# Synthetic Studies on Germacranolides: Synthesis of Optically Active 3-Benzoyloxy-6-oxo-13-nor-12,8-heliangolide

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Optically active (3*R*,7*R*,8*R*,1(10)*E*,4*Z*)-3-benzoyloxy-6-oxo-13-nor-1(10),4-germacradieno-12,8-lactone, a key synthetic intermediate for naturally occurring hiyodorilactone A, was prepared from (−)-carvone.

A group of sesquiterpene lactones with germacrane skeleton, named generically as "germacranolides," have been isolated from various plants.[1] Among them, 1(10)-*trans*-4-*cis*-germacranolides are called as "heliangolide." We have already reported several synthetic studies on 3-oxygenated heliangolides,[2] such as (−)-4,5-*cis*-3β-hydroxygermacranolide (**1**)[2c] isolated from *Tanacetum tanacetioides*, starting from optically active carvone using oxy-Cope rearrangement to construct the ten-membered ring. Since most of naturally occurring heliangolides possess acyloxyl group at C-8 position, which may enhance biological activities, we planned to synthesize 3,8-dihydroxylated heliangolide derivatives, such as hiyodorilactone A (**2**) which was isolated from *Eupatorium sachalinense* Makino by our group and showed a strong inhibitory activity in vivo against Ehrlich ascites carcinoma.[3] This compound **2** has already been synthesized by Still et al., who introduced the oxygen functional group at C-8 position by Baeyer-Villiger oxidation of a cyclobutanone ring under drastic conditions (anhydrous $H_2O_2$).[4]

In this paper, we would like to report another method to introduce oxygen functional group at C-8 position of the germacrane skeleton and the preparation of (3*R*, 7*R*, 8*R*, 1(10)*E*, 4*Z*)-3-benzoyloxy-6-oxo-13-nor-1(10),4-germacradieno-12,8-lactone (**3**) from (−)-carvone (**4**). The compound **3** is the antipode of **5**, which was a key intermediate on the total synthesis of hiyodorilactone A (**2**) by Still's group, except for the difference in the protecting group of the alcohol at C-3 position. If (+)-carvone, which is also commercially available at a higher price, is used as the starting material, the antipodal compound of **3** could be obtained. To construct the ten-membered ring, both we and Still's group had applied oxy-Cope rearrangemet to compounds **6** and **7**, respectively.

In order to introduce an oxygen functional group at C-8 position, we must use a compound which possesses a substituent (X) on the terminus of vinyl group of **6** as a substrate for oxy-Cope rearrangement to be able to transform into oxygen functional group at later stages. As a model compound, we first tried to prepare a compound **8** having ethoxyl group as X from isopiperitenone (**9**) and 2-ethoxyvinyllithium,[5] but it became clear that **8** decomposed via deethanolization upon purification and/or under the reaction conditions of oxy-Cope rearrangement. Then we decided to use 1-methylethylidene group, which could be transfered into oxygen by ozonolysis as X group of **6**. To determine the reaction conditions of oxy-Cope rearrangement, allenyl alcohol **10a** was prepared from isopiperitenone (**9**) and 3,3-dimethylallenyllithium (generated from 1,1-dimethylallene and methyllithium)[6] in 79% yield. When **10a** was refluxed with potassium hydride and 18-crown-6 in THF for 30 min (anionic oxy-Cope rearrangement),[2,4,7] piperitenone (**11**), which would be produced by the removal of dimethylallene followed by double bond isomerization, was obtained as a major product. When trimethylsilyl ether derivative of **10a** was heated at 150 °C without solvent under nitrogen atmosphere (siloxy-Cope rearrangement),[8] no reaction took place after 1 h. When **10a** was heated with almost ten equivalent moles of 1-methyl-2-pyrrolidinone at 120—130 °C for about 10 h (solvent-assisted oxy-Cope rearrangement),[9] the desired compound **12a** was produced (isolation yield: 25%) together with approximately the same amounts of the starting material **10a** and a bicyclic compound **13a**. The structure of **13a** was deduced from $^1$H NMR spectrum, and **13** would be formed via ene reaction.

