Synthetic Studies on Germacranolides. Synthesis of Optically Active 3-Oxygenated 13-Norheliangolides[1)]

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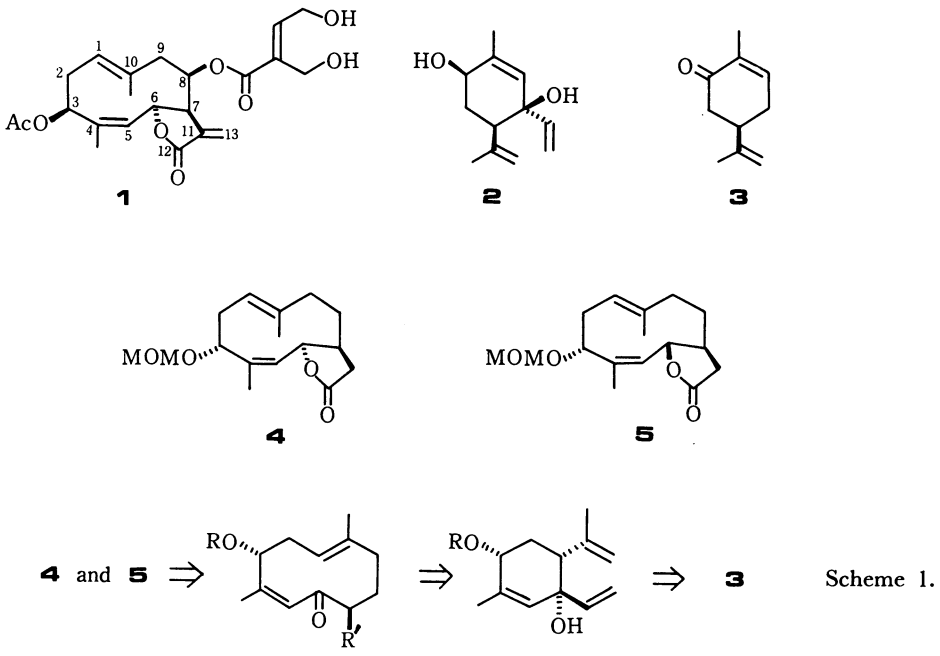
(Received June 25, 1984)

(3*R*,6*S*,7*S*,1(10)*E*,4*Z*)- and (3*R*,6*R*,7*S*,1(10)*E*,4*Z*)-3-Methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactones were synthesized from (−)-carvone, utilizing anionic oxy-Cope rearrangement to construct a ten-membered ring compound.

A group of germacrane-type sesquiterpene lactones are known as "germacranolides," and a large number of germacranolides have been isolated from various species of plants in these years.[2)] Among them, (1(10)*E*,4*E*)- and (1(10)*E*,4*Z*)-1(10),4-germacradienolides constitute a group of "germacrolides" and that of "heliangolides," respectively.[3)] Most of germacranolides possess an α-exomethylene structure on γ-lactone ring, and some of them show significant anti-tumor activities.[4)] One of us and co-workers have isolated several kinds of germacranolides from plants of the genus *Eupatorium*.[5)] Hiyodorilactone A (**1**), a heliangolide isolated from *Eupatorium sachalinense* Makino, showed a strong inhibitory activity *in vivo* against the Ehrlich ascites carcinoma.[5a)] Synthetic studies on germacrolides have already been reported by many groups.[6)] But, those on heliangolides have been reported by only two groups, one is our preliminary report[1)] and the other is the total synthesis of **1** by Still's group,[7)] although a number of (1*E*,5*Z*)-1,5-cyclodecadiene derivatives without a lactone moiety were synthesized by the route involving oxy-Cope rearrangement,[8)] pyrolysis,[9)] or cyclization.[10)] We chose optically active C(3) oxygenated 13-norheliangolides as synthetic targets, because most of natural heliangolides have an oxygen function at C(3) position[11)] and the introduction of an α-methylene group to the γ-lactone ring in the final stage of the synthesis has been well-investigated.[12)] In this paper, we wish to report the preparation of (1*S*,4*R*,6*R*)-1-ethenyl-3-methyl-6-(1-methylethenyl)-2-cyclohexene-1,4-diol (**2**) from (−)-carvone (**3**) and the synthesis of (3*R*,6*S*,7*S*,



Scheme 1.

