On the stereoselection of iodolactonizations of 3-silyloxyalk-5-enoic acids

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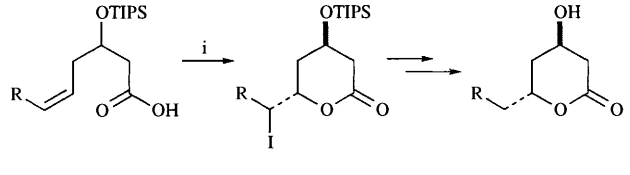
Iodolactonizations of 3-triisopropylsilyloxyalk-5-enoic acids (10b and 12) proceed by way of common transition-state geometry 23, in which the silyloxy group is positioned axially, presumably due to hydrogen bonding with the carboxylic acid group.

We have recently reported that iodolactonizations of the (*Z*)-3-silyloxyalk-5-enoates **1** result in predominant formation of the *trans*-disubstituted valerolactones **2** (Scheme 1), which are

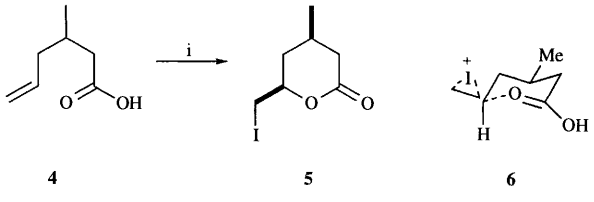


1 **2** **3**

TIPS = triisopropylsilyl

Scheme 1 *Reagents:* i, I_2, $NaHCO_3$, aq. MeCN

useful as precursors of hydroxyvalerolactones **3**, related to the key structural feature of the Mevinic acids.[1] As our interest at this stage was primarily in the synthesis of the latter structures, *via* deiodination of the initial major iodolactones **2**, we made no attempts to determine the stereochemistry at the iodine centre, beyond noting that all spectral data, as expected, indicated that a single diastereoisomer of these intermediates had been formed. Of more significance was the realization that predominant formation of the *trans* stereochemistry about the lactone ring was an unexpected outcome judging from many related results from similar cyclizations[2] and especially in view of the specific example of the iodolactonization of the methyl-substituted alkenoic acid **4**, which results in formation of largely the *cis*-isomer **5** (Scheme 2). A chair-like transition state model

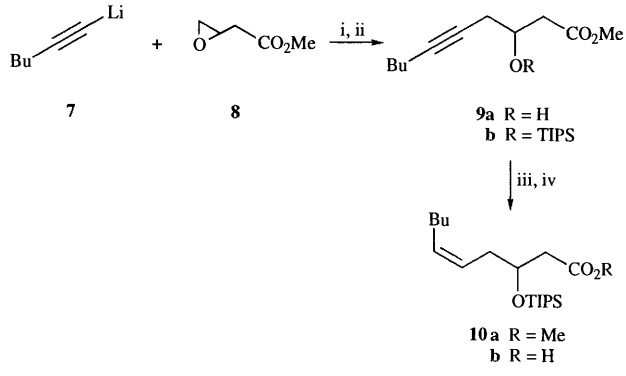


4 **5** **6**

Scheme 2 *Reagents:* i, I_2, $NaHCO_3$, aq. MeCN

6 readily explains this stereochemical outcome, in which the substituent methyl group is positioned pseudoequatorially and thus provides the observed control.[3] We speculated that the (*Z*)-stereochemistry of substrates **1** might be playing a key role leading to this unexpected result. In order to fully define the features of this cyclization, we realized that it would be necessary to examine similar cyclizations of the corresponding (*E*)-isomers and also to determine the stereochemistry at the iodine centres.[4] Herein, we report in full the outcome of these studies which have led to a plausible explanation of the observed stereochemistries in the iodolactones.

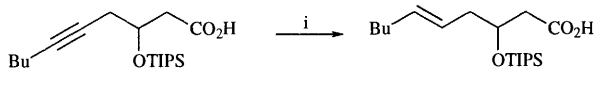
In our initial work,[1] we had prepared the (*Z*)-alkenoic acids **1** using a Wittig olefination reaction as a key step. A briefer approach was used in the present work which consisted of condensation of hex-1-ynyllithium **7** with the epoxy ester **8** under Yamaguchi–Hirao conditions.[5] The epoxy ester **8** was obtained by epoxidation of the methylbut-3-enoate using pertrifluoroacetic acid, generated from hydrogen peroxide–urea complex and trifluoroacetic acid.[6,7] The resulting hydroxy-ynoate **9a** was then sequentially protected, subjected to semi-hydrogenation and finally saponified to provide the required (*Z*)-alkenoic acid **10b** (Scheme 3). The intermediate



7 **8** **9a** R = H **b** R = TIPS **10a** R = Me **b** R = H

Scheme 3 *Reagents:* i, BF_3·OEt_2, THF, −78 °C, 4 h; ii, TIPSCl, imidazole, DMF, 20 °C, 72 h; iii, 5% $PdSO_4$, quinoline, H_2, EtOAc; iv, KOH, MeOH, 20 °C

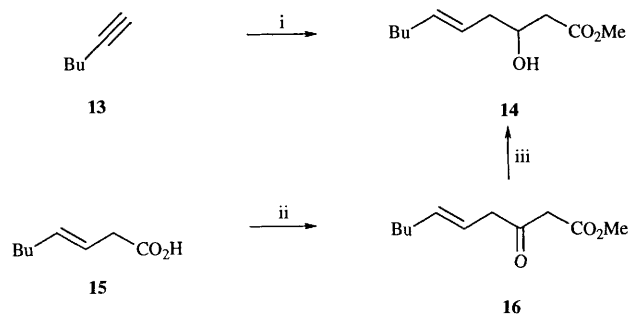
protected ynoate **9b** also served as a precursor to the corresponding (*E*)-alkenoic acid **12**, following saponification and dissolving metal reduction. (Scheme 4). Two alternative