Since the ten-membered-ring compound **12a** could be obtained in considerable yield, solvent-assisted oxy-Cope rearrangement reaction was applied to the compound **10b** having an additional hydroxyl group of a benzoylated form. The benzoyloxyl group was considered to be stable under the transformation reactions of **12b** into **3**.

The benzoyloxy ketone **14**, which was obtained from (−)-carvone (**4**) via carveol and carvyl benzoate, was treated with 3,3-dimethylallenyllithium[6] to afford **10b** in 29% yield. The alcohol **10b** was rearranged into the ten-membered-ring compound **12b** in 32% yield on heating with 1-methyl-2-pyrrolidinone at about 100 °C for 22 h. Other products, such as the bicyclic compound **13b**, were also formed, but these were not fully characterized. Ozonolysis of **12b** at −30 °C, adjusting the amount of ozone as less than 1 equivalent mole by pre-adsorption on a proper amount of silica gel, gave the desired diketone **15** in 21% yield. The diketone **15**

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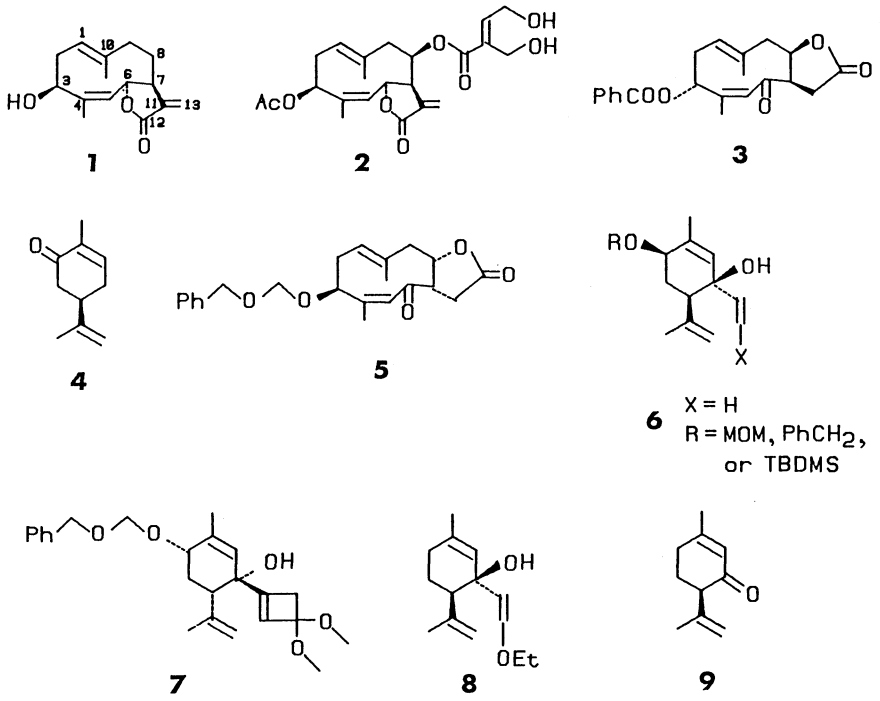

