Stereocontrol in organic synthesis using silicon-containing compounds. A synthesis of (−)-tetrahydrolipstatin using the alkylation of a β-silyl ester and the hydroboration of an allylsilane

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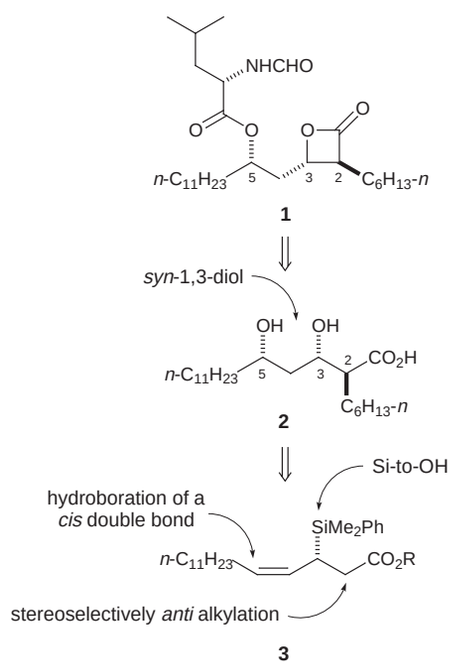
Conjugate addition of bis(*Z*-tridec-1-enyl)cuprate *Z*-10 to (5*S*)-1-[(*Z*)-3′-dimethyl(phenyl)silylprop-2-enoyl]-5-(trityloxymethyl)pyrrolidin-2-one *Z*-6 gave the 3*R*-imide *Z*-12. Subsequent enolate *n*-hexylation of the benzyl ester *Z*-13a derived from this imide gave the 2*R*,3*S*-ester *Z*-14a. Reduction of the ester group and protection of the alcohol as its TBDMS group gave the allylsilane (*Z*)(7*R*,8*S*)-7-(*tert*-butyldimethylsilyloxymethyl)-8-dimethyl(phenyl)silylhenicos-9-ene *Z*-15. Hydroboration–oxidation gave the 7*R*,8*S*,10*S*-alcohol 16. Protection of the C-10 hydroxy as its benzyl ether, removal of the silyl protecting group and oxidation gave (2*R*,3*S*,5*S*)-5-benzyloxy-3-dimethyl(phenyl)silyl-2-hexylhexadecanoic acid 19. Silyl-to-hydroxy conversion, β-lactone formation, and hydrogenolysis gave the known alcohol (3*S*,4*S*)-3-hexyl-4-[(*S*)-2′-hydroxytridecyl]oxetan-2-one 22, from which tetrahydrolipstatin 1 was prepared by a conventional esterification. Each of the stereochemistry determining steps, 4 ⟶ *Z*-6, 7 ⟶ *E*-8, *E*-8 ⟶ *Z*-9, *Z*-6 + *Z*-10 ⟶ *Z*-12, *Z*-13a ⟶ *Z*-14a and *Z*-15 ⟶ 16, took place with a remarkably high level of open-chain stereocontrol.

Introduction

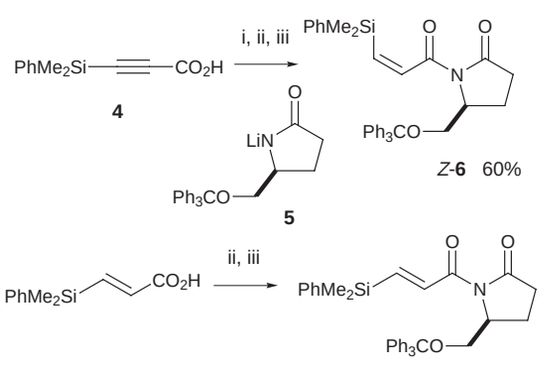
The esterase inhibitor, tetrahydrolipstatin **1**,[1] supports on its carbon skeleton a 1,3-relationship and a 1,2-relationship of exactly the kind that our synthetic methods controlling stereochemistry are able to solve (Scheme 1). The 1,3-relationship between C-3 and C-5 is that of a 1,3-diol **2**, where we must differentiate the two hydroxy groups in order to make the β-lactone without risk of δ-lactone formation. Hydroboration of a *cis* allylsilane **3**, can be expected to set up the masked diol with the correct *syn* relationship,[2] and with the two hydroxy groups about as well differentiated as they could possibly be. The 1,2-relationship between C-2 and C-3 is that which can be achieved by alkylation of an enolate carrying a β-silyl group **3**,[3] and conversion of the phenyldimethylsilyl group into a hydroxy with retention of configuration[4] can be carried out at an appropriate stage, after the C-5 hydroxy has been protected. We therefore need to make the β-silyl ester **3**, or a derivative of it, in an enantiomerically enriched state, for which we also have methods already developed.[5] We published a preliminary account[6] of how we were able to put these methods together to synthesise (−)-tetrahydrolipstatin, and we now report our work in full.



Scheme 1

Results and discussion

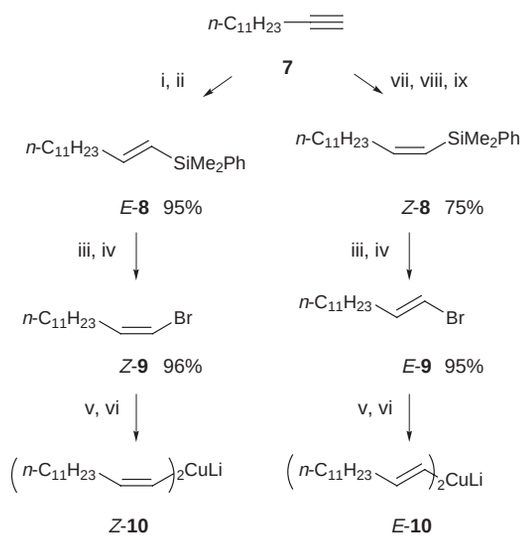
Our method for the control of absolute stereochemistry in the synthesis of β-silyl carbonyl compounds uses either the conjugate addition of a silylcuprate reagent to an α,β-unsaturated imide derived from Koga's chiral auxiliary **5**, or the conjugate addition of a carbon-based cuprate to a β-silylated α,β-unsaturated imide derived from the same auxiliary. In this case only the latter method will work, since we need the double bond between C-4 and C-5, and if it were present in the imide the silylcuprate would attack C-5 instead of C-3. We therefore made the β-silyl α,β-unsaturated imide *Z*-**6** from the acetylenic acid **4** (Scheme 2), choosing the *cis* double bond so that the product of the conjugate addition will be the enantiomer with the natural absolute configuration. We also prepared the *trans* isomer *E*-**6**, which we have made before,[5] in order to have



Scheme 2 *Reagents:* i, H_2, Lindlar; ii, $(COCl)_2$, CH_2Cl_2; iii, **5**

available for analytical purposes the diastereoisomer of the conjugate addition product.

We needed the double bond in the ester **3** to be *cis*, and were particularly happy, given how much of the stereochemistry was to be controlled by silicon to use it to control the double bond geometry too. A completely regioselective and *syn* stereospecific silyl-cupration[7] of the terminal acetylene **7** gave only the *trans* vinylsilane *E*-**8**, and bromodesilylation then gave the *cis* vinyl bromide *Z*-**9**, cleanly with inversion of configuration, as expected (Scheme 3).[8] We then prepared the cuprate *Z*-**10** from

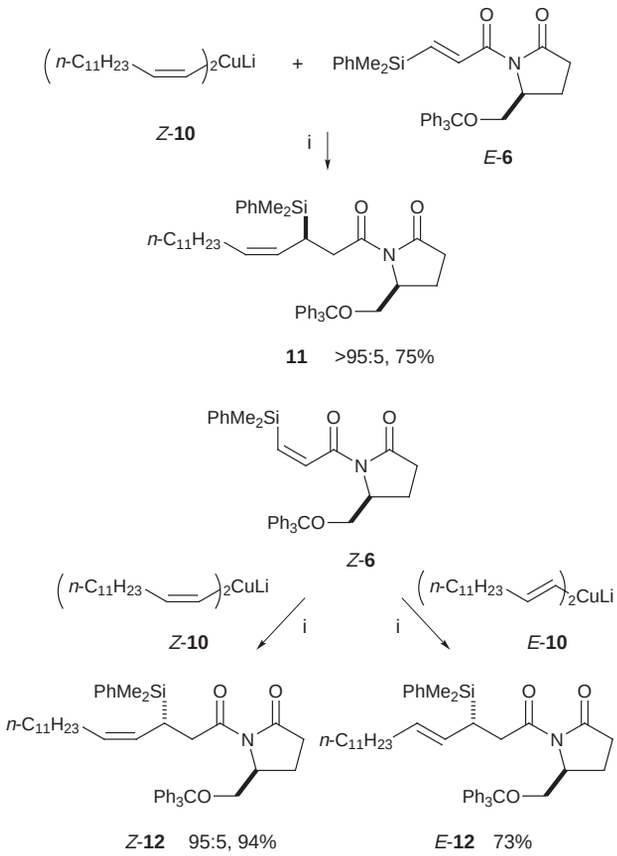


Scheme 3 *Reagents*: i, $(PhMe_2Si)_2CuLi{\cdot}LiCN$; ii, NH_4Cl, H_2O; iii, Br_2; iv, NaOMe; v, Li, Et_2O; vi, 0.5 equiv. $CuBr{\cdot}SMe_2$; vii, BuLi, $PhMe_2SiCl$; viii, $(c\text{-}C_6H_{11})_2BH$; ix, AcOH

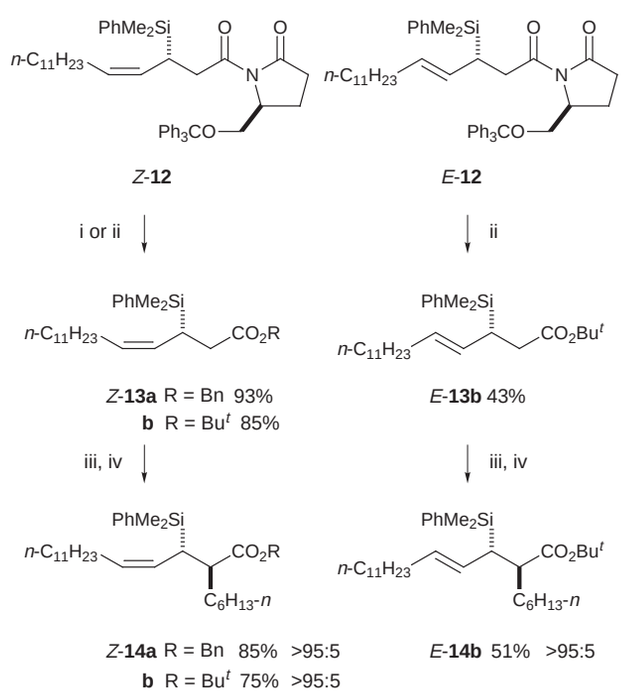
the bromide by halogen–lithium exchange, and coordination of two of the vinyllithium groups to one copper(I) ion. For comparisons later on, we also wanted the *trans* isomer *E*-**10**, which we made by the complementary route using *syn* reduction of the silylated acetylene to give the *cis* vinylsilane *Z*-**8**, and bromination, again with inversion, to give the *trans* vinyl bromide *E*-**9**.

