Asymmetric syntheses of panclicins A–E *via* [2+2] cycloaddition of alkyl(trimethylsilyl)ketenes to a β-silyloxyaldehyde

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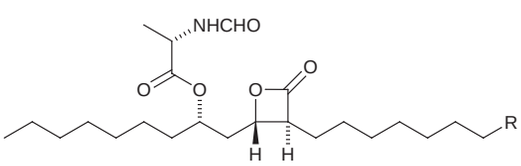
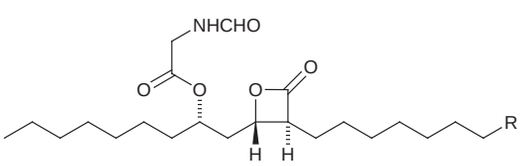
Panclicins A–E, pancreatic lipase inhibitors from *Streptomyces*, were synthesised in a modular fashion starting with three alkyl(trimethylsilyl)ketenes, two amino acids and a single aldehyde component, (3*R*)-3-(*tert*-butyldimethylsilyloxy)decanal 11. The lone stereocentre in 11 which governs the stereochemistry in subsequent steps was generated by Noyori asymmetric hydrogenation. The key step, a Lewis acid catalysed [2+2] cycloaddition of alkyl(trimethylsilyl)ketenes 13a–c to 11, gave three 3-trimethylsilyloxetan-2-ones with good 1,3-asymmetric induction. After *C*- and *O*-desilylation the amino acid side chains were introduced using a Mitsunobu inversion.

Introduction

Panclicins A–E **1**–**5** are potent pancreatic lipase inhibitors produced by *Streptomyces* sp. NR 0619.[1] Like lipstatin,[2,3] esterastin[4] and valilactone,[5] the panclicins contain a β-lactone structure with two alkyl chains one of which bears an α-*N*-formylamino acyloxy group. As inhibitors of pancreatic lipase, panclicins C, D and E are twice as potent as tetrahydrolipstatin (IC_{50} = 1.2 μM), which is marketed as an antiobesity agent.[6–8] Several syntheses of tetrahydrolipstatin have been reported[9–16] as have syntheses of lipstatin itself[17] and valilactone.[18] However, only one synthesis of panclicin D has been described to date.[19]



Panclicin A (**1**) R = $CH(CH_3)_2$
Panclicin B (**2**) R = $(CH_2)_2CH_3$

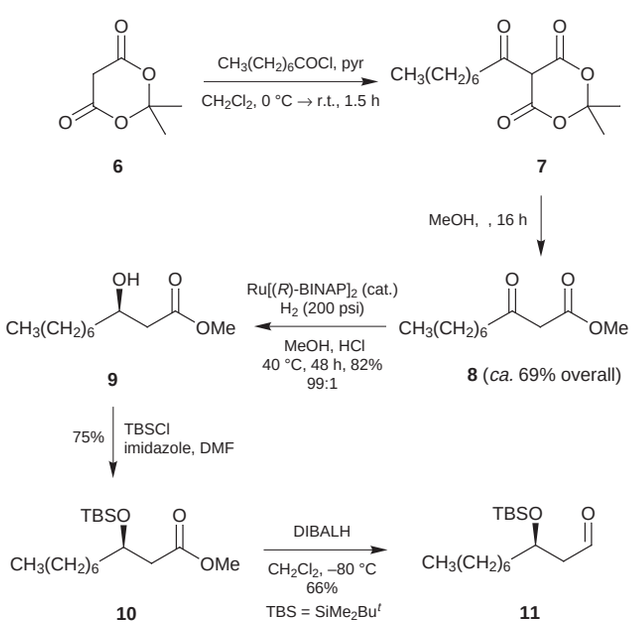


Panclicin C (**3**) R = $CH(CH_3)_2$
Panclicin D (**4**) R = $(CH_2)_4CH_3$
Panclicin E (**5**) R = $(CH_2)_2CH_3$

We now report a synthesis of panclicins A–E **1**–**5** which features a diastereoselective Lewis acid catalysed [2+2] cycloaddition of an alkyl(trimethylsilyl)ketene to a homochiral β-hydroxyaldehyde derivative. We also include some experiments relating to the stereochemistry of the key cycloaddition step, as well as a further refinement of our notion of the mechanism of the cycloaddition.

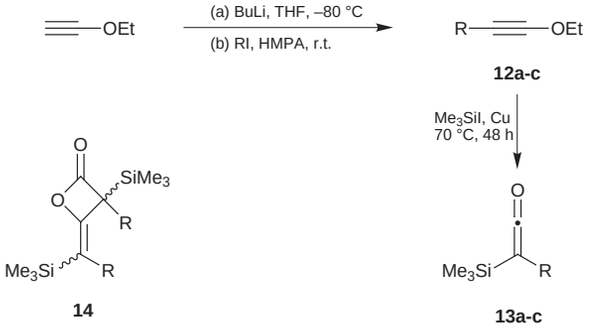
Results and discussion

The similarity in structure of the five panclicins invited a modular approach involving three alkyl(trimethylsilyl)ketenes, two amino acids and a single aldehyde component, (3*R*)-3-(*tert*-butyldimethylsilyloxy)decanal **11**, which harbours the 2-hydroxynonyl side chain common to all the panclicins. Since the lone stereogenic centre at C3 in aldehyde **11** controls the stereochemistry of all the subsequent steps in the synthesis, it was imperative that it be installed efficiently and economically. These requirements were satisfied by the five-step route depicted in Scheme 1. Acylation of Meldrum's acid (**6**) with



Scheme 1

octanoyl chloride followed by methanolysis of the crude intermediate **7** gave methyl 3-oxodecanoate (**8**) in 72% overall yield.[20] Catalytic asymmetric hydrogenation[21–23] of the β-keto ester to give **9** using [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride installed the requisite *R*-configured stereogenic centre in good yield and high enantiomeric ratio (99:1) according to NMR spectroscopic analysis of the Mosher ester derivative. The sequence was completed by first protecting the hydroxy function as its *tert*-butyldimethylsilyl (TBS) ether to give **10** followed by reduction of the ester to the aldehyde using DIBAL-H. The overall yield of **11** for the five-step sequence was 28%.



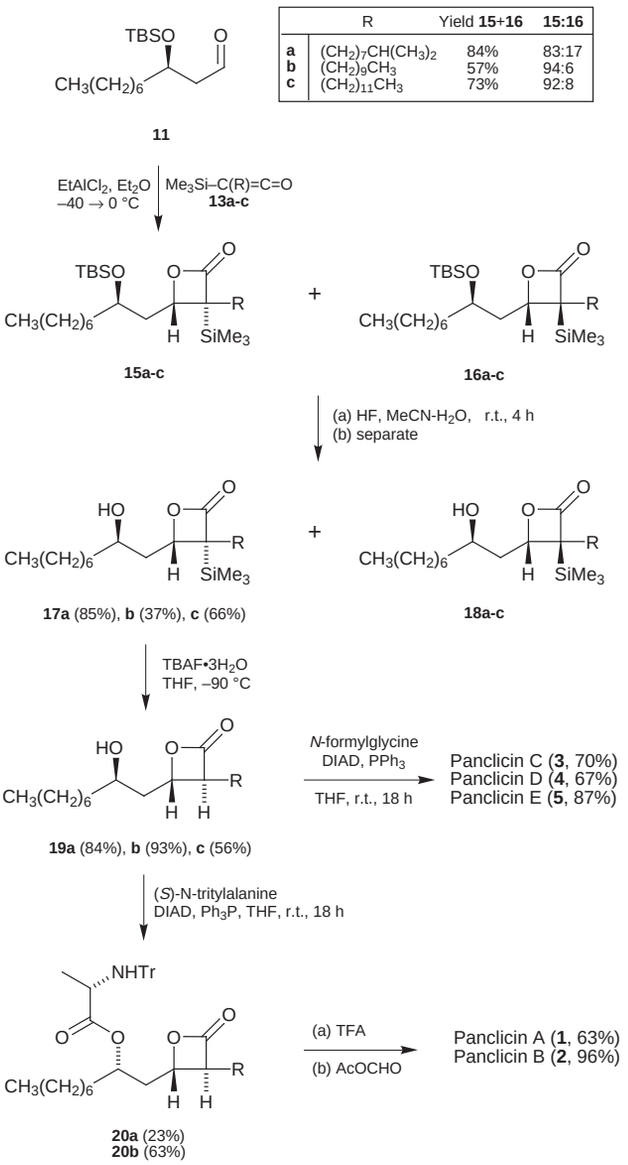
	R	Yield **12**	Yield **13**
a	$(CH_2)_9CH(CH_3)_2$	49%	50%
b	$(CH_2)_9CH_3$	68%	44%
c	$(CH_2)_{11}CH_3$	60%	44%

Scheme 2

The three alkyl(trimethylsilyl)ketenes **13a**–**c** were prepared by a modification of Sakurai's procedure[24] (Scheme 2). Thus alkylation of ethoxyethynyllithium with 1-iodo-8-methylnonane, 1-iododecane and 1-iododododecane gave the three ethoxyalkyne derivatives **12a**–**c**, respectively, in 49–68% yield. The ethoxyalkynes **12a**–**c** were slowly converted to the desired silylketenes **13a**–**c** on heating with *ca*. 1.5 equivalents of freshly prepared iodotrimethylsilane but under the reaction conditions, the silylketenes dimerised to the diketene derivatives **14a**–**c**. However, removal of the excess iodotrimethylsilane *in vacuo*, allowed thermolysis of the diketenes at 140–170 °C to the silylketenes **13a**–**c** which were isolated as stable, colourless oils which could be stored for several weeks at −20 °C.

The [2+2] cycloadditions of the three alkyl(trimethylsilyl)ketenes **13a**–**c** with the aldehyde **11** were performed using the conditions that had been previously optimised for our synthesis of tetrahydrolipstatin,[15] *i.e.* using ethylaluminium dichloride as Lewis acid and diethyl ether as solvent (Scheme 3). An inseparable mixture of four diastereoisomers was obtained from the cycloaddition and ^{1}H NMR spectroscopic analysis (300 MHz) of the crude reaction mixture revealed two sets of signals (dd) at δ 4.64–4.67 (J 11.0–11.6, 1.7–1.8 Hz) corresponding to the diastereoisomers **15a**–**c** and at δ 4.56–4.57 (J 11.0, 1.5 Hz) corresponding to the diastereoisomers **16a**–**c**. Both sets of signals were accompanied by unresolved small shoulders ascribable to the remaining two isomers (not shown) which together accounted for less than 10% of the total isomer distribution. By analogy with the tetrahydrolipstatin study,[15] both major isomers bore the correct *S* configuration at C4 and differed only in the stereochemistry at C3. The *R* configuration assigned to the preponderant isomers **15a**–**c** was deduced from NOE studies but firmer corroborative evidence was later gleaned from an analogue (*vide infra*).

