# A Short-step Synthesis of 14,15-Dinoreudesmanolides using Intramolecular Cyclization of an Allylsilane[1]

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14,15-Dinoreudesman-12,6-olides, α-methylene-γ-lactones fused to a *trans*-decalin ring with all three possible stereochemistries, were synthesized from a simple dialdehyde monoacetal *via* intramolecular cyclization of ethyl 5-(2-formylcyclohexyl)-2-(trimethylsilylmethyl)pent-2-enoate. The stereoselectivity of the cyclization reaction is described.

Sesquiterpenes containing an α-methylene-γ-lactone moiety are widely occurring natural products,[2] some of which have remarkable antitumour activity.[3] Among them, eudesmanolides are one of the major classes of natural sesquiterpene lactones, and a number of synthetic studies towards these compounds have been reported.[4] Most of these synthetic efforts include skeletal formation, lactonization, and α-methylenation in independent steps; a number of synthetic methods towards an α-methylene-γ-lactone moiety have also been reported.[5] For syntheses including one-step formation of all these three moieties, Semmelhack's group reported zinc(0)- or nickel(0)-promoted intramolecular cyclization reactions,[6] and this method was applied to the total synthesis of frullanolide[6b] and confertin,[6c] while chromium(II)-catalysed cyclization of ω-formyl-α-bromomethylacrylate was reported by Okuda *et al.*[7]

We planned to undertake these synthetic steps simultaneously, using intramolecular cyclization of an allylsilane with an ω-formyl group[8] for construction of the carbon framework, because an α-trimethylsilylmethyl-α,β-unsaturated ester group can be easily synthesized from the corresponding aldehyde by Wittig reaction[9] or cycloaddition,[10] which means the desired compound, an α-methylene-γ-lactone with the appropriate carbon framework, would be synthesized from an ω-protected α,ω-dialdehyde derivative[11] in only two or three steps (Scheme 1). Moreover, since the stereochemistry of cyclization is dependent on the choice of cyclizing reagent (acid or fluoride),[12] the configuration of the product lactone can be controlled by this method.

The initial study involving intermolecular reaction of α-trimethylsilylmethyl-α,β-unsaturated esters with some aldehydes was made by Hosomi *et al.*, but gave unsatisfactory yields.[13] Recently, we described intramolecular cyclization of ethyl 5-(2-formylcyclohexyl)-2-(trimethylsilylmethyl)pent-2-enoate, and a synthesis of all three possible stereoisomers of 14,15-dinoreudesmanolide [(**1**), (**2**), and (**3**)].[1,†] In the present paper, we report full details of this synthesis.

The starting material, *trans*-2-allylcyclohexanecarboxaldehyde (**5**),[14] was synthesized as follows. 2-Allylcyclohexanone, obtained from cyclohexanone and allyl bromide according to the known procedure,[15] was treated with $Ph_2POCH_2OMe$–$LiNPr^i_2$ (LDA)[16] in tetrahydrofuran (THF) to afford a mixture of enol ethers [(**4**), 89% yield], which was hydrolysed by 5% HCl–THF (1:4) to give a mixture of diastereoisomeric aldehydes (**5**) and (**6**) in 75% yield. The NMR spectrum of this mixture showed the ratio (**5**):(**6**) was *ca.* 1:1. The *trans*-compound (**5**) was obtained by base-catalysed equilibration (5% KOH–MeOH) of this mixture. The structure of product (**5**) was established by $^1$H NMR spectroscopy after addition of $Eu(fod)_3$.‡ Thus, irradiation of the aldehyde proton (d, *J* 3.5 Hz) simplified the adjacent proton into a double triplet (*J* 4, 10 Hz), which indicates that the two substituents of compound (**5**) have a *trans* configuration.

The first key intermediate, monoprotected dialdehyde derivative (**9**) was then synthesized easily from aldehyde (**5**) as shown in Scheme 2. The 'monoprotection' was first achieved by treatment of aldehyde (**5**) with ethylene glycol–pyridinium toluene-*p*-sulphonate (PPTS) to afford the acetal (**7**) (93% yield). The second carbonyl group was formed from the olefinic group by a hydroboration–oxidation sequence. Thus, hydroboration of compound (**7**) with disiamylborane gave the alcohol (**8**) (94% yield) after oxidative work-up, while 9-borabicyclo-[3.3.1]nonane (9-BBN) gave unsatisfactory results. This alcohol was further oxidized by pyridinium dichromate (PDC)[17] to obtain compound (**9**) (95% yield).

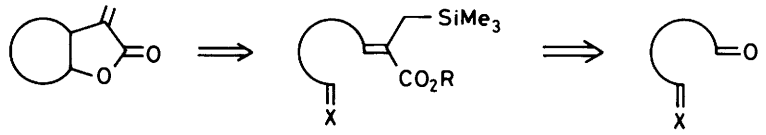
The next step was formation of α-trimethylsilylmethyl-α,β-unsaturated esters. The Wittig reaction of aldehyde (**9**) with $(EtO)_2POCH(CH_2SiMe_3)CO_2Et$–NaH in 1,2-dimethoxyethane (DME)[9] furnished two α,β-unsaturated esters, which were separated by silica gel column chromatography. Both products were shown to have an α-trimethylsilylmethyl-α,β-unsaturated ester moiety by spectral data. The chemical shifts of the olefinic protons in the NMR spectra showed that the major product (30% yield) was the (*Z*)-isomer (**10**),§ and the minor product (11% yield) was the (*E*)-isomer (**11**).

