Total Syntheses of Natural (+)-(4*R*,6*R*)-4-Hydroxy-6-pentylvalerolactone and of (−)-(6*R*)-Massoialactone

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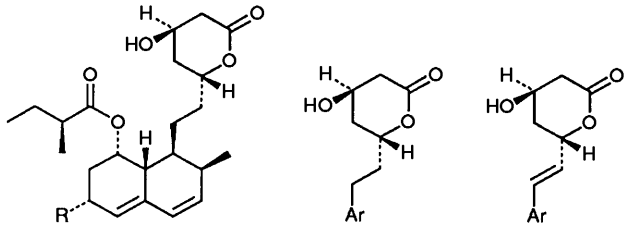
An asymmetric total synthesis and hence a confirmation of the absolute configuration of naturally occurring (+)-(4*R*,6*R*)-4-hydroxy-6-pentylvalerolactone **10**, a metabolite of *Cephalosporium recifei*, is described, starting from the yeast reduction product methyl (3*R*)-3-hydroxyhex-5-enoate **5**. The key step is a highly *trans*-selective kinetic iodolactonization of the unsaturated acid **16e**. Dehydration of the lactone **10** leads to natural (−)-(6*R*)-massoialactone **11**.

The ability of the mevinic acids, notably compactin **1a** and mevinolin **1b**, to inhibit cholesterol biosynthesis at the HMGCoA reductase stage[1] leading to mevalonic acid has stimulated a great deal of interest in the synthesis of these compounds[2] and of simpler, more readily available and potentially more potent analogues. Generally, the most active examples of such analogues are the arylethyl and arylethenyl lactones **2** and **3** in which the complex decalin system of the

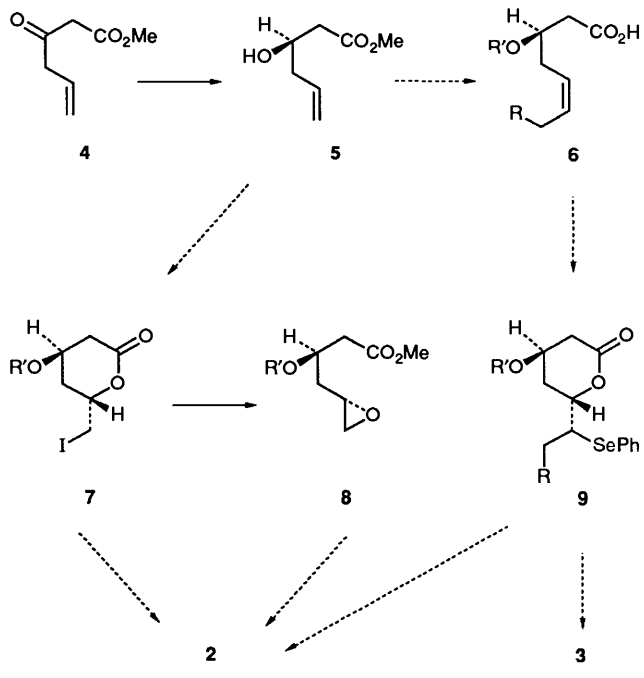


1a; R = H [(+)-compactin]
b; R = Me [(+)-mevinolin]

2 **3**

natural materials has been replaced by a more readily accessible benzenoid function.[3] We have recently described two alternative approaches to these types of analogues as outlined in Scheme 1.[4] The key starting material in these studies was the hydroxy ester **5** which was obtained in 78% enantiomeric excess from baker's yeast reduction of the corresponding keto ester **4**. In the first method, conversion of ester **5** into the iodo lactones **7** showed good selectivity in favour of the natural stereochemistry of the mevinic acids. These intermediates could then be converted into the mevinic acid analogues **2** either directly by radical coupling or by prior conversion into the epoxy ester **8**, followed by coupling with a copper-modified benzylic Grignard reagent.[5] As an alternative, the eventual 6-substituent of the valerolactone was introduced into ester **5**, before lactonization, by sequential ozonolysis and Wittig homologation. Subsequent selenolactonization of the resulting unsaturated acids **6** then gave seleno lactones **9** and hence both the saturated **2** and unsaturated **3** mevinic acid analogues by reductive or oxidative selenium elimination.

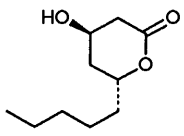
Herein, we describe an iodolactonization approach, based on the latter part of Scheme 1, which can be used in the unambiguous asymmetric synthesis of valerolactones and 2-pyrones in addition to mevinic acid analogues. The utility of this sequence is illustrated in syntheses of the natural enantiomer of 4-hydroxy-6-pentylvalerolactone **10** and of (−)-massoialactone **11**. The former lactone **10** is a metabolite of *Cephalosporium recifei* and neither the relative nor the absolute stereochemistry of the compound has been assigned.[6] However, the ^{1}H NMR



Scheme 1

spectrum [Fig. 3 in ref. 6] of the natural material strongly suggests that it possesses the *trans* configuration shown (structure **10**) by reason of a broad resonance for the 6-H (axial) and the relatively narrower band for the 4-H (equatorial) protons. By contrast, massoialactone (massoilactone) **11** is known to have the (6*R*) absolute configuration, initially determined from comparative ORD studies.[7] The compound has been isolated from a number of natural sources including massoy bark oil (*Cryptocarya massoia*),[8,9] cane molasses (in which it is a flavour component[10]), and jasmine flowers[11] as well as from the defence secretion of two species of formicin ants belonging to the *Camponotus* genus.[12] The gross structure has been confirmed by syntheses of racemic material[13] and the assignment of absolute stereochemistry confirmed by a synthesis of the non-natural (6*S*) enantiomer[9] and by separation of a racemic precursor by means of a chiral HPLC column and subsequent conversion into the natural (*R*)-lactone **11**.[14]