11 **12**

Scheme 4 *Reagents:* i, Li, Bu^{t}OH, $(NH_4)_2SO_4$, THF, −40 °C

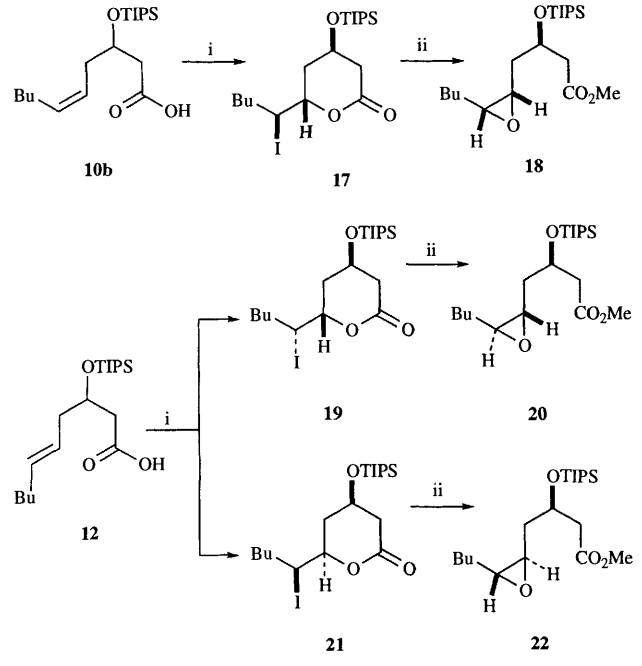
approaches to this substrate were also examined, the first of which provided a more direct preparation. (Scheme 5). Thus, hydroalumination[8] of hex-1-yne **13** followed by ate complex formation and BF_3-catalysed condensation[5] with the epoxy ester **8** provided the (*E*)-hydroxyalkenoate **14** directly. Alternatively, a Knoevenagel condensation[9] between hexanal and malonic acid gave (*E*)-oct-3-enoic acid **15**; subsequent acyl imidazole formation and condensation with the magnesium salt of monomethyl malonate[10] gave the keto-ester **16** which was then reduced using sodium borohydride in methanol to give the



Scheme 5 *Reagents:* i, a) Bu^i_2AlH hexane, 50 °C, 2 h; b) MeLi, Et_2O, −0 °C, 0.5 h; c) **8**, BF_3·OEt_2, −78 °C, 0.75 h; ii, a) Im_2CO, THF, 20 °C, 12 h; b) $MeO_2CCH_2CO_2H$–Pr^iMgBr, THF, 0–20 °C, 18 h; iii, $NaBH_4$, MeOH, 0 °C, 0.5 h

hydroxyalkenoate **14**. Subsequent protection and saponification of the latter then provided further samples of the required alkenoic acid **12**.

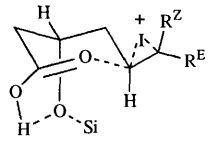
As expected,[1] iodolactonization of the (*Z*)-alkenoic acid **10b** using Bartlett's conditions,[3] gave predominantly (*ca.* 10:1) a single *trans*-disubstituted iodolactone **17** (Scheme 6); the minor



Scheme 6 *Reagents:* i, I_2, $NaHCO_3$, MeCN, H_2O, 0 °C, 4 h; ii, Na_2CO_3, MeOH, 20 °C, 16 h

product, whilst being visible in NMR spectrum of the crude reaction mixture, was not isolated. The product **17** was clearly a single diastereoisomer; the *trans* stereochemistry about the lactone ring was established by the presence, in the ^1H NMR spectrum, of a narrow resonance for the 3-H ($\omega_{\frac{1}{2}}$ = *ca.* 9 Hz), indicating that the 3-silyloxy group was positioned axially.[1] In addition, the 4-H_{ax} resonance showed only one large coupling to an axial proton (5-H) and the couplings between the 2- and 3-protons were small. Despite some flattening of the ring, due to the presence of the sp^2 carbon of the carbonyl group, when the 3-H is axial, larger couplings are observed (see below).[1] We were able to determine the stereochemistry at the iodine centre by subsequent treatment with methanolic sodium carbonate[11] which led to a good yield of the corresponding epoxy ester **18**. That this possessed a *cis*-stereochemistry about the epoxide ring was deduced from the coupling constant, $J_{5,6}$ = 4.1 Hz, indicative of such an arrangement[12] and by a consistency with the following results.

When the corresponding (*E*)-alkenoic acid **12** was similarly treated with iodine in aqueous acetonitrile, we obtained a



23

similar ratio of isomeric iodolactones (*ca.* 9:1) and were able to secure pure samples of each. The major isomer was also *trans* about the lactone ring, as the 3-H was clearly positioned equatorially (J = 3.5 Hz), and therefore differed only from the iodolactone **17** derived from the corresponding (*Z*)-alkenoic acid, in the stereochemistry at the iodine centre, and thus had structure **19**, indicative of a common transition state geometry for the formation of both major iodolactones. This was confirmed when this lactone was converted into the corresponding epoxy ester **20**, which showed $J_{5,6}$ = 2.2 Hz, indicative of a *trans* stereochemistry. The minor lactone isolated from cyclization of the (*E*)-alkenoic acid **12** provided some useful correlation data. This was clearly a *cis*-disubstituted valerolactone, in which both the 3- and 5-protons are positioned axially. The overall structure **21** was assigned by conversion into the corresponding epoxy ester **22**, which also had a *trans*-stereochemistry ($J_{5,6}$ = 2.2 Hz).

