The First Total Synthesis of (−)-Lipstatin

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A key step in the first total synthesis of the potent pancreatic lipase inhibitor (−)-lipstatin (**1**) is a diastereoselective Lewis acid-promoted [2 + 2] cycloaddition reaction between *n*-hexyl(trimethylsilyl)ketene (**4**) and (*R*)-(−)-(*Z*,*Z*)-3-[(*tert*-butyldimethylsilyl)oxy]-5,8-tetradecadienal (**3**), which is prepared from dimethyl (*S*)-(−)-malate.

Lipstatin (**1**) was isolated from *Streptomyces toxytricini* in 1987 by scientists from the Hoffmann-LaRoche company.[1] Both lipstatin and its tetrahydro derivative **2** are potent and irreversible inhibitors of pancreatic lipase—an enzyme which is essential for the absorption of dietary fat and therefore a useful lead for the development of novel antiobesity agents. Despite its lower activity, tetrahydrolipstatin (**2**, THL) has received far more attention in synthetic and biological studies[2] than its parent because THL is both simpler and more stable.[3] Thus, clinical studies have established its effectiveness in antiobesity treatment[4] and detailed structure–activity studies have revealed the importance of the 2-oxetanone ring in its activity.[5]

To date eight syntheses of THL have been reported,[6,7] most of which are based on the classic cyclodehydration procedure of Adam[8] to create the 2-oxetanone[9] ring from appropriate β-hydroxy carboxylic acid precursors. We now report full details and improvements to the first synthesis of (−)-lipstatin from (*R*)-(−)-(*Z*,*Z*)-3-[(*tert*-butyldimethylsilyl)oxy]-5,8-tetradecadienal (**3**), *n*-hexyl(trimethylsilyl)ketene (**4**), and (*S*)-*N*-formylleucine (**5**) (Figure 1).[10] A noteworthy feature of the synthesis is the use of a diastereoselective Lewis acid-catalyzed [2 + 2] cycloaddition to generate the 2-oxetanone ring which is amply precedented in the work of Zaitseva and coworkers published 30 years ago[11] and more recently used by us in an efficient synthesis of THL.[12]

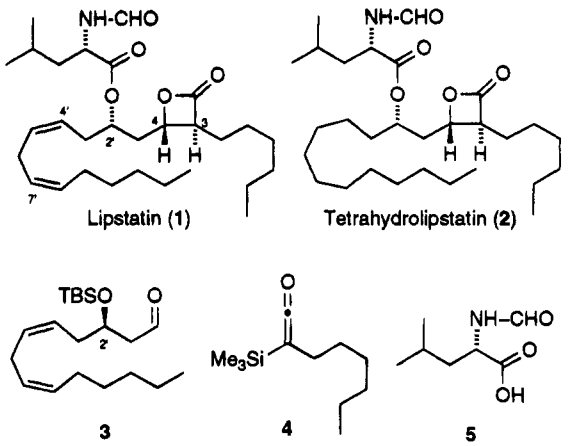

Figure 1. Lipstatin (**1**), THL (**2**), and key intermediates **3**, **4**, and **5**.

Synthesis of (*R*)-(−)-(*Z*,*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5,8-tetradecadienal (3). Two approaches to the scalemic aldehyde (**3**) were examined. In the first approach (Figure 2), a Wittig reaction involving the aldehyde **7** and the phosphorane derived from phosphonium salt **11** was used to form the (*Z*,*Z*)-diene moiety.[10] The stereogenic center at C2′ (lipstatin numbering) was created by a bakers' yeast reduction of the β-keto ester **6**[13] according to the procedure of Knight.[14] Unfortunately, the crucial asymmetric reduction step *en route* to **7** gave only 78% ee despite modifications like the use of benzene as solvent[15] or the use of the potassium salt of the corresponding carboxylic acid.[16]

Preparation of the phosphonium salt **11** began with the readily available acetal **8**[17] which was hydrolyzed and

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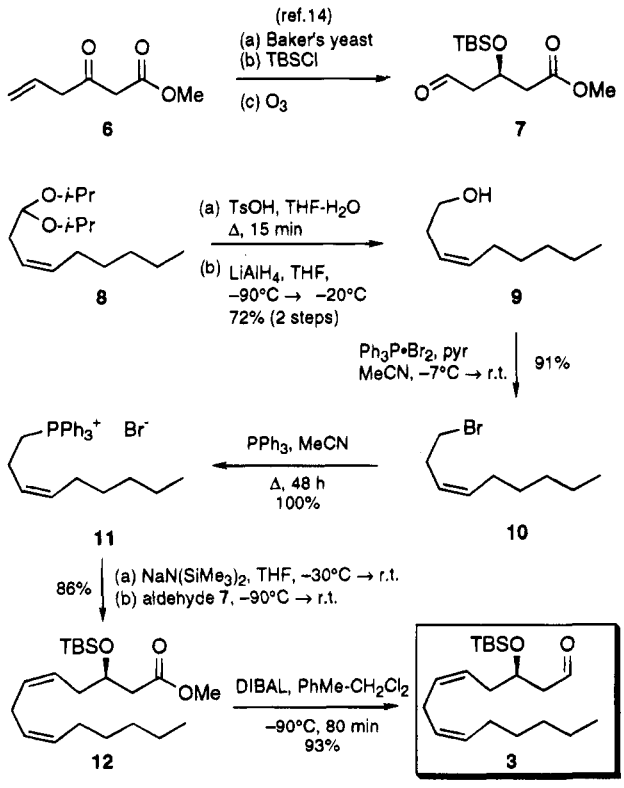

Figure 2. Preparation of dienic aldehyde **3** from β-keto ester **6**.

immediately reduced to the alcohol **9** (72% yield for the two steps). Alcohol **9** was converted first to the bromide **10** by the method of Viala[18] and then to the phosphonium salt in the usual way. The phosphorane derived from deprotonation of **11** with sodium hexamethyldisilazide underwent a Wittig reaction with aldehyde **7** to give the (*Z*,*Z*)-1,4-diene **12** in 86% yield and with ≥95% (*Z*)-stereoselectivity according to high-field NMR spectroscopy. Finally reduction of the ester function afforded the desired dienic aldehyde **3** in 52% overall yield from **8**.

