

Synthesis of a Stereoisomer of Frullanolide Utilizing the Intramolecular Cyclization of ω -Formyl-2-alkenylsilane

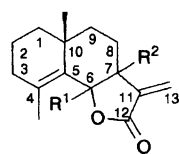
Chiaki KURODA,* Shigeru SHIMIZU, Takahiro HAISHIMA, and James Y. SATOH
Department of Chemistry, Rikkyo University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171
(Received January 20, 1993)

Synthesis of 10-epi-frullanolide (**3**) is reported via the intramolecular cyclization of ω -formyl- α -trimethylsilylmethyl- α,β -unsaturated ester. The cyclization precursor, ethyl (*Z*)-5-(2-formyl-1,3-dimethyl-2-cyclohexenyl)-2-trimethylsilylmethyl-2-pentenoate (**17**), was prepared from 2,6-dimethyl-2-cyclohexen-1-one through the dialdehyde monoacetal as the key intermediate. Cyclization of **17** with tetrabutylammonium fluoride produced the hydroxy ester having C(6 α)-H and C(7 β)-H, which was hydrolyzed, then subjected to Fujisawa's lactonization to afford **3**.

Eudesmanolides having α -methylene- γ -lactone moieties are widely-occurring natural sesquiterpenes with significant biological activities.^{1,2} Both frullanolide (**1**) and arbusculin B (**2**)³ are natural eudesman-6,12-olides, and are stereoisomers at C-6; frullanolide has *cis*-lactone and arbusculin B has *trans*-lactone. Interestingly, both enantiomers of **1** and **2** are found in nature,³ while a third stereoisomer, compound **3**, is not found as a natural product (Chart 1). Recently, one of the authors and his co-workers reported a revision of the Samek rule, which has often been used to determine the stereostructure of a lactone moiety, by comparing the NMR and MM2 of natural frullanolide with that of synthetic 10-epi-frullanolide (**3**).⁴ We showed the importance of the synthesis of the unnatural stereoisomer on natural products chemistry, while a number of synthetic studies targeting natural eudesmanolides have been reported.^{5,6}

We previously reported that the intramolecular cyclization of ω -formyl- α -trimethylsilylmethyl- α,β -unsaturated ester is an excellent method for synthesizing eudesmanolide derivatives, an α -methylene- γ -lactone ring fused to a decaline system, in a short step.⁷ By using this method, both the terpenoid carbon skeleton and the α -methylene- γ -lactone ring could be easily obtained from a simple dialdehyde monoacetal. Nishitani and Yamakawa have reported a similar reaction independently.⁸

In this paper, we report the details of the synthesis of **3** from 2,6-dimethyl-2-cyclohexen-1-one (**7**) via the fluoride-promoted intramolecular cyclization of ω -formyl-2-alkenylsilane **17**.

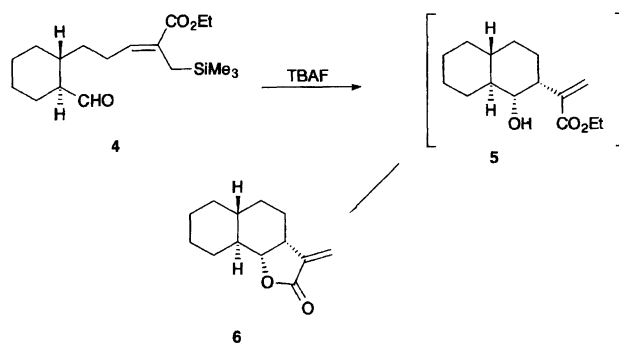


- 1** $R^1=R^2=\alpha\text{-H}$
2 $R^1=\beta\text{-H}, R^2=\alpha\text{-H}$
3 $R^1=R^2=\beta\text{-H}$

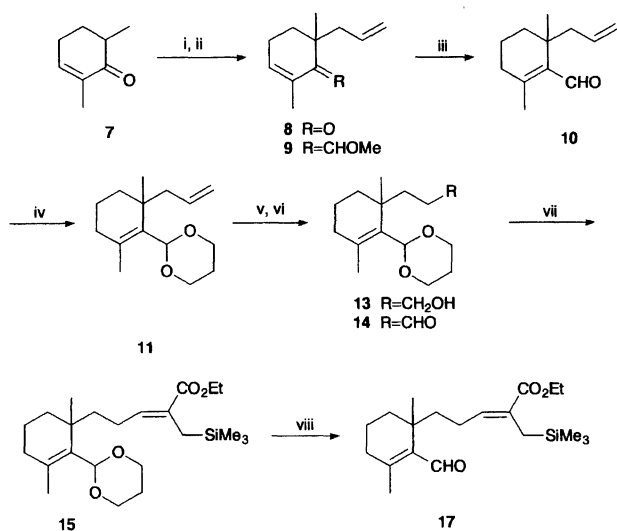
Chart 1.

