An Asymmetric Synthesis of (–)-Tetrahydrolipstatin

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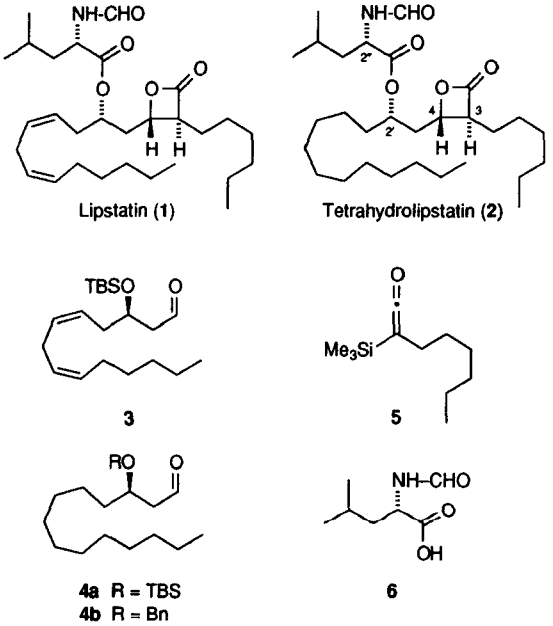
A key step in a short asymmetric synthesis of the potent pancreatic lipase inhibitor (–)-tetrahydrolipstatin (**2**) is a Lewis acid-catalysed [2+2] cycloaddition of *n*-hexyl(trimethylsilyl)ketene (**5**) to (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecanal (**4a**).

Obesity is one of the most prevalent conditions afflicting the Western world. It is estimated that 34 million people suffer from it in the USA alone[1]. For the majority the condition could be ameliorated by a radical change in diet because humans only have a very limited capacity for *de novo* fat biosynthesis. However, many patients find a low fat diet unpalatable and soon evade the strict regimen required. A key enzyme for the digestion of dietary fat is pancreatic lipase which cleaves free fatty acids from their triglyceride precursor. The resultant free fatty acids and monoglycerides are then incorporated into micelles and absorbed in the small intestine. Thus, if pancreatic lipase could be inhibited, dietary fat would pass into the gut without being absorbed.

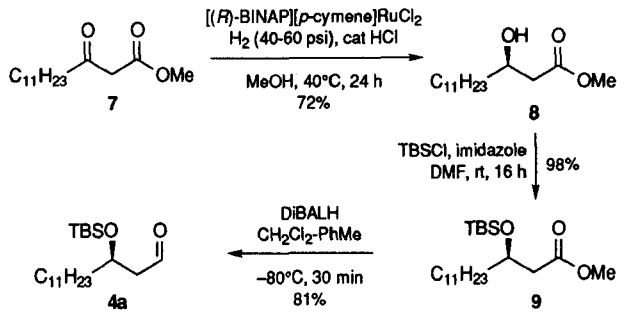
In 1987 scientists at the Hoffman La Roche company showed that lipstatin (**1**), a metabolite of *Streptomyces toxytricini*[2], is a potent and irreversible inhibitor of pancreatic lipase[3]. A striking feature of lipstatin and its tetrahydro derivative (**2**)[4], is the strained oxetanone ring[5] which is found in a number of microbial esterase inhibitors including esterastin[6], valilactone[7], ebelactones A and B[8], and antibiotic 1233A[9]. The enhanced reactivity of the oxetanone ring is central to the biological activity of lipstatin and tetrahydrolipstatin. It results in irreversible acylation of a serine residue at or near the active site of pancreatic lipase thereby rendering the enzyme inactive[10]. Recent clinical studies have shown that a diet supplemented by 50 mg of tetrahydrolipstatin per day leads to sustained weight loss in humans[11].

We now report details and improvements to our stereoselective synthesis of (–)-tetrahydrolipstatin[12] from three fragments: (*R*)-3-(*tert*-butyldimethylsilyloxy)tetradecanal (**4a**) (or the corresponding benzyl ether **4b**), *n*-hexyl(trimethylsilyl)ketene (**5**), and (*S*)-*N*-formylleucine (**6**). The key reaction in the sequence is a Lewis acid-catalysed [2+2] cycloaddition reaction between aldehydes **4a,b** and silylketene **5** to generate the crucial oxetanone ring. Our approach differs fundamentally from the seven previous syntheses of tetrahydrolipstatin [13-19] which first generated *β*-hydroxy carboxylic acid derivatives by various means and then accomplished the closure of the key oxetanone ring by the classical Adam procedure—intramolecular displacement of benzenesulfonate by carboxylate[20]. The cycloaddition can also be extended to the synthesis of (–)-lipstatin itself[21] by a similar sequence starting with (*Z,Z*)-(*R*)-3-(*tert*-butyldimethylsilyloxy)tetradeca-5,8-dienal (**3**).



Scheme 1

*Synthesis of Aldehydes **4a,b*** (Scheme 2). Aldehydes **4a,b** differing only in the hydroxyl protecting group, contain a single stereogenic centre which, after inversion, corresponds to C2' in tetrahydrolipstatin. The "incorrect" stereochemistry in **4a,b** was deliberately chosen as a stereocontrol element in the construction of the oxetanone ring and as a convenient vehicle for introducing the (*S*)-*N*-formylleucine at the end of the synthesis. Given the strategic and tactical significance of aldehydes **4a,b**, it was imperative to secure an efficient and highly enantioselective synthetic route. Thus, asymmetric catalytic hydrogenation of the *β*-keto ester **7**[17] using the commercial catalyst [(*R*)-BINAP][*p*-cymene]$RuCl_2$ in the presence of a small amount of HCl proceeded at readily accessible pressures (40-60 psi H_2 at 40°C)[22,23] to give the crystalline *β*-hydroxy ester **8** in 72% yield (≥97% ee)[24]. After protection of the hydroxyl group as a *tert*-butyldimethylsilyl ether, the ester function in **9** was converted to aldehyde **4a** using DiBALH. The corresponding *O*-benzyl protected aldehyde **4b** was prepared from **8** in two steps (62%) according to known procedures[14].

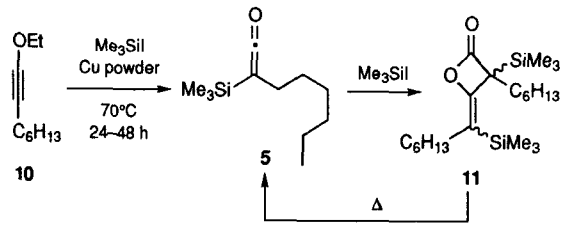


Scheme 2

*Synthesis of n-Hexyl(trimethylsilyl)ketene **5*** (Scheme 3). According to Sakurai and co-workers[25] *n*-butyl(trimethylsilyl)ketene is readily prepared by heating neat 1-ethoxy-1-hexyne with iodotrimethylsilane (TMSI) followed by direct distillation. Initial attempts to extend this method to the preparation of **5** from 1-ethoxy-1-octyne (**10**) were perplexed by variable yields, variable product quality or, in many cases, the reaction failed to initiate altogether. Three observations allowed us to minimise the apparent astrological caprice. First, the reaction invariably initiated provided the 1-ethoxy-1-octyne was carefully purified by fractional distillation, the TMSI prepared afresh *in situ*, and rigorous measures taken to exclude atmospheric moisture. Having initiated reaction we then noted that the silylketene product **5** dimerised in the presence of TMSI at a rate competitive with its

formation. However, by allowing the dimerisation to go to completion, and then removing all traces of TMSI *before distillation*, the diastereoisomeric mixture of putative dimers **11** could be thermolysed back to the silylketene by simply heating at 80°C at 0.5 mmHg. Best results were obtained in the ketene generating step by running the reaction in the presence of clean copper wire or copper powder leading to a decrease in reaction time accompanied by improved yields and product quality. Provided due care and attention was paid to the observations noted above, the silylketene **5** could be routinely prepared in 50-100 mmol quantities in yields ranging from 57-92%

The silylketene **5** was stable at r. t. and could be stored at -20°C for protracted periods without decomposition and its relative stability allowed manipulation in air without any special precautions. The infrared spectrum revealed an intense band at 2085 cm^{-1} and a low intensity signal at δ 13.1 (C=C=O) in the ^{13}C NMR spectrum indicative of the silylketene[26].