For reference, we carried out the conjugate addition of the vinylcuprate *Z*-**10** to the *trans* β-silylenone *E*-**6** that we have used before. With magnesium bromide to coordinate the two oxygen atoms of the imide, the nucleophile attacks *anti* to the trityloxymethyl group to give as the only detectable product (>95 : 5, ^{1}H NMR) the diastereoisomer **11** (Scheme 4). For the synthesis itself, we carried out the conjugate addition of the *cis* vinylcuprate *Z*-**10** to the *cis* β-silylenone *Z*-**6**. Attack *anti* to the trityloxymethyl group now gave largely the diastereoisomer *Z*-**12**, and, since we had both diastereoisomers, we were able to measure (^{1}H NMR) the degree of selectivity reliably (95 : 5). Again for reference purposes, we also prepared the *trans* imide *E*-**12** from the *trans* vinylcuprate *E*-**10**. This compound appeared (^{1}H NMR) to have the usual high degree of diastereoisomeric purity, but since we did not need to know the degree of enantiomeric purity of this compound reliably, we did not prepare the missing member of this quartet by treating the *trans* imide *E*-**6** with the *trans* vinylcuprate *E*-**10**.

We removed the chiral auxiliary by treating the imide *Z*-**12** with lithium benzyl oxide to give the benzyl ester *Z*-**13a** (Scheme 5), and presumably with the ratio of enantiomers the same as the ratio of diastereoisomers. We were now ready to control the relative stereochemistry between C-2 and C-3 by alkylation of the enolate derived from the ester *Z*-**13a**, which took place, as far as we could tell, with complete selectivity in favour of the *anti* isomer *Z*-**14a**. A vinyl or aryl group attached to the stereogenic centre has frequently been particularly effective in this respect, which is why we chose to deal with this



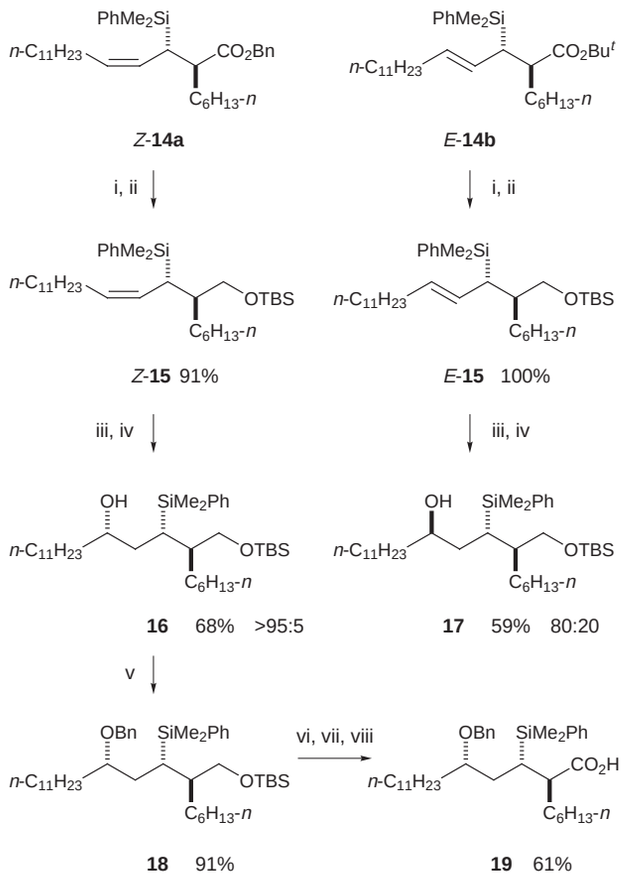
Scheme 4 *Reagent:* i, $MgBr_2$



Scheme 5 *Reagents:* i, BnOLi; ii, Bu^{t}OLi; iii, LDA; v, n-$C_6H_{13}I$

relationship before the hydroboration. We were also hopeful that, with a branched α-carbon, the ester might not be reduced by the hydroborating reagent, but this was not the case—we were unable to avoid reducing the ester group, even after making the *tert*-butyl ester *Z*-**14b** in place of the benzyl. We were able to isolate the diol, but all attempts to interrupt the reduction before it had gone to completion gave us only the alcohol derived from reduction of the ester group, but with the double bond intact. For reference later on, we also prepared the *tert*-butyl ester *E*-**14b**, starting with the *trans* imide *E*-**12**.

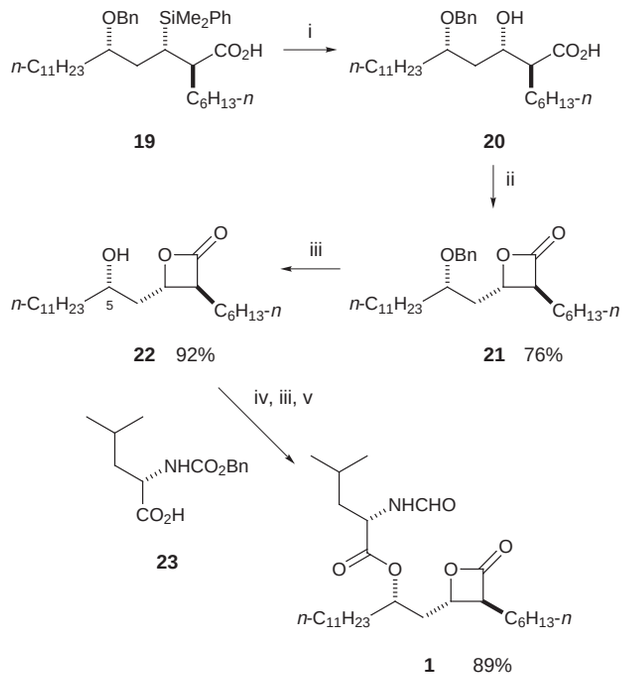
Unable to avoid the over-reduction, we reduced the ester *Z*-**14a** deliberately, protected the primary alcohol group as its *tert*-butyldimethylsilyl ether *Z*-**15**, and then carried out the hydroboration–oxidation reaction, which took place with high (>95 : 5) stereocontrol to give, as far as we could tell, only the *syn* isomer **16** (Scheme 6). Although this was very much the



Scheme 6 *Reagents:* i, $LiAlH_4$; ii, Bu^tMe_2SiCl, imidazole; iii, 9-BBN; iv, NaOH, H_2O_2; v, $BnOC(=NH)CCl_3$, TfOH; vi, TBAF; vii, PDC; viii, Jones

result we expected from our work with similar systems,[2] we checked that we were not being deceived by the diastereoisomer **16** having a ^{1}H NMR spectrum unresolved from its C-5 diastereoisomer. To prepare the 3,5-*anti* isomer **17**, we merely had to reduce the ester *E*-**14b** with a *trans* double bond in place of the *cis*, and subject the silyl ether *E*-**15** to hydroboration–oxidation. Although the stereoselectivity in the hydroboration was, as usual with a *trans* double bond, less impressive, the diastereoisomers proved to be easily distinguished, and there was no trace of any of the distinctive ^{1}H NMR signals of the *anti* isomer **17** in the spectrum of the *syn* isomer **16**. To avoid the formation of a δ-lactone later on, we protected the hydroxy group as its benzyl ether **18**, necessarily using the acid-catalysed method of ether formation,[9] since the standard base-catalysed method would have given a silyl ether by displacement of the phenyl group.[10] We then restored the correct oxidation level to the acid **19**.

The silyl-to-hydroxy conversion gave the β-hydroxy acid **20**, for which we were able to use, for the first time in a synthesis, one of our newly developed one-pot procedures.[4] We did not purify this intermediate but subjected it immediately to benzenesulfonyl chloride[11] to make the β-lactone **21**, and removed the protecting group. We obtained the known lactone **22**,[12] our first crystalline intermediate, in good overall yield for the three steps (Scheme 7). One recrystallisation served to give the enantiomerically and diastereomerically pure material, as judged by its sharp and correct melting point and optical



Scheme 7 *Reagents:* i, $Hg(OAc)_2$, AcOOH, AcOH; ii, $PhSO_2Cl$, Py; iii, H_2, Pd/C; iv, DCC, **23**, DMAP, DMF; v, AcOCHO

rotation. We knew that this recrystallisation was removing the 5% of enantiomer, which must have been present throughout. That one recrystallisation was enough, confirmed that both of the other steps controlling relative stereochemistry, *Z*-**13a** ⟶ *Z*-**14a** and *Z*-**15** ⟶ **16**, must have taken place with a very high level of stereoselectivity, remarkable for the fact that both of them were genuinely open-chain control, without any rings or cyclic transition structures. Curiously, although the alcohol **22** was known, none of the earlier syntheses of tetrahydrolipstatin[13,14,15,16] had used it as an intermediate, preferring instead to use its diastereoisomer at C-5 and a Mitsunobu inversion to attach the leucine residue. Two more recent syntheses have also adopted this tactic.[17] Nevertheless, we, and others since,[18,19] easily esterified the alcohol **22** with the leucine derivative **23** using dicyclohexylcarbodiimide. We then removed the benzyloxycarbonyl protecting group and replaced it with the formyl to give tetrahydrolipstatin **1**, identical (mp, mixed mp, rotation, ^{1}H NMR and mixed ^{1}H NMR) with an authentic sample.