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1(10)*E*,4*Z*)- and (3*R*,6*R*,7*S*,1(10)*E*,4*Z*)-3-methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactones (**4** and **5**)[13] from **2** utilizing anionic oxy-Cope rearrangement as a key step, in detail.

Retro-synthetic pathway is shown in Scheme 1.

The first stage of the synthesis was a preparation of the diol (**2**) from an easily available optically active compound. We chose (−)-carvone (**3**) as a starting material. Several carvone derivatives oxygenated at allylic position have already been derived from carvone by three groups; Still's group had obtained **6** in 37% yield by 6 step reactions,[7] Miyashita and Yoshikoshi had prepared **7** in about 40% yield through eight synthetic intermediates,[14] and Noma and Nishimura had obtained **7** in 10% yield by microbial one step oxidation.[15] To obtain a large amount of **6**-type compound from carvone, we planned a direct allylic oxidation reaction of carveol derivative. The good hydroxyl-protecting group to carveol was turned out to be ester-type one (acetate or benzoate). When (−)-*cis*-carveol (**8**),[16] prepared by reduction of (−)-carvone (**3**) with lithium aluminum hydride, was acetylated and then treated with *t*-butyl chromate, a corresponding ketone (**9**) was obtained in 41% yield. When Collins reagent [chromium(VI) oxide-pyridine complex] was used instead of *t*-butyl chromate as an oxidizing agent, the reaction rate was very slow, and oxidation with selenium (IV) oxide gave no desired compound. Reaction of **9** with 1.4 equivalent moles of vinylmagnesium bromide gave trienes, **10** and **2**, in 28 and 6% yields, respectively. The acetate (**10**) was hydrolyzed by potassium carbonate in aqueous methanol to afford **2** in 85% yield. (Consequently, **2** was obtained from **9** in 30% yield.) No diastereomer of **2** was obtained. The stereochemistry at the vinyl- and hydroxyl-carrying carbon atom of **2** was deduced from the formation mechanism. When the benzoate of carveol was utilized instead of acetate in these consecutive reactions, allylic oxidation step gave a worse result and Grignard step gave a better one, and overall yield was almost the same as in the case of acetate. Anionic oxy-Cope rearrangement reaction of the diol (**2**) was examined. The secondary hydroxyl group of **2** was protected by methoxymethyl (MOM) group and then the resulting triene (**11**) was treated with potassium hydride and 18-crown-6 in tetrahydrofuran under reflux affording a cyclodecadienone (**12**) in 67% yield. When **2** was directly treated with the same conditions as above, only complex mixture was obtained. Any ten-membered ring compound could not be obtained when acetyl (compound **10**), trimethylsilyl, *t*-butyldimethylsilyl, or *t*-butyldiphenylsilyl protecting groups was used instead of MOM group. Although the geometry of olefinic double bonds of **12** could have already been expected from the reaction fashion of oxy-Cope

