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

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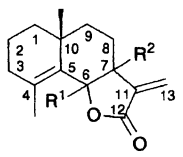
Synthesis of 10-epi-frullanolide (**3**) is reported via the intramolecular cyclization of ω-formyl-α-trimethylsilylmethyl-α,β-unsaturated ester. The cyclization precursor, ethyl (*Z*)-5-(2-formyl-1,3-dimethyl-2-cyclohexenyl)-2-trimethylsilylmethyl-2-pentenoate (**17**), was prepared from 2,6-dimethyl-2-cyclohexen-1-one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

Eudesmanolides having α-methylene-γ-lactone moieties are widely-occuring 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 intramoleclar cyclization of ω-formyl-α-trimethylsilylmethyl-α,β-unsaturated ester is an excellent method for synthesizing eudesmanolide derivatives, an α-methylene-γ-lacotone 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**.

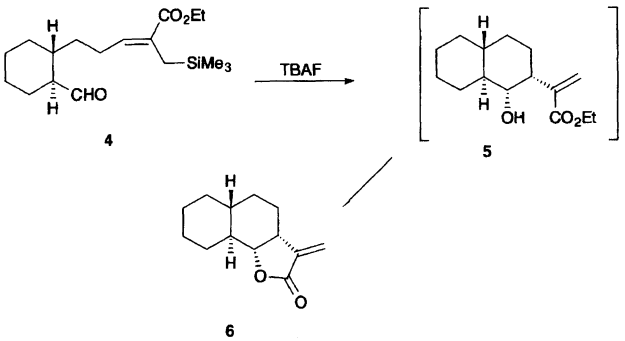


1 R^1=R^2=α-H
2 R^1=β-H, R^2=α-H
3 R^1=R^2=β-H

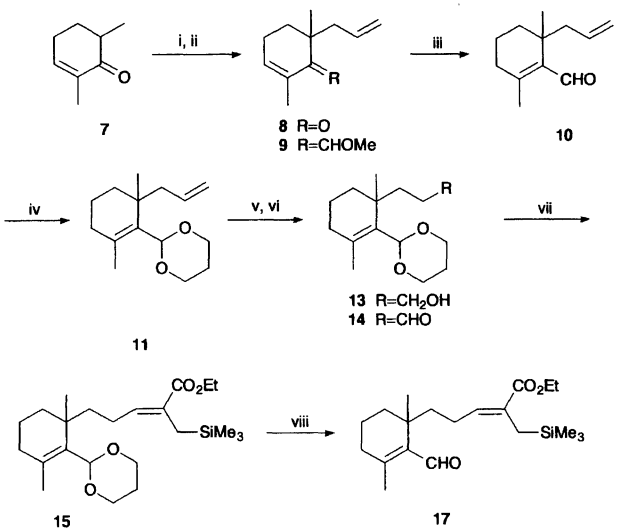
Chart 1.

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 ^{1}H 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, CH_2=$CHCH_2Br$, THF, −30 °C; ii, Ph_2POCH_2OMe, LDA, THF, room temperature; iii, 5% HCl, THF, reflux; iv, $HO(CH_2)_3OH$, 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, $(EtO)_2POCH(CO_2Et)CH_2SiMe_3$, NaH, DME, room temperature, viii, TsOH, acetone, reflux.

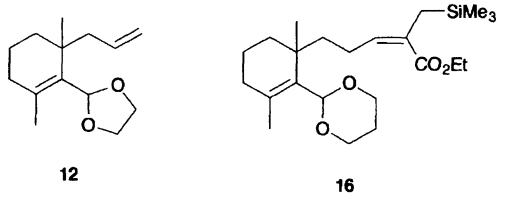
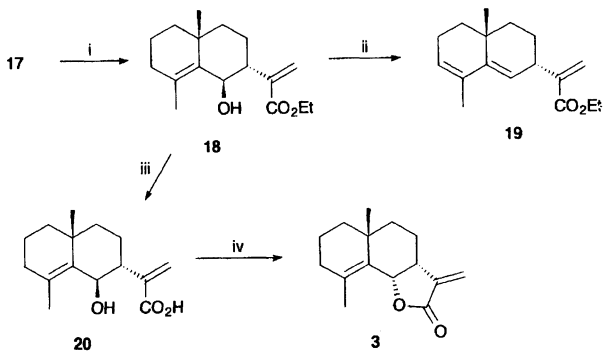


Chart 2.