To complete the synthesis of all five panclicins, the *tert*-butyldimethylsilyl protecting group was removed from **15a**–**c** with HF in aqueous acetonitrile and pure samples of the major isomers **17a**–**c** could then be obtained by column chromatography. *C*-Desilylation occurred on brief exposure to tetrabutylammonium fluoride (TBAF) in THF at −90 °C to give the crystalline *trans*-disubstituted β-lactone derivatives **19a**–**c** selectively. However, for preparative purposes, the tandem *O*-silylation and *C*-desilylation were best achieved without purification of intermediates and minor diastereoisomers removed by the easy recrystallisation of **19a**–**c** from pentane. Attempts to prepare panclicins A and B by direct Mitsunobu esterification of **19a** and **19b** with *N*-formylalanine were thwarted by the easy racemisation of the *N*-formylalanine residue under the reaction conditions. By contrast, Mitsunobu esterification with (*S*)-*N*-tritylalanine[25,26] occurred smoothly to give the ester derivatives **20a** (23%) and **20b** (63%). Removal of the trityl group with trifluoroacetic acid (TFA) followed by



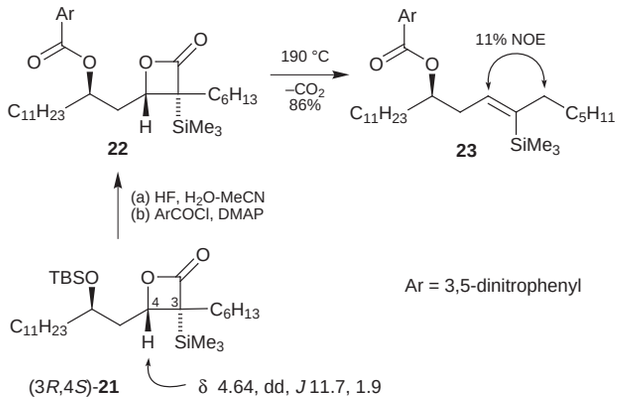
	R	Yield **15**+**16**	**15**:**16**
a	$(CH_2)_7CH(CH_3)_2$	84%	83:17
b	$(CH_2)_9CH_3$	57%	94:6
c	$(CH_2)_{11}CH_3$	73%	92:8

Scheme 3

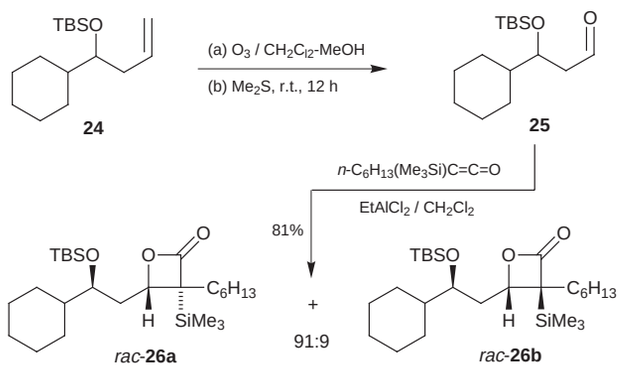
immediate *N*-formylation with formic acetic anhydride gave pure samples of panclicins A **1** and B **2** after column chromatography. Panclicins C **3**, D **4** and E **5** were obtained in 67–87% yield by direct Mitsunobu esterification of **19a**–**c** with *N*-formylglycine. The synthetic panclicins A–E obtained by our route were identical by high field ^{1}H and ^{13}C NMR spectroscopy and $[\alpha]_D$ with data reported for the natural products.[1]

Stereochemistry and mechanism of the Lewis acid catalysed [2+2] cycloaddition of silylketenes to aldehydes

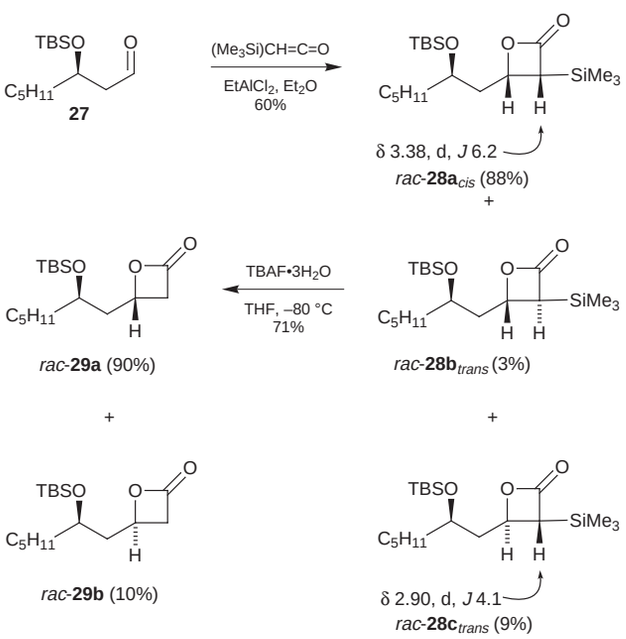
Our assignment of the (3*R*,4*S*) stereochemistry to the major cycloadducts **15a**–**c** was based on spectroscopic comparison with the analogous major cycloadduct **21** obtained in our previous tetrahydrolipstatin synthesis wherein the stereochemistry was ascertained by NOE analysis of the alkenylsilane **23** derived from thermolysis of the β-lactone **22** (Scheme 4).[15] In order to obtain a less convoluted and more secure assignment, we examined the cycloaddition of aldehyde *rac*-**25** with *n*-hexyl(trimethylsilyl)ketene using ethylaluminium dichloride as the Lewis acid (Scheme 5). Two cycloadducts *rac*-**26a**,**b** were formed in 81% yield and the relative stereochemistry of the major isomer (91% of the mixture), ascertained by X-ray crystallography, corroborated the (3*R*,4*S*) stereochemistry.[27] Moreover, we were able to show that the *n*-hexyl group on the silylketene did not markedly influence the stereochemistry of



Scheme 4



Scheme 5



Scheme 6

the cycloaddition under our conditions, since the cycloaddition of (trimethylsilyl)ketene[28] with the β-silyloxyaldehyde *rac*-**27** (Scheme 6) gave three inseparable β-lactone cycloadducts *rac*-**28a**–**c** (88 : 3 : 9) in 77% yield with the *cis*-β-lactone **28a** being the major product. The preference for *cis*-cycloadducts has also been noted by Yamamoto and co-workers using simple aldehydes devoid of proximate stereogenic centres.[29] Selective *C*-desilylation of β-lactones **28a**–**c** led to the corresponding β-lactones **29a**,**b** as a 9 : 1 mixture of two diastereoisomers (Scheme 6). This ratio, indicative of the 1,3-diastereoselectivity of the reaction, is similar to the ratio obtained with *n*-hexyl(trimethylsilyl)ketene and provides additional evidence for a strong stereoelectronic preference for the *cis* orientation of the aldehyde substituent and the trimethylsilyl group in the cycloaddition.

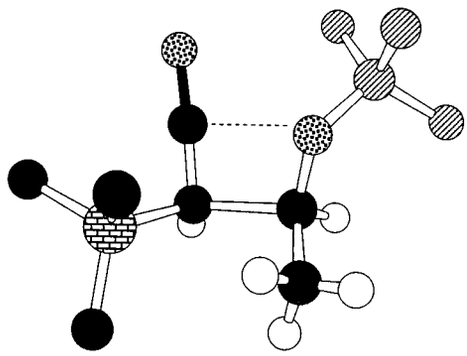
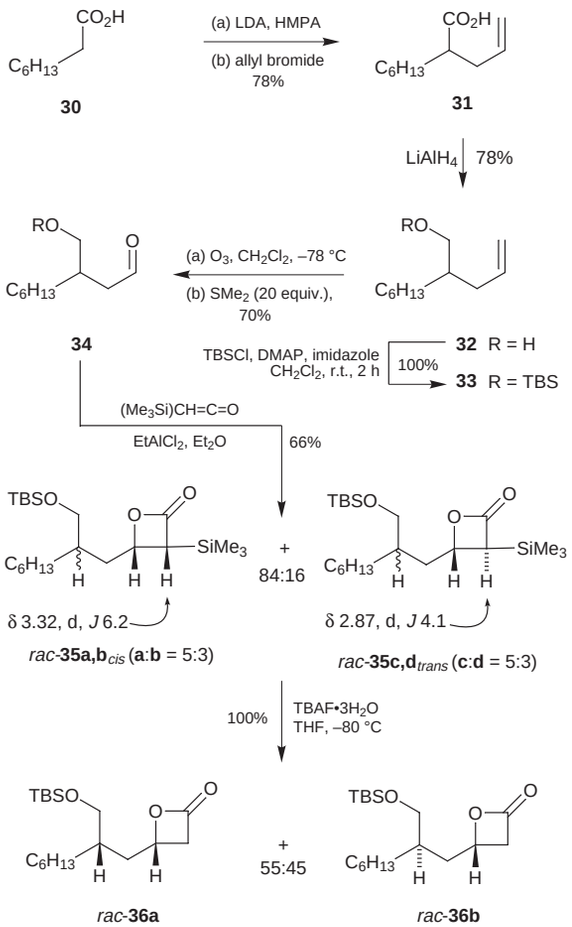


Fig. 1

In 1994 we proposed that the Lewis acid catalysed cycloaddition of silylketenes to aldehydes involved attack by the *nucleophilic* silylketene (terminal carbon atom) on an aldehyde–Lewis acid complex.[15] Such a mechanism, although not obvious, was based on experimental evidence from Zaitseva's group,[30,31] the high electron density of the terminal carbon atom of the trimethylsilylketene ($Me_3Si\mathbf{CH}{=}C{=}O$: δ_H 1.65; δ_C −0.3), and theoretical work from Tidwell and co-workers on the stability of silylketenes[32] together with preliminary theoretical studies by Yamabe *et al.* on the [2+2] cycloaddition.[33] More recently, *ab initio* calculations on the Lewis acid catalysed [2+2] cycloaddition of ketene to formaldehyde reported by Cossio and co-workers (with BH_3 as a model Lewis acid)[34,35] and us (with BF_3 as Lewis acid)[36] lent support to such a mechanism. Indeed, in both cases, calculations reveal prior formation of the C–C bond between the terminal carbon atom of the ketene and the carbon atom of the formaldehyde. Moreover, only a synperiplanar approach of the reactants was found which is in agreement with our proposed mechanism. We have also calculated at the semiempirical level, including solvation effects (AM1/RHF-COSMO), the influence of the introduction of a silyl (SiH_3) or a trimethylsilyl group on the ketene. Apart from an increase in the activation energy, which can be attributed to the remarkable stability of silylketenes, we found no significant changes on the reaction profile which remains concerted, but asynchronous, with a pronounced ionic character. Fig. 1 depicts a model of the transition state for the [2+2] cycloaddition of (trimethylsilyl)ketene and acetaldehyde catalysed by BF_3 which is extrapolated from the theoretical studies based on simpler systems.[37] The hydrogen atoms on the trimethylsilyl group have been omitted for clarity.

We previously speculated that the 1,3-diastereoselectivity observed in [2+2] cycloadditions to β-silyloxy aldehydes originates from an attractive electrostatic interaction between the aldehyde oxygen and the complexed β-silyloxy aldehyde resulting in a preferred conformation similar to that which would be expected for a chelated complex.[15] Indeed Zemribo and Romo[38] have performed [2+2] cycloadditions of (trimethylsilyl)ketene to β-benzyloxyaldehydes using a bidentate Lewis acid ($MgBr_2{\cdot}OEt_2$) and found that the diastereoselectivity is qualitatively and quantitatively similar to our observations using monodentate Lewis acids. One consequence of the electrostatic interaction model is that stereoselectivity should diminish with increasing distance of the alkoxy or silyloxy substituent from the aldehyde. Accordingly, we examined the [2+2] cycloaddition of (trimethylsilyl)ketene with γ-silyloxyaldehyde **34** in the presence of $EtAlCl_2$ (Scheme 7). A mixture of four inseparable β-lactones **35a**–**d** was obtained whose ratio (**a** : **b** : **c** : **d** = 50 : 34 : 10 : 6) was determined by NMR spectroscopy. Two *cis*-isomers **35a**,**b** were formed as the major products (84% of the mixture) and the two *trans*-isomers (**35c**,**d**) accounted for 16%



Scheme 7

of the mixture. *C*-Desilylation of β-lactones **35a**–**d** led to a 55:45 mixture of the two corresponding β-lactones **36a**,**b** (Scheme 7). Thus the remoteness of the silyloxy group resulted in a significant decrease in 1,3-diastereoselectivity of the reaction from 80% de (β-silyloxy) to 10% de (γ-silyloxy). Moreover, similar experiments performed on the corresponding *O*-benzyl ether gave a de of *ca*. 20% indicating that the diastereoselectivity is insensitive to the protecting group.