Results and Discussion

The previous model study on the synthesis of eudesmanolide derivatives suggested that tetrabutylammonium fluoride (TBAF) treatment of *Z*-2-(ethoxycarbonyl)allylsilane produces α -*cis*-lactone as the major product (Scheme 1).⁷ Since *Z*-allylsilane can be obtained as the major product against the *E*-isomer by Hoffmann's Wittig reaction,⁹ the synthesis of the cyclization precursor was carried out by a route parallel to the model study (Scheme 2). Thus, we chose 2,6-dimethyl-2-cyclohexen-1-one (**7**) as the starting material, which was prepared from diethyl ketone and acrylaldehyde according to the known procedure.¹⁰ The allylation of **7** was first carried out by using lithium diisopropylamide (LDA) and allyl bromide to give 6-allylated compound **8** in a 92% yield. Wittig one-carbon homologation of **8** gave enol ethers **9** as a mixture of geometrical isomers (93%), the ratio of which was determined to be 2:1 by ¹H NMR spectroscopy. These enol ethers **9** were hydrolyzed by HCl to afford α,β -unsaturated aldehyde **10** in a 94% yield. Protection of the aldehyde group by 1,3-propanediol or 1,2-ethanediol produced the corresponding acetals (**11** or **12**) in 100% and 90% yields, respectively (Chart 2). Since one of the dialdehyde functionalities was obtained as a protected form, the other aldehyde group was then synthesized from the olefinic group. Thus, hydroboration of the double bond using bis(1,2-dimethylpropyl)borane afforded



Scheme 1.



Scheme 2. Reagents and Conditions: i, LDA, $\text{CH}_2=\text{CHCH}_2\text{Br}$, THF, -30°C ; ii, $\text{Ph}_2\text{POCH}_2\text{OMe}$, LDA, THF, room temperature; iii, 5% HCl, THF, reflux; iv, $\text{HO}(\text{CH}_2)_3\text{OH}$, PPTS, PhH, reflux; v, a) bis(1,2-dimethylpropyl)borane, diglyme, room temperature, b) NaOH aq, H_2O_2 , 40°C ; vi, PDC, CH_2Cl_2 , room temperature; vii, $(\text{EtO})_2\text{POCH}(\text{CO}_2\text{Et})\text{CH}_2\text{SiMe}_3$, NaH, DME, room temperature; viii, TsOH, acetone, reflux.

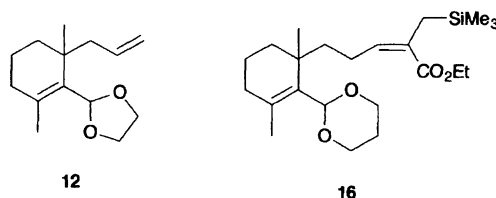


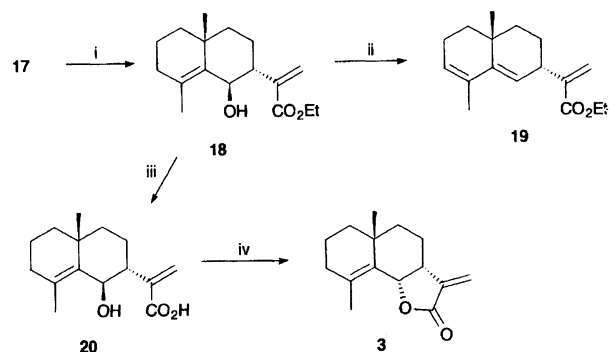
Chart 2.

alcohol **13** (96%), which was then oxidized by pyridinium dichromate (PDC) to yield dialdehyde monoacetal **14** (85%), the key intermediate described above. The α -trimethylsilylmethyl- α,β -unsaturated ester moiety was introduced by Hoffmann's Wittig reaction⁹⁾ on **14** using $(\text{EtO})_2\text{POCH}(\text{CO}_2\text{Et})\text{CH}_2\text{SiMe}_3/\text{NaH}$. The ^1H NMR spectrum of the crude product showed that it contained both *Z*-isomer **15** and *E*-isomer **16** in a ratio of 4:1. Thus, the olefinic protons of both **15** and **16** were observed at $\delta=6.57$ and 5.62 , respectively, while the corresponding protons for the *Z*- and *E*-isomers of the model compound were observed at $\delta=6.44$ and 5.55 , respectively.⁷⁾ *Z*-isomer **15** could be isolated from the crude product by alumina column chromatography (35% yield from **14**). Cyclization precursor **17** was then obtained by hydrolysis of the acetal with either aqueous HCl or *p*-toluenesulfonic acid (TsOH) in acetone, both of which gave satisfactory yields (81 and 97%, respectively). The same compound **17** could be obtained from **12** utilizing the same sequence, however

the yields were unsatisfactory (total yield 3.4%). Compared with the model study, the cyclization reaction did not occur even when an excess amount of TsOH was used in the hydrolysis step.

