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Studies on the Terpenoids and Related Alicyclic Compounds. XXVIII.[1] Chemical Transformations of α-Santonin into C-8 Lactonized Eudesmanolides: Yomogin and Diastereoisomers of Dihydrograveolide

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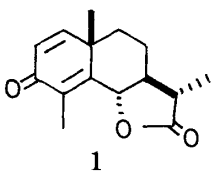
The chemical transformations of α-santonin (**1**), a C-6 lactonized eudesmanolide, into C-8 lactonized eudesmanolides, *i.e.*, yomogin (**2**) and four diastereoisomers of dihydrograveolide (**36**—**39**), are described. Transposition of 6,13-olide into 8,13-olide in eudesmanolides was investigated. Allylic oxidation of the trienone (**12**) with *tert*-butyl chromate gave 3,8-dioxotriene (**20**) and 3,6-dioxotriene (**22**). Reductive lactonization of **20** gave 11α- and 11β-methyl *cis*-lactones (**30** and **31**). Yomogin (**2**) was synthesized from the *cis*-lactones (**32** and **33**) by phenylselenenylation and deselenoxylation procedures. Catalytic reduction of **30** and **31** gave diastereoisomers of dihydrograveolide (**36**—**39**).

Keywords——sesquiterpene lactone; α-methylene-γ-lactone; synthesis; α-santonin; yomogin; dihydrograveolide; allylic oxidation; bromination–dehydrobromination; selective reduction; transposition of lactone

The eudesmane sesquiterpenoids possessing a 6,13-olide moiety, as typically seen in α-santonin (**1**), are widely distributed in the family Compositae. Many kinds of C-8 lactonized eudesmanolides having the α-methylene-γ-lactone moiety as a biologically active structural feature are also well-known,[2] for example, yomogin (**2**), telekin (**3**), pinnatifidin (**4**), graveolide (**5**), alantolactone (**7**), ivalin (**8**), *etc.*



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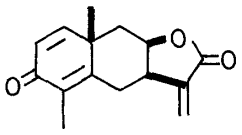

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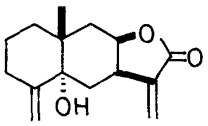

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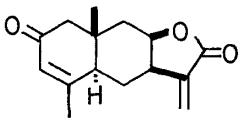

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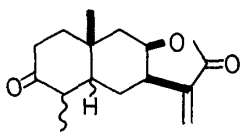

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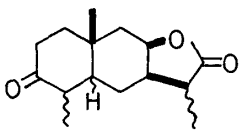

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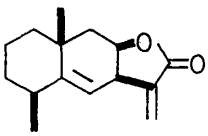

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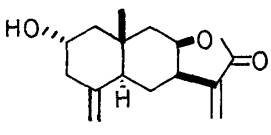

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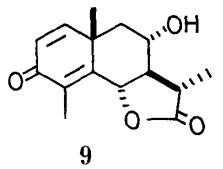

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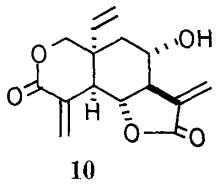

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In this paper, the authors wish to report the chemical transformations of α-santonin (**1**) into yomogin (**2**)[3,4] and dihydrograveolide (**6**). These transformations involve transposition of the lactone from 6,13- to 8,13-olide.

Geissman[5] reported the isolation of yomogin (**2**) from *Artemisia princeps*, which was collected in the garden of the University of Tokyo, Japan, and its structural determination. The cross-conjugated dienone moiety of yomogin (**2**) is closely related to that of α-santonin (**1**) and **2** contains an α-methylene C-8 lactone moiety.

Transposition of the lactone at C-8 to C-6 has been reported by Naemura[6] in the total synthesis of artemisin (**9**) and also by Grieco *et al.*[7] in the total synthesis of vernolepin (**10**). However, the transposition of the lactone from C-6 to C-8 in eudesmanolides has not been reported yet. For the purpose of the synthesis of the C-8 lactonized eudesmanolides yomogin (**2**), telekin (**3**), and pinnatifidin (**4**) from α-santonin (**1**), introduction of an oxygen function at the C-8 position of **1** is necessary, but has not yet been achieved.

Introduction of an oxygen function at the allylic position of cyclohexenes,[8] terpenoids and steroids[9] by oxidation procedures has been reported, so allylic oxidations of the trienone derivative (**12**) were attempted. The preparation of the trienone (**12**) by the dehydrobromination of 6-bromide (**11c**) was reported,[10] but the yield was not satisfactory. Thus, an improved method for the preparation of the trienone (**12**) from the known dienone (**11b**) was sought. Dehydrogenation of **11b** with dichlorodicyanobenzoquinone (DDQ) in diphenyl ether at 150—160 °C for 48 h, and with chloranil in refluxing *tert*-butanol for 24 h, furnished the starting material. Mincione *et al.*[11] reported that the dehydrogenation of 3-ketosteroids with $PdCl_2$ in *tert*-butanol at 80 °C for 20 h gave α,β-unsaturated ketones, but when this procedure was applied to the dienone (**11b**), all the starting dienone was recovered. Bromination of the dienone ester (**11b**) with 1.2 molar eq of Br_2 in $CHCl_3$ gave the dibromide (**13**), mp 116—119 °C, in 22.5% yield and recovered **11b** in 42% yield without the desired 6-bromide (**11d**). The stereoformula of the dibromide (**13**) was assigned by ^1H nuclear magnetic resonance (NMR) spectroscopy. A singlet olefinic proton signal attributable to the C-1 proton in the α-bromoenone moiety appeared at δ 7.16 and the 6α-proton signal appeared at δ 5.50 ($W_{1/2}$ = 5 Hz). The chemical shift of the angular methyl signal is lower ($\Delta\delta$ 0.35 ppm) than that of **11b** because of the 1,3-diaxial bromine effect, which was previously reported by us.[12] Therefore, the C-6 bromine is assumed to have β-configuration. Catalytic reduction of **11b** with Wilkinson catalyst, $[(Ph_3P)_3RhCl]$, according to the procedure of Piers *et al.*[13] gave the 3-oxo-4-ene (**14**) in 91% yield. Treatment of the enone (**14**) with 2 molar eq of bromine gave the dibromide (**15**), mp 125—127 °C and tribromide (**16**), mp 149—150 °C, whose structures were assigned by NMR spectroscopy. Dehydrobromination of the dibromide (**15**) with lithium bromide (LiBr) and lithium carbonate (Li_2CO_3) in dimethylformamide (DMF) according to the procedure reported by Corey *et al.*[14] gave the desired trienone (**12**) in 91% yield, whereas **15** was treated with diazabicyclo[5.4.0]undecene (DBU) to give only the ene-bromide (**17**). The formation mechanism of **17** may be assumed to be as shown in Chart 1. Treatment of the tribromide (**16**) with LiBr–Li_2CO_3 in DMF or DBU in benzene gave the trienone-bromide (**18**), mp 122—124 °C.

The practical preparation of the trienone (**12**) was carried out as follows. Bromination of the enone (**14**) with 2 molar eq of bromine followed by dehydrobromination by Corey's procedure[14] without purification gave **12** in 40—50% overall yield. An alternative convenient preparation of **12** was also examined. The dienone ester (**11b**) was converted into the enol-acetate (**19**), which was brominated with pyridine perbromide to yield the 6β-bromide (**11d**). Dehydrobromination of **11d** with DBU in refluxing benzene for 30—50 min gave **12**. The overall yield of **12** was 66% from **19**.

Allylic oxidation of **12** with chromium trioxide–pyridine complex for 8 d under conditions similar to those reported by Dauben *et al.*[9] for steroid olefins gave two ketones (**20**:

