$ +28.2° (c = 2.3, $CHCl_3$).

Methyl (1*S*,2*S*,3*S*,5*S*)-3-Triethylsiloxy-5-(2-chloro-2-methylethyl)-2-methylcyclopentane-1-carboxylate (**6**) --- A solution of the chloride (**5**)(30 mg, 0.13 mmol), triethylamine (42 mg, 0.42 mmol), and triethylsilyl chloride (47 mg, 0.31 mmol) in DMF (1 ml) was stirred at ambient temperature for 3 h. The mixture was treated with water and extracted with ethyl acetate. The extract was washed with brine and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (50:1, v/v) afforded the silyl ether (**6**)(44 mg, 99%) as a colorless oil; ir ($CHCl_3$): 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.47-0.63 (6H, m, 3×$SiCH_2$) 0.87-0.99 (9H, m, 3×$SiCH_2$*Me*), 1.05 (3H, d, J = 6.7 Hz, Me), 1.46 and 1.54 (each 3H, each s, 2×Me), 1.80 (1H, ddd, J = 7.3, 10.4, and 13.4 Hz, 2-H), 1.96-2.07 (2H, m, 4-H_2), 2.41 (1H, dd, J = 8.5 and 9.8 Hz, 1-H), 2.83 (1H, ddd, J = 5.5, 8.5, and 10.3 Hz, 5-H), 3.65-3.74 (1H, m, 3-H), 3.70 (3H, s, OMe); ms *m/z* Calcd for $C_{15}H_{28}O_3ClSi$ requires: 319.1496 (M^+-29). Found: 319.1498 (M^+-29). Anal. Calcd for $C_{15}H_{28}O_3ClSi$: C, 58.51; H, 9.53. Found: C, 58.78; H, 9.79. $[\alpha]_D$ +37.5° (c=2.2, $CHCl_3$).

Methyl (3*S*,4*S*)-4-Triethylsiloxy-3,7-dimethyl-6-octanoate (**7**) --- A solution of **6** (200mg, 0.57 mmol) was treated with 3 equiv. of samarium diiodide (prepared from samarium metal and 1,2-diiodoethane) in THF-HMPA (50 ml, 20:1 v/v) at ambient temperature for 5 min. The mixture was treated with sat. $NaHCO_3$ solution, and then diluted with ether. The insoluble material was removed off by filtration and the filtrate was washed with brine and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-dichloromethane (7:1, v/v) afforded **7** (154 mg, 85.5%) as a colorless oil; ir ($CHCl_3$); 1740 cm^{-1}; nmr ($CDCl_3$) δ 0.53–0.62 (6H, m, 3×$SiCH_2$), 0.89 (3H, d, J = 6.1 Hz, Me), 0.92-0.98 (9H, m, $SiCH_2$*Me*), 1.61 and 1.70 (each 3H, each br s, 2×Me), 2.05-2.19 (4H, m, 2-H, 3-H, and 5-H_2), 2.44-2.50 (1H, m, 2-H), 3.59-3.64 (1H, m, 4-H), 3.66 (3H, s, OMe), 5.07-5.13 (1H, m, 5-H); ms *m/z* Calcd for $C_{15}H_{29}O_3Si$ requires: 285.1884 (M^+-29). Found: 285.1884 (M^+-29). $[\alpha]_D$ -0.4 °(c=1.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{29}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.70; H, 11.15.

(3*S*,4*S*)-3-Methyl-4-dimethylallyl-γ-butyrolactone (**8**) --- A solution of the silyl ether (**7**)(190 mg, 0.61 mmol) in THF (10 ml) containing 10% hydrochloric acid (5 ml) was stirred at room temperature for 0.5 h. The solution was basified with sat. $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) afforded **8** (54 mg, 92%) as a colorless oil; ir ($CHCl_3$): 1750 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (3H, d, J = 6.7 Hz, Me), 1.64 and 1.72 (each 3H, each s, 2×Me), 2.17-2.73 (5H, m, C*H*Me and 2×CH_2), 4.40-4.47 (1H, m, CHO), 5.09-5.16 (1H, m, C=CH); $[\alpha]_D$ -87.5° (c = 1.8, AcOEt).

