Synthesis of Cadinanolide Type of Tricyclic α-Methylene-γ-lactone Using Intramolecular Cyclization of α-Trimethylsilylmethyl-α,β-Unsaturated Ester with Cyclic Ketone

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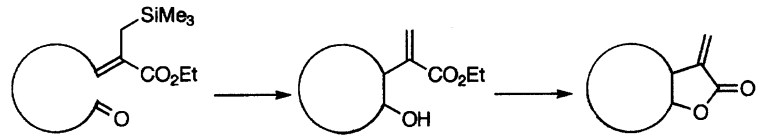
Fluoride-promoted intramolecular cyclization of ethyl 6-(2-oxocyclohex-1-yl)-2-(trimethylsilylmethyl)hex-2-enoate afforded ethyl 2-(1-hydroxybicyclo[4.4.0]decan-2-yl)acrylate as the major product, together with tricyclic α-methylene-γ-lactone, a model compound of cadinanolides. The former product was also converted to γ-lactone. The cyclization reaction promoted by $TiCl_4$ gave the hydroxy ester and its dehydrated product. Both Lewis acid- and fluoride-promoted cyclizations gave a *trans*-decaline system mainly. This stereoselectivity is completely different from that of Reformatsky cyclization observed by Dreiding and co-workers.

Sesquiterpenes having α-methylene-γ-lactone moieties are widely occurring natural products[1] with some biological activities.[2] We developed a synthetic strategy for α-methylene-γ-lactones fused to various carbocycles using intramolecular cyclization of α-trimethylsilylmethyl-α,β-unsaturated ester with aldehyde,[3,4] namely the intramolecular Hosomi reaction[5,6] (Scheme 1). Using this method, cyclization of allylsilane can be done via two different processes, a Lewis acid-promoted cationic process and a fluoride-promoted anionic process, and thus the stereochemistry of α-methylene-γ-lactones can be controlled by choosing the cyclization reagent, acid or fluoride. Following us, Nishitani and co-workers also developed similar methods.[7] We have prepared eudesman-6,12-olide,[3a] guaian-6,12-olide,[3b] and -8,12-olide[3c] types of tricyclic α-methylene-γ-lactones by this method, and Nishitani et al. synthesized menthanolide[7c] and diplophyllin.[7d] However, since all of these types of compounds have a γ-lactone moiety derived from a *secondary* alcohol, the cyclization study is limited to *ω-formyl* allylsilane, and no study was done on intramolecular cyclization of *keto* allylsilane giving a lactone moiety derived from a *tertiary* alcohol, such as cadinanolides.[8] A few synthetic studies targeted to cadinanolides have been reported, including formation of a tricyclic ring system by lactonization via hydroxy nitrile,[9] and thermolysis of a photo-adduct,[10] while Dreiding and co-workers reported a synthesis of cadinanolides by an intramolecular Reformatsky reaction between 2-(ethoxycarbonyl)allylzinc bromide and cyclic ketone.[11] We planned to synthesize a cadinanolide type of tricyclic α-methylene-γ-lactone by our method, intramolecular cyclization of functionalized allylsilane with ketone, in which a silicon atom is used instead of zinc atom appeared in the Dreiding's strategy. In contrast to the reaction with aldehyde depicted in Scheme 1, there must be two problems. First, ketone is normally less reactive than aldehyde against a nucleophile, in this case allylsilane, which has reduced nucleophilicity due to a conjugating ester group. The second problem is that the *tertiary* hydroxyl group of the cyclization product eliminates much more easily than a *secondary* hydroxyl group. Here we report that tetrabutylammonium fluoride (TBAF)-promoted cyclization, an anionic process, gives satisfactory results for this purpose. The stereochemistry of the cyclization is also described.

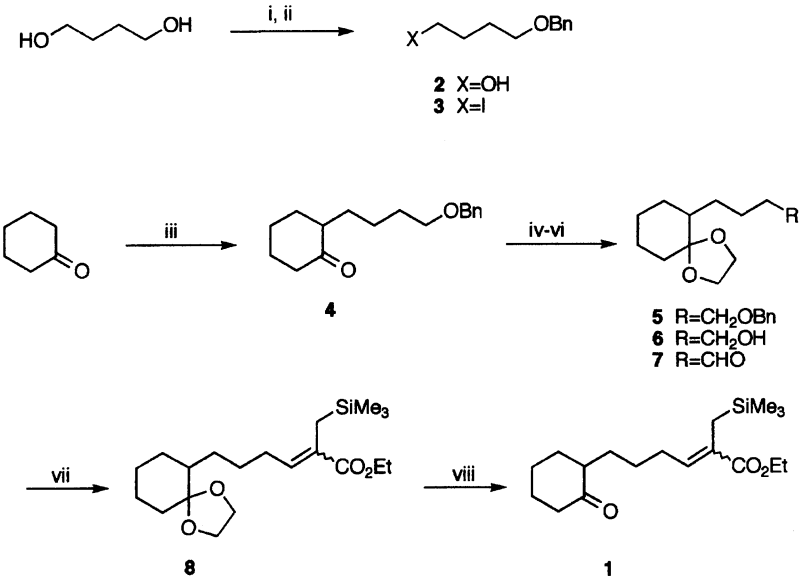
Results and Discussion

The cyclization precursor **1** was synthesized according to Scheme 2. First, 1-benzyloxy-4-iodobutane (**3**) was prepared from butane-1,4-diol by monobenzylation (**2**; 60%) followed by iodination by I_2/Ph_2PCl/imidazole[12] (64%). This was coupled with cyclohexanone using $KN(SiMe_3)_2$[13] as a base to afford **4** in 82% yield. Acetalization (**5**; 94%) followed by removal of benzyl group by hydrogenolysis yielded alcohol **6** (96%), which was treated by Swern oxidation to give keto-aldehyde derivative **7** (98%). An α-trimethylsilylmethyl-α,β-unsaturated ester moiety was then introduced by Hoffmann's method[3,4] giving **8** in 51% yield as a mixture of *Z*- and *E*-isomers. The ratio of the two isomers was determined to be $Z:E=2:1$ from olefinic signals in the ^{1}H NMR spectrum. Finally acetal was hydrolyzed to give **1** in 97% yield. Unfortunately, the two isomers could not be separated at both **8** and **1**, and the mixture of *Z*- and *E*-isomers was used in the following study.

