Total Synthesis of (−)-Tetrahydrolipstatin

Stephen Hanessian,* Ashok Tehim, and Ping Chen

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station A, Montréal, H3C 3J7 Quebec, Canada

Received July 21, 1993•

The total synthesis of (−)-tetrahydrolipstatin utilizing two approaches is described. In the first, L-malic acid was used as a chiral template to obtain enantiomerically pure (*R*)-3-(benzyloxy)-tetradecanal (11) which was chain-extended using 1-(trimethylsilyl)-2-nonene and a Lewis acid. This advanced intermediate was further elaborated to the target compound in good overall yield. The second approach utilized lauraldehyde as a starting material and capitalizes on an asymmetric allylboronation (91% ee). The product could be obtained enantiomerically pure by conversion to the (*R*)-acetoxymandelate ester and hydrolysis. Oxidative cleavage of the terminal double bond led to 11 which was further extended using 1,3- and 1,2-asymmetric induction based on existing neighboring chirality. The synthesis of tetrahydrolipstatin using the second approach comprises seven steps from 11 and proceeds in 38% overall yield.

Lipstatin (1) and its tetrahydro derivative **2** are representative members of a recently discovered class of β-lactone antibiotics of microbial origin[1] which also comprise valilactone,[2] esterastin,[3] ebelactone,[4] and L-659,-699[5] (Figure 1). Extensive studies at the Hoffmann-La Roche laboratories[6] have demonstrated that **1** and **2** are potent inhibitors of pancreatic lipase, thus making these compounds ideal candidates for the reduction of fat absorption through diet in man. Indeed, phase II clinical studies now in progress[7] have demonstrated excellent prognosis for a marketable product against obesity and as a cholesterol-lowering agent. In view of their interesting structures, and the important biological activity *in vivo*, it is not surprising that a number of groups have already reported on their results concerning total syntheses of tetrahydrolipstatin. The first synthesis of enantiomerically pure tetrahydrolipstatin **2** was reported by Barbier and Schneider[8] from the Roche-Basel group who obtained a mixture of diastereoisomers from a racemic mixture of alcohols after esterification with *N*-formylleucine. Subsequently, two other syntheses were reported[9] in which methyl (3*R*)-hydroxytetradecanoate, obtained from the corresponding β-keto ester by asymmetric reduction,[10] was used as starting material.

In 1989, Pons and Kocienski[11] described their total synthesis of **2** from (*R*)-3-(benzyloxy)tetradecanal obtained in 84% ee by the asymmetric reduction[12] of a precursor ynone followed by further elaboration. A key transformation in this synthesis was the diastereoselective [2 + 2] cycloaddition of the aldehyde with an appropriate (trimethylsilyl)ketene leading to four diastereoisomeric β-lactones from which the desired isomer could be isolated in 55–61% yield. Fleming and Lawrence[13] reported another interesting synthesis of **2** in which organosilicon chemistry and an asymmetric Michael addition step played important roles. Davies and co-workers[14] have elaborated the β-propiolactone portion via a stereoselective aldol reaction involving a chiral organoiron reagent. Finally, Uskokovic and co-workers[15] have described a synthesis of **2** based on the utilization of a cyclopentadiene alkylation-asymmetric hydroboration protocol en route to a key intermediate. A new route to the previously reported key intermediate lactone has been recently reported.[16]

We report herein our efforts in this area which have culminated with the total synthesis of (−)-**2** in an efficient and diastereocontrolled manner using two conceptually different strategies. The disconnective analysis shown in Figure 2 illustrates a plan which explores the stereocontrolled condensation of an aldehyde with a suitably functionalized nucleophilic 2-nonenyl partner (M = H, Sn, Si, etc.). The terminal double bond in the resulting product was to be utilized as a precursor to the carboxylic acid group, and subsequent transformations leading to the intended target molecule would follow a previously established protocol.[8,9] This plan to achieve the stereocontrolled synthesis of **2** is operationally different from the previous approaches[8,9]1,[11–16] in that it capitalizes on internal asymmetric induction by a resident alkoxy group originally derived from L-malic acid. With such a plan in mind we had to address a number of issues such as (a) the nature of the nucleophilic reagent, and particularly the terminal "activator" M (Figure 2), (b) the level of diastereoselection in the condensation reaction, and (c) an

• Abstract published in *Advance ACS Abstracts,* December 1, 1993.

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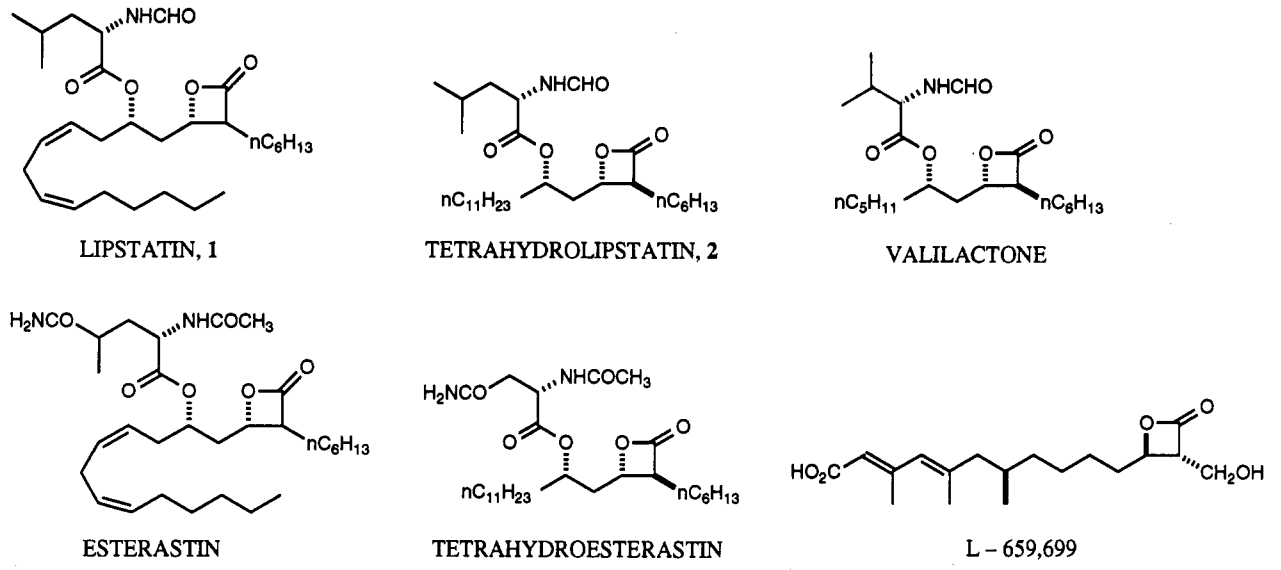


Figure 1.

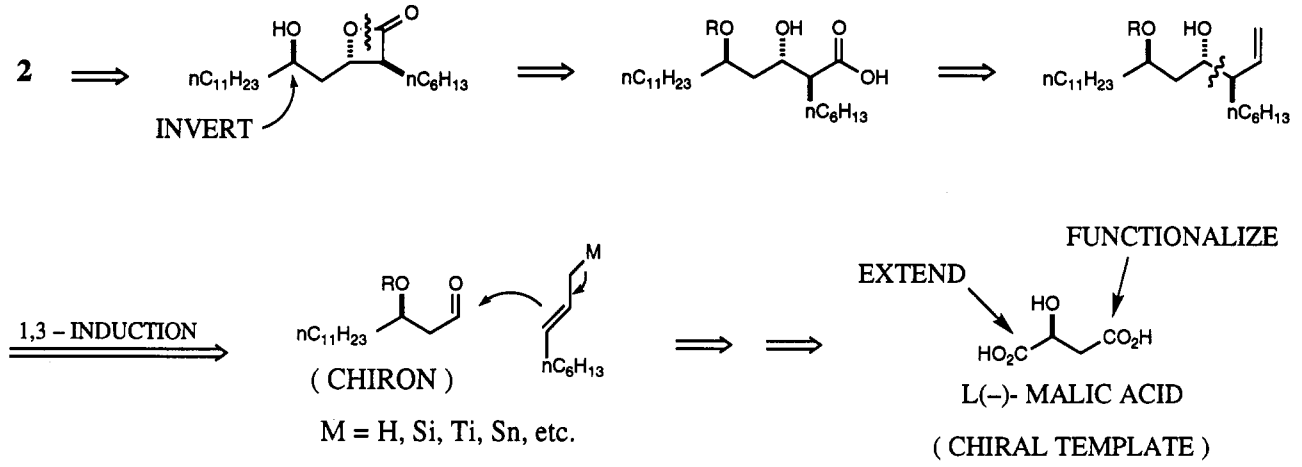
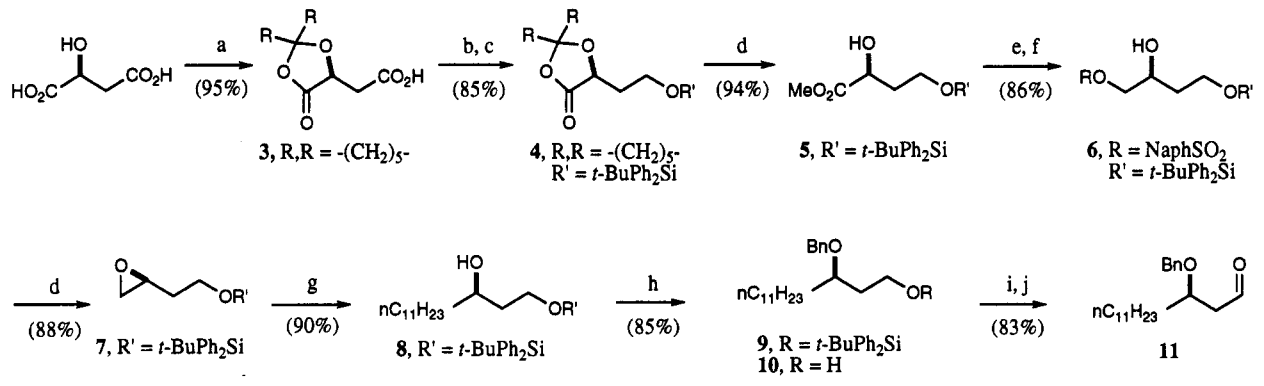


Figure 2.

Scheme I[a]



[a] Key: (a) cyclohexanone, BF_3·Et_2O; (b) BH_3–DMS, $B(OMe)_3$; (c) t-$BuPh_2SiCl$, imidazole, DMF; (d) Cat. NaOMe, MeOH; (e) BH_3–DMS, cat. $NaBH_4$; (f) Naph-SO_2Cl, cat. DMAP, py; (g) n-$C_{10}H_{21}Li$, BF_3·Et_2O; (h) $PhCH_2OC(CCl_3)$=NH, CF_3CO_2H, (i) 48% HF–CH_3CN (5:95)–CH_2Cl_2; (j) PDC, CH_2Cl_2.

alternate access to the aldehyde that would lead to material of very high enantiomeric purity.

Total Synthesis of Tetrahydrolipstatin from L-Malic Acid. In order to ensure the high enantiomeric purity of this aldehyde, we sought an approach that relied on the chemical manipulation of the readily available L-malic acid as a chiral template (Scheme I). Thus, the resident hydroxyl group would ultimately be part of the β-hydroxy aldehyde motif 11. Through a series of uneventful transformations, L-malic acid was converted into the known[17] epoxide 7 based on methodology developed in our group[18] (Scheme I). Some notable operational differences in our protocol involved the chemoselective

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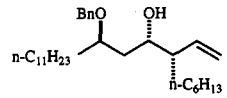
Table I. Lewis Acid Catalyzed Reaction of 11 with (*E*)-1-(Trimethylsilyl)-2-nonene and Diastereomeric Ratio of the Products



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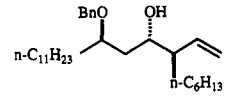

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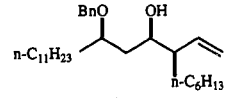

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entry	Lewis acid (equiv)	additive (equiv)	method[a]	time (h)	diastereomeric ratio[b] 14:12:16
1	$TiCl_4$ (1.1)	(control)[c]	A	1.0	1:1.6:1
2		MgBr2 (1.0)	A	1.0	2.7:2.5:1
3		LiBr2 (1.0)	A	1.0	4.6:5.3:1
4		ZnBr2 (1.0)	A	1.0	22:13:1
5		ZrCl4 (1.0)	A	starting material decomposed	
6		Ti(o-iPr)4 (1.0)	B	1.0	3.8:1.1:1
7		ZrCp2Cl2 (1.0)	A	2.0	13:10:1
8		ZrCp2Cl2 (1.0)	C	1.0	8.0:2.4:1
9		TiCp2Cl2 (1.0)	C	1.0	8.0:12:1
10		Eu(hfc)3 (1.0)	A	starting material decomposed	
11	$SnCl_4$ (1.1)	(control)	A	>5.0	8.6:9.5:1
12		ZnBr2 (1.0)	A	>4.0	7.0:6.3:1
13	$AlEtCl_2$ (1.0)		A	starting material decomposed	
14	$AlEt_2Cl$ (1.0)		A	starting material decomposed	
15	$TiCl_4$ (1.0) at −40 °C		D	1.0	11:7:1
16	$SnCl_4$ (1.0) at −40 °C		D	3.0	17:6.5:1

[a] Method A: Lewis acid was added to the solution of aldehyde in CH_2Cl_2 at −78 °C, and the mixture was stirred for 15 min for the complexation, followed by addition of solution of allylsilane in CH_2Cl_2. Method B: Lewis acid and additive were premixed by addition of $Ti(O\text{-}i\text{-}Pr)_4$ to the $TiCl_4$ in CH_2Cl_2. This premixed Lewis acid was added to the solution of aldehyde in CH_2Cl_2 at −78 °C, and after 15 min, the solution of allylsilane in CH_2Cl_2 was added. Method C: Lewis acid was added to the mixture of aldehyde, allylsilane, and additive in CH_2Cl_2 at −78 °C. Method D: Lewis acid was added to the mixture of aldehyde and allylsilane in CH_2Cl_2 at −78 °C. [b] Ratios determined by HPLC analysis of TBDMS ether and by weight (entries 1, 9). [c] With (*Z*)-2-nonenyltrimethylsilane, the ratio of 14:12:16 was 9:3:1, respectively.

reduction of the lactone–acid derivative **3** to the corresponding O-protected lactone alcohol **4**, manipulation of the lactone function to give the [(2-naphthyl)sulfonyl]-oxy derivative **6**, and base-catalyzed formation of an epoxide **7**. The epoxide **7** was thus prepared in high overall yield and on a multigram scale. Treatment of **7** with *n*-decyllithium in the presence of an equimolar quantity of $BF_3{\cdot}Et_2O$ in a mixture of ether and THF at −78 °C[19] resulted in a smooth opening of the oxirane ring to give the expected (3*R*)-1,3-dihydroxytetradecane derivative **8** in 90% yield. At this point, a choice of a protective group had to be made, and after a number of model studies, we opted for benzylation which was done using benzyl 2,2,2-trichloroacetimidate as a reagent[20] to give **9**. Subsequent desilylation and oxidation of the resulting alcohol with PDC gave the target aldehyde **11** in excellent overall yield (~63%) from the epoxide **7**. The physical properties of **11**, including its optical rotation, compared very favorably with those reported by Barbier and Schneider[9] who had previously established the very high enantiomeric purity of their aldehyde.