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 reaction[9] on **14** using $(EtO)_2POCH(CO_2Et)CH_2SiMe_3$/NaH. The ^{1}H 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 δ=6.57 and 5.62, respectively, while the corresponding protons for the *Z*- and *E*-isomers of the model compound were observed at δ=6.44 and 5.55, respectively.[7] *Z*-isomer **15** could be isolated from the crude product by alumina column chromatography (35% yield form **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 cyclizaiton 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 ^{1}H NMR (signals of the α-methylene ester) spectra. The stereochemistry at C(6) was determined to have C(6α)–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 δ=1.24 by a 1,3-diaxial interaction with the C(6β)–OH group. It was suggested that **18** had C(7β)–H from its signal in the ^{1}H 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 ^{1}H 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}), ^{1}H 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, $[Me_2N{=}CClNMe_2]^+Cl^-$, 2,4,6-trimethylpyridine, MeCN, room temperature.

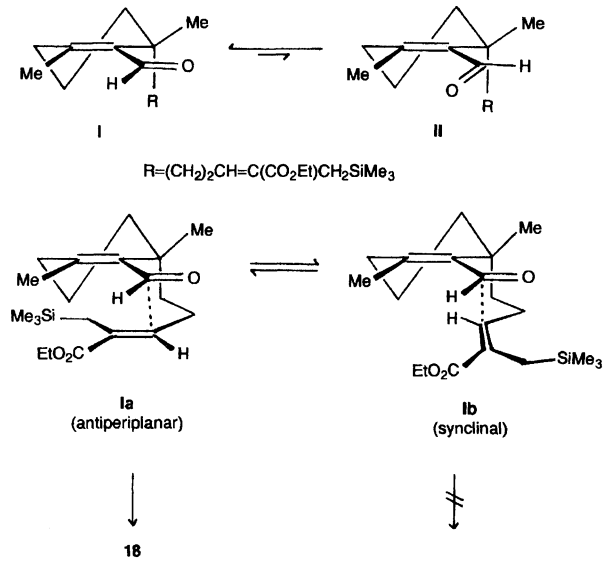
C(10)–Me was irradiated, which means that **3** had C-(6β)–H and C(7β)–H.

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(6β)–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. ^{1}H and ^{13}C 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 ($CHCl_3$=7.25) for all compounds having a trimethylsilyl group and for all ^{13}C NMR spectra. Both low-resolution 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 Na_2SO_4 or $MgSO_4$ were used for drying of extracted organic layers. For reactions requiring dry solvents, tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from $LiAlH_4$; diglyme, CH_2Cl_2, and hexane were distilled from CaH_2.



Scheme 4.