The second approach to aldehyde **3** (Figure 3) was developed in order to circumvent the low ee in the asymmetric reduction step in Figure 2. Thus the ester function adjacent to the hydroxyl group in enantiomerically pure dimethyl (*S*)-(−)-malate (**13**) was selectively reduced with BH_3•SMe_2 in the presence of a catalytic amount of $NaBH_4$ according to the procedure of Moriwake.[19] The primary hydroxyl function of the resultant diol **14** was converted to the tosylate **15**[20] and the remaining alcohol protected as its *tert*-butyldimethylsilyl ether. Attempts to displace the tosylate with carbon nucleophiles (e.g. organocuprates[21]) were thwarted by the base sensitivity caused by the ester function; therefore the ester was first converted, *via* aldehyde **17**, to the diisopropyl acetal **18** whereupon nucleophilic displacement occurred cleanly and efficiently on heating with NaCN in DMSO.[22] The resultant nitrile **19** was converted to aldehyde **20** on reduction with DIBAL and a Wittig reaction performed as before gave the fully

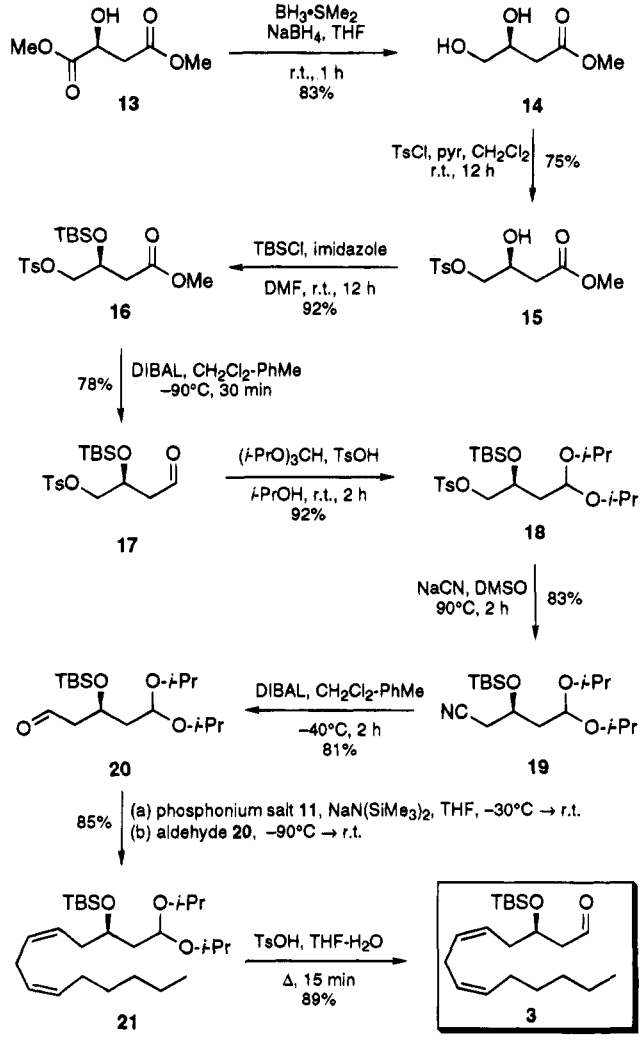

Figure 3. Preparation of dienic aldehyde **3** from dimethyl (*S*)-malate (**13**).

protected (*Z*,*Z*)-diene **21** in good yield and high (≥95%) (*Z*)-stereoselectivity. Finally hydrolysis of the acetal gave the desired dienal **3** in 21% overall yield from **13**. The regrettable length of the second route was compensated by the higher enantiomeric purity of the final product and the low cost of the starting material.

Synthesis of Lipstatin (1) from Dienal 3. The diastereoselective Lewis acid-catalyzed [2 + 2] cycloaddition which is the cornerstone of our synthetic plan was conducted by adding a solution of silylketene **4**[12] (1.5 equiv) in Et_2O to a solution of the dienal **3** (1.0 equiv) and $EtAlCl_2$ (1.1 equiv) in Et_2O at −45 °C followed by warming to −20 °C (Scheme 1). The inseparable mixture of four diastereoisomeric 2-oxetanones **22a**−**d**,[23] obtained in 91% yield, was first submitted to *O*-desilylation[24] with HF in MeCN followed by *C*-desilylation using TBAF in THF. The 2-oxetanone **24** having the desired stereochemistry at all three stereogenic centers was isolated in 64% overall yield from the mixture **23a**−**d** after column chromatography on silica gel. Finally esterifi-

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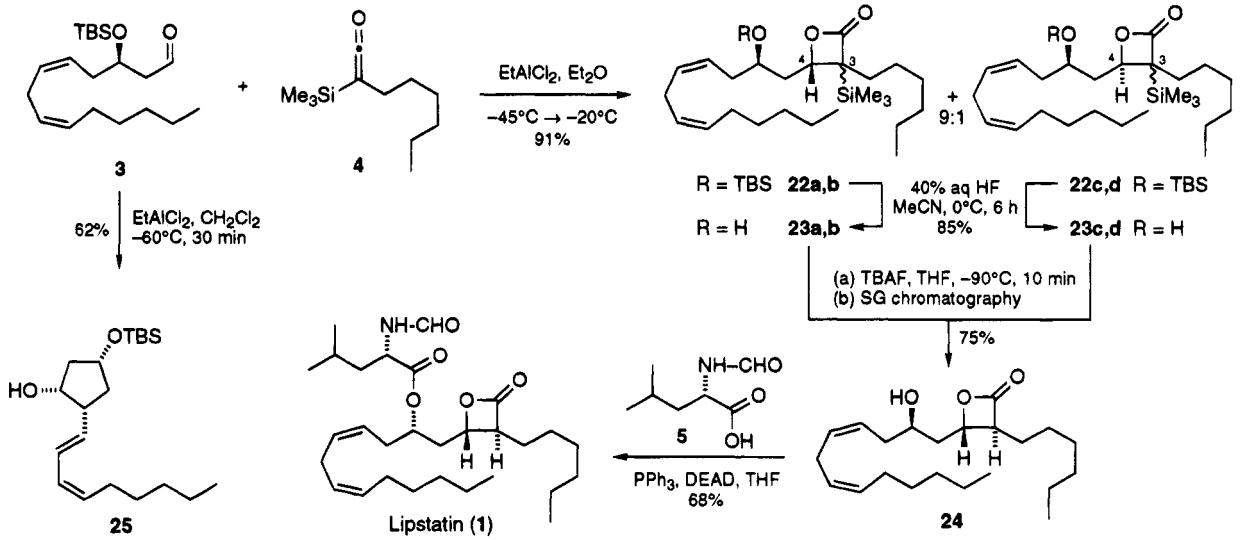
(24) Having a free hydroxy group, as in **23**, is a prerequisite to the selective obtention of *trans* 2-oxetanone **24** (for a discussion, see ref 12b).