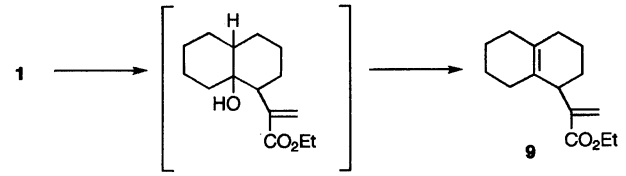
Lewis acid-promoted cyclization of **1** was first attempted. When **1** was treated with $Et_2O{\cdot}BF_3$ or $EtAlCl_2$, carbocyclization proceeded, however, only dehydrated product **9** was afforded in 75 and 83% yields, respectively. This is because the *tertiary* hydroxyl group in the intermediate is easy to eliminate in the acidic conditions used, as mentioned above (Scheme 3). Hydroxy ester **10** was obtained in 64% yield, in addition to **9**, when $TiCl_4$ was used as a Lewis acid.



Scheme 1.



Scheme 2. Reagents and conditions: i, $PhCH_2Br$, NaH, DMF, 0 °C; ii, I_2, Ph_2PCl, imidazole, toluene, r.t.; iii, $KN(SiMe_3)_2$, **3**, THF, r.t.; iv, ethylene glycol, PPTS, benzene, reflux; v, H_2, Pd–C, EtOH, r.t.; vi, $(COCl)_2$, DMSO, Et_3N, −60 °C; vii, $(EtO)_2P(O)CH(CO_2Et)CH_2SiMe_3$, NaH, DME, r.t.; viii, PPTS, acetone, reflux.



Scheme 3. Treatment of **1** with Lewis acid.

Conversion of **10** into a lactone was attempted but the result was unsatisfactory (Chart 1).

Fluoride-promoted cyclization of **1** was next done by treatment with 3 molar amount of TBAF in tetrahydrofuran (THF) at 0 °C to afford hydroxy ester **11** and a cadinanolide type

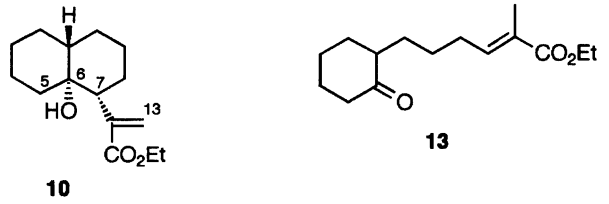
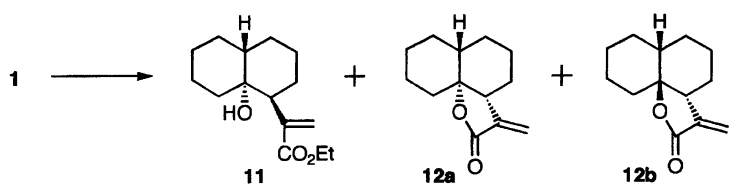


Chart 1.

of tricyclic lactone **12** in 69 and 12% yields, respectively (Scheme 4). The lactone was found to consist of mostly **12a** together with a small amount of **12b** (**12a** : **12b** = 13 : 1). We recently reported that the stereochemistry of the fluoride-promoted intramolecular cyclization of functionalized allylsilane with aldehyde does not depend on the geometry of the allylsilane.[14] Therefore, in this case, although the two geometrical isomers of α-trimethylsilylmethyl-α,β-unsaturated esters (*Z*)-**1** and (*E*)-**1** were not separated, it can be assumed that each isomer gave the same products, **11** and **12**.

Treatment of **1** with CsF in acetonitrile gave the same hydroxy ester **11** in low yield (5%) together with protiodesilylated product **13** (24%) as an inseparable mixture. Compound **13** was found to consist of only *E*-isomer (Chart 1). This must be the result of desilylation from (*Z*)-**1**,[3b] or equilibration of desilylated products of (*E*)- and (*Z*)-**1** under basic conditions.

The hydroxy ester **11** was further converted into the third lactone **15**. Thus the ester group was hydrolyzed by treatment with NaH in THF[3a] (98% yield) or KOH aq in MeOH (58% yield) giving **14**, which was lactonized according to Vorbruggen's method[15] using $Me_2NCH(OCH_2CMe_3)_2$ in



Scheme 4. Treatment of **1** with TBAF.

Table 1. ^{1}H NMR Data of Hydroxy Esters and Lactones[a)]

Compound	7-H	13*E*-H	13*Z*-H
10	2.63 (dd, 3, 13 Hz)	5.65 (d, 1.5 Hz)	6.23 (d, 1.5 Hz)
11	3.00 (br d, 6 Hz)	5.90 (s)	6.29 (s)
12a	2.58 (ddt, 7, 8, 1.5 Hz)	5.49 (d, 1.5 Hz)	6.12 (d, 1.5 Hz)
12b	2.55 (dq, 12, 3 Hz)	5.29 (d, 3 Hz)	6.03 (d, 3.5 Hz)
15	2.65 (dq, 6, 3 Hz)	5.41 (d, 3 Hz)	6.23 (d, 3.5 Hz)

a) Measured in $CDCl_3$ using the signal of $CHCl_3$ ($\delta = 7.25$) as a standard.

boiling toluene (95% yield). This lactonization method is known to include Walden inversion at the hydroxy-bearing carbon[15,16] (Scheme 5).