In conclusion, the syntheses of panclicins A–E reported herein together with our previous syntheses of lipstatin[17] and tetrahydrolipstatin[15] expands the scope of Lewis acid catalysed [2+2] cycloaddition of alkyl(trimethylsilyl)ketenes to β-silyloxyaldehydes as a general and stereoselective method for the synthesis of β-lactones. The stereocontrol exerted by the silyloxy substituent on the aldehyde component diminishes with increasing distance from the carbonyl group in accord with a conformational effect resulting from electrostatic interaction between the silyloxy substituent and the carbonyl–Lewis acid complex. Further studies on the effect of proximate substituents on the stereochemistry of the cycloaddition are in progress.

Experimental

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a nitrogen atmosphere. Solvents were dried by distillation from calcium hydride for dichloromethane, *N*,*N*-dimethylformamide, pyridine, triethylamine and cyclohexane or sodium and benzophenone for diethyl ether (referred to as ether) and tetrahydrofuran. Organic extracts were dried over $MgSO_4$ or Na_2SO_4 (as specified) and evaporated at aspirator pressure on a rotary evaporator.

All reactions were monitored by thin layer chromatography (TLC) with Macherey-Nagel Duren Alugram Sil G/UV_{254} aluminium foil sheets. Compounds were visualised with UV and/or phosphomolybdic acid in ethanol. Column chromatography was performed on Merck Kieselgel 60 (0.04–0.063 mm, 230–400 mesh) and run under pressure.

Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR Spectrophotometer, using NaCl plates or quartz cell. Peak intensities are defined as strong (s), medium (m) or weak (w). ^{1}H NMR spectra were recorded in Fourier Transform mode on a JEOL GX-270 and 250 and Bruker AC 300 and AMX 400 spectrometers, ^{13}C NMR spectra were recorded on Jeol GX-270 and Brüker AC-300 and AMX 400 spectrometers. ^{1}H chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.27). Coupling constants (J) are given in Hz. ^{13}C NMR spectra are quoted relative to $CDCl_3$ (δ 77.1) as an internal standard in which C–H coupling was analysed using the distortionless enhancement by phase transfer (DEPT) spectral editing technique with second pulses at 90 and 135°. C–H coupling is indicated by an integer 0–3 in parentheses following the ^{13}C chemical shift value denoting the number of coupled protons. Mass spectra were obtained from the mass spectrometry services at the Department of Chemistry at the University of Southampton and SmithKline Beecham, Brockham Park. The values given are in atomic mass units (amu), followed in parentheses by the peak intensity relative to the base peak 100%. Accurate mass determinations and low resolution mass spectra were made on compounds purified by either distillation or column chromatography and estimated to be at least 95% pure by NMR spectroscopy and TLC. Combustion analyses were conducted at the University College of London.

Methyl 3-oxodecanoate 8

Octanoyl chloride (33 cm^3, 191 mmol) was added dropwise to a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione **6** (Aldrich, 25 g, 173 mmol) in pyridine (900 cm^3) and CH_2Cl_2 (150 cm^3) at 0 °C. The cooling bath was removed and the reaction was stirred at ambient temperature for 1.5 h and then washed with 2 M HCl (3 × 100 cm^3) and H_2O (3 × 100 cm^3). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a dark brown–red oil which was dissolved in MeOH (100 cm^3) and refluxed for 16 h. The solvent was removed *in vacuo* and the residue was dissolved in benzene (100 cm^3) and washed successively with 10% aq. K_2CO_3 (2 × 50 cm^3) and H_2O (2 × 50 cm^3). The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo* to give a red–dark brown oil (33.8 g) which was purified by column chromatography (SiO_2, hexanes:ether = 1:5) to give the title compound (25 g, 125 mmol, 72%) as a pale yellow oil, ν_{max}(film)/cm^{-1} 2929s, 2856s, 1748s, 1718s, 1654m, 1628m; δ_H(270 MHz, $CDCl_3$) 3.68 (3H, s, OMe), 3.40 (2H, s, $COCH_2CO$), 2.48 (2H, t, J 7.36, CH_2CO), 1.61–1.43 (2H, m, CH_2), 1.33–1.10 (8H, m, 4 × CH_2), 0.82 (3H, distorted t, J 7.1, Me); δ_C(67.5 MHz, $CDCl_3$) 202.9 (0), 167.8 (0), 52.33 (3), 49.1 (2), 43.12 (2), 31.7 (2), 29.1 (2), 29.0 (2), 23.5 (2), 22.7 (2), 14.1 (3); *m*/*z* (CI mode, NH_3) 218 [(M + NH_4)$^+$, 100%], 201 [(M + H)$^+$, 25].

Methyl (*R*)-3-hydroxydecanoate 9

A Parr autoclave was charged with a solution of the keto ester **8** (2.30 g, 11.5 mmol) in methanol (20 cm^3). [(*R*)-(+)-2,2′-Bis-(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride (Aldrich, 9.29 mg, 0.01 mmol) and 2 M HCl (0.02 cm^3) were added and the mixture stirred under H_2 at 200 psi at 40 °C for 48 h. The cooled reaction mixture was concentrated *in vacuo* and the residue was dissolved in Et_2O (30 cm^3) and washed with saturated aqueous sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes:ether = 1:1) to give the title compound (1.9 g, 9.4 mmol, 82%) as a colourless oil, $[\alpha]_D^{20}$ −13.5 (*c* 2.5, $CHCl_3$) {lit.,[39] $[\alpha]_D^{20}$ −15.7 (*c* 2.06, $CHCl_3$)}; ν_{max}(film)/cm^{-1} 3441m, 2927s, 2856m, 1740s, 1438m; δ_H(270 MHz, $CDCl_3$) 4.04–3.88 (1H, m, OH), 3.67 (3H, s, OMe), 3.01 (1H, br s, HCO*H*), 2.48

(1H, dd, *J* 16.2, 3.7, $COCH_AH_BCO$), 2.38 (1H, dd, *J* 16.2, 8.8, $COCH_AH_BCO$), 1.60–1.14 (12H, br m, 6 × CH_2), 0.84 (3H, distorted t, *J* 6.6, Me); δ_C(67.5 MHz, $CDCl_3$) 173.6 (0), 68.1 (1), 51.8 (3), 41.3 (2), 36.7 (2), 31.9 (2), 29.6 (2), 29.3 (2), 25.6 (2), 22.7 (2), 14.2 (3); *m*/*z* (CI mode, NH_3) 220 [$(M + NH_4)^+$, 97%], 203 [$(M + H)^+$, 100], 185 (35). ^{19}F NMR analysis of the Mosher ester derivative established an ee of 98%.

Methyl (*R*)-3-(*tert*-butyldimethylsilyloxy)decanoate 10

A three-necked round-bottomed flask fitted with a magnetic stirrer and thermometer was charged with a solution of the hydroxy ester **9** (1.00 g, 5.0 mmol) in DMF (5 cm^3). With ice-bath cooling, imidazole (851 mg, 12.5 mmol) in DMF (5 cm^3) was added, followed by the dropwise addition of TBSCl (980 mg, 6.5 mmol) in DMF (5 cm^3). The cooling bath was removed and the mixture stirred for 16 h at room temp. The mixture was poured into H_2O (100 cm^3) with stirring and the product extracted into hexane (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, hexanes : ether = 6 : 1) to give the title compound (1.17 mg, 3.70 mmol, 75%) as a colourless oil, $[a]_D^{20}$ −14.5 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2955s, 2929s, 2857s, 1744s; δ_H(270 MHz, $CDCl_3$) 4.11 (1H, app. quintet, *J* 5.9, CHOTBS), 3.64 (3H, s, OMe), 2.45–2.38 (2H, app. dd, *J* 5.9, 1.5, $COCH_2CO$), 1.54–1.40 (2H, m, CH_2), 1.40–1.17 (10H, br s, 5 × CH_2), 0.85 (12H, br s), 0.05 and 0.02 (3H each, s, Me_2Si); δ_C(67.5 MHz, $CDCl_3$) 172.3 (0), 69.5 (1), 51.3 (3), 42.5 (2), 37.6 (2), 31.8 (2), 29.6 (2), 29.2 (2), 25.9 (3C, 3), 25.7 (2), 22.8 (2), 17.9 (0), 14.0 (3), −4.6 (3), −4.9 (3); *m*/*z* (APCI, MeCN) 317 $(M + H)^+$.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)decanal 11

To a three-necked round-bottomed flask with stirrer and under N_2 was added a solution of ester **10** (547 mg, 1.73 mmol) in CH_2Cl_2 (4 cm^3). The reaction mixture was cooled to −80 °C whereupon DIBAL-H (1.5 M in toluene, 1.27 cm^3, 1.90 mmol) was added dropwise at a rate sufficient to maintain the temperature at −80 °C. The mixture was then stirred at −80 °C for 30 min. The cooling bath was removed and a saturated aqueous solution of ammonium chloride (2 cm^3) was added followed by 2 M HCl (4 cm^3). The reaction was left to warm up to room temp. The reaction was then washed with H_2O (3 × 10 cm^3) and the aqueous layer extracted with CH_2Cl_2 (3 × 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* and the residue was purified *via* column chromatography (SiO_2, hexanes : EtOAc = 6 : 1) to give the title compound (327 mg, 1.14 mmol, 66%) as a colourless oil [HRMS (CI mode, NH_3): Found, $(M + H)^+$, 287.2401. $C_{16}H_{34}O_2Si+H$ requires 287.2406]; $[a]_D^{20}$ −0.1 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2955s, 2928s, 2959s, 1728s, 1255s; δ_H(270 MHz, $CDCl_3$) 9.82 (1H, t, *J* 2.5, CHO), 4.18 (1H, app. quintet, *J* 5.8, HCOTBS), 2.52 (2H, app. dd, *J* 5.8, 2.5, $COCH_2CO$), 1.60–1.40 (2H, m, CH_2), 1.40–1.05 (10H, br s, 5 × CH_2), 0.96 (12H, br s), 0.09 and 0.08 (3H each, s, Me_2Si); δ_C(67.5 MHz, $CDCl_3$) 202.5 (1), 68.4 (1), 50.9 (2), 38.0 (2), 31.9 (2), 29.7 (2), 29.3 (2), 25.9 (3C, 3), 25.2 (2), 22.8 (2), 18.1 (0), 14.2 (3), −4.3 (3), −4.6 (3); *m*/*z* (CI mode, NH_3) 304 $[(M + NH_4)^+$, 25%], 287 $[(M + H)^+$, 88], 243 (100), 229 (77), 132 (33).