Scheme 1. Synthesis of Lipstatin (1) from Dienic Aldehyde 3 and Ketene 4: Preparation of Cyclopentanediol 25



cation of the hydroxy-2-oxetanone **24** with (*S*)-*N*-formylleucine under Mitsunobu conditions[25] proceeded with clean inversion of stereochemistry to give (−)-lipstatin in 68% yield. The identity of the synthetic (−)-lipstatin was confirmed by comparison with published data[1b,26] and by hydrogenation to (−)-tetrahydrolipstatin which was identical by high-field ^1H and ^{13}C NMR spectroscopy, mp, and $[\alpha]_D$ with an authentic sample prepared as previously described.[12b]

Two aspects of the cycloadditon reaction deserve further comment. First the stereochemistry of the cycloaddition appears to parallel that previously observed in the synthesis of THL,[12b] reflecting the high level of 1,3-induction (ca. 9:1) exerted by the stereogenic center in dienal **3**. Secondly, the absence of any products derived from a competing intramolecular ene reaction[27,28] between the aldehyde function and the proximate alkene at C4' of the dienal **3** is both welcome and surprising. Separate experiments established that an ene reaction was possible though highly solvent dependent. Thus, treatment of the racemic dienal **3** with $EtAlCl_2$ in CH_2Cl_2 at −60 °C in the absence of silylketene **4** led to the cyclopentanol **25** in 62% yield (Scheme 1),[29] whereas the same reaction conducted in the presence of silylketene led to [2 + 2] cycloaddition with no evidence of competing ene cyclization. On the other hand, treatment of dienal **3** with $EtAlCl_2$ in Et_2O in the absence of silylketene gave none of the ene product **25** at low temperature while many unidentified products were formed at 0 °C.

In conclusion, we have accomplished the first total synthesis of (−)-lipstatin (**1**) in 8% overall yield from dimethyl (*S*)-(−)-malate and 40% overall from dienal **3**. Moreover, we have provided further evidence of (a) the value of silyl-stabilized ketenes as synthetic reagents, (b) their ability to react cleanly and efficiently with aldehydes in the presence of a sensitive 1,4-diene moiety, and (c) the efficiency of (*Z*)-selective Wittig chain elongation for the synthesis of (*Z*,*Z*)-1,4-dienes. Further investigation of the scope, stereochemistry, and mechanism of the [2 + 2] cycloaddition reaction is currently underway.

Experimental Section

Anhydrous THF and Et_2O were prepared by distillation over sodium benzophenone ketyl under an argon atmosphere. CH_2Cl_2 was distilled over P_2O_5. Anhydrous DMF and CH_3CN were obtained from Aldrich Chemical Co. and used as received. All starting materials were obtained from commercially available sources unless otherwise specified. Chromatography refers to flash chromatography using Merck silica gel (230−400 mesh).

(*Z*)-Non-3-en-1-ol (9). A solution of acetal **8**[17] (9.16 g, 37.8 mmol) and *p*-TsOH (0.1 M in H_2O, 19 mL) in THF (750 mL) was refluxed (in a prewarmed oil bath) for 15 min. The solution was then cooled, diluted with pentane (1.5 L), washed with water and brine, dried quickly over $MgSO_4$, and evaporated *in vacuo*. The resulting crude aldehyde was then diluted in THF (11 mL) and added to a stirred suspension of $LiAlH_4$ (1.44 g, 37.8 mmol) in THF (150 mL) at −90 °C. The reaction mixture was allowed to warm to −20 °C, the reaction was quenched with 2 N HCl (76 mL), and the mixture was stirred overnight at room temperature. After extraction with Et_2O and usual treatment of the organic layer, chromatography (Et_2O/pentane, 30/70) of the residue gave alcohol **9** (3.90 g, 27.2 mmol, 72%). Crude aldehyde: ^1H NMR (200 MHz, $CDCl_3$) δ 9.65 (broad s, 1H), 5.76−5.02 (m, 2H), 3.18 (d, J = 6.9 Hz, 2H), 2.05−1.98 (m, 2H), 1.40−1.28 (m, 6H), 0.88 (t like, J = 6.3 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 199.3 (d), 135.6 (d), 118.0 (d), 42.6 (t), 31.5 (t), 29.0 (t), 27.6 (t), 22.6 (t), 14.1 (q). **9**: ^1H NMR (200 MHz, $CDCl_3$) δ 5.47 ($^1/_2$ ABX_2, J_{AB} = 10.9, J = 7.1 Hz, 1H), 5.31 ($^1/_2$ ABX_2, J_{AB} = 10.9, J = 7.1 Hz, 1H), 3.55 (t, J = 6.8 Hz, 2H), 2.89 (broad s, 1H), 2.26 (q, J = 6.8 Hz, 2H), 2.08−1.92 (m, 2H), 1.40−1.15 (m, 6H), 0.84 (t, J = 6.4 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 132.8 (d), 125.0 (d), 62.1 (t), 31.4 (t), 30.7 (t), 29.3 (t), 27.2 (t), 22.5 (t), 13.9 (q); IR (film) ν 3320, 1660, 1055 cm^{-1}. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.04. Found: C, 76.04; H, 12.02.

1-Bromo-3-nonene (10). To a solution of alcohol **9** (2.55 g, 17.95 mmol) and pyridine (2.30 mL, 28.70 mmol) in CH_3CN (36 mL) at −7 °C was added $Ph_3P{\cdot}Br_2$ (9.84 g, 23.30 mmol) in 5 portions. The reaction mixture was stirred for 10 min at −7 °C and then for 1 h at room temperature before being directly chromatographed on silica gel (Et_2O/pentane, 10/90) to give bromide **10** (3.35 g, 16.33 mmol, 91%): ^1H NMR (200 MHz, $CDCl_3$) δ 5.54 ($^1/_2$ ABX_2, J_{AB} = 10.8, J = 7.2 Hz, 1H),

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(29) The attribution of an *all-syn* relationship between the three substituents of the cyclopentane ring rest upon two dimensional homo- and heteronuclear experiments and selective irradiations (^1H, 400 MHz) of the protons *gem* to the substituents.

5.36 ($^1/_2$ ABX$_2$, J_{AB} = 10.8, J = 7.0 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 2.62 (q, J = 7.2 Hz, 2H), 2.10−1.98 (m, 2H), 1.48−1.22 (m, 6H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 133.2 (d), 125.8 (d), 32.6 (t), 31.5 (t), 30.9 (t), 29.3 (t), 27.4 (t), 22.6 (t), 14.1 (q); IR (film) ν 3012, 1655 cm^{-1}.