The structures of these cyclization products were identified based on the ^{1}H NMR spectral data listed in Table 1. The stereochemistry of **10** was first established from axial coupling ($J = 13$ Hz) observed for 7-H[#] and NOE observed between 7-H and 5β-H.[#] The structure of **11** could next be identified from the fact that **11** gives lactone with inversion at C(6)[#] and that the signal of 7-H is low-field shifted with a small J-value, indicating equatorial orientation. Since the lactone **15** was obtained from **11**, the structure of **15** was also established. As for the stereochemistry of **12a** and **12b**, there are only two more possibilities since *trans*-lactone fused to *trans*-decaline can be ruled out. Then we could identify their structures by comparison of J-values observed for 7-H with that of calculated[##] based on the dihedral angle obtained by commercial Chem3D and the equation reported by Haasnoot et al.[17] As described in Table 2, observed and calculated J-values agreed for both **12a** and **12b**. The stereochemistry of the lactone moiety is also supported by J-values of both 13*E*-H and 13*Z*-H,[#] which depend on the dihedral angle H(7)–C(7)–C(12)–C(13).[18] Thus a small J-value ($J_{7-13} = 1.5$ Hz) observed for **12a** is consistent with a small dihedral angle (36.5°), and a large J-value ($J_{7-13} = 3$ or 3.5 Hz) for **12b** is consistent with the large angle (97.7°). Conformations of the three lactones are illustrated in Chart 2.

The explanation of the stereochemical outcome is easier than the case of the synthesis of eudesmanolides[3a)] or guaianolides.[3b,3c)] It is known that the mechanism of two cyclization processes, anionic and cationic, are different.[19] Thus Lewis acid-promoted reaction of allylsilane involves a thermodynamically controlled process while the fluoride-promoted reaction involves a kinetically controlled process. The stereochemistry of $TiCl_4$-promoted cyclization is rationalized by the intermediate **A**, a cation stabilized by silicon atom having the thermodynamically most favorable *trans*-fused chair–chair decaline system with an equatorial side chain. It is also possible to explain the stereochemistry by chelation of the titanium atom (**B**),[7b)] based on the fact that the treatment with $Et_2O{\cdot}BF_3$ or $EtAlCl_2$ did not afford hydroxy ester **10** (Scheme 6). For the product **9**, it is impossible to assume any stereochemistry of the intermediate since **9** has no stereochemical information.

Table 2. Calculated J-Values of **12a** and **12b**

Structure	Dihedral angle		Calculated J-value (Hz)[a)]	
	7-8α	7-8β	7-8α	7-8β
12a	160.0°	43.4°	11.6 (8)	6.3 (7)
12b	180.0°	61.6°	13.1 (12)	2.9 (3)

a) Observed J-values are shown in parenthesis.

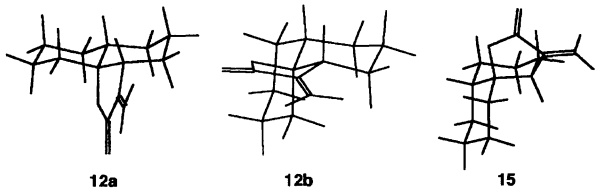
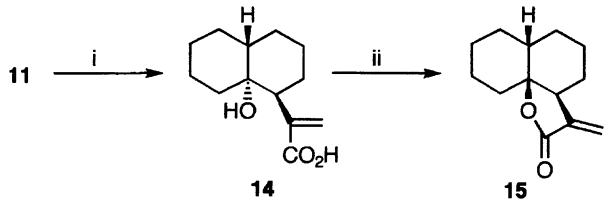
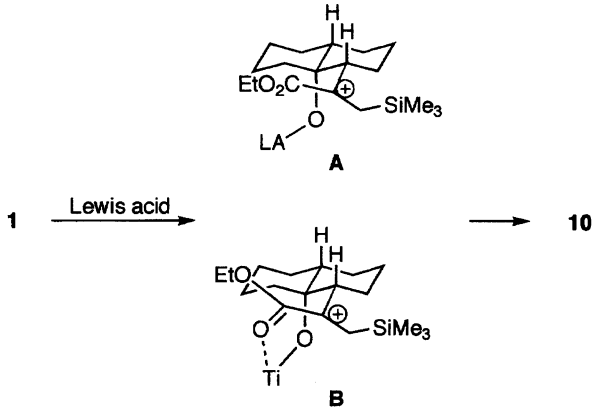


Chart 2.

Both the major product **11** and the minor product **12a** of TBAF-promoted cyclization is to be explained by an antiperiplanar attack[20] (**C**) and synclinal attack[20] (**D**) of fluorinated allylsilane[5] on carbonyl, respectively. The very minor prod-



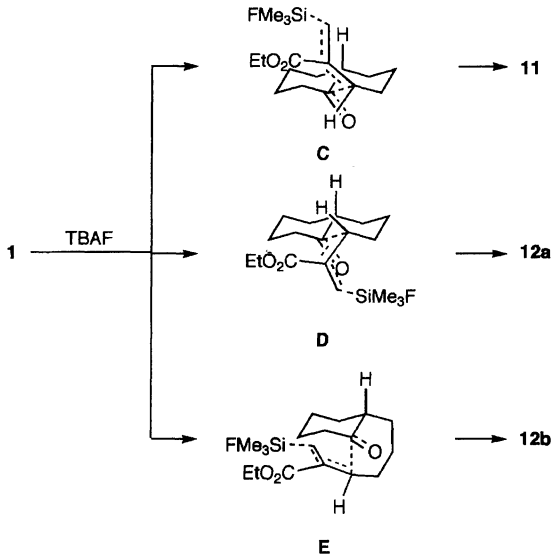
Scheme 5. Reagents and conditions: i, NaH, THF, reflux, then HCl; ii, $Me_2NCH(OCH_2CMe_3)_2$, toluene, reflux.