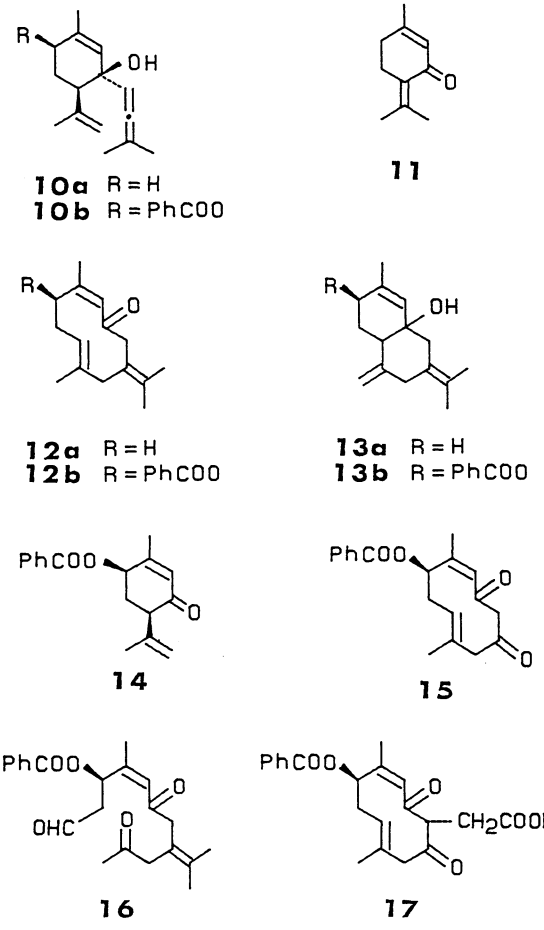

was accompanied by almost the same amount of a compound, which would have structure **16**, formed by cleavage of the non-conjugated trisubstituted double bond of **12b**. Signals of $^1$H NMR showed that diketone **15** existed as approximately 1 : 1 mixture of two conformational isomers at room temperature.

Table 1. Main Proton Signals of **3** and **5** at 270 MHz $^1$H NMR

| Position | **3** | | | **5**[a] | | |
|---|---|---|---|---|---|---|
| | $\delta$ | | $J$/Hz | $\delta$ | | $J$/Hz |
| 1-H | 5.1 | m[b] | | 4.94 | dd | 12 and 5 |
| 3-H | 6.48 | dd | 11.6 and 4.2 | 5.31 | dd | 12 and 4 |
| 5-H | 6.14 | br s | | 6.09 | br s | |
| 7-H | 3.63 | td | 12.6 and 8.1 | 3.56 | td | 13 and 8 |
| 8-H | 5.11 | m[b] | | 5.04 | ddd | 13, 8, and 3 |
| 11-H | 2.41 | dd | 18.1 and 8.1 | 2.36 | dd | 18 and 8 |
| | 3.25 | dd | 18.1 and 12.6 | 3.19 | dd | 18 and 13 |

a) Analyzed a copy of spectral chart sent from Prof. Still. b) Overlapped each other.

Diketone **15** was treated with sodium hydride followed by ethyl bromoacetate to give a diketo ester **17** in 44% yield. This compound **17** was also observed as a 1 : 2 mixture of two conformers by $^1$H NMR at room temperature. When temperature was raised up to 45 °C, a set of olefinic methyl signals ($\delta$ ca. 1.95) having smaller chemical shift differences at room temperature coalesced into a singlet in the 270 MHz $^1$H NMR spectrum. Stereochemistry at C-7 of **17** was assumed as 7$\alpha$-H by considering the reaction pathway. That is, the enolate ion generated with sodium hydride would have a more stable 6*Z*-double bond, and the electrophile would attack from the peripheral side of the ten-membered ring to give 7$\alpha$-H configuration compound. Similar argument has also been made in previous papers.[2] This stereochemical assignment was confirmed by subsequent transformation into $\gamma$-lactone **3**.

Treatment of **17** with sodium borohydride in ethanol gave a $\gamma$-lactone (**3**; $\nu_{C=O}$ 1780 $cm^{-1}$) as a major product (45% yield). The stereostructure of **3** was deduced to 8*R* or *cis*-lactone from Dreiding model consideration. It was very difficult to construct *trans*-lactone by Dreiding model, while it was fairly easy to make *cis*-lactone. This stereochemical assignment was confirmed by direct comparison of 270 MHz $^1H$ NMR spectra of **3** and **5**. In Table 1 were listed assignments, chemical shifts, and coupling constants of the main proton signals of **3** and **5** for comparison.