The fluoride-promoted cyclization reaction of **17** was then examined (Scheme 3). In contrast to the model study, treatment of **17** with TBAF did not produce lactones. Instead, hydroxy ester **18** was obtained in a 45% yield. The structure of **18** was deduced from its IR (OH absorption) and ^1H NMR (signals of the α -methylene ester) spectra. The stereochemistry at C(6) was determined to have C(6 α)-H by its small *J*-value ($J_{6,7}=2$ Hz) and the low-field shift of the C(10)-Me signal, which appeared at $\delta=1.24$ by a 1,3-diaxial interaction with the C(6 β)-OH group. It was suggested that **18** had C(7 β)-H from its signal in the ^1H NMR spectrum ($W_{1/2}=7$ Hz). Although the stereochemistry of **18** could finally be established by its conversion to **3**, the failure of acid- or base-promoted direct lactonization confirmed the stereochemistry. Thus, when **18** was treated with TsOH, only dehydrated product **19** was afforded in a quantitative yield. The diene structure of **19** was deduced from two new olefinic protons appearing in the ^1H NMR spectrum (see the Experimental section). Treatment of **18** with NaH gave hydrolyzed acid **20** (87%) instead of lactone. These results could easily be rationalized by the fact that **18** had both a C(6)-OH group and a C(7)-side chain with axial orientations.

The lactone **3** could be formed from **20** in an 18% yield with inversion at C(6) by utilizing Fujisawa's method.¹¹⁾ The resulting lactone was found to have an α -methylene- γ -lactone moiety from its IR (1750 cm^{-1}), ^1H NMR, and mass spectra ($M^+=232$). The spectral data of **3** was not consistent with frullanolide (**1**) nor arbusculin B (**2**). This fact reveals the structure of **3** as 10-*epi*-frullanolide, the third possible stereoisomer of both **1** and **2**. The *cis*-lactone structure was determined from NOE between C(6)-H and C(7)-H. NOE was also observed at both the C(6)-H and C(7)-H signals when



Scheme 3. Reagents and Conditions: i, TBAF, THF, 0°C ; ii, TsOH, acetone, room temperature; iii, NaH, THF, room temperature; iv, $[\text{Me}_2\text{N}=\text{CCINMe}_2]^+\text{Cl}^-$, 2,4,6-trimethylpyridine, MeCN, room temperature.

C(10)–Me was irradiated, which means that **3** had C(6 β)–H and C(7 β)–H.

The stereochemistry of the cyclization reaction of **17** by TBAF was not consistent with the model study (Scheme 1), in which the hydroxy ester having C(6 β)–H (**5**) was proposed to be formed initially. The stereoselectivity observed for the reaction of **17** can be rationalized based on Majetich's analysis of the enone system (Scheme 4).¹²⁾ Thus, the orientation of the aldehyde group is limited to **I** or **II** owing to its conjugating double bond. However, sterical congestion with the C(4)–Me group makes it preferable to take conformation **I** over **II**. Attack by an allylsilane moiety on this aldehyde from the β -side is blocked by the bulky C(10)–Me group, and therefore the reaction takes place from the α -side. The formation of **18** is the result of an antiperiplanar α -side attack (**Ia**) rather than a synclinal attack (**Ib**).

In conclusion, 10-epi-frullanolide (**3**) was synthesized via intramolecular cyclization between 2-(ethoxycarbonyl) allylsilane and the conjugated aldehyde. It was found that the stereochemical feature of the cyclization reaction is different from the model study owing to the presence of a conjugated double bond and/or methyl substituents.

Experimental

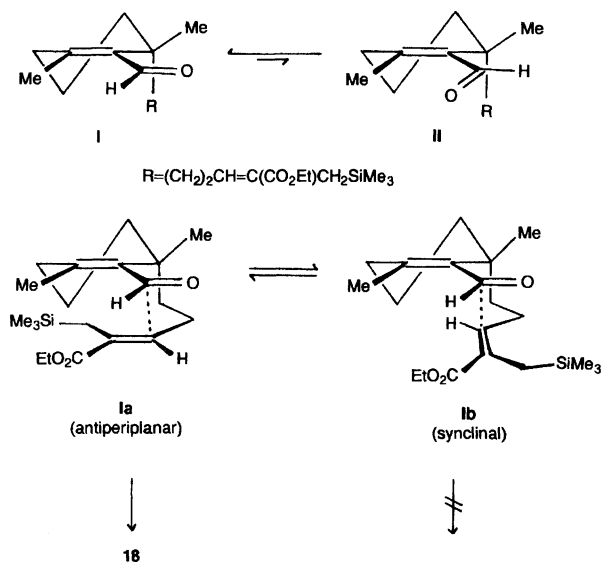
General Procedures. UV spectra were taken on a Hitachi 220A ultraviolet spectrometer. IR spectra were determined on a Hitachi 215 or Hitachi 270-30 spectrometer. ¹H and ¹³C NMR spectra were measured on Hitachi Perkin-Elmer R-20A (60 MHz), R-900 (90 MHz), JEOL GSX-400 (400 MHz), and GX-270 (270 MHz) spectrometers. Chemical shifts are reported downfield from tetramethylsilane on the δ scale (ppm), while chloroform was used as an internal standard ($\text{CHCl}_3=7.25$) for all compounds having a trimethylsilyl group and for all ¹³C NMR spectra. Both low-reso-

lution and high-resolution mass spectra were obtained on a JEOL JMS-D300 or SX102A mass spectrometer. Analytical TLC was performed on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200 and C-300, Florisil (100–200 mesh), or ICN Alumina N Act 1 were used for column chromatography. Anhydrous Na₂SO₄ or MgSO₄ were used for drying of extracted organic layers. For reactions requiring dry solvents, tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from LiAlH₄; diglyme, CH₂Cl₂, and hexane were distilled from CaH₂.