Since the second key intermediate, an ω-formyl-α-trimethylsilylmethyl-α,β-unsaturated ester, had been prepared in a protected form, the cyclization reactions for both the (*Z*)- and the (*E*)-isomer were next examined. When compound (**10**) was treated with a catalytic amount of *p*-TsOH (PTSA) in acetone (reflux; 3 h), the acetal was hydrolysed to afford aldehyde (**12**) (99% yield). However, if compound (**10**) was treated with an excess of PTSA in acetone (reflux; 7 h), the desired lactone (**1**) was obtained in 78% yield. The structure of compound (**1**) was deduced from spectral data, and the stereochemistry was decided as C(6α)-H and C(7α)-H from *J*-values of these protons in the NMR spectrum, and by decoupling experiments. Since the same lactone (**1**) was obtained by the same acid treatment of aldehyde (**12**) (reflux; 5.5 h), the product was assumed to be formed from acetal (**10**) *via* the aldehyde (**12**).

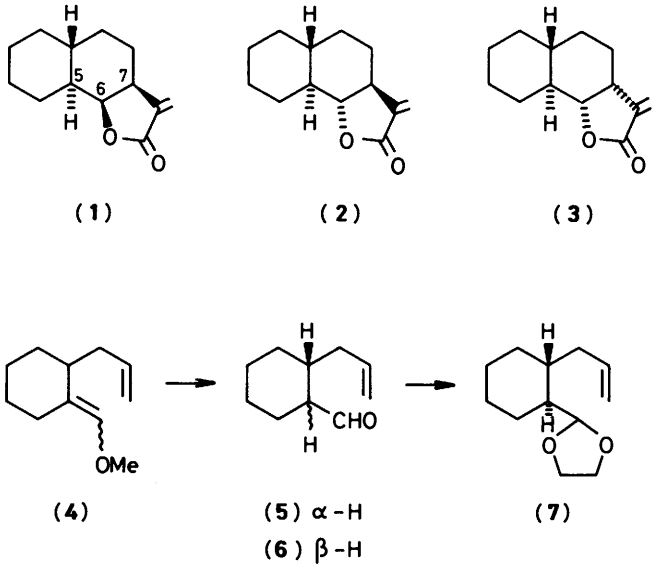
† Recently, Nishitani and Yamakawa reported an intramolecular cyclization independently: K. Nishitani and K. Yamakawa, *Tetrahedron Lett.*, 1987, **28**, 655.

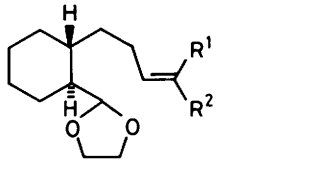
‡ $Eu(fod)_3$ = europium tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-octane-3,5-dionate).

§ The olefinic proton of $(Z)$-$Cl[CH_2]_3CH{=}C(CH_2SiMe_3)CO_2Et$ is reported to resonate at δ 6.45: H. M. R. Hoffmann and R. Henning, *Helv. Chim. Acta*, 1983, **66**, 828.



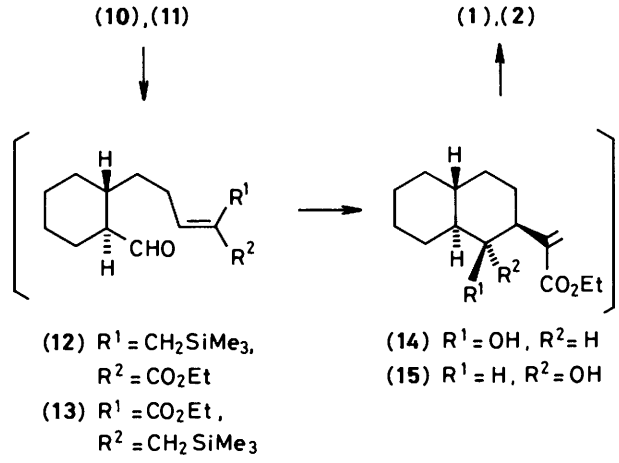

Scheme 1.




Scheme 2.

To determine the relationship between geometry of the α-trimethylsilylmethyl-α,β-unsaturated ester and configuration of the lactone, we next examined the acid-catalysed cyclization of the (*E*)-isomer (**11**). When this isomer was treated under the same reaction conditions (excess of PTSA in acetone; reflux; 6 h), the isomeric lactone (**2**) was obtained in 78% yield. The coupling pattern of C(6)-H and C(7)-H in the NMR spectrum showed that compound (**2**) had a *trans*-lactone structure with C(6β)-H. The intermediates of this cyclization reaction are presumed to be (**13**) and (**15**), which were isolated if the reaction mixture was quenched after a short reaction time (Table 1). The




Scheme 3.