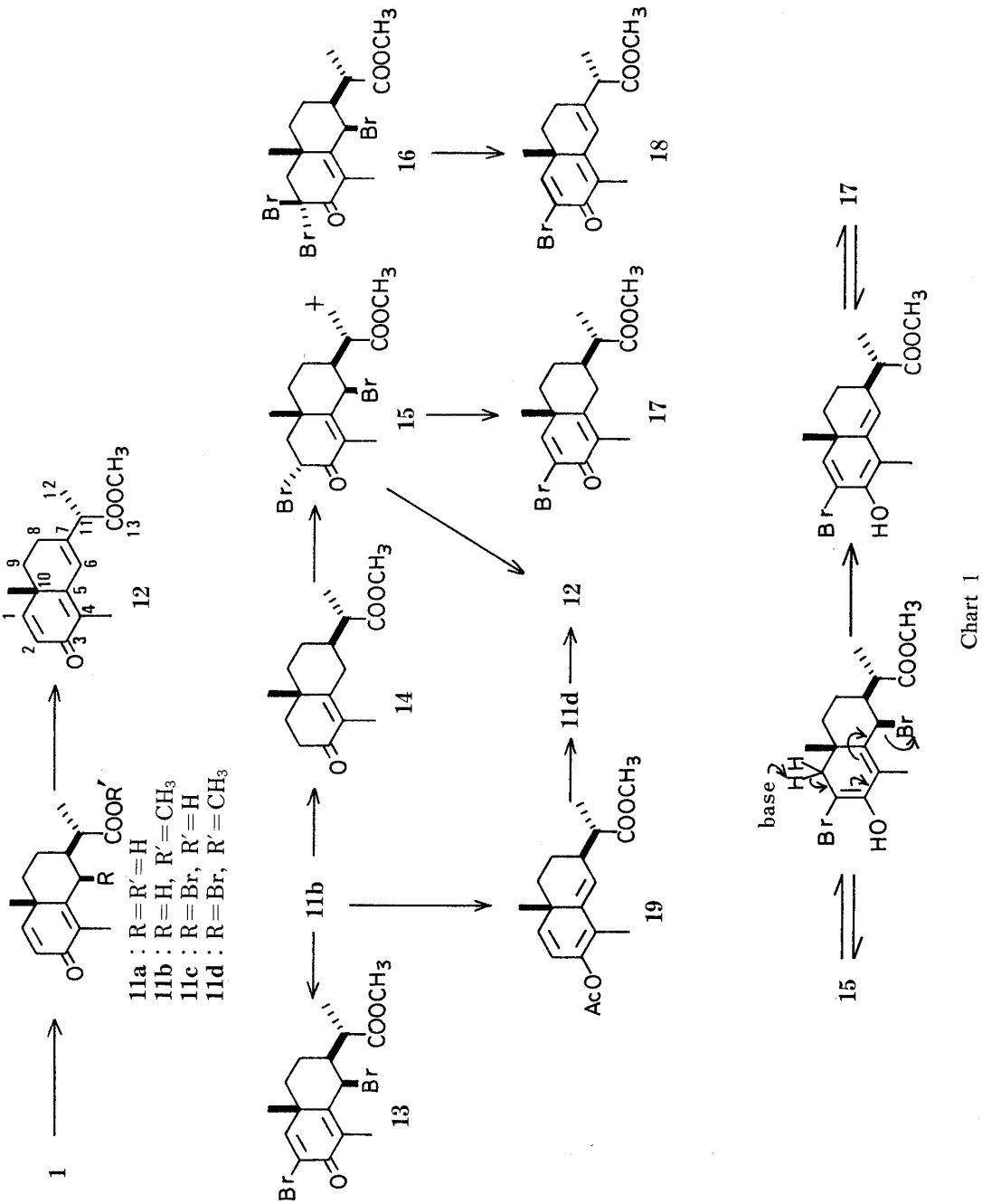


Chart 1

mp 127.5—129 °C and **21**: mp 95—97 °C) in 3.5 and 8% yields, respectively, together with 31% yield of the starting material (**12**). The ketone (**20**) showed characteristic absorption bands due to $\alpha,\beta,\gamma,\delta$-unsaturated dienone at λ_{max} 310 nm and ν 1670, 1646, and 1618 cm^{-1} in the ultraviolet (UV) and infrared (IR) spectra, respectively. High-resolution mass measurement and elemental analysis of **20** indicated the molecular formula $C_{16}H_{18}O_4$. From these spectral data, the structure of the ketone (**20**) was confirmed to be methyl 3,8-dioxoeudesm-1,4,6-trienoate. The other ketone (**21**) had the molecular formula $C_{16}H_{20}O_4$ as determined by high-resolution mass measurement. An α,β-unsaturated ketone moiety was apparent from its UV (λ_{max} 245.5 nm) spectrum. From these spectral data, the structure was assumed to be a 3,8-dioxo-1,4-diene (**21**) or 3,6-dioxo-1,4-diene (**23b**). Nishikawa and Morita[15] synthesized the diketone (**23b**), mp 81 °C, from α-santonin *via* three steps; the physical and spectral data are different from those of the diketone (**21**), and therefore the structure of the diketone (**21**) was confirmed to be methyl 3,8-dioxoeudesm-1,4-dienoate.

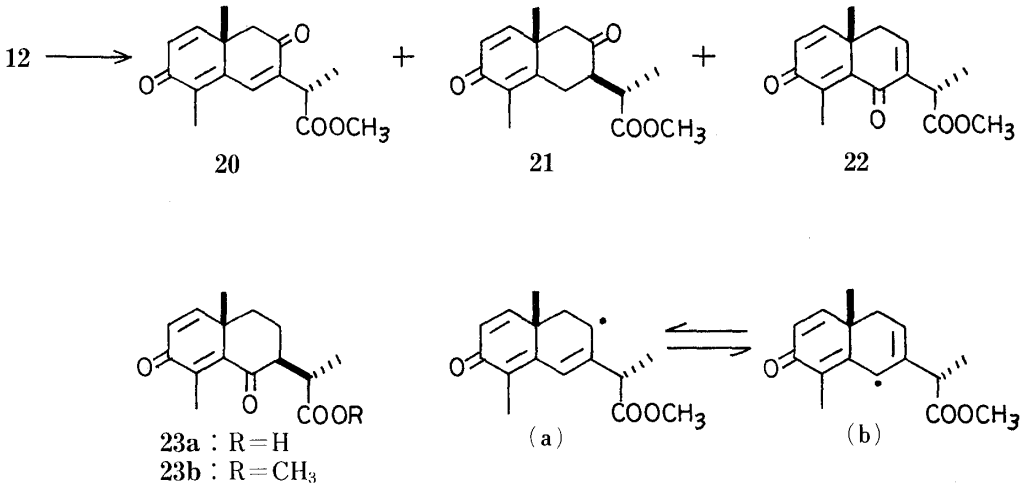


Chart 2

Next, the *tert*-butyl chromate oxidation method[16] was investigated. Refluxing a carbon tetrachloride solution of the trienone (**12**) with *tert*-butyl chromate containing acetic anhydride for 3 d gave a mixture of two ketones (**20**: 25—37% yield, and **22**: 11—16% yield). This oxidation was investigated under various conditions, but selective preparation of the desired diketone (**20**) was not achieved. The minor enone (**22**), mp 103—105 °C showed the same molecular ion peak as that of the ketone (**20**) at *m/z* 274 on mass spectrometry. The α,β-unsaturated ketone moiety was confirmed by the IR (1728, 1652, and 1628 cm^{-1}) and UV (λ_{max} 253 and 280 nm) spectra. Thus, the structure of the enone (**22**) was shown to be methyl 3,6-dioxoeudesm-1,4,7-trienoate. These enones (**20** and **22**) are probably produced *via* two allylic radicals (**a** and **b**) as intermediates.

In order to prepare C-8 lactonized eudesmanolide, 3,8-dioxo-triene (**20**) was reduced with lithium aluminum hydride to give two products (**24**: mp 70—72 °C in 17% yield, and **25**: 24% yield). High-resolution mass measurement of **24** indicated the molecular formula $C_{16}H_{20}O_4$. Compound **24** showed an $\alpha,\beta,\gamma,\delta$-unsaturated ketone chromophore (λ_{max} 308 nm) in its UV spectrum but no absorption band due to a hydroxyl group in its IR spectrum. In the NMR spectrum of **24**, a singlet signal appeared at δ 7.33 due to an olefinic proton, but no doublet signal due to C-1,2 olefinic protons. From these spectral data, the structure of **24** was confirmed to be methyl 3,8-dioxoeudesm-4,6-dienoate. The oily product **25** showed a molecular ion at *m/z* 276 in its mass spectrum (MS). Its UV spectrum showed α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated ketone chromophores (λ_{max} 227 and 307 nm) and a hydroxyl absorption band (3450 cm^{-1}) was seen in its IR spectrum. The NMR spectrum of **25** showed three olefinic