The conclusion is therefore that a likely transition state geometry which accounts for the observed major products [**17** and **19**] is as depicted in formula **23** wherein the silyloxy group is unexpectedly positioned axially, presumably due to hydrogen bonding with the carboxylic acid function. Thus, the products will only differ at the iodine stereocentre, the stereochemistry of which is directly related to that of the precursor alkene geometry. A similar proposal has been put forward by Yoshida and his colleagues to account for the stereoselection in various iodocyclizations of pentene diols.[13] Hopefully, this conclusion will be of use in future synthetic planning.

Experimental

General

Infra red spectra were obtained using a Perkin-Elmer 1720 FTIR spectrometer using liquid films on sodium chloride plates. ^1H NMR spectra were obtained using a Perkin-Elmer R32a instrument operating at 90 MHz where indicated, or a Bruker WM-250 instrument operating at 250 MHz. A JEOL EX270 spectrometer operating at 67.5 MHz was used to obtain ^{13}C NMR spectra. All spectra were recorded using dilute solutions in deuteriochloroform, with tetramethylsilane (Me_4Si) as the internal standard. Mass spectra were obtained in the EI mode using either an AEI MS 902 or a VG 7070E instrument operating at 70 eV.

Unless stated otherwise, all reactions were performed under dry nitrogen, with the exclusion of light in cases of iodine-containing reactants or products, and all organic solutions from aqueous work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. SG chromatography refers to column chromatography using silica gel [SORBSIL® C60-H (40–60 μm)] and the eluents specified. Petrol refers to light petroleum (bp 60–80 °C), and ether refers to diethyl ether.

All compounds reported herein are racemates.

Methyl 3-hydroxydec-5-ynoate 9a

Butyllithium (38.7 ml of a 1.6 mol l^{-1} solution in hexanes; 62 mmol) was added dropwise to a stirred solution of hex-1-yne (5.31 g, 64.7 mmol) in dry tetrahydrofuran (80 ml) maintained below −70 °C using an acetone–solid carbon dioxide bath. After 0.5 h, BF_3·Et_2O (7.63 ml, 62 mmol) was added dropwise followed, after a further 10 min, by a solution of the epoxy ester **8** (6.96 g, 60 mmol) in tetrahydrofuran (10 ml). The resulting

solution was stirred at this temperature for 4 h then poured into saturated aqueous ammonium chloride (200 ml). The product was extracted into ethyl acetate (3 × 50 ml) and the combined extracts dried and evaporated. SG chromatography [ethyl acetate–petrol (1 : 4)] gave the *hydroxy ester* **9a** (10.0 g, 84%) as a clear oil, ν_{max}/cm^{-1} 3448, 1738, 1437, 1162 and 1058; δ_H 0.91 (3 H, t, *J* 7.1, 10-CH_3), 1.37–1.48 (4 H, m, 8- and 9-CH_2), 2.14–2.19 (2 H, m, 7-CH_2), 2.39–2.42 (2 H, m, 4-CH_2), 2.52 (1 H, dd, *J* 16.3 and 8.7, 2-CH_AH$_B$), 2.67 (1 H, dd, *J* 16.3 and 3.8, 2-CH$_A$$H_B$), 3.78 (3 H, s, OCH_3) and 4.05–4.20 (1 H, m, 3-H); δ_C 13.46 (10-CH_3), 18.23, 21.84, 26.70 (all CH_2), 30.89 (4-CH_2), 40.73 (2-CH_2), 51.68 (OCH_3), 66.83 (3-CH), 75.06 (5-C), 83.36 (6-C) and 172.78 (1-CO); *m/z* 180 ($M^+ - H_2O$, 7%), 103 (100), 81 (18), 71 (51) and 61 (23) [Found: C, 66.9; H, 9.3. $C_{11}H_{18}O_3$ requires C, 66.6; H, 9.2%].

Methyl 3-triisopropylsilyloxydec-5-ynoate 9b

Triisopropylsilyl chloride (0.366 g, 1.9 mmol) was added to a stirred solution of the hydroxy ester **9a** (0.238 g, 1.2 mmol) and imidazole (0.211 g, 3.1 mmol) in dry dimethylformamide (6 ml). The resulting solution was stirred at ambient temperature for 72 h then diluted with water and extracted with ether (3 × 100 ml). The combined extracts were were dried and the residue purified by SG chromatography [9% ethyl acetate in petrol] to give the *silyl ether* **9b** (0.426 g, 98%) as a colourless oil, ν_{max}/cm^{-1} 1736, 1465, 1109 and 1069; δ_H 0.89 (3 H, t, *J* 7.1, 10-CH_3), 0.91–1.15 (21 H, m, TIPS), 1.31–1.72 (4 H, m, 8- and 9-CH_2), 2.10–2.21 (2 H, m, 7-CH_2), 2.41–2.43 (2 H, m, 4-CH_2), 2.60 (1 H, dd, *J* 15.0 and 6.3, 2-CH_ACH$_B$), 2.79 (1 H, dd, *J* 15.0 and 5.1, 2-CH$_A$CH_B), 3.74 (3 H, s, OCH_3) and 4.10–4.30 (1 H, m, 3-H); δ_C 12.41 (3 × CHSi), 13.58 (10-CH_3), 17.80 (6 × CH_3CHSi), 18.42, 21.80, 28.01, 30.51 (all CH_2), 40.01 (2-CH_2), 51.37 (OMe), 68.31 (3-CH), 75.60 (C), 84.10 (C) and 171.01 (1-CO); *m/z* 311 ($M^+ - Pr^i$, 7%), 131 (35), 103 (29) and 61 (30) [Found: $M^+ - Pr^i$, 311.2039. $C_{17}H_{31}O_3Si$ requires *M*, 311.2042].