1-Ethoxy-10-methylundec-1-yne 12a

A three-necked round-bottomed flask was charged with THF (50 cm^3) and then ethoxyacetylene (3.07 g, 43.7 mmol) was added. The solution was cooled to −80 °C. Butyllithium (1.60 M in hexanes, 31.1 cm^3, 49.8 mmol) was added dropwise and the mixture was stirred for 1 h. Hexamethylphosphoramide (16.7 cm^3, 94.2 mmol) was then added dropwise while the temperature was maintained at −80 °C and the reaction mixture was stirred for a further 30 min. 1-Iodo-8-methylnonane **39** (9.64 g, 35.95 mmol) (for preparation see later) in THF (10 cm^3) was added and the solution allowed to warm up to room temp. and stirred for 24 h. The mixture was hydrolysed with water (100 cm^3), stirred for 1 h and the organic layer was extracted with ether (3 × 200 cm^3). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified *via* rapid column chromatography (SiO_2, hexanes containing 0.5% NEt_3) to give the title compound (4.5 g, 21.4 mmol, 49%) as a colourless oil, ν_{max}(film)/cm^{-1} 2927s, 2855s, 2272s, 1467m, 1223s; δ_H(270 MHz, $CDCl_3$) 4.0 (2H, q, *J* 6.6, CH_3CH_2O), 2.10 (2H, t, *J* 6.6, $CH_2C\equiv$), 1.61–1.09 (16H, m), 0.86 (6H, d, *J* 6.6, Me_2CH); δ_C(67.5 MHz, $CDCl_3$) 89.3 (0), 73.7 (2), 39.3 (2), 39.0 (2), 37.3 (0), 29.8 (2), 29.2 (2), 28.8 (2), 27.9 (1), 27.4 (2), 22.6 (2C, 3), 17.2 (2), 14.3 (3); *m*/*z* (EI mode) 167 $[(M - CHMe_2)^{\cdot+}$, 5%], 85 (100).

1-Ethoxydodec-1-yne 12b

Reaction of ethoxyacetylene (4.58 g, 65.3 mmol) and 1-iododecane (14.4 g, 53.7 mmol) according to the procedure described above gave the title compound (7.67 g, 36.5 mmol, 68%) as a colourless oil, ν_{max}(film)/cm^{-1} 2926s, 2855s, 2272s; δ_H(270 MHz, $CDCl_3$) 4.01 (2H, q, *J* 7.0, CH_3CH_2O), 2.11 (2H, t, *J* 6.9, $CH_2C\equiv$), 1.34 (3H, t, *J* 6.9, OCH_2CH_3), 1.27 (16H, m, 8 × CH_2), 0.88 (3H, br t, *J* 6.6, Me); δ_C(67.5 MHz, $CDCl_3$) 89.3 (0), 73.8 (2), 37.4 (0), 31.9 (2), 29.8 (2), 29.8 (2), 29.6 (2), 29.3 (2), 29.2 (2), 28.8 (2), 22.7 (2), 17.2 (2), 14.3 (3), 14.1 (3); *m*/*z* (APCI, MeCN) 211 $(M + H)^+$.

1-Ethoxytetradec-1-yne 12c

Reaction of ethoxyacetylene (4.68 g, 66.7 mmol) and 1-iodododecane (16.5 g, 55.7 mmol) according to the procedure described above gave the title compound (11.6 g, 52.2 mmol, 60%) as a colourless oil, ν_{max}(film)/cm^{-1} 2923s, 2853s, 2271s, 1223s, 869m; δ_H(300 MHz, $CDCl_3$) 4.01 (2H, q, *J* 7.1, CH_3CH_2O), 2.11 (2H, t, *J* 6.6, $CH_2C\equiv$), 1.51 (20H, m, 10 × CH_2), 1.34 (3H, t, *J* 7.0, CH_3CH_2O), 0.89 (3H, distorted t, *J* 7.0, Me); δ_C(67.5 MHz, $CDCl_3$) 89.4 (0), 73.9 (2), 37.5 (0), 32.1 (2), 29.9 (2C, 2), 29.8 (3C, 2), 29.5 (2), 29.4 (2), 29.0 (2), 22.8 (2), 17.4 (2), 14.5 (3), 14.2 (3); *m*/*z* (APCI, MeCN) 239 $(M + H)^+$.

8-Methylnonyl(trimethylsilyl)ketene 13a

A flame-dried 50 cm^3 round-bottomed flask fitted with a reflux condenser and magnetic stirrer was charged with hexamethyldisilane (7.6 cm^3, 37.2 mmol). With rigorous exclusion of moisture, the mixture was warmed to 80 °C whereupon freshly sublimed iodine (8.6 g, 33.9 mmol) was added slowly over 1 h *via* a sealed tube connected to one of the necks of the flask with a glass joint. The reaction mixture was heated at 80 °C for a further 1 h. The reaction mixture was then cooled to room temp. and copper powder (307 mg, 4.8 mmol) was added. The reaction mixture was stirred for 5 min at room temp. and then the alkoxy alkyne **12a** (4.38 g, 20.8 mmol) was added dropwise and the mixture heated at 70 °C for 48 h. The reaction was then cooled and the excess iodotrimethylsilane removed *in vacuo* and the crude product was distilled using a Kugelrohr apparatus to yield the desired ketene **13a** (2.63 g, 10.3 mmol, 50%) as a pale yellow oil, bp 140 °C (bath)/7 mmHg; ν_{max}(film)/cm^{-1} 2955s, 2926m, 2856m, 2085s, 1251m, 840s; δ_H(300 MHz, $CDCl_3$) 1.91 (2H, t, *J* 7.3, $CH_2C=$), 1.62–1.05 (13H, m), 0.88 (6H, d, *J* 6.6, Me_2C), 0.17 (9H, s, Me_3Si); δ_C(75 MHz, $CDCl_3$) 182.4 (0), 39.0 (2), 31.6 (2), 30.5 (2), 29.8 (2), 29.5 (1), 29.4 (2C, 2), 22.6 (2C, 3), 22.0 (2), 12.8 (0), −0.9 (3C, 3); *m*/*z* (CI mode, NH_3) 255 $[(M + H)^+$, 4%], 201 (99), 129 (100), 73 (92).

***n*-Decyl(trimethylsilyl)ketene 13b**

By the same procedure alkoxy alkyne **12b** (1.0 g, 4.75 mmol) gave the title compound (529 mg, 2.08 mmol, 44%) as a pale yellow oil after Kugelrohr distillation, bp 140 °C (bath)/7 mmHg; ν_{max}(film)/cm^{-1} 2956m, 2926s, 2855m, 2086s, 1466m, 1251m, 841s; δ_H(300 MHz, $CDCl_3$) 1.91 (2H, t, *J* 7.4, $CH_2C=$), 1.53–1.20 (16H, m), 0.89 (3H, t, *J* 7.0, Me), 0.16 (9H, s, Me_3Si);

δ_C(75 MHz, $CDCl_3$) 182.5 (0), 32.1 (2), 31.8 (2), 29.7 (2C, 2), 29.5 (2C, 2), 29.3 (2), 22.8 (2), 22.2 (2), 14.3 (3), 13.0 (0), −0.8 (3C, 3); *m*/*z* (CI mode, NH_3) 255 [$(M + H)^+$, 50%], 170 (32), 90 (100).

n-Dodecyl(trimethylsilyl)ketene 13c

By the same procedure alkoxyalkyne **12c** (5.0 g, 21.0 mmol) gave the title compound (3.53 g, 12.51 mmol, 44%) as a pale yellow oil after Kugelrohr distillation, bp 170 °C (bath)/0.4 mmHg; ν_{max}(film)/cm^{-1} 2956m, 2925s, 2854m, 2086s, 1251m, 841m; δ_H(300 MHz, $CDCl_3$) 1.91 (2H, t, *J* 7.4, CH_2C=), 1.54–1.21 (20H, m), 0.89 (3H, distorted t, *J* 6.6, Me), 0.16 (9H, s, Me_3Si); δ_C(75 MHz, $CDCl_3$) 182.5 (0), 32.1 (2), 31.8 (2), 30.0 (4C, 2), 29.8 (2C, 2), 29.5 (2), 22.8 (2), 22.2 (2), 14.3 (3), 13.0 (0), −0.8 (3C, 3); *m*/*z* (CI mode, NH_3) [$(M + NH_4)^+$, 16%], 283 [$(M + H)^+$, 32], 90 (86), 35 (53).

(2′*R*,3*R*,4*S*)-3-(8-Methylnonyl)-3-trimethylsilyl-4-(2′-hydroxynonyl)oxetan-2-one 17a and its (3*S*)-epimer 18a

A round-bottomed flask fitted with a magnetic stirrer and thermometer was charged with a solution of the aldehyde **11** (1.89 g, 6.60 mmol) in ether (20 cm^3) and cooled to −50 °C. Ethylaluminium dichloride in hexane (7.25 cm^3, 7.25 mmol, 1 M in hexane) was added dropwise. The mixture was stirred at −50 °C for 10 min and then a solution of the silyl ketene **13a** (2.48 g, 9.76 mmol) in ether (5 cm^3) was added dropwise. The reaction was allowed to warm to −4 °C, and quenched with water. The reaction mixture was then extracted into ether (3 × 15 cm^3), the organic layers combined and dried ($MgSO_4$) and then concentrated *in vacuo* to give a pale yellow oil (3.2 g, 90%). The crude product was purified *via* column chromatography (SiO_2, hexanes : ether = 99 : 1) to give the β-lactones **15a** and **16a** (2.99 g, 5.53 mmol, 84%) as an inseparable mixture of diastereoisomers which was dissolved in acetonitrile (30 cm^3). The solution was cooled in an ice bath and hydrogen fluoride (0.32 cm^3, 48% aq.) was added dropwise. After addition was complete, the ice bath was removed and the mixture was stirred for 4 h at room temp. whereupon saturated aq. $NaHCO_3$ was added to quench excess hydrogen fluoride. The reaction was then concentrated *in vacuo* and the residue extracted into ether (3 × 20 cm^3). The combined ethereal extracts were washed with saturated aq. $NaHCO_3$ (3 × 30 cm^3), dried ($MgSO_4$) and concentrated to give a viscous colourless oil which was purified *via* column chromatography (SiO_2, hexanes : ether = 5 : 1) to give pure **17a** (2.00 g, 4.69 mmol, 85%) as a viscous, colourless oil, $[\alpha]_D^{18}$ −57.4 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3452m, 2855s, 1800s, 1466m, 1254m, 846s; δ_H(300 MHz, $CDCl_3$) 4.71 (1H, dd, *J* 11.0, 2.2, CHOC=O), 3.85–3.71 (1H, m, *H*COH), 2.11–1.88 (2H, m, OH and $CH_AH_BCOCH_2$), 1.84–1.65 (3H, m, $CH_AH_BCOCH_2$), 1.57–1.07 (25H, m), 0.85 (9H, distorted d, *J* 6.6, Me_2CH and Me), 0.20 (9H, s, Me_3Si); δ_C(75 MHz, $CDCl_3$) 174.1 (0), 76.3 (1), 68.4 (1), 54.8 (0), 39.8 (2), 39.0 (2), 38.1 (2), 31.8 (2), 30.6 (2), 29.9 (2), 29.8 (2), 29.5 (2C, 2), 29.4 (2), 29.2 (2), 27.9 (1), 27.3 (2), 26.1 (2), 25.5 (2), 22.6 (2C, 3), 14.1 (3), −1.0 (3C, 3); *m*/*z* (CI mode, NH_3) 427 [$(M + H)^+$, 26%], 409 (100), 337 (33), 73 (27).