As previously mentioned, one of our objectives was to explore the reactivity of **11** vis-a-vis a number of nucleophilic reagents derived from 2-nonene and to assess the degree of diastereoselectivity in the coupled product. It appeared that the simplest case would engage **11** and *trans*-2-nonene in an ene reaction[21] which could lead to the homo allylic alcohol structure expressed in Figure 2. Unfortunately, numerous attempts at effecting an ene reaction in the presence of a variety of Lewis acids ($SnCl_4$, $TiCl_4$, $AlCl_3$, $AlEtCl_2$) resulted in discouragingly poor yields of the desired condensation product. We were also attracted by a recent report by Collins and co-workers,[22] in which aliphatic and aromatic aldehydes were shown to react with the dimethyl dicyclopentadienyltitanium complex of butadiene resulting in excellent anti selectivity. Accordingly, the dicyclopentadienyltitanium complex of 1,3-nonadiene was prepared following the general procedure described by Collins.[22] However, reaction with the aldehyde **11** led to the wrong regioisomeric condensation product.

We next turned our attention to the prospects of a Lewis acid-mediated condensation between the aldehyde **11** and a 2-alkenylsilane having the appropriate length. The Lewis-acid catalyzed condensation of allylsilanes with aldehydes is a well-known and frequently used reaction for chain elongation in the aldol sense.[23] However, examples of γ-carbon-substituted 2-alkenylsilanes (crotylsilanes and a higher homologs) are not as abundant in applications to total synthesis.[24] In model studies using racemic **11**, it was found that the reaction of **11** with allyltrimethylsilane in CH_2Cl_2 catalyzed by $SnCl_4$ at −78 °C proceeded smoothly to afford the diol derivative corresponding to the general homoallylic alcohol structure shown in Figure 2 in over 80% yield. The *anti*-orientation of the newly generated secondary alcohol group was assumed based on previous elegant studies by Reetz, Heathcock, and co-workers.[23,25] Following several model studies in which a variety of Lewis acids were used, we directed our attention to the use of $TiCl_4$, and we proceeded to investigate the role of additives as well as the stereochemistry of the 2-alkenylsilane. Preliminary studies in which **11** was allowed to react with pure (*Z*)- and (*E*)-1-

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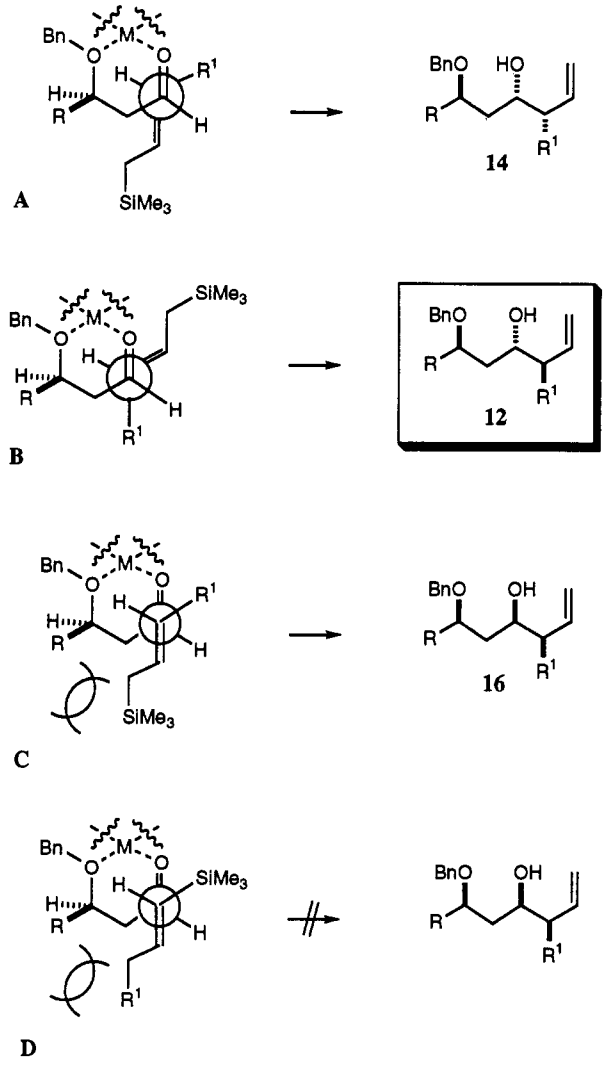
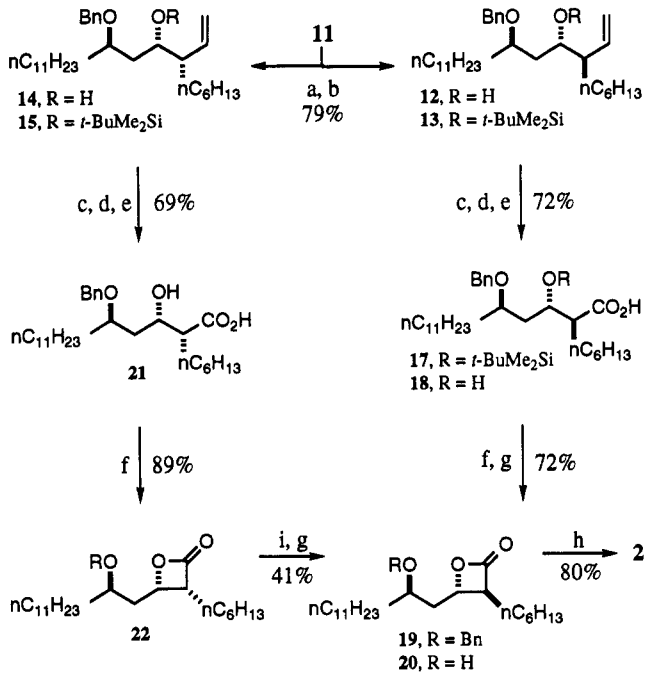


Figure 3.

(trimethylsilyl)-2-nonene in the presence of $TiCl_4$ at −78 °C proceeded efficiently within 1 h to give, in each case, a mixture of three of the four possible diastereomers which were chromatographically separable as their TBDMS ethers (Table I). In the case of the *Z*-olefin, one of the isomers later shown to be **14** was distinctly enriched (9:3:1:0), while the *E*-olefin gave an almost equal distribution of the same three isomers with a slight penchant for the desired isomer **12**. Interestingly none of the fourth isomer was formed in either case. Since the isomers were separable, as their TBDMS ethers, we proceeded with a previously planned sequence of oxidative cleavage of the terminal double bond in each isomer, desilylation and cyclization to the corresponding β-lactone. Analysis of ^1H NMR spectra of the resulting lactones revealed that **14** was in fact the *syn* isomer. Table I lists a variety of additives and the ratios of isomers as determined by the above protocol.

The most promising additive was found to be an equimolar amount of $TiCp_2Cl_2$, especially when the $TiCl_4$ was added to a mixture of the aldehyde, the silane, and the additive at −78 °C (Table I, entry 9). This combination produced a 1:1.5:0.12 ratio of isomers **14**, **12**, and **16**, respectively. Figure 3 illustrates a set of transition states that could be responsible for the observed results. In analogy to previous studies involving α- and β-alkoxyaldehydes,[23,25] it is reasonable to assume the existence of chelated structures in which the metal M consists of the

Scheme II[a]



[a] Key: (a) (*E*)-*n*-$C_6H_{13}CH{=}CHCH_2SiMe_3$, $TiCl_4$, Cp_2TiCl_2, CH_2Cl_2, −78 °C; (b) *t*-$BuMe_2SiCl$ imidazole, DMF, 55 °C; (c) O_3, −78 °C; then Me_2S; (d) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, $CH_3CH{=}C(CH_3)_2$, H_2O, 0 °C → rt; (e) 48% HF–CH_3CN (5:95)–CH_2Cl_2; (f) $PhSO_2Cl$, Py; (g) H_2, 10% Pd–C, EtOAc; (h) (*S*)-*N*-formyl leucine, Ph_3P, DEAD, THF; (i) LDA, THF −78 °C; then AcOH (42% of **22** recovered).

$TiCp_2Cl_2$ species. Apparently, there is sufficient steric interaction between the (trimethylsilyl)methyl group and the side chain R in the transition state leading to **16** to greatly minimize its formation. Transition state D which could lead to the fourth and undetected diastereomer shows an even greater steric congestion compared to C (R and R^1 groups). The distinction between the transition states leading to **12** and **14** is less evident. Nevertheless, there appears to be a better selection in favor of **12** which may be due to a more favorable disposition of the 2-nonenyltrimethylsilyl moiety vis-a-vis the chelated aldehyde in one of the possible rotamers. As seen from Table I, subtle variations in the nature of the additives and in the order of addition of reagents and reacting partners greatly influences the ratio of the diastereoisomeric alcohols **12**, **14**, and **16**. In view of the known lower degree of selectivity associated with 6-membered chelates compared to 5-membered chelates in such reactions,[23,25] it is of interest that conditions were found to somewhat favor the desired isomer **12**. Since the elaboration of **12** toward the synthesis of **2** was expecteed to proceed according to well-established precedents[8,9] once the β-hydroxy acid level was attained, a major challenge was to subsequently find a means of converting isomer **14** into **12**. The *syn* isomer **14** differs from **12** only in the configuration of the allyl-bearing carbon atom. The plan was to attempt a configurational inversion at that center at an opportune time in the remaining sequence.

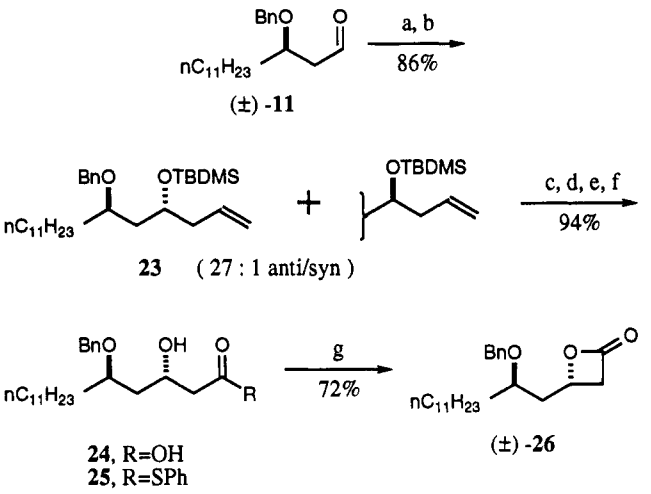
The major isomer **12** obtained in enantiomerically pure form was oxidatively cleaved to the corresponding aldehyde (Scheme II). However, numerous attempts to oxidize this aldehyde to the corresponding acid were fraught with problems resulting in complex mixtures. Finally, oxidation with sodium chlorite in phosphate buffer as described for other aldehydes[26] resulted in the formation of the expected

acid **17** in excellent overall yield, which was used without further purification. The subsequent steps leading to **2** were performed uneventfully.[8,9] Thus, desilylation of **17** gave the hydroxy acid **18** which was transformed into the β-lactone **19** in the presence of benzenesulfonyl chloride.[27] Catalytic debenzylation afforded the corresponding hydroxy lactone **20**, which when treated with *N*-formylleucine under the conditions of the Mitsunobu reaction[28] gave the target molecule **2**, isolated as a crystalline solid with physical properties identical to those reported for the natural product.[8,9] From a practical standpoint, it is of interest to note that **2** is produced from the known[9] aldehyde **11** in *eight steps and in 24% overall yield* without recycling the unwanted isomer.

As previously mentioned, it was our intention to explore ways in which the *syn* isomer **14** could also be transformed into the natural product. We relied on a method reported by Mulzer and Kerkmann[29] for the enolization and reprotonation of α,β-substituted β-lactones. Thus, the *syn* isomer **15** resulting from the condensation and O-protection was subjected to the same sequence of reactions as for the *anti*-isomer **13** to give the *syn*-β-lactone **22** in high overall yield (Scheme II). Treatment of **22** with LDA in THF at −78 °C, followed by protonation at the same temperature, gave a 1:1 ratio of lactones **19** and **22** in 83% yield. In view of the nature of the substrate and the size of the electrophile, a greater discrimination of the two faces of the enolate with a proton is not possible under the conditions tried. Quenching with sterically hindered acids (pivalic, camphorsulfonic)[30] did not change the original ratio observed as when acetic acid was used. Thus, keeping the recycling option in mind, the overall yield of **2** from **11** can be increased to about 33%.