6-Allyl-2,6-dimethyl-2-cyclohexen-1-one (8). To a stirred solution of LDA [prepared from BuLi (3.8 cm³, 9.5 mmol; 2.5 mol dm⁻³ solution in hexane) and diisopropylamine (2.8 cm³) in dry THF (30 cm³)] was added dropwise a solution of **7** (1.03 g, 8.29 mmol) in THF (2.7 cm³) at –78 °C under Ar. After being stirred for 1 h, allyl bromide (1.3 cm³, 15 mmol) was added, and the mixture was stirred at –30 °C for 4 h. Water (10 cm³) was added and the product was extracted with Et₂O. Evaporation of the solvent and silica-gel (50 g) column chromatography using hexane–AcOEt (4 : 1) as eluent gave **8** (1.25 g, 92%) as an oil; UV (EtOH) 235 nm (ϵ 8000); IR (neat) 1665 (C=O) and 1640 (C=C) cm⁻¹; ¹H NMR (CDCl₃) δ =1.07 (3H, s, *t*-CH₃), 1.76 (3H, br s, C=C–CH₃), 5.05 (2H, m, CH=CH₂), 5.73 (1H, m, CH=CH₂), and 6.65 (1H, m, C=CH); ¹³C NMR (CDCl₃) δ =16.22, 21.60, 22.58, 33.19, 41.00, 43.99, 117.60, 133.72, 134.05, 143.37, and 203.47; MS *m/z* (rel intensity) 164 (*M*⁺; 26), 149 (11), 136 (8), 123(15), and 82 (100). Found: C, 80.65; H, 9.96%. Calcd for C₁₁H₁₆O: C, 80.44; H, 9.82%.

5-Allyl-1,5-dimethyl-6-methoxymethylene-1-cyclohexene (9). To a stirred solution of LDA [prepared from BuLi (13.6 cm³, 21.9 mmol; 1.61 mol dm⁻³ solution in hexane) and diisopropylamine (6 cm³) in dry THF (25 cm³)] was added dropwise a solution of Ph₂POCH₂OMe (4.54 g, 18.5 mmol) in THF (120 cm³) at –78 °C under Ar and the mixture was stirred for 10 min. A solution of **8** (2.56 g, 15.6 mmol) in THF (20 cm³) was added and the mixture was allowed to warm to room temperature. After being stirred for 15 h, the reaction was quenched by addition of saturated aqueous NH₄Cl, and the mixture was extracted with Et₂O. After evaporation of the solvent, the crude product was chromatographed on silica gel (50 g) using hexane–benzene (1 : 1) as eluent to afford **9** (2.80 g, 93%; a mixture of geometrical isomers) as an oil; UV (EtOH) 240 nm (ϵ 19000); IR (neat) 1640 (C=C), 1615 (C=C), and 1135 (C–O) cm⁻¹; ¹H NMR (CDCl₃) δ =1.01 (3H, s, *t*-CH₃ of major isomer), 1.17 (3H, s, *t*-CH₃ of minor isomer), 1.75 (3H, d, *J*=1.5 Hz, C=C–CH₃ of minor isomer), 1.99 (3H, d, *J*=2 Hz, C=C–CH₃ of major isomer), 3.56 (3H, s, OCH₃ of major isomer), 3.60 (3H, s, OCH₃ of minor isomer), 4.92–5.01 (2H, m, CH=CH₂), 5.34 (1H, br s, C=CH of major isomer), 5.44 (1H, br s, C=CH of minor isomer), 5.79 (1H, m, CH=CH₂), 5.81 (1H, s, C=CHOCH₃ of major isomer), and 6.02 (1H, s, C=CHOCH₃ of minor isomer); ¹³C NMR (CDCl₃) δ =23.12, 23.78, 25.55, 35.15, 35.43, 42.58, 59.90, 116.43, 121.13, 124.34, 130.78, 135.93, and 143.43 (major isomer), and 20.69, 22.54, 25.51, 35.25, 36.50, 43.62, 59.98, 115.86, 122.28, 123.49, 130.56, 136.80, and 144.41 (minor isomer); MS *m/z* (rel intensity) 192 (*M*⁺; 31), 151 (100), and 129 (47). Found: *m/z* 192.1511 (*M*⁺). Calcd for C₁₃H₂₀O: *M*, 192.1515.