Scheme 6.

#For numbering of cadinanolides, see Ref. 1. The numbering is partly inserted in the structure **10**.

##See also Ref. 11 for structural discussion based on dihedral angle and coupling constant.



Scheme 7.

uct **12b** must be the result of an antiperiplanar attack from the opposite side (**E**) (Scheme 7).

In conclusion, the utility and the limitations of the cyclization of α-trimethylsilylmethyl-α,β-unsaturated ester in the short-step synthesis of the cadinanolide type of tricyclic α-methylene-γ-lactone was revealed. Despite the prediction, the reaction of ester-conjugated allylsilane with ketone did not show any electrical or sterical problems. However elimination of the resultant *tertiary* alcohol went much faster than the lactonization in acidic conditions except with $TiCl_4$ treatment. TBAF was found to be a good reagent in such cases. The stereochemistry of the cyclization reaction can be summarized that (1) cationic conditions ($TiCl_4$) give A/B-*trans*-6,7-*cis* product mainly and (2) anionic conditions (TBAF) give A/B-*trans*-6,7-*trans* product mainly. It is interesting that none of these stereoselectivities are the same as the anionic process of Reformatsky cyclization reported by Dreiding and co-workers,[11] in which the A/B-*cis*-6,7-*cis* product was obtained mainly. This means that the stereochemistry of the product can be controlled by the choice of reaction; i.e. allylsilane of cationic conditions, allylsilane of anionic conditions, and the Reformatsky reaction.

Experimental

General Procedures. UV spectra were measured on a JASCO Ubest-50 spectrometer. IR spectra were taken on a Hitachi 270-30 spectrometer. Both ^1H and ^{13}C NMR spectra were measured on a JEOL GSX-400 (400 MHz for ^1H; 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported on the δ scale (ppm) with tetramethylsilane ($Me_4Si = 0.00$) or chloroform ($CHCl_3 = 7.25$) as an internal standard. The signal of the solvent ($CDCl_3 = 77.00$) was used as a standard for all ^{13}C NMR spectra. Both low-resolution mass spectra (MS) and high-resolution mass spectra were obtained on a JEOL SX-102A mass spectrometer with EI method. Analytical TLC was done on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200, C-300, or Florisil (100—200 mesh) 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, 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF) were distilled from $LiAlH_4$; hexane, toluene, and CH_2Cl_2 were distilled from CaH_2; *N*,*N*-dimethylformamide (DMF) was distilled from 4A molecular sieve.

4-Benzyloxybutan-1-ol (2). Sodium hydride (2.24 g, 56.0 mmol; 60% oil-coated) was washed with dry hexane to remove coated oil, and to this was added dry DMF (50 cm^3) under Ar. Butane-1,4-diol (4.9 cm^3, 55.4 mmol) was added at 0 °C, and after 10 min of stirring, benzyl bromide (7.5 cm^3, 63.1 mmol) was added at once, and the stirring was continued for 20 min. Water was added and the mixture was extracted with Et_2O. After drying and evaporation of the solvent, the residue was chromatographed on silica gel (50 g) using hexane–AcOEt (9 : 1) as eluent to give **2** (5.97 g, 60%) as an oil; IR (neat) 3400 (OH) and 1105 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = Me_4Si) $\delta = 1.66$ (4H, m, CH_2CH_2), 2.67 (1H, br, OH), 3.50 (2H, t, $J = 6$ Hz, $C\underline{H}_2OBn$), 3.59 (2H, t, $J = 6$ Hz, $C\underline{H}_2OH$), 4.50 (2H, s, $C\underline{H}_2Ph$), and 7.32 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta = 26.45$, 29.84, 62.37, 70.20, 72.88, 127.52, 127.58 (2C), 128.28 (2C), and 138.04; MS *m*/*z* (rel intensity) 180 (M^+; 42), 107 (100), and 92 (57). Found: *m*/*z* 180.1177 (M^+). Calcd for $C_{11}H_{16}O_2$: M, 180.1151.

4-Benzyloxy-1-iodobutane (3). To a stirred solution of **2** (5.72 g, 31.7 mmol) in dry toluene (50 cm^3) was added imidazole (4.53 g) and Ph_2PCl (7.0 cm^3, 38.1 mmol). I_2 (7.26 g, 28.6 mmol) was added and the mixture was stirred at room temperature for 30 min. An aqueous solution of $NaHCO_3$ was added, the mixture was extracted with Et_2O, and the ethereal layer was washed with $Na_2S_2O_3$ solution. Drying and evaporation of the solvent followed by silica-gel (50 g) column chromatography using hexane–AcOEt (99 : 1) as eluent afforded **3** (5.88 g, 64%) as an oil; IR (neat) 1225 (CH_2I) and 1105 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = Me_4Si) $\delta = 1.71$ (2H, m, CH_2), 1.93 (2H, m, CH_2), 3.19 (2H, t, $J = 7$ Hz, CH_2I), 3.48 (2H, t, $J = 7$ Hz, $C\underline{H}_2OBn$), 4.49 (2H, s, $C\underline{H}_2Ph$), and 7.32 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta = 6.81$, 30.32, 30.54, 68.93, 72.85, 127.52, 127.53 (2C), 128.32 (2C), and 138.32; MS *m*/*z* (rel intensity) 290 (M^+; 24), 183 (M−OCH_2Ph; 83), and 163 (M−I; 100). Found: *m*/*z* 290.0153 (M^+). Calcd for $C_{11}H_{15}IO$: M, 290.0169.