Our syntheses[15] began with conversion of the initial yeast reduction product **5** into the corresponding triisopropylsilyl (TIPS) ether **12** (87%). Ozonolysis then provided the aldehydo ester **13** in 91% isolated yield. Subsequent Wittig homolog-



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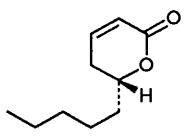

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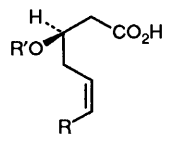
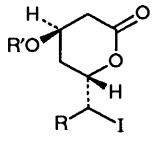
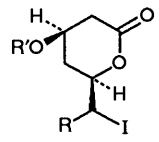
Table 1





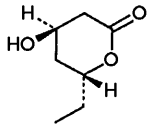


16	R	R′	17	18	Combined yield
a;	H	TBDMS[4]	4	1	84%[4]
b;	H	TIPS[4]	5.5	1	81%[4]
c;	Me	H	2.4	1	54%
d;	Me	TBDMS	6.1	1	77%
e;	Bu	TIPS	10.5	1	93%

ation using pentyl(triphenyl)phosphonium bromide proceeded smoothly to give the (*Z*)-alkene **14** in excellent yield, contaminated by some 8% of the corresponding (*E*)-isomer. The lactonization precursor **16e** was then secured by selective hydrolysis with methanolic potassium hydroxide. For comparison purposes, the lower heptenoate homologue **15a** was similarly prepared from the corresponding t-butyl(dimethyl)-silyl (TBDMS)-protected aldehydoester.[4] In this case, only poor selectivity was observed in attempted selective hydrolysis of the methyl ester function and so the silyl ether function was first hydrolysed using aq. hydrogen fluoride to give the hydroxy ester **15b** which was subsequently saponified to give the hydroxy acid **16c**. This was then converted into the silyl acid **16d** by silylation and selective hydrolysis of the resulting silyl ester function by reaction with aq. potassium carbonate.

Iodolactonization of the unsaturated acids **16c–e** was effected by using the kinetic procedure of Bartlett *et al.*[16] to give, in each example, mixtures of *trans* and *cis* iodo lactones **17c–e** and **18c–e** (see Table 1 for ratios). The relative stereochemistries were determined primarily by consideration of the coupling constants exhibited by the deiodinated hydroxy lactones **19–21**. Typically, the *trans* isomers (**19** and **21**) showed a narrow resonance for the 4-H with other coupling constants, especially those of the axial protons at C-3 and C-5, indicating that this proton was in an equatorial position and hence *trans* to the clearly axial 6-H, on the assumption that the smaller hydroxy group adopts an axial position in a chair-like conformation. In contrast, the corresponding data for the other isomers observed showed that both the 4- and the 6-proton were positioned axially, and hence that these had the *cis* configurations (**20a** and **20b**).

The reasons for the stereoselectivities observed in this type of iodolactonization (Table 1) are not entirely clear. For example, similar cyclizations of 3-substituted hexenoic acids give mainly the *cis*-4,6-disubstituted valerolactones, probably by way of a chair-like transition state with both pendant groups in pseudoequatorial positions.[16] The general trend shown in Table 1 is that increases in the sizes of the distal substituent and of the 3-oxy group in the starting unsaturated acids **16** are additive in favour of the *trans* iodo lactones **17**. This implies that the 3-oxy substituent could be forced to adopt largely a pseudoaxial position to lessen steric compression caused by the large iodonium atom in a chair-like transition state. An alternative explanation is that the cyclizations proceed largely through a boat-like transition state which would at least allow the two pendant groups to adopt pseudoequatorial positions. Further work is underway to attempt to define this feature more fully.



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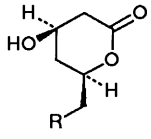
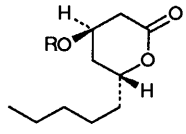


20a; R = Me
b; R = Bu

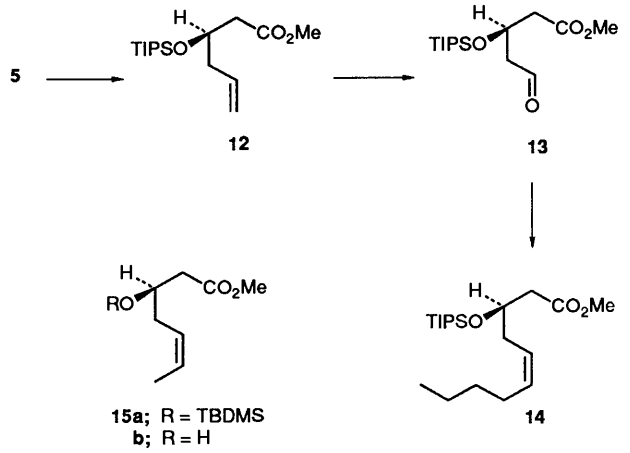


21a R = TIPS
21b R = H

The major, *trans*-isomer **21b** formed from iodolactonization of acid **16e** showed spectral data identical with those reported for 4-hydroxy-6-pentylvalerolactone isolated from *C. recifei*.[6] Further, the synthetic sample showed $[\alpha]_D$ +29.4° (*c* 1.4, $CHCl_3$), corrected to +37.7° on the basis of a 78% enantiomeric enrichment of the starting hydroxy ester **5**.[4] The natural material was found to have $[\alpha]_D$ +27.4° (*c* 11.7, $CHCl_3$).[6] The (4*R*,6*R*) absolute stereochemistry is therefore established for this metabolite.

Finally, dehydration of hydroxy lactone **21b** with phosphoryl trichloride in warm pyridine gave an excellent yield of massoialactone **11** which was identical in all respects, including optical rotation after adjustment, with the natural material.[7–14]

In summary, the foregoing methodology should be applicable to the synthesis and hence the determination of absolute configuration of a range of related hydroxyvalerolactones as well as many related dihydro- and tetrahydro-pyran-2-ones.