Experimental

General

The standard aqueous work-up referred to below involved the addition of aqueous ammonium chloride (adjusted to pH 8 by the addition of aqueous ammonia) to the reaction mixture, extraction with diethyl ether (2–3 ×), and separation of the ether layers, which were dried (Na_2SO_4) and evaporated under reduced pressure. Ether refers to diethyl ether.

3-Dimethyl(phenyl)silylprop-1-ynoic acid 4

Ethynyldimethyl(phenyl)silane[20] (10 g) in THF (20 cm^3) was added to methylmagnesium chloride (3 mol dm^{-3} in THF, 40 cm^3) at 0 °C. The mixture was stirred at room temperature for 2 h. Carbon dioxide was bubbled through the solution at −23 °C for 30 min and at room temperature for 2 h. Hydrochloric acid (1 mol dm^{-3}, 100 cm^3) was added and the mixture extracted with hexane. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the *acid* **4** (12.6 g, 99%); R_f(hexane–EtOAc, 1 : 1) 0.17 (streak); ν_{max}(film)/cm^{-1} 3500–2400 (OH), 2180 (C≡C), 1680 (CO), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 9.0–8.0 (1 H, br, OH), 7.60–7.32 (5 H, m, Ph)

and 0.51 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 157.4, 134.0, 133.6, 130.1, 128.1, 95.4, 95.0 and −2.0; *m*/*z* 204 (0.4%, M^+), 189 (0.5, M − Me), 161 (25, M − CO_2 + H), 160 (20, M − CO_2), 145 (100, M − CO_2 − Me) and 137 (20, MePhSiOH) (Found: M^+, 204.0618. $C_{11}H_{12}O_2$ requires *M*, 204.0606).

(*Z*)-3-Dimethyl(phenyl)silylprop-1-enoic acid

The acid **4** (12.8 g, 62.7 mmol) was hydrogenated in methanol (100 cm^3) over palladium (10% on $BaSO_4$, 1 g) in the presence of quinoline (20 cm^3) for 3 h. The mixture was filtered over Celite after 1 equivalent of hydrogen (1405 cm^3) had been consumed. Evaporation under reduced pressure gave the *acid* (8.2 g, 64%) as prisms, mp 101–103 °C; R_f(hexane–EtOAc, 1:1) 0.62; $\nu_{max}(CH_2Cl_2)$ 3500–2000 (OH), 1700 (CO), 1600 (C=C), 1248 (SiMe) and 1118 (SiPh); $\delta_H(CDCl_3)$ 11.0 (1 H, br, OH), 7.57–7.32 (5 H, m, Ph), 6.85 (1 H, d, *J* 14.3, SiC*H*=CH), 6.58 (1 H, d, *J* 14.3, SiCH=C*H*) and 0.47 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 172.0, 153.8, 138.7, 135.4, 133.6, 128.9, 127.7 and −2.2; *m*/*z* 206 (0.8%, M^+), 205 (1.5, M − H), 191 (100, M − Me), 137 (20, MePhSiOH), 135 (100, $PhMe_2Si$) and 129 (60, M − Ph) (Found: C, 64.05; H, 6.75; M^+, 206.0747. $C_{11}H_{14}O_2Si$ requires C, 64.05; H, 6.85%; *M*, 206.0763).

(5*S*)-1-[(*Z*)-3′-Dimethyl(phenyl)silylprop-2-enoyl]-5-(trityloxymethyl)pyrrolidin-2-one *Z*-6

Oxalyl chloride (1.53 cm^3) was added to the alkenoic acid (1.67 g) in dichloromethane (15 cm^3). One drop of DMF was added, the mixture warmed to room temperature, stirred for 1 h and the solvent evaporated under reduced pressure. *n*-Butyllithium (1.6 mol dm^{-3} in hexane, 4.6 cm^3) was added to a solution of the lactam[21] (2.68 g) in THF (5 cm^3) at −20 °C to give the lithium salt **5**. After 20 min the mixture was cooled to −78 °C and a solution of the crude acid chloride in THF (10 cm^3) added. The mixture was warmed to room temperature and stirred for 30 min. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 3:1) gave the *amide* (3.68 g, 94%) as prisms, mp 104–106 °C (from hexane); $[a]_D^{20}$ −109.7 (*c* 20.5 in $CHCl_3$); R_f(hexane–EtOAc, 3:1) 0.60; $\nu_{max}(CDCl_3)$ 1733 (CO), 1670 (CO), 1248 (SiMe) and 1112 (SiPh); $\delta_H(CDCl_3)$ 7.88 (1 H, d, *J* 14.1, SiC*H*=CH), 7.61–7.58 (2 H, m, *m*-SiPh), 7.43–7.20 (18 H, m, *o*- and *p*-SiPh and 3 × Ph), 6.78 (1 H, d, *J* 14.1, SiCH=C*H*), 4.44 (1 H, m, CHN), 3.58 (1 H, dd, *J* 3.9 and 9.7, $CH_ACH_BOCPh_3$), 3.15 (1 H, dd, *J* 2.5 and 9.7, $CH_AH_BOCPh_3$), 2.98 (1 H, dt, *J* 17.9 and 10.3, $NCOCH_ACH_B$), 2.50 (1 H, ddd, *J* 17.9, 9.2 and 2.4, $NCOC_ACH_BH_B$), 2.00 (2 H, m, $COCH_2CH_2$), 0.47 (3 H, s, $SiMe_AMe_B$) and 0.44 (3 H, s, $SiMe_AMe_B$); $\delta_C(CDCl_3)$ 176.3, 165.9, 149.5, 143.7, 139.5, 138.0, 133.6, 128.7, 128.6, 128.0, 127.6, 127.2, 87.1, 64.0, 56.6, 33.1, 21.2, −1.7 and −2.3; *m*/*z* 545 (3%, M^+), 530 (30, M − Me), 302 (15, M − CPh_3) and 243 (100, CPh_3) (Found: C, 76.5; H, 6.50; N, 2.50; M^+, 545.2382. $C_{35}H_{35}NO_3Si$ requires C, 77.0; H, 6.45; N, 2.55%; *M*, 545.2386).

Tridec-1-yne 7

Bromoundecane (5.13 cm^3, 22.9 mmol) was added to a slurry of lithium acetylide–ethylenediamine complex (3.06 g, 33 mmol) in DMSO (15 cm^3) at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. Standard aqueous work-up and chromatography (SiO_2, hexane) gave tridecyne[22] (4.13 g, 100%); R_f(hexane) 0.47; ν_{max}(film)/cm^{-1} 3310 (=CH) and 2120 (C=C); $\delta_H(CDCl_3)$ 2.17 (2 H, td, *J* 7.0 and 2.6, CH_2C=CH), 1.93 (1 H, t, *J* 2.6, C=CH), 1.50–1.20 (18 H, m, CH_2) and 0.87 (3 H, t, *J* 6.6, Me); $\delta_C(CDCl_3)$ 84.7, 68.0, 31.9, 29.6 (2), 29.5, 29.4, 29.1, 28.8, 28.5, 22.7, 18.4 and 14.1; *m*/*z* 165 (0.2%, M − Me), 151 (0.5, M − Et), 109 (15, C_8H_{13}), 95 (50, C_7H_{11}), 82 (55, C_6H_{10}), 81 (100, C_6H_9), 67 (70, C_5H_7) and 55 (50, C_4H_7) (Found: M^+ − Me, 165.1648. $C_{12}H_{21}$ requires *M* − Me, 165.1644).

(*E*)-1-Dimethyl(phenyl)silyltridec-1-ene *E*-8

The silyllithium reagent[23] (1.14 mol dm^{-3} in THF, 73.3 cm^3, 83.6 mmol) was added over 2 min to a slurry of copper(I) cyanide (3.74 g, 41.9 mmol) in THF (50 cm^3) at 0 °C. The mixture was stirred at 0 °C for 20 min and cooled to −78 °C. Tridec-1-yne (5.7 g, 31.7 mmol) was added in ether (15 cm^3) and the mixture stirred 2 h, and for a further 30 min at 0 °C. The reaction was quenched with aqueous ammonium chloride and filtered over Celite. The aqueous layer was extracted with ether, and the organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography (SiO_2, hexane) gave the *vinylsilane* (10.5 g, 95%); R_f(hexane) 0.51; ν_{max}(film)/cm^{-1} 1610 (C=C), 1245 (SiMe) and 1110 (SiPh); $\delta_H(CDCl_3)$ 7.54–7.32 (5 H, m, Ph), 6.12 (1 H, dt, *J* 18.5 and 6.2, SiCH=C*H*), 5.74 (1 H, dt, *J* 18.5 and 1.4, SiC*H*=CH), 2.13 (2 H, m, CH=CHCH_2), 1.40–1.20 (18 H, m, CH_2), 0.88 (3 H, t, *J* 6.6, Me) and 0.31 (6 H, s, $SiMe_2$); *m*/*z* 316 (6%, M^+), 301 (40, M − Me), 162 (30, M − $C_{11}H_{22}$), 161 (30, M − $C_{11}H_{23}$), 135 (50, $PhMe_2Si$) and 121 (100, MePhSiH) (Found: M^+, 316.2572. $C_{21}H_{36}Si$ requires *M*, 316.2586).