Triphenyl[(*Z*)-3-nonenyl]phosphonium Bromide (11). A solution of bromide **10** (5.54 g, 27 mmol) and PPh_3 (14.15 g, 54 mmol) in CH_3CN (30 mL) was refluxed under argon for 48 h. The excess PPh_3 was eliminated by chromatography (Et_2O/pentane, 50/50) before a change of eluent (CH_2Cl_2/MeOH, 90/10) allowed the purification of phosphonium salt **11** (12.62 g, 27 mmol, quantitative yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00−7.55 (m, 15H), 5.53 ($^1/_2$ ABX$_2$, J_{AB} = 10.7, J = 7.0 Hz, 1H), 5.34 ($^1/_2$ ABX$_2$, J_{AB} = 10.7, J = 7.4 Hz, 1H), 3.90−3.60 (m, 2H), 2.50−2.30 (m, 2H), 1.80−1.64 (m, 2H), 1.25−1.06 (m, 6H), 0.79 (t, J = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 134.6 (d) (d, J = 2.9 Hz, 3C), 133.0 (d) (d, J = 9.9 Hz, 6C), 130.0 (d) (d, J = 12.5 Hz, 6C), 132.0 (d), 125.3 (d) (d, J = 14.5 Hz), 117.4 (s) (d, J = 85.9 Hz, 3C), 30.7 (t), 28.3 (t), 26.5 (t), 21.8 (t), 22.3 (t) (d, J = 48.8 Hz), 19.6 (t) (d, J = 3.3 Hz), 13.4 (q); IR (CH_2Cl_2) ν 3037, 1588, 1486, 1440, 1260, 1113, 997 cm^{-1}. Anal. Calcd for $C_{27}H_{32}BrP$: C, 69.38; H, 6.90. Found: C, 69.34; H, 6.93.

Methyl (*R*)-(*Z*,*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5,8-tetradecadienoate (12). To a solution of dry phosphonium salt **11** (7.90 g, 16.9 mmol) in THF (225 mL) and toluene (45 mL), at −30 °C under argon, was added $NaN(SiMe_3)_2$ (2 M in THF, 7.8 mL, 15.6 mmol). After 2 h of stirring at room temperature, the orange solution was cooled to −90 °C and a solution of aldehyde **7**[14] (3.39 g, 13 mmol) in THF (15 mL) was added dropwise. The mixture was then allowed to warm to room temperature overnight, and the reaction was quenched with aqueous saturated NH_4Cl (60 mL) and water (15 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Ester **12** (4.14 g, 11.2 mmol, 86%) was obtained by chromatography (Et_2O/pentane, 3/97) of the crude product: $[\alpha]^{24}_D$ −26.7° (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.54−5.25 (m, 4H), 4.20 (quint like, J = 6.1 Hz, 1H), 3.67 (s, 3H), 2.78 (t like, J = 6.1 Hz, 2H), 2.48−2.40 (m, 2H), 2.36−2.24 (m, 2H), 2.10−1.98 (m, 2H), 1.43−1.18 (m, 6H), 0.90 (t, J = 5.4 Hz, 3H), 0.88−0.79 (broad s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.3 (s), 130.9 (d), 130.6 (d), 127.4 (d), 124.8 (d), 69.5 (d), 51.5 (q), 42.2 (t), 35.6 (2C) (t), 31.6 (t), 29.4 (t), 27.3 (t), 22.6 (t), 25.9 (q), 25.8 (2C) (q), 18.0 (s), 14.1 (q), −4.4 (q), −4.9 (q); IR (film): ν 1740, 1255, 1100, 835 cm^{-1}; HRMS *m*/*z* calcd for $C_{17}H_{31}O_3Si$ [(M − *t*-Bu)$^+$] 311.2042, found 311.2030.

(*R*)-(*Z*,*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5,8-tetradecadienal (3) (from Ester 12). To a solution of ester **12** (3.86 g, 10.47 mmol) in CH_2Cl_2 (50 mL) at −90 °C was added slowly, over 1 h, DIBAL (1.5 M in toluene, 7.7 mL, 11.52 mmol). The solution was stirred for 20 min at the same temperature, and then the reaction was quenched with aqueous saturated NH_4Cl (3 mL) and 1 N HCl (6 mL). The so-formed salts were filtered and rinsed with CH_2Cl_2. The combined organic layers were evaporated *in vacuo*, and the resulting residue was chromatographed (Et_2O/pentane, 6/94) to yield aldehyde **3** (3.31 g, 9.74 mmol, 93%): $[\alpha]^{24}_D$ −19.5° (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.81 (t, J = 2.4 Hz, 1H), 5.56−5.24 (m, 4H), 4.25 (quint, J = 5.9 Hz, 1H), 2.77 (t, J = 6.3 Hz, 2H), 2.53 (dd, J = 5.9, 2.4 Hz, 2H), 2.36−2.29 (m, 2H), 2.15−2.00 (m, 2H), 1.43−1.19 (m, 6H), 0.88 (broad s, 12H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 202.2 (d), 131.2 (d), 130.7 (d), 127.2 (d), 124.5 (d), 68.1 (d), 50.5 (t), 35.7 (t), 31.6 (t), 29.3 (t), 27.3 (t), 25.8 (t), 22.6 (t), 25.9 (q) (3C), 18.0 (s), 14.1 (q), −4.3 (q), −4.7 (q); IR (film) ν 3010, 1735, 1655, 1260, 1010, 840 cm^{-1}; HRMS *m*/*z* calcd for $C_{16}H_{29}O_2Si$ [(M − *t*-Bu)$^+$] 281.1937, found 281.1932. Anal. Calcd for $C_{20}H_{38}O_2Si$: C, 70.94; H, 11.31. Found: C, 70.85; H, 11.30.

Methyl (*S*)-3,4-Dihydroxybutanoate (14). To a solution of dimethyl (*S*)-(−)-malate (**13**) (29.57 g, 182.4 mmol) in THF (380 mL), under argon at 20 °C, was added, dropwise over 15 min, a BH_3−DMS complex (10 M, 18.6 mL, 186 mmol). After 30 min of stirring, $NaBH_4$ (345 mg, 9.12 mmol) was added in parts, and 30 min later the reaction was quenched by slowly adding MeOH (120 mL). After another 30 min, solvents were eliminated *in vacuo*, and the crude material was purified by chromatography (EtOAc) to give diol **14** (20.31 g, 151.4 mmol, 83%): $[\alpha]^{27}_D$ −24.6° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.15−4.03 (m, 1H), 3.60 ($^1/_2$ ABX, J_{AB} = 11.5, J = 3.5 Hz, 1H), 3.47 ($^1/_2$ ABX, J_{AB} = 11.5, J = 6.5 Hz, 1H), 3.67 (s, 3H), 2.54−2.46 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.4 (s), 68.4 (d), 58.2 (t), 51.5 (q), 37.6 (t); IR (film) ν 3375, 1730, 1050 cm^{-1}.