2-(4-Benzyloxybutyl)cyclohexanone (4). To a stirred solution of $KN(TMS)_2$ (40 cm^3, 20.0 mmol; 0.5 mol dm^{-3} solution in toluene) in dry THF (50 cm^3) at −60 °C under Ar was added cyclohexanone (1.9 cm^3, 18.3 mmol). After being stirred at −60 °C for 1.5 h, a solution of **3** (5.88 g, 20.3 mmol) in THF (22 cm^3) was added, and the mixture was stirred at room temperature for 3 h. An aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with pentane–Et_2O (9 : 1). The organic layer was washed with dilute HCl aq, $NaHCO_3$ aq, and dried. Evaporation of the solvent followed by silica-gel (200 g) column chromatography using hexane–AcOEt (97 : 3) as eluent yielded **4** (3.90 g, 82% from cyclohexanone) as an oil; IR (neat) 1715 (C=O) and 1105 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = Me_4Si) $\delta = 1.16$—2.41 (15H, m), 3.46 (2H, t, $J = 7$ Hz, $C\underline{H}_2OBn$), 4.49 (2H, s, $OC\underline{H}_2Ph$), and 7.23—7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) $\delta = 23.74$, 24.80, 27.93, 29.10, 29.81, 33.78, 41.88, 50.59, 70.16, 72.79, 127.35, 127.50 (2C), 128.21 (2C), 138.57, and 213.06; MS *m*/*z* (rel intensity) 260 (M^+; 54), 151 (25), 111 (26), and 91 (100). Found: *m*/*z* 260.1758 (M^+). Calcd for $C_{17}H_{24}O_2$: M, 260.1777.

2- (4- Benzyloxybutyl)- 1, 1- ethylenedioxycyclohexane (5). Compound **4** (776 mg, 2.98 mmol) was dissolved in benzene (100 cm^3), and to this was added ethylene glycol (10 cm^3) and pyridinium *p*-toluenesulfonate (205 mg). A Dean–Stark water separator was attached and the mixture was refluxed for 8 h. An aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with Et_2O

and dried. After evaporation of the solvent, the crude product was chromatographed on silica gel (5 g) using hexane–AcOEt (9 : 1) as eluent to afford **5** (850.1 mg, 94%) as an oil; IR (neat) 1105 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = Me_4Si) δ = 1.05—1.83 (15H, m), 3.46 (2H, t, J = 7 Hz, C<u>H</u>$_2$OBn), 3.90 (4H, m, OCH_2CH_2O), 4.49 (2H, s, OC<u>H</u>$_2$Ph), and 7.22—7.34 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ = 23.80, 24.06, 24.36, 27.73, 28.85, 30.04, 34.54, 44.47, 64.53, 64.64, 70.38, 72.73, 110.77, 127.32, 127.48 (2C), 128.21 (2C), and 138.63; MS *m/z* (rel intensity) 304 (M^+; 35), 213 (92), 155 (45), 99 (100), and 91 (43). Found: *m/z* 304.2001 (M^+). Calcd for $C_{19}H_{28}O_3$: M, 304.2039.

4-(2,2-Ethylenedioxycyclohex-1-yl)butan-1-ol (6). A suspension of 10% Pd–C (1.49 g) in EtOH (100 cm^3) was prepared and the reaction atmosphere was replaced by H_2. To this was added a solution of **5** (2.803 g, 9.21 mmol) in EtOH (10 cm^3), and the resulted suspension was stirred at room temperature for 2 h. The catalyst was filtered off, and after evaporation of the solvent, the residue was chromatographed on silica gel (5 g) using hexane–AcOEt (1 : 1) to give **6** (1.886 g, 96%) as an oil; IR (neat) 3450 (OH) and 1095 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.01—1.80 (15H, m), 1.89 (1H, br, OH), 3.58 (2H, t, J = 7 Hz, C<u>H</u>$_2$OH), and 3.83—3.95 (4H, m, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ = 23.54, 23.71, 24.31, 27.58, 28.81, 32.92, 34.46, 44.38, 62.53, 64.48, 64.59, and 110.78; MS *m/z* (rel intensity) 214 (M^+; 48), 171 (37), 155 (44), 141 (10), 113 (15), and 99 (100). Found: *m/z* 214.1574 (M^+). Calcd for $C_{12}H_{22}O_3$: M, 214.1570.

4-(2,2-Ethylenedioxycyclohex-1-yl)butanal (7). To a stirred solution of $(COCl)_2$ (1.2 cm^3) in dry CH_2Cl_2 (50 cm^3) was added dimethyl sulfoxide (1.99 cm^3) at −60 °C under Ar. After 2 min of stirring, a solution of **6** (1.500 g, 7.00 mmol) in CH_2Cl_2 (10 cm^3) was added, and the mixture was stirred for 1 h. Et_3N (7.8 cm^3) was added, and after 5 min of further stirring, the flask was warmed to room temperature slowly. An aqueous solution of NH_4Cl was added and the mixture was extracted with Et_2O, dried, and the solvent was evaporated off to afford crude product **7** (1.454 g, 78%), which was used in the next step without purification. **7**: IR (neat) 2725 (CHO), 1730 (C=O), and 1100 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.05—1.82 (13H, m), 2.39 (2H, m, C<u>H</u>$_2$CHO), 3.48—3.97 (4H, m, OCH_2CH_2O), and 9.73 (1H, t, J = 2 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ = 20.09, 23.68, 24.38, 27.64, 28.93, 34.46, 44.16, 44.33, 64.51, 64.62, 110.56, and 202.77; MS *m/z* (rel intensity) 212 (M^+; 71), 185 (100), 183 (69), 170 (54), 156 (61), 125 (51), and 79 (66). Found: *m/z* 212.1416 (M^+). Calcd for $C_{12}H_{20}O_3$: M, 212.1413.