**Table 1.** Acid-catalysed cyclization of compound (**11**).

| | Products (yield; %) | | |
|---|---|---|---|
| Time (h) | (**13**) | (**15**) | (**2**) |
| 1 | 45 | 44 | |
| 4 | | 28 | 51 |
| 6 | | | 78 |

**Table 2.** Fluoride-catalysed cyclization of compound (**12**).

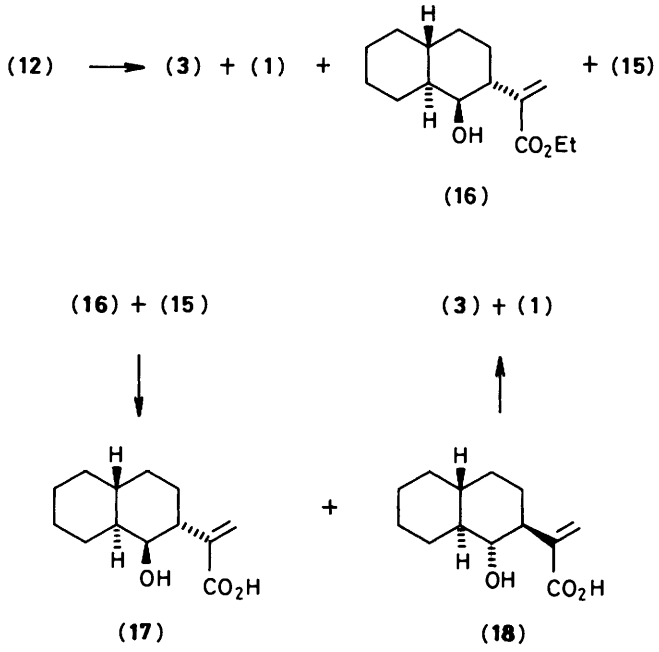
| TBAF | | | Products (yield; %) | | |
|---|---|---|---|---|---|
| (mol equiv.) | *T*/°C | *t*/h | (**3**) + (**1**) | (**16**) + (**15**) | Recovered (**12**) |
| 1.3 | 0 | 0.4 | 22 | 33 | |
| 1.1 | −5 | 1.5 | 65 | 9 | |
| 0.2 | −5 | 4 | 57 | 11 | 25 |

structure of intermediate (**15**) was deduced to have C(6β)-H and C(7α)-H stereochemistry according to the coupling pattern observed for C(7)-H in the NMR spectrum. The results revealed in Table 1 indicate that the cyclization of both isomers (**10**) and (**11**) proceeds as depicted in Scheme 3, where the postulated intermediate (**14**) was not isolated.

On the other hand, it is well known that fluoride ion catalyses the cyclization of allylsilanes with various carbonyl groups.[8] Thus, treatment of aldehyde (**12**) with tetrabutylammonium fluroide (TBAF) gave all four possible stereoisomers, two of them lactones [(**1**) and (**3**)], and the others hydroxy esters [(**15**) and (**16**)]. The lactone (**3**) was obtained as the major product when aldehyde (**12**) was treated with TBAF (1.1 mol equiv.) at −5 °C for 1.5 h (Table 2). Although the two lactones could not be separated by column chromatography, the ratio (**3**):(**1**) was determined as 19:1 by GLC analysis. The lactone (**3**) should have the stereochemistry C(6β)-H and C(7β)-H. This was confirmed from the $^1$H NMR spectrum, and from decoupling experiments between C(6)-H (δ 4.18) and C(7)-H (δ 3.16).

The hydroxy esters (**15**) and (**16**) were also inseparable by column chromatography, and the ratio was found to be 1:3 by GLC. To determine the stereochemistry of compounds (**15**) and (**16**), this mixture was converted into lactones as follows. First, in order to lactonize directly, the mixture was treated with NaH in dry THF; however, hydrolysed products (**17**) and (**18**) were obtained instead of lactones (Scheme 4). These hydroxy acids were then treated with *N,N*-dimethylformamide dineopentyl acetal[18] to yield lactones with inversion at C-6. The obtained lactones were found to be identical with compound (**3**), the major isomer, and compound (**1**), the minor isomer, by $^1$H NMR spectroscopy. Thus, the structures of the hydroxy esters, obtained by fluoride-catalysed cyclization of aldehyde (**12**), were established to be (**16**) as the major isomer and (**15**) as the minor isomer.

The *trans*-decalin ring system of the obtained lactones (**1**), (**2**), and (**3**) were established by chemical shifts and coupling patterns of 5-H in the NMR spectra (see Experimental section), which were determined by addition of Eu(fod)$_3$ and/or irradiation of 6-H. Thus, it was found that epimerization at C-5 had not occurred in the acid or fluoride treatments.