Through repeated chromatography of the mixture resulting from the above reaction a sample sufficiently enriched (*ca*. 70%) in isomer (2′*R*,3*S*,4*S*)-3-(8-methylnonyl)-4-[2′-hydroxynonyl]-oxetan-2-one **18a** was obtained and the following assignments could be made, δ_H(300 MHz, $CDCl_3$) 4.64 (1H, dd, *J* 10.3, 2.2, CHOC=O), 3.93–3.73 (1H, m, *H*COH), 2.14–1.64 (4H, m, CH_2COCH_2), 1.61–1.09 (26H, m), 0.86 (9H, Me_2CH and Me), 0.21 (9H, s, Me_3Si); δ_C(75 MHz, $CDCl_3$) 174.2 (0), 73.8 (1), 68.2 (1), 53.2 (0), 39.5 (2), 39.0 (2), 38.2 (2), 38.0 (2), 37.0 (2), 31.8 (2), 29.8 (2), 29.5 (2), 29.4 (2), 29.2 (2), 27.9 (1), 27.3 (2), 26.7 (2), 26.2 (2), 25.5 (2), 22.6 (2C, 3), 14.1 (3), −3.3 (3C, 3).

(2′*R*,3*R*,4*S*)-3-*n*-Decyl-3-trimethylsilyl-4-(2′-hydroxynonyl)-oxetan-2-one 17b

The cycloaddition described above starting with the aldehyde **11** (353 mg, 1.23 mmol) and silyl ketene **13b** (445.4 mg, 1.8 mmol) gave the β-lactones **15b** and **16b** (427 mg, 0.78 mmol, 57%) as an inseparable mixture of diastereoisomers. Deprotection of a sample (360 mg, 0.65 mmol) with HF in acetonitrile gave the major isomer **17b** (104 mg, 0.24 mmol, 37%) as a colourless oil which crystallised in the freezer, mp ~0 °C (Found: C, 70.38; H, 12.02%. $C_{25}H_{50}O_3Si$ requires C, 70.36; H, 11.81%); $[\alpha]_D^{22}$ −64 (*c* 2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3452s, 2959s, 2924s, 2854s, 1803s, 1466m, 1254s, 846s; δ_H(300 MHz, $CDCl_3$) 4.73 (1H, dd, *J* 11.4, 2.3, CHOC=O), 3.90–3.76 (1H, m, *H*COH), 2.07–1.63 (5H, m), 1.56–1.05 (28H, m), 0.89 (6H, distorted t, *J* 6.8, 2 × Me), 0.23 (9H, s, Me_3Si); δ_C(75 MHz, $CDCl_3$) 174.2 (0), 76.4 (1), 68.7 (1), 55.0 (2), 38.9 (2), 38.3 (2), 32.0 (2), 31.9 (2), 30.8 (2), 30.1 (2), 29.7 (3C, 2), 29.6 (2), 29.5 (2), 29.4 (2C, 2), 26.3 (2), 25.6 (2), 22.8 (2), 14.3 (2C, 3), −1.2 (3C, 3); *m*/*z* (APCI, MeCN) 427 $(M + H)^+$.

(2′*R*,3*R*,4*S*)-3-*n*-Dodecyl-3-trimethylsilyl-4-(2′-hydroxynonyl)-oxetan-2-one 17c

The cycloaddition described above starting with the aldehyde **11** (2.03 g, 7.09 mmol) and silyl ketene **13c** (2.99 g, 10.6 mmol) gave the β-lactones **15c** and **16c** (2.95 g, 5.18 mmol, 73%) as an inseparable mixture of diastereoisomers. Deprotection of the mixture (3.20 g, 5.62 mmol) with HF in acetonitrile as described above returned pure **17c** (1.7 g, 3.47 mmol, 66%) as a viscous, colourless oil after purification by column chromatography; $[\alpha]_D^{18}$ −75.0 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3458m, 2925s, 2855s, 1803s, 1466m, 1254s, 846s; δ_H(300 MHz, $CDCl_3$), 4.71 (1H, dd, *J* 11.0, 1.8, HCOC=O), 3.85–3.69 (1H, m, *H*COH), 2.05–1.65 (5H, m, CH_2COCH_2 and OH), 1.55–1.16 (32H, m), 0.87 (6H, distorted t, *J* 6.6, 2 × Me), 0.21 (9H, s, Me_3Si); δ_C(75 MHz, $CDCl_3$) 174.1 (0), 76.3 (1), 68.4 (1), 54.8 (1), 39.8 (2), 38.1 (2), 31.9 (2), 31.8 (2C, 2), 30.6 (2), 29.9 (2), 29.6 (2C, 2), 29.5 (2), 29.4 (2C, 2), 29.3 (2), 29.2 (2), 26.1 (2), 25.5 (2), 22.7 (2), 22.6 (2), 14.1 (2C, 3), −1.0 (3C, 3); *m*/*z* (APCI, MeCN) 455 $(M + H)^+$.

(2′*R*,3*S*,4*S*)-3-[8-Methylnonyl]-4-(2′-hydroxynonyl)oxetan-2-one 19a

To a solution of the β-lactones **17a** and **18a** (1.71 g, 4.01 mmol) in THF (25 cm^3) at −90 °C was added dropwise a solution of TBAF·$3H_2O$ (1.38 g) in THF (5.0 cm^3). After stirring for 15 min the reaction mixture was poured into rapidly stirred ice/water overlaid with ether (10 cm^3). The product was extracted into ether (3 × 20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give a white crystalline solid (1.57 g) from which the major diastereoisomer **19a** (1.3 g, 3.67 mmol, 91%) was obtained *via* column chromatography (SiO_2, hexanes : ether = 1 : 1) as a white crystalline compound which was recrystallised from pentane to give pure **19a** (1.21 g, 3.39 mmol, 84%), mp 50–52 °C (Found: C, 74.57; H, 12.13%. $C_{22}H_{42}O_3$ requires C, 74.52; H, 11.94%); $[\alpha]_D^{18}$ −43.1 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 3460w, 3021s, 1815m, 1220s, 774s; δ_H(270 MHz, $CDCl_3$) 4.49 (1H, overlapping dt, *J* 4.4, CHOC=O), 3.86–3.71 (1H, m, *H*COH), 3.24 (1H, td, *J* 11.6, 4.1, CHC=O), 2.15–2.05 (1H, br s, OH), 1.96–1.60 (4H, m, CH_2COCH_2), 1.56–1.10 (25H, m), 0.89–0.82 (9H, m, Me_2CH and Me); δ_C(67.5 MHz, $CDCl_3$) 171.9 (0), 75.8 (1), 68.4 (1), 56.6 (1), 42.0 (2), 39.1 (2), 38.2 (2), 31.9 (2), 29.9 (2), 29.6 (1), 29.5 (2C, 2), 29.4 (2), 29.3 (2), 28.0 (2), 27.8 (2), 27.4 (2), 26.9 (2), 25.5 (2), 22.7 (2C, 3), 14.2 (3); *m*/*z* (EI mode) 354 [$(M)^{\cdot+}$, 6%], 182 (83), 69 (100).

(2′*R*,3*S*,4*S*)-3-*n*-Decyl-4-(2′-hydroxynonyl)oxetan-2-one 19b

To a solution of the β-lactone **17b** (104 mg, 0.19 mmol) in THF (1 cm^3) at −90 °C was added dropwise a solution of TBAF·$3H_2O$ (68.90 mg) in THF (0.1 cm^3). After stirring for 15 min the reaction mixture was poured into rapidly stirred ice/water overlaid with ether (5 cm^3). The product was extracted into ether (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give a white crystalline solid (95 mg) which was recrystallised from

pentane to give pure *trans* isomer **19b** (80 mg, 0.23 mmol, 93%), mp 55–56 °C (Found: C, 74.56; H, 12.17%. $C_{22}H_{42}O_3$ requires C, 74.52; H, 11.94%); $[\alpha]_D^{22}$ −34.4 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3019s, 2976m, 2929m, 1815m, 1212s, 766s; δ_H(300 MHz, $CDCl_3$) 4.50 (1H, app. quintet, *J* 4.4, HCOC=O), 3.84–3.69 (1H, m, *H*COH), 3.25 (1H, td, *J* 7.4, 4.0, CHC=O), 2.05–1.96 (1H, br s, OH), 1.96–1.65 [4H, m, CH_2C(OH)CH_2], 1.56–1.18 (28H, m), 0.87 (6H, distorted t, *J* 6.6, 2 × Me); δ_C(75 MHz, $CDCl_3$) 171.9 (0), 75.8 (1), 68.5 (1), 56.6 (1), 42.0 (2), 38.2 (2), 32.0 (2), 31.9 (2), 30.8 (2), 29.7 (2C, 2), 29.6 (2C, 2), 29.5 (2), 29.4 (2), 27.8 (2), 26.9 (2), 25.6 (2), 22.8 (2C, 2), 14.2 (2C, 3); *m*/*z* (CI mode, NH_3) 372 [(M + NH_4)$^+$, 100%], 355 [(M + H)$^+$, 35%], 337 (10).

Column chromatography of the mother liquors (SiO_2, hexanes : ether = 1 : 1) gave the *cis*-isomer (2′R,3R,4S)-3-n-*decyl*-4-(2′-*hydroxynonyl*)*oxetan*-2-*one* **18b** (91 mg, 0.26 mmol, 8%), mp ~0 °C; $[\alpha]_D^{22}$ −12 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3424m, 2926s, 2855s, 1823s, 1466m, 1118m, 819m; δ_H(300 MHz, $CDCl_3$) 4.90 (1H, ddd, *J* 10.3, 6.3, 2.2, HCOC=O), 3.91–3.78 (1H, m, *H*COH), 3.71–3.59 (1H, overlapping dt, *J* 7.6, CHC=O), 1.91–1.68 (4H, m, $COCH_2CO$ and CH_2CC=O), 1.68–1.80 (29H, m), 0.89 (6H, distorted t, *J* 6.6, 2 × Me); δ_C(75 MHz, $CDCl_3$) 172.4 (0), 72.9 (1), 68.1 (1), 52.7 (1), 38.3 (2), 37.6 (2), 32.0 (2), 31.9 (2), 29.7 (2C, 2), 29.6 (2), 29.5 (2C, 2), 29.4 (2), 27.7 (2), 25.6 (2), 25.2 (2), 24.3 (2), 22.8 (2C, 2), 14.3 (2C, 3); *m*/*z* (CI mode, NH_3) 372 [(M + NH_4)$^+$, 100%], 355 [(M + H)$^+$, 35], 337 (12).

(2′*R*,3*S*,4*S*)-3-*n*-Dodecyl-4-(2′-hydroxynonyl)oxetan-2-one 19c

Desilylation of the β-lactone **17c** (1.81 g, 3.98 mmol) in THF (15 cm^3) at −90 °C with TBAF·3H_2O (1.37 g, 4.36 mmol) in THF (5.0 cm^3) as described above gave **19c** (945 mg, 2.47 mmol, 62%) as a white crystalline solid after column chromatography (SiO_2, hexanes : ether = 3 : 1). Recrystallisation from pentane afforded pure **19c** (850 mg, 2.22 mmol, 56%), mp 54–56 °C (Found: C, 75.06; H, 12.19%. $C_{24}H_{46}O_3$ requires C, 75.34; H, 12.12%); $[\alpha]_D^{18}$ −35.7 (*c* 0.98, $CHCl_3$); ν_{max}(film)/cm^{-1} 3589w, 2928s, 2856s, 1815s, 1466m, 772m; δ_H(300 MHz, $CDCl_3$) 4.40 (1H, overlapping dt, *J* 4.25, HCOC=O), 3.78–3.64 (1H, m, HCO), 3.15 (1H, td, *J* 11.2, 3.7, HCC=O), 1.85–1.57 (4H, m, CH_2COCH_2), 1.45–1.05 (33H, m), 0.77 (6H, distorted t, *J* 6.5, 2 × Me); δ_C(75 MHz, $CDCl_3$) 171.7 (0), 75.6 (1), 68.4 (1), 56.5 (1), 41.8 (2), 38.1 (2), 31.9 (2C, 2), 29.6 (2C, 2), 29.5 (2C, 2), 29.3 (2C, 2), 29.2 (2), 27.7 (2), 26.8 (2), 25.4 (2), 22.7 (2), 22.6 (2C, 2), 15.2 (2), 14.1 (2C, 3); *m*/*z* (APCI, MeCN) 383 (M + H)$^+$.