After the completion of our first synthesis of **2**, we explored another approach that would capitalize on the high stereoselectivity of allylsilane methodology,[23,24] eventually leading to the β-lactone **26** as shown in Scheme III. In view of the susceptibility of 3-substituted β-lactones to self-condensation, lactone formation was effected using the phenylthio ester[31] rather than the benzenesulfonyl chloride mediated cyclization[27] used in the case of **18** (Scheme II). Unfortunately, treatment of **26** with LDA at −78 °C followed by addition of *n*-hexyl bromide or iodide under a variety of conditions resulted in loss of starting material with little if any alkylation. Evidently, the enolate undergoes irreversible intermolecular condensation with concomitant β-elimination as observed by Mulzer and Kerkmann[29] in related systems. Another reaction for exploring the allylsilane methodology shown in Scheme III was the prospect of introducting the *n*-hexyl moiety via alkylation of the dianion of the methyl ester of **24**, as previously demonstrated by Fräter[32] in simpler systems. To this end we considered a "totally asymmetric" approach to **2** as shown in Figure 4.

Scheme III[a]



[a] Key: (a) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2, −78 C°; (b) *t*-$BuMe_2SiCl$, imidazole, DMAP, DMF, 60 °C; (c) O_3, MeOH, CH_2Cl_2, −78 °C; (d) $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH; 0 °C; (e) 48% HF–CH_3CN, CH_2Cl_2; (f) PhSH, DCC, DMAP, CH_2Cl_2; (g) $Hg(OTf)_2$, Na_2HPO_4, CH_3CN, 4-Å sieves.

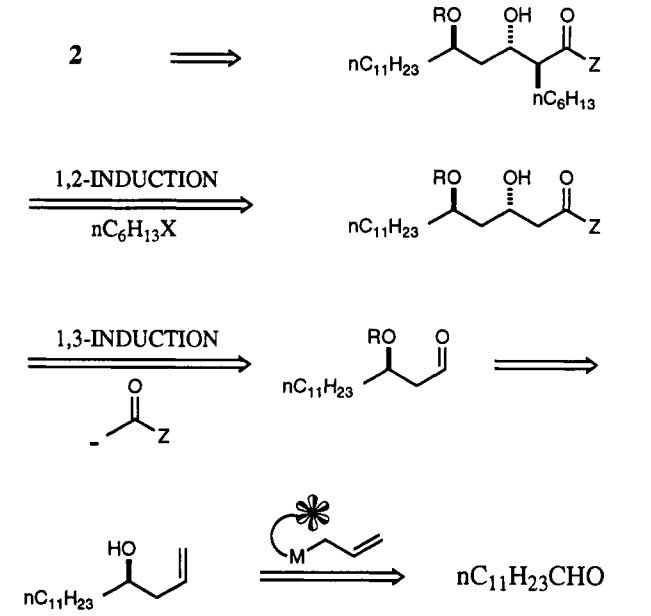


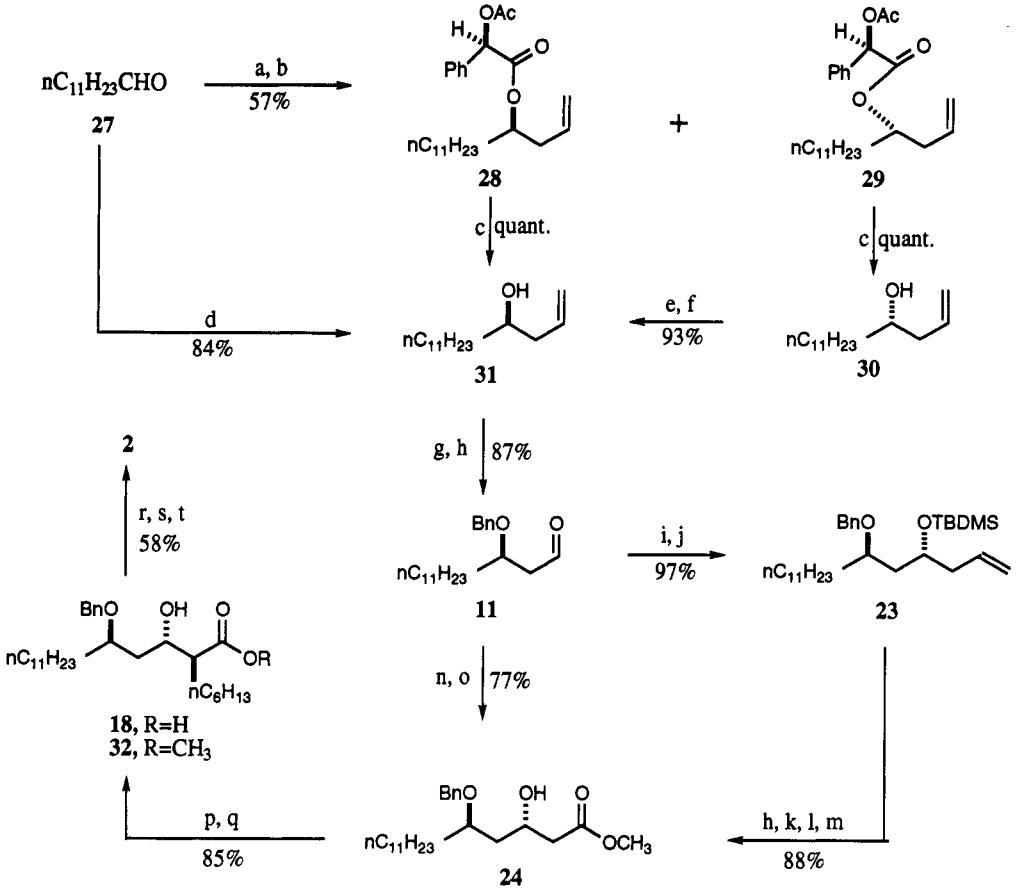
Figure 4.

Asymmetric Synthesis of Tetrahydrolipstatin from Lauraldehyde. We envisaged a strategy that would rely on an asymmetric allylation of lauraldehyde to provide an enantiomerically enriched homoallylic alcohol. The aldehyde obtained from this intermediate would be engaged in another asymmetric two-carbon elongation process relying on 1,3-induction. Finally, alkylation of the corresponding dianion was expected to occur under the control of the β-oriented alkoxide in a 1,2-asymmetric induction process,[32] leading to the known seco acid.

In order to have access to authentic epimeric homoallylic alcohols, we initially relied on the prospects of separating a mixture of two diastereomers. Indeed, treatment of lauraldehyde **27** with allylmagnesium bromide followed by esterification with *O*-acetyl-D-mandelic acid gave the diastereomeric esters **28** and **29** which could be easily separated by chromatography (Scheme IV). Deacylation of **28** led to the optically pure homoallylic alcohol **31**. The diastereomeric **29** could be converted to the desired **31** by

(26) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(27) Adam, W.; Baera, J.; Liu, J.-C., *J. Am. Chem. Soc.* **1972**, *94*, 2000. Adam, W.; Martinez, G.; Thompson, J. *J. Org. Chem.* **1981**, *46*, 3359 and references cited therein; see also extensive citations in ref 26.
(28) Mitsunobu, O. *Synthesis* **1981**, 1.
(29) Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620.
(30) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733.
(31) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874. See also: Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176 for extensive references on β-lactones.
(32) Fräter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269. Fräter, G. *Helv. Chim. Acta* **1979**, *62*, 2825.

Scheme IV[a]



[a] Key: (a) allylmagnesium bromide; (b) (*R*)-*O*-acetylmandelic acid, DCC, DMAP; (c) 2 N KOH, MeOH; (d) $Ipc_2BCH_2CH{=}CH_2$, Et_2O; (e) *p*-nitrobenzoic acid, Ph_3P, DEAD; (f) K_2CO_3, MeOH; (g) KH, $PhCH_2Br$; (h) O_3, MeOH–CH_2Cl_2; (i) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$; (j) *t*-$BuMe_2SiCl$, imidazole; (k) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$; 1.48% HF–CH_3CN (5:95); (m) CH_2N_2; (n) $CH_2{=}C(SPh)OTBDMS$, $TiCl_4$; (o) CF_3SO_3Ag, MeOH–CH_2Cl_2; (p) LDA, *n*-$C_6H_{13}I$; (q) 1 N KOH, MeOH; (r) $PhSO_2Cl$, Py; (s) H_2, 10% Pd–C; (t) (*S*)-*N*-formylleucine, Ph_3P, DEAD.

desterification and inversion of configuration via a modified Mitsunobu reaction.[33]

After exploring a number of conditions, it was found that asymmetric allylation of **27** was best achieved with allyl diisocampheylborane[34] at −100 °C where an ee of 91% was obtained. Although the yield was somewhat higher (84%) at −78 °C, the ee of the resulting alcohol **31** was 82%. Benzylation and oxidative cleavage led to the known aldehyde[9,11] **11** in 87% yield. The homoallylic alcohol **31** prepared via this route could also be obtained enantiomerically pure by conversion to the *O*-acetylmandelate ester followed by hydrolysis. Treatment of **11** with allyltrimethylsilane in the presence of titanium tetrachloride gave, after protection of the resulting alcohol, **23** and its epimer in a ratio of 27:1. It is of interest that under essentially the same conditions the (*E*)-1-(trimethylsilyl)-2-nonene gave a mixture of homoallylic alcohols, thus demonstrating the critical effect of the presence of an alkyl group in the reagent. The formation of **23** can be rationalized based on the transition-state models **A** shown in Figures 3 (**14**, R^1 = H). Having the enantiomerically pure **23** in hand, we proceeded to manipulate the double bond via oxidative cleavage followed by desilylation and esterification to give the β-hydroxy ester **24**. A much more expeditious route was investigated with the exciting prospects of 1,3-asymmetric induction during a two-carbon acetate extension. Thus, treatment of **11** with the *O-tert*-butyldimethylsilyl ketene acetal derived from phenylthio acetate in the presence of titanium tetrachloride[35] led to the corresponding the β-hydroxy derivative with greater than 21:1 selectivity in favor of the desired diastereomer. Treatment of the phenyl thioester with methanol in the presence of silver triflate gave the methyl ester **24**, identical to the product obtained from the four-step route from **23**. Unfortunately, treatment of **11** with the *O-tert*-butyldimethylsilyl ketene acetal of methyl acetate[36] led to a much poorer selectivity in favor of **24** (~3:1). The highly stereoselective addition of the phenylthioacetate to the β-(benzyloxy) aldehyde **11** can be rationalized based on transition state **A** or **A′** in Figure 5. It is possible that a transition state corresponding to **A** is more favored in the presence of the phenylthio group compared to a methoxy group. It is also of interest to point out that the use of $BF_3{\cdot}Et_2O$ or $SnCl_4$ as Lewis acids led to modest yields and poor selectivity (59%, 6:1 ratio, and 70% 15:1 ratio, respectively).

There now remained the task of performing a stereoselective *n*-hexylation of the dianion of **24**, as previously taught by Fräter[32] in simpler β-hydroxy esters and applied to an analog of tetrahydrolipstatin.[9] Clearly, the main concerns in the case of **24** were the presence of the second

(33) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(34) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.
(35) Gennari, C.; Beretta, M. G.; Bernadi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893 and references cited therein.
(36) See, for example: Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 217. See also ref 25.

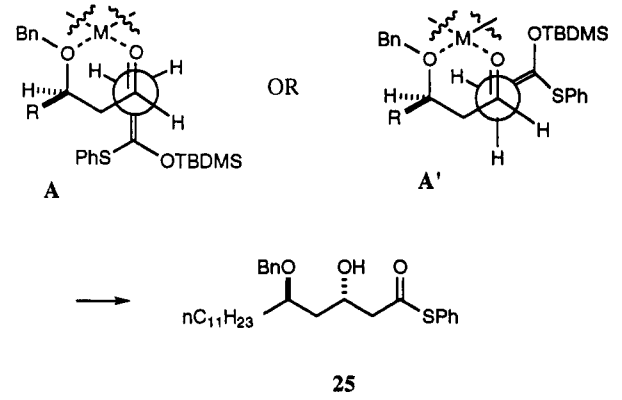


Figure 5.

alkoxy group, albeit remotely situated with regard to the enolate dianion, and the influence of the C_{11} hydrophobic chain. Treatment of the dianion of **24** in THF containing 10% HMPA with *n*-hexyl iodide at −50 °C[32,37] led to the desired α-alkylated ester **32** in high yield and with excellent selectivity (40:1). After saponification, this product gave hydroxy acid **18** identical in all respects to that obtained from the L-malic acid route. Completion of the synthesis was done according to the previously established protocol described above.

Conclusion

We have described two new routes to (−)-tetrahydrolipstatin **2**, each exploiting the influence of resident chirality in C–C bond-forming reactions. Both routes depend on the use of a single protective group and utilize the β-(benzyloxy)aldehyde **11** as a chiron. In the first route 2-nonenylsilane chemistry was utilized in the diastereoseletive branching and C-allylation of **11**, with a modest preference for the desired *anti/anti* orientation of the three stereogenic centers (Table I, **11** → **12**, **14**, 1.5:1 ratio). Interestingly only two of four possible diastereomers were formed. The second route relied on the utilization of an achiral aldehyde to prepare **11** via an asymmetric allylboronation. The highly enriched homoallylic alcohol (91% ee) could be further purified by separation of the corresponding *O*-acetyl mandelate ester to eventually provide the key aldehyde **11** in enantiomerically pure form. Alternatively, **11** could also be obtained by separation of a diastereomeric mixture of racemic homoallylic alcohols (five steps, 25% overall yield). With the known **11** in hand, the second route utilizes sequential, highly stereoselective reactions involving 1,3- and 1,2-asymmetric induction in assembling the full complement of functional and structural features present in the intended target. Starting from **11**, which is available in large quantity,[8,9] the route comprises only seven steps which can be accomplished in 38% overall yield.