(*Z*)-1-Bromotridec-1-ene *Z*-9

Bromine (0.45 cm^3, 8.75 mmol) was added to the vinylsilane ***E*-8** (2.77 g, 8.75 mmol) in dichloromethane (20 cm^3) at −78 °C and stirred for 10 min. Sodium sulfite (1 g) and methanol (10 cm^3) were added at −78 °C and the mixture stirred for 10 min. The still cold mixture was poured into saturated aqueous sodium sulfite and extracted with pentane. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Freshly prepared sodium methoxide (1 mol dm^{-3} in MeOH, 11 cm^3) was added to the crude dibromide in methanol (10 cm^3) at 0 °C. The solution was stirred at 0 °C for 1 h and at room temperature for 2 h. Standard aqueous work-up and chromatography (SiO_2, hexane) gave the *vinyl bromide* (2.19 g, 96%); R_f(hexane) 0.64; ν_{max}(film)/cm^{-1} 1623 (C=C); $\delta_H(CDCl_3)$ 6.12 (1 H, dt, *J* 6.9 and 1.2, CH=C*H*Br), 6.07 (1 H, q, *J* 6.9, C*H*=CHBr), 2.17 (2 H, m, CH_2C=CHBr), 1.40–1.20 (18 H, m, CH_2) and 0.87 (3 H, t, *J* 6.4, Me); *m*/*z* 260 (5%, M^+), 162 (5, M − C_8H_{16}), 97 (65, C_7H_{13}), 83 (80, C_6H_{11}), 69 (75, C_5H_9), 57 (100, C_4H_9) and 55 (70, C_4H_7) (Found: M^+ 260.1149. $C_{13}H_{25}Br$ requires *M*, 260.1139).

1-Dimethyl(phenyl)silyltridec-1-yne

Tridec-1-yne (2.0 g) was stirred with butyllithium (1.6 mol dm^{-3}, 7.5 cm^3) in THF (10 cm^3) for 30 min, and then refluxed with chlorodimethyl(phenyl)silane (1.8 g) for 18 h. Standard work-up gave the *ethynylsilane* (3.04 g, 86%); R_f(hexane) 0.32; ν_{max}(film)/cm^{-1} 2170 (C=C), 1250 (SiMe) and 1115 (SiPh); $\delta_H(CDCl_3)$ 7.63–7.34 (5 H, m, Ph), 2.26 (2 H, t, *J* 7.0, CH_2C=C), 1.50 (2 H, m, CH_2CH_2C=C), 1.40–1.20 (16 H, m, CH_2), 0.88 (3 H, t, *J* 6.6, Me) and 0.38 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 137.8, 133.7, 129.3, 127.8, 109.7, 82.3, 32.0, 29.7 (×2), 29.6, 29.4, 29.2, 28.9, 28.7, 22.8, 20.0, 14.2 and −0.5; *m*/*z* 314 (0.1%, M^+), 299 (60, M − Me), 135 (100, $PhMe_2Si$) and 121 (50, MePhSiH) (Found: M^+, 314.2454. $C_{21}H_{34}Si$ requires *M*, 314.2430).

(*Z*)-1-Dimethyl(phenyl)silyltridec-1-ene *Z*-8

The ethynylsilane (2.34 g) and dicyclohexylborane (8 mmol) were stirred in THF (7 cm^3) at room temperature for 2 h. Acetic acid (1.2 cm^3) was added and the mixture stirred for a further 1 h. Water was added, and the organic layer washed with aqueous sodium hydrogen carbonate (saturated, 100 cm^3), dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography of the residue [SiO_2, light petroleum (bp 30–40 °C)] gave the *vinylsilane* (2.04 g, 87%); R_f(hexane) 0.49; ν_{max}(film)/cm^{-1} 1605 (C=C), 1250 (SiMe) and 1110 (SiPh); $\delta_H(CDCl_3)$ 7.56–7.31 (5 H, m, Ph), 6.42 (1 H, dt, *J* 14 and 7.4, SiCH=C*H*), 5.61 (1 H, dt, 14 and 1.1, SiC*H*=CH), 2.00 (2 H, m, CH_2CH=CH), 1.25 (18 H, m, CH_2), 0.88 (3 H, t, *J* 6.6, Me) and 0.37 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 151.1, 139.8, 133.7, 128.8, 127.7, 126.4, 33.8, 32.0, 29.7 (×2), 29.6 (×2), 29.5, 29.4, 29.3, 22.7, 14.1 and −0.8; *m*/*z* 316 (21%, M^+), 301 (50, M − Me), 162 (50, M − $C_{11}H_{22}$), 161 (50, M − $C_{11}H_{23}$), 135 (85, $PhMe_2Si$) and

121 (100, MePhSiH) (Found: M^+, 316.2577. $C_{21}H_{36}Si$ requires *M*, 316.2586).

(*E*)-1-Bromotridec-1-ene *E*-9

This was prepared in the same way as the vinyl bromide *Z*-**9** from the vinylsilane *Z*-**8** (1.93 g) to give the *vinyl bromide* (1.62 g, 95%); R_f(hexane) 0.61; ν_{max}(film)/cm^{-1} 1620 (C=C) and 930 (*trans*-CH=CH); δ_H($CDCl_3$) 6.16 (1 H, dt, *J* 13.5 and 7.0, C*H*=CHBr), 5.99 (1 H, dt, *J* 13.5 and 1.2, CH=C*H*Br), 2.00 (2 H, m, CH_2CH=CH), 1.37–1.20 (18 H, m, CH_2) and 0.87 (3 H, t, *J* 6.5, Me); δ_C($CDCl_3$) 138.3, 104.0, 32.9, 31.9, 29.63 (×2), 27.56, 29.4, 29.3, 29.0, 28.6, 22.7 and 14.1; *m*/*z* 260 (3%, M^+), 162 (3, M − C_7H_{14}), 148 (5, M − C_8H_{16}), 97 (60, C_7H_{13}), 83 (70, C_6H_{11}), 69 (75, C_5H_9), 57 (100, C_4H_9) and 55 (70, C_4H_7) (Found: M^+, 260.1122. $C_{13}H_{25}Br$ requires *M*, 260.1140).

(5*S*)-1-[(*Z*)-(3′*R*)-3′-Dimethyl(phenyl)silylhexadec-4′-enoyl]-5-(trityloxymethyl)pyrrolidin-2-one *Z*-12

The vinyl bromide *Z*-**9** (2.95 g, 11.3 mmol) in ether (20 cm^3) was added to lithium wire (containing 1% Na, 300 mg, 13 mmol) at −20 °C and stirred for 3 h. The resulting vinyllithium was added to copper bromide–dimethyl sulfide complex[24] (1.16 g, 5.65 mmol) in THF (32 cm^3) and dimethyl sulfide (16 cm^3) at −40 °C, stirred for 30 min and cooled to −78 °C. A slurry of the lactam *Z*-**6** (2.43 g, 4.45 mmol) and anhydrous magnesium bromide[25] (4.36 g) in THF (30 cm^3) was added very slowly to the cuprate. After complete addition, the mixture was stirred at −78 °C for 1 h and warmed to 0 °C over 90 min. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 20:1 and then 10:1) gave an inseparable mixture (5:95) of **11** and the *allylsilane* (3.06 g, 94%); $[\alpha]_D^{20}$ −26.3 (*c* 1.63 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.44; ν_{max}(film)/cm^{-1} 1740 (CO), 1695 (CO) and 1600 (C=C); δ_H($CDCl_3$) 7.55–7.50 (2 H, m, *o*-SiPh), 7.37–7.14 (18 H, m, CPh_3, *m*- and *p*-SiPh), 5.23 (1 H, dt, *J* 10.9 and 6.8, SiCHCH=C*H*), 5.05 (1 H, t, *J* 10.9, SiCHC*H*=CH), 4.39 (1 H, m, CHN), 3.34 (1 H, dd, *J* 9.6 and 4.4, C$H_A$$H_B$-OCPh$_3$), 3.17 (1 H, dd, *J* 16.4 and 11.4, SiCHC$H_A$$H_B$), 3.13 (1 H, m, CH_ACH_BOCPh$_3$), 2.81 (1 H, dt, *J* 17.8 and 10.2, NCOC$H_A$$H_B$), 2.73 (1 H, dd, *J* 16.4 and 3.0, SiCHCH$_A$CH_B), 2.61 (1 H, td, *J* 11.4 and 3.0, SiCH), 2.10–1.80 (4 H, m, NCO-CH_2CH_2 and CH_2), 1.24 (18 H, m, CH_2), 0.87 (3 H, t, *J* 6.6, Me), 0.33 (3 H, s, Si*Me*$_A$Me$_B$) and 0.30 (3 H, s, SiMe$_A$*Me*$_B$); δ_C($CDCl_3$) 176.1, 173.4, 143.6, 137.2, 134.1, 129.8, 129.5, 129.1, 128.9, 128.5, 127.8, 127.1, 127.1, 86.9, 63.9, 56.6, 37.2, 33.0, 31.9, 29.7, 29.6, 29.5, 29.3, 27.6, 24.0, 22.7, 21.0, 14.1, −4.4 and −5.3; *m*/*z* 727 (5%, M^+), 484 (4, M − CPh_3), 243 (100, CPh_3) and 135 (35, $PhMe_2Si$) (Found: M^+, 727.4492. $C_{48}H_{61}NO_3Si$ requires *M*, 727.4420). The ratio of isomers was determined by integration of the $SiMe_2$ signals in the ^{1}H NMR spectrum.

(5*S*)-1-[(*Z*)(3′*S*)-3′-Dimethyl(phenyl)silylhexadec-4′-enoyl]-5-(trityloxymethyl)pyrrolidin-2-one 11

This was made in the same way as the allylsilane *Z*-**12** from the vinylcuprate *Z*-**10** (1.02 mmol) and the lactam *E*-**6**[5] (187 mg, 0.34 mmol) to give the *allylsilane* (188 mg, 75%); $[\alpha]_D^{20}$ −23.9 (*c* 2.98 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.44; ν_{max}(film)/cm^{-1} 1740 (CO), 1690 (CO) and 1600 (SiPh); δ_H($CDCl_3$) 7.57–7.50 (2 H, m, *o*-SiPh), 7.44–7.10 (18 H, m, CPh_3, *m*- and *p*-SiPh), 5.25 (1 H, dt, *J* 10.8 and 6.8, SiCHCH=C*H*), 5.12 (1 H, t, *J* 10.8, SiCHC*H*=CH), 4.30 (1 H, m, CHN), 3.43 (1 H, dd, *J* 9.7 and 4.3, CH_ACH$_B$OCPh$_3$), 3.20–3.11 (2 H, m, CH$_A$$H_B$OCPh$_3$ and SiCHCH_ACH$_B$), 2.84 (1 H, dt, *J* 18.3 and 10.5, NCOCH_A-CH$_B$), 2.64 (1 H, m, SiCHCH$_A$CH_B), 2.41 (1 H, m, NCOCH$_A$-CH_B), 2.28 (1 H, m, SiCH), 2.00–1.80 (4 H, m, $NCOCH_2C$$H_2$ and CH_2), 1.25 (18 H, m, CH_2), 0.88 (3 H, t, *J* 6.5, Me), 0.324 (3 H, s, Si*Me*$_A$Me$_B$) and 0.321 (3 H, s, SiMe$_A$*Me*$_B$); δ_C($CDCl_3$) 175.8, 173.3, 143.6, 137.0, 134.1, 129.2, 129.0, 128.7, 128.5, 127.8, 127.5, 127.0, 86.9, 63.7, 56.7, 37.9, 33.0, 31.0, 29.7, 29.64, 29.60, 29.5, 29.3, 27.6, 23.9, 22.6, 21.1, 14.1, −4.6 and −5.1; *m*/*z* 727 (2%, M^+), 485 (6, M − CPh_3 + H), 243 (100, CPh_3) and 135 (20, $PhMe_2Si$) (Found: M^+, 727.4463. $C_{48}H_{61}NO_3Si$ requires *M*, 727.4420). The diastereoisomer *Z*-**12** was not detectable (^{1}H NMR).