Methyl (*S*)-3-Hydroxy-4-(tosyloxy)butanoate (15). To a solution of diol **14** (19 g, 141.6 mmol) and pyridine (61 mL) in CH_2Cl_2 (630 mL), at 0 °C under argon, was added in portions tosyl chloride (7 g, 141.6 mmol), and the solution was stirred at room temperature overnight. The reaction mixture was then washed with an aqueous saturated $CuSO_4$ solution to obtain a colorless organic layer. The aqueous layer was extracted with CH_2Cl_2, and combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo*. Filtration of the residue over silica gel gave **15** (30.55 g, 106.2 mmol, 75%): $[\alpha]^{28}_D$ −6.7° (*c* 1, $CHCl_3$); mp 82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 4.32−4.18 (m, 1H), 4.04 (d, J = 5.1 Hz, 2H), 3.70 (s, 3H), 2.60−2.52 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.9 (s), 145.2 (s), 132.5 (s), 130.0 (d) (2C), 128.0 (d) (2C), 72.1 (t), 65.9 (d), 52.0 (q), 37.3 (t), 21.6 (q); IR (film) ν 3620, 1735, 1610, 1370, 1200, 1185, 990 cm^{-1}.

Methyl (*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(tosyloxy)butanoate (16). To a solution of monotosylate **15** (3.59 g, 12.45 mmol) in DMF (12 mL) were added a solution of *t*-$BuMe_2$SiCl (2.81 g, 18.84 mmol) in DMF (7 mL) and then a solution of imidazole (1.69 g, 24.82 mmol) in DMF (7 mL). The solution was stirred overnight at room temperature, then diluted with Et_2O, and washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* and the residue purified by chromatography (Et_2O/pentane, 25/75) to give **16** (4.63 g, 11.45 mmol, 92%): $[\alpha]^{21}_D$ −18.3° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 4.29 (quint, J = 5.6 Hz, 1H), 3.94 (d, J = 5.6 Hz, 2H), 3.65 (s, 3H), 2.50−2.38 (m, 2H), 2.45 (s, 3H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.8 (s), 144.9 (s), 132.7 (s), 129.8 (d) (2C), 127.9 (d) (2C), 72.2 (t), 67.1 (d), 51.6 (q), 39.2 (t), 25.5 (q) (3C), 21.6 (q), 17.8 (s), −4.8 (q), −5.2 (q); IR (film) ν 1740, 1600, 1365, 1190, 1175, 980, 840 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_6SSi$: C, 53.70; H, 7.51; S, 7.96. Found: C, 53.67; H, 7.48; S, 7.90.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(tosyloxy)butanal (17). To a solution of methyl ester **16** (3.88 g, 9.64 mmol) in CH_2Cl_2 (50 mL) at −90 °C was added dropwise DIBAL (1.5 M in toluene, 7.1 mL, 10.6 mmol) so that the temperature did not exceed −75 °C. After 30 min of stirring, the reaction was quenched with aqueous saturated NH_4Cl (2.8 mL) and 1 N HCl (5.4 mL). After filtration over silica gel, the solvent was eliminated *in vacuo* and the residue purified by chromatography (Et_2O/pentane, 50/50) to give aldehyde **17** (2.81 g, 7.52 mmol, 78%): $[\alpha]^{22}_D$ −12.2° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.72 (dd, J = 1.6, 3.2 Hz, 1H), 7.78 (broad d, J = 8.2 Hz, 2H), 7.35 (broad d, J = 7.9 Hz, 2H), 4.38 (quint like, J = 5.5 Hz, 1H), 3.98 ($^1/_2$ ABX, J_{AB} = 9.9, J = 5.2 Hz, 1H), 3.90 ($^1/_2$ ABX, J_{AB} = 9.9, J = 5.3 Hz, 1H), 2.62−2.57 (m, 2H), 2.45 (s, 3H), 0.81 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 199.6 (d), 145.0 (s), 132.5 (s), 129.9 (d) (2C), 127.8 (d) (2C), 72.2 (t), 65.5 (d), 47.6 (t), 25.5 (q) (3C), 21.5 (q), 17.8 (s), −4.8 (q), −5.2 (q); IR (film) ν 3040, 1735, 1605, 1370, 1190, 990, 840 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_5SSi$: C, 54.81; H, 7.57; S, 8.60. Found: C, 54.80; H, 7.53; S, 8.50.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-(tosyloxy)butanal Diisopropyl Acetal (18). To a solution of aldehyde **17** (2.60 g, 6.98 mmol) in *i*-PrOH (70 mL) was added isopropyl orthoformate[17] (3.98 g, 20.94 mmol) and a catalytic amount of *p*-TsOH. The reaction, monitored by TLC, was over after 2 h at room temperature and then quenched with water. Extraction with Et_2O provided the organic layer which was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by chromatography (Et_2O/pentane, 80/20) to give acetal **18** (3.06 g, 6.42 mmol, 92%): $[\alpha]^{24}_D$ 4.1° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H),