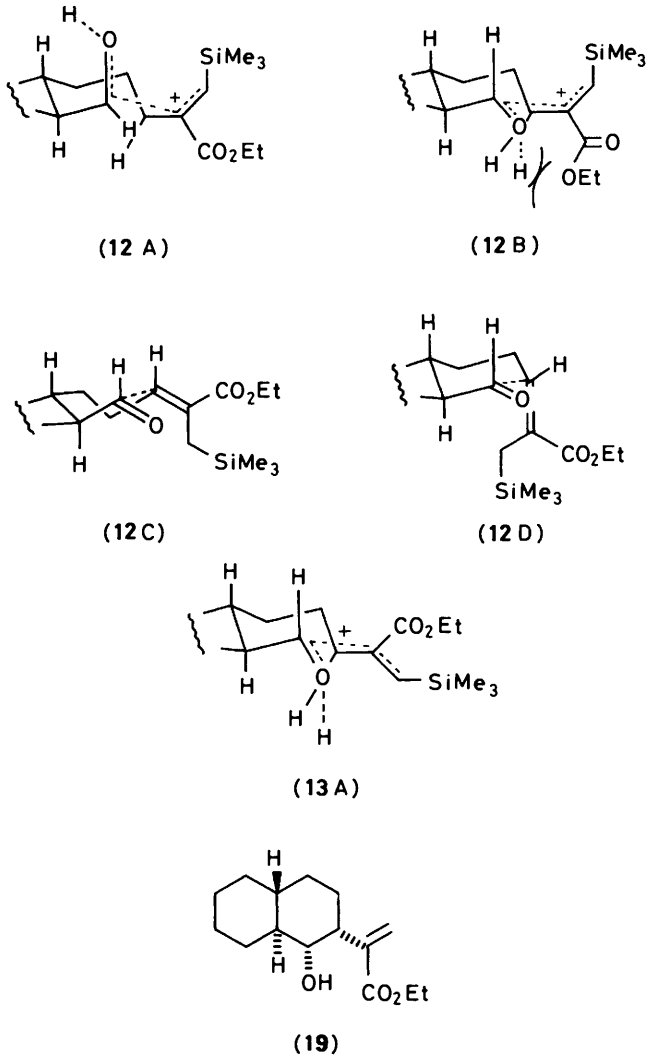



**Scheme 4.**

Attempts to rationalize the diastereoselectivity of acid-catalysed cyclization reactions have made use of the conformation of protonated transition states.[12,19] Our results indicate that (**12A**) is the predominant conformation for cyclization of (**10**) *via* (**12**). Thus conformation (**12B**), which has two equatorial substituents at C-6 and C-7, is not favoured by an interaction between two oxygen functionalities. In contrast, the diastereoselective formation of lactone (**2**) from (**11**) *via* (**13**) is explained by conformation (**13A**), where two substituents at C-6 and C-7 are both equatorial.

According to Majetich *et al.*, the diastereoselectivity produced by fluoride-catalysed cyclization is considered to be under kinetic control.[12] Although fluoride-catalysed cyclization of aldehyde (**12**) gave all four possible stereoisomers, the major product was lactone (**3**), which is proposed to be formed *via* hydroxy ester (**19**). This result shows that (**12C**) or (**12D**) is a favourable conformation, and that the product was formed through one of these conformations.

In conclusion, the stereochemistry of the cyclization reaction was shown to depend on the geometry of the α-trimethylsilyl-methyl-α,β-unsaturated ester and on the cyclizing reagent. Thus, α-methylene-γ-lactone moieties with various stereochemistries can be synthesized by this method, which leads to a new short-step synthetic strategy towards eudesmanolides of various stereochemistries.




## Experimental

M.p.s were obtained on a Mel-temp capillary melting point apparatus (Laboratory Devices) and are uncorrected. UV spectra were measured on a Hitachi 220A ultraviolet spectrometer. IR spectra were taken on a Hitachi 215 or Hitachi 270-30 spectrometer. NMR spectra were determined on a Hitachi Perkin-Elmer R-20A (60 MHz), R-900 (90 MHz), R-250 (250 MHz), JEOL G-270 (270 MHz), GSX-400 (400 MHz), or Varian EM-390 (90 MHz) spectrometer. Chemical shifts are reported downfield from tetramethysilane, unless noted otherwise, on the δ scale (ppm). Both low-resolution and high-resolution mass spectra were obtained on a JEOL JMS-D300 mass spectrometer at an ionization potential of 70 eV. Analytical TLC was performed on precoated TLC plates (Kieselgel 60 F254, layer thickness 0.2 mm). Wakogel C-200 or Florisil (100–200 mesh) were used for column chromatography. Alumina column chromatography was made with ICN Alumina N, Act I. GLC was carried out on a Hitachi 023 equipped with a flame-ionization detector and a 1 m length column of 2% OV-1. For reactions required dry solvents, THF

and DME were distilled from $LiAlH_4$; diglyme, $CH_2Cl_2$, hexane, and toluene were distilled from $CaH_2$.