Methyl (*Z*)-3-triisopropylsilyloxydec-5-enoate 10a

5% Palladium on barium sulfate (0.036 g) was suspended in dry ethyl acetate (1.5 ml) and treated with quinoline (33 μl). The resulting mixture was stirred at ambient temperature for 10 min before the silyl ether **9b** (0.42 g) was added. The mixture was then stirred under an atmosphere of hydrogen in the dark until no more gas was absorbed (*ca.* 1 h) and filtered through Celite. The filtrate was washed with 1 mol l^{-1} hydrochloric acid (10 ml), saturated aqueous sodium hydrogencarbonate (10 ml) and saturated brine (10 ml), then dried and evaporated to leave the (*Z*)-*alkenoate* **10a** (0.40 g, 95%) as a colourless oil, ν_{max}/cm^{-1} (film) 1741, 1465 and 1103; δ_H 0.89 (3 H, t, *J* 7.1, 10-CH_3), 0.92–1.17 (21 H, m, TIPS), 1.31–1.71 (4 H, m, 8- and 9-CH_2), 2.10–2.13 (2 H, m, 7-CH_2), 2.41–2.44 (2 H, m, 4-CH_2), 2.60 (1 H, dd, *J* 15.0 and 6.7, 2-CH_AH$_B$), 2.79 (1 H, dd, *J* 15.0 and 4.1, 2-CH$_A$$H_B$), 3.74 (3 H, OCH_3), 4.01–4.09 (1 H, m, 3-H), 5.35–5.42 (1 H, m, =CH) and 5.55–5.60 (1 H, m, =CH); δ_C 12.44 (3 × CHSi), 13.91 (10-CH_3), 18.00 (6 × CH_3CHSi), 22.43, 27.24, 31.86, 35.54 (all CH_2), 42.08 (2-CH_2), 51.63 (OCH_3), 66.31 (3-CH), 124.35 (=CH), 132.79 (=CH) and 171.73 (CO); *m/z* 313 ($M^+ - Pr^i$, 4%), 131 (100), 71 (65), 61 (41) and 55 (47) [Found: $M^+ - Pr^i$, 313.2180. $C_{17}H_{33}O_3Si$ requires *M*, 313.2199].

(*Z*)-3-Triisopropylsilyloxydec-5-enoic acid 10b

The alkenoate **10a** (0.4 g, 1.2 mmol) was dissolved in methanol (7 ml) containing potassium hydroxide (0.556 g) and the solution stirred at ambient temperature overnight, then evaporated to dryness. The residue was dissolved in water and the solution washed with ether (25 ml) then acidified using 2 mol l^{-1} hydrochloric acid (4.5 ml) and extracted with chloroform (3 × 15 ml). The combined extracts were dried and evaporated to leave the *acid* **10b** (0.38 g, 95%), an oil, which showed ν_{max}/cm^{-1} (film) 3664, 1713 and 1103; δ_H 0.90 (3 H, t, *J* 7.1, 10-CH_3), 1.05–1.18 (21 H, m, TIPS), 1.31–1.71 (4 H, m, 8- and 9-CH_2), 1.93–2.25 (2 H, m, 7-CH_2), 2.45–2.49 (2 H, m, 4-CH_2), 2.60 (1 H, dd, *J* 15.3 and 8.0, 2-CH_AH$_B$), 2.65 (1 H, dd, *J* 15.3 and 5.9, 2-CH$_A$$H_B$), 4.10–4.09 (1 H, m, 3-H), 5.35–5.42 (1 H, m, =CH) and 5.55–5.60 (1 H, m, =CH); δ_C 12.47 (3 × CHSi), 13.98 (10-CH_3), 18.08 (6 × CH_3CHSi), 22.39, 27.22, 31.79, 40.71 (all CH_2), 41.51 (2-CH_2), 69.52 (3-CH), 124.13 (=CH), 132.99 (=CH) and 175.53 (CO); *m/z* 299 ($M^+ - Pr^i$, 87%), 201 (20), 157 (44), 131 (80), 71 (30) and 43 (100) [Found: $M^+ - Pr^i$, 299.2037. $C_{16}H_{31}O_3Si$ requires *M*, 299.2042].

3-Triisopropylsilyloxydec-5-ynoic acid 11

The acetylenic ester **9b** (0.52 g) was saponified according to the foregoing method to give the *ynoic acid* **11** (0.50 g, 95%) as a colourless oil, ν_{max}/cm^{-1} 3500, 1714, 1465, 1109 and 1069; δ_H 0.89 (3 H, t, *J* 7.0, 10-CH_3), 1.05–1.10 (21 H, m, TIPS), 1.31–1.47 (4 H, m, 8- and 9-CH_2), 2.11–2.17 (2 H, m, 7-CH_2), 2.43–2.46 (2 H, m, 4-CH_2), 2.58 (1 H, dd, *J* 15.1 and 6.6, 2-CH_ACH$_B$), 2.78 (1 H, dd, *J* 15.1 and 5.0, 2-CH$_A$CH_B) and 4.26–4.30 (1 H, m, 3-H); δ_C 12.40 (3 × CHSi), 13.53 (10-CH_3), 17.95 (6 × CH_3CHSi), 18.39, 21.89, 27.82, 30.91 (all CH_2), 41.62 (2-CH_2), 68.56 (3-CH), 75.62 (C), 83.09 (C) and 177.18 (1-CO); *m/z* 297 ($M^+ - Pr^i$, 10%), 131 (65), 85 (45), 71 (100) and 61 (37) [Found: $M^+ - Pr^i$, 297.1902. $C_{16}H_{29}O_3Si$ requires *M*, 297.1886].