15a; R = TBDMS
b; R = H

TIPS = $SiPr^i_3$
TBDMS = $SiMe_2Bu^t$

Experimental

General Details.—For general details, see ref. 4. For NMR, *J*-values are given in Hz. The enantiomeric enrichment (ee) of the methyl (−)-(3*R*)-3-hydroxyhex-5-enoate **5** used in all the following reactions is 78%.[4] All products should therefore be regarded as having this order of optical purity.

Methyl (3R)-3-(*Triisopropylsiloxy*)*hex*-5-*enoate* **12**.—Imidazole (3.71 g, 55 mmol) was added to a stirred solution of triisopropylsilyl chloride (5.05 g, 22 mmol) and methyl (3*R*)-3-hydroxyhex-5-enoate **5**[4] (3.14 g, 22 mmol; 78% ee) in dry dimethylformamide (DMF) (6 cm^3). The resulting solution was stirred at ambient temperature for 48 h, then poured into pentane (70 cm^3). The resulting solution was washed with water

(3 × 20 cm^3), then dried and concentrated to give, after chromatography over silica gel eluted with diethyl ether–hexanes (1:20), the *silyl ether* **12** (5.67 g, 87%) as an oil, $[\alpha]_D$ − 23.9° (*c* 1.3, $CHCl_3$); ν_{max}/cm^{-1} 1739 and 1646; δ_H 0.68 (21 H, br s, 6 × *Me*CH and 3 × MeC*H*), 1.86–2.20 (4 H, m, 2 × CH_2), 3.28 (3 H, s, OMe), 3.99 [1 H, p, *J* 6.3, CH(OSi)], 4.55–4.86 (2 H, m, C*H*$_2$=CH) and 5.26–5.70 (1 H, m, CH_2=C*H*); *m/z* 257 (85%, $C_{13}H_{25}O_3Si$, M − C_3H_7), 145 (100, $C_7H_{17}OSi$), 117 (22, $C_5H_{13}OSi$) and 89 (21, C_3H_9OSi) [Found: (M^+ − C_3H_7), 257.1568. $C_{13}H_{25}O_3Si$ requires *m/z* 257.1570].

Methyl (3R)-4-*Formyl*-3-(*triisopropylsiloxy*)*butanoate* **13**.—A solution of the foregoing methyl hex-5-enoate **12** (2.00 g, 6.67 mmol) in dry dichloromethane (60 cm^3) cooled to −70 °C was treated with ozonized oxygen until the solution became blue in colour. Excess of ozone was removed in a stream of dry nitrogen, then dimethyl sulphide (1.2 cm^3) was added and the mixture was warmed to ambient temperature. Following the addition of more dimethyl sulphide (4.0 cm^3), the solution was kept at 40 °C for 48 h, then cooled and evaporated. The residue was dissolved in pentane (50 cm^3) and washed with water (3 × 20 cm^3), dried, and evaporated to give the aldehyde **13** (1.82 g, 91%) as a pale yellow oil which decomposed upon attempted distillation, but which was ≥95% pure according to both TLC analysis and NMR data and which showed $[\alpha]_D$ −6.7° (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 1725; δ_H 1.09 (21 H, br s, Pr^i_3Si), 2.68 (2 H, d, *J* 6.3, CH_2CO), 2.76 (2 H, dt, *J* 5.4 and 1.8, C*H*$_2$CHO), 3.72 (3 H, s, OMe), 4.80 [1 H, p, *J* 5.4, CH(OSi)] and 9.86 (1 H, t, *J* 1.8, CHO).

Methyl (3R,5Z)-3-(*Triisopropylsiloxy*)*dec*-5-*enoate* **14**.—Butyllithium (4 cm^3 of a 1.5 mol dm^{-3} solution in hexanes, 6 mmol) was added dropwise to a stirred suspension of pentyl(triphenyl)phosphonium bromde (2.29 g, 6 mmol) in dry tetrahydrofuran (THF) (100 cm^3) maintained at 20 °C. The resulting mixture was stirred at ambient temperature for 20 min, when a solution of the aldehyde **13** (1.79 g, 6 mmol) in THF (2 cm^3) was added in one portion. After a further 30 min, the mixture was poured into pentane (100 cm^3) and the resulting suspension was washed with water. The organic phase was dried, filtered and evaporated. Chromatographic purification of the resulting oil gave the *alkene* **14** (1.80 g, 85%) as an oil, $[\alpha]_D$ −22.6° (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} 1737; δ_H 0.79–1.38 [7 H, m, Me(CH_2)$_2$], 1.07 (21 H, br s, Pr^i_3Si), 1.89–2.19 (2 H, m, C*H*$_2$CH=), 2.33 [2 H, br t, *J* 6.3, =CHC*H*$_2$CH(O)], 2.47 (2 H, d, *J* 6.3, CH_2CO), 3.62 (3 H, s, OMe), 4.34 (1 H, p, *J* 6.3, CHOSi) and 5.24–5.65 (2 H, m, 2 × =CH); *m/z* 313 (100%, $C_{17}H_{33}O_3Si$, M − C_3H_7), 281 (12, $C_{16}H_{29}O_2Si$, M − Pr^i − MeOH) and 145 (43, $C_7H_{17}OSi$) [Found: (M^+ − C_3H_7) 313.2181. $C_{17}H_{33}O_3Si$ requires *m/z*, 313.2198] [Found: C, 67.6; H, 11.5. $C_{20}H_{40}O_3Si$ requires C, 67.4; H, 11.3%].

At 400 MHz, the sample could be seen to contain *ca.* 8% of the corresponding (*E*)-isomer.