Scheme 3

Cycloaddition of Silylketene 5 to Aldehydes 4a,b (Scheme 4). The [2+2] cycloaddition of trimethylsilylketene to aldehydes catalysed by BF_3•OEt_2 was first reported by Zaitseva and co-workers in 1975[27,28] and since then the reaction has been exploited intermittently by others for the synthesis of oxetanones[29-31]. However, asymmetric induction by proximate stereogenic centres was not an issue previously addressed. In the event, cycloaddition of silylketene **5** to aldehydes **4a,b** generated 4 diastereoisomers whose ratio was easily assayed by integration of the ^1H NMR signals (500 MHz) arising from the single proton at C4 on the oxetanone ring of the corresponding deprotected alcohols **12c–15c** (*vide infra*). From the results summarised in Table 1, we see that the yield and diastereoselectivity depended strongly on the Lewis acid catalyst but not the protecting group. Under the optimum conditions, the aldehyde **4a** underwent cycloaddition with silylketene **5** (1.5 equiv) in the presence of $EtAlCl_2$ (1.1 equiv) in Et_2O–toluene (ca 5:1) at –40 → 0°C to give the oxetanones **12a–15a** in 90% yield on a 1–5 mmol scale and 79% yield on a 35 mmol scale.

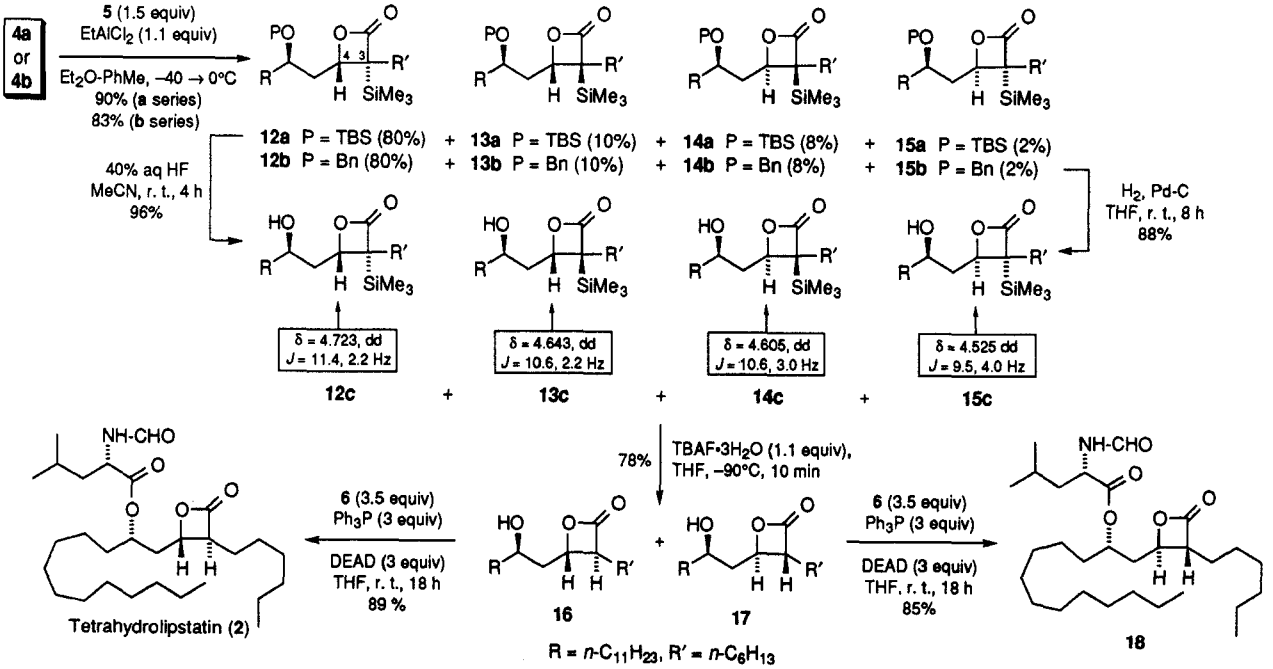
Table 1. Diastereoselectivity in the Cycloaddition of Aldehydes **4a,b** and *n*-Hexyl(trimethylsilyl)ketene (**5**).

Aldehyde	Lewis Acid	Yield	%12	%13	%14	%15
4a (TBS)	BF_3•OEt_2	75%	61	34	4	1
	$AlCl_3$	65%	80	10	8	2
	$EtAlCl_2$	95%	80	10	8	2
4b (Bn)	BF_3•OEt_2	75%	44	41	8	7
	$EtAlCl_2$	70%	80	10	8	2

All reactions were performed in Et_2O on a 1 mmol scale (1.1 equiv. of Lewis acid) under identical conditions. When $EtAlCl_2$ was used as the Lewis acid, the solvent also contained about 20% toluene.

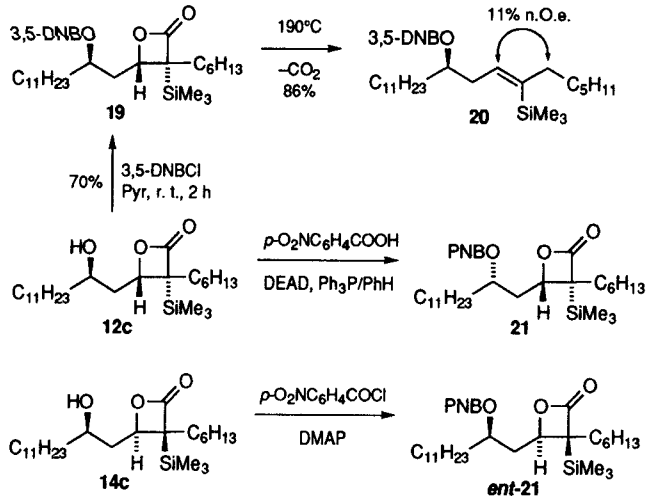
To complete the synthesis of (–)-tetrahydrolipstatin, the mixture of adducts **12a–15a** was deprotected with HF in MeCN to the 4 sensitive diastereoisomeric alcohols **12c–15c** from which a pure sample of **12c** could be isolated by column chromatography. For preparative purposes though, the mixture of **12c–15c** was best treated immediately with TBAF•$3H_2O$ (1.1 equiv) in THF at –90°C for 10 min to give two hydroxy oxetanones **16** and **17** (9:1) from which the bulk of the major isomer **16** could be isolated by direct crystallisation. Similarly deprotection of the benzyl ethers **12b–15b** by catalytic hydrogenolysis produced **12c–15c** (88% yield) which were then desilylated as described above. Thus, the mixtures of adducts **12a,b–15a,b** could be converted to crystalline hydroxy oxetanone **16** without the need for diastereoisomer separation.

The final step of the sequence involved esterification of hydroxy oxetanone **16** with (*S*)-*N*-formylleucine (**6**) under Mitsunobu conditions to accomplish the requisite inversion of configuration at C2′. The tetrahydrolipstatin thus obtained (89% yield) gave mp, $[\alpha]_D$, and ^1H NMR data comparable with those reported by the Hofmann La Roche group[14]. Similarly, Mitsunobu esterification of the alcohol **17** gave the (3*R*,4*R*)-diastereoisomer **18** of tetrahydrolipstatin.