(*E*)-3-Triisopropylsilyloxydec-5-enoic acid 12

Ammonia (50 ml) was condensed into a stirred mixture of the foregoing ynoic acid **11** (0.42 g, 1.2 mmol), *tert*-butyl alcohol (0.12 g, 1.47 mmol) and ammonium sulfate (1.94 g, 14.7 mmol) in dry tetrahydrofuran (25 ml), maintained below −70 °C using an acetone–solid carbon dioxide bath. The temperature of the mixture was then raised to −40 °C and maintained at this level during the addition of lithium chips (0.054 g, 8.9 mmol) over 5 min and for the subsequent 2 h. No further coolant was added to the bath as the mixture was left stirring for 16 h while the bulk of the ammonia evaporated. The residue was diluted with water (100 ml) and extracted with chloroform (3 × 50 ml). The combined extracts were dried and evaporated to leave the (E)-*alkenoic acid* **12** (0.475 g, 95%) as a colourless oil which showed ν_{max}/cm^{-1} (film) 3500, 1713, 1464 and 1106; δ_H 0.89 (3 H, t, *J* 7.1, 10-CH_3), 1.05–1.17 (21 H, m, TIPS), 1.31–1.40 (4 H, m, 8- and 9-CH_2), 1.95–2.05 (2 H, m, 7-CH_2), 2.20–2.29 (2 H, m, 4-CH_2), 2.47 (1 H, dd, *J* 15.2 and 5.9, 2-CH_AH$_B$), 2.57 (1 H, dd, *J* 15.2 and 4.1, 2-CH$_A$$H_B$), 4.17–4.27 (1 H, m, 3-H), 5.30–5.42 (1 H, m, =CH) and 5.55–5.60 (1 H, m, =CH); δ_C 12.42 (3 × CHSi), 13.89 (10-CH_3), 18.01 (6 × CH_3CHSi), 22.19, 31.47, 32.33, 40.75 (all CH_2), 41.48 (2-CH_2), 69.44 (3-CH), 124.64 (=CH), 134.52 (=CH) and 177.45 (CO); *m/z* 299 ($M^+ - Pr^i$, 2%), 131 (45), 89 (51), 85 (100) and 71 (52) [Found: $M^+ - Pr^i$, 299.2035].

(*E*)-Methyl 3-hydroxydec-5-enoate 14

***Via* vinylalane.** Diisobutylaluminium hydride (27 ml of a 1 mol l^{-1} solution in hexane; 27 mmol) was added to a solution of hexyne (3.1 ml, 27 mmol) in hexane (90 ml), maintained at −78 °C, and the resulting solution stirred and heated to 50 °C for 2 h, before recooling to −30 °C. Methyllithium (18.5 ml of a 1.4 mol l^{-1} solution in ether, 26 mmol) and ether (90 ml) were added and the resulting suspension stirred at 0 °C for 0.5 h before cooling to −78 °C. Methyl 3,4-epoxybutanoate **8** (3 g, 26 mmol) was then added dropwise followed by BF_3·Et_2O (3.18 ml, 26 mmol). The resulting solution was stirred at −78 °C for 0.75 h then quenched using methanol (15 ml) followed, after 10 min, by 1 mol l^{-1} hydrochloric acid (60 ml). The mixture was extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried and evaporated to leave a colourless oil. SG chromatography [15% ethyl acetate–petrol] separated the *hydroxy ester* **14** (3.28 g, 63%), a colourless oil, ν_{max}/cm^{-1} (film) 3417 and 1732; δ_H 0.90 (3 H, t, *J* 6.4, 10–CH_3), 1.20–1.40 (4 H, m, 8- and 9-CH_2), 2.01–2.05 (2 H, m, 7-CH_2), 2.10–2.14 (2

H, m, 4-CH_2), 2.45 (1 H, dd, *J* 15.7 and 9.8, 2-CH_AH_B), 2.52 (1 H, dd, *J* 15.7 and 3.8, 2-CH_AH_B), 3.71 (3 H, s, OCH_3), 4.05–4.20 (1 H, m, 3-H), 5.35–5.45 (1 H, m, =CH) and 5.55–5.65 (1 H, m, =CH); δ_C 13.92 (10-CH_3), 22.22, 31.55, 32.32, 39.91 (all CH_2), 40.44 (2-CH_2), 51.80 (OCH_3), 67.75 (3-CH), 124.82 =CH), 138.70 (=CH) and 173.26 (CO); *m/z* [NH_3, CI] 218 ($M^+ + NH_4$, 85%), 201 (20), 183 (100), 169 (5) and 151 (10) [Found: C, 65.4; H, 9.9. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%].

From (*E*)-oct-3-enoic acid 15. Malonic acid (15.60 g, 150 mmol), piperidine (5 drops) and xylene (200 ml) were brought to reflux under a Dean and Stark water separator, then hexanal (5 g, 50 mmol) was added dropwise over a period of 5 min. Heating was continued until no more gas/water generation was observed (*ca.* 3 h), then the mixture was cooled and the bulk of the volatiles evaporated. The residue was dissolved in ether (200 ml) and the solution washed with water (3 × 50 ml) then extracted with 2 mol l^{-1} aqueous sodium carbonate (3 × 50 ml). The combined aqueous extracts were cooled to 0 °C and carefully acidified using 2 mol l^{-1} hydrochloric acid then extracted with ethyl acetate (3 × 30 ml). The combined organic extracts were dried and evaporated to leave (*E*)-3-octenoic acid **15** (5.10 g, 72%) as a colourless oil, ν_{max}/cm^{-1} (film) 3150–2850, 1711 and 1418; δ_H(90 MHz) 0.91 (3 H, t, *J* 6.9, 8-CH_3), 1.30–1.38 (4 H, m, 6- and 7-CH_2), 1.95–2.20 (2 H, m, 5-CH_2), 3.11 (2 H, d, *J* 6.0, 2-CH_2), 5.65–6.10 (2 H, m, 2 × =CH) and 9.45 (1 H, br s, OH); δ_C 14.72 (8-CH_3), 23.40, 27.35, 31.72, 33.01 (all CH_2), 124.07 (=CH), 136.23 (=CH) and 179.02 (CO), which was used without further purification.