Experimental Section

Melting points and boiling points are uncorrected. ^{1}H NMR spectra were recorded on a 300-MHz Varian spectrometer in $CDCl_3$ with TMS (δ 0) or $CHCl_3$ (δ 7.265) as reference. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CHCl_3$ (δ 76.90) as reference. In some cases ^{1}H NMR assignments were supported by appropriate homonuclear correlation experiments (COSY). *J* values are expressed in Hz. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer as solutions or films. Mass spectra were recorded on a Kratos MS-50 spectrometer by using electron ionization (EI) at 70 eV, chemical ionization (CI), or by the fast atom bombardment (FAB) techniques. Optical rotations were measured at 25 °C at the sodium line with a Perkin-Elmer Model 241 spectropolarimeter. Elemental analyses were obtained from Guelph Chemical Laboratories Ltd. of Guelph, Ontario (Canada). Ozonolysis was performed by employing a Welsbach T-408 ozonator. Flash chromatography was performed on 230-400-mesh silica gel. Thin-layer chromatography (TLC) was performed on glass plates coated with a 0.02-mm layer of silica gel 60 F-254 purchased from Merck. Tetrahydrofuran and diethyl ether were distilled from potassium or sodium benzophenone ketyl immediately prior to use. Methylene chloride and toluene were distilled from CaH_2 immediately prior to use. Acetonitrile, pyridine, triethylamine, and diisopropylamine were all distilled from CaH_2 and stored over molecular sieves.

(5*S*)-(2,2-Cyclohexylidene-4-oxo-1,3-dioxolan-5-yl)acetic Acid (3). To a suspension of L-(−)-malic acid (5.0 g, 37.3 mmol) in dry diethyl ether (100 mL) cooled at 0 °C was added, dropwise *via* syringe, freshly distilled cyclohexanone (3.9 mL, 37.3 mmol) and BF_3·Et_2O (6.7 mL, 54.1 mmol). The suspension gradually turned into a clear solution, and the mixture was stirred for 1 h at 0 °C. The ice bath was then removed, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ether (200 mL) and washed with 10% aqueous NaOAc (3 × 40 mL). The combined aqueous phases were extracted with ether, and the combined organic layers were washed once with saturated aqueous NaCl (20 mL) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded crude acid **3** as a thick pale yellow oil which solidified on standing.

Recrystallization (ether–hexane) afforded 8.0 g (100%) of **3** as off-white crystals mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.48 (bs, 1H, CO_2H), 4.71 (dd, J_1 = 3.98, J_2 = 6.48, 1H, OC*H*CO_2), 2.90 (d of AB, J = 3.98, 6.48, J_{AB} = 17.21, 2H, CH_2-CO_2), 1.60–1.89 (m, 8H, cyclic CH_2's), 1.30–1.58 (m, 2H, cyclic CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.97, 171.82, 112.04, 69.87, 36.07, 36.02, 35.14, 24.23, 22.82, 22.75. IR (CCl_4): 3450, 2940, 1780, 1720, 1370, 1280, 1220, 1150, 1110, 940 cm^{-1}. MS (high resolution): *m/z* M$^+$ ($C_{10}H_{14}O_5$) calcd 214.0841, found 214.0835. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.29; H, 6.72.

(5*S*)-[1′-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-2,2-cyclohexylidene-1,3-dioxolan-4-one (4). To a mixture of 2.0 M BH_3·DMS complex (28.5 mL, 57.0 mmol) and $B(OMe)_3$ (6.9 mL, 57.0 mmol) in 50 mL of dry THF cooled at 0 °C was added, dropwise *via* a syringe, a solution of **3** (4.3 g, 20 mmol) in 20 mL of dry THF. The reaction mixture was stirred overnight at room temperature and cooled to 0 °C, and 20 mL of MeOH was added dropwise *via* syringe. The mixture was stirred for 1 h, and the solvent was removed under reduced pressure to afford a thick oil. This process was repeated twice with MeOH (30 mL × 2) to afford as a colorless oil (4 g, 100%).

To a solution of the preceding alcohol (3.66 g, 18.3 mmol) in 60 mL of dry CH_2Cl_2 cooled at 0 °C was added imidazole (1.87 g, 27.4 mmol) in small portions, followed by a solution of *tert*-butyldiphenylsilyl chloride (6.5 g, 23.7 mmol) in 25 mL of dry DMF, dropwise *via* a syringe. The mixture was stirred for 2 h at 0 °C and then 3 h at room temperature. The reaction mixture was partitioned between 100 mL of ether and 30 mL of water. The aqueous layer was extracted with ether (100 mL × 3), and the combined organic layers were washed once with saturated aq NaCl and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate (20:1 → 10:1)) afforded 6.82 g (85%) of **4** as a colorless, viscous oil, $[\alpha]_D$ −5.83° (*c* 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 4H, Ph-H's), 7.36–7.46 (m, 6H, Ph-H's), 4.65 (dd, J_1 = 4.20, J_2 = 8.27, 1H, OC*H*CO_2), 3.87 (m, 2H, CH_2OSi), 1.92, 2.18 (m, 2H, OCHCH_2), 1.40–1.88 (m, 10H, cyclic CH_2's), 1.06 [s, 9H, C(CH_3)$_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.42, 135.42, 135.38, 133.41, 133.36, 129.51, 127.49, 111.11, 70.32, 59.19, 36.63, 35.26, 34.65, 26.62, 24.37, 22.89, 22.80, 19.03. IR (film): 2930, 2850, 1795, 1420, 1365, 1290, 1260, 1200, 1150, 1100, 930, 820, 750, 730, 700 cm^{-1}. MS (high resolution): *m/z* M$^+$ ($C_{26}H_{34}O_4Si$) calcd

(37) Previously, ethylation was described in the case of an analog (ref 9). In our hands, it was imperative to generate the LDA with MeLi (and not BuLi, ref 9), as described by Fráter (ref 32).

438.2227, found 438.2185. Anal. Calcd for $C_{28}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.14; H, 7.83.

Methyl (2*S*)-4-[(*tert*-butyldiphenylsilyl)oxy]-2-hydroxybutyrate (5). To a solution of **4** (2.26 g, 5.0 mmol) in 20 mL of MeOH cooled at 0 °C was added, dropwise *via* syringe, a solution of 1.02 M NaOMe (2.46 mL, 2.5 mmol) in MeOH. The mixture was stirred for 15 min at 0 °C, and a suspension of Amberlite H^+ resin in MeOH was carefully added in small portions until the pH reached ca. 6.8. The suspension was then stirred for 20 min at room temperature, the resin was removed by filtration, and the filtrate was concentrated *in vacuo* to afford a viscous oil, which after flash chromatography (hexane–ethyl acetate (10:1)) yielded 1.85 g (94%) of the α-hydroxy ester **5** as a colorless oil, $[\alpha]_D$ +1.31° (*c* 1.07, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (m, 4H, Ph-H's), 7.37-7.46 (m, 6H, Ph-H's), 4.48 (ddd, J_1 = 3.89, J_2 = 5.40, J_3 = 7.85, 1H, OC*H*CO_2-Me), 3.87 (t, *J* = 5.93, 2H, CH_2OSi), 3.77 (s, 3H, CH_3), 3.25 (d, *J* = 5.40, 1H, OH), 2.02 (dt of AB, *J* = 7.85, *J* = 3.89, *J* = 5.43, *J* = 6.29, J_{AB} = 14.26, 2H, CH_2CHOH), 1.07 [s, 9H, C$(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.21, 135.44, 133.26, 133.19, 129.61, 127.59, 68.58, 60.48, 52.23, 26.71, 26.27, 19.03. IR (film): 3550, 2940, 2920, 2840, 1730, 1470, 1425, 1240, 1100, 820, 735, 700 cm^{-1}. MS (high resolution): *m/z* M^+ ($C_{21}H_{28}O_4Si$) calcd 372.1757, found: 372.1363. Anal. Calcd for $C_{21}H_{28}O_4Si$: C, 67.70; H, 7.58. Found: C, 67.89; H, 7.78.

(2*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-hydroxybutyl 2'-Naphthalenesulfonate (6). To the solution of **5** (1.80 g, 4.83 mmol) in 15 mL of dry THF was added, dropwise *via* a syringe, a solution of 2.0 M BH_3·DMS complex (2.46 mL, 4.93 mmol) in THF. The reaction mixture was stirred for 30 min at room temperature and $NaBH_4$ (91.4 mg, 2.42 mmol) was then added in small portions. The mixture was stirred for overnight at room temperature. The solution was cooled at 0 °C, and MeOH (1.0 mL) was added carefully, followed by Amberlite H^+ resin until pH ~7.0. Filtration followed by concentration *in vacuo* afforded 1.66 g (100%) of the 1,2-diol as an off-white powder (>95% purity by ^1H NMR) which was directly used in the next step without further purification.

To a cooled solution of the above diol (3.44 g, 10.0 mmol) in 60 mL of dry CH_2Cl_2 containing Et_3N (1.81 mL, 13.0 mmol) and DMAP (244 mg, 2.0 mmol) was added dropwise *via* syringe a solution of 2-naphthalenesulfonyl chloride (2.61 g, 11.5 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, water (20 mL) was added, the reaction mixture was stirred for another 20 min at room temperature, and ether (150 mL) was added. The aqueous layer was extracted with ether (3 × 100 mL), and the combined organic layers were washed once with saturated aqueous NaCl (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by flash chromatography (hexane–benzene–ethyl acetate (3:2:0.5)) afforded 4.59 g (86%) of **6** as an off-white solid, which was immediately used in the next step. ^1H NMR (300 MHz, $CDCl_3$): δ 8.54 (s, 1H, naphthalene-H), 7.88–8.01 (m, 4H, naphthalene-H's), 7.62–7.72 (m, 6H, 2 × naphthalene-H's and 4 × Ph-H's), 7.37–7.47 (m, 6H, Ph-H's), 4.06–4.23 (m, 3H, CH_2-SO_3 and CHOH), 3.83 (m, 2H, CH_2OSi), 1.74 (AB, J_{AB} = 5.66, 2H, CH_2-CHO), 1.03 [s, 9H, C$(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.31, 135.17, 132.80, 132.74, 132.55, 131.81, 129.70, 129.65, 129.54, 129.20, 127.93, 127.64, 122.37, 73.63, 68.38, 61.44, 34.57, 26.62, 18.84.

(2*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-1,2-epoxybutane (7). To the solution of **6** (3.84 g, 7.18 mmol) in 100 mL of MeOH was added a solution of 1.02 M NaOMe (7.04 mL, 7.18 mmol) in MeOH at 0 °C via a syringe. Upon completion of addition, the reaction mixture was stirred for 30 min at 0 °C and then 15 min at room temperature. A suspension of Amberlite H^+ resin in MeOH was added until pH ~ 7.0. Filtration followed by concentration *in vacuo* gave a syrup which was partitioned between hexane–ether (2:1, 200 mL) and water (50 mL). The aqueous layer was extracted with hexane–ether (2:1, 100 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and then with brine (30 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by flash chromatography (hexane–ethyl acetate (10:1 → 4:1)) afforded 2.35 g (94%) of the epoxide **2** as a white solid, mp 46.5–47.5 °C, $[\alpha]_D$ –6.57° (*c* 1.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 4H, Ph-H's), 7.39–7.45 (m, 6H, Ph-H's), 3.84 (m, 2H, CH_2OSi), 3.11 (m, 1H, CH_BO), 2.80 (dd, J_1 = 4.05, J_2 = 5.13, 1H, CH_AO), 2.53 (dd, J_1 = 2.75, J_2 = 5.13, 1H, CH_AO), 1.78 (AB, J_{AB} = 6.05, 2H, CH_2CH_2OSi), 1.07 [s, 9H, C$(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.42, 133.55, 133.50, 129.55, 127.57, 60.78, 50.00, 47.15, 35.58, 26.70, 19.06. IR (film): 2960, 2920, 2850, 1470, 1425, 1110, 840, 740, 700, 685, 610 cm^{-1}. MS (high resolution): *m/z* M^+ – *t*-BU ($C_{16}H_{17}O_2Si$): calcd 269.0998, found 269.1017. Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.43; H, 8.18.

(*R*)-1-[(*tert*-butyldiphenylsilyl)oxy]-3-hydroxytetradecane (8). Into a 50-mL round-bottomed flask containing lithium (484 mg, 0.07 mol) was added freshly distilled diethyl ether (11 mL) under argon atmosphere. The suspension was refluxed for 1 h, cooled to 15 °C, and treated with ca. 50 drops of a solution of *n*-decyl bromide (6.22 g, 28.12 mmol) in ether (5.6 mL) dropwise *via* a syringe. The reaction mixture was cooled to 7–10 °C, and after 5 min, when the suspension became slightly cloudy and bright spots appeared on the lithium metal, the remainder of the *n*-decyl bromide solution was added at an even rate over a period of 30 min while the internal temperature was maintained at below 10 °C. Upon completion of addition, the mixture was stirred further for 1 h at 10 °C. The suspension was then transferred into a small Kramer filter (Aldrich) by cannula and filtered to remove the excess lithium metal and lithium bromide. A solution of 0.894 M *n*-decyllithium was thus obtained by double titration.

To dry THF (40 mL) cooled to –78 °C was added BF_3·Et_2O (1.1 mL, 8.93 mmol) under argon atmosphere. The solution was stirred briefly for 1–2 min, followed by addition of the above-prepared solution of 0.894 M *n*-decyllithium (10.0 mL, 8.93 mmol) in ether. The solution of epoxide **7** (978 mg, 2.98 mmol) in ether (5.0 mL) was immediately added, and the reaction mixture was stirred for another 10 min at –78 °C. Saturated $NaHCO_3$ (aq) solution (5 mL) was added, and the dry ice–acetone bath was removed. Standard workup after extraction with ether followed by flash chromatography (hexane–ethyl acetate (20:1)) afforded 1.25 g (90%) of **8** as a colorless oil, $[\alpha]_D$ +5.79° (*c* 1.26, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 4H, Ph-H's), 7.38–7.45 (m, 6H, Ph-H's), 3.81–3.96 (m, 3H, CH_2OSi and C*H*OH), 3.18 (d, *J* = 2.60, 1H, O*H*), 1.69 (m, 2H, CH_2CH_2OSi), 1.44 (m, 4H, CH_2's), 1.28 (bs, 16H, CH_2's), 1.07 [s, 9H, C$(CH_3)_3$], 0.90 (t, *J* = 6.92, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.47, 133.08, 132.99, 129.69, 127.65, 71.61, 63.39, 38.40, 37.47, 31.81, 29.62, 29.53, 29.23, 26.74, 25.50, 22.57, 18.94, 13.97. IR (film): 3450, 2920, 2850, 1460, 1425, 1110, 1080, 820, 730, 700 cm^{-1}. MS (high resolution): *m/z* M^+ + H ($C_{30}H_{49}O_2Si$) calcd 469.3504, found 469.3512. Anal. Calcd for $C_{30}H_{48}O_2Si$: C, 76.86; H, 10.32. Found: C, 76.85; H, 10.44.