Methyl (1*R*,2*S*,3*R*,5*S*)-3-Benzoyloxy-5-isopropenyl-2-methylcyclopentane-1-carboxylate (**9**) --- To a stirred solution of the alcohol (**4**)(35 mg, 10.18 mmol) in THF (2 ml) were added triphenylphosphine (60 mg, 0.23 mmol), benzoic acid (35 mg, 0.29 mmol), and diethyl azodicarboxylate (40 mg, 0.23 mmol) at ambient temperature and the resulting solution was further stirred for 10 min. After dilution with ethyl acetate, the organic layer was washed with 2% NaOH solution and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (12:1, v/v) afforded the benzoate (**9**)(53 mg, 100%) as a colorless oil; ir ($CHCl_3$): 1650,1720

cm^{-1}; nmr ($CDCl_3$) δ 1.09 (3H, d, J = 6.7 Hz, Me), 1.73 (3H, s, Me), 1.78 (1H, ddd, J = 2.4, 7.9, and 15.3 Hz, 4-H), 2.39-2.61 (2H, m, 2-H and 4-H), 2.76 (1H, t, J = 11.0 Hz, 1-H), 2.99 (1H, dt, J = 8.5 and 10.4 Hz, 5-H), 3.72 (3H, s, OMe), 4.74 and 4.81 (each 1H, each s, $C=CH_2$), 5.45 (1H, dt, J = 2.5 and 6.1 Hz, 3-H), 7.45-8.03 (5H, m, aromatic protons). $[\alpha]_D$ -31.7° (c = 1.6, $CHCl_3$).

Methyl (1*R*,2*S*,3*R*,5*S*)-3-Hydroxy-5-isopropenyl-2-methylcyclopentane-1-carboxylate (**10**) --- To a stirred solution of the benzoate (*9*)(100 mg, 0.33 mmol) in THF (10 ml) was added 28% methanolic solution of sodium methoxide (0.2 ml, 0.99 mmol) and the resulting mixture was further stirred for 0.5 h. The solution was acidified by addition of acetic acid (69 mg) and diluted with ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1, v/v) afforded the benzoate (**10**)(66 mg, 100%) as a colorless oil; ir ($CHCl_3$) 1730 cm^{-1}; nmr($CDCl_3$) δ 1.05 (3H, d, J = 7.3, Me), 1.55 (1H, br s, OH), 1.59 (1H, ddd, J = 2.4, 7.9, and 14.0 Hz, 2-H), 1.73 (3H, s, Me), 2.12 (1H, ddd, J = 5.5, 7.3, and 11.0 Hz, 4-H), 2.42 (1H, ddd, J = 5.5, 7.3, and 11.0 Hz, 4-H), 2.63 (1H, t, J = 11.0 Hz, 1-H), 2.88 (1H, dt, J = 7.9 and 11.0 Hz, 5-H), 3.69 (3H, s, OMe), 4.19 (1H, dt, J = 2.4 and 6.1 Hz, 3-H), 4.72 and 4.78 (each 1H, each s, $C=CH_2$); ms *m/z* Calcd for $C_{11}H_{18}O_3$ requires: 198.1255 (M^+). Found: 198.1247 (M^+). $[\alpha]_D$ -7.8 °(c=2.1, $CHCl_3$).