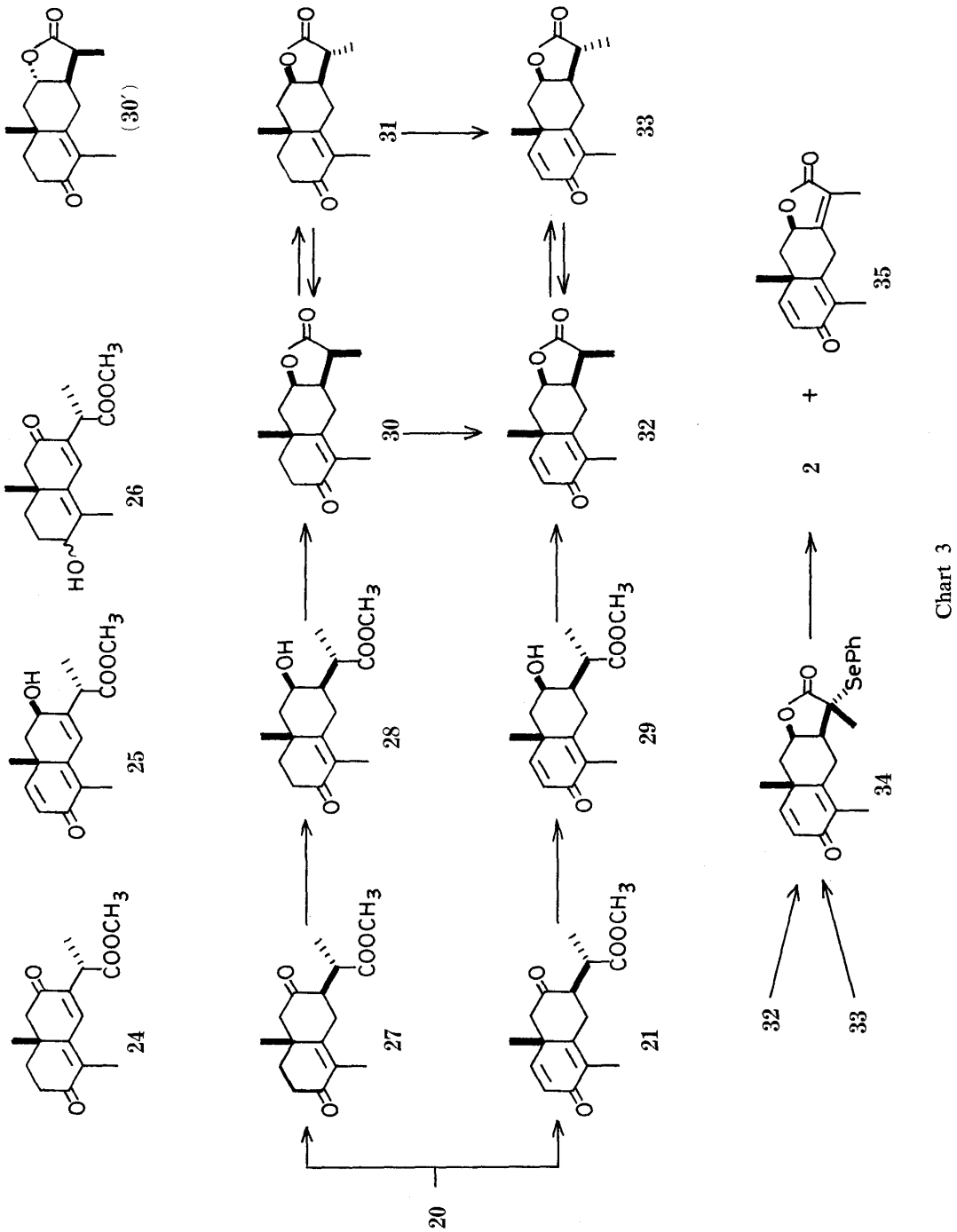


Chart 3

proton signals and a broad doublet signal (δ 4.40, $J=6$ Hz) due to the C-8 proton. From these spectral data, the structure of **25** was concluded to be methyl 8β-hydroxy-3-oxoeudesm-1,4,6-trienoate.

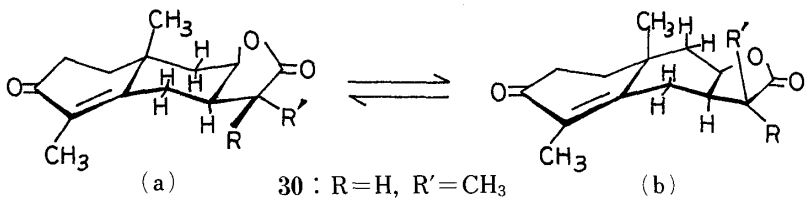
The reduction of **20** with lithium tri-*tert*-butoxyaluminum hydride gave **24** (26% yield) and a new reduction product (**26**) in 25% yield. Oxidation of the latter compound (**26**) gave **24**. Thus, the structure of **26** was confirmed to be methyl 3ξ-hydroxy-8-oxo-eudesm-4,6-dienoate. Reduction of **20** with sodium borohydride gave **25** and **26** in 50 and 16% yields, respectively.

For the purpose of lactonization, treatment of the 8β-hydroxy compound (**25**) with sodium hydroxide followed by acidification with hydrochloric acid gave a complex mixture, but no lactonized compound could be detected. This suggests that the lactonization is disturbed by the presence of the C-6 (7) double bond, presumably for steric reasons.

Therefore, selective catalytic reduction of the C-6 (7) double bond of **20** was carried out. Compound **20** was reduced with tris(triphenylphosphine)-chlororhodium[17] in benzene containing a small amount of ethanol under medium pressure of hydrogen for 3 or 4 d to give 87% yield of the 3,8-dioxo-4-ene (**27**) accompanied by a small amount of the diketo diene (**21**). Reduction of a mixture of **27** and **21** with sodium borohydride in methanol at -20 °C gave ketols (**28**: mp 128—138 °C and **29**: oil) in 58 and 24% yields respectively. The configuration of the C-8 hydroxyl groups of **28** and **29** should be β because of the half-height width (8 and 12 Hz, respectively) of the C-8 proton signal of **28** and **29**.

Treatment of **28** with aqueous sodium hydroxide followed by acidification with hydrochloric acid gave two lactones, (**30**) as a major product, mp 111—112 °C, and (**31**) as a minor product, mp 189 °C. Mass spectral and elemental analyses of **30** and **31** indicated the same molecular formula, $C_{15}H_{20}O_3$. The IR and UV spectra of **30** and **31** showed the presence of γ-lactone and enone moieties. Both lactones (**30** and **31**) were treated with potassium carbonate in refluxing xylene to give an equilibrium mixture of **30** and **31** in a 2 : 3 ratio. From these results, **30** and **31** should be C-11 epimers. Reduction of **27** with lithium tri-*tert*-butoxyaluminum hydride or sodium borohydride followed by 3 N sodium hydroxide without isolation of the alcohol (**28**), then acidification with hydrochloric acid gave lactones (**30**) in 64% yield, and (**31**) 11% yield.

The configuration of the γ-lactone and the conformation of ring B in **30** and **31** were investigated by NMR spectrometry. Physical data for **30** were not consistent with those of the *trans*-lactone (**30′**) derived from isoalantolactone (**40**) reported by Naemura and Nakazaki.[18] In compound **30**, signals due to the C-8 proton appeared as a quartet, $W_{1/2}=10$ Hz, at δ 4.45. This suggests that the γ-lactone is *cis*-fused to the cyclohexane ring B in the chair form. When **30** is in the more unstable conformation **30b**, ring B is in boat form, and the steric repulsion between the C-11 methyl and 6β-H is apparent in a Dreiding model. Therefore, **30** may exist preferentially with ring B in the chair form in the *cis*-lactone (**30a**).



30 : R=H, R′=CH$_3$
31 : R=CH$_3$, R′=H

Chart 4

The signal due to the C-8 proton in **31** appeared as a multiplet, $W_{1/2}=20$ Hz, at δ 4.50. On the basis of the molecular model, the coupling constant between the protons at C-8 and C-7 ($W_{1/2}=20$ Hz) suggested that the γ-lactone is *cis*-fused to the cyclohexane ring B in boat

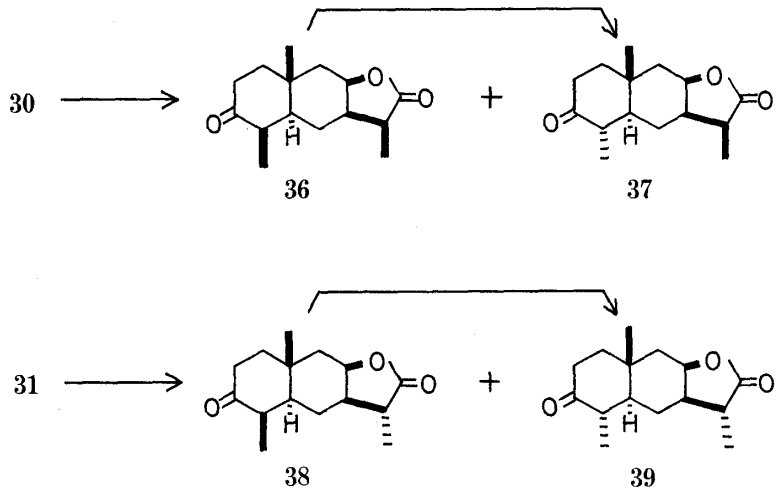
form (**31b**). It is considered that the conformation **31a** is less favorable because of the 1,3-diaxial interaction between the C-10 methyl group and C(8)–O bond of the γ-lactone ring. Therefore, the preferred conformation of **31** should be the boat form in ring B (**31b**).

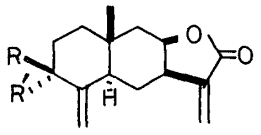
Treatment of the dienone alcohol (**29**) with alkali followed by acidification with hydrochloric acid provided the 8,13-olide (**32**), mp 180—180.5 °C, in 60% yield. In the NMR spectrum of **32**, the signal due to the C-8 proton appeared as a broad triplet at δ 4.50, $W_{1/2}$ = 10 Hz, which also supported the *cis*-lactone (**32**) structure.

Dehydrogenation of **30** with DDQ in refluxing dioxane gave the dienone (**32**) in 72% yield. Treatment of **31** under the same condition gave a dienone lactone (**33**), mp 135—136 °C, in 73% yield. Both C-11 epimers (**32** and **33**) were refluxed in xylene in the presence of potassium carbonate to give an equilibrium mixture of **32** and **33** in a 3:2 ratio. The configuration of the C-11 methyl of **32** should be β, in view of the above results. Phenylselenenylation of **32** according to Grieco's procedure,[19] gave a phenylselenide (**34**), mp 218—219 °C, in 42% yield. Compound **34** was also obtained from **33** by phenylselenenylation under the same conditions as used for the lactone (**32**). In the NMR spectrum of **34**, a singlet signal of the C-11 methyl group and multiplet signals of phenyl protons appeared at δ 1.60 and 7.2—7.7, respectively. Treatment of **34** with hydrogen peroxide in tetrahydrofuran produced a 1.2:1 mixture of exocyclic isomer, yomogin (**2**), and endocyclic isomer (**35**). Recrystallization of the mixture gave pure yomogin (**2**), mp 210—211 °C, in 37% yield. The IR and NMR spectra of **2** were identical with those of yomogin which was isolated from *Artemisia princeps* by Geissman.[5]

In 1973 d'Alcontres *et al.*[20] reported the isolation of graveolide from *Inula graveolens* and they proposed it to be a C-8 lactonized endesmanolide (**5**) based on some chemical transformations and spectroscopic data. Catalytic reduction of graveolide gave dihydrograveolide (**6**), mp 135—136 °C.