Scheme 4

Stereochemical Assignments (Schemes 5–7). The relative stereochemistry of the 4 diastereoisomeric adducts **12–15** was deduced from the following arguments. The major diastereoisomeric **12c** derived from adducts **12a,b**, when desilylated with TBAF•3H$_2$O, gave pure alcohol **16**. Since **16** was converted to tetrahydrolipstatin, adducts **12a,b** must have had the (4*S*) stereochemistry. Adduct **13c** could not be obtained pure but a mixture enriched in **13c** (ca 80%) was also converted to **16** and hence it too must have had the desired (4*S*) stereochemistry. Consequently the remaining two diastereoisomers **14c** and **15c** must have the (4*R*) stereochemistry. In order to assign the stereochemistry at the 3-position, alcohol **12c** was converted to the crystalline 3,5-dinitrobenzoate ester **19** which was pyrolysed at 190°C. An n.O.e. study of the resultant alkenylsilane **20** indicated (*Z*)-stereochemistry. Assuming retention of configuration[27,32] in the thermal extrusion of CO_2, the stereochemistry of the oxetanone ring must have the trimethylsilyl group and the C4 chain in a syn relationship. Hence the stereochemistry **12c** is that depicted in Scheme 4 and **13c** must be epimeric at C3.

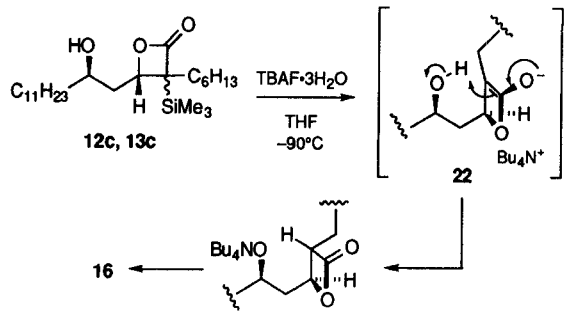


Scheme 5

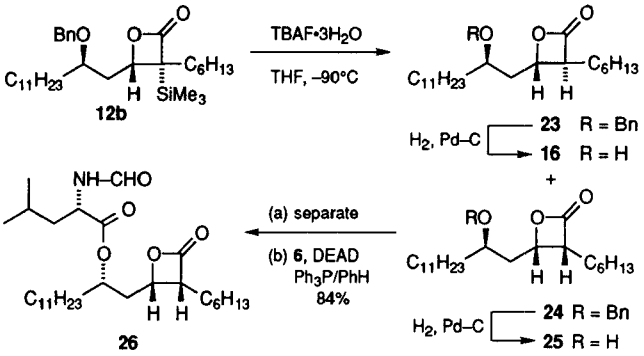
Compounds **14c** and **15c** were never obtained pure and therefore a tentative assignment had to be gleaned from mixtures. That **14c** and **15c** had the (4*R*) stereochemistry was established by the experiments decribed above. The stereochemistry of **14c** was assigned on the basis of the comparison of the *p*-nitrobenzoates derived from a mixture of **13c**, **14c**, and **15c** with the *p*-nitrobenzoate **21** obtained by Mitsunobu inversion of **12c**. The *p*-nitrobenzoate of **14c** is the enantiomer of **21** and hence displays the same NMR spectra. By a process of elimination, the relative stereochemistry of oxetanones **15** was assigned as depicted in Scheme 4.

The reduction in complexity in going from the 4 diastereoisomers **12c–15c** to only two diastereomers (**16** and **17**) on *C*-desilylation was fortuitous and since (**12c** + **13c**) : (**14c** + **15c**) = **16** : **17** (9 : 1), the desilylation must have proceeded through a common intermediate (**22** in the case of **12c** and **13c**) which underwent highly stereoselective protonation, perhaps by intramolecular proton transfer, to form the *anti*-substituted oxetanones as suggested in Scheme 6. The stereoselectivity of the process depended on having a free hydroxyl group in the side chain since *C*-desilylation of the benzyl ether **12b** (Scheme 7) gave **23** along with the syn diastereoisomer **24** in the ratio 2:1. Hydrogenolysis then furnished alcohols **16** and **25** respectively from which tetrahydrolipstatin and its 3-*epi* diastereoisomer **26** were obtained by Mitsunobu inversion as described above.

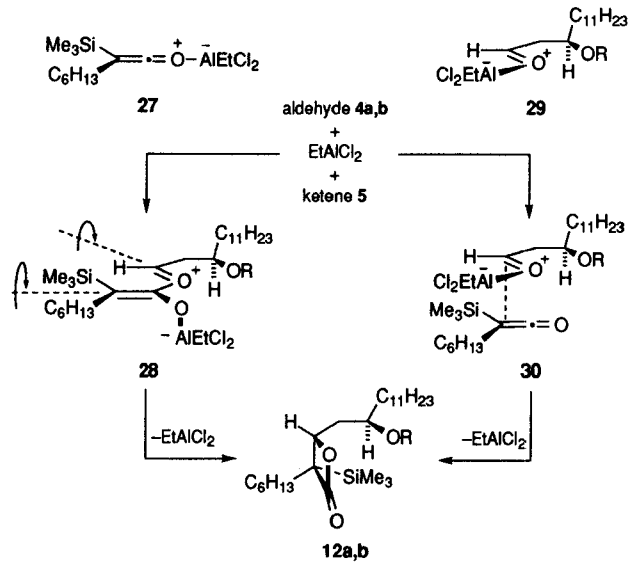
Stereochemistry of the Cycloaddition: a Hypothesis (Scheme 8). Previous workers recorded good levels of 1,3-asymmetric induction in the *chelation-controlled* addition of ester enolate[14,15] and allylmetal[19] nucleophiles to β-alkoxyaldehyde **4b** but the good diastereoselectivity



Scheme 6



Scheme 7



Scheme 8

observed in the [2+2] cycloaddition leading to **12a,b** was accomplished with the monocoordinate Lewis acids BF_3•OEt_2 and $EtAlCl_2$. In order to rationalise the selective formation of oxetanones **12a,b**, we have considered two stepwise mechanisms. The first, which strays the least from the analogous ketene-imine cycloaddition leading to azetidinones[33], entails addition of the aldehyde to the *electrophilic* silylketene complex **27** to give an intermediate **28** whose conformation is fixed by electrostatic interaction of the oxonium ion and the C2′ ether oxygen atoms. The stereochemistry is then governed by a conrotatory ring closure in which the torquoselectivity[34,35] results from minimisation of adverse steric factors. Torquoelectronic effects have recently been invoked to explain the stereoselectivity of ketene-imine cycloaddition reactions[36,37].

An alternative mechanism which reverses the electronic roles of the reactants is initiated by coordination of the Lewis acid to aldehydes

4a,b to generate an electrophilic complex in which the conformation **29** is, once again, favoured by electrostatic attraction between the two oxygen atoms (Scheme 8). In the second step, the *nucleophilic* silylketene selectively adds to the less hindered face of complex **30** in the manner shown to generate a cycloadduct which finally expels the Lewis acid affording the oxetanone ring. We prefer the second mechanism because the nucleophilic character of silylketenes is corroborated by experimental evidence from Zaitseva's laboratory[38,39]; spectroscopic evidence (δ_C = 13-18 in accord with very high electron density at TMS-*C*=C=O); as well as recent theoretical studies on the stability of silylketenes[40,41] and the mechanism of the uncatalysed cycloaddition of formaldehyde to ketene[42]. Furthermore, previous studies[43] indicate that the nucleophilic behaviour of ketenes may not be restricted to the electron-rich metalloketenes. Studies are underway to elucidate the mechanism.