(*R*)-3-(Benzyloxy)-1-[(*tert*-butyldiphenylsilyl)oxy]tetradecane (9). To a cooled solution of **8** (917 mg, 1.96 mmol) in dry CH_2Cl_2 was added, dropwise *via* a syringe, benzyl 2,2,2-trichloroacetimidate (727 mL, 3.91 mmol) and trifluoromethanesulfonic acid (92 μL, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, diluted with ether (20 mL), and partitioned between hexane (20 mL) and water (20 mL). The aqueous layer was extracted with hexane–ether (2:1, 2 × 20 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by flash chromatography (hexane–ethyl acetate (50:1 → 30:1)) afforded 934 mg (86%) of **9** as a colorless oil, $[\alpha]_D$ –5.49° (*c* 1.08, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 4H, Ph-H's), 7.37–7.49 (m, 6H, Ph-H's), 7.33 (m, 5H, Ph-H's), 4.52 (AB, J_{AB} = 11.50, 2H, CH_2OPh), 3.85 (dd of AB, *J* = 6.72, 6.68, 5.93, 5.88, J_{AB} = 10.24, 2H, CH_2OSi), 3.68 (m, 1H, C*H*OBn), 1.82 (m, 2H, CH_2CH_2OSi), 1.55 (m, 2H, CH_2), 1.32 (bs, 16H, CH_2's), 1.11 [s, 9H, C$(CH_3)_3$], 0.94 (t, *J* = 6.96, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.03, 135.47, 133.93, 129.42, 128.12, 127.58, 127.50, 127.19, 76.03, 70.90, 60.67, 37.07, 34.07, 31.82, 29.69, 29.54, 29.24, 26.81, 25.21, 22.57, 19.10, 13.98. IR (film): 2940, 2860, 1460, 1425, 1110, 1090, 820, 730, 700, 610 cm^{-1}. MS (high resolution): *m/z* M^+ + H ($C_{37}H_{55}O_2Si$) calcd, 559.3974, found 559.3994. Anal. Calcd for $C_{37}H_{54}O_2Si$: C, 79.51; H, 9.74. Found: C, 80.78; H, 9.64.

(*R*)-3-(Benzyloxy)tetradecan-1-ol (10). To a stirred solution of **9** (934 mg, 1.67 mmol) in CH_2Cl_2 (10 mL) was added, dropwise *via* a plastic syringe, a solution of 48% HF–CH_3CN (5:95, 10 mL). The reaction was completed after 3 h (monitored by TLC), and the mixture was partitioned between ether (20

mL) and water (10 mL). The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by flash chromatography (hexane–ethyl acetate (5:1)) afforded 530 mg (99%) of **10** as a colorless oil, $[\alpha]_D$ −30.92° (*c*, 1.12, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 5H, Ph-H's), 4.55 (AB, J_{AB} = 11.45, 2H, CH_2OPh), 3.70–3.84 (m, 2H, CH_2OH), 3.65 (m, 1H, $CHOBn$), 2.43 (bs, 1H, OH), 1.49–1.88 (m, 4H, CH_2's), 1.28 (bs, 18H, CH_2's), 0.90 (t, J = 6.95, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.41, 128.30, 127.69, 127.53, 78.40, 70.82, 60.60, 35.90, 33.39, 31.79, 29.68, 29.47, 29.20, 25.03, 22.54, 13.94. IR (film): 3400 (bs), 2920, 2850, 1465, 1450, 1085, 1060, 1025, 730, 695 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.62; H, 11.17.

(*R*)-3-(Benzyloxy)tetradecan-1-al (11). To a stirred suspension of PDC (1.56 g, 4.06 mmol) in dry CH_2Cl_2 (10 mL) was added, dropwise *via* a syringe, a solution of **10** (434 mg, 1.35 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at room temperature and diluted with ether (50 mL). The brown precipitate was removed by filtration through a short pad of Celite, and the solvent was removed *in vacuo* to afford a yellow oily residue, which after flash chromatography (hexane–ethyl acetate (10:1)) yielded 359 mg (83%) of aldehyde **11** as a colorless oil, $[\alpha]_D$ −14.25° (*c* 1.24, CH_2Cl_2) (lit.[9] $[\alpha]_D$ −13.8° ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (dd, J = 1.98, 2.60, 1H, CHO), 7.33 (s, 5H, Ph-H's), 4.55 (AB, J_{AB} = 11.46, 2H, OCH_2-Ph), 3.95 (m, 1H, $CHOBn$), 2.66 (dd of AB, J = 2.60, 7.17, 1.98, 4.79, J_{AB} = 16.25, 2H, CH_2CHO), 1.50–1.77 (m, 2H, CH_2CHOBn), 1.27 (m, 18H, CH_2's), 0.89 (t, J = 6.83, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.37, 138.18, 128.25, 127.61, 127.53, 74.29, 71.08, 48.21, 34.14, 31.77, 29.48, 29.42, 29.19, 24.96, 22.54, 13.94. IR (film): 2920, 2840, 1720, 1460, 1450, 1090, 1060, 730, 690, 670 cm^{-1}. MS (high resolution): m/z M^+ ($C_{21}H_{34}O_2$) calcd 318.2560, found 318.2478.

(*E*)-1-Bromo-1-octene. To a 100-mL round-bottomed flask charged with 1-octyne (2.76 g, 25.0 mmol) was added a 1.0 M solution of DIBAL-H (26.8 mL, 26.8 mmol) in hexane while the temperature was maintained at 25–35 °C. The mixture was stirred for 30 min at room temperature and then heated at 50 °C for 4 h. The resultant alkenylalane was cooled to −30 °C, diluted with dry ether (15 mL) and treated with NBS (5.35 g, 30.1 mmol) while the temperature was kept below −15 °C. The reaction mixture was gradually warmed to room temperature and stirred for another hour. The reaction mixture was poured slowly into a mixture of 6 N HCl (50 mL), pentane (10 mL), and some ice cubes (10 g). The layers were separated, and the aqueous phase was extracted with more pentane (2 × 10 mL). The combined organic extracts were washed successively with 1 N NaOH, 10% Na_2SO_3, and brine and dried over $MgSO_4$. Distillation afforded 4.47 g (93.4%) of (*E*)-1-bromo-1-octene as a colorless liquid, *E*/*Z* ratio >99:1 (300-MHz ^1H NMR), which was used as such.

(*Z*)-1-Bromo-1-octene. This compound was prepared essentially according to a literature precedent.[38] A mixture of 1-octyne (5.2 g, 47.0 mmol) and catecholborane (5.9 g, 47.0 mmol) was heated at 70 °C for 2.0 h. After being cooled to room temperature, water (50 mL) was added and the mixture was stirred for 2 h at room temperature to effect hydrolysis. The mixture was then cooled to 0 °C, and a white solid was collected by filtration. After washing with ice-cold water, after drying overnight at 0.2 mmHg, 4.99 g (68%) of 1-octenylboronic acid was obtained as an off-white solid, which was used immediately for the next reaction. To a solution of the preceding compound (1.56 g, 10 mmol) in Et_2O-CH_2Cl_2 (1:1, 20 mL) cooled at −20 °C was added bromine (512.4 μL 10 mmol) dropwise via a syringe. The mixture was stirred for 1 h at −20 °C, after which time a solution of 1.02M NaOMe (10 mL, 10.0 mmol) in MeOH was added and the mixture was stirred for another 1.0 hr at −20 °C. The mixture was warmed to −5 °C and water (10 mL) was added, followed by ether (50 mL). Successive washing with saturated $Na_2S_2O_3$, $NaHCO_3$ aqueous solutions and brine, drying over Na_2SO_4), followed by Kugelrohr distillation, afforded 1.64 g (86%) of *Z*-1-bromo-1-octene as a light yellow liquid; *Z*/*E* ratio: >95:5 (300 MHz ^1H NMR). The product was used as such.

(*E*)-1-(Trimethylsilyl)-2-nonene. To a suspension of $(PPh_3)_4$-Pd (577 mg, 0.5 mmol) in dry THF (10 mL) was added sequentially a 1.0 M solution of [(trimethylsilyl)methyl]magnesium chloride (10 mL, 10 mmol) in ether and the (*E*)- or (*Z*)-vinyl bromide (2.14 g, 9.0 mmol) at 0 °C. The mixture was stirred overnight at room temperature and treated with 3 N HCl (10 mL), and the mixture was extracted with hexane (3 × 25 mL). The organic layers were washed once with water and then saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Short-path column chromatography (eluted with hexane) afforded 1.45 g (81%) of (*E*)-1-(trimethylsilyl)-2-nonene as a colorless liquid. *E*/*Z* ratio ≥99:1 (300-MHz ^1H NMR). The *Z*- isomer was similarly prepared, essentially according to Negishi and co-workers.[39] The product was used as such.

(3*R*,4*S*,6*R*)-6-(Benzyloxy)-3-hexyl-4-hydroxy-1-heptadecene (12) and (3*S*,4*S*,6*R*)-6-Benzyloxy)-3-hexyl-4-hydroxy-1-heptadecene (14). To a stirred solution of aldehyde **11** (209 mg, 0.656 mmol) in dry CH_2Cl_2 (15 mL) cooled at −78 °C was added a suspension of CP_2TiCl_2 (196 mg, 0.788 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 30 min at −78 °C, followed by addition of a solution of **(*E*)-1-(trimethylsilyl)-2-nonene** (170 mg, 0.853 mmol, >99% *E*) in dry CH_2Cl_2 (5 mL). Finally, a solution of $TiCl_4$ (788 μL, 0.788 mmol, 1.0 M in CH_2Cl_2) was added dropwise *via* a syringe. The reaction mixture was stirred for 1.0 h at −78 °C, water (5 mL) was added, and the mixture was partitioned between ether (30 mL) and water (10 mL). The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were washed once with water (10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate (10:1)) afforded 265 mg 991%) of the title homoallylic alcohols as a colorless oils, which were derivatized immediately as their silyl ethers.

(3*R*,4*S*,6*R*)-6-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)-oxy]-3-hexyl-1-heptadecene (13) and (3*S*,4*S*,*R*)-6-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-3-hexyl-1-heptadecene (15). The mixture of **12** and **14** (191.2 mg, 0.215 mmol), *tert*-butyldimethylsilyl chloride (324 mg, 2.15 mmol), imidazole (293 mg, 4.30 mmol), and DMAP (105 mg, 0.86 mmol) in dry DMF (2.0 mL) was heated at 55 °C for 20 h. The reaction mixture was partitioned between ether (20 mL) and water (10 mL), the aqueous layer was extracted with ether (3 × 10 mL), the combined organic layers were washed with water (2 × 10 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. Flash chromatography (hexane–benzene (20:1 → 15:1)) afforded 71.3 mg of **15** and 128.3 mg of **13** together with 9.5 mg of the (3*S*,4*R*,6*R*) diastereomer **16** (overall 87%). For (3*R*,4*S*,6*R*)-**13**, $[\alpha]_D$ −17.01° (*c* 0.97 $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.33 (m, 5H, Ph-H's), 5.69 (ddd, J = 8.94, 10.31, 17.24, 1H, vinyl-H), 5.07 (dd, J = 2.20, 10.31, 1H, vinyl-H), 4.99 (dd, J = 1.63, 17.24, 1H, vinyl-H), 4.47 (AB, J_{AB} = 11.54, 2H, OCH_2Ph), 3.83 (m, 1H, $CHOBn$), 3.49 (m, 1H, $CHOSi$), 2.05 (m, 1H, $CHCH{=}CH_2$), 1.75 (m, 1H, $OCCH_ACO$), 1.41–1.61 (m, 3H, $OCCH_BCO$ and CH_2CO), 1.28 (m, 26H, CH_2's), 0.90 [s, 9H, $C(CH_3)_3$], 0.89 (t-like, 6H, 2 × CH_3), 0.05 (s, 3H, CH_3), 0.03 (s, 3H, CH_3). ^{13}C NMR (75 MHz, C_6D_6): δ 139.98, 139.75, 128.48, 127.61, 127.46, 116.47, 76.40, 73.30, 70.06, 51.02, 39.53, 34.27, 32.32, 32.27, 30.33, 30.17, 30.11, 30.09, 29.92, 29.78, 28.19, 26.28, 26.25, 25.39, 23.08, 23.04, 18.44, 14.31, 14.27, −3.98, −0.40. IR (film): 2940, 2920, 2840, 1450, 1250, 1060, 1020, 1000, 900, 830, 770, 720, 690, 670 cm^{-1}. MS (high resolution): m/z M^+ − *t*-Bu ($C_{32}H_{57}O_2Si$) calcd 501.4130, found 501.4147. For the (3*S*,4*S*,6*R*) diastereomer **15**, $[\alpha]_D$ −31.15° (c, 1.22, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27–7.37 (m, 5H, Ph-H's), 5.77 (ddd, J_1 = 8.02, J_2 = 10.50, J_3 = 17.27, 1H, vinyl-H), 5.07 (dd, J_1 = 2.12, J_2 = 10.50, 1H, vinyl-H), 4.99 (ddd, J_1 = 1.03, J_2 = 2.12, J_3 = 17.27, 1H, vinyl-H), 4.50 (AB, J_{AB} = 11.53, 2H, OCH_2Ph), 3.91 (m, 1H, $CHOBn$), 3.56 (m, 1H, $CHOSi$), 2.16 (m, 1H, $CHCH{=}CH_2$), 1.38–1.72 (m, 4H, $OCCH_2CO$ and CH_2CO), 1.28 (m, 28H, CH_2's), 0.90 [s, 9H, $C(CH_3)_3$], 0.89 (t-like, 6H, 2 × CH_3), 0.06 (s, 3H, CH_3), 0.03 (s, 3H, CH_3). IR (film): 2940, 2920, 2840, 1455, 1250, 1060,

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1020, 1000, 900, 830, 800, 770, 720, 690 cm^{-1}. MS (high resolution): m/z M$^+$ − t-Bu ($C_{32}H_{57}O_2Si$) calcd 501.4130, found 501.4102.