Methyl (1*S*,2*S*,3*R*,5*S*)-5-(2-Chloro-2-methylethyl)-4-hydroxy-5-methylcyclopetane-1-carboxylate (**11**) --- Addition of hydrogen chloride to **10** (100 mg, 0.50 mmol) was carried out as described for the preparation of **5** to give the chloride (**11**)(120 mg, 100%) as a colorless oil; ir ($CHCl_3$) 1730 and 3400 cm^{-1}; nmr ($CDCl_3$) δ 1.06 (3H, d, J = 6.7 Hz, Me), 1.52 and 1.57 (each 3H, each s, 2×Me), 1.62 (1H, br s, OH), 1.79 (1H, ddd, J = 1.2, 5.5, and 14.7 Hz, 4-H), 2.07 (1H, ddq, J = 4.3, 6.7, and 11.0 Hz, 2-H), 2.33 (1H, ddd, J = 4.3, 11.0, and 14.7 Hz, 4-H), 2.63-2.80 (2H, m, 1-H and 5-H), 3.72 (3H, s, OMe), 4.08 (1H, dt, J = 1.2 and 4.3 Hz, 3-H). $[\alpha]_D$ -4.7° (c=1.9, $CHCl_3$).

Methyl (1*S*,2*S*,3*R*,5*S*)-5-(2-Chloro-2-methylethyl)-3-triethylsiloxy-2-methylcyclopentane-1-carboxylate (**12**) -- Silylation of **11** (800 mg, 3.41 mmol) was carried out as described for the preparation of **6** to give the silyl ether (**12**)(1.18 g, 99%) as a colorless oil; ir ($CHCl_3$):1725 cm^{-1}; nmr ($CDCl_3$) δ 0.43-0.56 (6H, m, 3×$SiCH_2$), 0.83-0.96 (9H, m, 3×$SiCH_2$*Me*), 1.44 (3H, d, J = 3.1 Hz, Me), 1.62 (1H, ddd, J = 3.1, 6.7 and 9.8 Hz, 2-H), 1.95-2.15 (2H, m, 4-H_2), 2.56 (1H, dt, J = 7.3 and 9.8 Hz, 5-H), 3.63 (3H, s, OMe), 4.04 (1H, dt, J = 3.1 and 4.9 Hz, 3-H); ms *m/z* Calcd for $C_{15}H_{28}O_3Si$ requires: 321.1467 (M^+-29). Found 321.1475 (M^+-29). $[\alpha]_D$ -30.14 ° (c=2.0, $CHCl_3$).

Methyl (3*S*,4*R*)-4-Triethylsiloxy-3,7-dimethyl-6-octanoate (**13**) --- The fragmentation reaction of the chloride (**12**)(100 mg, 0.66 mmol) with samarium diiodide was carried out as described for the prepararion of **7** to provide the ester (**13**)(60 mg, 66%) as a colorless oil; ir ($CHCl_3$) 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.54-0.63 (6H, m, 3×$SiCH_2$), 0.85-0.89 (1H, m, 3-H), 0.90 (3H, d, J = 5.5 Hz, Me), 0.92-0.98 (9H, m, 3×$SiCH_2$*Me*), 1.60 and 1.70 (each 3H, each s, 2×Me), 2.04-2.51 (4H, m, 2-H_2 and 5-H_2), 3.58 (1H, dt, J = 3.7 and 6.1 Hz, 4-H), 3.66 (3H, s, OMe), 5.11-5.16 (1H, m, 6-H); ms *m/z* Calcd for $C_{15}H_{29}O_3Si$ requires: 285.1884 (M^+-29). Found

285.1882(M^+-29). $[\alpha]_D$ -10.9° (c=1.4, $CHCl_3$). Anal. Calcd for $C_{15}H_{29}O_3Si$: C, 64.92; H, 10.90. Found: C, 65.12; H, 11.19.

(+)-Eldanolide (1) --- The synthesis of (+)-eldanolide was achieved by treament of **13** (190 mg, 0.61 mmol) with 10% hydrochloric acid (2 ml) in THF (20 ml) as described for the preparation of **7** to give **1**(93 mg, 91%). The synthetic (+)-eldanolide was identical with the authentic specimen[8h] in all respects.

ACKNOWLEDGMENT

We thank Mrs. T. Ogata, Miss Y. Takahashi, and Miss N. Nagayama, Hoshi University, for microanalyses and spectral measurements.

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Received, 26th August, 1993