(5*S*)-1-[(*E*)(3′*R*)-3′-Dimethyl(phenyl)silylhexadec-4′-enoyl]-5-(trityloxymethyl)pyrrolidin-2-one *E*-12

This was prepared in the same way as the allylsilane *Z*-**12,** from the vinyl bromide *E*-**9** (1.4 g) and the lactam *Z*-**6** (1.15 g) to give the *allylsilane* (1.12 g, 73%); $[\alpha]_D^{21}$ −35.0 (*c* 1.3 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.43; ν_{max}(film)/cm^{-1} 1740 (CO), 1690 (CO) and 1600 (C=C); δ_H($CDCl_3$) 7.53–7.47 (2 H, m, *o*-SiPh), 7.36–7.14 (18 H, m, CPh_3, *m*- and *p*-SiPh), 5.27–5.11 (2 H, m, CH=CH), 4.38 (1 H, m, CHN), 3.36 (1 H, dd, *J* 9.7 and 4.5, C$H_A$$H_B$OCPh$_3$), 3.21 (1 H, dd, *J* 16.4 and 11.7, SiCHC$H_A$$H_B$), 3.14 (1 H, dd, *J* 9.7 and 2.9, CH$_A$$H_B$OCPh$_3$), 2.83 (1 H, dt, *J* 17.7 and 10.5, NCOCH_ACH$_B$), 2.71 (1 H, dd, *J* 16.4 and 3.1, SiCHCH$_A$CH_B), 2.25 (1 H, ddd, *J* 11.7, 7.6 and 3.1, SiCH), 2.10–1.80 (4 H, m, CH_2 and $COCH_2C$$H_2$), 1.25 (18 H, m, CH_2), 0.87 (3 H, t, *J* 6.6, Me), 0.31 (3 H, s, Si*Me*$_A$Me$_B$) and 0.29 (3 H, s, SiMe$_A$*Me*$_B$); δ_C($CDCl_3$) 176.1, 173.4, 143.6, 137.3, 134.1, 129.3, 129.2, 129.1, 128.5, 127.8, 127.7, 86.9, 63.8, 56.6, 36.3, 33.0, 32.7, 31.9, 29.8, 29.7 (×2), 29.5, 29.3, 29.1, 27.9, 22.7, 21.0, 14.1, −4.3 and −5.3; *m*/*z* 727 (5%, M^+), 712 (1, M − Me), 649 (5, M − C_6H_6), 484 (5, M − CPh_3), 243 (100, CPh_3) and 135 (50, $PhMe_2Si$) (Found: M^+, 727.4440. $C_{48}H_{61}NO_3Si$ requires *M*, 727.4220).

Benzyl (*Z*)(3*R*)-3-dimethyl(phenyl)silylhexadec-4-enoate *Z*-13a

The lactam *Z*-**12** (1.61 g) in THF (7 cm^3) was added to lithium benzyl oxide [prepared from *n*-butyllithium (1.6 mol dm^{-3} in hexane, 7.7 cm^3) and benzyl alcohol in THF (10 cm^3)] and stirred at room temperature for 24 h. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 10:1) gave the *ester* (0.95 g, 93%); $[\alpha]_D^{20}$ −12.7 (*c* 1.90 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.60; ν_{max}(film)/cm^{-1} 1730 (CO), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.57–7.44 (2 H, m, *o*-SiPh), 7.38–7.27 (8 H, m, CH_2*Ph*, *m*- and *p*-SiPh), 5.31 (1 H, dt, *J* 10.8 and 7.0, SiCHCH=C*H*), 5.08 (1 H, m, SiCHC*H*=CH), 5.02 (1 H, d, *J* 12.1, C$H_A$$H_B$Ph), 4.97 (1 H, d, *J* 12.1, CH$_A$$H_B$Ph), 2.55 (1 H, td, *J* 11.3 and 3.5, SiCH), 2.42 (1 H, dd, *J* 14.6 and 3.5, C$H_A$$H_B$-CO), 2.22 (1 H, dd, *J* 14.6 and 11.7, CH$_A$$H_B$CO), 2.00–1.80 (2 H, m, CH_2), 1.25 (18 H, m, CH_2), 0.88 (3 H, t, *J* 6.5, Me), 0.28 (3 H, s, Si*Me*$_A$Me$_B$) and 0.27 (3 H, s, SiMe$_A$*Me*$_B$); δ_C($CDCl_3$) 173.3, 136.7, 134.0, 130.0, 129.2, 128.4, 128.2, 128.0, 127.7, 66.1, 35.5, 31.9, 29.7, 29.6, 29.5, 29.4, 27.6, 25.1, 22.7, 14.1, −4.6 and −5.4; *m*/*z* 478 (0.04%, M^+), 463 (0.5, M − Me), 400 (2, M − C_6H_6), 387 (4, M − C_7H_7) and 135 (100, $PhMe_2Si$) (Found: M^+, 478.3236. $C_{31}H_{46}O_2Si$ requires *M*, 478.3267).

***tert*-Butyl (*Z*)(3*R*)-3-dimethyl(phenyl)silylhexadec-4-enoate *Z*-13b**

This was prepared in the same way as the benzyl ester *Z*-**13a**, from the lactam *Z*-**12** (1.98 g, 2.72 mmol) and lithium *tert*-butyl oxide (30 mmol), stirring for 48 h to give the *allylsilane* (1.03 g, 85%); R_f(hexane–EtOAc, 5:1) 0.64; ν_{max}(film)/cm^{-1} 1730 (CO) and 1250 (SiMe); δ_H($CDCl_3$) 7.50–7.47 (2 H, m, *o*-SiPh), 7.37–7.30 (3 H, m, *m*- and *p*-SiPh), 5.28 (1 H, dt, *J* 10.9 and 7.0, SiCHCH=C*H*), 5.08 (1 H, m, SiCHC*H*=CH), 2.50 (1 H, td, *J* 11.5 and 3.4, SiCH), 2.28 (1 H, dd, *J* 14.4 and 3.4, SiCHCH_A-CH$_B$), 2.04 (1 H, dd, *J* 14.4 and 11.5, SiCHCH$_A$CH_B), 2.00–1.80 (2 H, m, CH_2), 1.37 (9 H, s, Bu^t), 1.25 (18 H, m, CH_2), 0.88 (3 H, t, *J* 6.6, Me), 0.28 (3 H, s, Si*Me*$_A$Me$_B$) and 0.27 (3 H, s, SiMe$_A$*Me*$_B$); *m*/*z* 444 (2.4%, M^+), 443 (6, M − H), 309 (95, M − $PhMe_2Si$) and 135 (100, $PhMe_2Si$) (Found: M^+, 444.3404. $C_{28}H_{48}O_2Si$ requires *M*, 444.3423).

Benzyl (*Z*)(2*R*,3*S*)-3-dimethyl(phenyl)silyl-2-hexylhexadec-4-enoate *Z*-14a

This was prepared in the same way as the ester *Z*-**13b**, from the ester *Z*-**13a** (150 mg), to give the *allylsilane* (150 mg, 85%); $[\alpha]_D^{20}$

−21.4 (*c* 2.33 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.65; ν_{max}(film)/cm^{-1} 1730 (CO), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.52–7.46 (2 H, m, *o*-SiPh), 7.40–7.26 (8 H, m, CH_2-*Ph*, *m*- and *p*-SiPh), 7.35 (1 H, dt, *J* 10.8 and 7.2, SiCHCH=C*H*), 4.82 (1 H, d, *J* 12.5, OCH_ACH$_B$Ph), 4.75 (1 H, d, *J* 12.5, CH$_A$$H_B$Ph), 2.43 (2 H, m, SiCHCH), 1.90–1.80 (2 H, m, CH_2), 1.25–1.10 (28 H, m, CH_2), 0.85 (6 H, m, 2 × Me), 0.29 (3 H, s, SiMe_AMe$_B$) and 0.24 (3 H, s, SiMe$_A$$Me_B$); δ_C($CDCl_3$) 175.5, 137.5, 136.1, 134.2, 130.5, 128.4, 128.2, 128.0, 127.7, 127.5, 127.0, 65.7, 46.1, 31.9, 31.6, 30.6, 29.7–29.1 (m), 22.7, 22.6, 14.1, 14.0, −3.4 and −4.3; *m*/*z* 471 (1.2%, M − CH_2Ph) and 135 (100, $PhMe_2Si$) (Found: M$^+$ − CH_2Ph, 471.3693. $C_{37}H_{58}O_2Si$ requires *M* − CH_2Ph, 471.3658).

tert-Butyl (*Z*)(2*R*,3*S*)-3-dimethyl(phenyl)silyl-2-hexylhexadec-4-enoate *Z*-14b