In conclusion we have developed a practical and efficient synthesis of (–)-tetrahydrolipstatin which depends on only one protecting group and avoids the inherent detractions of chiral auxiliaries altogether. A single stereogenic centre created early in the synthesis by catalytic asymmetric hydrogenation under readily accessible conditions was used to control absolute and relative stereochemistry throughout. Minor deficiencies in stereocontrol during the cycloaddition were of little practical consequence since the desired diastereoisomer **16** could be obtained by crystallisation at a late stage of the synthesis without the need for arduous chromatographic separation. Finally, our synthesis of the oxetanone ring, alongside the route of Ley and co-workers[44], represents a novel departure from the cyclodehydration chemistry previously exploited for the synthesis of natural oxetanones[13-18,45-48] and it cogently illustrates the value of silylketenes as stable, readily available organic reagents.

Unless otherwise specified all yields quoted refer to compounds purified by column chromatography on silica gel with the eluant specified in parenthesis. Reactions requiring anhydrous conditions were conducted in a flame-dried apparatus under a static atmosphere of dry argon or nitrogen. Organic extracts were dried over $MgSO_4$ unless otherwise specified and evaporated at aspirator pressure on a rotary evaporator. Distillations in which the bath temperature is recorded were performed with a Kugelrohr apparatus.

^1H chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.27). ^{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 parenthesis following the ^{13}C chemical shift value denoting the number of coupled protons. Peak intensities in the infra-red spectra are defined as strong (s), medium (m), or weak (w). Accurate mass determinations (HRMS) and low resolution mass spectra (LRMS) were made on compounds purified by either distillation or column chromatography and estimated to be at least 95% pure by NMR spectroscopy and thin layer chromatography.

Methyl (*R*)-3-Hydroxytetradecanoate (8):
A Parr autoclave was charged with a solution of methyl 3-oxotetradecanoate (**7**)[24] (10 g, 39.06 mmol) in methanol (50 mL). [(*R*)-(+)-2,2′-*Bis*(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride (50 mg, 1000:1 substrate:catalyst) and hydrochloric acid (0.05 mL, 2 M) were added and the mixture stirred under hydrogen at 40–60 psi at 40°C for 24 h by which time reduction had ceased at ca 80% completion. To the cooled reaction mixture hexanes (20 mL) was added and the mixture filtered and concentrated under reduced pressure. The residue was crystallised from methanol. A second crystallisation from cold MeOH afforded pure hydroxy ester **8** (7.26 g, 28.1 mmol, 72%) as a white solid: mp 39–41°C (lit.[49] mp 39.4–40.6°C).

$[\alpha]_D$ (20°C) –17.1° (*c* = 1.02, $CHCl_3$); lit[49] $[\alpha]_D$(20°C) –18.5° (*c* = 1.05, $CHCl_3$).

^1H NMR (270 MHz, $CDCl_3$): δ = 4.07–3.94 (1H, m), 3.70 (3H, s), 2.94 (1H, d, *J* = 3.9 Hz), 2.51 (1H, dd, *J* = 16.4, 3.3 Hz), 2.43 (1H, dd, *J* = 16.4, 8.7 Hz), 1.58–1.37 (4H, m), 1.37–1.17 (16H, br), 0.89 (3H, distorted t, *J* = 6.5 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 173.7 (0), 68.2 (1), 51.9 (3), 41.3 (2), 36.7 (2), 32.1 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 25.6 (2), 22.8 (2), 14.3 (3).

LRMS (CI mode, NH_3): *m/z* = 276 [$(M+NH_3)^{+\bullet}$, 100%], 259 (96), 241 (36). $C_{15}H_{30}O_3$ = 258.4

A similar asymmetric hydrogenation conducted on a 30 g scale (117 mmol) required ca 80 h reaction time for 80% reaction.

Methyl (*R*)-3-(*tert*-Butyldimethylsiloxy)tetradecanoate (9):
A 250 mL 3-necked round-bottomed flask fitted with a magnetic stirrer and thermometer was charged with a solution of hydroxy ester **8** (14.8 g, 57.6 mmol) in DMF (30 mL). With ice-bath cooling, imidazole (9.8 g, 144 mmol) in DMF (25 mL) was added, followed by the dropwise addition of *tert*-butyldimethylsilyl chloride (11.3 g, 74.9 mmol) in DMF (25 mL). The cooling bath was removed and the mixture stirred for 16 h at r. t. The mixture was poured into water (500 mL) with stirring and the product extracted into hexanes (3 x 100 mL). The combined organic layers were dried, concentrated, and the residue (22 g) purified by column chromatography (5% ether in hexanes) to afford ester **9** (21.0 g, 56.5 mmol, 98%) as a colourless oil.

$[\alpha]_D$ (20°C) –16.6° (*c* = 1.045, $CHCl_3$).

IR (film): ν = 2927 s, 2986 s, 1743 s, 1463 m, 1437 m, 1255 s, 837 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.18 (1H, app quin, *J* = 6.0 Hz, CHOTBS), 3.6 (3H, s), 2.42 (2H, m), 1.55 (2H, m), 1.10–1.40 (20H, m), 0.70–0.90 (12 H, m), 0.055 and 0.035 (3H each, s).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.5 (0), 69.6 (1), 51.4 (3), 42.7 (2), 37.8 (2), 29.8 (3C, 2), 29.7 (3C, 2), 25.9 (3C, 3), 25.1 (2C, 2), 22.9 (2), 18.1 (0), 14.3 (3), –4.4 (3), –4.7 (3).

LRMS (CI mode, NH_3): m/z = 373 [$(M+1)^{+\bullet}$, 100%), 315 (83). $C_{21}H_{44}O_3Si$ =372.67

(*R*)-3-(*tert*-Butyldimethylsiloxy)tetradecanal (4a):
A 250 mL 3-necked round bottomed flask fitted with mechanical stirrer, thermometer and Ar line was charged with a solution of ester **9** (21.02 g, 56.5 mmol) in dichloromethane (100 mL), and cooled to –80°C. DiBALH (41.4 mL of 1.5 M in toluene, 62.1 mmol) was added dropwise at a rate sufficient to maintain the temperature at –80°C. The mixture was stirred at –80°C for 30 min, whereupon the cooling bath was removed and saturated ammonium chloride (15 mL) was added, followed by HCl (30 mL, 2M) and the mixture warmed to r. t. over 3 h. The solid was filtered and the filtrate washed with water, dried over MgSO4, concentrated under reduced pressure, and the residue (16.9 g) chromatographed on silica gel (5% ether in hexanes) to afford aldehyde **4a** (15.6 g, 45.7 mmol, 81%) as a colourless oil.

$[\alpha]_D$ (20°C) –3.0° (*c* = 2, $CHCl_3$).

IR (film): ν = 1729 s, 1464 s, 837 s, 776 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.79 (1H, dd, *J* = 2.5, 2.3 Hz), 4.17 (1H, app quin, *J* = 5.8 Hz), 2.49 (2H, app dd, *J* = 5.8, 2.5 Hz) 1.58–1.42 (2H, m), 1.37–1.12 (18H, br s), 0.96–0.78 (12H, br s), 0.06 (3H, s), 0.04 (3H, s).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 202.4 (1), 68.4 (1), 50.9 (2), 38.0 (2), 32.0 (2), 29.8 (2), 29.7 (2C, 2), 29.5 (2), 25.9 (2C, 2), 25.9 (3C, 3), 25.2 (2), 22.8 (2), 18.1 (0), 14.2 (3), –4.3 (3), –4.6 (3).

LRMS (EI mode): *m/z* = 342 (0.1%), 299 (1), 286 (22), 285 (100), 241 (14), 131 (58), 101 (79), 97 (30), 95 (18), 83 (30), 75 (51), 69 (30), 59 (25), 55 (22), 43 (21), 41 (29).

HRMS Found: $(M+H)^{+\bullet}$, 343.3004. ($C_{20}H_{42}O_2Si$+H) requires M, 343.3032.