(2′*S*,3*S*,4*S*)-3-(8-Methylnonyl)-4-{2′-[2″-(*N*-tritylamino)-propanoyloxy]nonyl}oxetan-2-one 20a

To a magnetically stirred solution of triphenylphosphine (667.0 mg, 2.54 mmol), *N*-tritylalanine[25,26] (97.0 mg, 0.29 mmol) and β-lactone **19a** (300 mg, 0.84 mmol) in THF (5 cm^3) was added dropwise at 0 °C diisopropyl azodicarboxylate (0.50 cm^3, 2.54 mmol). The reaction was stirred at 0 °C for 2 h and then allowed to warm up slowly to room temp. overnight. The mixture was concentrated *in vacuo* and triphenylphosphine oxide crystallised from ether–hexanes and filtered. The filtrate was concentrated and the residue purified by column chromatography (SiO_2, hexanes : ether = 20 : 1) to give **20a** (129 mg, 0.19 mmol, 23%) as a viscous colourless oil, $[\alpha]_D^{18}$ −2.17 (*c* 1.29, $CHCl_3$); ν_{max}(film)/cm^{-1} 2926s, 2855s, 1826s, 1732s; δ_H(300 MHz, $CDCl_3$) 7.58–7.45 (5H, m, aromatic H), 7.33–7.12 (10H, m, aromatic H), 4.50–4.35 (1H, m, C*H*NH), 4.21–4.05 (1H, m, HCOCOCN), 3.43–3.30 (1H, m, HCOC=O), 3.13 (1H, dt, *J* 11.8, 3.7, CHC=O), 2.75–2.60 (1H, m, NH), 2.04–1.61 (4H, m, CH_2COCH_2), 1.60–1.09 (28H, m), 0.96–0.81 (9H, m, Me_2CH and Me); δ_C(75 MHz, $CDCl_3$) 175.4 (0), 171.0 (0), 146.2 (3C, 0), 128.7 (6C, 1), 127.8 (6C, 1), 126.4 (3C, 1), 74.5 (1), 71.6 (1), 71.3 (0), 56.9 (1), 51.9 (1), 39.0 (2C, 2), 37.9 (2), 33.5 (2), 31.8 (2C, 2), 29.8 (2), 29.4 (1), 29.3 (2), 29.2 (2), 28.0 (1), 27.6 (2), 27.3 (2), 26.7 (2), 25.1 (2), 22.7 (2), 22.0 (2C, 3), 14.2 (3).

(2′*S*,3*S*,4*S*)-3-*n*-Decyl-4-{2′-[2″-(*N*-tritylamino)propanoyloxy]-nonyl}oxetan-2-one 20b

Reaction of β-lactone **19b** (42 mg, 0.12 mmol) and *N*-tritylalanine[25,26] (132 mg, 0.40 mmol) in THF (0.6 cm^3) with diisopropyl azodicarboxylate (0.07 cm^3, 0.36 mmol) and triphenylphosphine (93.5 mg, 0.36 mmol) according to the procedure described above gave the ester **20b** (50 mg, 0.06 mmol, 63%) as a viscous colourless oil, $[\alpha]_D^{22}$ −1.7 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 2826s, 2856s, 1827s, 1732s; δ_H(300 MHz, $CDCl_3$) 7.56–7.47 (6H, m, aromatic H), 7.36–7.13 (9H, m, aromatic H), 4.52–4.39 [1H, m, HCOC(O)CN], 4.23–4.11 (1H, m, MeCH), 3.45–3.30 (1H, m, HCOC=O), 3.20–3.05 (1H, dt, *J* 7.7, 3.9, HC=O), 2.77–2.62 (1H, m, NH), 2.03–1.90 [2H, m, $C(O)CH_2CO$], 1.89–1.57 (6H, m, 3 × CH_2), 1.44 (3H, d, *J* 7.0, MeCN), 1.40–1.10 (24H, m), 0.92 (6H, app. q, *J* 6.4, 2 × Me); δ_C(75 MHz, $CDCl_3$) 175.4 (0), 171.0 (0), 146.2 (3C, 0), 128.7 (6C, 1), 127.9 (6C, 1), 126.6 (3C, 1), 74.5 (1), 71.6 (1), 71.3 (0), 56.9 (1), 51.9 (1), 37.9 (2), 33.5 (2), 31.9 (2), 31.8 (2), 29.6 (2C, 2), 29.5 (2), 29.4 (2C, 2), 29.3 (2C, 2), 29.2 (2), 27.6 (2), 26.7 (2), 25.1 (2), 22.7 (2), 22.0 (3), 14.1 (2C, 3).

Panclicin A 1

The β-lactone **20a** (129 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (3.0 cm^3) under N_2 at 0 °C. Trichloroacetic acid–CH_2Cl_2 (1 : 1, 6.4 cm^3) was added dropwise to the stirring solution which was then warmed to room temp. After 10 min triisopropylsilane was added until the yellow colour of the reaction disappeared and the solvents were removed *in vacuo*. Formic acetic anhydride (4 cm^3) was then added to the residue dropwise. The mixture was diluted with ether (5 cm^3), washed with aqueous sodium hydrogen carbonate (3 × 5 cm^3), then with water (3 × 5 cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a clear oil (80 mg, 91%). The crude residue was purified *via* column chromatography (hexanes : ether = 1 : 4) to give a clear oil which slowly solidified to afford a solid product (70 mg, 0.15 mmol, 80%) which was recrystallised from pentane to give pure panclicin A (55 mg, 0.12 mmol, 63%) as a white crystalline solid, mp 53–55 °C (Found: C, 68.52; H, 10.25; N, 2.94%. $C_{26}H_{47}NO_5$ requires C, 68.84; H, 10.44; N, 3.09%); $[\alpha]_D^{18}$ −29 (*c* 0.61, $CHCl_3$) [lit.,[1] $[\alpha]_D^{25}$ −26 (*c* 1.27, $CHCl_3$)]. The product gave ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data identical to those reported for the natural product.[1]

Panclicin B 2

Treatment of β-lactone **20b** (46 mg, 0.07 mmol) in CH_2Cl_2 (1.2 cm^3) with trichloroacetic acid–CH_2Cl_2 (2.3 cm^3) as described above gave panclicin B (30 mg, 0.07 mmol, 96%) as a viscous colourless oil [HRMS (FAB mode, Ar): Found, (M + H)$^+$, 454.3533. $C_{26}H_{47}NO_5$+H requires *M*, 454.3532]; $[\alpha]_D^{22}$ −21 (*c* 0.16, $CHCl_3$) {lit.,[1] $[\alpha]_D^{25}$ −28 (*c* 0.94, $CHCl_3$)}. The product gave ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data identical to those reported for the natural product.[1]

Panclicin C 3

To a magnetically stirred solution of triphenylphosphine (333.0 mg, 1.27 mmol), *N*-formyl glycine (151.0 mg, 1.46 mmol) and β-lactone **19a** (150.0 mg, 0.42 mmol) in THF (2 cm^3) was added dropwise at 0 °C diisopropyl azodicarboxylate (0.25 cm^3, 1.27 mmol). The reaction was stirred at 0 °C for 2 h and then allowed to warm up slowly to room temp. overnight. The mixture was concentrated under reduced pressure and triphenylphosphine oxide crystallised from ether–hexanes and filtered. The filtrate was concentrated and the residue purified by column chromatography (hexanes : ether = 15 : 1) to give panclicin C (290 mg, 0.66 mmol, 70%) as a colourless oil [HRMS (FAB mode, Ar): Found, (M + H)$^+$, 440.3336. $C_{25}H_{45}NO_5$+H requires *M*, 440.3376]; $[\alpha]_D^{18}$ −18 (*c* 0.73, $CHCl_3$) {lit.,[1] $[\alpha]_D^{25}$ −20 (*c* 0.33, $CHCl_3$)}. The product gave ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data identical to those reported for the natural product.[1]

Panclicin D 4

Reaction of *N*-formyl glycine (107.6 mg, 1.04 mmol) and β-lactone **19b** (106 mg, 0.90 mmol) in THF (1.5 cm^3) with triphenylphosphine (235.9 mg, 0.91 mmol) and diisopropyl azodicarboxylate (0.18 cm^3, 0.90 mmol) as described above gave panclicin D (89 mg, 0.20 mmol, 67%) as a colourless oil, $[a]_D^{20}$ −19 (*c* 0.9, $CHCl_3$) {lit.,[1] $[a]_D^{25}$ −23 (*c* 0.3, $CHCl_3$)} [HRMS (FAB mode, Ar): Found, MH^+, 440.3344. $C_{25}H_{45}NO_5$+H requires *M*, 440.3376]. The product gave ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data identical to those reported for the natural product.[1]

***cis*-Panclicin D 4**

The experimental procedure for converting **17b** to panclicin D **4** was applied to **18b** on a 0.36 mmol scale to afford *cis*-**4** (30 mg, 0.07 mmol, 57%) as a clear oil [HRMS (FAB mode, Ar): Found, $(M + H)^+$, 440.3340. $C_{25}H_{45}NO_5$+H requires *M*, 440.3376]; $[a]_D^{22}$ −4.6 (*c* 0.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3414s, 1822m, 1746m, 1668m, 1521w; δ_H(300 MHz, $CDCl_3$) 8.27 (1H, br s, CHO), 6.21–6.04 (1H, br s, NH), 5.27–5.10 [1H, m, *H*COC(O)CH_2], 4.67 (1H, app. septet, *J* 2.9, HCOC=O), 4.14 (1H, dd, *J* 18.4, 5.9, CH_AH_BN), 4.03 (1H, dd, *J* 18.4, 5.2, CH_AH_BN), 3.72–3.60 (1H, m, CHC=O), 2.12–2.00 (1H, m, CH_AH_BCO), 1.95 (1H, dt, *J* 15.4, 3.9, CH_AH_BCO), 1.84–1.50 [4H, m, C(O)CCH_2 and CH_2CO], 1.41–1.19 (26H, m), 0.89 (6H, distorted t, *J* 6.6, 2 × Me); δ_C(75 MHz, $CDCl_3$) 171.6 (0), 169.5 (0), 161.1 (1), 73.4 (1), 72.8 (1), 53.6 (1), 40.3 (2), 34.9 (2), 34.2 (2), 32.0 (2), 31.9 (2), 29.7 (2C, 2), 29.5 (2), 29.4 (3C, 2), 29.2 (2), 27.6 (2), 25.4 (2), 24.2 (2), 22.8 (2C, 2), 14.3 (2C, 3).