3-(2-*Methoxymethylenecyclohexyl*)*prop*-1-*ene* (**4**).—To a stirred, ice-cooled solution of LDA, prepared from BuLi (25 ml, 33.5 mmol; 1.34M in hexane) and di-isopropylamine (7 ml) in dry THF (36 ml), was added a solution of $Ph_2POCH_2OMe$ (6.85 g, 27.8 mmol) in THF (150 ml) under $N_2$. After being stirred for 20 min at 0 °C the mixture was cooled to −60 °C and was treated dropwise with a solution of 2-allylcyclohexanone (3.2 g, 23.2 mmol) in THF (30 ml), and the reaction mixture was allowed to warm to room temperature slowly. After being stirred at room temperature for 24 h, the mixture was treated with aqueous $NH_4Cl$ and the product was extracted with $Et_2O$. Evaporation of solvent, followed by silica gel (50 g) column chromatography with hexane–$Et_2O$ (20:1) as eluant, gave *compound* (**4**) as an oil (3.43 g, 89%) (Found: $M^+$, 166.1329. $C_{11}H_{18}O$ requires $M$, 166.1358); $\nu_{max}$(neat) 1 680, 1 640, 1 450, 1 135, 995, 910, and 840 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$) 3.45 (3 × $\frac{2}{5}$ H, s, OMe), 3.49 (3 × $\frac{3}{5}$ H, s, OMe), 4.70–5.11 (2 H, m, CH=C$H_2$), 5.63 (1 H, br s, =C*H*OMe), and 5.34–6.20 (1 H, m, C*H*=$CH_2$); *m*/*z* 166 (7%, $M^+$), 149 (3), and 125 (100).

trans-2-(*Prop*-2-*enyl*)*cyclohexanecarboxaldehyde* (**5**).—A solution of compound (**4**) (4.63 g, 27.8 mmol) in 5% HCl–THF (450 ml; 1:4 ratio) was refluxed for 25 min. To this was added aqueous $NaHCO_3$ (with cooling), and the product was extracted with $Et_2O$. Evaporation of solvent afforded a mixture of aldehydes (**5**) and (**6**) (4.11 g, 97%), which showed one spot on TLC; $\delta_H$(60 MHz; $CCl_4$) 9.48 [($\frac{1}{2}$ H, d, *J* 3 Hz, CHO, due to (**5**)], 9.68 [($\frac{1}{2}$ H, s, CHO, due to (**6**)].

This mixture of aldehydes (**5**) and (**6**) (3.11 g) was dissolved in 5% KOH aq.–MeOH (160 ml; 1:1 ratio), and the solution was heated to reflux for 3 h. After cooling, the product was extracted with $Et_2O$. Evaporation of solvent afforded *compound* (**5**) (3.08 g) as an oil (Found: $M^+$, 152.1195. $C_{10}H_{16}O$ requires $M$, 152.1202); $\nu_{max}$(neat) 1 730, 1 640, 1 450, 1 000, and 915 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$) 4.70–5.17 (2 H, m, CH=C$H_2$), 5.38–6.18 (1 H, m, C*H*=$CH_2$), and 9.48 (1 H, d, *J* 3 Hz, CHO); *m*/*z* 152 (11%, $M^+$), 134 (24), and 57 (100).

3-[trans-2-(*Ethylenedioxymethyl*)*cyclohexyl*]*prop*-1-*ene* (**7**).—To a stirred solution of the aldehyde (**5**) (2.73 g, 17.9 mmol) in benzene (270 ml) and ethylene glycol (60 ml) was added a catalytic amount of PPTS. A Dean–Stark water separator was attached, and the mixture was refluxed for 5 h. Saturated aqueous $NaHCO_3$ was added and the product was extracted with $Et_2O$. After evaporation of solvent, the residue was chromatographed on neutral alumina (10 g; containing 10% of water) with hexane as eluant to yield *compound* (**7**) (3.26 g, 93%) as an oil (Found: C, 73.4; H, 10.3. $C_{12}H_{20}O_2$ requires C, 73.46; H, 10.27%); $\nu_{max}$(neat) 1 640, 1 445, 1 120, 1 035, and 910 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$) 3.81 (4 H, m, acetal), 4.73–5.14 (3 H, m, CH–C$H_2$ and acetal), and 5.35–6.13 (1 H, m, C*H*=$CH_2$); *m*/*z* 195 (0.8%, $M$ − H), 153 (18), and 73 (100).

3-[trans-2-(*Ethylenedioxymethyl*)*cyclohexyl*]*propan*-1-*ol* (**8**).—To stirred 2-methylbut-2-ene (6.6 ml. 62.3 mmol) cooled in an ice-bath was added dropwise a solution of sodium borohydride (630 mg, 16.7 mmol) in dry diglyme (15 ml) under $N_2$. Boron trifluoride–diethyl ether (1.5 ml, 12.2 mmol) was added dropwise to the vigorously stirred mixture at 0 °C, and the mixture was stirred for a further 6 h, and then treated dropwise with a solution of the propene (**7**) (242 mg, 1.23 mmol) in diglyme (5 ml), and the mixture was allowed to warm to room temperature. After the mixture had been stirred for 24 h, water (8 ml), 3M aqueous NaOH (8 ml), and 30% aqueous $H_2O_2$ (12 ml) were carefully added successively dropwise to the mixture cooled in an ice-bath. The mixture was stirred at 40 °C for 1.5 h, saturated aqueous NaCl was added, and the product was extracted with $Et_2O$. After evaporation of solvent, crude product (249 mg, 94%) was obtained. This showed one spot on TLC and was used in the next step without further purification. *Compound* (**8**) was an oil (Found: $M^+$, 214.1586. $C_{12}H_{22}O_3$ requires $M$, 214.1570); $\nu_{max}$(neat) 3 350, 1 445, 1 120, 1 050, and 945 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$) 3.40 (1 H, br, OH), 3.28–3.65 (2 H, m, C$H_2$OH), 3.81 (4 H, m, acetal), and 4.88 (1 H, br s, acetal); *m*/*z* 213 (5%, $M$ − H), 184 (2), 153 (11), and 73 (100).