1-Ethoxy-1-octyne (10):
A 1L 3 necked round bottomed flask fitted with mechanical stirrer, thermometer and cold finger condenser was immersed in a liquid N_2 / acetone bath at –40°C and charged with liquid ammonia (500 mL). Ferric nitrate (350 mg) was added followed by portionwise addition of sodium (30 g, 1.3 g atom). The reaction mixture was stirred under reflux until all the sodium had reacted as indicated by the change in colour from dark blue to dark grey. A pressure-equalised dropping funnel was fitted to the reaction vessel and chloracetaldehyde diethyl acetal (60 mL, 61 g, 0.4 mol) added dropwise. The reaction mixture was stirred under reflux for 4 h. 1-Iodohexane (47.2 mL, 67.8 g, 0.32 mol) was added dropwise and the mixture stirred overnight under reflux. The ammonia was evaporated from the clear orange solution by replacing the cold bath with a water bath at 35°C. The reaction was then quenched by dropwise addition of saturated aqueous ammonium chloride solution (300 mL) and the crude 1-ethoxy-1-octyne extracted into pentane (3 x 150 mL). After drying over $MgSO_4$, the pentane was removed by distillation through a fractionating column and the product purified by Spaltrohr distillation to afford 14.8 g (96 mmol, 30%) of pure 1-ethoxy-1-octyne as a clear, colourless oil [bp 30°C/0.2 mmHg] having spectroscopic data identical to those previously reported[50]. On one third the scale described here, the yield was 43-47%.

***n*-Hexyl(trimethylsilyl)ketene (5):**
A flame-dried 50 mL round-bottomed flask fitted with a reflux condenser and magnetic stirrer was charged with hexamethyldisilane (17.5 mL, 85.7 mmol). With rigorous exclusion of moisture, the mixture was warmed to 80°C whereupon freshly sublimed I_2 (19.8 g, 77.9 mmol) was added slowly in 100 mg portions over 1h 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 and cooled to r. t. before Cu (powder, 700 mg) was added. On addition of the Cu, the dark brown solution became pale yellow after stirring at r. t. for 5 min. 1-Ethoxy-1-octyne (14.8 g, 95.9 mmol) was added dropwise and the mixture heated at 70°C for 24-48 h. After cooling, the reflux condenser was replaced by a short path distillation apparatus and the excess iodotrimethylsilane removed (65°C, 20 mmHg). Distillation of the residual oil afforded *n*-hexyl(trimethylsilyl)ketene (**5**) (10.9 g, 55 mmol, 57%): bp 33.5°C / 0.2 mmHg.

IR (film): ν = 2957 s, 2927 s, 2857 s, 2085 s, 840 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.92 (2H, t, J = 7.1 Hz), 1.34–1.22 (8H, br s), 0.90 (3H, distorted t, J = 6.9 Hz), 0.16 (9H, s).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 183.2 (0), 32.1 (2), 29.9 (2), 29.6 (2), 22.9 (2), 22.2 (2), 14.3 (3), 13.1 (0, C=C=O), –0.7 (3, 3C).

LRMS (CI mode, NH_3): *m/z* = 199 [$(M+1)^{+\bullet}$, 84%), 90 (100). $C_{11}H_{22}OSi$ = 198.38

The reaction time depended to some extent on the quality of the 1-ethoxy-1-octyne used. To optimise the yield of ketene, the reaction should be followed by IR spectroscopy. The acetylene band at 2272 cm^{-1} diminishes and is replaced by a band due to the ketene at 2085 cm^{-1} and the ketene dimer at 1781 cm^{-1}. However, the reaction does not always reach completion, even with high quality 1-ethoxy-1-octyne and workup should be carried out after 48 h to avoid degradation of the ketene product. Ketene containing up to 5% 1-ethoxy-1-octyne can be carried though the next step without adverse effect. The yield described above is typical but yields as high as 92% have been observed on a 20 mmol scale.

3-Hexyl-3-trimethylsilyl-4-[(*R*)-2′-(*tert*-butyldimethylsilyloxy)tridecyl]-2-oxetanones (12a–15a):
A 250 mL 3-necked round-bottomed flask fitted with a magnetic stirrer, thermometer, Ar line, and pressure equalised dropping funnel was charged with a solution of silylketene **5** (13.6 g, 68.6 mmol) in ether (100 mL) and cooled to –50°C. Ethylaluminium dichloride in toluene (27.9 mL, 1.8 M, 50.3 mmol) was added dropwise, maintaining the temperature at –50°C. The mixture was stirred at –40°C for 10 min whereupon a solution of (*R*)-3-(*tert*-butyldimethylsiloxy)tetradecanal (**4a**) (15.6 g, 45.5 mmol) in ether (40 mL) was added dropwise. The mixture was warmed to –25°C and stirred for 30 min. The solution was allowed to warm to 0°C and poured into rapidly stirred ice water (200 mL). The crude product was extracted into ether, dried over $MgSO_4$ and concentrated under reduced pressure to afford 20.5 g of crude material which was purified by column chromatography (3% ether in hexanes) to give the oxetanones **12a–15a** (19.1 g, 36.1 mmol, 79%) as an inseparable mixture of the four diastereoisomers which were used in the next step without further purification.

^1H NMR (500 MHz, $CDCl_3$): 4.643 (dd, J = 11.7, 1.9 Hz, 80%), 4.635 (dd, J = 10.2, 2.0 Hz, 8%), 4.576 (dd, J = 10.0, 1.9 Hz, 2%), 4.566 (dd, J = 11.1, 1.9 Hz, 10%).

IR (film, isomeric mixture): ν = 1807 s, 1255 s, 837 s cm^{-1}.

The following signals corresponding to (3*R*,4*S*)-3-hexyl-3-trimethylsilyl-4-[(*R*)-2′-(*tert*-butyldimethylsilyloxy)tridecyl]-2-oxetanone (**12a**) could be assigned from the data collected on the mixture of diastereoisomers:

^1H NMR (270 MHz, $CDCl_3$): δ = 4.64 (1H, dd, J = 11.7, 1.9 Hz, CH–O–C=O), 3.94–3.77 (1H, m, CHOTBS), 2.0 (1H, dt, J = 11.6, 2.3 Hz), 1.83–1.62 (2H, m), 1.58–1.39 (2H, m), 1.39–1.12 (27H, m), 0.94–0.79 (15H, m), 0.22 (9H, s, Me_3Si), 0.12 and 0.08 (3H each, s, $SiMe_2$).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.5 (0), 76.2 (1, CH–OC=O), 69.0 (1, CH–OTBS), 54.6 (0, C-TMS), 39.7 (2, $OCHCH_2CHO$), 38.3 (2), 31.8 (2), 31.6 (2), 30.7 (2), 29.9 (2), 29.83 (3C, 2), 29.77 (2C, 2), 29.5 (2), 26.3 (2), 26.0 (3C,3), 24.8 (2), 22.9 (2), 22.7 (2), 18.2 (0), 14.3 (3), 14.2 (3), –1.2 (2C, 3), –3.1 (3), –4.0 (3), –4.6 (3).

LRMS (EI mode): *m/z* = 525 (0.5%), 483 (7), 331 (16), 300 (13), 299 (60), 286 (24), 285 (100), 147 (22), 131 (11), 101 (13), 75 (12), 73 (60), 59 (7), 43 (8).

HRMS (EI mode): Found $[M–Me]^{+\bullet}$, 525.4128. $C_{31}H_{64}O_3Si_2–CH_3$ requires M, 525.4159.

3-Hexyl-3-trimethylsilyl-4-[(*R*)-2′-(benzyloxy)tridecyl]-2-oxetanones (12b–15b):
Reaction of aldehyde **4b** (1.36 g, 4.27 mmol), silylketene **5** (1.27 g, 6.40 mmol), $EtAlCl_2$ (2.6 mL, 1.8 M in PhMe, 4.7 mmol) according to the procedure described above gave oxetanones **12b–15b** (1.83 g, 3.54 mmol, 83%) as a mixture of four chromatographically inseparable diastereoisomers in the ratio 80:10:8:2.