The ester *Z*-**13b** (365 mg) was added to LDA (0.24 mol dm^{-3} in THF, 3.4 cm^3) at −78 °C and the mixture stirred for 30 min. Iodohexane (0.74 cm^3) was added and the mixture stirred at −78 °C for 1 h and warmed to 0 °C over 1 h. Standard aqueous work-up gave the *allylsilane* (324 mg, 75%); R_f(hexane–EtOAc, 5:1) 0.72; ν_{max}(film)/cm^{-1} 1725 (CO), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.52–7.47 (2 H, m, *o*-SiPh), 7.36–7.29 (3 H, m, *m*- and *p*-SiPh), 5.30 (1 H, dt, *J* 11.8 and 6.8, SiCHCH=C*H*), 5.14 (1 H, m, SiCHC*H*=CH), 2.46 (1 H, dd, *J* 11.8 and 7.5, SiCH), 2.34 (1 H, m, COCH), 1.90–1.80 (2 H, m, CH_2), 1.39 (9 H, s, Bu^t), 1.25–1.20 (28 H, m, CH_2), 0.86 (6 H, m, 2 × Me) and 0.29 (6 H, s, $SiMe_2$); *m*/*z* 528 (1.6%, M$^+$), 457 (4, M − C_5H_{11}), 443 (5, M − C_6H_{15}), 309 (90, M − C_6H_{14} − $PhMe_2Si$) and 135 (100, $PhMe_2Si$) (Found: M$^+$, 528.4334. $C_{34}H_{60}O_2Si$ requires *M*, 528.4362).

tert-Butyl (*E*)(3*R*)-3-dimethyl(phenyl)silylhexadec-4-enoate *E*-13b

This was prepared in the same way as the benzyl ester *Z*-**13a**, from the lactam *E*-**12** (2.98 g), to give the *allylsilane* (0.78 g, 43%); R_f (hexane–EtOAc, 5:1) 0.64; ν_{max}(film)/cm^{-1} 1730 (CO) and 1250 (SiMe); δ_H($CDCl_3$) 7.49–7.45 (2 H, m, *o*-SiPh), 7.36–7.31 (3 H, m, *m*- and *p*-SiPh), 5.24 (2 H, m, SiCHCH=C*H*), 2.30–2.10 (3 H, m, $SiCHCH_2$), 1.94 (2 H, m, CH_2), 1.37 (9 H, s, Bu^t), 1.24 (18 H, m, CH_2), 0.87 (3 H, t, *J* 6.4, Me) and 0.26 (6 H, s, $SiMe_2$); *m*/*z* 444 (4%, M$^+$), 373 (10, M − C_5H_{11}), 310 (25, M − $PhMe_2Si$ + H), 155 (40, $C_{11}H_{23}$) and 135 (100, $PhMe_2Si$) (Found: M$^+$, 444.3428. $C_{28}H_{48}O_2Si$ requires *M*, 444.3423).

tert-Butyl (*E*)(2*R*,3*S*)-3-dimethyl(phenyl)silyl-2-hexylhexadec-4-enoate *E*-14b

This was prepared in the same way as the ester *Z*-**14b**, from the ester *E*-**13b** (220 mg), to give the *allylsilane* (132 mg, 51%); R_f(hexane–EtOAc, 5:1) 0.72; ν_{max}(film)/cm^{-1} 1725 (CO), 1250 (SiMe) and 970 (*trans*-CH=CH); δ_H($CDCl_3$) 7.52–7.46 (2 H, m, *o*-SiPh), 7.33–7.29 (3 H, m, *m*- and *p*-SiPh), 5.14 (2 H, m, SiCHC*H*=C*H*), 2.29 (1 H, m, SiCH), 2.08 (1 H, dt, *J* 3.2 and 6.7, COCH), 1.94 (2 H, m, CH_2), 1.45 (2 H, m, CH_2), 1.38 (9 H, s, Bu^t), 1.25–1.10 (26 H, m, CH_2), 0.88 (6 H, m, 2 × Me), 0.29 (3 H, s, SiMe_AMe$_B$) and 0.28 (3 H, s, SiMe$_A$$Me_B$); *m*/*z* 528 (1, M$^+$), 472 (1, M − C_4H_8), 457 (2, M − C_5H_{11}), 444 (5, M − C_6H_{14}), 309 (70, M − C_6H_{14} − $PhMe_2Si$) and 135 (100, $PhMe_2Si$) (Found: M$^+$, 528.4360. $C_{34}H_{60}O_2Si$ requires *M*, 528.4362).

(*Z*)(3*R*)-3-Dimethyl(phenyl)silylhexadec-4-en-1-ol

Hydroboration (9-BBN, 1.5 equiv., 4 h, room temperature)[2] of the allylsilane *Z*-**13a** (93 mg) gave a mixture of the starting material (52 mg, 56%) and the *alcohol* (23 mg, 32%); R_f(hexane–EtOAc, 3:1) 0.47; ν_{max}(film)/cm^{-1} 3350 (OH), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.51–7.26 (5 H, m, Ph), 5.34 (1 H, dt, *J* 11.0 and 7.0, SiCHCH=C*H*), 5.14 (1 H, t, *J* 11.0, SiCHC*H*=CH), 3.63–3.44 (2 H, m, CH_2OH), 2.10 (1 H, td, *J* 11.6 and 2.6, SiCH), 2.00–1.10 (23 H, CH_2, $SiCHCH_2$ and OH), 0.88 (3 H, t, *J* 6.1, Me), 0.28 (3 H, s, SiMe_AMe$_B$) and 0.27 (3 H, s, SiMe$_A$$Me_B$); *m*/*z* 259 (0.1%, M − Me) and 135 (100, $PhMe_2Si$) (Found: M$^+$ − Me, $C_{24}H_{42}OSi$ requires *M* − Me, 359.2770).

(3*R*,5*S*)-3-Dimethyl(phenyl)silylhexadecane-1,5-diol

Hydroboration (BH_3·THF, 2 equiv., 0 °C, 2 h)[2] of the allylsilane *Z*-**13a** (117 mg) gave the *diol* (20.1 mg, 18%); R_f(hexane–EtOAc, 3:1) 0.21; ν_{max}(film)/cm^{-1} 3300 (OH), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.55–7.28 (5 H, m, Ph), 3.76–3.40 (3 H, m, C*H*OH and CH_2OH), 2.30 (2 H, s, OH), 1.80–1.10 (25 H, m, CH_2 and $CH_2SiCHCH_2$), 0.88 (3 H, t, *J* 6.0, Me), 0.36 (3 H, s, SiMe_AMe$_B$) and 0.28 (3 H, s, SiMe$_A$$Me_B$); *m*/*z* 374 (0.2%, M − H_2O), 359 (0.3, M − Me − H_2O), 205 (50), 137 (50, MePhSiOH) and 135 (100, $PhMe_2Si$) (Found: M$^+$ − H_2O, 374.2991. $C_{24}H_{42}OSi$ requires *M* − H_2O, 374.3004).

(*Z*)(2*R*,3*S*)-3-Dimethyl(phenyl)silyl-2-hexylhexadec-4-en-1-ol

Hydroboration (9-BBN, 1.3 equiv., reflux, 3 h)[2] and oxidation of the allylsilane *Z*-**14b** (80 mg) gave, after chromatography (SiO_2, hexane–EtOAc, 5:1), the starting material (30 mg, 38%) and the *alcohol* (24 mg, 29%); R_f(hexane–EtOAc, 5:1) 0.50; ν_{max}(film)/cm^{-1} 3400 (OH), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.52–7.33 (5 H, m, Ph), 5.35 (2 H, m, CH=CH), 3.50–3.30 (3 H, m, CH_2OH and C*H*OH), 2.00–1.00 (32 H, m, CH_2 and SiCHCH), 0.87 (6 H, m, 2 × Me), 0.32 (3 H, s, SiMe_A-Me$_B$) and 0.29 (3 H, s, SiMe$_A$$Me_B$); δ_C($CDCl_3$) 138.6, 133.9, 130.6, 128.9, 127.7, 127.3, 65.7, 41.6, 41.9, 31.8, 30.3, 29.8, 29.6, 29.5, 29.4, 28.6, 28.0, 27.6, 22.7, 22.6, 14.1, 14.0, −3.1 and −3.4; *m*/*z* 457 (0.1%, M − Me), 306 (6, M − $PhMe_2SiOH$), 152 (5, $PhMe_2SiOH$) and 135 (100, $PhMe_2Si$) (Found: M$^+$ − H, 457.3847. $C_{30}H_{54}OSi$ requires *M* − H, 457.3866).

(*Z*)(7*R*,8*S*)-7-(*tert*-Butyldimethylsilyloxymethyl)-8-dimethyl-(phenyl)silylhenicos-9-ene *Z*-15

The ester *Z*-**14a** (1.87 g) in ether (20 cm^3) was added to a slurry of lithium aluminium hydride (0.7 g) in ether (20 cm^3) and stirred at 0 °C for 3 h. Standard aqueous work-up gave crude alcohol [R_f(hexane–EtOAc, 5:1) 0.47] which was stirred with imidazole (0.91 g) and *tert*-butylchlorodimethylsilane in DMF (20 cm^3) at room temperature for 1 h. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 10:1) gave the *allylsilane* (1.75 g, 91%); $[\alpha]_D^{20}$ −21.4 (*c* 2.33 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.74; ν_{max}(film)/cm^{-1} 1250 (SiMe); δ_H($CDCl_3$) 7.52–7.47 (2 H, m, *o*-SiPh), 7.35–7.28 (3 H, m, *m*- and *p*-SiPh), 5.35 (1 H, dt, *J* 11.4 and 7.0, SiCHCH=C*H*), 5.21 (1 H, t, *J* 11.4, SiCHC*H*=CH), 3.36 (1 H, dd, *J* 9.5 and 4.9, CH_ACH$_B$O), 3.20 (1 H, dd, *J* 9.5 and 8.4, CH$_A$CH_BO), 2.53 (1 H, dd, *J* 11.7 and 3.3, SiCH), 2.00–1.50 (3 H, m, SiCHC*H* and CH_2), 1.30–1.15 (28 H, m, CH_2), 0.86 (15 H, m, 2 × Me and Bu^t), 0.29 (3 H, s, SiMe_AMe$_B$Ph), 0.26 (3 H, s, Si$Me_A$$Me_B$Ph), −0.04 (3 H, s, Si$Me_AMe_B$Bu^t) and −0.06 (3 H, s, Si$Me_A$$Me_B$-Bu^t); *m*/*z* 515 (0.5%, M − Bu^t), 440 (0.5, M − TBDMSOH), 427 (1, M − $TBDMSOCH_2$), 379 (10, M − $PhMe_2Si$ − Bu^t), 365 (12, M − $PhMe_2Si$ − Bu^t − Me), 209 (50, $PhMe_2SiOSi$-Me_2) and 135 (100, $PhMe_2Si$) (Found: M$^+$ − Bu^t, 515.4113. $C_{36}H_{68}OSi_2$ requires *M* − Bu^t, 515.4104).