Thus the structure of **3** was shown to be (3*R*, 7*R*, 8*R*,1(10)*E*,4*Z*)-3-benzoyloxy-6-oxo-13-nor-1(10),4-germacradieno-12,8-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-181. Ultraviolet absorption (UV) and infrared (IR) spectra were measured on a Hitachi 340 and a Hitachi 260-30 spectrometer, respectively. Proton nuclear magnetic resonance ($^1H$ NMR) spectra were taken using a Varian EM390 (90 MHz) and a JEOL GX270 (270 MHz) at ambient temperature, unless otherwise noted. Chemical shifts were expressed in $\delta$ (ppm) downfield from tetramethylsilane as an internal standard and coupling constants in Hz. Mass spectra (MS) were run on a JEOL JMS-D300 mass spectrometer operating at 70 eV. Thin-layer chromatography (TLC) including preparative one was carried out on Kieselgel 60 $GF_{254}$ coated in 0.25 mm-thickness. Wakogel C-200 (Wako) was used for silica-gel column chromatography.

**(+)-3-Methyl-1$\alpha$-(3-methyl-1,2-butadienyl)-6$\beta$-(1-methylethenyl)-2-cyclohexen-1$\beta$-ol (10a).** To an ether solution of methyllithium (0.58 M (1M=1mol $dm^{-3}$); 23.5 mL) was added diisopropylamine (0.05 mL) followed by 4.2 mL of a mixture (4 : 7) of 3-methyl-1,2-butadiene and tetrahydrofuran (THF), dropwisely at room temperature under nitrogen atmosphere, and the mixture was stirred for 4 h. At −78 °C, (±)-isopiperitenone (1.25 g) in ether (5 mL) was added dropwise. After stirring for about 2 h at room temperature and addition of saturated brine, the reaction mixture was extracted with ether. Usual work-up afforded 1.77 g of oily residue. Pure **10a** (1.426 g) was obtained by Kugel-Rohr distillation (80 °C/0.05 mmHg; 1 mmHg=133.322 Pa): an oil, IR (neat) 3460, 1670, 1635, 965, and 890 $cm^{-1}$; $^1H$ NMR ($CCl_4$; 90 MHz) $\delta$=1.70 (9H, br s), 1.80 (3H, br s), 4.72 (1H, br s), 4.84 (1H, br s), 4.97 (1H, sept), and 5.28 (1H, br s); MS *m/z* (%) 218 ($M^+$, 6), 203 (5), 200 (100), 185 (55), 157 (57), and 143 (72); Found: *m/z* 218.1659. Calcd for $C_{15}H_{22}O$: M, 218.1669.

**(2*Z*,6*E*)-3,7-Dimethyl-9-(1-methylethylidenyl)-2,6-cyclodecadien-1-one (12a).** A solution of allenyl derivative (**10a**; 544 mg) in 6 mL of 1-methyl-2-pyrrolidinone was heated at 120—130 °C (bath temperature) for about 10 h under argon atmosphere. After cooling and addition of ether, the mixture was poured into water, and was extracted with ether as usual. $^1H$ NMR showed that the residue was consisted from three compounds, that is, the starting material **10a**, the objective ten-membered ketone **12a**, and a bicyclic compound **13a**, the ratio of which was almost 3 : 2 : 2, respectively. The residue was separated by column and preparative thin-layer chromatographies (solvent: hexane-ethyl acetate). **12a** (139 mg): white amorphous solid; IR (nujol) 1680, 1633, 1210, 1085, and 992 $cm^{-1}$; $^1H$ NMR ($CCl_4$; 90 MHz) $\delta$=1.35 (3H, br s), 1.77 (9H, br s), 4.94 (1H, br t, *J*=8 Hz), and 5.77 (1H, br s); MS *m/z* (%) 218 ($M^+$, 100), 200 (71), and 185 (49); Found: *m/z* 218.1666. Calcd for $C_{15}H_{22}O$: M, 218.1669. **13a**: an oil; IR (neat) 3350, 1660, 1640, 1255, 1090, and 965 $cm^{-1}$; $^1H$ NMR ($CCl_4$; 90 MHz) $\delta$=1.70 (9H, br s), 2.68 (1H, dd, *J*=14 and 3 Hz), 3.28 (1H, dd, *J*=14 and 3 Hz), 4.51 (1H, br s), 4.77 (1H, br s), and 5.27 (1H, br s); MS *m/z* (%) 218 ($M^+$, 20), 200 (61), 185 (35), 175 (100), and 157 (50); Found: *m/z* 218.1662. Calcd for $C_{15}H_{22}O$: M, 218.1669.