3-Hexyl-3-trimethylsilyl-4-[(*R*)-2′-hydroxytridecyl]-2-oxetanones (12c–15c):
From 12a–15a. A 100 mL round bottomed flask fitted with magnetic stirrer and Ar line was charged with a solution of oxetanones **12a–15a** (19.1 g, 35.4 mmol) in acetonitrile (150 mL) and cooled in ice. HF (2 mL, 40% aq) was added dropwise to the mixture which was stirred for 4 h at r. t. Tlc of the mixture (3% ether in toluene) showed a mixture of 4 spots having R_f 0.44 (**12c**), 0.31 (**13c**), 0.22 and 0.12. The solvent was removed under reduced pressure and the residue extracted into ether. The combined ethereal extracts were washed with water, dried over $MgSO_4$, concentrated, and the residue purified by column chromatography (3% ether in toluene) to give pure **12c** (7.63 g) together with a mixture containing all four isomers (6.18 g). The combined yield of **12c–15c** (13.8 g, 32.3 mmol) was 91%. On storage at –20°C overnight, the main isomer **12c** gave a white, low melting solid (mp ca 0°C).

From 12b–15b. The mixture of *O*-benzyl-oxetanones **12b–15b** (1.83 g, 3.54 mmol) in THF (30 mL) was hydrogenated over 10% Pd-C (225 mg) for 8 h at r. t. in the usual way to give **12c–15c** (1.33 g, 3.12 mmol, 88%).

(3R,4S)-3-Hexyl-3-trimethylsilyl-4-[(R)-2′-hydroxytridecyl]-2-oxetanone (**12c**):
$[\alpha]_D$ (20°C) –74° (*c* = 1.03, $CHCl_3$).

IR (film): ν = 3489 br, 1802 s, 1466 m, 1254 m, 846 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.73 (1H, dd, J = 1.7, 11.3 Hz, CH–O–C=O), 3.88–3.76 (1H, br, CH–OH), 2.00∠1.61 (33H, m), 0.89–0.69 (6H, overlapping distorted t), 0.22 (9H, s).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.2 (0, C=O), 76.4 (1, CH–O–C=O), 68.8 (1, CHOH), 55.1 (0, lactone C–$SiMe_3$), 39.95 (2) , 38.4 (2), 32.1 (2), 31.7 (2), 30.8 (2), 29.8 (3C, 2), 29.7 (3C, 2), 29.5 (2), 26.3 (2), 25.65 (2), 22.9 (2), 22.76 (2), 14.3 (3), 14.2 (3), –1.15 (3C, 3).

LRMS (CI mode, NH_3): *m/z* = 444 [$(M+NH_4)^{+\bullet}$, 22%], 427 ($M^{+\cdot}$, 43), 409 (49), 381 (16), 354 (29), 337 (84), 326 (19), 199 (18), 90 (100), 58 (14), 44 (21). $C_{25}H_{50}O_3Si$ = 426.75

(3S,4S)-3-Hexyl-3-trimethylsilyl-4-[(R)-2′-hydroxytridecyl]-2-oxetanone (**13c**):
Repeated chromatography of the mixture gave a sample sufficiently enriched (ca 80%) in isomer **13c** to allow the following assignments:

^1H NMR (270 MHz, $CDCl_3$): δ = 4.66–4.61 (1H, dd, J = 2.5, 10.5 Hz, CH–O–C=O), 3.88–3.78 (1H, br, CH-OH), 2.12–1.61 (6H, m), 1.59–1.02 (27H, m), 0.92–0.75 (6H, overlapping distortrd t), 0.17 (9H, s, $SiMe_3$).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 174.3 (0, C=O), 78.1 (1, CH–O–C=O), 68.2 (1, CHOH).

(3*S*,4*S*)-3-Hexyl-4-[(*R*)-2′-hydroxytridecyl]-2-oxetanone (16):
To a solution of **12c** (7.63 g, 18.4 mmol) in THF (40 mL) at –90° C was added dropwise a solution of TBAF•$3H_2O$ (6.2 g, 19.7 mmol) in THF (10 mL). After stirring for 10 min, the reaction mixture was poured into rapidly stirred ice/water (100 mL), overlaid with ether (50 mL). The product was extracted into ether, dried over $MgSO_4$ and concentrated under reduced pressure to afford 5.2 g of a colourless oil which crystallised from pentane (2 crops) at r. t. giving **16** (4.95 g, 14.0 mmol, 71%) as white needles mp 57-59°C (lit.[14] mp 58.8–59°C).

$[\alpha]_D$ (20°C) –42.1° (*c* = 1.02, $CHCl_3$); lit.[14] $[\alpha]_D$ –41.4° (*c* = 0.5, $CHCl_3$).

IR (KBr): ν = 3347 m, 3272 m, 1820 s, 1394 s, 1115 s, 819 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.51 (1H, dt, J = 4.2, 8.5 Hz, CH–O–C=O), 3.82–3.78 (1H, m, CH–OH), 3.27 (1H, dt, J = 4.0, 8.0 Hz, O=C–CH), 2.0–1.62 (3H, m), 1.58–1.15 (30H, m), 0.90–0.80 (6H, distorted t, J = 6.8 Hz, 2 x Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.8 (0, C=O), 75.8 (1, C–O–C=O), 68.7 (1, CHOH), 56.7 (1, CH–C=O), 42.0 (2), 38.3 (2), 37.8 (2), 32.1 (2), 31.7 (2), 29.8 (2), 29.7 (2), 29.5 (2), 29.4, (2), 29.1 (2), 27.9 (2), 26.9 (2), 25.6 (2), 25.2 (2), 22.8 (2), 22.7 (2), 14.3 (3), 14.2 (3).

(3*R*,4*R*)-3-Hexyl-4-[(*R*)-2′-hydroxytridecyl]-2-oxetanone (17):
A solution of hydroxy oxetanones **12c–15c** (3.14 g 7.39 mmol) in THF (30 mL) was treated with TBAF•$3H_2O$ (8.1 mmol) as described above and the crude product purified by column chromatography (5% ether in hexanes) to afford **16** (1.67 g, 4.76 mmol, 65%) along with its diastereoisomer **17** (0.23 g, 0.65 mmol, 9%) as a colourless oil which crystallised in cold pentane, mp 54–56°C.

$[\alpha]_D$ (20°C) +7.8° (*c* = 0.5, $CHCl_3$).

IR (KBr): ν = 3358 m, 1813 s, 1470 s, 1135 m, 837 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.47 (1H, dt, J = 6.4, 4.1 Hz, CH–O–C=O), 3.77 (1H, m, CHOH), 3.31 (1H, ddd, J = 3.9, 6.8, 8.2 Hz, CH–C=O), 2.1–1.2 (33H, m), 0.90 (6H, overlapping distorted t).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.5 (0, C=O), 76.4 (1, CHO–C=O), 69.5 (1, CHOH), 56.9 (1, CH–C=O), 41.3 (2), 37.8 (2), 32.1 (2), 31.7 (2), 29.8 (2C, 2), 29.7

(3C, 2), 29.5 (2), 29.1 (2), 28.0 (2), 26.9 (2), 25.6 (2), 22.9 (2), 22.7 (2), 14.3 (3), 14.2 (3).