We attempted the structural elucidation of dihydrograveolide by means of synthetic





40 : R=R'=H
41 : R=OH, R'=H

Chart 5

TABLE I. Physical and Spectral Data for Dihydrograveolide and Its Diastereoisomers

Compound	mp (°C)	$[\alpha]_D$ (°)	NMR (δ)				IR (cm^{-1})
			4-CH_3	10-CH_3	11-CH_3	8-H	
Dihydro-graveolide[20]	135—136		1.07 (d) J=5 Hz	1.02 (s)	1.19 (d) J=6.4 Hz	4.34 (m)[a]	1760, 1730
36	161—164	−23.9	1.12 (d) J=8 Hz	1.20 (s)	1.24 (d) J=7 Hz	4.51 (m) $W/2$=9	1753, 1743, 1705
37	173—174	−40.7	1.05 (d) J=7 Hz	1.18 (s)	1.23 (d) J=7 Hz	4.50 (m) $W/2$=9	1763, 1753, 1709
38	90—92	+96.4	1.11 (d) J=8 Hz	1.23 (s)	1.32 (d) J=8 Hz	4.73 (m) $W/2$=9	1754, 1702
39	114—116	+15.5	1.04 (d) J=7 Hz	1.21 (s)	1.32 (d) J=8 Hz	4.71 (m) $W/2$=9	1763, 1707

a) Coupling constants; $J_{7,8}$=9 Hz, $J_{8,9}$=3 Hz, $J_{8,9'}$=11 Hz.

correlation with hydrogenated yomogin. Catalytic reduction of both tetrahydroyomogins (**30** and **31**) with palladium charcoal gave four diastereoisomers of dihydrograveolide (**36**—**39**). Compounds **36** and **38** were epimerized by acid to **37** and **39**, respectively. Therefore, **36** and **38** should be epimers of **37** and **39** at C-4, respectively, and **36** and **38** should be unstable 4β-methyl isomers.

The physical and NMR data for **37** are identical with those reported for 3-oxo-4β,5α,7α,11α(H)-eudesman-8β,13-olide derived from (+)-3-epiisotelekin (**41**) by Geissman.[21] The structures of **36**—**39** were determined to be as shown in Chart 5 from the results described above.

These physical and spectral data for the four diastereoisomers of C-8 lactonized 3-oxoeudesmanolides (**36**—**39**) are not consistent with those of dihydrograveolide reported by d'Alcontres *et al.*[20] Thus, the A/B ring fusion should be *cis* in graveolide (**5**).

Experimental

All melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. NMR spectra were measured as solutions in $CDCl_3$ with a Hitachi R-24 spectrometer at 60 MHz and with JEOL JNM-4H-100 and FX-100 FT-NMR spectrometers at 100 MHz. Tetramethylsilane (TMS) was used as an internal reference. IR spectra were measured as KBr disks unless otherwise mentioned with Hitachi 215 and Hitachi-Perkin Elmer 225 grating spectrophotometers. UV spectra were measured as solutions in EtOH with a Hitachi 323 spectrophotometer. Mass spectra were recorder on a Hitachi RMU-7M double-focusing mass spectrometer at 70 eV, using direct insertion. High-resolution mass spectral data were determined with a Hitachi datalyzer 002 system connected on-line with the mass spectrometer. Specific rotations were measured as solutions in $CHCl_3$ with a Jasco DIP-SL digital polarimeter.

Wako silica gel C-200 (200 mesh) containing 2% fluorescence reagent 254 was used in column chromatography. Preparative thin-layer chromatography (TLC) was carried out using Merck silica gel HF_{254}.

Methyl 3-Oxoeudesm-1,4-dienoate (11b)——6-Dehydrosantoninic acid (**11a**), which was prepared from santonin (**1**) according to the known procedure,[10] was methylated with ethereal diazomethane to give the methyl ester (**11b**), $bp_{1.4}$ 153—157 °C. $[\alpha]_D^{23}$ −91.8° (c=0.77). UV nm (ε): 240 (11600). IR cm^{-1}: 1733, 1658, 1629, 1607. NMR δ: 1.23 (3H, s, 10-CH_3), 1.23 (3H, d, J=8 Hz, 11-CH_3), 1.91 (3H, d, J=1 Hz, 4-CH_3), 3.74 (3H, s, $COCH_3$), 6.22 (1H, d, J=10 Hz, 2-H), 6.75 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 262 (M^+, 50), 247 (5), 203 ($M^+ - CH_3COO$, 13), 175 (100), 159 (77).

Methyl 3-Oxo-2β,6β-dibromoeudesm-1,4-dienoate (13)——A solution of **11b** (300 mg, 1.14 mmol) in 10 ml of $CHCl_3$ containing one drop of 48% HBr–AcOH was treated dropwise over a period of 15 min with 220 mg (1.38 mmol) of Br_2 in 3 ml of $CHCl_3$. The mixture was stirred at room temperature for 3.5 h, then washed with 10% $NaHCO_3$, 10% $Na_2S_2O_3$, and H_2O, and dried. After removal of the $CHCl_3$ *in vacuo*, the product was separated by

preparative TLC with hexane–EtOAc (5 : 1) to give 108.3 mg (22.5%) of the 2,6-dibromoenone (**13**) as yellow crystals and 126 mg (42%) of **11b**. Recrystallization of **13** from hexane–EtOAc gave colorless needles, mp 116—119 °C. UV nm (ε): 207 (12000), 262 (13000). IR cm^{-1}: 1725, 1648, 1595. NMR δ: 1.30 (3H, d, J=7 Hz, 11-CH_3), 1.58 (3H, s, 10-CH_3), 2.04 (3H, s, 4-CH_3), 3.76 (3H, s, $COOCH_3$), 5.50 (1H, br d, $W_{1/2}$=5 Hz, 6-H), 7.16 (1H, s, 1-H). MS m/z (% rel. int.): 341 (12), 339 (M^+ − HBr, 12), 259 (M^+ − HBr − Br, 86), 199 (100), 172 (62).

Methyl 3-Oxo-eudesm-4-enoate (14)——Catalytic hydrogenation of **11b** (600 mg) was performed in benzene (30 ml) with $Rh(Ph_3P)_3Cl$ (120 mg) under an H_2 atmosphere for 8 h. Evaporation of the benzene gave a viscous oil, which was purified on a silica gel column with EtOAc–hexane (1 : 5) to give 550 mg (91%) of the 3-oxo-4-ene (**14**) as a yellow oil. $[\alpha]_D^{23}$ +93.0° (c=0.55). UV nm (ε): 247 (10500). IR ν_{max}^{film} cm^{-1}: 1736, 1665, 1613. NMR δ: 1.20 (3H, s, 10-CH_3), 1.20 (3H, d, J=7 Hz, 11-CH_3), 1.76 (3H, d, J=7 Hz, 4-CH_3), 3.75 (3H, s, $COOCH_3$). MS m/z (% rel. int.): 264 (M^+, 13), 249 (10), 205 (5), 177 (100).

Bromination of Methyl 3-Oxoeudesm-4-enoate (14)——a) With 3 Molar eq of Br_2: **14** (1.47 g, 5.56 mmol) in 60 ml of $CHCl_3$ was treated with Br_2 (2.9 g, 16 mmol) at room temperature for 6 h. Removal of the $CHCl_3$ *in vacuo* afforded crude methyl 3-oxo-2,2,6β-tribromoeudesm-4-enoate (**16**). Recrystallization from benzene–hexane afforded 642 mg (23%) of **16** as colorless needles, mp 149—150 °C. $[\alpha]_D^{24}$ −94.3° (c=2.1). UV nm (ε): 274 (10500). IR ν_{max} cm^{-1}: 1729, 1676, 1596. NMR δ: 1.28 (3H, d, J=7 Hz, 11-CH_3), 1.77 (3H, s, 10-CH_3), 2.00 (3H, s, 4-CH_3), 3.10, 3.12 (each 1H, d, J=15 Hz, 1-H_2), 3.76 (3H, s, $COOCH_3$), 5.37 (1H, br s, $W_{1/2}$=5 Hz, 6-H). MS m/z (% rel. int.): 423 (M^+ − Br, 52), 421 (M^+ − Br, 100), 419 (M^+ − Br, 53), 363 (8), 361 (14), 359 (8), 342 (M^+ − Br–HBr, 44), 340 (M^+ − Br–HBr, 43). *Anal.* Calcd for $C_{16}H_{23}Br_3O_3$: C, 38.35; H, 4.22; Br, 47.84. Found: C, 38.35; H, 4.18; Br, 47.47.

b) With 2 Molar eq of Br_2: The enone (**14**) (1.50 g, 5.7 mmol) was treated with Br_2 (2.0 g, 11 mmol) in 60 ml of $CHCl_3$ at room temperature for 1 h. Work-up as usual gave a crude product, which was recrystallized from benzene–hexane to give 618 mg of pale yellow crystals. This product was found to be a 1 : 1 mixture of dibromide (**15**) and tribromide (**16**) by NMR analysis. The residue from the mother liquor was recrystallized from benzene–hexane to give 583 mg (24%) of methyl 3-oxo-2α,6β-dibromoeudesm-4-enoate (**15**) as colorless columns, mp 125—127 °C. $[\alpha]_D^{24}$ −56.8° (c=1.6). UV nm (ε): 263 (11800). IR cm^{-1}: 1736, 1731, 1676, 1600. NMR δ: 1.28 (3H, d, J=7 Hz, 11-CH_3), 1.59 (3H, s, 10-CH_3), 1.90 (3H, s, 4-CH_3), 2.33 (2H, d, J=10 Hz, 1-H), 3.75 (3H, s, $COOCH_3$), 4.98 (1H, t, J=10 Hz, 2-H), 5.38 (1H, br s, $W_{1/2}$=5 Hz, 6-H). MS m/z (% rel. int.): 425, 423, 421 (M^+, 1) 343, 341 (M^+ − HBr, 100), 283 (22), 281 (22), 261 (14), 201 (40), 173 (66).