6-Allyl-2,6-dimethyl-1-cyclohexene-1-carbaldehyde (10). Compound **9** (2.00 g, 10.4 mmol) was dis-



Scheme 4.

solved in 5% HCl aq-THF (150 cm³; 1:4 ratio) and the solution was refluxed for 20 min. After being cooled to room temperature, aqueous NaHCO₃ (35 cm³) was added slowly and the mixture was extracted with Et₂O. Evaporation of the solvent followed by Florisil (50 g) column chromatography using hexane-Et₂O (20:1) as eluent afforded **10** (1.75 g, 94%) as an oil; UV (EtOH) 248 nm (ϵ 4000); IR (neat) 2765 (CHO), 1665 (C=O), 1640 (C=C), and 1615 (C=C) cm⁻¹; ¹H NMR (CDCl₃) δ =1.20 (3H, s, *t*-CH₃), 2.12 (3H, s, C=C-CH₃), 4.93–4.99 (2H, m, CH=CH₂), 5.66 (1H, m, CH=CH₂), and 10.13 (1H, s, CHO); ¹³C NMR (CDCl₃) δ =18.20, 19.40, 26.00, 35.57, 36.00, 36.37, 43.61, 116.91, 135.53, 139.38, 157.68, and 192.06; MS (rel intensity) *m/z* 178 (M⁺; 3), 163 (15), 137 (100), and 109 (37). Found: *m/z* 178.1365 (M⁺). Calcd for C₁₂H₁₈O: M, 178.1358.

6-Allyl-2,6-dimethyl-1-cyclohexene-1-carbaldehyde Trimethyleneacetal (11) and Ethyleneacetal (12).

To a solution of **10** (1.50 g, 8.41 mmol) in benzene (45 cm³) was added 1,3-propanediol (4 cm³) and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). A Dean-Stark water separator was attached, and the reaction mixture was refluxed for 4 h. After being cooled to room temperature, aqueous NaHCO₃ was added. Extraction with Et₂O followed by evaporation of the solvent gave an oily residue, which was chromatographed on neutral alumina (15 g) using hexane as eluent to yield **11** (1.98 g, 100%) as an oil; IR (neat) 1660 (C=C), 1640 (C=C), and 1150 (C-O) cm⁻¹; ¹H NMR (CDCl₃) δ =1.03 (3H, s, *t*-CH₃), 1.96 (3H, s, C=C-CH₃), 3.80 (2H, m, acetal), 4.18 (2H, m, acetal), 5.01 (2H, m, CH=CH₂), 5.02 (1H, s, OCHO), and 5.80 (1H, m, CH=CH₂); ¹³C NMR (CDCl₃) δ =18.76, 21.18, 25.61, 25.84, 33.38, 35.33, 36.53, 44.60, 67.67, 67.70, 100.95, 116.72, 134.47, 135.75, and 136.68; MS (rel intensity) *m/z* 236 (M⁺; 2), 221 (1), 205 (2), 195 (100), and 137 (44). Found: *m/z* 236.1809 (M⁺). Calcd for C₁₅H₂₄O₂: M, 236.1777.

By a similar procedure, **10** (1.93 g, 10.8 mmol) in benzene (190 cm³) was treated with 1,2-ethanediol (30 cm³) to give analogous ethyleneacetal **12** (2.17 g, 90%) as an oil; IR (neat) 1640 (C=C) and 1150 (C-O) cm⁻¹; ¹H NMR (CCl₄) δ =1.05 (3H, s, *t*-CH₃), 1.72 (3H, s, C=C-CH₃), 3.57–4.11 (2H, m, acetal), 4.70–5.10 (2H, m, CH=CH₂), 5.27 (1H, s, OCHO), and 5.36–6.15 (1H, m, CH=CH₂).

3-[2-(1,3-Dioxan-2-yl)-1,3-dimethyl-2-cyclohexenyl]-1-propanol (13). To a solution of NaBH₄ (800 mg) in dry diglyme (20 cm³) was added 2-methyl-2-butene (8.0 cm³) under Ar. The mixture was cooled in an ice bath and BF₃·OEt₂ (1.85 cm³, 15 mmol) was added dropwise with vigorous stirring. After being stirred at 0 °C for 6 h, a solution of **11** (359 mg, 1.52 mmol) in diglyme (5 cm³) was added. The mixture was allowed to warm to room temperature and stirred for 18 h. The flask was then cooled in an ice bath, and H₂O (9.5 cm³), aqueous NaOH (9.5 cm³; 3 moldm⁻³), and 35% H₂O₂ (8.5 cm³) were added dropwise successively. After being stirred at 40 °C for 1.5 h, saturated aqueous NaCl was added, and the mixture was extracted with Et₂O. Evaporation of the solvent gave the crude product, which was chromatographed on neutral alumina (5 g) using hexane-AcOEt (1:1) as eluent to give **13** (369 mg, 96%) as an oil; IR (neat) 3350 (OH), 1660 (C=C), 1140 (C-O), and 1085 (C-O) cm⁻¹; ¹H NMR (CCl₄) δ =1.00 (3H, s, *t*-CH₃), 1.85 (3H, s, C=C-CH₃), 3.28–4.30 (6H, m, acetal),

and 4.89 (1H, s, OCHO); MS (rel intensity) *m/z* 254 (M⁺; 22), 239 (7), 195 (86), and 59 (100). Found: *m/z* 254.1913 (M⁺). Calcd for C₁₅H₂₆O₃: M, 254.1883.