LRMS (CI mode, NH_3): m/z = 372 [$(M+NH_4)^{+\bullet}$, 100%] 355 ($M^{+\bullet}$, 22). $C_{22}H_{42}O_3$ = 354.57

(3*S*,4*S*)-3-Hexyl-4-[(*S*)-2′-[(*S*)-4″-methyl-2″-(*N*-formylamino)-pentanoyloxy]tridecyl]-2-oxetanone [Tetrahydrolipstatin, (2)]:
To a magnetically stirred solution of triphenylphosphine (9.33 g, 35.6 mmol), (*S*)-*N*-formylleucine (**6**) (6.43 g, 41.5 mmol) and oxetanone **16** (4.2 g, 11.9 mmol) in THF (25 mL) was added dropwise at 0°C diethyl azodicarboxylate (5.6 mL, 35.6 mmol) added dropwise. After 2 h at 0°C, the mixture was allowed to stir at r. t. overnight. The mixture was concentrated under reduced pressure and diethyl hydrazodicarboxylate crystallised from ether–hexanes and filtered. The filtrate was concentrated and the residue purified by column chromatography (10% ether in toluene) to afford a colourless oil which crystallised from pentane at –20°C, giving tetrahydrolipstatin (**2**) as a white solid (5.2 g, 89%): mp 40-42°C (lit.[14] mp 41–42.5°C)

$[\alpha]_D$ (20°C) –32.2° (c = 0.5, $CHCl_3$); lit.[14] $[\alpha]_D$ –33° (c = 0.36, $CHCl_3$).

IR (CCl_4): ν = 1839, 1740, 1695 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.22 (1H, s, NH–CHO), 6.03 (1H, d, J = 8.7 Hz, NH), 5.02 (1H, m, C2′-H), 4.68 (1H, ddd, J = 8.5, 8.5, 4.5 Hz, CH–NH), 4.29 (1H, ddd appearing as a symmetrical 5-line m, C4-H), 3.21 (1H, ddd, J = 7.8, 7.8, 4.0 Hz, C3-H), 2.17 (1H, ddd, J = 14.8, 7.2, 7.2 Hz, C1′-H_AH_B); 2.00 (1H, ddd, J = 14.8, 4.2, 4.1 Hz, C1′-H_AH_B), 1.84–1.18 (33H, m), 0.93 (6H, m, Me_2C), 0.85 (6H, distorted t, 2 x Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.1 (0), 171.0 (0), 160.8 (1), 75.0 (1), 72.9 (1), 57.2 (1), 49.8 (1), 41.7 (2), 38.9 (2), 34.2 (2), 32.1 (2), 31.6 (2), 29.8 (2C, 2), 29.7 (2C, 2), 29.6 (2), 29.5 (2), 29.1 (2), 27.8 (2), 26.9 (2), 25.3 (2), 25.0 (1), 23.0 (3), 22.9 (2), 22.7 (2), 21.9 (3), 14.3 (3), 14.2 (3).

(3*R*,4*R*)-3-Hexyl-4-[(*S*)-2′-[(*S*)-4″-methyl-2″-(*N*-formylamino)-pentanoyloxy]tridecyl]-2-oxetanone (18):
By the same Mitsunobu inversion procedure described above, hydroxyoxetanone **17** was converted to the tetrahydrolipstatin diastereoisomer **18** in 85% yield.

$[\alpha]_D$ (20°C) –3.0° (c = 0.3, $CHCl_3$).

IR(film): ν = 1839 s, 1740 s, 1695 s cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 8.12 (1H, s, NH–CHO), 5.94 (1H, br d, J = 7.7 Hz, NH), 5.02 (1H, m, C2′-H), 4.72 (1H, ddd, J = 8.9, 8.6, 4.3 Hz, CH–NH), 4.27 (1H, m, C4-H), 3.25 (1H, ddd, J = 5.3, 4.2, 1.4 Hz, C3-H), 2.05 (2H, m), 1.70 (7H, m), 1.30 (26H, m), 0.982 and 0.968 (3H, each, d, J = 6.2 Hz), 0.88 (6H, 2 overlapping distorted t).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2 (0), 170.8 (0), 160.7 (1), 74.3 (1), 72.8 (1), 56.8 (1), 49.8 (1), 41.9 (2), 39.1 (2), 34.2 (2), 32.1 (2), 31.6 (2), 29.9 (2), 29.8 (2C, 2), 29.7 (2), 29.6 (2), 29.5 (2C, 2), 29.1 (2), 27.8 (2), 26.9 (2), 25.1 (1), 23.0 (3), 22.8 (2), 22.7 (2), 22.1 (3), 14.3 (3), 14.1 (3).

LRMS (EI mode): m/z = 292 (100%), 114 (95), 96 (38), 69 (40).

HRMS (CI mode, NH_3): Found $[M+NH_4]^{+\bullet}$, 513.4271. $C_{29}H_{53}O_5N+NH_4$ requires M, 513.4264.

(3*S*,4*S*)-3-Hexyl-3-trimethylsilyl-4-[(*R*)-2′-3,5-(dinitrobenzoyloxy)tridecyl]-2-oxetanone (19):
To oxetanone **12c** (50 mg, 0.12 mmol) in THF (2 mL) was added 3,5-dinitrobenzoyl chloride (27.7 mg, 0.12 mmol) followed by pyridine (0.01 mL, 0.14 mmol). The reaction mixture was stirred at r. t. for 2 h before being poured into water. The aqueous phase was extracted with Et_2O and the organic fraction was dried and concentrated. Column chromatography (5% Et_2O in hexanes) yielded **19** (51.1 mg, 0.08 mmol, 70%) as a cream solid (mp 59–61°C) after recrystallisation from isopropanol.

IR (CCl_4): ν = 1805 s, 1730 s, 1629 m, 1548 s, 1345 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.24 (1H, s), 9.16 (2H, s), 5.42–5.28 (1H, m), 4.53 (1H, d, J = 10.8 Hz), 2.46–2.31 (1H, m), 2.24–2.13 (1H, m), 1.98–1.63 (4H, m), 1.53–0.96 (26H, m), 0.95–0.76 (6H, overlapping distorted t), 0.25 (9H, s).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 173.4 (0), 162.2 (0), 148.8 (0), 134.0 (0), 129.6 (1), 122.6 (1), 75.3 (1), 55.8 (0), 36.6 (2), 34.0 (2), 32.0 (2), 31.6 (2), 30.6 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.4 (2), 29.4 (2), 26.3 (2), 25.4 (2), 22.6 (2), 14.2 (3), 14.1 (3), –1.3 (3).

LRMS (CI mode, NH_3): m/z = 638 [$(M+NH_4)^{+\bullet}$, 11%], 90 (100).

Found: C, 61.45; H, 8.2%. $C_{32}H_{52}N_2O_8Si$ requires C 61.9; H, 8.45.

(*Z*)-(*R*)-10-[3,5-(Dinitrobenzoyloxy)-7-(trimethylsilyl)]-7-heneicosene (20):
Oxetanone **19** (7.6 mg, 0.01 mmol) in decalin (0.5 mL) was refluxed (189–191°C) for 2 h. Column chromatography (2% Et_2O in hexanes) yielded **20** (6.1 mg, 0.01 mmol, 86%) as a yellow oil.

IR (film): ν = 1730 s, 1628 m, 1548 s, 1460 m, 1344 s, 1276 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.24 (1H, t, J = 2.2 Hz), 9.15 (2H, d, J = 2.2 Hz), 5.92 (1H, dd, J = 7.8, 6.65 Hz), 5.29 (1H, tt, J = 7.3, 5.35 Hz), 2.60 (1H, dd, J = 14.8, 7.5 Hz), 2.55 (1H, dd, J = 12.1, 5.8 Hz), 2.05–1.98 (2H, m), 1.77 (2H, app quin, J = 7.4 Hz), 1.39–1.16 (26H, m), 0.88 (3H, distorted t, J = 6.8 Hz), 0.84 (3H, distorted t, J = 6.70 Hz), 0.16 (9H, s).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.3 (0), 148.8 (0), 143.8 (0), 136.1 (1), 134.6 (0), 129.5 (1), 122.3 (1), 77.7 (1), 38.7 (2), 36.8 (2), 34.1 (2), 32.0 (2), 31.9 (2), 30.9 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.6 (2), 29.5 (2), 29.5 (2), 29.2 (2), 25.7 (2), 22.8 (2), 22.7 (2), 14.2 (3), 14.2 (3), 0.48 (3C, 3).