(3R,5Z)-3-*Hydroxyhept*-5-*enoic Acid* **16c**.—Butyllithium (1.23 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 2 mmol) was added dropwise to a stirred suspension of ethyl(triphenyl)-phosphonium bromide (0.78 g, 2.1 mmol) in dry THF (30 cm^3) maintained at 20 °C. The resulting mixture was heated to 40 °C for 5 min, when a solution of methyl (3*R*)-3-[t-butyl(dimethyl)-siloxy]-4-formylbutanoate[4] (0.49 g, 1.8 mmol) in THF (2 cm^3) was added in one portion. After a further 5 min, the mixture was cooled and poured into pentane (50 cm^3) and the resulting suspension was washed with water (2 × 20 cm^3). The dried organic phase was evaporated: chromatography of the residue over silica gel eluted with diethyl ether–hexane (1:20) gave *methyl* (3R,5Z)-3-[*t-butyl*(*dimethyl*)*siloxy*]*hept*-5-*enoate* **15a** (0.27 g, 55%), $[\alpha]_D$ −28.4° (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 1746; δ_H 0.06 (6 H, s, 2 × SiMe), 0.90 (9 H, s, Bu^t), 1.64 (3 H, br d, *J* 4.5, *Me*C=CH), 2.31 (2 H, br t, *J* 6.3 =CHC*H*$_2$), 2.48 (2 H, d, *J* 6.3, CH_2CO), 3.72 (3 H, s, OMe), 4.26 (1 H, p, *J* 6.3, CHOSi) and 5.33–5.87 (2 H, m, 2 × =CH); *m/z* 241 (6%, $C_{13}H_{25}O_2Si$, M − OMe), 217 (43, $C_{10}H_{21}O_3Si$) and 215 (100, $C_{10}H_{19}O_3Si$, M − Bu^t) [Found: (M^+ − C_4H_9), 215.1113. $C_{10}H_{19}O_3Si$ requires *m/z* 215.1103].

Aq. hydrogen fluoride (7.5 cm^3 of a 40% solution) was added dropwise to a stirred solution of the foregoing silyl ether **15a** (0.51 g, 1.8 mmol) in acetonitrile (15 cm^3) maintained at 0 °C. After 3 h at this temperature, the solvent was removed under reduced pressure and the residue was partitioned between diethyl ether (60 cm^3) and water (20 cm^3). The separated organic phase was dried and concentrated, then chromatographed over silica gel with diethyl ether–hexane (3:7) as eluent to give *methyl* (3R,5Z)-3-*hydroxyhept*-5-*enoate* **15b** (0.19 g, 67%) as an oil, $[\alpha]_D$ −19.4° (*c* 0.98, $CHCl_3$); ν_{max}/cm^{-1} 3461, 1736 and 1657; δ_H(400 MHz) 1.64 (3 H, td, *J* 6.7 and 1.5, MeCH=), 2.26 (1 H, dt, *J* 14.5 and 6.4, C*H*$_a$H$_b$CH=), 2.33 (1 H, dt, *J* 14.5 and 6.5, CH$_a$*H*$_b$CH=), 2.45 (1 H, dd, *J* 16.4 and 8.8, C*H*$_a$H$_b$CO), 2.54 (1 H, dd, *J* 16.4 and 3.5, CH$_a$*H*$_b$CO), 2.96 (1 H, br s, OH), 3.72 (3 H, s, OMe), 4.07 [1 H, dddd, *J* 8.8, 6.4, 6.3 and 3.5, CH(OH)], 5.41–5.46 (1 H, m, =CH) and 5.65 (1 H, dtq, *J* 10.9, 6.7 and 1.2, =CH); δ_C 13.0 (Me), 34.0, 40.5 (both CH_2), 51.8 (OMe), 67.95 [CH(OH)], 125.25, 127.4 (both =CH) and 173.3 (CO); *m/z* 140 (15%, $C_8H_{12}O_2$, M − H_2O), 103 (100, $C_4H_7O_3$), 81 (17, C_6H_9) and 71 (73, $C_3H_3O_2$) [Found: (M^+ − H_2O), 140.0810. $C_8H_{12}O_2$ requires *m/z* 140.0837].

The sample contained 15% of the corresponding (*E*)-isomer.

Aq. 2 mol dm^{-3} sodium hydroxide (5 cm^3) was added to the foregoing ester **15b** (0.18 g) and the resulting mixture was stirred at ambient temperature for 16 h. After being washed with chloroform (2 × 5 cm^3), the resulting solution was acidified to pH 2 (2 mol dm^{-3} hydrochloric acid) and continuously extracted with chloroform for 24 h to give the *title acid* **16c** (0.16 g, 95%) as an oil, $[\alpha]_D$ −20.9° (*c* 0.76, $CHCl_3$); ν_{max}/cm^{-1} 3385 and 1711; *m/z* 126 (23%, $C_7H_{10}O_2$, M − H_2O), 89 (70, $C_3H_5O_3$), 71 (100, $C_3H_3O_2$), 58 (30, C_3H_6O), 56 (92, C_4H_8) and 55 (26, C_4H_7) [Found: (M^+ − H_2O), 126.0675. $C_7H_{10}O_2$ requires *m/z* 126.0680].

(3R,5Z)-3-[*t-Butyl*(*dimethyl*)*siloxy*]*hept*-5-*enoic Acid* **16d**.—Imidazole (0.31 g, 4.6 mmol) was added to a stirred solution of the foregoing hydroxy acid **16c** (0.092 g, 0.7 mmol) and t-butyl(dimethyl)silyl chloride (0.25 g, 1.6 mmol) in dry DMF (2 cm^3). The resulting solution was kept at 45 °C for 4 h, cooled, diluted with pentane (40 cm^3) and washed with water (2 × 10 cm^3) then dried, and concentrated under reduced pressure to afford the crude silyl ester (0.23 g) as an oil, ν_{max}/cm^{-1} 1724; δ_H 0.05 (6 H, s, 2 × MeSi), 0.24 (6 H, s, 2 × MeSi), 0.85 (9 H, s, Bu^t), 0.90 (9 H, s, Bu^t), 1.57 (3 H, br d, *J* 5.4, *Me*CH=), 2.24 (2 H, br t, *J* 6.3, =CHC*H*$_2$), 2.81 (2 H, d, *J* 5.4, CH_2CO), 4.13 [1 H, p, *J* 6.3, CH(OSi)] and 5.23–5.71 (2 H, m, 2 × =CH).