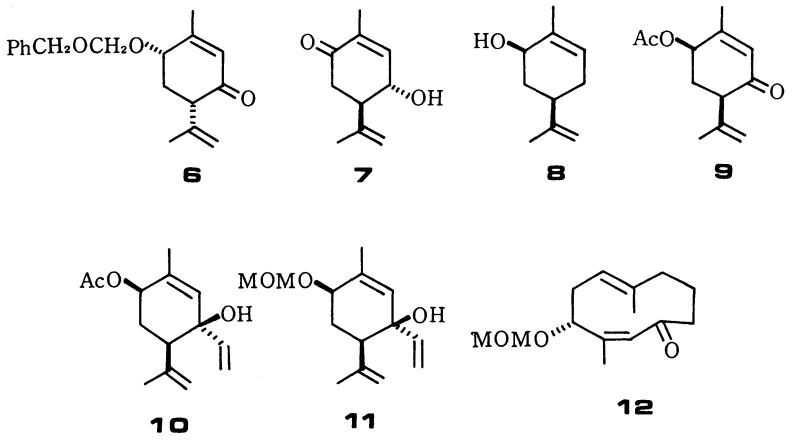


Table 1.[a] NOE data for **12**

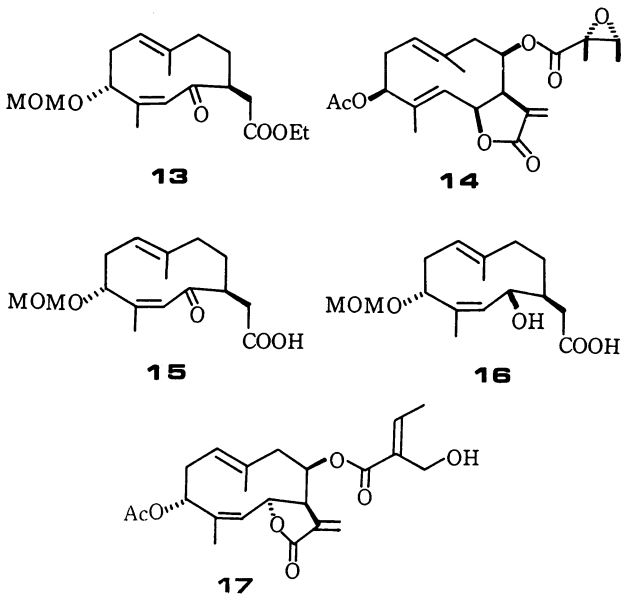
Irradiated proton(s)	Observed proton	NOE[b]
C(10)-CH_3 (δ=1.56, 3H, s)	C(1)-H (δ=5.03, 1H, t, $J_{1,2\alpha}=J_{1,2\beta}=8$ Hz)	2%
	C(2β)-H (δ=2.51, 1H, ddd, $J_{1,2\beta}=8$ Hz, $J_{2\alpha,2\beta}=13$ Hz, $J_{2\beta,3\beta}=5.5$ Hz)	7%
	C(3β)-H (δ=4.88, 1H, dd, $J_{2\alpha,3\beta}=11$ Hz, $J_{2\beta,3\beta}=5.5$ Hz)	10%
C(4)-CH_3 (δ=1.79, 3H, s)	C(1)-H	15%
	C(5)-H (δ=6.07, 1H, s)	20%
C(2β)-H	C(3β)-H	12%

a) Assignment of signals was determined by decoupling experiments. b) Accuracies are about ±2%.

rearrangement, it was confirmed by NOE experiments. The result shown in Table 1 can only be interpreted based on the (1(10)*E*,4*Z*)-structure (**A**).[8] The ketone (**12**) was treated with lithium diisopropylamide followed by ethyl bromoacetate to give a keto ester (**13**) stereoselectively as a sole product in 74% yield. The stereochemistry at C(7) of **13** would be *S*(7α-H) from the reaction pathway as the following. That is, the enolate ion generated with lithium diisopropylamide would have a more stable 6*Z*-double bond, which can conjugate with 4*Z*-double bond, while the corresponding 6*E*-enolate can not do. On the enolate ion, methoxymethoxyl group at C(3) would take an equatorial form (**B**). Then, the electrophile would attack from the less hindered outer side of the ten-membered ring to give 7α-H configuration compound. This stereochemical assignment was supported by the following transformation into *cis*-lactone (**5**).