3-[trans-2-(*Ethylenedioxymethyl*)*cyclohexyl*]*propanal* (**9**).—To a stirred solution of compound (**8**) (249 mg, 1.16 mmol) in dry $CH_2Cl_2$ (12 ml) was added PDC (680 mg). After the mixture had been stirred for 24 h at room temperature, $Et_2O$ (*ca.* 15 ml) was added. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to a minimum amount of solvent. This was chromatographed on neutral alumina (5 g; containing 10% of water) with hexane–$Et_2O$ (1:1) as eluant to yield *compound* (**9**) (235 mg, 95%) as an oil (Found: $M$ − H, 211.1353. $C_{12}H_{20}O_3$ requires $M$ − H, 211.1335); $\nu_{max}$(neat) 2 710, 1 710, 1 445, 1 120, 1 030, and 945 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$) 3.82 (4 H, m, acetal), 4.82 (1 H, br s, acetal), and 9.71 (1 H, t, *J* 1.5 Hz, CHO); *m*/*z* 211 (0.8%, $M$ − H), 153 (4), and 73 (100).

(Z)- *and* (E)-*Ethyl* 5-[2-(*Ethylenedioxymethyl*)*cyclohexyl*]-2-(*trimethylsilylmethyl*)*pent*-2-*enoate* (**10**) *and* (**11**).—Into a 30 ml three-necked flask was placed NaH (118 mg, 2.46 mmol; 50% in mineral oil) under $N_2$, and the mineral oil was removed by washing with dry hexane (3 ×). Dry DME (5 ml) was added and the flask was cooled to 0 °C. To this stirred mixture was added a solution of ethyl diethylphosphonacetate (440 μl, 2.22 mmol) in DME (2 ml). After the mixture had been stirred at room temperature for 1.5 h, a solution of (iodomethyl)trimethylsilane (400 μl, 2.70 mmol) in DME (2.5 ml) was added all at once. The mixture was heated to 70 °C for 3 h, cooled to 0 °C, and another batch of NaH (96 mg, 2.00 mmol) was added. After the mixture had been stirred at room temperature for 1.5 h, a solution of the aldehyde (**9**) (301 mg, 1.42 mmol) in DME (2.5 ml) was added dropwise at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$, and the products were extracted with $Et_2O$. The crude product was purified by silica gel (6 g) column chromatography with hexane–AcOEt (20:1) as eluant. Chromatography was continued until the *title esters* (**10**) (155 mg, 30%) and (**11**) (55 mg, 11%) were obtained as oils.

For (**10**) (Found: C, 65.3; H, 9.8. $C_{20}H_{36}O_4Si$ requires C, 65.17; H, 9.84%); $\lambda_{max}$(EtOH) 232 nm (ε 7 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(neat) 1 715, 1 640, 1 450, 1 255, 1 045, and 855 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$; $CHCl_3$ as internal standard) −0.04 (9 H, s, $SiMe_3$), 1.26 (3 H, t, *J* 7 Hz, $OCH_2$*Me*), 1.73 (2 H, br s, C$H_2SiMe_3$), 3.77 (4 H, m, acetal), 4.08 (2 H, q, *J* 7 Hz, O$CH_2$Me), 4.82 (1 H, br s, acetal), and 6.44 (1 H, t, *J* 7 Hz, CH=C<); *m*/*z* 368 (3%, $M^+$), 339 (8), 323 (2), 295 (3), 153 (38), and 73 (100).

For (**11**) (Found: C, 65.3; H, 9.8%); $\lambda_{max}$(EtOH) 233 nm (7 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(neat) 1 715, 1 630, 1 245, 1 155, and 850 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$; $CHCl_3$ as internal standard −0.09 (9 H, s, $SiMe_3$), 1.25 (3 H, t, *J* 7 Hz, $OCH_2$*Me*), 1.64 (2 H, br s, C$H_2SiMe_3$), 3.25 (4 H, m, acetal), 4.07 (2 H, q, *J* 7 Hz, O$CH_2$Me), 4.83 (1 H, br s, acetal), and 5.55 (1 H, t, *J* 7 Hz, CH=C<); *m*/*z* 368 (6%, $M^+$), 339 (27), 323 (8), 295 (10), 153 (58), and 73 (100).

(Z)-*Ethyl* 5-(2-*Formylcyclohexyl*)-2-(*trimethylsilylmethyl*)-*pent*-2-*enoate* (**12**).—To a stirred solution of compound (**10**) (78 mg, 0.21 mmol) in acetone (15 ml) was added a catalytic amount of PTSA. The mixture was refluxed for 3 h, saturated aqueous $NaHCO_3$ was added, and the product was extracted with $Et_2O$.