Panclicin E 5

Reaction of *N*-formylglycine (187 mg, 1.81 mmol) and β-lactone **19c** (200 mg, 0.52 mmol) in THF (1.5 cm^3) with triphenylphosphine (409 mg, 1.56 mmol) and diisopropyl azodicarboxylate (0.31 cm^3, 1.56 mmol) as described above gave panclicin E (212 mg, 0.45 mmol, 87%) as a colourless oil [HRMS (FAB mode, Ar): Found, $(M + H)^+$, 468.3685. $C_{27}H_{49}NO_5$+H requires *M*, 468.3689]; $[a]_D^{18}$ −24.4 (*c* 0.25, $CHCl_3$) {lit.,[1] $[a]_D^{25}$ −27 (*c* 1.21, $CHCl_3$)}. The product gave ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data identical to those reported for the natural product.[1]

3-Trimethylsilyl-4-[2′-(*tert*-butyldimethylsilyloxy)heptyl]-oxetan-2-ones 28a–c

A solution of aldehyde **27**[40] (129 mg, 0.5 mmol) in dry Et_2O (1 cm^3) was cooled at −50 °C under argon before a solution of trimethylsilylketene (68 mg, 0.6 mmol) in dry Et_2O (0.5 cm^3) was added. Ethylaluminium dichloride (0.6 cm^3 of a 1 M solution in hexanes, 0.6 mmol) was added dropwise at that temperature. After 1 h stirring, the reaction was quenched with water (3 cm^3) and the aqueous phase was extracted with ether (3 × 3 cm^3). The organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes : ether = 97 : 3) to yield β-lactones **28a**–**c** (144 mg, 0.39 mmol, 77%) as a mixture of diastereoisomers ($\mathbf{a}_{cis}$: $\mathbf{b}_{trans}$: $\mathbf{c}_{trans}$ = 88 : 3 : 9) according to 400 MHz NMR spectroscopy of the mixture, ν_{max}(film)/cm^{-1} 1815s, 1260s, 850s, 780m; δ_H(200 MHz, $CDCl_3$) **28a**$_{cis}$ 4.80 (1H, ddd, *J* 10.6, 6.2, 2.7, CHOC=O), 3.85 (1H, m, CHOTBS), 3.38 (1H, d, *J* 6.2, CHC=O), 1.90–1.20 (10H, m, 5 × CH_2), 0.92 (9H, s, Bu^t), 0.87 (3H, distorted t, Me), 0.24 (9H, s, $SiMe_3$), 0.08 (6H, s, $SiMe_2$); δ_C(100.6 MHz, $CDCl_3$) **28a**$_{cis}$ 170.9 (0), 70.6 (1), 68.7 (1), 45.9 (1), 40.5 (2), 38.1 (2), 31.9 (2), 25.9 (3C, 3), 24.3 (2), 22.6 (2), 18.1 (0), 14.0 (3), −1.1 (3C, 3), −4.3 (3), −4.8 (3); δ_H(200 MHz, $CDCl_3$) **28c**$_{trans}$ 4.51 (1H, dt, *J* 8.9, 4.1, CHOC=O), 2.90 (1H, d, *J* 4.1, CHC=O); *m*/*z* (EI mode) 315 $[(M - Bu^t)^{\bullet+}$, 2%], 201 (100).

4-[2′-(*tert*-Butyldimethylsilyloxy)heptyl]oxetan-2-ones 29a,b

To a stirred solution of lactones **28a**–**c** (56 mg, 0.15 mmol) in THF (1 cm^3) at −80 °C under argon, was slowly added a solution of TBAF·$3H_2O$ (75 mg, 0.24 mmol) in THF (1 cm^3). Once the addition was completed, the mixture was stirred for a further 30 min at the same temperature. Hydrolysis was then carried out with five drops of a saturated aqueous NH_4Cl solution, diethyl ether (5 cm^3) was added and extraction was performed with diethyl ether (3 × 5 cm^3). The combined organic phases were washed with brine (5 cm^3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes : ether = 95 : 5) to give β-lactones **29a**,**b** (32 mg, 0.11 mmol, 71%) as a (9 : 1) mixture of diastereoisomers according to 400 MHz NMR spectroscopy of the mixture) (Found: C, 63.89; H, 10.72%. $C_{16}H_{32}O_3Si$ requires C, 63.95; H, 10.73%); ν_{max}(film)/cm^{-1} 1830s, 1260m, 1130m, 840s, 780s; δ_H(400 MHz, $CDCl_3$) major isomer **29a** 4.69–4.62 (1H, m), 3.87–3.80 (1H, m), 3.53 (1H, part A of ABX system, J_{AB} 16.3, J_{AX} 5.8), 3.08 (1H, part B of ABX system, J_{AB} 16.3, J_{BX} 4.3), 1.88 (1H, part A of ABXY system, J_{AB} 14.1, J_{AX} 8.5, J_{AY} 3.1), 1.82 (1H, part B of ABXY system, J_{AB} 14.1, J_{BX} 9.2, J_{BY} 4.8), 1.53–1.37 (2H, m), 1.32–1.18 (6H, m), 0.89 (12H, br s), 0.07 (3H, s), 0.06 (3H, s); minor isomer **29b** 3.52 (1H, part A of ABX system, J_{AB} 16.3, J_{AX} 7.1), 3.11 (1H, part B of ABX system, J_{AB} 16.3, J_{BX} 4.4); δ_C(50.3 MHz, $CDCl_3$) major isomer **29a** 168.6 (0), 69.1 (1), 68.9 (1), 43.6 (2), 42.0 (2), 38.0 (2), 32.0 (2), 24.4 (2), 22.7 (2), 25.9 (3, 3C), 18.1 (0), 14.1 (3), −4.3 (3), −4.7 (3).

2-Allyloctanoic acid 31

Octanoic acid (4.8 cm^3, 30 mmol) was added dropwise, at −20 °C, to a THF solution of LDA [prepared from diisopropylamine (10.5 ml, 75 mmol), butyllithium (52 cm^3 of a 1.5 M solution in hexanes, 78 mmol) and THF (130 cm^3)]. Hexamethylphosphoramide (6.8 cm^3, 39 mmol) was added to the yellow mixture and the cooling bath removed. The mixture was allowed to stir at ambient temperature for 1 h and then cooled to 0 °C whereupon freshly distilled allyl bromide (3.4 cm^3, 39 mmol) was added dropwise to the resulting orange solution. After stirring at room temp. for 12 h, the mixture was hydrolysed with saturated aqueous ammonium chloride (15 cm^3) and concentrated *in vacuo*. The residue was partitioned between ether (90 cm^3) and 20% aqueous HCl (30 cm^3). The organic phase was washed with 20% HCl (4 × 30 cm^3), the combined aqueous portions were extracted with ether (3 × 30 cm^3) and the combined organic solutions were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes : ether = 70 : 30) to give the title compound **31** (4.3 g, 23 mmol, 78%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3070m, 1730s, 1690w, 910m; δ_H(200 MHz, $CDCl_3$) 5.78 (1H, ddt, *J* 17.0, 10.1, 6.8, CH=), 5.15–5.00 (2H, m, $=CH_2$), 2.55–2.15 (3H, m, $CHCH_2C$=), 1.80–1.20 (10H, m, 5 × CH_2), 0.88 (3H, distorted t, *J* 6.6, Me); δ_C(50.3 MHz, $CDCl_3$) 182.6 (0), 135.2 (1), 116.9 (2), 45.3 (2), 36.2 (1), 31.7 (2), 31.6 (2), 29.2 (2), 27.2 (2), 22.6 (2), 14.1 (3).

4-(Hydroxymethyl)decene 32[41]

To a stirred solution of $LiAlH_4$ (835 mg, 22 mmol) in ether (25 cm^3) at 0 °C, was added dropwise a solution of carboxylic acid **31** (1.84 g, 10 mmol) in ether (25 cm^3). The mixture was stirred at room temp. for 3 h and then cooled to 0 °C. Water (0.8 cm^3) was added dropwise followed by NaOH (0.8 cm^3 of a 2.5 M aqueous solution) and finally water (1.7 cm^3). The mixture was then stirred vigorously at room temp. for 20 min. The resulting white solid was removed by filtration and the residue washed with ether (200 cm^3). The filtrate was dried over $MgSO_4$ and concentrated *in vacuo* to yield alcohol **32** (1.645 g, 9.7 mmol, 97%) as a colourless oil, ν_{max}(film)/cm^{-1} 3400s, 3010m, 1650m; δ_H(200 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 17.2, 10.1, 7.1, CH=), 5.15–4.95 (2H, m, $=CH_2$), 3.56 (2H, distorted d, *J* 5.8, CH_2OH), 2.13 (2H, distorted t, *J* 7.1, CH_2C=), 1.70–1.45 (1H, m), 1.40–1.20 (10H, m, 5 × CH_2), 0.89 (3H, distorted t, *J* 6.6, Me);

δ_C(50.3 MHz, $CDCl_3$) 137.1 (1), 116.0 (2), 65.2 (2), 40.3 (1), 35.6 (2), 31.8 (2), 30.6 (2), 29.6 (2), 26.9 (2), 22.6 (2), 14.0 (3).

4-[(*tert*-Butyldimethylsilyloxy)methyl]decene 33

To a solution of alcohol **32** (0.85 g, 5.0 mmol), imidazole (1.36 g, 20 mmol) and 4-dimethylaminopyridine (0.03 g, 0.25 mmol) in CH_2Cl_2 (15 cm^3) was added at room temp. a solution of *tert*-butyldimethylsilyl chloride (867 mg, 5.75 mmol) in CH_2Cl_2 (5 cm^3). The mixture was stirred for 2 h, and concentrated *in vacuo*. The residue was partitioned between water (20 cm^3) and ether (20 cm^3) and the aqueous phase was extracted with ether (3 × 10 cm^3). The organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, hexanes : ether = 95 : 5) to give **33** (1.42 g, 5.0 mmol, 100%) as a colourless oil; ν_{max}(film)/cm^{-1} 2880m, 1280m, 1120s, 850s, 790m; δ_H(400 MHz, $CDCl_3$) 5.80 (1H, ddt, *J* 17.1, 10.0, 7.2, CH=), 4.98 (1H, ddt, *J* 17.1, 2.2, 1.4, $=CH_{trans}$), 4.96 (1H, ddt, *J* 10.0, 2.2, 1.3, $=CH_{cis}$), 3.46 (1H, part A of ABX system, J_{AB} 9.1, J_{AX} 5.5, CH_AH_BOTBS), 3.43 (1H, part B of ABX system, J_{AB} 9.1, J_{BX} 6.0, CH_AH_BOTBS), 2.10 (1H, part A of ABX_2 system, J_{AB} 14.0, J_{AX2} 6.8, CH_AH_BC=), 1.99 (1H, part B of ABX_2 system, J_{AB} 14.0, J_{BX2} 7.1, CH_AH_BC=), 1.51 (1H, m), 1.32–1.20 (10H, m, 5 × CH_2), 0.87 (9H, s, Bu^t), 0.86 (3H, t, *J* 7.0, Me), 0.01 (6H, s, $SiMe_2$); δ_C(50.3 MHz, $CDCl_3$) 137.4 (1), 115.8 (2), 65.1 (2), 40.5 (1), 35.7 (2), 32.0 (2), 30.6 (2), 29.8 (2), 27.0 (2), 26.0 (3C, 3), 22.8 (2), 18.4 (0), 14.2 (3), −5.3 (2C, 3).