(2*S*,3*S*,5*R*)-5-(Benzyloxy)-2-hexyl-3-hydroxyhexadecanoic Acid (18). Ozone was carefully and slowly bubbled into a stirred solution of **13** (100 mg, 0.179 mmol) in MeOH–CH_2Cl_2 (3:1, 4 mL) cooled at −78 °C. Upon completion of the oxidation (ca. 4.5 h), Me_2S (1 mL) was added, followed by Et_3N (0.2 mL), and the dry ice–acetone bath was removed. The mixture was slowly warmed to room temperature and stirred for 1 h. The solvent was removed *in vacuo*, and the oily residue was dissolved in 2-methyl 2-butene (1 mL) and t-BuOH (1 mL). The mixture was cooled at 0 °C, and to this was added, dropwise *via* a syringe, a solution of sodium chlorite (202 mg, 1.79 mmol, 80%) and NaH_2PO_4·H_2O (296 mg, 2.15 mmol) in water (1 mL). The mixture was stirred for 3 h at 0 °C and for 30 min at room temperature and then partitioned between ether (10 mL) and water (5 mL). The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic layers were washed once with saturated aqueous NaCl (5 mL). The solvent was removed under reduced pressure, and the crude acid was redissolved in CH_2Cl_2 (1 mL). A solution of 48% HF–CH_3CN (5:95, 1 mL) was added, and the mixture was stirred for 5 h at room temperature. The reaction was partitioned between ether (10 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo* followed by flash chromatography ($CHCl_3$–EtOH (98:2 → 95:5)) afforded 60 mg (72%) of β-hydroxy acid **18** as a colorless oil, $[\alpha]_D$ −27.6° (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5 H, Ph-H's), 4.56 (AB, J_{AB} = 11.29, 2H, OC*H*$_2$Ph), 4.09 (ddd, J = 2.09, 5.00, 10.11, 1H, C*H*OBn), 3.74 (m, 1H, C*H* OH), 2.38 (dt, J_d = 9.21, J_t = 5.14, 1H, C*H*CO_2H), 1.48–1.93 (m, 4H, CH_2's), 1.27 (m, 28H, CH_2's), 0.89 (t, J = 6.83, 3H, CH_3), 0.88 (t, J = 6.55, 3H, CH_3). ^{13}C NMR (75 MHz, C_6D_6): δ 137.98, 128.34, 127.85, 127.68, 76.75, 71.32, 69.12, 51.65, 37.90, 33.30, 31.80, 31.51, 29.67, 29.53, 29.24, 29.09, 27.13, 25.27, 22.58, 22.49, 14.01, 13.94. IR (film): 3420 (bs), 2930, 2860, 1720, 1470, 1460, 1200, 1060, 900, 830, 730, 690 cm^{-1}. MS (high resolution): m/z M$^+$ ($C_{29}H_{50}O_4$) calcd 462.3711, found 462.3718.

(3*S*,4*S*)-3-Hexyl-4[(*R*)-2-hydroxytridecyl]-2-oxetanone (20). To a stirred solution of **18** (52 mg, 0.112 mmol) in dry pyridine (2 mL) cooled at 0 °C was added, dropwise *via* a syringe, benzenesulfonyl chloride (28.7 μL, 0.225 mmol). The light yellow solution was stirred for overnight at 0 °C and diluted with ether (10 mL). Water (4 mL) was added, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed once with water (2 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure afforded the crude β-lactone **20** as a light yellow oil. The residue was dissolved in ethyl acetate (4 mL) and treated with 10% Pd–C (50 mg), and the suspension was hydrogenated overnight. Removal of the catalyst by filtration and flash chromatography (hexane–ethyl acetate (10:1)) gave 28.7 mg (72%) of **20** as a white powder. Recrystallizatiopn from pentane–ether afforded 28.2 mg of an analytically pure sample as a white crystals, mp 61–61.5 °C, $[\alpha]_D$ −40.79 °C (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50 [dt, J_d = 8.28, J_t = 4.00, 1H C(4)-H], 3.81 (m, 1H, C*H*OH), 3.26 [ddd, J = 4.00, 7.04, 8.01, 1H, C(3)-H], 1.68–1.98 (m, 5H, CH_2's), 1.18–1.54 (m, 30H, CH_2's), 0.88 (t-like, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.40, 75.40, 68.44, 56.55, 41.77, 38.02, 31.79, 31.39, 29.50, 29.44, 29.39, 29.21, 28.85, 27.63, 26.65, 25.28, 22.55, 22.40, 13.96, 13.87. IR (film): 3420 (bs), 2930, 2860, 1720, 1470, 1460, 1200, 1060, 900, 830, 730, 690 cm^{-1}. MS (high resolution): m/z M$^+$ ($C_{22}H_{42}O_3$) calcd 354.3136, found 354.3122. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.50; H, 11.71.

Tetrahydrolipstatin (2). To a stirred mixture of **20** (16 mg, 0.045 mmol), triphenylphosphine (14.3 mg, 0.054 mmol) and (*S*)-*N*-formylleucine (9.0 mg, 0.056 mmol) in dry THF cooled at 0 °C was added diethyl azodicarboxylate (9.1 μL, 0.056 mmol) *via* a syringe.[8,9] The reaction mixture was then stirred overnight at room temperature. Removal of solvent under reduced pressure followed by flash chromatography (toluene–ethyl acetate (4:1)) afforded 19.2 mg (85.8%) of tetrahydrolipstatin **2** as white crystals, mp 40–41 °C, $[\alpha]_D$ −33.04° (*c* 0.79, $CHCl_3$) (lit.[8,9] mp 40–42 °C; $[\alpha]_D$ −33° ($CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H, NHC*H*O), 5.92 (d, J = 8.5 Hz, 1H, N*H*), 5.03 [m, 1H, $CH_3(CH_2)_{10}$C*H*O], 4.69 (ddd, J = 8.90, 8.90, 4.70 Hz, 1H, C*H*NH), 4.29 (ddd, appearing as a symmetric five-line m, 1H, lactone OC*H*), 3.22 (ddd, J = 7.60, 7.60, 4.10 Hz, 1H, lactone O=CC*H*), 2.17 (ddd, J = 15.3, 7.70, 7.70 Hz, 1H, OCHC*H*$_A$CH$_B$CHO), 1.97 (ddd, J = 15.3, 4.50, 4.50 Hz, 1H, OCHCH$_A$CH$_B$CHO), 1.50–1.88 (m, 7H, CH_2's), 1.20–1.48 (m, 23H, CH_2's), 0.97 (d, J = 4.52 Hz, 6H, 2 × CH_3), 0.88 (t-like, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.83, 170.67, 160.50, 74.66, 72.64, 56.91, 49.48, 41.45, 38.59, 33.94, 31.79, 31.36, 29.50, 29.43, 29.32, 29.23, 29.19, 28.85, 27.50, 26.59, 24.98, 24.77, 22.77, 22.57, 22.40, 21.62, 14.02, 13.92. IR (CCl_4): 2970, 2940, 2870, 1835, 1745, 1705, 1500, 1470, 1200, 1120 cm^{-1}. MS (high resolution): m/z M$^+$ + H ($C_{29}H_{54}NO_5$) calcd 496.4004, found 496.3990. Anal. Calcd for $C_{29}H_{53}NO_5$: C, 70.26; H, 10.78. Found: C, 70.32; H, 10.64.

(2*S*,3*S*,5*R*)-5-(Benzyloxy)-2-hexyl-3-hydroxyhexadecanoic Acid (21). Ozone was carefully bubbled into a stirred solution of **15** (80 mg, 0.143 mmol) in MeOH–CH_2Cl_2 (3:1, 4 mL) cooled at −78 °C. After ca. 4.5 h, Me_2S (1 mL) was added, and the dry ice–acetone bath was removed. The mixture was slowly warmed to room temperature and stirred for 1 h. The solvent was removed *in vacuo*, and the oily residue was dissolved in 2-methyl 2-butene (1 mL) and t-BuOH (1 mL). The mixture was cooled at 0 °C, and to this was added, dropwise *via* a syringe, a solution of sodium chlorite (162 mg, 1.43 mmol, 80%) and NaH_2PO_4·H_2O (237 mg, 1.72 mmol) in water (1 mL). The mixture was stirred for 3 h at 0 °C and then 30 min at room temperature. The reaction mixture was worked up and desilylated as described for **18**. Flash chromatography ($CHCl_3$–EtOH (98:2 → 95:5)) afforded 46 mg (69%) of **21** as a white solid, $[\alpha]_D$ −21.68° (*c* 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.41 (m, 5H, Ph-H's), 4.56 (AB, J_{AB} = 11.39, 2H, OC*H*$_2$Ph), 4.21 (m, 1H, C*H*OBn), 3.76 (m, 1H, C*H*OH), 2.53 (m, 1H, C*H*CO_2H), 1.43–1.90 (m, 33H, CH_2's), 0.89 (t-like, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.77, 137.74, 128.41, 127.82, 71.29, 68.96, 50.54, 35.16, 32.86, 31.81, 31.52, 29.54, 29.49, 29.25, 29.14, 27.51, 27.35, 25.44, 22.59, 22.48, 14.02, 13.95. IR (film): 3450, 2940, 2860, 1750, 1710, 1470, 1460, 1070 cm^{-1}. MS (High resolution): m/z M$^+$ + H ($C_{29}H_{51}O_4$) calcd 463.3789, found 463.3745.

(3*R*,4*S*)-3-Hexyl-4[(*R*)-2-hydroxytridecyl]-2-oxetanone (22). To a cooled and stirred solution of **21** (33 mg, 0.072 mmol) in dry pyridine (0.5 mL) was added, dropwise *via* a syringe, benzenesulfonyl chloride (24 μL 0.143 mmol) at 0 °C. The light yellow solution was stirred overnight at 0 °C and diluted with ether (10 mL). Water (2 mL) was added, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed once with water (2 mL) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by flash chromatography (hexane–ethyl acetate (20:1)) afforded 28.1 mg (89%) of **22** as a colorless oil, $[\alpha]_D$ −43.6° (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.38 (m, 5H, Ph-H's), 4.83 (m, 1H, lactone OC*H*), 4.53 (AB, J_{AB} = 11.18, 2H, OC*H*$_2$Ph), 3.57–3.69 (m, 2H, C*H*OBn and lactone O=CC*H*), 1.17–1.86 (m, 33H, CH_2's), 0.89 (t-like, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.23, 138.30, 128.36, 127.78, 127.65, 75.39, 72.69, 71.76, 52.36, 35.33, 34.09, 31.83, 31.37, 29.71, 29.56, 29.50, 29.26, 28.90, 27.37, 24.69, 24.07, 22.60, 22.44, 14.03, 13.93. IR ($CHCl_3$): 2930, 2855, 1815, 1725, 1600, 1465, 1450, 1118, 1060. MS (High resolution): m/z M$^+$ ($C_{29}H_{48}O_3$) calcd 444.3605, found 444.3611. Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.36; H, 10.84.

Epimerization of *Cis* β-Lactone 22 Into *Trans* β-Lactone 19. To a stirred solution of diisopropylamine (12 μL, 0.086 mmol) in dry THF (1 mL) cooled at 0 °C was added, dropwise *via* a syringe, a solution of 1.6 M n-BuLi (51 μL, 0.082 mmol) in hexane. The mixture was stirred for 10 min at 0 °C. To this solution of LDA cooled at −78 °C was added, *via* a syringe, a solution of **22** (18 mg, 0.04 mmol) in dry THF (1 mL). The reaction mixture was stirred for 20 min at −78 °C and quenched by addition of glacial acetic acid (5 μL, 0.086 mmol). The mixture was stirred briefly for 2 min and poured into a solution of saturated $NaHCO_3$ (2 mL). Standard workup (ether extraction, brine washing, and drying over Na_2SO_4) afforded, after removal of solvent under reduced pressure, 15 mg (83%) of **22** and **19** as a 1:1 mixture of *cis* and *trans* isomers, respectively (^{1}H NMR, 300 MHz). Flash chromatography (hexane/ethyl acetate (20:1)) afforded 7.4 mg

(41%) of the *trans* β-lactone **19** as a colorless oil and 7.6 mg (42%) of recovered *cis* β-lactone **22**.