The acid **15** (1.23 g, 8.67 mmol) in tetrahydrofuran (5 ml) was added dropwise to a solution of 1,1-carbonyl diimidazole (1.73 g, 10.4 mmol) in tetrahydrofuran (20 ml) maintained at 0 °C under an argon atmosphere. The mixture was then stirred in the dark for 12 h without further cooling. In a separate preparation, an ice-cold solution of isopropylmagnesium bromide (26 mmol) in tetrahydrofuran (40 ml) was added dropwise to a solution of methyl hydrogen malonate (1.53 g, 13 mmol) in tetrahydrofuran (10 ml), maintained at 0 °C. After 20 min, the resulting mixture was stirred without cooling for 20 min, then at 40 °C for a further 20 min before cooling back to 0 °C. To this mixture was slowly added the above acyl imidazolide solution and the resultant mixture stirred without further cooling for 18 h, then poured into a stirred, ice-cold mixture of 2 mol l^{-1} aqueous phosphoric acid (140 ml) and ethyl acetate (60 ml). The separated aqueous phase was further extracted with ethyl acetate (3 × 50 ml) and the combined organic solutions washed with saturated aqueous sodium hydrogen carbonate (3 × 30 ml) then dried and evaporated. SG chromatography [4:1 hexanes–ethyl acetate] then separated methyl (*E*)-3-oxodec-5-enoate **16** (1.01 g, 58%) as a colourless oil, ν_{max}/cm^{-1} (film) 1738 and 1727; δ_H 0.89 (3 H, t, *J* 7.0, 10-CH_3), 1.23–1.38 (4 H, m, 8- and 9-CH_2), 2.04 (2 H, td, *J* 6.6 and 6.4, 7-CH_2), 3.22 (2 H, d, *J* 6.1, 4-CH_2), 3.49 (2 H, s, 2-CH_2), 3.73 (3 H, s, OCH_3), 5.51 (1 H, dt, *J* 14.8 and 6.6, 6-H) and 5.57 (1 H, dt, *J* 14.8 and 6.1, 5-H); δ_C 13.38 (10-CH_3), 25.62, 31.41, 32.34, 46.91, 48.26 (all CH_2), 52.22 (OCH_3), 120.96 (=CH), 136.40 (=CH), 167.66 (CO) and 201.08 (CO); *m/z* 198 (M^+, 4%), 139 (7), 125 (29), 101 (25), 97 (39), 69 (25) and 31 (100) [Found: M^+, 198.1248. $C_{11}H_{18}O_3$ requires *M*, 198.1256].

To a stirred solution of the keto-ester **16** (0.79 g, 4 mmol) in dry methanol (8 ml) maintained at 0 °C was added sodium borohydride (0.152 g, 4 mmol). After 0.5 h, TLC indicated completion of the reduction and water (3 ml) was added. The bulk of the methanol was evaporated and the residue partitioned between water (10 ml) and ethyl acetate (30 ml). The separated organic layer was dried and evaporated and the residue subjected to SG chromatography [3:2 hexanes–ethyl acetate] to give the *hydroxy ester* **14** (0.57 g, 71%) as a colourless oil, displaying identical spectral and analytical properties to the previous sample.

(3*RS*,5*SR*,6*SR*)-6-Iodo-3-triisopropylsilyloxydecan-5-olide 17
Sodium hydrogen carbonate (0.096 g, 1.14 mmol) was added to a stirred, ice-cold solution of the (*Z*)-alkenoic acid **10b** (0.13 g, 0.38 mmol) in acetonitrile (1.5 ml) and water (0.5 ml). After 5 min, iodine (0.29 g, 1.14 mmol) was added and the mixture stirred for 4 h at 0 °C. The mixture was then diluted with ether (40 ml) and washed with saturated aqueous sodium thiosulfate until the excess iodine was removed, then water (15 ml), then dried and evaporated. SG chromatography [15% ether–petrol] gave the *iodolactone* **17** (0.162 g, 91%) as a colourless oil, ν_{max}/cm^{-1} (film) 1748, 1464, 1342 and 1248; δ_H 0.92 (3 H, t, *J* 6.7, 10-CH_3), 1.05–1.08 (21 H, m, TIPS), 1.22–1.45 (4 H, m, 8- and 9-CH_2), 1.50–1.65 (1 H, m, 7-H_A), 1.86 (1 H, ddd, *J* 13.7, 9.9 and 4.8, 4-H_{ax}), 2.12 (1 H, dddd, *J* 13.7, 4.0, 3.0 and 1.4, 4-H_{eq}), 2.09–2.13 (1 H, m, H_B), 2.63 (1 H, dd, *J* 17.6 and 3.7, 2-CH_AH_B), 2.68 (1 H, ddd, *J* 17.6, 3.0 and 1.4, 2-CH_AH_B), 4.12 (1 H, ddd, *J* 9.9, 4.0 and 2.6, 5-H), 4.43 (1 H, partly obscured ddd, *J ca.* 12, 2.6 and 2.6, 6-H) and 4.48 (1 H, m, $\omega_{\frac{1}{2}}$ = *ca.* 9 Hz, 3-H); δ_C 12.29 (3 × CHSi), 13.93 (10-CH_3), 17.72 (6 × CH_3CHSi), 21.89, 31.91, 35.88, 35.93 (all CH_2), 38.96 (6-CH), 39.41 (2-CH_2), 63.59 (3-CH), 77.23 (5-CH) and 169.41 (CO); *m/z* 425 ($M^+ - Pr^i$, 5%), 297 (10), 157 (100), 99 (45) and 57 (40) [Found: $M^+ - Pr^i$, 425.0986. $C_{16}H_{30}IO_3Si$ requires *M*, 425.1011].