4-[(*tert*-Butyldimethylsilyloxy)methyl]nonanal 34

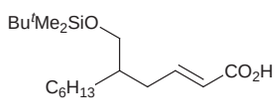
A solution of alkene **33** (1.38 g, 4.8 mmol) in CH_2Cl_2 (60 cm^3) was ozonised for 30 min at −78 °C. When the reaction was over (TLC), the excess ozone was flushed with nitrogen and dimethyl sulfide (7.3 cm^3, 100 mmol) was added and the solution allowed to warm up to room temp. and then refluxed for 24 h. The solvents were removed *in vacuo* and the residual oil purified by column chromatography (SiO_2, hexanes : ether = 97 : 3) to yield the aldehyde **34** (963 mg, 3.4 mmol, 70%) as a colourless oil, ν_{max}(film)/cm^{-1} 1750s, 1480s, 1280s, 1120s, 850s, 790m; δ_H(200 MHz, $CDCl_3$) 9.74 (1H, distorted t, *J* 2.3, CHO), 3.61 (1H, part A of ABX system, J_{AB} 9.9, J_{AX} 4.5, CH_AH_BOTBS), 3.38 (1H, part B of ABX system, J_{AB} 9.9, J_{BX} 7.3, CH_AH_BOTBS), 2.50–2.25 (2H, m, CH_2CHO), 1.70–1.50 (1H, m), 1.40–1.10 (10H, m, 5 × CH_2), 0.86 (12H, br s, Me and Bu^t), 0.01 (6H, s, $SiMe_2$); δ_C(50.3 MHz, $CDCl_3$) 203.1 (1), 65.9 (2), 46.8 (2), 36.6 (1), 31.8 (2), 31.2 (2), 29.5 (2), 27.0 (2), 25.9 (3C, 3), 22.7 (2), 18.3 (0), 14.1 (3), −5.0 (2C, 3).

4-[2′-(*tert*-Butyldimethylsilyloxymethyl)octyl]-3-trimethylsilyl-oxetan-2-one 35

A solution of aldehyde **34** (287 mg, 1 mmol) in dry Et_2O (3 cm^3) was cooled down to −80 °C before a solution of trimethylsilylketene (114 mg, 1.2 mmol) in dry Et_2O (2 cm^3) was added. Ethylaluminium dichloride (0.5 cm^3 of a 1 M solution in hexanes, 0.5 mmol) was then slowly added and the reaction mixture was stirred for 2 h. The mixture was then allowed to warm up to −50 °C whereupon hydrolysis with water (1 drop) was carried out at the same temperature. The mixture was allowed to warm up to room temp., filtered through Celite, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes : ether = 97 : 3) to give β-lactones **35a**–**d** (265 mg, 0.66 mmol, 66%) as a mixture of diastereoisomers (**a**$_{cis}$: **b**$_{cis}$: **c**$_{trans}$: **d**$_{trans}$ = 50 : 34 : 10 : 6) according to 400 MHz NMR spectroscopy of the mixture, ν_{max}(film)/cm^{-1} 1820s, 1270m, 1115m, 860s, 790m; δ_H(400 MHz, $CDCl_3$) **35a**$_{cis}$ 4.72 (1H, m, HCOC=O), 3.62 (1H, part A of ABX system, J_{AB} 10.1, J_{AX} 4.0, CH_AH_BOTBS), 3.52 (1H, part B of ABX system, CH_AH_BOTBS), 3.32 (1H, d, *J* 6.2, CHC=O), 1.98–1.80 (1H, m), 1.75–1.60 (2H, m, $CHCH_2CHO$), 1.36–1.18 (10H, m, 5 × CH_2), 0.87 (12H, br s, Me and Bu^t), 0.21 (9H, s, $SiMe_3$), 0.05 (6H, s, $SiMe_2$); δ_C(100.6 MHz, $CDCl_3$) **35a**$_{cis}$ 171.0 (0), 72.9 (1), 64.6 (2), 46.5 (1), 38.0 (1), 35.4 (2), 31.8 (2C, 2), 29.5 (2), 26.9 (2), 25.9 (3C, 3), 22.7 (2), 18.2 (0), 14.1 (3), −1.0 (3C, 3), −5.5 (2C, 3); *m*/*z* (EI mode) 343 [(M − Bu^t)$^{\cdot+}$, 4%], 229 (100).

Characteristic NMR signals attributable to the minor diastereoisomers: δ_H(400 MHz, $CDCl_3$) **35b**$_{cis}$ 3.33 (1H, d, *J* 6.2, CHC=O); **35c**$_{trans}$ 4.41 (1H, m, HCOC=O), 2.87 (1H, d, *J* 4.1, CHC=O); δ_C(100.6 MHz, $CDCl_3$) **35b**$_{cis}$ 171.06 (0), 72.5 (1), 65.0 (2), 46.6 (1), 38.2 (1), 35.41 (2), −5.4 (2C, 3); **35c**$_{trans}$ 170.9 (0), 71.8 (1), 64.9 (2), 48.9 (1), −3.0 (2C, 3); **35d**$_{trans}$ 71.6 (1), 65.6 (2), −2.9 (2C, 3).

Further elution gave (*E*)-5-(*tert*-butyldimethylsilyloxymethyl)undec-2-enoic acid **37** (30 mg, 0.09 mmol, 9%) as a



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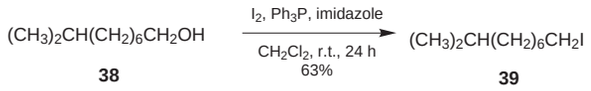
colourless oil, ν_{max}(film)/cm^{-1} 3010s, 1730s, 1680m, 1290m, 1130m, 860s, 790m; δ_H(400 MHz, $CDCl_3$) 7.06 (1H, dt, *J* 15.6, 7.7, CH_2CH=), 5.81 (1H, d, *J* 15.6, $CHCO_2H$), 3.50 (1H, part A of ABX system, J_{AB} 10.1, J_{AX} 4.6, CH_AH_BOTBS), 3.41 (1H, part B of ABX system, J_{AB} 10.1, J_{BX} 6.4, CH_AH_BOTBS), 2.31 (1H, part A of distorted ABX_2 system, J_{AB} 14.3–14.8, J_{AX} 6.3–6.6, CH_AH_BC=), 2.19 (1H, part B of distorted ABX_2 system, J_{AB} 14.3–1.48, J_{BX} 6.3, CH_AH_BC=), 1.63 (1H, m), 1.30–1.21 (10H, m, 5 × CH_2), 0.87 (12H, br s, Me and Bu^t), 0.03 (6H, s, $SiMe_2$); δ_C(50.3 MHz, $CDCl_3$) 171.9 (0), 151.5 (1), 121.8 (1), 65.0 (2), 40.3 (1), 34.4 (2), 31.9 (2), 30.8 (2), 29.6 (2), 27.0 (2), 26.0 (3C, 3), 22.7 (2), 18.3 (0), 14.2 (3), −5.4 (2C, 3); *m*/*z* (EI mode) 271 [(M − Bu^t)$^{\cdot+}$, 46%], 253 (67), 75 (100).

4-[2′-(*tert*-Butyldimethylsilyloxymethyl)octyl]oxetan-2-ones 36a,b

To a stirred solution of lactones **35a**–**d** (152 mg, 0.38 mmol) in THF (1.5 cm^3) at −80 °C under argon, was slowly added a solution of TBAF·$3H_2O$ (145 mg, 0.46 mmol) in THF (1.5 cm^3). Once the addition was complete, the mixture was stirred for a further 30 min at the same temperature. Hydrolysis was then carried out with 10 drops of saturated aqueous NH_4Cl solution, diethyl ether (10 cm^3) was added and extraction was performed with diethyl ether (3 × 10 cm^3). The combined organic phases were washed with brine (10 cm^3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes : ether = 95 : 5) to give β-lactones **36a**,**b** (125 mg, 0.38 mmol, 100%) as a 55 : 45 mixture of diastereoisomers according to 400 MHz NMR spectroscopic analysis (Found: C, 65.78; H, 11.07%. $C_{18}H_{36}O_3Si$ requires C, 65.80; H, 11.04%); ν_{max}(film)/cm^{-1} 1850s, 1270m, 1140s, 850s, 790s; δ_H(400 MHz, $CDCl_3$) major isomer **36a** 4.63 (1H, m, CHOC=O), 3.58 (1H, part A of ABX system, J_{AB} 10.2, J_{AX} 4.2, CH_aHOTBS), 3.50 (1H, part A of ABX system, J_{AB} 16.3, J_{AX} 5.7, CH_aHC=O), 3.44 (1H, part B of ABX system, J_{AB} 10.2, J_{BX} 5.9, CHH_bOTBS), 3.06 (1H, part B of ABX system, J_{AB} 16.3, J_{BX} 4.3, CHH_bC=O), 1.84 (1H, part A of ABXY system, J_{AB} 15.8, J_{AX} 4.1, J_{AY} 7.4, $CHCH_aHCHO$), 1.79 (1H, part B of ABXY system, J_{AB} 15.8, J_{BX} 3.4, J_{BY} 7.3, $CHCHH_bCHO$), 1.35–1.15 (9H, m), 0.87 (12H, br s, CH_3 and Bu^t), 0.02 (6H, s, $SiMe_2$); minor isomer **36b** (distinguishable signals) 4.68 (1H, m, CHOC=O), 1.95 (1H, part A of ABX_2 system, J_{AB} 14.0, J_{AX} 7.0, $CHCH_aHCHO$), 1.70 (1H, part B of ABX_2 system, J_{AB} 14.0, J_{BX} 6.4, $CHCHH_bCHO$); δ_C(100.6 MHz, $CDCl_3$) major isomer **36a** 168.7 (0), 70.6 (1), 64.9 (2), 43.6 (2), 37.8 (1), 37.2 (2), 31.8 (2), 31.5 (2), 29.6 (2), 26.9 (2), 22.7 (2), 25.9 (3, 3C), 18.3 (0), 14.1 (3), −5.4 (3, 2C); minor isomer **36b** (distinguishable signals) 168.6 (0), 70.3 (1), 65.6 (2), 43.4 (2), 37.9 (1), 37.3 (2).



38 **39**

Scheme 8

1-Iodo-8-methylnonane 39

To a solution of imidazole (75.6 mg, 1.11 mmol) and triphenylphosphine (107.5 mg, 0.1 mmol) in CH_2Cl_2 (3 cm^3) at 0 °C was added I_2 (104 mg, 0.41 mmol). A solution of the alcohol **38**[42] (58 mg, 0.37 mmol) in CH_2Cl_2 (1 cm^3) was then added slowly and the mixture warmed to room temp., covered in foil and stirred for a further 24 h. The mixture was shaken with aqueous sodium thiosulfate (5%, 3 cm^3). The organic layer was separated and the aqueous layer washed with ether (3 × 5 cm^3). The combined layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave a colourless oil. Hexane (5 cm^3) was added and the resulting white precipitate was removed by filtration. The filtrate was concentrated *in vacuo* to give iodoalkane **39** (62 mg, 0.23 mmol, 63%) as a pale yellow oil, ν_{max}(film)/cm^{-1} 2954s, 2926s, 2854s, 1465m; δ_H(300 MHz, $CDCl_3$) 3.18 (2H, t, *J* 12.9, CH_2I), 1.82 (2H, app. quintet, *J* 7.0, CH_2), 1.65–1.09 (11H, m, 5 × CH_2 and CH), 0.86 (6H, d, *J* 6.6, Me_2C); δ_C(67.5 MHz, $CDCl_3$) 39.1 (2), 33.7 (2), 30.7 (2), 29.8 (1), 28.7 (2), 28.0 (2), 27.4 (2), 22.8 (2C, 3), 7.3 (2); *m*/*z* (EI mode) 267 [$(M - H)^{\cdot +}$, 20%], 141 (40), 85 (76), 57 (100).

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