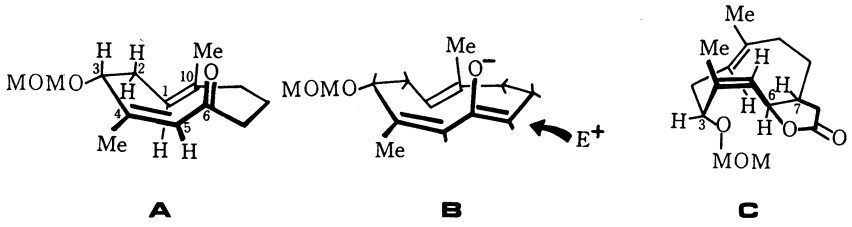
The keto ester (**13**) was reduced with sodium borohydride in ethanol to give a lactone (**5**) in 12% yield, together with more polar products which were suggested to be a keto alcohol (19%) and a diol (15%). The stereochemistry of **5** was decided to be 6*R*(6α-H) and 7*S*(7α-H) (**C**) from the NMR spectrum as follows. The methoxymethoxyl group at C(3α) is in axial conformation judging from the coupling constant of C(3β)-H (t, *J*=3 Hz). The chemical shift of C(6)-H (δ 6.01) is fairly low, which could be explained that C(6)-H is situated at the close position to the C(3α)-axial methoxymethoxyl oxygen, meaning that C(6)-H is α-oriented; large *J* values (7 and 11 Hz) observed for C(6)-H lead to a *cis*-lactone structure with C(6α)-H and C(7α)-H configuration for **5**. The *cis* lactone structure is also compatible with the formation mechanism that a hydride would attack C(6) carbonyl carbon preferentially from the less hindered outer side of the ten-membered ring. Consequently, the absolute stereostructure of **5** is established as (3*R*,6*R*,7*S*,1(10)*E*,4*Z*)-3-methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactone.

No natural heliangolide possessing (6α-H,7α-H)-12,6-lactone has been known, even though several germacrolides of this type have been known (*e.g.* ursinolide A (**14**)).[17] In order to obtain *trans*-lactone, we planned to lactonize the hydroxy acid (**16**) with inversion at C(6) stereochemistry by activating the hydroxyl group. The keto ester (**13**) was hydrolyzed with potassium carbonate in aqueous methanol, and the resulting keto acid (**15**) was reduced with lithium borohydride to afford **16**. As the hydroxy acid (**16**) was easily lactonized into *cis*-lactone (**5**), **16** without purification was treated with *N*,*N*-dimethylformamide dineopentyl acetal in boiling toluene[18] to afford a lactone (**4**) in 15% yield from **13**.[19] The stereochemistry of the lactone (**4**), which has different physical data from those of *cis*-lactone (**5**), must have been *trans* (6*S*,7*S*), which was convincingly suggested from the formation mechanism.[18] The NMR spectral data were also compatible with the structure **4** when compared with those of natural heliangolide, eupasimplicin A (**17**).[20] Thus, the structure of **4** including the absolute stereochemistry was shown to be (3*R*,6*S*,7*S*,1(10)*E*,4*Z*)-3-methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactone.



Experimental

General Procedures. All melting points were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and uncorrected. Optical rotation was determined on a JASCO polarimeter DIP-SL. Ultraviolet absorption (UV) and infrared (IR) spectra were measured on a Hitachi 340 and a Hitachi 260-30 spectrometer, respectively. Mass (MS) spectra were run on a JEOL JMS-D300 mass spectrometer operating at 70 eV. Proton nuclear magnetic resonance (^{1}H NMR) spectra were taken using a Varian EM390 (90 MHz), a JEOL FX90Q (90 MHz), and a Brucker



WH270 (270 MHz). Chemical shifts were expressed in δ (ppm) downfield from tetramethylsilane as an internal standard and coupling constants in Hz. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 GF_{254} coated in 0.25 mm-thickness. Wakogel C-200 (Wako) and Florisil (100—200 mesh) were used for column chromatography. Liquid Chromatograph Model ALC/GPS 202/401 (Waters Assoc.) was used for high performance liquid chromatography (HPLC).