(3*RS*,5*SR*,6*RS*)- and (3*RS*,5*RS*,6*SR*)-6-Iodo-3-triisopropylsilyloxydecan-5-olide [19 and 21]
Iodolactonization of the (*E*)-alkenoic acid **12** (0.504 g, 1.47 mmol) by the above procedure gave a crude product (0.90 g) which was separated by SG chromatography [15% ether–petrol] to give (i) the trans-*lactone* **19** (0.54 g, 78%) as a colourless oil, ν_{max}/cm^{-1} (film) 1748, 1464, 1342 and 1248; δ_H 0.92 (3 H, t, *J* 7.0, 10-CH_3), 1.05–1.08 (21 H, m, TIPS), 1.13–1.42 (4 H, m, 8- and 9-CH_2), 1.49–1.65 (1 H, m, 7-H_A), 1.71–1.91 (2 H, m, 4-H_{ax} and 7-H_B), 2.21 (1 H, dddd, *J* 13.9, 3.6, 3.6 and *ca.* 1.4, 4-H_{eq}) 2.64–2.69 (2 H, m, 2-CH_2), 4.27–4.37 (2 H, m, 5- and 6-H), and 4.48 (1 H, br p, *J ca.* 3.5, 3-H); δ_C 12.31 (3 × CHSi), 14.14 (10-CH_3), 18.24 (6 × CH_3CHSi), 22.12, 31.81, 35.65, 35.77 (all CH_2), 39.66 (2-CH_2), 41.04 (6-CH), 63.83 (3-CH), 77.79 (5-CH) and 169.34 (CO); *m/z* 425 ($M^+ - Pr^i$, 5%), 297 (10), 157 (100), 99 (45) and 57 (40) [Found: $M^+ - Pr^i$, 425.0998], and (ii) the cis-*lactone* **21** (0.050 g, 8%) as a colourless oil, ν_{max}/cm^{-1} (film) 1748, 1464, 1344 and 1250; δ_H 0.93 (3 H, t, *J* 6.7, 10-Me), 1.05–1.10 (21 H, m, TIPS), 1.26–1.36 (4 H, m, 8- and 9-CH_2), 1.55–1.62 (1 H, m, 7-H_A), 1.72–1.87 (2 H, m, 4-H_A and 7-H_B), 2.45–2.53 (1 H, obscured m, 4-H_B), 2.51 (1 H, dd, *J* 17.1 and 8.3, 2-H_A), 2.85 (1 H, ddd, *J* 17.1, 5.2 and 1.2, 2-H_B), 3.97 (1 H, ddd, *J* 11.1, 6.0 and 3.0, 5-H), 4.23 (1 H, ddd, *J* 6.2, 6.2, and 6.0, 6-H) and 4.30 (1 H, dddd, *J* 8.6, 8.6, 5.2 and 5.2, 3-H); δ_C 12.19 (3 × CHSi), 13.97 (10-CH_3), 16.02 (6 × CH_3CHSi), 21.91, 31.55, 35.04, 38.13 (all CH_2), 39.11 (6-CH), 40.37 (2-CH_2), 64.25 (3-CH), 78.90 (5-CH) and 169.41 (CO) [Found: $M^+ - Pr^i$, 425.1007].

(3*RS*,5*SR*,6*RS*)-Methyl 5,6-epoxy-3-triisopropylsilyloxydecanoate 18
Sodium carbonate (16.1 mg, 0.16 mmol) was added to a solution of the (3*RS*,5*SR*,6*SR*)-iodolactone **17** (45 mg, 0.09 mmol), derived from the (*Z*)-alkenoic acid **10b**, in dry methanol (1.6 ml) and the resulting mixture stirred at ambient temperature for 16 h. The solvent was evaporated and the residue partitioned between water (1 ml) and ether (3 ml). The separated organic phase was dried and evaporated to give the (3RS,5SR,6RS)-*epoxy ester* **18** (18 mg, 76%) as a colourless oil, ν_{max}/cm^{-1} (film) 1741, 1463, 1381, 1170 and 1096; δ_H 0.92 (3 H, t, *J* 6.9, 10-CH_3), 1.10–1.27 (21 H, m, TIPS), 1.35–1.60 (6 H, m, 7-, 8- and 9-CH_2), 1.68 (1 H, ddd, *J* 14.4, 7.8 and 4.1, 4-CH_ACH_B), 1.94 (1 H, ddd, *J* 14.4, 6.1 and 3.9, 4-CH_ACH_B), 2.65 (2 H, dd, *J* 6.4 and 2.2, 2-CH_2), 2.92 (1 H, ddd, *J* 7.8, 4.1, and 3.9, 5-H), 3.13 (1 H, ddd, *J* 7.9, 7.9 and 4.1, 6-H), 3.67 (3 H, s,

OCH_3) and 4.55 (1 H, dddd, *J* 6.4, 6.4, 6.1 and 4.1, 3-H); δ_C 12.45 (3 × CHSi), 14.00 (10-CH_3), 18.06 (6 × CH_3CHSi), 22.59 (9-CH_2), 27.35 (8-CH_2), 27.65 (7-CH_2), 35.31 (4-CH_2), 41.83 (2-CH_2), 51.50 (OCH_3), 53.05 (5-CH), 56.26 (6-CH), 67.78 (3-CH) and 171.59 (CO); *m*/*z* 329 (90%, $M^+ - Pr^i$), 259 (31), 255 (27), 227 (77), 217 (43), 157 (61), 131 (85), 103 (78) and 75 (100) [Found: $M^+ - Pr^i$, 329.2116. $C_{17}H_{33}O_4Si$ requires *M*, 329.2148].