**(−)-*cis*-Carvyl Benzoate ((3*R*, 5*R*)-3-Benzoyloxy-2-methyl-5-(1-methylethenyl)cyclohexene) and (4*R*, 6*R*)-4-Benzoyloxy-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-one (14).** A solution of (−)-carvone (**4**; 50 g) in dry ether (150 mL) was added dropwise over 30 min to a stirring suspension of lithium aluminium hydride (6.5 g) in dry ether (300 mL) at about 0 °C. After additional 30 min stirring at room temperature, water and 2 M hydrochloric acid were added, successively. Ether extraction followed by removal of the solvent was performed as usual to afford carveol.[10] Benzoyl chloride (60 mL) was added to a solution of carveol in pyridine (300 mL) at about 0 °C, and the mixture was stirred at room temperature for 8 h. After addition of methanol (100 mL) followed by saturated brine, organic solvents were removed in vacuo, and the reaction mixture was extracted with ether as usual to afford crude carvyl benzoate. Kugel-Rohr distillation (170 °C, 0.5 mmHg) of a part of this crude material afforded the analytical sample of carvyl benzoate: $[\alpha]_D^{22}$ +13.3° (*c* 1.25, EtOH); UV (EtOH) 229.5 nm ($\varepsilon$ 14280); IR (neat) 1725, 1645, 1270, and 1115 $cm^{-1}$; $^1H$ NMR ($CDCl_3$; 270 MHz) $\delta$=1.71 (3H, br s), 1.74 (3H, s), 4.74 (2H, s), 5.6—5.8 (2H, m), 7.4—7.6 (3H, m), and 8.0—8.1 (2H, m); MS *m/z* (%) 256 ($M^+$, 5), 213 (15), 134 (14), 119 (19), and 105 (100); Found: C, 79.48%; H, 7.72%; and *m/z* 256.1466. Calcd for $C_{17}H_{20}O_2$: C, 79.65%; H, 7.86%; and M, 256.1464.

A solution of the crude carvyl benzoate in carbon tetrachloride (50 mL) was added to a carbon tetrachloride solution (700 mL) of *t*-butyl chromate (prepared from 130 g of chromium(VI) oxide). Acetic anhydride (200 mL) and acetic acid (70 mL) was added, and the whole was refluxed for 16 h. After filtration and addition of a solution of oxalic acid (160 g) in 1.2 L of water and then solid oxalic acid (50 g), the reaction mixture was extracted with ether. The ether layer was washed with aqueous sodium hydrogensulfite, saturated sodium hydrogencarbonate aqueous solution, and saturated brine, successively, and dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was chromatographed on a column of silica gel (800 g). Elution with hexane-ethyl acetate (8 : 1) afforded 28 g of the unreacted carvyl benzoate and 21 g of the objective allyl-oxidation product **14**: an oil, $[\alpha]_D^{22}$ +27.9° (*c* 0.143, EtOH); UV (EtOH) 232.5 nm ($\varepsilon$ 27600); IR (neat) 1725, 1680, 1645 (sh), 1265, and 1115 $cm^{-1}$; $^1H$ NMR ($CDCl_3$; 270 MHz) $\delta$=1.75 (3H, s), 2.02 (3H, br s), 4.85 (1H, br s), 5.00 (1H, br s), 5.95—6.05 (2H, m), 7.4—7.7 (3H, m), and 8.05—8.15 (2H, m); MS *m/z* (%) 270 ($M^+$, 1.5), 202 (3), 148 (7), 105 (100), and 77 (25); Found: C, 75.31; H, 6.87, and *m/z* 270.1262. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71, and M, 270.1256.