(*E*)(7*R*,8*S*)-7-(*tert*-Butyldimethylsilyloxymethyl)-8-dimethyl-(phenyl)silylhenicos-9-ene *E*-15

This was prepared in the same way as the allylsilane *Z*-**15**, from the ester *E*-**14b** (119 mg), to give the *allylsilane* (130 mg, 100%); R_f(hexane–EtOAc, 5:1) 0.74; ν_{max}(film)/cm^{-1} 1250 (SiMe); δ_H($CDCl_3$) 7.50–7.46 (2 H, m, *o*-SiPh), 7.34–7.28 (3 H, m, *m*- and *p*-SiPh), 5.21 (2 H, m, SiCHCH=C*H*), 3.37 (1 H, dd, *J* 9.6 and 4.8, CH_AH$_B$O), 3.25 (1 H, t, *J* 9.6, CH$_A$CH_B), 2.10 (1 H, m, SiCH), 1.96 (2 H, m, CH_2), 1.30–1.10 (28 H, m, CH_2), 0.86 (15 H, m, 2 × Me and Bu^t), 0.28 (3 H, s, SiMe_AMe$_B$Ph), 0.25 (3 H, s, SiMe$_A$$Me_B$Ph), −0.03 (3 H, s, Si$Me_AMe_B$Bu^t) and −0.04 (3 H, s, SiMe$_A$$Me_B$Bu^t); *m*/*z* 515 (0.2%, M − Bu^t), 440 (1, M − TBDMSOH), 427 (0.5, M − $TBDMSOCH_2$), 379 (12,

M − $PhMe_2Si$ − Bu′), 365 (12, M − $PhMe_2Si$ − Bu′ − Me), 209 (20, $PhMe_2SiOSiMe_2$) and 135 (100, $PhMe_2Si$) (Found: M^+ − Bu′, 515.4086. $C_{36}H_{68}OSi_2$ requires *M* − Bu′, 515.4104).

(7*R*,8*S*,10*S*)-7-(*tert*-Butyldimethylsilyloxymethyl)-8-dimethyl-(phenyl)silylhenicosan-10-ol 16

Hydroboration (9-BBN, 10 equiv., 24 h, reflux)[2] and oxidation, of the allylsilane *Z*-**15** (250 mg) gave the *alcohol* (177 mg, 68%); $[\alpha]_D^{20}$ −4.3; R_f(hexane–EtOAc, 5:1) 0.59; ν_{max}(film)/cm^{-1} 3450 (OH) and 1250 (SiMe); δ_H($CDCl_3$) 7.52–7.47 (2 H, m, *o*-SiPh), 7.35–7.30 (3 H, m, *m*- and *p*-SiPh), 3.58 (2 H, dd overlying br m, *J* 10.4 and 6.1, CH_AH_BOSi and C*H*OH), 3.40 (1 H, t, *J* 10.4, CH_ACH_BOSi), 3.70 (2 H, m, CH_2), 1.30–1.10 (32 H, m, CH_2 and SiCHCH), 0.88 (15 H, m, 2 × Me and Bu′), 0.31 (3 H, s, $SiMe_AMe_BPh$) and 0.29 (3 H, s, $SiMe_AMe_BPh$), 0.01 (3 H, s, $SiMe_AMe_BBu^t$) and −0.01 (3 H, s, $SiMe_AMe_BBu^t$); δ_C($CDCl_3$) 139.2, 133.9, 128.8, 127.7, 70.9, 66.2, 40.8, 37.9, 34.4, 31.9, 31.8, 30–29 (m), 26.1, 25.9, 22.7, 22.6, 20.2, 18.2, 14.12, 14.07, −2.7, −3.1, −5.3 and −5.4; *m*/*z* 575 (0.2%, M − Me), 533 (1, M − Bu′), 209 (30, $PhMe_2SiOSiMe_2$) and 135 (100, $PhMe_2Si$) (Found: M^+ − Me, 575.4712. $C_{36}H_{70}O_2Si_2$ requires *M* − Me, 575.4680). The diastereoisomer **17** was not detectable (^{1}H NMR).

(7*R*,8*S*,10*R*)-7-(*tert*-Butyldimethylsilyloxymethyl)-8-dimethyl-(phenyl)silylhenicosan-10-ol 17

This was prepared in the same way as the alcohol **16**, from the allylsilane *E*-**15** (127 mg), to give a mixture of the alcohols **16** and **17** (1:4, 70 mg, 59%); $[\alpha]_D$ −15.8 (*c* 1.00 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.59; ν_{max}(film)/cm^{-1} 3400 (OH) and 1250 (SiMe); δ_H($CDCl_3$) 7.51–7.47 (2 H, m, *o*-SiPh), 7.34–7.30 (3 H, m, *m*- and *p*-SiPh), 3.57 (1 H, dd, *J* 10.4 and 5.1, CH_ACH_BO), 3.44 (1 H, t, *J* 10.4, CH_ACH_BO), 3.20 (1 H, m, C*H*OH), 2.94 (1 H, s, OH), 1.70–1.15 (31 H, m, SiCH and CH_2), 0.88 (15 H, m, CH_2 and Bu′), 0.32 (6 H, s, $SiMe_2Ph$), 0.02 (3 H, s, $SiMe_AMe_BBu^t$) and 0.00 (3 H, s, $SiMe_AMe_BBu^t$); δ_C($CDCl_3$) 139.0, 133.8, 128.9, 127.7, 72.8, 64.4, 41.0, 37.6, 32.2, 31.9, 31.7, 30–29.4 (m), 28.3, 25.9, 25.7, 22.8, 22.7, 22.6, 18.2, 14.1, 14.0, −3.0, −3.2 and −5.3; *m*/*z* 533 (0.4%, M − Bu′) and 135 (100, $PhMe_2Si$) (Found: M^+ − Bu′, 533.4247. $C_{36}H_{70}O_2Si_2$ requires *M* − Bu′, 533.4210). The isomer ratio was determined from the ^{13}C NMR spectrum.

(7*R*,8*S*,10*S*)-10-Benzyloxy-7-(*tert*-butyldimethylsilyloxymethyl)-8-dimethyl(phenyl)silylhenicosane 18

The alcohol **16** (1.9 g) was stirred in cyclohexane (30 cm^3) and dichloromethane (30 cm^3) with benzyl trichlorobenzylacetimidate[9] (1.5 cm^3) and trifluoromethansulfonic acid (0.15 cm^3) at room temperature for 30 min. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 10:1) gave the *benzyl ether* (1.99 g, 91%); R_f(hexane–EtOAc, 5:1) 0.57; ν_{max}(film)/cm^{-1} 1250 (SiMe); δ_H($CDCl_3$) 7.51–7.47 (2 H, m, *o*-SiPh), 7.35–7.26 (8 H, m, CH_2Ph, *m*- and *p*-SiPh), 4.34 (2 H, s, CH_2Ph), 3.34 (2 H, m, CH_2OTBDMS), 3.22 (1 H, m, C*H*OBn), 1.60–1.13 (34 H, m, CH_2 and SiCHCH), 0.87 (15 H, m, Bu′ and 2 × Me), 0.31 (3 H, s, $SiMe_AMe_BPh$), 0.29 (3 H, s, $SiMe_AMe_BPh$) and −0.01 (6 H, s, $SiMe_2Bu^t$); *m*/*z* 665 (0.2%, M − Me), 623 (0.5, M − Bu′), 209 (25, $PhMe_2SiOSiMe_2$), 135 (100, $PhMe_2Si$) and 91 (60, $PhCH_2$) (Found: M^+ − Me, 665.5203. $C_{42}H_{73}O_2Si_2$ requires M − Me, 665.5149).

(2*R*,3*S*,5*S*)-5-Benzyloxy-3-dimethyl(phenyl)silyl-2-hexylhexadecan-1-ol

Tetrabutylammonium fluoride (1 mol dm^{-3} in THF, 30 cm^3) was added to the silyl ether **18** (1.99 g) and the mixture stirred at room temperature for 1 h. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 10:1) gave the *alcohol* (1.62 g, 98%); $[\alpha]_D^{20}$ +2.3 (*c* 1.8 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.40; ν_{max}(film)/cm^{-1} 3400 (OH), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.53–7.38 (2 H, m, *o*-SiPh), 7.36–7.26 (8 H, m, CH_2Ph, *m*- and *p*-SiPh), 4.34 (2 H, s, CH_2Bn), 3.52–3.43 (3 H, m, CH_2OH and C*H*OBn), 1.60–1.17 (34 H, m, CH_2 and SiCHCH), 0.87 (3 H, t, *J* 6.5, Me_A), 0.85 (3 H, t, *J* 6.7, Me_B), 0.33 (3 H, s, $SiMe_AMe_B$) and 0.32 (3 H, s, $SiMe_AMe_B$); *m*/*z* 551 (0.003%, M − Me), 165 (12, $PhCH_2OSiMe_2$), 135 (100, $PhMe_2Si$) and 91 (100, CH_2Ph) (Found: M^+ − Me, 551.4280. $C_{37}H_{62}O_2Si$ requires *M* − Me, 551.4284).