6-Allyl-2,6-dimethyl-2-cyclohexen-1-one (8). To a stirred solution of LDA [prepared from BuLi (3.8 cm^3, 9.5 mmol; 2.5 mol dm^{-3} solution in hexane) and diisopropylamine (2.8 cm^3) in dry THF (30 cm^3)] was added dropwise a solution of **7** (1.03 g, 8.29 mmol) in THF (2.7 cm^3) at −78 °C under Ar. After being stirred for 1 h, allyl bromide (1.3 cm^3, 15 mmol) was added, and the mixture was stirred at −30 °C for 4 h. Water (10 cm^3) was added and the product was extracted with Et_2O. 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}; ^{1}H NMR ($CDCl_3$) δ=1.07 (3H, s, t-CH_3), 1.76 (3H, br s, C=C–CH_3), 5.05 (2H, m, CH=C$\underline{H}_2$), 5.73 (1H, m, C$\underline{H}$=CH_2), and 6.65 (1H, m, C=CH); ^{13}C NMR ($CDCl_3$) 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 $C_{11}H_{16}O$: 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 cm^3, 21.9 mmol; 1.61 mol dm^{-3} solution in hexane) and diisopropylamine (6 cm^3) in dry THF (25 cm^3)] was added dropwise a solution of Ph_2POCH_2OMe (4.54 g, 18.5 mmol) in THF (120 cm^3) 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 cm^3) 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 NH_4Cl, and the mixture was extracted with Et_2O. 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}; ^{1}H NMR ($CDCl_3$) δ=1.01 (3H, s, t-CH_3 of major isomer), 1.17 (3H, s, t-CH_3 of minor isomer), 1.75 (3H, d, J=1.5 Hz, C=C–CH_3 of minor isomer), 1.99 (3H, d, J=2 Hz, C=C–CH_3 of major isomer), 3.56 (3H, s, OCH_3 of major isomer), 3.60 (3H, s, OCH_3 of minor isomer), 4.92—5.01 (2H, m, CH=C$\underline{H}_2$), 5.34 (1H, br s, C=CH of major isomer), 5.44 (1H, br s, C=CH of minor isomer), 5.79 (1H, m, C$\underline{H}$=CH_2), 5.81 (1H, s, C=C$\underline{H}$$OCH_3$ of major isomer), and 6.02 (1H, s, C=C$\underline{H}$$OCH_3$ of minor isomer); ^{13}C NMR ($CDCl_3$) 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 $C_{13}H_{20}O$: M, 192.1515.

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

solved in 5% HCl aq–THF (150 cm^3; 1:4 ratio) and the solution was refluxed for 20 min. After being cooled to room temperature, aqueous $NaHCO_3$ (35 cm^3) was added slowly and the mixture was extracted with Et_2O. Evaporation of the solvent followed by Florisil (50 g) column chromatography using hexane–Et_2O (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 ($CDCl_3$) δ=1.20 (3H, s, *t*-CH_3), 2.12 (3H, s, C=C–CH_3), 4.93—4.99 (2H, m, CH=C$\underline{H}_2$), 5.66 (1H, m, C$\underline{H}$=CH_2), and 10.13 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) 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 $C_{12}H_{18}O$: 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 cm^3) was added 1,3-propanediol (4 cm^3) 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 $NaHCO_3$ was added. Extraction with Et_2O 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 ($CDCl_3$) δ=1.03 (3H, s, *t*-CH_3), 1.96 (3H, s, C=C–CH_3), 3.80 (2H, m, acetal), 4.18 (2H, m, acetal), 5.01 (2H, m, CH=C$\underline{H}_2$), 5.02 (1H, s, OCHO), and 5.80 (1H, m, C$\underline{H}$=CH_2); ^{13}C NMR ($CDCl_3$) 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 $C_{15}H_{24}O_2$: M, 236.1777.

By a similar procedure, **10** (1.93 g, 10.8 mmol) in benzene (190 cm^3) was treated with 1,2-ethanediol (30 cm^3) 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 (CCl_4) δ=1.05 (3H, s, *t*-CH_3), 1.72 (3H, s, C=C–CH_3), 3.57—4.11 (2H, m, acetal), 4.70—5.10 (2H, m, CH=C$\underline{H}_2$), 5.27 (1H, s, OCHO), and 5.36—6.15 (1H, m, C$\underline{H}$=CH_2).