**(1*R*,4*R*,6*R*)-4-Benzoyloxy-3-methyl-1-(3-methyl-1,2-butadienyl)-6-(1-methylethenyl)-2-cyclohexen-1-ol (10b).** To a

mixture of butyllithium (1.2 mL; 1.8 M hexane solution), THF (3 mL), and several drops of diisopropylamine was added a mixture (3 : 1) of 3-methyl-1,2-butadiene and THF, dropwise at room temperature. After stirring for 1 h, the mixture was added dropwise into a solution of **14** (280 mg) in THF (5 mL) at −78 °C, and was stirred for 1 h at −60 °C and then 10 min at 0 °C. Saturated ammonium chloride aqueous solution was added, and the reaction mixture was exracted with ether as usual. After evaporation, the residue was separated by column chromatography ($SiO_2$ 16 g). Elution with hexane-ether (20 : 1) afforded the objective compound **10b** (100 mg): an oil, $[\alpha]_D^{19}$ +83.0° (*c* 1.73, EtOH), IR (neat) 3530, 1715, 1640, and 1275 $cm^{-1}$; $^1H$ NMR ($CDCl_3$; 270 MHz) $\delta$=1.71 (3H, d, *J*=3 Hz), 1.74 (3H, d, *J*=3 Hz), 1.76 (3H, br s), 1.86 (3H, br s), 4.82 (1H, br s), 5.00 (1H, br s), 5.09 (1H, sept, *J*=3 Hz), 5.58 (1H, br s), 5.62 (1H, dd, *J*=10 and 7 Hz), 7.4—7.65 (3H, m), and 7.95—8.1 (2H, m); MS *m/z* (%) 338 ($M^+$, 0.6), 320 (0.8), 271 (5), 216 (5), 122 (7), and 105 (100); Found: *m/z* 338.1852. Calcd for $C_{22}H_{26}O_3$: M, 338.1880.

**(4*R*, 2*Z*, 6*E*)-4-Benzoyloxy-3,7-dimethyl-9-(1-methylethylidenyl)-2,6-cyclodecadien-1-one (12b).** A solution of **10b** (277 mg) in 2.8 mL of 1-methyl-2-pyrrolidinone was heated at 105 °C (bath temperature) for 22 h under argon atmosphere. After cooling to room temperature and the addition of ether, the whole was poured into water and was extracted as usual. After evaporation, the residue was separated by silica gel (15 g) column chromatography. Elution with hexane-ether (20 : 1) afforded 153 mg of recovered starting material **10b** and 40 mg of the objective ketone **12b**. **12b**: white crystals, mp 153—155.5 °C (recrystallized from ether); $[\alpha]_D^{19}$ −150° (*c* 0.44, $CHCl_3$); UV (EtOH) 230 nm ($\varepsilon$ 21100); IR (KBr) 1720, 1690, 1645, and 1280 $cm^{-1}$; $^1H$ NMR ($CDCl_3$; 270 MHz) $\delta$=1.61 (3H, br s), 1.79 (3H, br s), 1.86 (3H, s), 1.93 (3H, br s), 5.15 (1H, br t, *J*=8 Hz), 6.11 (1H, dd, *J*=11 and 6 Hz), 6.13 (1H, br s), 7.35—7.6 (3H, m), and 8.0—8.1 (2H, m); MS *m/z* 338 ($M^+$, 10), 320 (3), 295 (2), 233 (2), 216 (23), 198 (25), 173 (22), 122 (17), and 105 (100); Found: C, 78.03; H, 7.52; and *m/z* 338.1875. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74; and M, 338.1880.