The crude ester (0.23 g) was stirred at ambient temperature with potassium carbonate (0.23 g) in a mixture of methanol (7 cm^3), water (3 cm^3) and THF (3 cm^3) for 1 h. The resulting mixture was concentrated under reduced pressure to *ca.* 3 cm^3, cooled to 0 °C, acidified to pH 4 with aq. potassium hydrogen sulphate, and finally extracted with diethyl ether (3 × 10 cm^3). The combined extracts were dried and evaporated. Chromatography of the residue over silica gel with diethyl ether–hexane (3:7) as the eluent then gave the *acid* **16d** (0.12 g, 79%) as an oil, $[\alpha]_D$ − 16.4° (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3085, 2690 and 1703; δ_H 0.04 (3 H, s, MeSi), 0.06 (3 H, s, MeSi), 0.86 (9 H, s, Bu^t), 1.60 (3 H, br d, *J* 6.3, *Me*CH=), 2.27 (2 H, br t, *J* 6.3, =CHC*H*$_2$), 2.46 (2 H, d, *J* 6.3, CH_2CO), 4.17 [1 H, p, *J* 6.3, CH(OSi)], 5.13–5.78 (2 H, m, 2 × =CH) and 12.20 (1 H, br s, OH); *m/z* 203 (20%, $C_9H_{19}O_3Si$, M − C_4H_7), 201 (42, $C_9H_{17}O_3Si$, M − Bu^t), 159 (22,

$C_7H_{15}O_2Si$), 101 (30, C_4H_9OSi) and 75 (100, C_2H_7OSi) [Found: ($M^+ - C_4H_7$), 203.1081. $C_9H_{19}O_3Si$ requires *m/z* 203.1101].

(3R,5Z)-3-(*Triisopropylsiloxy*)*dec*-5-*enoic Acid* **16e**.—A solution of potassium hydroxide (0.26 g, 4.7 mmol) in methanol (7 cm^3) was added to the ester **14** (0.28 g, 0.8 mmol) and the resulting solution was stirred at ambient temperature for 16 h. The solvent was then evaporated off under reduced pressure and the residue was dissolved in water, the solution acidified to pH 2 (2 mol dm^{-3} hydrochloric acid), and finally extracted with diethyl ether (3 × 25 cm^3). The combined extracts were concentrated and the residue was purified by chromatography over silica gel with diethyl ether–hexane (1:10) as eluent to give the *title acid* **16e** (0.23 g, 86%) as an oil, $[\alpha]_D$ −10.2° (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2690 and 1701; δ_H 0.90 (3 H, br t, *J* 6.3, *Me*CH_2), 1.11 (21 H, br s, Pr$^i_3$Si), 1.20 (4 H, m, 2 × CH_2), 1.93–2.25 (2 H, m, C*H*$_2$=CH), 2.46 [2 H, br t, *J* 6.3, =CHC*H*$_2$CH(O)], 2.63 (2 H, d, *J* 6.3, CH_2CO), 4.43 [1 H, p, *J* 6.3, CH(OSi)], 5.32–5.79 (2 H, m, 2 × =CH) and 10.17 (1 H, br s, OH); *m/z* 299 (87%, $C_{16}H_{31}O_3Si$, M − C_3H_7), 201 (20, $C_9H_{17}O_3Si$), 157 (44, $C_8H_{17}OSi$) and 131 (80, $C_6H_{15}OSi$) [Found: ($M^+ - C_3H_7$), 299.2017. $C_{16}H_{31}O_3Si$ requires *m/z* 299.2041].

(4R,6R)- *and* (4R,6S)-6-*Ethyl*-4-*hydroxy*-3,4,5,6-*tetrahydro*-2H-*pyran*-2-*one* **19** *and* **20a**.—*Method* (*a*). *From* (3R,5Z)-3-*hydroxyhept*-5-*enoic acid* **16c**. Anhydrous sodium hydrogen carbonate (1.08 g, 13 mmol) was added to a stirred solution of (3*R*,5*Z*)-3-hydroxyhept-5-enoic acid **16c** (0.062 g, 0.4 mmol) in acetonitrile (1.4 cm^3) maintained at 0 °C and the resulting suspension was stirred for 5 min. Iodine (0.33 g, 1.3 mmol) was then added and the mixture was stirred at 0 °C for 3 h in the dark. The mixture was then diluted with diethyl ether (50 cm^3) and the solution was then washed successively with aq. sodium thiosulphate and brine. Evaporation of the dried organic phase gave a mixture of *trans*- and *cis*-iodo lactone **17c** and **18c** (0.062 g, 54%) in the ratio 71:29, as an oil, ν_{max}/cm^{-1} 1720; δ_H(400) 1.73–1.97 (1 H, m, *cis*- and *trans*-5-H), 1.97 (0.87 H, d, *J* 7.1, *cis*-Me), 2.01 (2.13 H, d, *J* 6.9, *trans*-Me), 2.16 (0.71 H, m, *trans*-5-H), 2.45–2.56 (0.58 H, m, *cis*-3- and 5-H), 2.70 (1.42 H, d, *J* 3.3, *trans*-3-H_2), 2.93 (0.29 H, dd, *J* 17.2 and 4.8, *cis*-3-H), 3.91 (1 H, br s, OH), 3.95 (0.71 H, dt, *J* 11.7 and 3.4, *trans*-6-H_{ax}), 4.24–4.30 (1.29 H, m, *cis*- and *trans*-CHI and *cis*-6-H_{ax}), 4.34 (0.29 H, m, $w_{\frac{1}{2}}$ *ca.* 16 Hz, *cis*-4-H) and 4.45 (0.71 H, p, *J* 3.3, *trans*-4-H_{eq}); *m/z* 143 (7%, $C_7H_{11}O_3$, M − I), 125 (58, $C_7H_9O_2$, M − I − H_2O), 83 (10, C_5H_7O) and 57 (100, C_3H_5O) [Found: (M^+ − I − H_2O), 125.0593. $C_7H_9O_2$ requires *m/z* 125.0602].