(3*R*,4*S*)-3-Hexyl-4-[(*S*)-2′-(*p*-nitrobenzoyloxy)tridecyl]-2-oxetanone (21):
Mitsunobu esterification of oxetanone **12c** using *p*-nitrobenzoic acid gave ester **21** as a pale yellow oil.

^1H NMR (270 MHz, $CDCl_3$): δ = 8.20–8.35 (4H, AA′BB′), 5.28 (1H, quin with fine splitting, J = 6.4 Hz), 4.525 (1H, dd, J = 11.3, 2.3 Hz), 2.31 (1H, ddd, J = 15.0, 10.5, 5.25 Hz), 2.15 (1H, ddd, J = 15.0, 6.75, 2.25 Hz), 1.65–1.90 (2H, m), 1.1–1.5 (27H, m), 0.8–1.0 (6H, overlapping distorted t), 0.25 (3H, s), 0.08 (6H, s).

C-Desilylation of Oxetanone 12b:
To a solution of oxetanone **12b** (154 mg) in THF (1 mL) cooled to –80°C, was added dropwise TBAF (0.25 mL of a 1 M solution in THF, 0.25 mmol). After 5 min. the reaction was quenched at –80°C by the slow addition of water (1 mL). On warming to r. t. the mixture was extracted with Et_2O, dried ($MgSO_4$) and concentrated to yield a yellow oil (111 mg) which was purified by column chromatography (4% Et_2O in hexanes) to give in order of elution **23** (44 mg, 0.09 mmol, 43% from **12b**) and **24** (30 mg, 0.06 mmol, 29%).

(3S,4S)-3-Hexyl-4-[(R)-2′-(benzyloxy)tridecyl]-2-oxetanone (**23**):
$[\alpha]_D$ +0.5° (c = 2, $CHCl_3$)

IR (film): ν = 1828 s, 1465 s, 1121 s cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 7.39–7.24 (5H, m), 4.61 (1H, d, J = 9.5 Hz), 4.47–4.43 (2H, m), 3.61 (1H, app quin, J = 6.35 Hz), 3.22 (1H, dt, J = 7.6, 4.0 Hz), 1.94 (2H, t, J = 7.4 Hz), 1.81–1.47 (4H, m), 1.4–1.0 (26H, m), 0.88 (3H, t, J = 6.85 Hz), 0.87 (3H, t, J = 6.8 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.0 (0), 138.6 (0), 128.6 (2C, 1), 128.0 (2C, 1), 127.9 (1), 75.9 (1), 75.7 (1), 71.7 (2), 56.8 (1), 40.0 (2), 34.1 (2), 32.1 (2), 31.7 (2), 29.9 (2), 29.8 (2C, 2), 29.7 (2C, 2), 29.6 (2), 29.1 (2), 27.9 (2), 26.9 (2), 24.9 (2), 22.9 (2), 22.7 (2), 14.4 (3), 14.2 (3).

LRMS (CI mode, NH_3): m/z = 462 [$(M+NH_4)^{+\bullet}$, 100%], 445 [$(M+H)^{+\bullet}$, 27].

(3R,4S)-3-Hexyl-4-[(R)-2′-(benzyloxy)tridecyl]-2-oxetanone (**24**):
^1H NMR (270 MHz, $CDCl_3$): δ = 7.41–7.25 (5H, m), 4.85 (1H, q, J = 8.5 Hz), 4.62 (1H, d, J = 11.4 Hz), 4.44–4.40 (2H, m), 3.61 (1H, app quin, J = 5.7 Hz), 1.96 (2H, t, J = 6.4 Hz), 1.81–1.46 (4H, m), 1.4-1.0 (26H, s), 0.88 (6H, m).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.4 (0), 138.6 (0), 128.6 (2C, 1), 128.0 (2C, 1), 127.9 (1), 75.7 (1), 73.0 (1), 72.0 (2), 52.7 (1), 35.6 (2), 34.4 (2) 32.1 (2), 31.6 (2), 30.0 (2), 29.9 (2), 29.8 (3C, 2), 29.5 (2C, 2), 29.2 (2), 27.6 (2), 24.3 (2), 22.9 (2), 22.7 (2), 14.3 (3), 14.2 (3).

(3*R*, 4*S*)-3-Hexyl-4-[(*R*)-2′-hydroxytridecyl]-2-oxetanone (25):
Hydrogenolysis of oxetanone **24** (123 mg, 0.28 mmol) in THF (4 mL) with Pd/C (10%, 31 mg) at atmospheric pressure in the usual way afforded **25** (57 mg, 0.16 mmol, 58%) as a pale yellow oil after column chromatography (20% EtOAc in hexanes).

IR (film): ν = 3648-3119 br, 1823 s, 1120 m cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 4.89 (1H, ddd, J = 10.6, 6.5, 2.5 Hz), 3.86–3.79 (1H, m), 3.64 (1H, dt, J = 8.3, 7.0 Hz), 2.13–1.96 (1H, s, br), 1.92-1.66 (2H, m), 1.54–1.46 (2H, m), 1.36–1.23 (28H, m), 0.88 (3H, t, J = 6.85 Hz), 0.87 (3H, t, J = 6.8 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.4 (0), 72.9 (1), 68.1 (1), 52.7 (1), 38.3 (2), 37.6 (2), 32.0 (2), 31.6 (2), 29.8 (2), 29.8 (2), 29.7 (2), 29.7 (2), 29.5 (2), 29.2 (2), 27.6 (2), 25.6 (2), 24.3 (2), 22.8 (2), 22.7 (2), 14.3 (3), 14.2 (3).

LRMS (CI mode, NH_3): m/z = 372 [$(M+NH_4)^{+\bullet}$, 100%], 355 [$(M+H)^{+\bullet}$, 38].

(3*R*4*S*)-3-Hexyl-4-[(*S*)-2′-[(*S*)-4″-methyl-2″-(*N*-formylamino)-pentanoyloxy]tridecyl]-2-oxetanone (26):
By the same Mitsunobu inversion procedure described above, hydroxyoxetanone **25** (46 mg, 0.13 mmol), triphenylphosphine (42 mg, 0.16 mmol), (*S*)-*N*-formylleucine (**6**) (28 mg, 0.18 mmol), and diethyl azodicarboxylate (28 µl, 0.18 mmol) gave the tetrahydrolipstatin diastereoisomer **26** (54 mg, 0.11 mmol, 84%) as a pale yellow oil. after column chromatography (hexanes: chloroform: dioxane/ 3:1:0.4).

$[\alpha]_D$ (20°C) = –9.5° (*c* = 1, $CHCl_3$).

IR (CCl_4): ν = 3436-3131 br, 1824 s, 1798 s, 1740 s, 1689 s cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$) δ = 8.22 (1H, s), 6.05 (1H, d, *J* = 8.1 Hz), 5.09 (1H, m), 4.69 (2H, m), 3.67 (1H, m), 2.08–1.84 (2H, m), 1.81–1.45 (12H, m), 1.42–1.06 (21H, m), 0.94 (6H, d, *J* = 5.6 Hz), 0.86 (6H, distorted t, *J* = 6.8 Hz).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.1 (0), 171.6 (0), 161.1 (1), 73.1 (1), 72.5 (1), 53.5 (1), 49.9 (1), 41.4 (2), 34.6 (2), 34.2 (2), 32.0 (2), 31.6 (2), 29.8 (2C, 2), 29.7 (2), 29.6 (2), 29.5 (2), 29.2 (2C, 2), 27.5 (2), 25.3 (2), 25.0 (1), 24.2 (2), 23.0 (3), 22.8 (2), 22.6 (2), 21.9 (3), 14.2 (3), 14.1 (3).

LRMS (CI mode, NH_3): *m/z* = 513 [$(M+NH_4)^{+\bullet}$, 100%] 496 [$(M+H)^{+\bullet}$, 23], 470 (27), 86 (39).

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