(−)-cis-Carvyl Acetate ((3R,5R)-3-Acetoxy-2-methyl-5-(1-methylethenyl)cyclohexene). To a solution of 6.7 g of (−)-*cis*-carveol (**8**) in 100 ml of pyridine was added 20 ml of acetic anhydride and the whole was stirred for about 12 h. After addition of 30 ml of methanol and removal of solvent *in vacuo*, the reaction mixture was extracted with ether as usual. After the removal of impurities at 40 °C under reduced pressure (10 mmHg; 1 mmHg=133.322 Pa), 8.11 g of acetate was obtained: bp 82—83 °C/2 mmHg; $[\alpha]_D^{11}$ −54.4° (*c* 6.99, EtOH); IR (neat) 1740, 1645, and 1240 cm^{-1}; NMR ($CDCl_3$) δ=1.62 (3H, br s), 1.72 (3H, s), 2.07 (3H, s, $-OCOCH_3$), 4.70 (2H, s, $-\underset{|}{C}=CH_2$), 5,42 (1H, br, C(1)-H), and 5.55 (1H, br, C(3)-H); MS *m/z* (%) 194 (M^+, 0.4), 152 (39), 134 (56), and 84 (100).

Allylic Oxidation of (−)-cis-Carvyl Acetate. To a solution of 5.0 g of (−)-*cis*-carvyl acetate in 70 ml of carbon tetrachloride was added 70 ml of a carbon tetrachloride solution of *t*-butyl chromate (prepared from 13 g of chromium(VI) oxide), 20 ml of acetic anhydride, and 7 ml of acetic acid, and the whole was refluxed for 1 d. A solution of oxalic acid (16 g) in 120 ml of water and then 50 g of oxalic acid were added. After removal of precipitate, ether was added for extraction. The ether layer was washed with aqueous sodium hydrogensulfite, saturated sodium hydrogencarbonate aqueous solution, and saturated brine, successively, and dried over sodium sulfate. After evaporation of solvent, the residue was chromatographed on a column of silica gel (80 g). Elution with hexane–ether (5:1) afforded 2.35 g of the unreacted starting material, and elution with hexane–ether (2:1) gave (4*R*,6*R*)-4-acetoxy-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-one (**9**, 1.22 g): an oil, $[\alpha]_D^{14}$ −52.2° (*c* 6.50, EtOH); IR (neat) 1740, 1680, 1635, and 1235 cm^{-1}; UV (EtOH) 228 nm (ε 9800); ^1H NMR ($CDCl_3$) δ=1.72 (3H, s, $CH_2=\underset{|}{C}-CH_3$), 1.91 (3H, s, C(3)-$CH_3$), 2.13 (3H, s, $-OCOCH_3$), 3.11 (1H, dd, *J*=4.5 and 13.5 Hz, C(6)-H), 4.79 and 4.95 (each 1H, br s, $-\underset{|}{C}=CH_2$), 5.7 (1H, br, C(4)-H), and 5.92 (1H, br s, C(2)-H); MS *m/z* (%) 208 (M^+, 0.5), 166 (17), and 98 (100); Found: *m/z* 208.1090. Calcd for $C_{12}H_{16}O_3$: 208.1097.

Grignard Reaction of the Keto Acetate (9). The Grignard reagent was prepared by heating the mixture of small pieces of magnesium ribbon (110 mg), 7 ml of dry tetrahydrofuran (dry THF; freshly distilled from lithium aluminum hydride), and vinyl bromide (0.35 ml) under nitrogen atmosphere. To the Grignard reagent cooled at 0 °C with ice-bath, a solution of **9** (675 mg) in THF (3.5 ml) was added, and the mixture was stirred for 20 min at room temperature. After addition of saturated ammonium chloride solution, the mixture was extracted with ether and then subjected to separation by silica gel (20 g) column chromatography. Elution with hexane–ether (5:1) gave **10** (157.0 mg), elution with hexane–ether (4:1) gave starting material (**9**; 189.1 mg), and then elution with hexane–ether (1:1) gave **2** (35.2 mg). (1*S*, 4*R*,6*R*)-4-Acetoxy-1-ethenyl-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-ol (**10**): an oil, $[\alpha]_D^{14}$ −29.9° (*c* 5.58, EtOH); IR (neat) 3500, 1735, 1635, and 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.68 (3H, t, *J*=0.5 Hz, $CH_2=\underset{|}{C}-CH_3$), 1.79 (3H, s, C(3)-Me), 2.09 (3H, s, $-OCOCH_3$), 4.8—5.5 (6H, m), and 5.87 (1H, dd, *J*=10 and 17 Hz, $-\underset{|}{C}-CH=CH_2$); MS *m/z* (%) 194 [$(M-42)^+$, 3], 176 (8), and 125 (100). Fragment ion peak due to $(M-CH_2CO)^+$ was observed at *m/z* 194.1308. Calcd for $C_{12}H_{18}O_2$: M-C_2H_2O, 194.1307. (1*S*,4*R*,6*R*)-1-Ethenyl-3-methyl-6-(1-methylethenyl)-2-cyclohexene-1,4-diol (**2**): crystals, mp 142.5—144.5 °C, $[\alpha]_D^{16}$ −23.9° (*c* 2.80, EtOH); IR (KBr disk) 3320, 3250, and 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.80 (6H, s), 4.1 (1H, br, C(4)-H), 4.8—5.3 (5H, m), and 5.86 (1H, dd, *J*=10 and 17 Hz, $-\underset{|}{C}-CH=CH_2$); MS *m/z* (%) 194 (M^+, 0.2), 176 (1), 161 (5), and 126 (100). Found: C, 73.92%; H, 9.22%. Calcd for $C_{12}H_{18}O_2$: C, 74.19%; H, 9.34%.