The mixture of iodo lactones **17c** and **18c** (0.065 g, 0.2 mmol) and tributyltin hydride (0.21 g, 0.7 mmol) were refluxed together in THF (1 cm^3) for 3 h and then the solvent was removed under reduced pressure. ^{1}H NMR analysis of the residue showed the same 70:30 isomer ratio as in the starting iodo lactones. Subsequent chromatography over silica gel eluted with diethyl ether gave (i) the (4R,6R)-trans-*lactone* **19** (0.0145 g, 42%), the less polar isomer, as an oil, $[\alpha]_D$ + 20.5° (*c* 0.64, $CHCl_3$); ν_{max}/cm^{-1} 3525 and 1716; δ_H(400 MHz) 1.02 (3 H, t, *J* 7.5, *Me*CH_2), 1.62–1.81 (3 H, m, MeC*H*$_2$ and 5-H_{ax}), 1.97 (1 H, dddd, *J* 14.4, 3.9, 3.1 and 1.6, 5-H_{eq}), 2.45 (1 H, br s, OH), 2.65 (1 H, ddd, *J* 17.6, 3.6 and 1.6, 3-H_{eq}), 2.75 (1 H, dd, *J* 17.6 and 4.9, 3-H_{ax}), 4.41 (1 H, m, $w_{\frac{1}{2}}$ 10.6 Hz, 4-H_{eq}) and 4.67 (1 H, dddd, *J* 11.4, 6.9, 5.5 and 3.1, 6-H_{ax}); δ_C 9.3 (Me), 28.4, 35.3 and 38.6 (all CH_2), 62.6 and 77.2 (both CH) and 170.9 (CO); *m/z* 144 (1%, $C_7H_{12}O_3$, M^+), 115 (70, $C_5H_7O_3$, M − Et), 97 (53, $C_5H_5O_2$, M − Et − H_2O), 73 (99, $C_3H_5O_2$) and 43 (100, C_2H_3O) (Found: M^+, 144.0780. $C_7H_{12}O_3$ requires M, 144.0786), and (ii) the (4R,6S)-cis-*lactone* **20a** (0.0045 g, 13%) as an oil, ν_{max} 3380 and 1720; δ_H(400 MHz) 1.01 (3 H, t, *J* 7.5, *Me*CH_2), 1.58 (1 H, ddd, *J* 13.6, 11.8 and 9.4, 5-H_{ax}), 1.60–1.83 (3 H, m, CH_3CH_2 and OH), 2.26 (1 H, dddd, *J* 13.6, 5.3, 3.0 and 1.4, 5-H_{eq}), 2.46 (1 H, dd, *J* 17.1 and 8.0, 3-H_{ax}), 2.92 (1 H, ddd, *J* 17.1, 6.0 and 1.4, 3-H_{eq}), 4.15 (1 H, dddd, *J* 9.4, 8.0, 6.0 and 5.3, 4-H_{ax}) and 4.25 (1 H, dddd, *J* 11.8, 6.6, 5.5 and 3.0, 6-H_{ax}); δ_C 9.3 (Me), 28.6, 37.5 and 39.6 (all CH_2), 64.1 and 78.5 (both CH) and 170.8 (CO); *m/z* 144 (4%, $C_7H_{12}O_3$, M^+), 115 (100, $C_5H_7O_3$, M − Et), 97 (58, $C_5H_5O_2$, M − Et − H_2O) and 73 (90, $C_3H_5O_2$) (Found: M^+, 144.0786).

Method (*b*). *From* (3R,5Z)-3-[*t*-*butyl*(*dimethyl*)*siloxy*]*hept*-5-*enoic acid* **16d**. Iodolactonization as described above but of the silyl ether **16d** (0.11 g, 0.5 mmol) gave the iodo lactones **17d** and **18d** (0.117 g, 77%), in a *trans*:*cis* ratio of *ca.* 6:1, which were not separated. The mixture showed ν_{max}/cm^{-1} 1730; δ_H 0.06 (6 H, s, 2 × MeSi), 0.85 (9 H, s, Bu^t), 1.70–2.05 (m, Me and 5-H), 2.39–2.63 (m, 3- and 5-H), 2.76–2.83 (m, 3-H) and 4.14–4.33 (m, CHI, CHOSi and 6-H).

Deiodination was carried out exactly as described below with tributyltin hydride and was followed by removal of the silyl protecting group with 40% aq. HF as in the following reaction, but for 3 h at 0 °C. The overall yield for the two steps was 58% on a 70 mg scale after chromatography. The final product had a *trans*:*cis* ratio of 86:14, and subsequent separation by column chromatography gave samples of the lactones **19** and **20a** which showed identical spectral data with those given in method (a).