**Quantification of an Amount of Ozone.** Some known amount of silica gel, which had been activated for several hours at 110 °C, was packed into a U-shaped glass tube, one end of which was connected with an ozonator and the other end was introduced into potassium iodide aqueous solution. At −78 °C, ozone was passed through the tube to be adsorbed on the silica-gel surface. When the potassium iodide solution was colored, the silica gel was judged to be saturated with ozone. Nitrogen stream was passed through the tube at room temperature to liberate the adsorbed ozone, which was then introduced into 2% aqueous solution of potassium iodide for titration. The potassium iodide solution containing iodide was acidified with sulfuric acid, and was titrated with standard sodium thiosulfate aqueous solution. As the result, it was turned out that 1.16% (w/w) ozone was adsorbed on the silica gel.[11]

**(3*R*, 1(10)*E*, 4*Z*)-3-Benzoyloxy-11,12,13-trinor-1(10),4-germacradiene-6,8-dione (15).** A solution of ketone **12b** (64 mg) in methanol (2 mL) and dichloromethane (1 mL) was stirred at −30 °C with introduction of ozone which was liberated from the saturated surface of 510 mg of the silica gel by nitrogen stream. (Calculated amount of ozone was 6.1 mg; 0.68 equivalent mole.) Acetic acid (0.2 mL) and zinc powder (ca. 50 mg) were added, and the mixture was stirred at 0 °C to room temperature for 15 min. After removal of excess zinc powder by filtration, the reaction mixture was diluted with ether, poured into water, and then was exracted with ether as usual. After evaporation, the residue was separated by preparative TLC (benzene-ether (5 : 1)). Together with the unreacted material **12b** (8.7 mg; $R_f$ 0.7) and a compound (probably **16**; 8 mg; $R_f$ 0.2), 10.8 mg of diketone (**15**; $R_f$ 0.3) was obtained. **15**: an oil, $[\alpha]_D^{18}$ −130° (*c* 0.27, $CHCl_3$); UV (EtOH) 230 nm ($\varepsilon$ 18100); IR (neat) 1730, 1720, 1680, 1640, and 1280 $cm^{-1}$; $^1H$ NMR ($CCl_4$; 90 MHz) $\delta$=1.48 (1.5H, br s), 1.74 (1.5H, br s), 1.90 (1.5H, br s), 1.98 (1.5H, br s), ca. 5.3 (1H, m), 6.02 (1H, br s), 6.22 (0.5H, dd, *J*=11 and 5 Hz), 6.41 (0.5H, dd, *J*=11 and 4 Hz), ca. 7.4 (3H, m), and ca. 8.0 (2H, m); MS *m/z* (%) 312 ($M^+$, 4.5), 190 (7), 172 (11), 122 (7), and 105 (100); Found: *m/z* 312.1356. Calcd for $C_{19}H_{20}O_4$: M, 312.1350.