Ethyl 6-(2,2-Ethylenedioxycyclohex-1-yl)-2-(trimethylsilylmethyl)hex-2-enoate (8). To a stirred suspension of NaH (455.3 mg, 11.4 mmol; 60% in mineral oil which was removed by washing with dry hexane) in dry DME (50 cm^3) was added $(EtO)_2P(O)CH_2CO_2Et$ (2.0 cm^3, 10.1 mmol) at 0 °C under Ar. After being stirred for 30 min, ICH_2SiMe_3 (1.85 cm^3, 12.5 mmol) was added and the mixture was heated to 70 °C for 4 h. This was cooled to 0 °C again, and a second portion of NaH (378.8 mg, 9.47 mmol) was added. After being stirred at room temperature for 1.5 h, a solution of **7** (1.454 g, 6.85 mmol) in DME (20 cm^3) was added, and the mixture was stirred at room temperature for 16 h. An aqueous solution of NH_4Cl was added, the mixture was extracted with Et_2O, and dried. Evaporation of the solvent followed by silica-gel (70 g) column chromatography using hexane–AcOEt (19 : 1) as eluent gave **8** (1.2777 g, 51%) as an oil; UV (hexane) λ_{max} = 232 nm (ε 10000); IR (neat) 1710 (C=O), 1250 (C–O), and 1090 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) assigned for *Z*-isomer δ = −0.05 (9H, s, $SiMe_3$), 1.02—1.82 (13H, m), 1.24 (3H, t, J = 7 Hz, OCH_2C<u>H</u>$_3$), 1.76 (2H, br s, C<u>H</u>$_2$$SiMe_3$), 2.03 (2H, m, C<u>H</u>$_2$CH=C), 3.81—3.95 (4H, m, OCH_2CH_2O), 4.11 (2H, q, J = 7 Hz, OC<u>H</u>$_2$$CH_3$), and 6.56 (1H, t, J = 7 Hz, CH=C), assigned for *E*-isomer δ = −0.06 (9H, s, $SiMe_3$), 1.02—1.82 (13H, m), 1.25 (3H, t, J = 7 Hz, OCH_2C<u>H</u>$_3$), 1.68 (2H, br s, C<u>H</u>$_2$$SiMe_3$), 2.35 (2H, m, C<u>H</u>$_2$CH=C), 3.81—3.95 (4H, m, OCH_2CH_2O), 4.12 (2H, q, J = 7 Hz, OC<u>H</u>$_2$$CH_3$), and 5.62 (1H, t, J = 8 Hz, CH=C); ^{13}C NMR ($CDCl_3$) assigned for *Z*-isomer δ = −1.25 (3C), 14.10, 17.04, 23.67, 26.73, 27.89, 28.87, 29.40, 29.87, 34.48, 44.40, 60.09, 64.45, 64.55, 110.59, 129.74, 138.33, and 168.11, assigned for *E*-isomer δ = −1.86 (3C), 13.92, 23.70, 23.85, 24.36, 27.61, 27.64, 28.82, 31.40, 34.54, 44.42, 59.74, 64.45, 64.55, 110.63, 129.03, 138.88, and 168.19; MS *m/z* (rel intensity) 368 (M^+; 57), 353 (14), 310 (19), 295 (18), 195 (36), 185 (52), 155 (42), and 99 (100). Found: *m/z* 368.2380 (M^+). Calcd for $C_{20}H_{36}O_4Si$: M, 368.2384.

Ethyl 6-(2-Oxocyclohex-1-yl)-2-(trimethylsilylmethyl)hex-2-enoate (1). A solution of **8** (24.3 mg, 0.0659 mmol) in acetone (10 cm^3) was refluxed for 3 h together with a small amount of *p*-toluenesulfonic acid. After addition of $NaHCO_3$ aq, acetone was partly removed by a rotary evaporator. Extraction with Et_2O and drying followed by silica-gel (5 g) column chromatography using hexane–AcOEt (4 : 1) as eluent yielded **1** (20.7 mg, 97%) as an oil; IR (neat) 1710 (C=O), 1640 (C=C), and 1250 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) assigned for *Z*-isomer δ = −0.03 (9H, s, $SiMe_3$), 1.16—2.40 (15H, m), 1.26 (3H, t, J = 7 Hz, OCH_2C<u>H</u>$_3$), 1.78 (2H, br s, C<u>H</u>$_2$$SiMe_3$), 4.14 (2H, q, J = 7 Hz, OC<u>H</u>$_2$$CH_3$), and 6.56 (1H, t, J = 7 Hz, CH=C), assigned for *E*-isomer δ = −0.04 (9H, s, $SiMe_3$), 1.16—2.40 (15H, m), 1.28 (3H, t, J = 7 Hz, OCH_2C<u>H</u>$_3$), 1.70 (2H, br s, C<u>H</u>$_2$$SiMe_3$), 4.15 (2H, q, J = 7 Hz, OC<u>H</u>$_2$$CH_3$), and 5.63 (1H, t, J = 8 Hz, CH=C); ^{13}C NMR ($CDCl_3$) assigned for *Z*-isomer δ = −1.09 (3C), 14.25, 17.29, 24.89, 26.46, 27.99, 29.25, 29.28, 33.87, 41.99, 50.62, 60.35, 130.20, 138.05, 168.33, and 213.13, assigned for *E*-isomer δ = −1.68 (3C), 14.25, 24.03, 24.84, 27.33, 28.02, 29.09, 29.65, 33.92, 41.97, 50.53, 60.00, 129.47, 138.62, 168.40, and 213.30; MS *m/z* (rel intensity) 324 (M^+; 35), 309 (28), 278 (11), 227 (13), 213 (17), 200 (14), 185 (90), 183 (46), and 73 (100). Found: C, 66.39; H, 9.76%. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94%.