Dehydrobromination of Dibromide (15)——a) With LiBr–Li_2CO_3: **15** (250 mg, 0.59 mmol) was added to a suspension of LiBr (105 mg) and Li_2CO_3 (110 mg) in 5 ml of DMF at 125—130 °C. The mixture was heated at the same temperature for 30 min, then cooled. The product was extracted with CH_2Cl_2. Evaporation of CH_2Cl_2 *in vacuo* furnished a crude product, which was purified by preparative TLC with hexane–EtOAc (5 : 1) to give 118.2 mg (91%) of methyl 3-oxoeudesm-1,4,6-trienoate (**12**).[10]

b) With DBU: A solution of **15** (120 mg, 0.28 mmol) in benzene (7 ml) was heated under reflux with DBU (98 mg, 0.64 mmol) for 1.5 h. Evaporation of the benzene followed by preparative TLC with hexane–EtOAc (5 : 1) gave 12.4 mg (13%) of methyl 3-oxo-2-bromoeudesm-1,4-dienoate (**17**) as an oil. UV nm (ε): 206 (10100), 254 (12700). IR ν_{max}^{film} cm^{-1}: 1726, 1643, 1604. NMR δ: 1.23 (3H, d, J=7 Hz, 11-CH_3), 1.27 (3H, s, 10-CH_3), 1.96 (3H, d, J=1 Hz, 4-CH_3), 3.74 (3H, s, $COOCH_3$), 7.23 (1H, s, 1-H). MS m/z (% rel. int.): 342, 340, (M^+, 17), 327 (6), 325 (7), 239, 237 (40), 201 (M^+ − Br–$COOCH_3$, 25), 174 (72), 173 (100).

Methyl 3-Oxo-2-bromoeudesm-1,4,6-trienoate (18)——A mixture of **16** (200 mg), LiBr (53 mg) and Li_2CO_3 (44 mg) in 5 ml of DMF was heated at 125—130 °C for 1 h. Work-up as described above followed by TLC separation with hexane–EtOAc (5 : 1) gave 105 mg (78%) of the trienone (**18**). Recrystallization from benzene–hexane yielded colorless needles, mp 122—124 °C. $[\alpha]_D^{20}$ +370.5° (c=1.46). UV nm (ε): 238 (12800), 267 (7360), 317 (11600). IR cm^{-1}: 1730, 1675, 1610. NMR δ: 1.23 (3H, s, 10-CH_3), 1.41 (3H, d, J=7 Hz, 11-CH_3), 2.03 (3H, s, 4-CH_3), 3.32 (1H, q, J=7 Hz, 11-H), 3.73 (3H, s, $COOCH_3$), 6.52 (1H, br s, $W_{1/2}$=5 Hz, 6-H), 7.21 (1H, s, 1-H). MS m/z (% rel. int.): 340, 338 (M^+, 55), 259 (M^+ − Br, 47), 199 (M^+ − HBr − $COOCH_3$, 100).

Conversion of 14 into 12——The enone (**14**) (10 g, 3.8 mmol) was treated with 13.4 g (7.4 mmol) of Br_2 in 400 ml of $CHCl_3$ with stirring at room temperature for 1 h. The crude bromide was dehydrobrominated with LiBr (4.3 g) and Li_2CO_3 (4.1 g) in 150 ml of DMF with stirring at 125—130 °C for 45 min. Usual work-up gave a crude oil, which was separated on a silica gel column with hexane–EtOAc (5 : 1) to give 1.34 g (10% yield from **14**) of methyl 3-oxo-2-bromoeudesm-1,4-dienoate (**18**) and 5.47 g (56% yield from **14**) of 3-oxo-1,4,6-trienone (**12**).

Acetylation of 11b——The diene (**11b**) (13 g) and 1.3 g of *p*-TsOH were dissolved in 110 ml of isopropenyl acetate and the mixture was heated under reflux for 3 d. After removal of the excess isopropenyl acetate, the mixture was chromatographed on a silica gel column with hexane–EtOAc (30 : 1) to afford 11.7 g (78%) of the enol acetate (**19**) as a yellow oil. IR ν_{max}^{film} cm^{-1}: 1755, 1730, 1210, 1165. NMR δ: 1.15 (3H, s, 10-CH_3), 1.15 (3H, d, J=7 Hz, 11-CH_3), 1.71 (3H, s, 4-CH_3), 2.20 (3H, s, $OCOCH_3$), 3.70 (3H, s, $COOCH_3$), 5.4 (1H, d, J=3 Hz, 6-H), 5.65 (2H, s, 1,2-H). MS m/z (% rel. int.): 304 (M^+, 9), 262 (17), 175 (100), 159 (31).

Methyl 3-Oxoeudesm-1,4,6-trienoate (12)——A stirred solution of the enolacetate (**19**) (11.2 g) in a mixture of $CHCl_3$ (120 ml) and CCl_4 (30 ml) was treated with 11 g of freshly prepared pyridine perbromide[23] at 5—10 °C. The reaction was found to be complete after 30 min as judged by TLC (hexane–EtOAc 4 : 1). After usual work-up,

evaporation of the solvent gave 13.5 g of the 6β-bromide (**11d**) as a yellow–brown oil, which was chromatographed on a silica gel column. The product was recrystallized from hexane–EtOAc to give colorless prisms, mp 104—105 °C. IR cm^{-1}: 1725, 1655, 1630, 1155. NMR δ: 1.22 (3H, d, J=7 Hz, 11-CH_3), 1.53 (3H, s, 10-CH_3), 1.98 (3H, s, 4-CH_3), 2.72 (1H, m, 1-H), 3.76 (3H, s, $COOCH_3$), 5.52 (1H, br s, 6-H), 6.24 (1H, d, J=10 Hz, 2-H), 6.70 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 342, 340 (M^+, 1), 261 (M^+ − Br, 36), 201 (66), 173 (100).

A solution of the crude **11d** (13.5 g) in 500 ml of benzene was treated with 6.76 g of DBU. The mixture was stirred at 80 °C for 90 min. After usual work-up, evaporation of the benzene left a brown oil, which was chromatographed on a silica gel column with hexane–EtOAc (10 : 1) to give 6.30 g (66% yield from **19**) of the trienone (**12**).[10]

Allylic Oxidation of the Trienone (12)——a) Using *tert*-Butyl Chromate: A refluxing anhydrous CCl_4 (500 ml) solution of **12** (1.73 g, 6.6 mmol) was treated dropwise with a CCl_4 solution of *tert*-butyl chromate reagent,[16] prepared from 8.04 g (80 mmol) of CrO_3 and 20.3 ml of *tert*-BuOH containing 7.3 ml of Ac_2O. The mixture was refluxed for 72 h. After cooling, the mixture was diluted with 500 ml of $CHCl_3$ and washed with 10% $NaHSO_3$, 10% $NaHCO_3$, H_2O and brine. Removal of the solvent *in vacuo* left a crude product, which was chromatographed over silica gel with hexane–EtOAc (5 : 1) to afford a mixture of enones. The mixture was separated by preparative TLC to give 674 mg (37%) of methyl 3,8-dioxoeudesm-1,4,6-trienoate (**20**) and 296 mg (16%) of methyl 3,6-dioxoeudesm-1,4,7-trienoate (**22**). Recrystallization of **20** from hexane–EtOAc gave pale yellow prisms, mp 127.5—129 °C. $[\alpha]_D^{22}$ +256° (c=1.66). UV nm (ε): 252 (6900), 310 (16400). IR cm^{-1}: 1735, 1670, 1646, 1618, 1597, 1208. NMR δ: 1.35 (3H, s, 10-CH_3), 1.43 (3H, d, J=7 Hz, 11-CH_3), 2.08 (3H, s, 4-CH_3), 2.56 (2H, AB q, J=15 Hz, 9-H), 3.67 (3H, s, $COOCH_3$), 3.78 (1H, q, J=7 Hz, 11-H), 6.33 (1H, d, J=10 Hz, 2-H), 6.83 (1H, d, J=10 Hz, 1-H), 7.50 (1H, s, 6-H). MS m/z (% rel. int.): 274 (M^+, 52), 259 (25), 242 (60), 227 (24), 215 (77), 214 (100), 200 (33), 199 (44), 187 (46). *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.98; H, 6.72. Recrystallization of **22** from hexane–EtOAc gave yellow prisms, mp 103—105 °C. $[\alpha]_D^{22}$ −234.4° (c=1.88). UV nm (ε): 253 (10500), 280 (8300). IR cm^{-1}: 1728, 1652, 1628, 1209. NMR δ: 1.33 (3H, s, 10-CH_3), 1.37 (3H, s, J=7 Hz, 11-CH_3), 2.05 (3H, s, 4-CH_3), 2.59 (2H, d, J=4.5 Hz, 9-H), 3.64 (3H, s, $COOCH_3$), 3.67 (1H, q, J=7 Hz, 11-H), 6.32 (1H, d, J=10 Hz, 2-H), 6.78 (1H, t, J=4.5 Hz, 8-H), 6.84 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 274 (M^+ 21), 259 (21), 242 (37), 227 (100), 215 (36), 199 (84), 171 (31). *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.74; H, 6.76.