7.33 (d, J = 8.3 Hz, 2H), 4.68 (t, J = 5.4 Hz, 1H), 4.03–3.89 (m, 3H), 3.78 (sept, J = 6.1 Hz, 2H), 2.44 (s, 3H), 1.72 (t like, J = 5.4 Hz, 2H), 1.16 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H), 1.11 (d, J = 6.1 Hz, 3H), 1.07 (d, J = 6.1 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 144.7 (s), 133.0 (s), 129.8 (d) (2C), 128.0 (d) (2C), 97.1 (d), 74.0 (t), 68.3 (d) (2C), 67.5 (d), 40.5 (t), 25.8 (q) (3C), 23.4 (q), 23.3 (q), 22.8 (q), 22.2 (q), 21.6 (q), 18.0 (s), −4.4 (q), −4.9 (q); IR (film) ν 1605, 1375, 1195, 1185, 1020, 840 cm^{-1}. Anal. Calcd for $C_{23}H_{42}O_6SSi$: C, 58.19; H, 8.92; S, 6.75. Found: C, 58.08; H, 8.94; S, 6.80.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-cyanobutanal Diisopropyl Acetal (19). A solution (orange) of acetal **18** (510 mg, 1.07 mmol) and NaCN (68 mg, 1.4 mmol) in DMSO (2 mL) was heated at 90 °C for 2 h, cooled to 0 °C, diluted with Et_2O (2 mL), and poured in water (2 mL). After extraction of the aqueous layer with Et_2O (3 × 10 mL), the combined organic layers were washed with water (5 mL) and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by chromatography (Et_2O/pentane, 80/20) to give nitrile **19** (293 mg, 0.89 mmol, 83%): $[\alpha]^{21}_D$ −6.2° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.69 (t, J = 5.0 Hz, 1H), 4.11 (broad quint, J = 5.5 Hz, 1H), 3.82 (sept, J = 6.1 Hz, 2H), 2.65 ($^1/_2$ ABX, J_{AB} = 16.6, J = 4.7 Hz, 1H), 2.54 ($^1/_2$ ABX, J_{AB} = 16.6, J = 5.7 Hz, 1H), 1.92–1.82 (m, 2H), 1.18 (d, J = 6.1 Hz, 6H), 1.14 (d, J = 6.1 Hz, 6H), 0.91 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 117.9 (s), 97.1 (d), 68.4 (d) (2C), 65.2 (d), 42.8 (t), 26.6 (t), 25.6 (q) (3C), 23.3 (q), 23.1 (q), 22.6 (q), 22.3 (q), 17.8 (s), −4.7 (q) (2C); IR (film) ν 2230, 1390, 1370, 1105, 840 cm^{-1}; HRMS m/z calcd for $C_{14}H_{28}NO_2Si$ [(M − O-*i*-Pr)$^+$] 270.1889, found 270.1875.

(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5,5-diisopropoxypentanal (20). To a solution of nitrile **19** (1.7 g, 5.31 mmol) in CH_2Cl_2 (90 mL), under argon at −40 °C, was added dropwise DIBAL (1.5 M in toluene, 5.3 mL, 7.96 mmol). After 15 min of stirring at the same temperature, the reaction was quenched with AcOH/H_2O (1/1) (1.5 mL) and the solution allowed to warm to 0 °C over 15 min. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), washed with water (15 mL) and brine (15 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by chromatography (Et_2O/pentane, 10/90) to give aldehyde **20** (1.43 g, 4.30 mmol, 81%); $[\alpha]^{24}_D$ 3.1° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.77 (t, J = 2.1 Hz, 1H), 4.67 (t, J = 5.3 Hz, 1H), 4.31 (quint like, J = 5.5–6.1 Hz, 1H), 3.81 (sept, J = 6.2 Hz, 1H), 3.80 (sept, J = 6.2 Hz, 1H), 2.63 ($^1/_2$ ABMX, J_{AB} = 15.8, J = 5.0, 2.0 Hz, 1H), 2.51 ($^1/_2$ ABMX, J_{AB} = 15.8, J = 6.3, 2.9 Hz, 1H), 1.95–1.72 (m, 2H), 1.16 (d, J = 6.2 Hz, 6H), 1.12 (d, J = 6.2 Hz, 6H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 202.2 (d), 97.5 (d), 68.2 (d), 68.1 (d), 65.3 (d), 51.1 (t), 43.6 (t), 25.7 (q) (3C), 23.4 (q), 23.2 (q), 22.8 (q), 22.3 (q), 17.9 (s), −4.5 (q) (2C); IR (film) ν 1730, 1380, 1370, 1260, 1100, 1010, 835 cm^{-1}; HRMS m/z calcd for $C_{14}H_{29}O_3Si$ [(M − O-*i*-Pr)$^+$] 273.1886, found 273.1884.

(*R*)-(*Z*,*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5,8-tetradecadienal Diisopropyl Acetal (21). To a solution of dry phosphonium salt **11** (3.63 g, 7.76 mmol) in THF (100 mL) and toluene (12 mL), at −30 °C under argon, was added NaN(SiMe$_3$)$_2$ (1 M in THF, 6.9 mL, 6.9 mmol). After 2 h of stirring at room temperature, the orange solution was cooled to −90 °C, and a solution of aldehyde **20** (1.43 g, 4.31 mmol) in THF (10 mL) was added dropwise. The mixture was then allowed to warm to room temperature overnight, and the reaction was quenched with aqueous saturated NH_4Cl (22 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Acetal **21** (8.24 g, 6.60 mmol, 85%) was obtained by chromatography (Et_2O/pentane, 10/90) of the crude product: $[\alpha]^{24}_D$ −28.5° (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.46–5.28 (m, 4H), 4.70 (dd, J = 6.2, 4.9 Hz, 1H), 3.91–3.77 (m, 3H), 2.78 (t, J = 5.6 Hz, 2H), 2.27 (t, J = 5.5 Hz, 2H), 2.09–1.99 (m, 2H), 1.76–1.68 (m, 2H), 1.39–1.25 (m, 6H), 1.18 (d, J = 7.4 Hz, 6H), 1.15 (d, J = 6.6 Hz, 6H), 0.92–0.78 (m, 12H), 0.07 (broad s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 130.4 (d), 130.0 (d), 127.7 (d), 125.6 (d), 98.3 (d), 69.2 (d), 67.9 (d), 67.7 (d), 43.0 (t), 35.5 (t) (2C), 31.6 (t), 29.4 (t), 27.3 (t), 22.6 (t), 25.9 (q) (3C), 23.6 (q), 23.3 (q), 22.9 (q), 22.6 (q), 18.1 (s), 14.1 (q), −4.0 (q), −4.6 (q); IR (film) ν 3025, 1655, 1385, 1375, 840 cm^{-1}; HRMS m/z calcd for $C_{23}H_{45}O_2Si$ [(M − O-*i*-Pr)$^+$] 381.3187, found 381.3191.

(*R*)-(*Z*,*Z*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5,8-tetradecadienal (3) (from Acetal 21). A solution of acetal **21** (1.04 g, 2.36 mmol) and *p*-TsOH (0.1 M in H_2O, 1.2 mL) in THF (47 mL) was refluxed (in a prewarmed oil bath) for 15 min. The solution was then cooled, diluted with pentane (100 mL), washed with water and brine, quickly dried over $MgSO_4$, and evaporated *in vacuo*. Flash chromatography (Et_2O/pentane, 7/93) of the crude product provided aldehyde (*R*)-(−)-**3** (710 mg, 2.10 mmol, 89%): $[\alpha]^{18}_D$ −26.8° (*c* 1.1, $CHCl_3$).