Treatment of 1 with Et_2O·BF_3. To a stirred solution of **1** (24.2 mg, 0.0746 mmol) in dry CH_2Cl_2 (10 cm^3) was added Et_2O·BF_3 (0.16 cm^3, 1.30 mmol) under Ar. After being stirred at room temperature for 3 h, an aqueous solution of $NaHCO_3$ was added, the mixture was extracted with Et_2O, and dried. Evaporation of the solvent followed by silica-gel (2 g) column chromatography using hexane–AcOEt (19 : 1) as eluent afforded ethyl 14,15-dinorcadina-1(6),11(13)-dien-12-oate (**9**)# (13.1 mg, 75%) as an oil; IR (neat) 1720 (C=O), 1630 (C=C), and 1255 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.23—1.94 (14H, m), 1.30 (3H, t, J = 7 Hz, OCH_2C<u>H</u>$_3$), 3.15 (1H, br s, 7-H), 4.18 (1H, dq, J = 11, 7 Hz, OC<u>H</u>$H$$CH_3$), 4.22 (1H, dq, J = 11, 7 Hz, OCH<u>H</u>CH_3), 5.38 (1H, dd, J = 1, 2 Hz, 13*E*-H), and 6.27 (1H, d, J = 2 Hz, 13*Z*-H); ^{13}C NMR ($CDCl_3$; DEPT) δ = 14.21 (CH_3), 17.68 (CH_2), 23.18 (CH_2), 23.38 (CH_2), 27.78 (CH_2), 28.81 (CH_2), 30.45 (CH_2), 30.56 (CH_2), 40.42 (CH), 60.55 (CH_2), 125.63 (CH_2), 127.85 (C), 131.63 (C), 142.80 (C), and 167.59 (CO); MS *m/z* (rel intensity) 234 (M^+; 48), 205 (37), 189 (35), 188 (35), 160 (100), 131 (34), 117 (30), and 91 (40). Found: *m/z* 234.1633 (M^+). Calcd for $C_{15}H_{22}O_2$: M, 234.1621.

Treatment of 1 with $TiCl_4$. To a stirred solution of **1** (174.8 mg, 0.539 mmol) in dry CH_2Cl_2 (30 cm^3) was added a solution of $TiCl_4$ (1.65 cm^3, 1.65 mmol; 1 mol dm^{-3} in CH_2Cl_2) under Ar. After being refluxed for 1 h, water was added, and the mixture was extracted with Et_2O and dried. The crude product was chromatographed on silica gel (10 g) using hexane–AcOEt (99 : 1) as

eluent to obtain **9** (37.0 mg, 32% based on consumed material), recovered **1** (14.6 mg), and ethyl 6α-hydroxy-14,15-dinor-7βH-cadin-11(13)en-12-oate (**10**)# (79.2 mg, 64% based on consumed material) as an oil; IR (neat) 3460 (OH), 1715 (C=O), 1625 (C=C), and 1265 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.15—1.49 (10H, m), 1.23 (1H, dt, J = 5, 13 Hz, 5β-H), 1.29 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.53 (1H, tq, J = 4, 13 Hz, 4α-H), 1.65 (1H, br d, J = 13 Hz, 5α-H), 1.73 (1H, m, 9α-H), 1.84 (1H, dq, J = 4, 13 Hz, 8α-H), 1.98 (1H, br, OH), and 4.20 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), see Table 1 for 7-H, 13E-H, and 13Z-H; NOE was observed between δ = 2.63 (7-H, irradiated) and 1.23 (5β-H, observed); ^{13}C NMR ($CDCl_3$; DEPT) δ = 14.15 (CH_3), 21.68 (CH_2), 26.05 (CH_2), 26.13 (CH_2), 27.78 (CH_2), 28.58 (CH_2), 28.94 (CH_2), 37.18 (CH_2), 45.06 (CH), 48.72 (CH), 60.99 (CH_2), 71.38 (C), 126.27 (CH_2), 142.36 (C), and 168.45 (CO); MS m/z (rel intensity) 252 (M^+; 17), 235 (6), 206 (74), 189 (13), 178 (100), 163 (58), 135 (24), 108 (35), and 98 (35). Found: m/z 252.1750 (M^+). Calcd for $C_{15}H_{24}O_3$: M, 252.1726.

Treatment of 1 with TBAF. To a stirred solution of TBAF (53.7 mg, 0.205 mmol) in dry THF (10 cm^3) was added a solution of **1** (20.7 mg, 0.0638 mmol) in THF (10 cm^3) at 0 °C under Ar. After being stirred at 0 °C for 1 h, an aqueous solution of NH_4Cl was added, and the mixture was extracted with Et_2O and dried. Evaporation of the solvent followed by silica-gel (8 g) column chromatography using hexane–AcOEt (97 : 3) gave hydroxy ester **11** (11.1 mg, 69%) and a mixture of lactones **12a** and **12b** (1.6 mg, 12%).

Ethyl 6α-Hydroxy-14,15-dinor-7αH-cadin-11(13)en-12-oate (11):# IR (neat) 3540 (OH), 1720 (C=O), 1625 (C=C), and 1270 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.11—1.68 (15H, m), 1.29 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.09 (1H, ddt, J = 12, 13, 6 Hz, 8β-H), and 4.19 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), see Table 1 for 7-H, 13E-H, and 13Z-H; ^{13}C NMR ($CDCl_3$) δ = 14.18, 21.30, 21.58, 25.89, 26.37, 27.96, 29.11, 36.15, 38.14, 44.49, 61.00, 72.95, 124.65, 143.45, and 168.61; MS m/z (rel intensity) 252 (M^+; 2), 234 (1), 206 (20), 189 (7), 178 (100), 163 (19), 149 (13), 135 (10), 121 (11), 108 (19), and 98 (16). Found: m/z 252.1727 (M^+). Calcd for $C_{15}H_{24}O_3$: M, 252.1726.