b) Using CrO_3–Pyridine Complex: A CH_2Cl_2 solution of CrO_3–pyridine complex[24] (13.1 g) was added to a CH_2Cl_2 solution of **12** (900 mg in 100 ml). The mixture was stirred at room temperature for 74 h, and a further 10 g of the reagent was added then stirring was continued for another 114 h. After usual work-up, removal of the solvent *in vacuo* gave 815 mg of an oil, which was chromatographed on a silica gel column. Elution with hexane–EtOAc (10 : 1) gave two fractions. The less polar band gave 252 mg of an oily product, which was separated by preparative TLC (benzene–EtOAc 1 : 1) to give 77 mg (8%) of methyl 3,8-dioxoeudesm-1,4-dienoate (**21**), mp 95—97 °C, and 278 mg (31%) of **12**. Compound **21**: High-resolution MS: mol. wt. 276.1361 $C_{16}H_{20}O_4$ Found: M^+, 276.1369. UV nm (ε): 245.5 (12600). IR cm^{-1}: 1735, 1660, 1630. NMR δ: 1.18 (3H, s, 10-CH_3), 1.25 (3H, d, J=7 Hz, 11-CH_3), 2.02 (3H, s, 4-CH_3), 2.70 (1H, q, J=7 Hz, 7-H), 3.70 (3H, s, $COOCH_3$), 6.20 (1H, d, J=10 Hz, 2-H), 6.68 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 276 (M^+, 13), 258 (7), 201 (11), 199 (10), 189 (33), 173 (19), 161 (31), 134 (100), 106 (40). The polar band gave 32 mg (3.5%) of the 3,8-dioxotriene (**20**), mp 127.5—129 °C which was identical with an authentic specimen.

Methyl 2,6-Dioxoeudesm-1,4-dienoate (23b)——According to the procedure reported by Nishikawa,[15] 0.3 g of NaOH in a small amount of H_2O was added to a solution of 1.0 g of santonin (**1**) in 50 ml of 75% EtOH. The resulting light red solution was warmed on a water bath until the color disappeared. After removal of the EtOH *in vacuo*, the aq. solution was added dropwise to an 80% AcOH solution of CrO_3 (1.5 g in 40 ml) and the mixture was stirred at room temperature for 30 min. After the excess oxidizing reagent had been decomposed with $NaHSO_3$, the mixture was extracted with benzene. The benzene layer was extracted with 10% $NaHCO_3$, and then the alkaline extract was acidified with HCl and extracted with EtOAc. Removal of the EtOAc *in vacuo* gave 928 mg (87%) of 3,6-dioxoeudesm-1,4-dienoic acid (**23a**), which was recrystallized from benzene–hexane to give 820 mg (77%) of colorless prisms, mp 139—140 °C (reported[15] mp 102—105 °C as monohydrate). $[\alpha]_D^{22}$ −128° (c=1.87). UV nm (ε): 248.5 (11800). IR cm^{-1}: 3200, 1720, 1695, 1640, 1615. NMR (C_6D_6) δ: 0.65 (3H, d, 10-CH_3), 1.03 (3H, s, J=7 Hz, 11-CH_3), 2.03 (3H, s, 4-CH_3), 2.50 (1H, quintet, J=7 Hz, 11-H), 2.73 (1H, m, J=7 Hz, , 7-H), 6.08 (1H, d, J=10 Hz, 2-H), 6.25 (1H, d, J=10 Hz, 1-H), 10.16 (1H, COOH). *Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.48; H, 7.00.

Methylation of **23a** (100 mg) with ethereal diazomethane gave the methyl ester (**23b**), which was recrystallized to give colorless prisms, mp 83 °C (reported[15] mp 81 °C). UV nm (ε): 249 (12800). IR cm^{-1}: 1733, 1696, 1659, 1628. NMR δ: 1.14 (3H, s, 10-CH_3), 1.20 (3H, d, J=7 Hz, 11-CH_3), 1.83 (3H, s, 4-CH_3), 2.84 (2H, m, 7-, 11-H), 3.68 (3H, s, $COOCH_3$), 6.26 (1H, d, J=10 Hz, , 2-H), 6.80 (1H, d, J=10 Hz, , 1-H). MS m/z (% rel. int.): 276 (M^+, 25), 261 (10), 245 (28), 244 (57), 230 (16), 229 (100), 201 (23), 173 (27).

Reduction of 20 with $LiAlH_4$——**20** (100 mg) in 5 ml of tetrahydrofuran (THF) was treated with 10 mg of $LiAlH_4$ at −75——70 °C for 4 h. After usual work-up, the product was extracted with EtOAc. Removal of the EtOAc *in vacuo* gave a crude brown oil (99 mg), which was separated by preparative TLC using 2% MeOH–CH_2Cl_2 to give 17 mg (17%) of methyl 3,8-dioxoeudesm-4,6-dienoate (**24**) and 24 mg (24%) of methyl 3-oxoeudesm-1,4,6-trienoate

(**25**). Recrystallization of **24** gave light yellow prisms, mp 70—72 °C. High-resolution MS: mol. wt. 276.1360 $C_{16}H_{20}O_4$ Found: M^+, 276.1337. UV nm (ε): 308 (22320). IR cm^{-1}: 1740, 1665, 1600. NMR δ: 1.27 (3H, s, 10-CH_3), 1.38 (3H, d, J=7 Hz, 11-CH_3), 1.93 (3H, s, 4-CH_3), 2.50 (4H, m, 2, 9-H), 3.65 (3H, s, $COOCH_3$), 3.70 (1H, m, 11-H), 7.33 (1H, s, 6-H). MS m/z (% rel. int.): 276 (M^+, 28), 244 (64), 217 (43), 216 (100). Compound **25** as a yellow oil. UV nm: 227, 307. IR ν_{max}^{film} cm^{-1}: 3450, 1735, 1650, 1610. NMR δ: 1.38 (3H, s, 10-CH_3), 1.43 (3H, d, J=7 Hz, 11-CH_3), 1.92 (3H, s, 4-CH_3), 3.48 (1H, q, J=7 Hz, 11-H), 3.70 (3H, s, $COOCH_3$), 4.40 (1H, br d, J=6 Hz, 8-H), 6.20 (1H, d, J=10 Hz, 2-H), 6.60 (1H, s, 6-H), 6.80 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 276 (M^+, 11), 261 (16), 244 (64), 243 (14), 239 (31), 216 (39), 201 (47), 189 (100), 173 (42).

Reduction of 20 with LiAlH (*tert*-BuO)$_3$——A solution of **20** (80 mg) in THF (5 ml) was treated with 240 mg of LiAlH (*tert*-BuO)$_3$. The mixture was stirred at −75——70 °C for 1 h, at −40 °C for 1 h, and at −10—0 °C for 3 h, then 5% HCl was added, and the whole was extracted with EtOAc. Evaporation of the EtOAc gave 80 mg of a yellow oil, which was separated by preparative TLC with CH_2Cl_2–MeOH (50:1) to give 21 mg (26%) of methyl 3,8-dioxoeudesm-4,6-dienoate (**24**), 20 mg (25%) of methyl 8-oxo-3ξ-hydroxyeudesm-4,6-dienoate (**26**), and 12 mg (14%) of methyl 3-oxo-8β-hydroxyeudesm-1,4,6-trienoate (**25**). Compound **26**: UV nm: 246, 308. IR ν_{max}^{film} cm^{-1}: 3450, 1735, 1665, 1620. NMR (60 MHz) δ: 1.20 (3H, s, 10-CH_3), 1.35 (3H, d, J=7 Hz, 11-CH_3), 2.00 (3H, s, 4-CH_3), 3.70 (3H, s, $COOCH_3$), 4.30 (1H, m, 3-H), 7.30 (1H, s, 6-H). MS m/z (% rel. int.): 278 (M^+, 19), 276 (27), 246 (33), 244 (63), 218 (89), 216 (100).

Reduction of 20 with $NaBH_4$——A MeOH solution of **20** (100 mg in 5 ml) was treated with 15 mg of $NaBH_4$ at room temperature for 2 h. After usual work-up, the product was separated by preparative TLC with CH_2Cl_2–MeOH (50:1) to give 50 mg of **25** and 16.5 mg of **26**, which were identified by comparing the NMR spectra with those of authentic specimens.