Hydrolysis of the Acetate (10). A mixture of **10** (1.13 g) and potassium carbonate (1.8 g) in 80% aqueous methanol (120 ml) was stirred at room temperature for 1 h. After removal of methanol *in vacuo*, ether extraction was carried out as usual, and white crystals of **2** (786.7 mg) was afforded.

Methoxymethylation of the Diol (2). To a solution of **2** (174 mg) in dry acetonitrile (35 ml) were added triethylamine (3.5 ml) and methoxymethyl chloride (1.2 ml), and the mixture was refluxed for 8 h. After addition of saturated aqueous solution of sodium hydrogencarbonate and removal of acetonitrile *in vacuo*, ether extraction was done as usual. The mixture was separated by Florisil (20 g) column chromatography. Elution with hexane–ether (9:1) afforded 90.2 mg of methoxymethyl ether (**11**) and elution with ether gave unreacted diol (**2**; 55.2 mg). (1*S*,4*R*,6*R*)-1-Ethenyl-4-methoxymethoxy-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-ol (**11**): an oil, $[\alpha]_D^{16}$ −61.2° (*c* 4.25, EtOH); IR (neat) 3480 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.79 (6H, s), 3.40 (3H, s, $-OCH_2OCH_3$), 4.05 (1H, br t, *J*=7.5 Hz, C(4)-H), 4.65 and 4.76 (each 1H, A and B parts of an ABq, *J*=6 Hz, $-OCH_2OCH_3$), 4.7—5.1 (5H, m), and 5.84 (1H, dd, *J*=10 and 17 Hz, $-\underset{|}{C}-CH=CH_2$); MS *m/z* (%) 193 [$(M-MOM)^+$, 4], 170 (36), and 108 (100). The fragment ion peak due to $(M-MOM)^+$ was observed at *m/z* 193.1236. Calcd for $C_{12}H_{17}O_2$: M-C_2H_5O, 193.1228.

Cyclodecadienone (12): (3R,1(10)E,4Z)-3-Methoxymethoxy-11,12,13-trinor-1(10),4-germacradien-6-one.[8] All the reactions were carried out under argon atmosphere. To a solution of potassium hydride (17 mg) in 10 ml of dry THF were added a THF (3 ml) solution of **11** (85.8 mg) and a solution of 18-crown-6 (107 mg) in THF (1.5 ml). After the mixture was refluxed for 1 h, the whole was cooled to room temperature, and subjected to ether extraction as usual. The products were separated by Florisil (7 g) column chromatography. Elution with hexane–ether (7:1) afforded the recovered starting material (**11**; 29.6 mg), and elution with hexane–ether (2:1) gave the cyclodecadienone (**12**; 37.5 mg): crystals, mp 52—53 °C (recrystallization from hexane), $[\alpha]_D^{11}$ −110.6° (*c* 3.02, EtOH); IR (film) 1680 and 1630 cm^{-1}; UV (EtOH) 235 nm (ε 5300); ^1H NMR ($CDCl_3$) δ=3.42 (3H, s, $-OCH_2OCH_3$), 4.65 and 4.67 (each 1H, A and B parts of an ABq, *J*=6 Hz, $-OCH_2OCH_3$), and signals listed in Table 1; MS *m/z* (%) 238 (M^+, 8), 193 (19), 169 (50), 81 (95), and 45 (100). Found: C, 70.47%; H, 9.57%. Calcd for $C_{14}H_{22}O_3$: C, 70.56%; H, 9.30%.