(±)-6-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-1-heptadecene (23). To the solution of racemic aldehyde **11** (783.9 mg, 2.46 mmol) in dry CH_2Cl_2 (30 mL) cooled at −78 °C was added a 1 M solution of $TiCl_4$ (2.71 mL, 2.71 mmol) in CH_2Cl_2 dropwise via syringe. The resulting light yellow suspension was stirred briefly for 10 min, followed by the addition of a solution of allyltrimethylsilane (430.4 μL 2.71 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 20 min, water (10 mL) was added, and the mixture was processed as described for **12**. Removal of solvnt *in vacuo* followed by flash chromatography (hexane–ethyl acetate (10:1)) afforded 763 mg (86%) of homoallylic alcohols, as a colorless oil, which were derivatized immediately as their silyl ethers. The mixture (606.1 mg, 1.68 mmol), *tert*-butyldimethylsilyl chloride (317 mg, 2.10 mmol), and DMAP (205.4 mg, 1.68 mmol) in dry DMF (5 mL) were heated overnight at 50–60 °C. Water was added, and the mixture was then partitioned between ether (40 mL) and water (10 mL). The aqueous layer was extracted with ether, and the combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate (40:1)) afforded 798.8 mg (100%) of **23** as a colorless oil (27:1, *anti/syn*). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27–7.38 (m, 5H, Ph-H's), 5.86 (m, 1H, vinyl-H), 5.07 (m, 2H, vinyl-H's), 4.57 (d, J = 11.36, 1H, OCH_APh), 4.45 (d, J = 11.36, 1H, OCH_BPh), 3.99 (m, 1H, CHOBn), 3.61 (m, 1H, CHOSi), 2.27 (m, 2H, CH_2CH=CH$_2$), 1.51–1.78 (m, 4H, OCCH_AH$_B$CO and CH_2-CO), 1.29 (m, 18H, CH_2's), 0.92 [s, 9H, C(CH_3)$_3$], 0.90 (t-like, 3H, CH_3), 0.09 (s, 3H, CH_3), 0.07 (S, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.07, 134.73, 128.17, 127.42, 127.21, 116.85, 76.06, 70.10, 68.90, 42.58, 33.74, 31.83, 29.74, 29.55, 29.27, 25.83, 25.60, 24.82, 22.60, 17.98, 14.03, −3.05, −4.10, −4.65. IR (film): 2960, 2940, 2860, 1470, 1260, 1090, 1070, 980, 840, 810, 780, 740, 700 cm^{-1}. MS (high resolution): m/z M$^+$ + H ($C_{30}H_{55}O_2Si$), calcd 475.3974, found 475.3920.

Phenyl (±)-5-(Benzyloxy)-3-hydroxyhexadecanethioate (25). Ozone was carefully passed into a stirred solution of **23** (798.8 mg, 1.68 mmol) in MeOH–CH_2Cl_2 (1:1, 30 mL **cooled** at −78 °C. Upon completion of the reaction (monitored by TLC, ca. 40 min), Me_2S (5 mL) was added, followed by Et_3N (1 mL), and the dry ice–acetone bath was removed. The mixture was slowly warmed to room temperature and stirred for 1.0 h. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography (hexane–ethyl acetate (20:1)) to afford 802.0 mg (100%) of aldehyde as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (t, J = 2.49, 1H, CHO), 7.27–7.35 (m, 5H, Ph-H's), 4.57 (d, J = 11.38, 1 H, OCH_APh), 4.40 (d, J = 11.38, 1H, OCH_BPh), 4.38 (m, 1H, SiOCH), 3.58 (m, 1H, BnOCH), 2.61 (ddd, J = 2.26, 5.42, 15.75, 1H, O=CHCH_A), 2.50 (ddd, J = 2.94, 5.42, 15.75, 1H, O=CHCH_B), 1.49–1.78 (m, 3H, CH_2's), 1.27 (bs, 18H, CH_2's), 0.89 (t-like, 3H, CH_3), 0.88 [s, 9H, C(CH_3)$_3$], 0.07 (s, 3H, CH_3), 0.06 (s, 3H, CH_3).

To the solution of the above aldehyde (802.0 mg, 1.68 mmol) in 2-methyl 2-butene (10 mL) and *t*-BuOH (25 mL) cooled at 0 °C was added, dropwise *via* a pipet, a solution of sodium chlorite (1.75 g, 15.43 mmol, 80%) and NaH_2PO_4·H_2O (1.61 g, 11.64 mmol) in water (10 mL). The mixture was stirred for 15 min at 0 °C and then 10 min at room temperature. The reaction mixture was then partitioned between ether and water and processed as described for **18**. Removal of solvent under reduced pressure afforded 826 mg (100%) of the crude acid as a colorless oil. A solution of 48% HF–CH_3CN (5:95, 10 mL) was added to the preceding compound in 10 mL of CH_2Cl. The mixture was stirred for 1 h at room temperature. The reaction mixture was partitioned between ether and water. The aqueous phase was extracted with ether and then processed as usual. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate–acetic acid (5:1:1)) afforded 614.4 mg (97%) of the β-hydroxy acid **24** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27–7.40 (m, 5H, Ph-H's), 4.61 (d, J = 11.38, 1H, OCH_APh), 4.51 (d, J = 11.38, 1H, OCH_BPh), 4.34 (m, 1H, CHOBn), 3.63 (m, 1H, CHOH), 2.52 (s, 1H, CH_ACO$_2$), 2.50 (d, J = 1.29, CH_BCO$_2$), 1.47–1.86 (m, 4H, CH_2's), 1.27 (m, 18H, CH_2's), 0.89 (t, J = 6.71, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.98, 138.02, 128.27, 127.81, 127.59, 76.26, 71.15, 65.03, 41.41, 39.60, 33.37, 31.75, 29.60, 29.47, 29.43, 29.18, 25.03, 22.52, 13.96. IR (film): 3420, 2940, 2860, 2680, 1720, 1460, 1280, 1100, 1070, 740, 7000 cm^{-1}. MS (high resolution): m/z M$^+$ ($C_{23}H_{38}O_4$) calcd 378.2771, found 378.2777.

To a stirred mixture of **24** (150 mg, 0.396 mmol) and DMAP (24.2 mg, 0.198 mmol) in dry CH_2Cl_2 cooled at 0 °C was added benzenethiol (61 μL 0.594 mmol), followed by 1,3-dicyclohexylcarbodiimide (123 mg, 0.594 mmol). The mixture was stirred for 5 min at 0 °C and then 2 h at room temperature. Precipitated urea was removed by filtration through a plug of silica gel, and the filtrate was evaporated *in vacuo* to yield the crude thio ester **25**. Flash chromatography (hexane/ethyl acetate (10:1)) afforded 165.5 mg (89%) of **25** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 5H, SPh-H's), 7.27–7.35 (m, 5H, Ph-H's), 4.60 (d, J = 11.35, 1H, OCH_APh), 4.50 (d, J = 11.35, 1H OCH_BPh), 4.39 (m, 1H, CHOBn), 3.72 (m, 1H, CHOH), 3.22 (d, J = 3.66, 1H, OH), 2.83 [d, J = 3.66, 1H, CH_AC(=O)SPh], 2.81 [d, J = 3.66, 1H, CH_BC(=O)SPh], 1.45–1.80 (m, 4H, CH_2's), 1.26 (bs, 18H, CH_2's), 0.88 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.07, 138.22, 134.29, 129.46, 129.14, 128.37, 127.87, 127.65, 127.22, 76.29, 71.26, 65.72, 50.60, 39.76, 33.43, 31.81, 29.68, 29.52, 29.49, 29.25, 25.12, 22.59, 14.03. IR (film): 3460 (bs), 2940, 2860, 1710, 1480, 1470, 1460, 1440, 1090, 1070, 1030, 750, 700, 690 cm^{-1}. MS (high resolution): m/z M$^+$ + H ($C_{29}H_{43}O_3$) calcd 471.2935, found 471.2913.

(±)-4-[2-(Benzyloxy)tridecyl]-2-oxetanone (26). To a stirred mixture of thioester **25** (159.0 mg, 0.338 mmol), Na_2HPO_4 (384.0 mg, 2.70 mmol), and activated powdered 4-Å molecular sieves (three spatula full) in dry acetonitrile (10 mL) was added freshly prepared mercuric (II) trifluoromethanesulfonate (264.2 mg, 0.676 mmol) in small portions. The reaction mixture was stirred for 15–20 min at room temperature. Ether was added, and the white solid was removed by filtration through a short pad of Celite. Removal of solvent followed by flash chromatography (hexane–ethyl acetate (10:1 → 5:1)) afforded 87.3 mg (72%) of β-lactone **26** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.39 (m, 5H, Ph-H's), 4.71 (m, 1H, lactone OCH), 4.61 (d, J = 11.36, 1H, OCH_APh), 4.43 (d, J = 11.36, 1H, OCH_B-Ph), 3.62 (m, 1H, CHOBn), 3.52 (dd, J = 5.81, 16.39, 1H, lactone O=CCH_A), 3.13 (dd, J = 4.33, 16.39, 1H, lactone O=CCH_B), 1.44–1.74 (m, 2H, OCHCH_2), 1.27 (bs, 18H, CH_2's), 0.89 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.29, 138.16, 128.32, 127.66, 127.61, 75.57, 71.37, 68.96, 43.36, 39.80, 33.74, 31.77, 29.60, 29.49, 29.43, 29.20, 24.63, 22.55, 13.99. IR (film): 2930, 2860, 1835 (β-lactone C=O), 1470, 1455, 1130, 1090, 1070, 880, 820, 740, 700 cm^{-1}. MS (high resolution): m/z M$^+$ ($C_{23}H_{36}O_3$) calcd 360.2664, found 360.2644.

(4*R*)-4-[(2*R*)-Acetoxy-2-phenylacetoxy]pentadec-1-ene (28). To a stirred solution of lauraldehyde (5.18 g, 23.48 mmol) in dry THF (40 mL) cooled at −10 °C was added a 1 M solution of allylmagnesium bromide (35.2 mL, 35.2 mmol) in ether dropwise via syringe. The reaction mixture was stirred for 1 h at −10 °C, saturated aqueous NH_4Cl (50 mL) was added, and the mixture was partitioned between ether (300 mL) and water (30 mL). The organic layer was washed once with water (15 mL) and brine (30 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography (hexane–ethyl acetate (24:1 → 16:1)) afforded 3.87 g (61%) of the homoallylic alcohol as a colorless oil which solidified below 0 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 5.76–5.92 (m, 1H, CH=CH$_2$), 5.10–5.20 (m, 2H, CH=CH_2), 3.64 (brm, 1H, CHOH), 2.26–2.37 (m, 1H, CH_ACH=), 2.07–2.20 (m, 1H, CH_B-CH=), 1.58 (d, J = 3.85, OH), 1.41–1.53 (brm, 4H, CH_2's), 1.26 (bs, 18H, CH_2's), 0.88 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.80, 117.87, 77.32, 76.47, 70.51, 41.79, 36.66, 31.78, 29.53, 29.48, 29.22, 25.54, 22.55, 13.98. IR (film): 3360 (br), 3080, 2930, 2860, 1645, 1470, 910. MS (high resolution): m/z M$^+$ ($C_{15}H_{30}O$) calcd 226.2298, found 226.2269.

To a stirred solution of (*R*)-(−)-*O*-acetylmandelic acid (4.97 g, 25.6 mmol) and DMAP (1.24 g, 10.15 mmol) in dry CH_2Cl_2 (46 mL) cooled at 0 °C was added dropwise a solution of homoallylic alcohol (4.6 g, 20.33 mmol) in CH_2Cl_2 (46 mL) followed by a solution of DCC (5.25 g, 25.45 mmol) in CH_2Cl_2 (40 mL) via cannula. The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature, and stirred for 1 h. The white precipitate was removed by filtration through a small pad of SiO_2 and the pad washed with CH_2Cl_2 (5 × 70 mL). The filtrate

was concentrated *in vacuo* to afford a residue, which after flash chromatography (hexane–benzene (1:9)) yielded 7.8 g (94%) of the mandelate esters **28** and **29** as colorless oils.

For **28**, $[\alpha]_D$ −41.84° (*c* 1.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.03–7.48 (m, 5H, Ph-H's), 6.01 (s, 1H, PhC*H*), 5.3–5.5 (m, 1H, C*H*=CH_2), 5.01–5.12 (m, 1H, C*H*OCO), 4.65–4.80 (m, 2H, CH=CH_2), 2.02 (bt, 2H, CH_2CH=), 1.73 (s, 1H, CH_3CO_2), 1.1–1.62 (brm, 24H, CH_2's), 0.91 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, C_6D_6): δ 169.91, 168.68, 134.71, 133.39, 129.14, 128.74, 128.21, 117.61, 75.32, 74.69, 38.78, 34.08, 32.32, 30.09, 30.01, 29.95, 29.81, 25.54, 23.1, 20.18, 14.36. IR (film): 3680, 3620, 3020, 2930, 2860, 2400, 1740, 1740, 1525, 1430, 1375, 1235, 1050, 930. MS (high resolution): *m/z* M^+ ($C_{25}H_{38}O_4$) calcd 402.2771, found 402.2794.

For **29**, $[\alpha]_D$ −71.66° (*c* 3.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.5 (m, 5H, Ph-*H*'s), 5.88 (s, 1H, PhC*H*), 5.66–5.82 (m, 1H, C*H*=CH_2), 5.03–5.12 (m, 2H, CH=CH_2), 4.86–4.98 (m, 1H, C*H*OCO), 2.29–2.38 (bt, 2H, CH_2CH=), 2.2 (s, 1H, CH_3CO_2), 1.0–1.48 (brm, 24H, CH_2's), 0.89 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.12, 168.44, 133.92, 133.08, 128.99, 128.51, 127.5, 117.8, 74.89, 74.77, 74.57, 38.38, 38.32, 33.13, 31.80, 29.49, 29.3, 29.24, 29.05, 24.58, 22.57, 20.65, 20.56, 14.01. IR (film): 3680, 3620, 3030, 2940, 2860, 2400, 1745, 1525, 1500, 1470, 1460, 1375, 1240, 1050, 925. MS (high resolution): *m/z* M^+ ($C_{25}H_{38}O_4$) calcd 402.2771, found 402.2765.

(*R*)-4-Hydroxypentadec-1-ene (31). To a stirred solution of **28** (3.15 g, 7.84 mmol) in MeOH (50 mL) was added dropwise 2 N KOH (19.6 mL, 39.21 mmol). The reaction mixture was heated at 75 °C for 6 h, cooled, and concentrated *in vacuo*. The residue was diluted with water (10 mL), acidified in cold 1 N HCl, and extracted with ether (3 × 100 mL). The combined organic extract washed with water (20 mL) and brine (20 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography (hexane-ethyl acetate (16:1 → 12:1)) afforded 1.7 g (quantitative) of **31** as a colorless oil, $[\alpha]_D$ +5.78° (*c* 2.89, $CHCl_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.79, 117.87, 70.50, 41.79, 36.66, 31.77, 29.52, 25.54, 13.98. MS: *m/z* 226.22 (M^+), 225.21 ($M^+ - 1$).