Methyl 3,8-Dioxoeudesm-4-enoate (27)——**20** (640 mg) was dissolved in 60 ml of benzene containing a few drops of EtOH and reduced in an H_2 atmosphere, (3 kg/cm^2) with 200 mg of $RhCl[PPh_3]_3$ catalyst for 4 d. Removal of the solvent *in vacuo* gave an oil, which was purified by silica gel column chromatography to give 563 mg (87%) of a pale yellow oil (**27**). High-resolution MS: mol. wt. 278.1517 $C_{16}H_{22}O_4$ Found: M^+, 278.1539. $[\alpha]_D^{30}$ +87.7° (c=1.03). UV nm (ε): 244 (14800). IR ν_{max}^{film} cm^{-1}: 1735, 1710, 1665, 1630, NMR δ: 1.22 (3H, s, 10-CH_3), 1.25 (3H, d, J=7 Hz, 11-CH_3), 1.82 (3H, s, 4-CH_3), 3.65 (3H, s, $COOCH_3$). MS m/z (% rel. int.): 278 (M^+, 11), 263 (4), 247 (15), 246 (42), 208 (30), 191 (100), 173 (24). Bis-2,4-dinitrophenylhydrazone of **27**, red needles, mp 183—185 °C (from EtOH–hexane). *Anal.* Calcd for $C_{28}H_{30}N_4O_{10}$: C, 52.66; H, 4.74; N, 17.55. Found: C, 52.53; H, 4.74; N, 17.32.

Reduction of 20 with $RhCl[PPh_3]_3$ Followed by $NaBH_4$——Catalytic reduction of **20** with $RhCl[PPh_3]_3$ catalyst was carried out for 2—3 d under the same conditions as described above. The oily products were composed of mainly **27** and a small amount of **21** together with the 3,8-dioxo-4,6-diene (**24**) as judged from NMR analysis. The above mixture (70 mg) was dissolved in MeOH (3 ml) and treated with $NaBH_4$ (5 mg), then the mixture was stirred at −20—−18 °C for 30 min. After decomposition of the excess reagent with AcOH, the products were extracted with EtOAc. Evaporation of the EtOAc *in vacuo* yielded an oily product, which was separated by preparative TLC with hexane–EtOAc (1:1) to afford 41 mg (58%) of methyl-3-oxo-8β-hydroxyeudesm-4-enoate (**28**) and 17 mg (24%) of methyl-3-oxo-8β-hydroxyeudesm-1,4-dienoate (**29**). Recrystallization of **28** from EtOAc–hexane gave colorless needles, mp 128—138 °C (lactonization occurred on heating). $[\alpha]_D^{23}$ +50.0° (c=0.14). UV nm (ε): 250 (17360). IR cm^{-1}: 3430, 1730, 1650, 1608. NMR δ: 1.22 (3H, d, J=7 Hz, , 11-CH_3), 1.49 (3H, s, 10-CH_3), 1.72 (3H, s, 4-CH_3), 3.68 (3H, s, $COOCH_3$), 4.16 (1H, m, $W_{1/2}$=8 Hz, 8-H). MS m/z (% rel. int.): 280 (M^+, 16), 262 (M^+-H_2O, 51), 248 (M^+-CH_3OH, 57), 202 (74), 173 (100). Compound **29** as an oil: IR ν_{max}^{film} cm^{-1}: 3400, 1735, 1660, 1620, 1605. NMR (60 MHz) δ: 1.32 (3H, d, J=7 Hz, 11-CH_3), 1.45 (3H, s, 10-CH_3), 1.89 (3H, s, 4-CH_3), 3.78 (3H, s, $COOCH_3$), 4.20 (1H, q, $W_{1/2}$=12 Hz, 8-H), 6.22 (1H, d, J=10 Hz, 2-H), 6.80 (1H, d, J=10 Hz, 1-H).

3-Oxoeudesm-4-en-8β,13-olides (30 and 31) from 27——A THF solution of **27** (302 mg in 15 ml) was treated with 330 mg of LiAlH (*tert*-BuO)$_3$ at room temperature for 30 min. Then 6 ml of 3 N NaOH was added, and the alkaline solution was stirred for 40 min; 8 ml of 3 N HCl was added, and the whole was stirred for 30 min, then extracted with EtOAc. Removal of the EtOAc *in vacuo* gave 277 mg of a crude solid, which was separated by preparative TLC with ether–hexane (5:1) to give 28.5 mg (11%) of 3-oxo-11β(*H*)-eudesm-4-en-8β,13-olide (**31**) and 173 mg (64%) of 3-oxo-11α(*H*)-eudesm-4-en-8β,13-olide (**30**). Recrystallization of **31** from EtOAc–hexane gave colorless prisms, mp 189 °C $[\alpha]_D^{23}$ +143.7° (c=0.52). UV nm (ε): 247 (15740). IR cm^{-1}: 1766, 1752, 1656, 1623. NMR δ: 1.25 (3H, s, 10-CH_3), 1.30 (3H, d, J=7 Hz, 11-CH_3), 1.74 (3H, s, 4-CH_3), 4.50 (1H, m, $W_{1/2}$=20 Hz, 8-H). MS m/z (% rel. int.): 248 (M^+, 100), 233 (30), 230 (27), 206 (64), 175 (64), 159 (84), 133 (87). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.44; H, 8.24. Recrystallization of **30** from EtOAc–hexane gave colorless columns, mp 111—112 °C. $[\alpha]_D^{23}$ +130.4° (c=0.29). UV nm (ε): 246 (11440). IR cm^{-1}: 1760, 1743, 1658, 1616. NMR δ: 1.21 (3H, d, J=7 Hz, 11-CH_3), 1.23 (3H, s, 10-CH_3), 1.73 (3H, s, 4-CH_3), 4.45 (1H, q, $W_{1/2}$=10 Hz, 8-H). MS m/z (% rel. int.): 248 (M^+, 80), 233 (27), 230 (38), 206 (50), 175 (74), 133 (100). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.39; H, 8.46.

Lactonization of 28——a): **28** (7 mg) was heated at 160—170 °C for 45 min. After cooling, the resulting solid was purified by preparative TLC to give **30** (5.5 mg), mp 96—102 °C.

b): A THF solution of **28** (59 mg in 1 ml) was treated with 1 ml of 3 N NaOH. The mixture was stirred at room temperature for 30 min, then 3 ml of 3 N HCl was added and the whole was stirred for 1 h. Extraction with EtOAc

gave a crude product, which was separated by preparative TLC with hexane–EtOAc (1 : 1) to give **31** (11.4 mg) as colorless crystals and **30** (47 mg); these products were identical with authentic samples (mixed mp, IR, and NMR spectra).

Epimerization of Lactones 30 and31——A xylene solution of each lactone (**30** and **31**, 10 mg in 1 ml) with 100 mg of K_2CO_3 was heated at reflux temperature. The reaction was monitored by GLC and the products were isolated by preparative TLC. The results are summarized below:

Reaction time (d)		1	2	3	4	5	5*
Products ratio **31**/**30**[a]	A[b]	80/20	67/33	65/35	65/35	65/35	60/40
	B[c]	36/64	47/53	56/44	61/39	63/37	63/37

a) All products ratios except * were measured by GLC.
b) Starting material was **31**.
c) Starting material was **30**.
* Product ratios were determined after separation by preparative TLC.

3-Oxo-11α(*H*)-eudesm-1,4-dien-8β,13-olide (32)——a) Lactonization of **29**: A THF solution of **29** (55 mg in 1 ml) was stirred with 3 N NaOH (1 ml) followed by addition of 3 N HCl (2 ml) described above. The products were purified by preparative TLC with hexane–EtOAc (1 : 1) to give 31 mg (64%) of 11β-methyl-8β,13-olide (**32**). Recrystallization from hexane–EtOAc afforded 19 mg of colorless plates, mp 180—180.5 °C. $[\alpha]_D^{23}$ −117.5° (c=0.22). UV nm (ε): 240 (11330), 263 (shoulder). IR cm^{-1}: 1775, 1655, 1625, 1603. NMR δ: 1.27 (3H, d, J=7 Hz, 11-CH_3), 1.29 (3H, s, 10-CH_3), 1.58 (1H, dd, J=15, 4 Hz, 6α-H), 1.92 (3H, s, 4-CH_3), 2.56 (1H, dd, J=17, 15 Hz, 6β-H), 4.50 (1H, m, $W_{1/2}$=10 Hz, 8-H), 6.21 (1H, d, J=10 Hz, 2-H), 6.77 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 246 (M^+, 100), 231 (17), 218 (15), 173 (99), 172 (79), 145 (66), 144 (66). *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.25; H, 7.53.

b) Dehydrogenation of **30**: A dioxane solution of **30** (140 mg in 10 ml) was refluxed with 180 mg of DDQ for 27 h. After cooling, the precipitate was filtered off. The filtrate was concentrated *in vacuo*, and the residue was separated by preparative TLC with hexane–EtOAc (1 : 1) to give 14 mg of unchanged **30** and 101 mg (72%) of **32** as colorless plates, mp 176—179 °C, Recrystallization from hexane–EtOAc gave 66.7 mg of colorless plates, mp 180—180.5 °C; this product was identical (mixed mp, IR, and NMR spectra) with an authentic sample of **32**.