3-[2-(1,3-Dioxan-2-yl)-1,3-dimethyl-2-cyclohexenyl]propanal (14). To a stirred solution of **13** (370 mg, 1.45 mmol) in CH₂Cl₂ (15 cm³) was added PDC (900 mg) all at once and the mixture was stirred at room temperature for 1 d. Et₂O (ca. 20 cm³) was added and the resulting precipitate was filtered off. The filtrate was evaporated under reduced pressure until the solvent was at a minimum and the residual solution was passed through neutral alumina using Et₂O as eluent in order to remove any remaining PDC. After evaporation of the solvent, the crude product **14** (311 mg, 85%), which showed one spot on TLC, was used in the next step without purification. **14**: an oil; IR (neat) 2700 (CHO), 1720 (C=O), 1145 (C-O), and 1085 (C-O) cm⁻¹; ¹H NMR (CCl₄) δ =1.03 (3H, s, *t*-CH₃), 1.82 (3H, s, C=C-CH₃), 3.4–4.2 (4H, m, acetal), 4.87 (1H, s, OCHO), and 9.65 (1H, m, CHO); MS (rel intensity) *m/z* 252 (M⁺; 21), 237 (22), 224 (13), 209 (22), 195 (81), 137 (63), and 87 (100). Found: *m/z* 252.1722 (M⁺). Calcd for C₁₅H₂₄O₃: M, 252.1726.

Ethyl (Z)-5-[2-(1,3-Dioxan-2-yl)-1,3-dimethyl-2-cyclohexenyl]-2-trimethylsilylmethyl-2-pentenoate (15). NaH (175 mg, 3.6 mmol; 50% in mineral oil) was placed in a 30 cm³ three-necked flask under Ar, and the mineral oil was removed by washing with dry hexane. To this was added DME (6.5 cm³), then a solution of (EtO)₂POCH₂CO₂Et (0.65 cm³, 3.3 mmol) in DME (2 cm³) dropwise in an ice bath. After being stirred for 1.5 h, a solution of (iodomethyl)trimethylsilane (0.58 cm³, 3.9 mmol) in DME (3 cm³) was added and the mixture was warmed to 70 °C for 3 h. This was cooled to 0 °C again, and a second portion of NaH (142 mg, 3.0 mmol) was added. After being stirred at room temperature for 30 min, a solution of **14** (546 mg, 2.16 mmol) in DME (3 cm³) was added at 0 °C, and the reaction mixture was stirred at room temperature for 16 h. Aqueous NH₄Cl was then added to quench the reaction and the resulting aqueous mixture was extracted with Et₂O. Evaporation of the solvent gave a crude product containing **15** and **16**: ¹H NMR (CDCl₃) δ =6.57 (1H, t, *J*=7 Hz, C=CH of **15**) and 5.62 (1H, t, *J*=7 Hz, C=CH of **16**). Alumina (5 g) column chromatography using hexane as eluent afforded **15** (310 mg, 35%) as an oil; UV (EtOH) 238 nm (ϵ 10000); IR (neat) 1705 (C=O), 1630 (C=C), and 1090 (C-O) cm⁻¹; ¹H NMR (CCl₄) δ =-0.05 (9H, s, SiMe₃), 0.99 (3H, s, *t*-CH₃), 1.25 (3H, t, *J*=7 Hz, OCH₂CH₃), 1.73 (2H, s, CH₂SiMe₃), 1.82 (3H, s, C=C-CH₃), 3.4–4.3 (4H, m, acetal), 4.06 (2H, q, *J*=7 Hz, OCH₂CH₃), 4.84 (1H, s, OCHO), and 6.40 (1H, t, *J*=7 Hz, C=CH); MS (rel intensity) *m/z* 408 (M⁺; 12), 393 (4), 379 (9), 349 (35), 335 (18), 303 (19), 195 (92), 137 (64), 87 (73), and 73 (100). Found: *m/z* 408.2714 (M⁺). Calcd for C₂₃H₄₀O₄Si: M, 408.2697.

Ethyl (Z)-5-(2-Formyl-1,3-dimethyl-2-cyclohexenyl)-2-trimethylsilylmethyl-2-pentenoate (17). To a stirred solution of **15** (71 mg, 0.17 mmol) in acetone (15 cm³) was added a catalytic amount of TsOH. The mixture was heated under reflux for 5 h, cooled to room temperature, and aqueous NaHCO₃ was added. Extraction with Et₂O and evaporation of the solvent gave a crude product, which was chromatographed on silica gel (3 g) using hexane-AcOEt (50:1) as eluent to yield **17** (59 mg, 97%) as an