(*Z*,*Z*)-3-Hexyl-3-(trimethylsilyl)-4-[2′-[(*tert*-butyldimethylsilyl)oxy]-4′,7′-tetradecadienyl]-2-oxetanone (22). (A) Preparation in Diethyl Ether. To a solution of aldehyde **3** (475 mg, 1.40 mmol) in Et_2O (11 mL) at −45 °C was added $EtAlCl_2$ (1 M in hexanes, 1.68 mL, 1,68 mmol) and 5 min later a solution of ketene **4**[12b] (416 mg, 2.10 mmol) in Et_2O (4 mL). The reaction mixture was allowed to warm to −20 °C, while the advancement of the reaction was monitored by TLC. Once the reaction was over, standard workup (hydrolysis with ice–water, extraction with Et_2O, drying of the extract over $MgSO_4$, and evaporation of solvent *in vacuo*) led to the crude material. Upon chromatography (Et_2O/pentane, 3/97), β-lactone **22** was obtained as a mixture[23] of diastereomers (687 mg, 1.29 mmol, 91%). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (dtt, J = 10.8, 7.2, 1.2 Hz, 1H), 5.41–5.32 (m, 2H), 5.28 (dtt, J = 10.7, 7.0, 1.3 Hz, 1H), 4.61 (dd, J = 11.8, 1.8 Hz, 1H), 3.91–3.85 (m, 1H), 2.75 (broad t, J = 7.2 Hz, 2H), 2.35–2.20 (m, 2H), 2.08–1.92 (m, 2H), 1.76–1.63 (m, 2H), 1.35–1.24 (m, 16H), 0.89 (broad s, 15H), 0.18 (s, 9H), 0.08 (broad s, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.3 (s), 130.8 (d), 130.7 (d), 127.3 (d), 124.7 (d), 75.8 (d), 68.5 (d), 54.4 (s), 39.3 (t), 36.2 (t), 31.6 (t) (2C), 30.5 (t), 29.6 (t), 29.4 (t), 27.3 (t) (2C), 26.2 (t), 22.64 (t), 22.57 (t), 25.9 (q) (3C), 18.1 (s), 14.1 (q) (2C), −1.4 (q) (3C), −4.1 (q), −4.9 (q); IR (film) ν 3016, 1808, 1260, 845 cm^{-1}; HRMS m/z calcd for $C_{27}H_{51}O_3Si_2$ [M − *t*-Bu)$^+$] 479.3376, found 479.3373.

(B) Preparation in Dichloromethane. To a solution of aldehyde **3** (100 mg, 0.29 mmol) and ketene **4** (95 mg, 0.48 mmol) in CH_2Cl_2 (1.2 mL) at −60 °C under argon was added dropwise $EtAlCl_2$ (1 M in hexanes, 0.33 mL, 0.33 mmol). After 15 min of stirring at the same temperature, the reaction was quenched with ice–water, and the mixture was extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated. β-Lactone **22** (106 mg, 0.20 mmol, 68%) was purified from the residue by chromatography (Et_2O/pentane, 3/97).

(*Z*,*Z*)-3-Hexyl-3-(trimethylsilyl)-4-(2′-hydroxy-4′,7′-tetradecadienyl)-2-oxetanone (23). To a solution of β-lactones **22** (687 mg, 1.27 mmol) in CH_3CN (25 mL) at 0 °C was added HF (40% aqueous, 1.5 mL). The reaction mixture was stirred for 6 h at the same temperature and then filtered over silica gel. The cake was rinsed with Et_2O and the organic layer evaporated *in vacuo*. The residue was purified by chromatography (Et_2O/pentane, 80/20) to give β-lactones **23** (458 mg, 1.08 mmol, 85%). Major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.62–5.23 (m, 4H), 4.72 (dd, J = 11.1, 2.2 Hz, 1H), 3.95–3.78 (m, 1H), 2.81 (t, J = 6.8 Hz, 2H), 2.31 (t, J = 6.8 Hz, 2H), 2.10–1.97 (m, 2H), 1.82–1.70 (m, 2H), 1.48–1.17 (m, 16H), 0.91–0.85 (m, 6H), 0.22 (broad s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.1 (s), 132.4 (d), 130.9 (d), 127.1 (d), 124.5 (d), 76.2 (d), 68.0 (d), 55.0 (s), 39.3 (t), 36.1 (t), 31.6 (t) (2C), 30.6 (t), 29.6 (t), 29.3 (t), 27.3 (t), 26.1 (t), 25.8 (t), 22.6 (t) (2C), 14.1 (q), −1.3 (q) (3C); IR (film) ν 3480, 1825, 1120, 845 cm^{-1}; HRMS m/z calcd for $C_{14}H_{25}O_2Si$ [(M − $C_{11}H_{21}O$)$^+$] 253.1624, found 253.1623.

(3*S*,4*S*,2′*R*)-(*Z*,*Z*)-3-Hexyl-4-(2′-hydroxy-4′,7′-tetradecadienyl)-2-oxetanone (24). To a solution of β-lactones **23** (700 mg, 1.46 mmol) in THF (26 mL) at −90 °C was added dropwise a solution of TBAF (521 mg, 2 mmol) in THF (4 mL). After 10 min, the reaction mixture was quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by chromatography (Et_2O/pentane, 25/

75) to give pure *trans*-β-lactone **24** (436 mg, 1.09 mmol, 75%): $[\alpha]^{22}_D$ −49.7° (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (dtt, *J* = 10.7, 7.4, 1.4 Hz, 1H), 5.43−5.25 (m, 2H), 5.28 (dtt, *J* = 10.6, 7.2, 1.5 Hz, 1H), 4.47 (dt, *J* = 8.5, 4.3 Hz, 1H), 3.86−3.74 (m, 1H), 3.24 (ddd, *J* = 8.0, 7.0, 4.0 Hz, 1H), 2.79 (broad t, *J* = 7.2 Hz, 2H), 2.38−2.22 (m, 2H), 2.05−1.95 (m, 2H), 1.96−1.68 (m, 4H), 1.45−1.24 (m, 14H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.8 (s), 132.3 (d), 130.8 (d), 127.0 (d), 124.3 (d), 75.6 (d), 67.8 (d), 56.5 (d), 41.3 (t), 35.9 (t), 31.5 (t) (2C), 29.3 (t), 29.0 (t), 27.7 (t), 27.2 (t), 26.7 (t), 25.8 (t), 22.54 (t), 22.52 (t), 14.1 (q) (2C); IR (film) ν 3480, 3010, 1825, 1120 cm^{-1}; HRMS *m*/*z* calcd for $C_{22}H_{38}O_3$ [M^+] 350.282 08, found 350.2819.