Keto Ester (13): *Ethyl (3R,7S,1(10)E,4Z)-3-Methoxymethoxy-6-oxo-13-nor-1(10),4-germecradien-12-oate.* A mixture of 1 ml of dry THF, 0.053 ml of diisopropylamine, and 0.24 ml of butyllithium (1.56 M hexane solution; 1 M=1 mol dm^{-3}) was stirred at −70 °C under nitrogen atmosphere, and a THF (1.5 ml) solution of **12** (74.7 mg) was added and the mixture was stirred at −70 °C for 45 min. Ethyl bromoacetate (0.15 ml) was added and the mixture was stirred at −23 °C (Dry Ice in carbon tetrachloride) for 5 h. Water was added and the mixture was extracted with ether as usual. Products were separated by Florisil (6 g) column chromatography. Elution with hexane–ethyl acetate (19:1) gave starting material (**12**; 26.2 mg). Elution with hexane–ethyl acetate (9:1) afforded the keto ester (**13**; 48.4 mg): an oil, $[\alpha]_D^{12}$ −39.5° (*c* 6.45, EtOH); IR (neat) 1735, 1680, and 1630 cm^{-1}; UV (EtOH) 238 nm (ε 5800); ^1H NMR ($CDCl_3$) δ=1.24 (3H, t, *J*=7 Hz, $-COOCH_2\underline{CH_3}$), 1.52 (3H, s, C(10)-Me), 1.80 (3H, s, C(4)-Me), 3.42 (3H, s, $-OCH_2OC\underline{H_3}$), 4.11 (2H, q, *J*=7 Hz, $-COOC\underline{H_2}CH_3$), 4.65 (2H, s, $-OC\underline{H_2}OCH_3$), 4.91 (1H, dd, *J*=6 and 11.5 Hz, C(3β)-H), 5.01 (1H, t, *J*=7 Hz, C(1)-H), and 6.23 (1H, br s, C(5)-H); MS *m/z* (%) 324 (M^+, 4), 255 (40), and 45 (100). Found: *m/z* 324.1948. Calcd for $C_{18}H_{28}O_5$: M, 324.1937.

Sodium Borohydride Reduction of the Keto Ester (13). Sodium borohydride (*ca.* 70 mg) was added to an ethanol solution (15 ml) of the keto ester (**13**; 76.3 mg), and the mixture was stirred at room temperature for 2 d. After addition of acetone to decompose the excess sodium borohydride and removal of solvent *in vacuo*, the products were extracted with ether as usual. The products were separated by Florisil (7 g) column chromatography. Elution with hexane–ethyl acetate (4:1) afforded the recovered starting material (**13**; 17.8 mg), the lactone (**5**; 5.2 mg), and a keto alcohol (9.8 mg). Elution with ethyl acetate gave a diol (7.5 mg). (3*R*, 6*R*,7*S*,1(10)*E*,4*Z*)-3-Methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactone (**5**): an oil, $[\alpha]_D^{24}$ −110° (*c* 0.70, EtOH); IR (neat) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.46 (3H, s), 1.75 (3H, s), 3.36 (3H, s, $-OCH_2OC\underline{H_3}$), 4.36 (1H, t, *J*=3 Hz, C(3β)-H), 4.51 and 4.65 (each 1H, A and B parts of an ABq, *J*=6.5 Hz, $-OC\underline{H_2}OCH_3$), 5.37 (2H, m, C(1)-H and C(5)-H), and 6.01 (1H, dd, *J*=7 and 11 Hz, C(6)-H); MS *m/z* (%) 280 (M^+, 6), 248 (10), and 159 (100). Found: *m/z* 280.1656. Calcd for $C_{16}H_{24}O_4$: M, 280.1673.