(4R,6S,1′S)-6-(1′-*Iodopentyl*)-4-(*triisopropylsiloxy*)-3,4,5,6-*tetrahydro*-2H-*pyran*-2-*one* **17e**.—Anhydrous sodium hydrogen carbonate (0.91 g, 11 mmol) was added to a stirred solution of the acid **16e** (0.12 g, 0.4 mmol) in dry acetonitrile (1.2 cm^3) maintained at 0 °C. After 5 min, iodine (0.28 g, 1.1 mmol) was added and the resulting mixture was stirred at 0 °C for a further 3 h in the dark. After dilution with diethyl ether (50 cm^3), the reaction mixture was washed successively with aq. sodium thiosulphate and brine, and was then dried and evaporated to leave the sensitive *iodolactone* **17e** (0.15 g, 93%), which showed ν_{max}/cm^{-1} 1734; δ_H(400 MHz) 0.92 (3 H, t, *J* 7.0, *Me*CH_2), 1.06–1.60 (21 H, m, Pr$^i_3$Si), 1.79–2.09 (7 H, m, 3 × CH_2 and 5-H_a), 2.12 (1 H, m, 5-H_b), 2.60–2.70 (2 H, m, 3-H_2), 4.05–4.18 (1 H, m, CHI) and 4.41–4.50 (2 H, m, 4- and 6-H); δ_C 12.1 and 12.4 (both CH), 17.8 and 18.0 (both Me), 21.9, 31.9, 35.8 and 35.9 (all CH_2), 39.1 (CH), 39.4 (CH_2), 63.6 and 77.6 (both CH) and 169.6 (CO); *m/z* 425 (5%, $C_{16}H_{30}IO_3Si$, M − C_3H_7), 297 (10, $C_{16}H_{29}O_3Si$, M − C_3H_7 − HI) and 157 (100, $C_8H_{17}OSi$) [Found: (M^+ − C_3H_7), 425.1009. $C_{16}H_{30}IO_3Si$, requires *m/z* 425.1011].

Also visible was *ca.* 10% of a second isomer [(4*R*,6*R*,1′*R*)-**18e**], with characteristic resonances at δ_H 2.46–2.55 (m), 2.84–2.98 (m), 3.98–4.05 (m) and 4.26–4.40 (m).

(4R,6R)-4-*Hydroxy*-6-*pentyl*-3,4,5,6-*tetrahydro*-2H-*pyran*-2-*one* **21b**.—A solution of tributyltin hydride (0.78 g, 2.7 mmol) in dry THF (4 cm^3) was added to the foregoing iodo lactones **17e** and **18e** (0.39 g, 0.9 mmol) and the resulting solution was refluxed for 3 h, then cooled and evaporated. Chromatography of the residue over silica gel eluted with diethyl ether–hexane (1:10) afforded (i) the *cis*-siloxy lactone **20b** (0.044 g, *ca.* 15%) which showed δ_H 0.90 (3 H, t, *J* 7.0, *Me*CH_2), 1.07 (21 H, br s, Pr$^i_3$Si), 1.14–2.40 (10 H, m), 2.44 (1 H, dd, *J* 17.1 and 8.1, 3-H_{ax}), 2.89 (1 H, ddd, *J* 17.1, 6.7, and *ca.* 1.5, 3-H_{eq}) and 3.39–4.46 (2 H, m, 4- and 6-H), contaminated with *ca.* 20% of tin residues and (ii) the *trans*-siloxylactone **21a** (0.24 g, 86%), δ_H 0.90 (3 H, t, *J* 7.0, *Me*CH_2), 1.08 (21 H, br s, Pr$^i_3$Si), 1.18–2.16 (10 H, m), 2.64 (2 H, d, *J* 3.6, 3-H_2), 4.34–4.56 (1 H, m, 4-H_{eq}) and 4.56–4.96 (1 H, m, 6-H_{ax}), contaminated with *ca.* 10% of tin residues.

The crude *trans*-siloxy lactone **21a** (0.233 g, 0.68 mmol) was dissolved in acetonitrile (20 cm^3) and the solution was stirred at 0 °C while aq. hydrogen fluoride (4 cm^3 of a 40% solution) was added dropwise. The resulting solution was stirred at this temperature for 7 h and was then concentrated under reduced

pressure and the residue was partitioned between water (20 cm^3) and chloroform (40 cm^3). The separated organic phase was dried and evaporated to provide a residue, which was chromatographed over silica gel with diethyl ether as eluent to give the hydroxylactone **21b** (0.11 g, 87%) as an oil, $[\alpha]_D$ + 29.4° (*c* 1.4, $CHCl_3$) {lit.,[6] $[\alpha]_D$ +27.4° (*c* 11.7, $CHCl_3$)}; ν_{max}/cm^{-1} 3420 and 1718; δ_H(400 MHz) 0.90 (3 H, t, *J* 6.9, *Me*CH_2), 1.20–1.74 (8 H, m, 4 × CH_2), 1.73 (1 H, ddd, *J* 14.5, 11.1 and 3.3, 5-H_{ax}), 1.98 (1 H, dddd, *J* 14.5, 3.8, 3.0 and 1.6, 5-H_{eq}), 2.63 (1 H, ddd, *J* 17.7, 3.7 and 1.6, 3-H_{eq}), 2.72 (1 H, dd, *J* 17.7 and 4.9, 3-H_{ax}), 2.81 (1 H, br s, OH), 4.37 (1 H, m, 4-H) and 4.71 (1 H, dddd, *J* 11.1, 7.8, 4.9 and 3.0, 6-H_{ax}); δ_C 14.0 (Me), 22.6, 24.6, 31.6, 35.5, 35.9 and 38.9 (all CH_2), 62.7 and 76.2 (both CH) and 171.4; *m/z* 130 (2%, $C_6H_{10}O_3$), 115 (100, $C_5H_7O_3$), 97 (71, $C_5H_5O_2$) and 73 (94, $C_3H_5O_2$) [Found: ($M^+ - C_5H_{11}$), 115.0407. Calc. for $C_5H_7O_3$: *m/z* 115.0395]. All the foregoing data are in excellent agreement with those reported for the natural material.[6]