(2*R*,3*S*,5*S*)-5-Benzyloxy-3-dimethyl(phenyl)silyl-2-hexylhexadecanoic acid 19

The alcohol (1.62 g, 2.86 mmol) and PDC[26] (3.3 g, 8.60 mmol) were stirred in DMF (25 cm^3) at room temperature for 2 h. Chromatography of the solution (SiO_2, hexane–EtOAc, 5:1) gave the aldehyde (1.41 g, 88%). Jones' reagent[27] (2.5 cm^3, 6.7 mmol) was added to the aldehyde in acetone (50 cm^3). The mixture was stirred at 0 °C for 45 min. The solvent was removed under reduced pressure and chromatography (SiO_2, hexane–EtOAc, 5:1) gave the *acid* **19** (0.96 g, 62%); $[\alpha]_D^{20}$ +19.2 (*c* 2.7 in $CHCl_3$); R_f(hexane–EtOAc, 5:1) 0.40; ν_{max}(film)/cm^{-1} 3500–2300 (OH), 1700 (CO), 1250 (SiMe) and 1110 (SiPh); δ_H($CDCl_3$) 7.52–7.49 (2 H, m, *o*-SiPh), 7.35–7.26 (8 H, m, C_2Ph, *m*- and *p*-SiPh), 4.44 (1 H, d, *J* 11.5, CH_AH_BPh), 4.32 (1 H, d, *J* 11.5, CH_ACH_BPh), 3.40 (1 H, m, C*H*OBn), 2.52 (1 H, m, $CHCO_2H$), 1.70–1.10 (33 H, m, CH_2 and SiCH), 0.87 (6 H, m, 2 × Me), 0.35 (3 H, s, $SiMe_AMe_B$) and 0.32 (3 H, s, $SiMe_AMe_B$); *m*/*z* 580 (0.1%, M^+), 565 (0.7, M − Me), 503 (4, M − Ph), 472 (5, M − BnOH), 135 (60, $PhMe_2Si$) and 91 (100 CH_2Ph) (Found: M^+, 580.4296. $C_{37}H_{60}O_3Si$ requires *M*, 580.4314).

(2*S*,3*S*,5*S*)-5-Benzyloxy-3-hydroxy-2-hexylhexadecanoic acid 20

The silyl acid **19** (43 mg) and mercuric acetate (30 mg) were stirred in peracetic acid (15% in AcOH, 1 cm^3) at room temperature for 3 h. Chromatography (SiO_2, Et_2O), gave the *hydroxy acid* (13 mg, 38%); R_f(hexane–EtOAc, 1:1) 0.20; ν_{max}(film)/cm^{-1} 3400–2400 (OH); δ_H($CDCl_3$) 7.36–7.29 (5 H, m, Ph), 4.67 (1 H, d, *J* 11.2, CH_ACH_BOBn), 4.40 (1 H, d, *J* 11.2, CH_ACH_BOBn), 3.94 (1 H, dt, *J* 9.8 and 3.0, C*H*OH), 3.75 (1 H, ddd, *J* 13.7, 7.0 and 3.2, C*H*OBn), 2.35 (1 H, ddd, *J* 9.2, 6.0 and 3.0, $CHCO_2H$), 1.75 (33 H, CH_2 and OH) and 0.87 (6 H, m, 2 × Me); δ_C($CDCl_3$) 176.3, 137.4, 128.7, 128.0, 127.9, 80.3, 72.3, 70.6, 51.7, 38.5, 33.0, 31.9, 31.6, 29.8, 29.6, 29.5, 29.3, 29.1, 27.2, 24.3, 22.7, 22.5, 14.1 and 14.0; *m*/*z* 460 (0.5%, M − 2 × H), 338 (1, M − $C_7H_8O_2$), 123 (1, $C_7H_7O_2$), 105 (40, PhCO) and 91 (100, $PhCH_2$) (Found: M^+ − 2 × H, 460.3527. $C_{29}H_{50}O_4$ requires *M* − 2 × H, 460.3553).

(3*S*,4*S*)-4-[(*S*)-2′-Benzyloxytridecyl]-3-hexyloxetan-2-one 21

The silyl acid **19** (0.8 g) and mercuric acetate (1 g) were stirred in peracetic acid (30 cm^3) at room temperature for 18 h. The solvent was evaporated under reduced pressure. Standard aqueous work-up and chromatography (SiO_2, Et_2O–Me_2CO, 1:1) gave crude hydroxy acid, which was dissolved in pyridine (50 cm^3) at 0 °C. Benzenesulfonyl chloride (6 cm^3) was added and the mixture stirred at 0 °C for 15 h. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 3:1) gave the *lactone* (0.46 g, 76%); R_f(hexane–EtOAc, 3:1) 0.6; ν_{max}(CH_2Cl_2) 1825 (lactone CO); δ_H($CDCl_3$) 7.35–7.25 (5 H, m, Ph), 4.54 (1 H, d, *J* 11.5, CH_AH_BPh), 4.41 (1 H, d, *J* 11.5, CH_ACH_BPh), 4.40 (1 H, m, CHOCO), 3.50 (1 H, m, $C_{11}CHO$), 3.24 (1 H, dt, *J* 4 and 7.5, $CHCO_2$), 2.15 (1 H, dt, *J* 14.4 and 6.5, $OCHCH_AH_BCHO$), 1.90 (1 H, m, $OCHCH_AH_BCHO$), 1.50–1.20 (30 H, m, 15 × CH_2) and 0.86 (6 H, m, 2 × Me); *m*/*z* 338 (0.1%, M − PhCHO), 275 (0.8, M − $C_{10}H_{17}O_2$), 107 (20, $PhCH_2O$) and 91 (100, $PhCH_2$) (Found: M^+ − PhCHO, 338.3180. $C_{29}H_{48}O_3$ requires *M* − PhCHO, 338.3184).

(3*S*,4*S*)-3-Hexyl-4-[(*S*)-2′-hydroxytridecyl]oxetan-2-one 22

The benzyl ether **21** (0.46 g) and palladium (10% on charcoal, 1 g) were stirred in THF (20 cm^3) under hydrogen for 15 h. Filtration and chromatography (SiO_2, hexane–EtOAc, 3:1)

gave the alcohol[12] (0.34 g, 92%) as needles mp 64–65 °C (lit.[12] mp 64.5–65.5 °C); $[\alpha]_D^{20}$ −15.3 (*c* 1.2 in CH_2Cl_2) (lit.[12] $[\alpha]_D$ −15); R_f(hexane–EtOAc, 3:1) 0.40; ν_{max}(film)/cm^{-1} 3600 (OH), 1820 (lactone C=O); $\delta_H(CDCl_3)$ 4.46 (1 H, dt, *J* 4.1 and 6.5, CHOCO), 3.76 (1 H, m, C*H*OH), 3.30 (1 H, ddd, *J* 8.5, 6.8 and 4.0, CHCO), 2.00–1.15 (33 H, m) and 0.87 (6 H, m, 2 × Me); $\delta_C(CDCl_3)$ 171.4, 76.2, 69.3, 56.7, 41.1, 37.6, 31.9, 31.5, 29.6, 29.54, 29.5, 29.3, 28.9, 27.8, 26.7, 25.4, 22.6, 22.5, 14.1 and 14.0.

(*S*)-1′-[(2″*S*,3″*S*)-3″-Hexyl-4″-oxooxetan-2″-yl]methyldodecyl (*S*)-*N*-formylleucinate (tetrahydrolipstatin) 1

DCC (167 mg) and (S)-*N*-(benzyloxycarbonyl)leucine **23** (418 mg) were stirred in dichloromethane (6 cm^3) at 0 °C for 15 min. The solvent was evaporated under reduced pressure and the residue dissolved in DMF (5 cm^3) and added to a solution of the alcohol (56 mg) and DMAP (15 mg) in DMF (1 cm^3). The mixture was stirred at room temperature for 1 h. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 3:1) gave *N*-CBz-protected ester, R_f(hexane–EtOAc, 3:1) 0.50, which was stirred with palladium (10% on charcoal, 100 mg) in THF (10 cm^3) under hydrogen at room temperature for 4 h. The solution was filtered over Celite and evaporated under reduced pressure. The crude residue was stirred with formic acetic anhydride (0.2 cm^3) in dichloromethane (0.5 cm^3) at room temperature for 15 min. Standard aqueous work-up and chromatography (SiO_2, hexane–EtOAc, 3:1) gave tetrahydrolipstatin (69 mg, 89%) as an amorphous solid mp 40–41 °C (lit. mp 43 °C,[1] 41–42.5 °C,[13] 40–42 °C,[14,15] 40–41 °C,[16,17,18] 42–43 °C[19]); $[\alpha]_D^{25}$ −33.4 (*c* 1.33 in $CHCl_3$) {lit. $[\alpha]_D^{20}$ −32 (*c* 1 in $CHCl_3$),[1] $[\alpha]_D^{20}$ −34.45 (*c* 1 in $CHCl_3$),[13] $[\alpha]_D^{20}$ −33 (*c* 0.36 in $CHCl_3$),[14,15] $[\alpha]_D^{20}$ −31.2 (*c* 0.5 in $CHCl_3$),[16] $[\alpha]_D$ −33 ($CHCl_3$),[17] $[\alpha]_D^{20}$ −31.8 (*c* 0.37 in $CHCl_3$),[18] $[\alpha]_D^{25}$ −34.58 (*c* 0.96 in $CHCl_3$)[19]}; $\nu_{max}(CHCl_3)$ 1825 (lactone CO), 1740 ($NHCO_2$) and 1695 (NHCHO); $\delta_H(CDCl_3)$ 8.20 and 8.05 (1 H, s and d, *J* 7, NHC*H*O), 5.93 (1 H, d, *J* 9, NH), 5.02 (1 H, m, CHOleucine), 4.67 (1 H, dt, *J* 4.5 and 8.5, C*H*NH), 4.28 (1 H, 5-line m, lactone CHOCO), 3.20 (1 H, dt, *J* 4.0 and 7.5, lactone CHCO), 2.15 (1 H, dt, *J* 14.7 and 7.8, $OCHCH_AH_BCHO$), 1.98 (1 H, dt, *J* 14.7 and 4.5, $OCHCH_AH_BCHO$), 1.90–1.20 (33 H, m, 15 × CH_2 and Me_2CHCH_2), 0.95 (6 H, d, *J* 5.1, $CHMe_2$) and 0.87 (6 H, m, 2 × Me); $\delta_C(CDCl_3)$ 171.9, 170.8, 160.9, 74.7, 72.6, 56.9, 49.6, 41.3, 38.6, 34.0, 31.8, 31.4, 29.6 (2C), 29.5, 29.4, 29.3, 28.9, 27.6, 26.6, 25.0, 24.8, 22.8, 22.5, 21.7, 14.1 and 14.0.

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