Hydrolysis of the Keto Ester (13). As it was rather hard to separate **13** from **12** by Florisil column chromatography, the hydrolysis of a mixture of **12** and **13** was examined. To the mixture of **12** and **13** (35.6 mg) was added potassium carbonate (45 mg) in 80% aqueous methanol (3 ml), and the whole was stirred at room temperature for 8 h. After addition of water and evaporation of methanol, the mixture was extracted with ether. Aqueous layer was adjusted to approximately pH 3 by addition of dil. HCl, and was extracted with dichloromethane several times. From the ether layer 14.0 mg of **12** was recovered, and from the dichloromethane layer 18.3 mg of keto acid (**15**) was obtained. (3*R*,7*S*,1(10)*E*,4*Z*)-3-Methoxymethoxy-6-oxo-13-nor-1(10),4-germacradien-12-oic acid (**15**): an oil; IR (neat) 3400—2500 (br), 1710, and 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.52 (3H, s, C(10)-Me), 1.80 (3H, s, C(4)-Me), 3.07 (3H, s, $-OCH_2OC\underline{H_3}$), 4.63 (2H, s, $-OC\underline{H_2}OCH_3$), 4.96 (2H, m, C(1)-H and C(3β)-H), 6.20 (1H, m, C(5)-H), and 7.83 (1H, br, −COOH).

(3R,6S,7S,1(10)E,4Z)-3-Methoxymethoxy-13-nor-1(10),4-germacradieno-12,6-lactone (4). A mixture of the keto acid (**15**; 23.3 mg) in dry THF (2 ml) and about 10 mg of lithium borohydride was stirred at room temperature for 20 h. After addition of water and evaporation of THF, dil.HCl was gradually added to pH 4—5, and dichloromethane extraction was carried out several times. The extract was dried over sodium sulfate, and was concentrated into *ca.* 1 ml *in vacuo*. Toluene (6 ml) was added and the solvent (mainly dichloromethane) was removed under atmospheric pressure to give toluene solution (*ca.* 4 ml). To this toluene solution was added 0.03 ml of *N,N*-dimethylformamide dineopentyl acetal in toluene (0.4 ml), and the mixture was refluxed for 2 h. After removal of solvent, the reaction mixture was charged onto silica gel (*ca.* 3 g) column chromatography. Elution with benzene–ethyl acetate (5:1) gave 3.2 mg of *trans*-lactone (**4**), which was purified through HPLC (μ-Porasil; CH_2Cl_2). **4**: an oil, $[\alpha]_D^{19}$ +61° (*c* 0.04, EtOH); IR (neat) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.59 (3H, s, C(4)-Me), 1.75 (3H, br, C(10)-Me), 3.37 (3H, s, $-OCH_2OC\underline{H_3}$), 4.20 (1H, dd, *J*=6 and 9.5 Hz, C(3β)-H), 4.48 and 4.57 (each 1H, A and B parts of an ABq, *J*=7 Hz, $-OC\underline{H_2}OCH_3$), 4.55 (1H, br, C(1)-H), and 5.12 (2H, br, C(5)-H, and C(6β)-H) [Corresponding signals of eupasimplicin A (**17**)[20]: δ=5.60 (1H, dd, *J*=5 and 11 Hz, C(3β)-H) and 5.25 (2H, br, C(5)-H and C(6β)-H]; MS m/z (%) 280 (M^+, 1), 282 (12), and 81 (100). Found: *m/z* 280.1672. Calcd for $C_{16}H_{24}O_4$: M, 280.1672.

The authors with to thank Dr. Hajime Nagano, Ochanomizu University, for valuable discussions, Professor W. Clark Still, Columbia University, for the kind sending of the preprint on the total synthesis of hiyodorilactone A (**1**),[6] and Professor Tatsuo Miyazawa and Dr. Tatsushi Murae, Faculty of Science, the University of Tokyo, for the measurement of ^1H NMR spectra at 270 MHz.

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