**Ethyl (3*R*, 7*R*, 1(10)*E*, 4*Z*)-3-Benzoyloxy-6,8-dioxo-13-nor-1(10),4-germacradien-12-oate (17).** To a mixture of 5 mg of 50% sodium hydride in oil dispersion and 1 mL of THF was added a solution of diketone **15** (19.6 mg) in THF (1 mL) at 0 °C. After stirring for 30 min at room temperature, large excess amount of ethyl bromoacetate (0.03 mL) was added at 0 °C, and the mixture was stirred for 1.5 h at room temperature. Saturated brine was added, and the reaction mixture was extracted with ether as usual. After evaporation, the residue was separated by preparative TLC (hexane-ether (1 : 2)). Together with the starting material **15** (3.3 mg, $R_f$ 0.4), 9.2 mg of diketo ester **17** ($R_f$ 0.6) was obtained. **17**: white crystals, mp 148—149.5 °C (recrystallized from ether); $[\alpha]_D^{14}$ −160° (*c* 0.18, $CHCl_3$); UV (EtOH) 230 nm ($\varepsilon$ 21300); IR (KBr) 1725, 1680, 1635, and 1280 $cm^{-1}$; $^1H$ NMR ($CDCl_3$; 270 MHz) $\delta$=1.25 (3H, t, *J*=7 Hz), 6.29 (1H, br s), ca. 7.5 (3H, m), and ca. 8.0 (2H, m). Other signals could be assigned to one of two conformational isomers, the ratio of which was almost 2 : 1. The major isomer: $\delta$=1.72 (3H, br s), 1.96 (3H, br s), 2.45 (1H, q, *J*=11.7 Hz), 2.90, 2.95, 3.44, and 3.49 (2H, ABq, *J*=13.7 Hz), 4.02 (1H, t, *J*=7.1 Hz), 4.12 (2H, q, *J*=7.1 Hz), 5.11 (1H, br dd, *J*=12 and 5 Hz), and 6.35 (1H, dd, *J*=11.7 and 3.8 Hz). The minor isomer: $\delta$=1.65 (3H, br s), 1.98 (3H, br s), 2.17 (1H, ddd, *J*=12, 12, and 7.8 Hz), 3.00, 3.04, 3.21, and 3.26 (2H, ABq, *J*=11.5 Hz), 4.24 (1H, dd, *J*=8.5 and 5.9 Hz), 4.13 (2H, q, *J*=7.1 Hz), 5.50 (1H, br t, *J*=8 Hz), and 6.25 (1H, dd, *J*=12 and 5.7 Hz). MS *m/z* (%) 398 ($M^+$, 8), 276 (11), 212 (25), 122 (28), and 105 (100); Found: *m/z* 398.1723. Calcd for $C_{23}H_{26}O_6$: M, 398.1729.

**(3*R*, 7*R*, 8*R*, 1(10)*E*, 4*Z*)-3-Benzoyloxy-6-oxo-13-nor-1(10),4-germacradieno-12,8-lactone (3).** To a solution of diketo ester **17** (4.4 mg) in ethanol (2 mL) and dichloromethane (0.1 mL) was added sodium borohydride (1 mg) at 0 °C, and the mixture was stirred for 1 h. After addition of acetone to destroy the excess hydride reagent, the reaction mixture was acidified by addition of dil. HCl. After concentration of the solution in vacuo, ether extraction as the usual work-up, and evaporation, the residue was separated by preparative TLC (hexane-ethyl acetate (2 : 1)). Togethr with the unreacted material **17** (0.9 mg, $R_f$ 0.6), lactone **3** (1.4 mg, $R_f$ 0.3) was obtained. **3**: white crystals, mp 149—150.5 °C (recrystallized from $CHCl_3$); $[\alpha]_D^{19}$ −190° (*c* 0.14, $CHCl_3$); UV (EtOH) 232 nm ($\varepsilon$ 18100); IR (Nujol) 1780, 1730, 1710, 1680, 1620, 1275, and 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$=1.57 (3H, br s), 1.94 (3H, br s), ca. 2.4 (2H, m), 2.41 (1H, dd, *J*=18.1 and 8.1 Hz), ca. 2.6 (2H, m), 3.25 (1H, dd, *J*=18.1 and 12.6 Hz), 3.63 (1H, td, *J*=12.6 and 8.1 Hz), 5.1 (2H, m), 6.14 (1H, br s), 6.48 (1H, dd, *J*=11.6 and 4.2 Hz), 7.4—7.7 (3H, m), and 8.0—8.15

(2H, m); MS *m/z* (%) 354 ($M^+$, 2), 232 (7), 214 (13), 122 (11), and 105 (100); Found: *m/z* 354.1481. Calcd for $C_{21}H_{22}O_5$: M, 354.1467.

The authors wish to thank Professor W. Clark Still, Columbia University, for the kind sending of a copy of 270 MHz $^1H$ NMR spectrum of their synthetic intermediate **5**.

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