oil; UV (EtOH) 241 nm (ϵ 13000); IR (neat) 2750 (CHO), 1700 (C=O), 1665 (C=O), 1630 (C=C), 1610 (C=C), 1245 (C-O), and 1170 (C-O) cm^{-1} ; ^1H NMR (CDCl_3) δ = -0.05 (9H, s, SiMe_3), 1.16 (3H, s, $t\text{-CH}_3$), 1.24 (3H, t, J = 7 Hz, OCH_2CH_3), 1.73 (2H, s, CH_2SiMe_3), 2.09 (3H, s, C=C- CH_3), 4.11 (2H, q, J = 7 Hz, OCH_2CH_3), 6.51 (1H, t, J = 7 Hz, C=CH), and 10.10 (1H, s, CHO); ^{13}C NMR (CDCl_3) δ = -1.04 (3C), 14.25, 17.10, 18.33, 19.41, 24.33, 26.03, 35.55, 35.96, 37.87, 60.30, 129.73, 138.76, 139.64, 157.65, 168.32, and 191.86; MS (rel intensity) m/z 350 (M^+ ; 18), 335 (19), 321 (6), 304 (7), and 295 (14). Found: m/z 350.2282 (M^+). Calcd for $\text{C}_{20}\text{H}_{34}\text{O}_3\text{Si}$: M, 350.2278.

Ethyl 6-Hydroxyeudesmane-4,11(13)-dien-12-oate (18). To a stirred solution of TBAF (92 mg, 0.35 mmol) in dry THF (20 cm^3) was added dropwise a solution of **17** (86 mg, 0.25 mmol) in THF (6 cm^3) at 0 °C under Ar. After being stirred for 80 min, to the mixture was added aqueous NH_4Cl . The mixture was then extracted with Et_2O and the solvent was evaporated. Alumina (5 g) column chromatography using hexane-AcOEt (20:1 and 10:1) as eluents afforded **18** (31 mg, 45%) as an oil; IR (neat) 3400 (OH), 1700 (C=O), and 1615 (C=C) cm^{-1} ; ^1H NMR (CCl_4) δ = 1.24 (3H, s, 10-Me), 1.29 (3H, t, J = 7 Hz, OCH_2CH_3), 1.72 (3H, s, 4-Me), 3.04 (1H, m, $W_{1/2}$ = 7 Hz, 7-H), 4.04 (2H, q, J = 7 Hz, OCH_2CH_3), 4.63 (1H, d, J = 2 Hz, 6-H), 5.26 (1H, s, 13E-H), and 6.25 (1H, s, 13Z-H); MS (rel intensity) m/z 278 (M^+ ; 21), 250 (44), 232 (47), and 217 (100). Found: m/z 278.1883 (M^+). Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$: M, 278.1883.

Ethyl Eudesmane-3,5,11(13)-trien-12-oate (19). To a stirred solution of **18** (15 mg, 0.054 mmol) in acetone (15 cm^3) was added a small amount of $\text{TsOH}\cdot\text{H}_2\text{O}$ all at once and the mixture was stirred at room temperature for 25 min. Aqueous NaHCO_3 was added and the acetone was partly removed by evaporation under reduced pressure. This aqueous mixture was extracted with Et_2O , dried, and the solvent was evaporated to yield **19** (14 mg, 100%) as an oil; IR (neat) 1720 (C=O), 1630 (C=C), and 1130 (C-O) cm^{-1} ; ^1H NMR (CDCl_3) δ = 0.99 (3H, s, 10-Me), 1.30 (3H, t, J = 7 Hz, OCH_2CH_3), 1.54 (3H, s, 4-Me), 3.54 (1H, br t, J = 6 Hz, 7-H), 4.22 (2H, t, J = 7 Hz, OCH_2CH_3), 5.37 (1H, d, J = 5 Hz, 6-H), 5.40 (1H, t, J = 1.5 Hz, 13E-H), 5.55 (1H, m, 3-H), and 6.23 (1H, d, J = 1.5 Hz, 13Z-H); MS (rel intensity) m/z 260 (M^+ ; 100), 245 (26), 231 (21), 214 (20), 199 (16), 186 (61), 171 (40), and 95 (59).

6-Hydroxyeudesmane-4,11(13)-dien-12-oic Acid (20). To a stirred suspension of NaH (13 mg, 0.27 mmol; 50% in mineral oil, which was removed by washing with dry hexane) in dry THF (7 cm^3) was added a solution of **18** (23 mg, 0.083 mmol) in THF (7 cm^3) at room temperature under Ar. The mixture was stirred for 1 d, then to this was added an aqueous solution of NH_4Cl , and the resulting solution was acidified to pH ca. 1 by addition of dilute HCl. Extraction with Et_2O followed by evaporation of the solvent gave an oily residue, which was chromatographed on silica gel (3 g) using hexane-AcOEt (3:1) as eluent to afford **20** (18 mg, 87%) as an oil; IR (neat) 3300 (OH), 3500-2200 (COOH), 1695 (C=O), and 1620 (C=C) cm^{-1} ; ^1H NMR (CDCl_3) δ = 1.24 (3H, s, 10-Me), 1.72 (3H, s, 4-Me), 3.12 (1H, m, 7-H), 4.72 (1H, br s, 6-H), 5.43 (1H, s, 13E-H), and 6.35 (1H, s, 13Z-H); MS (rel intensity) m/z 250 (M^+ ; 14), 232 (83), 227 (100), and 171 (25). Found: m/z 232.1445 ($\text{M}-\text{H}_2\text{O}$). Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: M, 232.1464.