After evaporation of solvent, the resulting crude product was chromatographed on silica gel (2 g) with hexane–AcOEt (15:1) as eluant to give the *oxo ester* (**12**) (68 mg, 99%) as an oil (Found: $M^+$, 324.2138. $C_{18}H_{32}O_3Si$ requires $M$, 324.2122); $\lambda_{max}$(EtOH) 229 nm (23 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(neat) 2 710, 1 725, 1 710, 1 640, 1 450, 1 250, and 855 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$; $CHCl_3$ as internal standard) −0.09 (9 H, s, $SiMe_3$), 1.21 (3 H, t, $J$ 7 Hz, $OCH_2Me$), 1.68 (2 H, br s, $CH_2SiMe_3$), 4.04 (2 H, q, $J$ 7 Hz, $OCH_2Me$), 6.38 (1 H, t, $J$ 7 Hz, CH=C<), and 9.44 (1 H, d, $J$ 3 Hz, CHO); $m/z$ 324 (3%, $M^+$), 309 (12), 296 (22), 185 (49), and 73 (100).

*Acid-catalysed Cyclization of Compound* (**10**).—To a stirred solution of compound (**10**) (76 mg, 0.21 mmol) in acetone (20 ml) was added PTSA (97 mg, 0.51 mmol; monohydrate) all at once, and the mixture was refluxed for 7 h. The same work-up described for compound (**12**), followed by silica gel (4 g) column chromatography with hexane–AcOEt (10:1) as eluant, gave *lactone* (**1**) (33 mg, 78%) as crystals; m.p. 46.5–47.5 °C (from hexane) (Found: C, 75.6; H, 8.9. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.79%); $\lambda_{max}$(EtOH) 210 nm (8 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(KBr) 1 760, 1 665, 1 455, 1 265, 1 150, and 950 $cm^{-1}$; $\delta_H$(400 MHz; $CDCl_3$) 1.25 [1 H, br t, $J$ 11 Hz, 5-H, determined after addition of Eu(fod)$_3$], 2.88 (1 H, ddd, $J$ 5, 7, 11 Hz, 7-H), 4.27 (1 H, dd, $J$ 2.5, 4.5 Hz, 6-H), 5.50 (1 H, d, $J$ 1 Hz, >C=C$H$H), and 6.06 (1 H, d, $J$ 1.5 Hz, >C=CH$H$); $m/z$ 206 (28%, $M^+$), 178 (100), and 134 (56).

*Acid-catalysed Cyclization of Compound* (**11**).—By the same procedure described for the cyclization of compound (**10**), the ester (**11**) (32 mg, 0.087 mmol) was refluxed with PTSA (48 mg, 0.25 mmol) in acetone (12 ml) for 6 h. Purification of the product by silica gel (3 g) column chromatography with hexane–AcOEt (20:1) afforded *lactone* (**2**) (14 mg, 78%) as crystals; m.p. 75–77 °C (Found: $M^+$, 206.1295. $C_{13}H_{18}O_2$ requires $M$, 206.1307); $\lambda_{max}$(EtOH) 209 nm (9 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(KBr) 1 765, 1 450, 1 260, 1 130, 990, and 965 $cm^{-1}$; $\delta_H$(400 MHz; $CDCl_3$) 1.43 (1 H, dq, $J$ 3.5, 10 Hz, 5-H), 2.49 (1 H, tq, $J$ 3, 11 Hz, 7-H), 3.45 (1 H, t, $J$ 11 Hz, 6-H), 5.37 (1 H, d, $J$ 3.5 Hz, >C=C$H$H), and 6.06 (1 H, d, $J$ 3 Hz, >C=CH$H$); $m/z$ 206 (8%, $M^+$), 178 (100), and 134 (92).

For isolation of intermediates, ester (**11**) (20 mg, 0.054 mmol) was refluxed with PTSA (29 mg, 0.15 mmol) in acetone (5 ml) for 1 h. Separation of the products by silica gel (5 g) column chromatography with hexane–AcOEt (20:1 and 10:1) as eluants yielded *compound* (**13**) (8 mg, 45%) and *compound* (**15**) (6 mg, 44%) as oils.

For (**13**) (Found: $M^+$, 324.2117. $C_{18}H_{32}O_3Si$ requires $M$, 324.2122); $\nu_{max}$(neat) 1 730, 1 720, 1 630, 1 250, and 855 $cm^{-1}$; $\delta_H$(60 MHz; $CCl_4$; benzene as internal standard) 0.04 (9 H, s, $SiMe_3$), 1.37 (3 H, t, $J$ 7 Hz, $OCH_2Me$), 1.75 (2 H, br s, $CH_2SiMe_3$), 4.18 (2 H, q, $J$ 7 Hz, $OCH_2Me$), 5.62 (1 H, t, $J$ 7 Hz, CH=C<), and 9.54 (1 H, d, $J$ 3 Hz, CHO); $m/z$ 324 (8%, $M^+$), 309 (20), 296 (27), 185 (76), and 73 (100).

For (**15**) (Found: $M^+$, 252.1729. $C_{15}H_{24}O_3$ requires $M$, 252.1726); $\nu_{max}$(neat)3 500, 1 720, 1 630, 1450, 1 260, and 1 160 $cm^{-1}$; $\delta_H$(270 MHz; $CDCl_3$) 1.31 (3 H, t, $J$ 7 Hz, $OCH_2Me$), 2.55 (1 H, ddd, $J$ 3.5, 9.5, 12.5 Hz, 7-H), 3.19 (1 H, dt, $J$ 5.5, 9.5 Hz, 6-H), 4.22 (1 H, q, $J$ 7 Hz, $OCH_2Me$), 5.63 (1 H, s, >C=C$H$H), and 6.25 (1 H, d, $J$ 1 Hz, >C=CH$H$); $m/z$ 252 (10%, $M^+$), 234 (14), 224 (14), and 206 (100).