3-Oxo-11β(*H*)-eudesm-1,4-dien-8β,13-olide (33)——**31** (150 mg) was treated with 190 mg of DDQ as described above. After usual work-up, the product was separated by preparative TLC to give 10.6 mg of unchanged **31** and 108 mg (73%) of dienone (**33**). Recrystallization from hexane–EtOAc gave colorless prisms, mp 135—136 °C. $[\alpha]_D^{25}$ −92.5° (c=0.59). UV nm (ε): 240 (11900), 263 (shoulder). IR cm^{-1}: 1762, 1658, 1629 1607. NMR δ: 1.32 (3H, s, 10-CH_3), 1.33 (3H, s, J=7 Hz, 11-CH_3), 1.59 (1H, dd, J=15, 4 Hz, 6α-H), 1.92 (3H, s, 4-CH_3), 2.38 (1H, dd, J=17, 15 Hz, 6β-H), 4.64 (1H, q, J=3.5 Hz, 8-H), 6.18 (1H, d, J=10 Hz, 2-H), 6.73 (1H, d, J=10 Hz, 1-H). MS m/z (% rel. int.): 246 (M^+, 100), 231 (11), 218 (11), 173 (65), 172 (48), 145 (45), 144 (44), 135 (37). *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.29; H, 7.47.

Epimerization of Lactones (32 and 33)——Epimerization of **32** and **33** was performed under the same conditions as described for **30** and **31**. The results are summarized below:

Reaction time (d)		1	2	3	5
Products ratio[a] **32**/**33**	A[b]	98/2	78/22	60/40	62/38
	B[c]	5/95	21/79	40/60	60/40

a) All product ratios were measured by GLC analysis.
b) Starting material was **32**.
c) Starting material was **33**.

Phenylselenenylation of 32——**32** (65 mg, 0.246 mmol) in anhydrous THF (0.4 ml) was treated with lithium diisopropylamide (LDA) (0.7 mmol) at −78 °C for 30 min. The resulting deep-red enolate solution was treated with PhSeSePh (156 mg, 0.5 mmol) in THF (0.4 ml) containing hexamethylphosphoramide (HMPA) (0.09 ml, 0.5 mmol) at −78 °C for 3 h. Usual work-up gave yellow crystals, which were chromatographed on a silica gel column to give 44.8 mg (42%) of **34**. Recrystallization from hexane–EtOAc gave colorless prisms, mp 218—219 °C. High-resolution MS: mol. wt. 402.0732 $C_{21}H_{22}O_3Se$ Found: M^+, 402.0709. $[\alpha]_D^{25}$ −138.5° (c=0.29). UV nm (ε): 232 (10700), 263 (shoulder). IR cm^{-1}: 1760, 1657, 1624, 1610. NMR δ: 1.28 (3H, s, 10-CH_3), 1.60 (3H, s, 11-CH_3), 1.91 (3H, s, 4-CH_3), 5.05 (1H, m, $W_{1/2}$=10 Hz, 8-H), 6.22 (1H, d, J=10 Hz, 2-H), 6.75 (1H, d, J=10 Hz, 1-H), 7.20—7.70 (5H, m, PhSe).

MS *m/z* (% rel. int.): 402 (M^+, 100), 400 (53), 245 ($M^+ - PhSe$, 96), 244 ($M^+ - PhSeH$, 77), 227 (55), 199 (53), 173 (57), 135 (95).

Phenylselenenylation of 33——The enolate of **33**, prepared from **33** (50 mg, 0.203 mmol) and LDA (0.81 mmol), was treated with PhSeSePh (125 mg, 0.4 mmol) by the same method as described above. Usual work-up followed by preparative TLC with hexane–EtOAc (1 : 1) gave two compounds. The less polar compound **34** (15 mg, 19%), mp 195—200 °C, had IR and NMR spectra identical with those of an authentic sample. The polar compound **32** (22.6 mg, 45%), mp 176—178 °C, had IR and NMR spectra identical with those of authentic **32**.

(−)-Yomogin (2)——**34** (45 mg) was treated with 35% H_2O_2 (0.1 ml) in THF at 0 °C for 30 min. Evaporation of the solvent *in vacuo* gave 28 mg of a solid, which was found to be an equimolar mixture of exocyclic and endocyclic olefins (**2** and **35**) by NMR analysis. The mixture was digested with EtOAc to afford colorless prisms, which were filtered and washed with EtOAc–hexane to give 10 mg (37%) of (−)-yomogin (**2**), mp 208—211 °C. Recrystallization from EtOAc–hexane gave colorless prisms, mp 210—211 °C, whose physical and spectral data were in good agreement with those of natural yomogin.[5] High-resolution MS: mol. wt. 244.1099. $C_{15}H_{16}O_3$ Found: M^+, 244.1099. $[\alpha]_D^{22}$ −96.6° ($c=0.6$). UV nm (ε): 212 (12950), 238 (12800), 263 (shoulder). IR cm^{-1}: 1764, 1656, 1620, 1607. NMR δ: 1.32 (3H, s, 10-CH_3), 1.93 (3H, s, 4-CH_3), 4.48 (1H, q, $J=3.5$ Hz, 8-H), 5.72, 6.26 (each 1H, br s, $=CH_2$), 6.22 (1H, d, $J=10$ Hz, 2-H), 6.77 (1H, d, $J=10$ Hz, 1-H). MS *m/z* (% rel. int.): 244 (M^+, 36), 229 (19), 183 (40), 120 (60), 105 (100). *Anal.* Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.51; H, 6.62.

The residual oil (16 mg) from the filtrate was found to be **35** on the basis of NMR analysis. NMR (60 MHz) δ: 1.22 (3H, s, 10-CH_3), 2.00 (6H, br s, 4,11-CH_3), 4.90 (1H, m, 8-H), 6.32 (1H, d, $J=10$ Hz, 2-H), 6.83 (1H, d, $J=10$ Hz, 1-H).

Hydrogenation of 30——The enone (**30**) (206 mg) was reduced over 10% Pd-C (65 mg) in 20 ml of acetone under an H_2 atmosphere. After usual work-up, separation of the products by preparative TLC with benzene–EtOAc (5 : 1) gave 69.5 mg (33.5%) of 3-oxo-4β(*H*)-eudesman-8β,13-olide (**37**) and 123.4 mg (59%) of 3-oxo-4α(*H*)-eudesman-8β,13-olide (**36**). Recrystallization of **37** from hexane–EtOAc afforded colorless needles, mp 173—174 °C (reported[22] mp 173—174 °C). $[\alpha]_D^{23}$ −40.7° ($c=0.71$). IR cm^{-1}: 1763, 1753, 1709. NMR δ: 1.05 (3H, d, $J=7$ Hz, 4-CH_3), 1.18 (3H, s, 10-CH_3), 1.23 (3H, d, $j=7$ Hz, 11-CH_3), 4.50 (1H, m, $W_{1/2}=9$ Hz, 8-H). MS *m/z* (% rel. int.): 250 (M^+, 51), 121 (100). *Anal.* Calcd for $C_{15}H_{23}O_3$: C, 71.97; H, 8.86. Found: C, 71.97; H, 8.86. Recrystallization of **36** from hexane–EtOAc gave colorless columns, mp 161—164 °C. $[\alpha]_D^{23}$ −23.9° ($c=0.63$). IR cm^{-1}: 1753, 1747, 1705. NMR δ: 1.12 (3H, d, $J=8$ Hz, v-CH_3), 1.20 (3H, s, 10-CH_3), 1.23 (3H, d, $J=7$ Hz, 11-CH_3), 4.51 (1H, m, $W_{1/2}=9$ Hz, 8-H). MS *m/z* (% rel. int.): 250 (M^+, 49), 121 (100). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.94.

Epimerization of 36——An EtOH solution of **36** (112 mg in 10 ml) was treated with 2 ml of 10% HCl at reflux temperature for 1.5 h. After evaporation of the EtOH, the residue was extracted with EtOAc. Removal of the solvent afforded 103.5 mg (92%) of pale yellow crystals, mp 166—171 °C, which were identical with **37** (comparison of IR spectra).

Hydrogenation of 31——The enone **31** (100 mg) was reduced over 10% Pd-charcoal (30 mg) in acetone (10 ml) under an H_2 atmosphere. The 3-oxo-4α-methyl compound (**39**) (47.5 mg, 47%) and 3-oxo-4β-methyl compound (**38**) (41.3 mg, 41%) were obtained by preparative TLC with benzene–EtOAc (5 : 1). Recrystallization of **39** from hexane–EtOAc gave colorless columns, mp 120—122 °C. $[\alpha]_D^{20}$ +15.5° ($c=0.58$). IR cm^{-1}: 1763, 1707. NMR δ: 1.04 (3H, d, $J=7$ Hz, 4-CH_3), 1.21 (3H, s, 10-CH_3), 1.32 (3H, d, $J=8$ Hz, 11-CH_3), 4.71 (1H, m, $W_{1/2}=9$ Hz, 8-H). MS *m/z* (% rel. int.): 250 (M^+, 51), 193 (42), 121 (100). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.83; H, 8.86. Recrystallization of **38** from hexane–EtOAc gave colorless needles, mp 98—102 °C. $[\alpha]_D^{20}$ +96.4° ($c=0.09$). IR cm^{-1}: 1754, 1702. NMR δ: 1.11 (3H, d, $J=8$ Hz, 4-CH_3), 1.23 (3H, s, 10-CH_3), 1.32 (3H, d, $J=8$ Hz, 11-CH_3), 4.73 (1H, m, $W_{1/2}=9$ Hz, 8-H). MS *m/z* (% rel. int.): 250 (M^+, 43), 193 (36), 121 (100).

Epimerization of 38——An EtOH solution of **38** (12.5 mg in 0.5 ml) was treated with 0.5 ml of 10% HCl. After work-up in the same manner as described for **36**, 12.1 mg (96%) of yellow crystals, mp 103—110 °C, was obtained; this product was identical with **39** on the basis of IR spectral comparison.

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