(3*S*,4*S*)-3-Hexyl-4-[(*S*)-2′-[[(*S*)-4″-methyl-2″-(*N*-formylamino)pentanoyl]oxy]-(*Z*,*Z*)-trideca-4′,7′-dienyl]-2-oxetanone [(−)-Lipstatin, 1]. To a solution of alcohol **24** (360 mg, 1.03 mmol), PPh_3 (324 mg, 1.24 mmol), and (*S*)-*N*-formylleucine (213 mg, 1.34 mmol) in THF (11 mL) at 0 °C was added dropwise DEAD (0.21 mL, 1.34 mmol). The reaction mixture was stirred for 2 h at 0 °C then allowed to warm to room temperature (ca. 1 h). Once the reaction was over, THF was eliminated *in vacuo* and the residue diluted in Et_2O−hexane (9 mL of a 1:1 mixture). The formed precipitate was filtered off and washed with the same mixture (6 mL). After evaporation *in vacuo* of the solvents, the residue was purified by chromatography on silica gel (EtOAc/pentane, 25/75) to give pure (−)-lipstatine (**1**) as pale yellow oil (345 mg, 0.70 mmol, 68%): $[\alpha]^{24}_D$ −18.2° (*c* 1, $CHCl_3$) [lit.[1b] $[\alpha]^{22}_D$ −19° (*c* 1, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s) and 8.02 (d, *J* = 12.0 Hz) (CHO), 5.93 (d, *J* = 8.0 Hz, NH), 5.52 (dtt, *J* = 10.8, 7.4, 1.6 Hz, $C^{5'}H$), 5.39 (dtt, *J* = 10.7, 7.2, 1.6 Hz, $C^{8'}H$), 5.30 (dtt, *J* = 10.8, 7.4, 1.5 Hz, $C^{4'}H$), 5.26 (dtt, *J* = 10.7, 7.2, 1.5 Hz, $C^{7'}H$), 5.03−4.97 (m, $C^{2'}H$), 4.67 (td, *J* = 8.9, 4.4 Hz, CHN), 4.27 (td, *J* = 8.0, 4.5 Hz, C^4H), 3.19 (td, *J* = 7.1, 4.0 Hz, C^3H), 2.76 (t, *J* = 7.4 Hz, $C^{6'}H_2$), 2.50−2.42 (m, ½ ABMX) and 2.41−2.32 (m, ½ ABMX) ($C^{3'}H_2$), 2.15 (½ ABX_2, J_{AB} = 14.9, *J* = 8.1 Hz) and 2.02−1.98 (m, ½ ABX_2) ($C^{1'}H_2$), 2.05−1.97 (m, $C^{9'}H_2$), 1.80−1.60 (m, C^3-CH_2), 1.85−1.20 (m, 17H [8 × CH_2 + $CHMe_2$]), 0.87 (t, *J* = 6.8 Hz) and 0.86 (t, *J* = 6.8 Hz) (2 × CH_2CH_3), 0.94 (d, *J* = 6.3 Hz) and 0.94 (d, *J* = 6.0 Hz) [$CH(CH_3)_2$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 and 170.7 (C^2 and COO), 160.9 (CHO), 132.1 ($C^{5'}$), 130.7 ($C^{8'}$), 126.7 ($C^{7'}$), 122.8 ($C^{4'}$), 74.6 (C^4), 71.9 ($C^{2'}$), 56.8 (C^3), 49.5 (CNH), 37.9 ($C^{1'}$), 31.7 ($C^{3'}$), 27.1 ($C^{9'}$), 25.6 ($C^{6'}$), 24.7 ($CHMe_2$), 22.7 and 21.5 [$CH(CH_3)_2$], 41.1, 31.3 (2C), 29.1, 28.8, 27.5, 26.5, 22.4 and 22.3 (9 × CH_2), 13.9 and 13.8 (2 × CH_2CH_3); IR (film) ν 3329, 1822, 1740, 1671, 1521, 1464, 1382, 1193, 1124 cm^{-1}; HRMS *m*/*z* calcd for $C_{29}H_{49}NO_5$ [M^+] 491.361 05, found 491.3629. Anal. Calcd for $C_{29}H_{49}NO_5$: C, 70.84; H, 10.04; N, 2.85. Found: C, 70.51; H, 10.10; N, 2.89.

(1*R,2*R**,4*R**)-(1′*E*,3′*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(1′,3′-octadienyl)cyclopentanol (25).** To a solution of aldehyde **3** (96 mg, 0.28 mmol) in CH_2Cl_2 (2.5 mL) at −60 °C under argon was added dropwise $EtAlCl_2$ (1 M in hexanes, 0.31 mL, 0.31 mmol). After 30 min of stirring at the same temperature, the reaction was quenched with ice−water and the mixture extracted with Et_2O. The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. A flash chromatography (Et_2O/pentane, 20/80) of the crude product provided dienic cyclopentanol **25** (60 mg, 0.17 mmol, 62%): ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (ddt, *J* = 15.2, 11.9, 1.0 Hz, 1H), 5.99 (broad t, *J* = 10.9 Hz, 1H), 5.85 (dd, *J* = 15.2, 8.3 Hz, 1H), 5.31 (dt, *J* = 10.8, 7.6 Hz, 1H), 4.38−4.33 (m, 1H), 4.10−4.05 (m, 1H), 2.52 (qd, *J* = 8.7, 4.6 Hz, 1H), 2.22−2.10 (m, 2H), 1.85 (broad t, *J* = 4.0 Hz, 2H), 1.68 (ddd, *J* = 13.9, 9.0, 3.2 Hz, 1H), 1.38−1.32 (m, 1H), 1.31−1.22 (m, 6H), 0.86 (broad s, 12H), 0.04 (broad s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.8 (d), 130.9 (d), 128.5 (d), 126.7 (d), 76.5 (d), 74.0 (d), 48.3 (d), 44.4 (t), 40.3 (t), 31.6 (t), 29.4 (t), 27.8 (t), 25.9 (q) (3C), 22.6 (t), 18.0 (s), 14.1 (q), −4.8 (q) (2C); IR (film) ν 3514, 1654, 1367, 1255, 1108, 894, 835 cm^{-1}. Anal. Calcd for $C_{20}H_{38}O_2$: C, 70.95; H, 11.32. Found: C, 70.41; H, 11.13.

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Supporting Information Available: ^{13}C NMR spectra of compounds **10**, **12**, **15**, **19**, **20**, **21**, **23**, and **24** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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