*Fluoride-catalysed Cyclization of Compound* (**12**).—To a stirred solution of compound (**12**) (29 mg, 0.089 mmol) in dry THF (7 ml) under Ar at −5 °C was added dropwise a solution of TBAF (26 mg, 0.099 mmol) in THF (7 ml). The reaction mixture was stirred at −5 °C for 1.5 h, then saturated aqueous $NH_4Cl$ was added. The products were extracted with $Et_2O$, and were separated by silica gel (5 g) column chromatography with hexane–AcOEt (50:1) as eluant to yield lactones (**3**) and (**1**) (total 12 mg, 65%), and hydroxy esters (**15**) and (**16**) (total 2 mg, 9%). The mixture of lactones (**3**) and (**1**) was an oil; GLC (**3**):(**1**) 19:1 [Found: $M^+$, 206.1308, due to (**3**), detected by total ion monitor. Calc. for $C_{13}H_{18}O_2$: $M$, 206.1307]; $\lambda_{max}$(EtOH) 209 nm (13 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(neat) 1 760, 1 660, 1 445, 1 260, 1 100, and 985 $cm^{-1}$; $\delta_H$(400 MHz; $CDCl_3$) 0.86 (1 H, dq, $J$ 3, 10 Hz, 5-H), 3.16 (1 H, m, $w_{\frac{1}{2}}$ 16 Hz, 7-H), 4.18 (1 H, dd, $J$ 8, 9 Hz, 6-H), 5.47 (1 H, d, $J$ 3 Hz, >C=C$H$H), and 6.27 (1 H, d, $J$ 3 Hz, >C=CH$H$); $m/z$ 206 (12%, $M^+$), 178 (100), and 134 (64).

The mixture of (**15**) and (**16**) was an oil (Found: $M^+$, 252.1709. Calc. for $C_{15}H_{24}O_3$: $M$, 252.1726); $\nu_{max}$(neat) 3 520, 1 715, 1 625, 1 445, 1 270, 1 170, 1 095, and 1 035 $cm^{-1}$; $\delta_H$(60 MHz; $CDCl_3$) 1.32 (3 H, t, $J$ 7 Hz, $OCH_2Me$), 3.76 (1 H, m, $w_{\frac{1}{2}}$ 4 Hz, 6-H), 4.22 (2 H, q, $J$ 7 Hz, $OCH_2Me$), 5.67 (1 H, br s, >C=C$H$H), and 6.25 (1 H, br s, >C=CH$H$); $m/z$ 252 (4%, $M^+$), 234 (15), 224 (10), and 206 (100).

*Hydrolysis of Hydroxy Esters* (**15**) *and* (**16**).—NaH (23 mg, 0.48 mmol; 50% suspension in mineral oil) was placed in a three-necked flask under $N_2$, and was washed with dry hexane (3 ×). To this was added dry THF (10 ml) and a solution of the mixture of compounds (**15**) and (**16**) (20 mg, 0.079 mmol) in dry THF (4 ml). The mixture was stirred at room temperature for 24 h, water (*ca.* 5 ml) was added, and the pH was adjusted to *ca.* 1 by dil. HCl. The product was extracted with $CH_2Cl_2$ and chromatographed on silica gel (1 g) with hexane–AcOEt (5:1 and 1:1) as eluants to yield a mixture of hydroxy acids (**17**) and (**18**) (17 mg, 96%) as an oil (Found: $M^+$, 224.1395. Calc. for $C_{13}H_{20}O_3$: requires $M$, 224.1413); $\lambda_{max}$(EtOH) 206 nm (8 000 $dm^3$ $mol^{-1}$ $cm^{-1}$); $\nu_{max}$(neat) 3 500–2 500, 1 700, 1 620, 1 240, and 1 040 $cm^{-1}$; $\delta_H$(60 MHz; $CDCl_3$) 3.85 (1 H, m, 6-H), 5.83 (1 H, br s, >C=C$H$H), and 6.43 (1 H, br s, >C=CH$H$); $m/z$ 224 (1%, $M^+$), 206 (32, $M - H_2O$), 178 (45), 111 (78), and 67 (100).

*Lactonization of Hydroxy Esters* (**17**) *and* (**18**).—To a refluxing solution of a mixture of compounds (**17**) and (**18**) (11 mg, 0.049 mmol) in dry toluene (10 ml) was added dropwise a solution of *N,N*-dimethylformamide dineopentyl acetal (33 mg, 0.14 mmol) in toluene (10 ml). After refluxing for 30 min, most of the solvent was distilled off under reduced pressure. The resulting oil was chromatographed on silica gel (2 g) with hexane–AcOEt (40:1) as eluant to give a mixture of lactones (**3**) and (**1**) (9 mg, 89%); GLC (**3**):(**1**) 3:1.

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