A Mixture of 14,15-Dinor-7βH-cadin-11(13)en-6,12-olide (12):# IR (neat) 1765 (C=O), 1670 (C=C), and 1260 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.19—2.00 (15H, m), see Table 1 for 7-H, 13E-H, and 13Z-H; ^{13}C NMR ($CDCl_3$) assigned for **12a**: δ = 21.49, 21.73, 25.88, 25.92, 28.67, 29.50, 38.45, 40.72, 45.06, 84.57, 120.35, 142.55, and 170.64; MS m/z (rel intensity) 206 (M^+; 100), 178 (7), 163 (100), 135 (17), 91 (23), and 79 (31). Found: m/z 206.1305 (M^+). Calcd for $C_{13}H_{18}O_2$: M, 206.1307. The ratio of two isomers was found to be **12a** : **12b** = 13 : 1 from olefinic signals in the ^1H NMR spectrum.

Treatment of 1 with CsF. To a stirred solution of CsF (69.5 mg, 0.458 mmol) in dry acetonitrile (15 cm^3) was added a solution of **1** (22.7 mg, 0.0699 mmol) in acetonitrile (8 cm^3) under Ar. The mixture was heated to reflux for 3 h and then water was added. Acetonitrile was partly removed by a rotary evaporator, and the mixture was extracted with Et_2O and dried. After evaporation of the solvent, the resultant residue was chromatographed on silica gel (2 g) using hexane–AcOEt (97 : 3) as eluent to yield an inseparable mixture of **11** and **13** (5.1 mg, 29%) as an oil. The molar ratio of the products were determined to be **11** : **13** = 1 : 4.5 from the signals of the olefinic protons in the ^1H NMR spectrum. Thus yields of **11** and **13** were calculated to be 5 and 24%, respectively. The following spectral data due to compound **13** was collected from a mixture with **11**.

Ethyl 6-(2-Oxocyclohex-1-yl)-2-methylhex-2-enoate (13): IR (neat) 1715 (C=O), 1655 (C=C), and 1265 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.16—2.41 (15H, m), 1.27 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.81 (3H, d, J = 1.5 Hz, $C{=}CCH_3$), 4.17 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), and 6.72 (1H, tq, J = 7, 1.5 Hz, CH=C); ^{13}C NMR ($CDCl_3$) δ = 12.36, 14.27, 24.91, 26.26, 28.00, 28.81, 29.19, 33.91, 42.03, 50.61, 60.38, 127.92, 141.91, 168.25, and 213.71.

6α-Hydroxy-14,15-dinor-7αH-cadin-11(13)en-12-oic Acid (14).# To a stirred suspension of NaH (65.3 mg, 1.63 mmol; 60% in oil, which was removed by washing with dry hexane) in dry THF (10 cm^3) was added a solution of **11** (11.6 mg, 0.0460 mmol) in THF (5 cm^3) under Ar. The mixture was heated to reflux for 3 h, cooled to room temperature, and dilute HCl aq was added to about pH 1. This was extracted with Et_2O and dried. After evaporation of the solvent, the residue was chromatographed on silica gel (2 g) using hexane–AcOEt (97 : 3) as eluent to afford **14** (10.1 mg, 98%) as an oil; IR (neat) 3470 (OH), 1700 (C=O), 1625 (C=C), and 1260 cm^{-1} (C–O); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.11—1.68 (15H, m), 2.10 (1H, ddt, J = 12, 13, 6 Hz, 8β-H), 3.01 (1H, br d, J = 6 Hz, 7-H), 6.04 (1H, s, 13E-H), and 6.47 (1H, s, 13Z-H); ^{13}C NMR ($CDCl_3$) δ = 21.22, 21.52, 25.88, 26.33, 27.89, 29.06, 36.10, 38.13, 43.92, 73.10, 127.17, 142.45, and 173.14; MS m/z (rel intensity) 224 (M^+; 13), 206 (100), 178 (94), 163 (79), 149 (65), 135 (45), 121 (57), 111 (99), and 98 (74). Found: m/z 224.1432 (M^+). Calcd for $C_{13}H_{20}O_3$: M, 224.1413.

14,15-Dinor-7αH-cadin-11(13)en-6β,12-olide (15).# A solution of **14** (4.1 mg, 0.0183 mmol) in toluene (5 cm^3) was heated to reflux, and to this was added slowly *N*,*N*-dimethylformamide dineopentyl acetal (0.02 cm^3, 0.0717 mmol). After being refluxed for additional 1 h, the solvent was evaporated off. The residue was chromatographed on silica gel (2 g) using hexane–AcOEt (97 : 3) as eluent to give **15** (3.6 mg, 95%) as an oil; IR (neat) 1755 (C=O) and 1670 cm^{-1} (C=C); ^1H NMR ($CDCl_3$; ref = $CHCl_3$) δ = 1.23—1.77 (12H, m), 1.84—2.05 (3H, m), see Table 1 for 7-H, 13E-H, and 13Z-H; ^{13}C NMR ($CDCl_3$; DEPT) δ = 20.21 (CH_2), 20.77 (CH_2), 22.40 (CH_2), 23.89 (CH_2), 27.60 (CH_2), 28.15 (CH_2), 31.33 (CH_2), 40.30 (CH), 46.92 (CH), 85.81 (C), 119.14 (CH_2), 139.13 (C), and 170.60 (CO); MS m/z (rel intensity) 206 (M^+; 74), 163 (100), 149 (19), 135 (14), 121 (19), 108 (30), 98 (25), and 79 (25). Found: m/z 206.1314 (M^+). Calcd for $C_{13}H_{18}O_2$: M, 206.1307.

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