10-Epi-frullanolide (3). To a stirred solution of $\text{Me}_2\text{NCONMe}_2$ (0.1 cm^3 , 0.82 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (5 cm^3) was added $(\text{COCl})_2$ (0.07 cm^3 , 0.80 mmol) all at once. After being heated to 60 °C for 2 h, the solvent was removed under reduced pressure. MeCN (4 cm^3) was added, and to this was added dropwise a solution of **20** (30 mg, 0.12 mmol) and 2,4,6-trimethylpyridine (0.08 cm^3) in MeCN- Et_2O (35 cm^3 ; 3:4 ratio). After being stirred at room temperature for 1 d, the mixture was extracted with Et_2O . Evaporation of the solvent and silica-gel (5 g) column chromatography using hexane-AcOEt (100:1) as eluent afforded **3** (5 mg, 18%) as an oil; IR (neat) 1750 (C=O) and 1660 (C=C) cm^{-1} ; ^1H NMR (CDCl_3) δ = 1.03 (3H, s, 10-Me), 1.77 (3H, s, 4-Me), 3.29 (1H, dtt, J = 5, 2.5, and 7.5 Hz, 7-H), 5.31 (1H, d, J = 7 Hz, 6-H), 5.53 (1H, d, J = 2.5 Hz, 13E-H), and 6.19 (1H, d, J = 2.5 Hz, 13Z-H); MS (rel intensity) m/z 232 (M^+ ; 50), 217 (100), and 171 (23). Found: m/z 232.1478 (M^+). Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: M, 232.1464.

We thank Dr. Hiroshi Hirota, University of Tokyo, Dr. Masato M. Ito, and Dr. Takashi Niitsu, Soka University, for the measurements of the mass spectra. Thanks are also due to the staff of the Central Research Laboratories of Nitto Chemical Industry Co., Ltd. for the measurements of the NMR spectra.

References

- 1) N. H. Fischer, E. J. Olivier, and H. D. Fischer, *Fortschr. Chem. Org. Naturst.*, **38**, 47 (1979).
- 2) For a recent review of natural eudesmanolides see: B. M. Fraga, *Nat. Prod. Rep.*, **7**, 61 (1990); **7**, 515 (1990); **9**, 217 (1992).
- 3) Y. Asakawa, J. C. Muller, G. Ourisson, J. Foussereau, and G. Ducombs, *Bull. Soc. Chim. Fr.*, **1976**, 1465; For more examples see Ref. 1.
- 4) M. Tori, S. Yoshimura, C. Kuroda, and Y. Asakawa, *Chem. Lett.*, **1990**, 2117.
- 5) C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White, "The Total Synthesis of Natural Products," ed by J. ApSimon, Wiley, New York (1983), Vol. 5.
- 6) For recent examples on the synthesis of eudesmanolides see: I. G. Collado, J. G. Madero, G. M. Massanet, and F. R. Luis, *J. Org. Chem.*, **56**, 3587 (1991); G. Blay, M. L. Cardona, B. Garcia, and J. R. Pedro, *J. Org. Chem.*, **56**, 6172 (1991); M. Ando, T. Wada, and K. Isogai, *J. Org. Chem.*, **56**, 6235 (1991); Y. Amate, J. L. Breton, A. Garcia-Granados, A. Martinez, M. E. Onorato, and A. S. de Buruaga, *Tetrahedron*, **46**, 6939 (1990); K. Tomioka, F. Masumi, T. Yamashita, and K. Koga, *Tetrahedron*, **45**, 643 (1989); M. Tada and A. Kanamori, *Chem. Lett.*, **1989**, 1085.
- 7) C. Kuroda, S. Shimizu, and J. Y. Satoh, *J. Chem. Soc., Chem. Commun.*, **1987**, 286; *J. Chem. Soc., Perkin Trans. 1*, **1990**, 519.
- 8) K. Nishitani and K. Yamakawa, *Tetrahedron Lett.*, **28**, 655 (1987); K. Nishitani, H. Fukuda, and K. Yamakawa, *Heterocycles*, **33**, 97 (1992).
- 9) R. Henning and H. M. R. Hoffmann, *Tetrahedron Lett.*, **23**, 2305 (1982).
- 10) Ciba-Geigy A. -G., Brit. Patent 1565849 (1980);

Chem. Abstr., **94**, P30328w (1981).

11) T. Fujisawa, T. Mori, K. Fukumoto, and T. Sato, *Chem. Lett.*, **1982**, 1891.

12) G. Majetich, K. Hull, A. M. Casares, and V. Khetani, *J. Org. Chem.*, **56**, 3958 (1991); G. Majetich, J. Defauw, and C. Ringold, *J. Org. Chem.*, **53**, 50 (1988).