(6R)-6-*Pentyl*-5,6-*dihydro*-2H-*pyran*-2-*one* (*Massoialactone*) **11**.—A solution of phosphoryl trichloride (0.064 g, 0.42 mmol) in dry pyridine (0.5 cm^3) was added to a stirred solution of the hydroxy lactone **21b** (0.065 g, 0.34 mmol) in pyridine (1 cm^3) cooled to 0 °C. The cooling bath was then removed and, after 15 min, the mixture was heated to 65 °C and maintained at this temperature for 5 h. The cooled solution was diluted with diethyl ether, washed successively with 2 mol dm^{-3} hydrochloric acid and water, and then dried and evaporated. The residue was pure according to TLC and NMR analysis and was identified as massoialactone **11** (0.054 g, 92%), a pale yellow oil, which showed $[\alpha]_D$ −82.4° (*c* 2.7, $CHCl_3$) (corrected to $[\alpha]_D$ − 105.6° on the basis of an ee of 78% in the starting material) {lit.,[14] $[\alpha]_D$ −109° (*c* 9.1, $CHCl_3$); highest lit. value quoted}; ν_{max}/cm^{-1} 1715; δ_H(400 MHz) 0.90 (3 H, *J* 6.8, *Me*CH_2), 1.26–1.86 (8 H, m, 4 × CH_2), 2.31 (1 H, dddd, *J* 18.3, 10.8, 3.0 and 2.4, 5-H_a), 2.37 (1 H, ddt, *J* 18.3, 5.3 and 1.2, 5-H_b), 4.43 (1 H, ddt, *J* 10.8, 7.3 and 5.3, 6-H), 6.01 (1 H, ddd, *J* 9.7, 2.4 and 1.2, 3-H) and 6.90 (1 H, ddd, *J* 9.7, 5.4 and 3.0, 4-H); δ_H 13.9, (Me), 22.5, 24.5, 29.4, 31.5 and 34.8 (all CH_2), 78.0, 121.3 and 145.2 (all CH), and 164.6 (CO); *m/z* 168 (2%, $C_{10}H_{16}O_2$, M^+), 97 (100, $C_5H_5O_2$, $M - C_5H_{11}$) and 68 (94, C_4H_4O) (Found: M^+, 168.1143. Calc. for $C_{10}H_{16}O_2$: M, 168.1149). These data are identical in all respects with those of the natural material.[7–14]

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References

1 For reviews, see A. Endo, *J. Med. Chem.*, 1985, **28**, 401; L. Vega and S. Grundy, *J. Am. Med. Assoc.*, 1987, **257**, 33.
2 For a comprehensive review see T. Rosen and C. H. Heathcock, *Tetrahedron*, 1986, **42**, 4909. For some recent synthetic studies, see D. L. J. Clive, K. S. Keshava Murthy, A. G H. Wee, J. S. Prasad, G. V. J. Da Silva, M. Majewski, P. C. Anderson, R. D. Haugen and L. D. Heerze, *J. Am. Chem. Soc.*, 1988, **110**, 6914; S. D. Burke, K. Takeuchi, C. W. Murtiashaw and D. W. M. Liang, *Tetrahedron Lett.*, 1989, **30**, 6299; A. E. DeCamp, T. R. Verhoeven and I. Shinkai, *J. Org. Chem.*, 1989, **54**, 3207.
3 G. E. Stokker, W. F. Hoffman, A. W. Alberts, E. J. Cragoe, Jr., A. A. Deana, J. L. Gilfilan, J. W. Huff, F. C. Novello, J. D. Prugh, R. L. Smith and A. K. Willard, *J. Med. Chem.*, 1985, **28**, 347; W. F. Hoffman, A. W. Alberts, E. J. Cragoe, Jr., A. A. Deana, B. E. Evans, J. L. Gilfilan, N. P. Gould, J. W. Huff, F. C. Novello, J. D. Prugh, K. E. Rittle, R. L. Smith, G. E. Stokker and A. K. Willard, *J. Med. Chem.*, 1986, **29**, 159; G. E. Stokker, A. W. Alberts, P. S. Anderson, E. J. Cragoe, Jr., A. A. Deana, J. L. Gilfilan, J. Hirshfield, W. J. Holtz, W. F. Hoffman, J. W. Huff, T. J. Lee, F. C. Novello, J. D. Prugh, C. S. Rooney, R. L. Smith and A. K. Willard, *J. Med. Chem.*, 1986, **29**, 170, and references therein.
4 F. Bennett, D. W. Knight and G. Fenton, *J. Chem. Soc., Perkin Trans. 1*, in the press; F. Bennett and D. W. Knight, *Tetrahedron Lett.*, 1988, **29**, 4625.
5 Y. Guindon, C. Yoakin, M. A. Bernstein and H. E. Morton, *Tetrahedron Lett.*, 1985, **26**, 1185; B. D. Roth and W. H. Roark, *Tetrahedron Lett.*, 1988, **29**, 1255.
6 R. F. Vesonder, F. H. Stodola and W. K. Rohwedder, *Can. J. Biochem.*, 1972, **50**, 363.
7 L. Crombie and P. A. Firth, *J. Chem. Soc. C*, 1968, 2852.
8 M. Meijer, *Recl. Trav. Chim. Pays-Bas*, 1940, **59**, 191.
9 K. Mori, *Agric. Biol. Chem.*, 1976, **40**, 1617, and references therein.
10 T. Hashizume, N. Kikuchi, Y. Sasaki and I. Sasata, *Agric. Biol. Chem.*, 1968, **32**, 1306.
11 R. Kaiser and D. Lamparsky, *Tetrahedron Lett.*, 1976, 1659.
12 G. W. K. Cavill, D. V. Clark and F. B. Whitfield, *Aust. J. Chem.*, 1968, **21**, 2819.
13 L. Crombie, *J. Chem. Soc.*, 1955, 1007, 2535; S. Abe and K. Sato, *Bull. Chem. Soc. Jpn.*, 1956, **29**, 88; A. Nobuhara, *Agric. Biol. Chem.*, 1968, **32**, 1016.
14 W. K. Pirkle and P. E. Adams, *J. Org. Chem.*, 1980, **45**, 4117.
15 For a preliminary report, see F. Bennett, D. W. Knight and G. Fenton, *Heterocycles*, 1989, **29**, 639.
16 P. A. Bartlett, D. P. Richardson and J. Myerson, *Tetrahedron*, 1984, **40**, 2317.

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