3-[2-(1,3-Dioxan-2-yl)-1,3-dimethyl-2-cyclohexenyl]-1-propanol (13). To a solution of $NaBH_4$ (800 mg) in dry diglyme (20 cm^3) was added 2-methyl-2-butene (8.0 cm^3) under Ar. The mixture was cooled in an ice bath and BF_3·OEt_2 (1.85 cm^3, 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 cm^3) 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 H_2O (9.5 cm^3), aqueous NaOH (9.5 cm^3; 3 mol dm^{-3}), and 35% H_2O_2 (8.5 cm^3) were added dropswise succesively. After being stirred at 40 °C for 1.5 h, saturated aqueous NaCl was added, and the mixture was extracted with Et_2O. 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 (CCl_4) δ=1.00 (3H, s, *t*-CH_3), 1.85 (3H, s, C=C–CH_3), 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 $C_{15}H_{26}O_3$: 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 CH_2Cl_2 (15 cm^3) was added PDC (900 mg) all at once and the mixture was stirred at room temperature for 1 d. Et_2O (ca. 20 cm^3) 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 Et_2O 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 (CCl_4) δ=1.03 (3H, s, *t*-CH_3), 1.82 (3H, s, C=C–CH_3), 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 $C_{15}H_{24}O_3$: 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 cm^3 three-necked flask under Ar, and the mineral oil was removed by washing with dry hexane. To this was added DME (6.5 cm^3), then a solution of $(EtO)_2POCH_2CO_2Et$ (0.65 cm^3, 3.3 mmol) in DME (2 cm^3) dropwise in an ice bath. After being stirred for 1.5 h, a solution of (iodomethyl)trimethylsilane (0.58 cm^3, 3.9 mmol) in DME (3 cm^3) 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 cm^3) was added at 0 °C, and the reaction mixture was stirred at room temperature for 16 h. Aqueous NH_4Cl was then added to quench the reaction and the resulting aqueous mixture was extracted with Et_2O. Evaporation of the solvent gave a crude product containing **15** and **16**: ^1H NMR ($CDCl_3$) 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 (CCl_4) δ=−0.05 (9H, s, $SiMe_3$), 0.99 (3H, s, *t*-CH_3), 1.25 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 1.73 (2H, s, C$\underline{H}_2$$SiMe_3$), 1.82 (3H, s, C=C–$CH_3$), 3.4—4.3 (4H, m, acetal), 4.06 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 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 $C_{23}H_{40}O_4Si$: 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 cm^3) was added a catalytic amount of TsOH. The mixture was heated under reflux for 5 h, cooled to room temperature, and aqueous $NaHCO_3$ was added. Extraction with Et_2O 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 ($CDCl_3$) $\delta=-0.05$ (9H, s, $SiMe_3$), 1.16 (3H, s, t-CH_3), 1.24 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.73 (2H, s, $C\underline{H}_2SiMe_3$), 2.09 (3H, s, C=C–CH_3), 4.11 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 6.51 (1H, t, $J=7$ Hz, C=CH), and 10.10 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) $\delta=-1.04$ (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 $C_{20}H_{34}O_3Si$: 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) $\delta=1.24$ (3H, s, 10-Me), 1.29 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.72 (3H, s, 4-Me), 3.04 (1H, m, $W_{1/2}=7$ Hz, 7-H), 4.04 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 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 $C_{17}H_{26}O_3$: 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 $TsOH\cdot H_2O$ 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 ($CDCl_3$) $\delta=0.99$ (3H, s, 10-Me), 1.30 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.54 (3H, s, 4-Me), 3.54 (1H, br t, $J=6$ Hz, 7-H), 4.22 (2H, t, $J=7$ Hz, $OC\underline{H}_2CH_3$), 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 (CO$\underline{O}$H), 1695 (C=O), and 1620 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.24$ (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 ($M-H_2O$). Calcd for $C_{15}H_{20}O_2$: M, 232.1464.

10-Epi-frullanolide (3). To a stirred solution of $Me_2NCONMe_2$ (0.1 cm^3, 0.82 mmol) in $ClCH_2CH_2Cl$ (5 cm^3) was added $(COCl)_2$ (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 ($CDCl_3$) $\delta=1.03$ (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 $C_{15}H_{20}O_2$: M, 232.1464.

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