(3*RS*,5*SR*,6*SR*)-Methyl 5,6-epoxy-3-triisopropylsilyloxydecanoate 20

The (3*RS*,5*SR*,6*RS*)-iodolactone **19** (0.40 g, 0.85 mmol), derived as the major product from the (*E*)-alkenoic acid **12**, was treated with sodium carbonate in methanol as in the above experiment to give the (3RS,5SR,6SR)-*epoxy ester* **20** (0.19 g, 75%) as a colourless oil, ν_{max}/cm^{-1} (film) 1741, 1463, 1371, 1176 and 1060; δ_H 0.91 (3 H, t, *J* 6.9, 10-CH_3), 1.05–1.07 (21 H, m, TIPS), 1.36–1.44 (4 H, m, 8- and 9-CH_2), 1.51–1.62 (2 H, m, 7-CH_2), 1.68 (1 H, ddd, *J* 14.3, 7.1 and 3.8, 4-C$H_A$$CH_B$), 1.94 (1 H, ddd, *J* 14.3, 6.4 and 4.3, 4-CH_ACH_B), 2.58–2.71 (3 H, m, 6-H and 2-CH_2), 2.86 (1 H, ddd, *J* 7.1, 4.3, and 2.2, 5-H), 3.66 (3 H, s, OCH_3) and 4.47 (1 H, dddd, *J* 6.4, 6.4, 3.8 and 2.6, 3-H); δ_C 12.71 (3 × CHSi), 14.25 (10-CH_3), 18.33 (6 × CH_3CHSi), 22.81 (9-CH_2), 28.39 (8-CH_2), 31.97 (7-CH_2), 39.97 (4-CH_2), 42.07 (2-CH_2), 51.79 (OCH_3), 55.10 (5-CH), 58.55 (6-CH), 67.80 (3-CH) and 172.22 (CO); *m*/*z* 329 (76%, $M^+ - Pr^i$), 259 (22), 255 (30), 227 (79), 217 (41), 157 (67), 131 (85), 103 (79) and 75 (100) [Found: $M^+ - Pr^i$, 329.2129].

(3*RS*,5*RS*,6*RS*)-Methyl 5,6-epoxy-3-triisopropylsilyloxydecanoate 22

The (3*RS*,5*RS*,6*SR*)-iodolactone **21** (40 mg, 0.80 mmol), obtained as the minor product from the (*E*)-alkenoic acid **12**, was treated with sodium carbonate in methanol as in the above experiment to give the (3RS,5RS,6RS)-*epoxy ester* **22** (15 mg, 70%) as a colourless oil, ν_{max}/cm^{-1} (film) 1741, 1463, 1371, 1174 and 1095; δ_H 0.92 (3 H, t, *J* 6.9, 10-CH_3), 1.07–1.17 (21 H, m, TIPS), 1.27–1.45 (6 H, m, 7-, 8- and 9-CH_2), 1.70–1.72 (1 H, m, 4-H), 1.82–1.85 (1 H, m, 4-H), 2.53 (2 H, app. dd, *J* 6.3 and 1.7, 2-CH_2), 2.66 (1 H, ddd, *J* 5.3, 5.3 and 2.2, 6-H), 2.79 (1 H, ddd, *J* 5.6, 4.1, and 2.2, 5-H), 3.67 (3 H, s, OCH_3) and 4.54 (1 H, p, *J* 6.3, 3-H); δ_C 12.46 (3 × CHSi), 13.91 (10-CH_3), 18.03 (6 × CH_3CHSi), 22.48 (9-CH_2), 27.98 (8-CH_2), 31.63 (7-CH_2), 40.07 (4-CH_2), 42.70 (2-CH_2), 51.48 (OCH_3), 55.13 (5-CH), 58.89 (6-CH), 67.91 (3-CH) and 171.68 (CO); *m*/*z* 329 (89%, $M^+ - Pr^i$), 259 (27), 255 (35), 227 (65), 217 (44), 157 (64), 131 (89), 103 (80) and 75 (100) [Found: $M^+ - Pr^i$, 329.2123].

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References

1 F. Bennett, D. W. Knight and G. Fenton, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1543.
2 P. A. Bartlett, *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, Orlanda, 1984, vol. 3, p. 144.
3 P. A. Bartlett, D. P. Richardson and J. Myerson, *Tetrahedron*, 1984, **40**, 2317; W. Bartmann, G. Beck, E. Granzer, H. Jendralla, B. V. Kerekjarto and G. Wess, *Tetrahedron Lett.*, 1986, **27**, 4709.
4 S. B. Bedford, G. Fenton, D. W. Knight and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6505.
5 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391.
6 M. S. Cooper and H. Heaney, *Synlett*, 1990, 533.
7 For a preparation of homochiral epoxy ester **8**, see M. Larcheveque and S. Henrot, *Tetrahedron*, 1990, **46**, 4277.
8 G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.*, 1969, **89**, 2754; A. Alexakis and D. Jachiet, *Tetrahedron*, 1989, **45**, 6197.
9 N. Ragoussis, *Tetrahedron Lett.*, 1987, **28**, 93.
10 H. A. Bates and H. Rapoport, *J. Am. Chem. Soc.*, 1979, **101**, 1259.
11 P. A. Bartlett and J. Myerson, *J. Org. Chem.*, 1979, **44**, 1625.
12 H. Booth, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1969, **5**, 149.
13 Y. Tamaaru, M. Hojo, S. Kawamura, S. Sawada and Z. Yoshida, *J. Org. Chem.*, 1987, **52**, 4062.

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