(*S*)-Hydroxypentadec-1-ene (30). To a stirred solution of **29** (0.511 g, 1.27 mmol) in MeOH (8 mL) was added dropwise 2 N KOH (3.18 mL, 6.35 mmol). The reaction mixture was heated at 75 °C for 6 h, cooled and concentrated *in vacuo*. The residue was diluted with water (1.5 mL), acidified in cold 1 N HCl, and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (3 mL) and brine (3 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash chromatography (hexane–ethyl acetate (16:1 → 12:1)) afforded 0.28 g (quantitative) of **30** as a colorless oil: $[\alpha]_D$ −6.63° (*c* 1.69, $CHCl_3$).

Synthesis of 31 from 30. To a stirred solution of **30** (0.254 g, 1.12 mmol) and Ph_3P (1.44 g, 5.5 mmol) in dry ether–toluene (3:1) was added *p*-nitrobenzoic acid (0.826 g, 4.94 mmol) followed by dropwise addition of DEAD (0.87 mL, 5.5 mmol) at room temperature. The reaction mixture was stirred for 30 min and the solvent removed *in vacuo* to afford a residue, which after flash chromatograhy (hexane–ethyl acetate (49:1 → 39:1)) yielded 0.392 g (93%) of the *p*-nitrobenzoate ester as a colorless oil, $[\alpha]_D$ +17.46° (*c* 2.63, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (bdd, 4H, Ph-*H*'s), 5.73-5.89 (m, 1H, C*H*=CH_2), 5.16-5.16 (m, 1H, C*H*OCO), 5.04–5.16 (m, 2H, CH=CH_2), 2.47 (bt, 2H, CH_2-CH=), 1.62–1.80 (m, 2H, CH_2), 1.20–1.45 (m, 20H, CH_2's), 0.88 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.19, 150.4, 136.03, 133.2, 130.5, 123.37, 117.97, 75.29, 38.49, 33.5, 31.78, 29.48, 29.41, 29.34, 29.3, 29.2, 25.2, 22.55, 13.95. IR (film): 2920, 2850, 1720, 1605, 1530, 1350, 1280, 1120, 1100, 1015. MS (high resolution): *m/z* $M^+ + H$ ($C_{22}H_{34}NO_4$) calcd 376.2489, found 376.2498. Treatment of the ester with K_2CO_3 in methanol afforded **31** in quantitative yield.

(*R*)-4-Hydroxypentadec-1-ene (31) via Asymmetric Allylation. To a stirred solution of (−)-*B*-methoxydiisopinocampheylborane (Ipc_2BOCH_3, 0.325 g, 1.03 mmol) in dry ether (1 mL) in a Schlenk tube cooled at 0 °C was added a 1 M solution of allylmagnesium bromide 0.99 mL, 0.99 mmol) dropwise via syringe. Following completion of addition, the reaction mixture was warmed to room temperature and stirred for 1 h, and the solvent was removed under vacuum. The residue was extracted with pentane (3 × 1 mL), and the salts were allowed to settle. The clear supernatant was transferred into another Schlenk tube using a double-tipped needle through a Kramer filter. Evaporation of pentane afforded pure *B*-allyldiisopinocampheylborane. Anhydrous ether (1.5 mL) was added, and the resulting stirred solution was cooled to −100 °C. A solution of lauraldehyde (0.23 mL, 1.03 mmol) in ether (1 mL) was added dropwise via syringe. The reaction mixture was stirred at −100 °C for 30 min, and methanol (0.1 mL) was added. The reaction mixture was then warmed to 0 °C and treated with 3 N NaOH (0.75 mL) and 30% H_2O_2 (0.31 mL). The reaction mixture was next refluxed at 50 °C for 1 h and then partitioned between ether (100 mL) and water (5 mL). The aqueous layer was extracted with ether (5 × 25 mL), the combined organic layers were washed once with water (2.5 mL) and brine (10 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash chromatography (hexane-ethyl acetate (24:1 → 19:1)) afforded 0.148 g (65%, ee 91%) of the homoallylic alcohol **31** as a colorless oil, $[\alpha]_D$ +5.52° (*c* 1.05, $CHCl_3$). The enantiomeric purity was determined by transformation to the mandelate ester with (*R*)-(−)-*O*-acetylmandelic acid (DCC, DMAP) and integration of the benzylic proton signal [^1H NMR (300 MHz, C_6D_6)] at δ 6.04, in comparison to the ester derived from racemic **31**. Asymmetric allylation at −78 °C gave **31** with ~82% ee and in 84% yield.

(*R*)-3-(Benzyloxy)tetradecan-1-al (11). To a stirred mixture of KH (2.94 g, 25.64 mmol) in dry THF (15 mL) at 0 °C was added dropwise a solution of 3.87 g (17.0 9 mmol) of enantiomerically pure **31**, obtained from **28** as described above, in THF (55 mL). The reaction mixture was stirred at 0 °C for 15 min, stirred at room temperature for 10 min, and finally recooled to 0 °C. DMF (10 mL) was added followed by dropwise addition of benzyl bromide (2.44 mL, 20.51 mmol), and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h and recooled to 0 °C. An ether–water mixture (9:1, 50 mL) was added dropwise, and the mixture was partitioned between ether (200 mL) and water (20 mL). The organic layer washed once with water (20 mL) and brine (30 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography (hexane-ethyl acetate (49:1 → 32:1)) afforded 5.23 g (97%) of product as a colorless oil: $[\alpha]_D$ +14.67° (*c*, 3.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27–7.43 (m, 5H, Ph-*H*'s), 5.83–5.98 (m, 1H, C*H*=CH_2), 5.06–5.18 (m, 2H, CH=CH_2), 4.60 (d, *J* = 11.72, 1H, OCH_APh), 4.52 (d, *J* = 11.72, 1H, OCH_BPh), 3.43–3.54 (m, 1H, C*H*OBn), 2.28–2.46 (m, 2H, CH_2CH=), 1.20–1.69 (br, 24H, CH_2's), 0.92 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.99, 135.08, 128.16, 127.59, 127.28, 116.58, 78.58, 70.82, 38.28, 33.77, 31.82, 29.64, 29.52, 29.24, 25.27, 22.57, 13.96. IR (film): 3070, 3038, 2940, 2860, 1645, 1500, 1470, 1460, 1350, 1100, 1070, 918. MS (high resolution): *m/z* M^+ ($C_{22}H_{36}O$) calcd 316.2768, found 316.2766.

Ozone was slowly bubbled into a stirred solution of the above olefin (2.08 g, 6.57 mmol) in MeOH–CH_2Cl_2 (1:1, 60 mL) cooled at −78 °C. Upon completion of the oxidation (ca. 60 min), Me_2S (9 mL) was added, followed by Et_3N (0.9 mL). The reaction mixture was slowly warmed to room temperature and stirred for 3 h and the solvent removed *in vacuo*. Flash chromatography (hexane–ethyl acetate (32:1 → 16:1)) afforded 1.92 (92%) of aldehyde **11** as a colorless oil, $[\alpha]_D$ −14.51° (*c* 2.92, $CHCl_3$) (lit.[9] $[\alpha]_D$ −13.8° (c, 1, $CHCl_3$)), ^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (dd, J_{d1} = 1.98, J_{d2} = 2.60, 1H, C*H*O), 7.33 (s, 5H, Ph-*H*'s), 4.55 (AB, J_{AB} = 11.46, Δν = 11.70, 2H, OCH_2Ph), 3.95 (m, 1H, C*H*OBn), 2.66 (dd, of AB, J_{d1} = 2.60, $J_{d1'}$ = 7.17, J_{d2} = 1.98, $J_{d\,2'}$ = 4.79, J_{AB} = 16.25, Δν = 31.79, 2H, CH_2CHO), 1.50–1.77 (m, 2H, CH_2-CHOBn), 1.27 (m, 18H, CH_2's), 0.89 (t, *J* = 6.83, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.37, 138.18, 128.25, 127.61, 127.53, 74.29, 71.08, 48.21, 34.14, 31.77, 29.48, 29.42, 29.19, 24.96, 22.54, 13.94. IR (film): 2920, 2840, 1720, 1460, 1460, 1450, 1090, 1060, 730, 690, 670 cm^{-1}. MS (high resolution): *m/z* M^+ ($C_{21}H_{34}O_2$) calcd 318.2560, found 318.2478.

(4*S*,6*R*)-6-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-1-heptadecene (23). To a stirred solution of enantiomerically pure aldehyde **11** (82.6 mg, 0.259 mmol) in dry CH_2Cl_2 (40 mL) cooled at −78 °C was added, dropwise via syringe, a 1.0 M solution of $TiCl_4$ (285 μL, 0.285 mmol) in CH_2Cl_2. The resulting light yellow suspension was stirred briefly for 10 min, followed by the addition of allyltrimethylsilane (45 μL, 0.285 mmol). The mixture was stirred for 30 min, and water (4 mL) was added. The mixture

was then partitioned between ether (50 mL) and water (4 mL). The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were washed once with water (5 mL) and brine (5 mL) and dried over $MgSO_4$. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate (16:1 → 9:1)) afforded 89 mg (98%) of homoallylic alcohol as a colorless oil, which was derivatized immediately.

The mixture of homoallylic alcohol (89 mg, 0.247 mmol), *tert*-butyldimethylsilyl chloride (46 mg, 0.308 mmol), and DMAP (30 mg, 0.247 mmol) in dry DMF (0.7 mL) was heated for overnight at 50–60 °C. The reaction mixture was diluted with ether (20 mL) and poured into water (5 mL). The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic layers were washed once with water (3 mL) and brine (5 mL) and dried over $MgSO_4$. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate (19:1)) afforded 116 mg (99%) of **23** as a colorless oil, $[\alpha]_D$ −28.46° (*c* 2.27, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.27–7.38 (m, 5H, Ph-*H*'s), 5.86 (m, 1H, vinyl-*H*), 5.07 (m, 2H, vinyl-*H*'s), 4.57 (d, *J* = 11.36, 1H, OCH_APh), 4.45 (d, *J* = 11.36, 1H, OCH_BPh), 3.99 (m, 1H, C*H*OBn), 3.61 (m, 1H, C*H*OSi), 2.27 (m, 2H, $CH_2CH{=}CH_2$), 1.51–1.78 (m, 4H, $OCCH_AH_BCO$ and CH_2CO), 1.29 (m, 18H, CH_2's), 0.92 [s, 9H, $C(CH_3)_3$], 0.90 (t-like, 3H, CH_3), 0.09 (s, 3H, CH_3), 0.07 (S, 3H, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 139.07, 134.73, 128.17, 127.42, 127.21, 116.85, 76.06, 70.10, 68.90, 42.58, 41.85, 33.74, 31.83, 29.74, 29.55, 29.27, 25.83, 25.60, 24.82, 22.60, 17.98, 14.03, −3.05, −4.10, −4.65. IR (film): 2960, 2940, 2860, 1470, 1260, 1090, 1070, 980, 840, 810, 780, 740, 700 cm^{-1}. MS (high resolution): *m/z* M^+ + H ($C_{30}H_{55}O_2Si$) calcd 475.3974, found 475.3920.

Methyl (3*S*,5*R*)-5-(Benzyloxy)-3-hydroxydecanoate (24). From 23. Ozone was carefully passed into a stirred solution of olefin (73.8 mg, 0.155 mmol) in MeOH–CH_2Cl_2 (1:1, 3 mL) cooled at −78 °C. Upon completion of the reaction (monitored by TLC) Me_2S (350 μL) was added, followed by Et_3N (35 μL), and the dry ice–acetone bath was removed. The mixture was slowly warmed to room temperature and stirred for 1 h. The solvent was removed *in vacuo*, and aldehyde was used as such for the next step. To the stirred solution of the aldehyde in 2-methyl 2-butene (1 mL) and *t*-BuOH (1 mL) cooled at 0 °C was added, dropwise *via* a pipet, a solution of sodium chlorite (159 mg) and $NaH_2PO_4{\cdot}H_2O$ (146 mg) in water (1 mL). The mixture was stirred for 30 min at 0 °C and then 3 h at room temperature. The reaction mixture was then partitioned between ether (50 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 15 mL), and the combined organic layers were washed once with water (5 mL) and brine (5 mL) and then dried over anhydrous $MgSO_4$. Removal of solvent under reduced pressure afforded crude acid as a colorless oil. To the solution of the above-obtained acid in CH_2Cl_2 (0.5 mL) was added a solution of 48% HF–CH_3CN (5:95, 0.5 mL). After 4 h, the reaction mixture was partitioned between ether (50 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic layers were washed with water (3 mL) and brine (5 mL) and dried over anhydrous $MgSO_4$. Removal of solvent *in vacuo* afforded crude β-hydroxy acid as a colorless oil, which was esterified by dropwise addition of diazomethane. Removal of solvent *in vacuo* followed by flash chromatography (hexane–ethyl acetate (5.7:1)) afforded 53.7 mg (88%) of **24** as a colorless oil, $[\alpha]_D$ −19.0° (*c* 2 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.38 (m, 5H, Ph-*H*'s), 4.60 (d, *J* = 11.26, 1H, OCH_APh), 4.51 (d, *J* = 11.36, 1H, OCH_BPh), 4.27–4.36 (m, 1H, C*H*OBn), 3.71 (s, 1H, CO_2CH_3), 3.68–3.80 (m, 1H, C*H*OH), 2.53–2.80 (br, 1H, O*H*), 2.48 (d, *J* = 6.27, 2H, $CH_2CO_2CH_3$), 1.46–1.82 (m, 4H, CH_2's), 1.27 (bs, 18H, CH_2's), 0.88 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.87, 138.31, 128.30, 127.80, 127.57, 76.34, 71.30, 65.06, 51.59, 41.54, 39.94, 33.52, 31.80, 29.68, 29.48, 29.24, 25.12, 22.58, 14.02. IR (film): 3480 (bs), 2920, 2850, 1740, 1450, 1435, 1200, 1170, 1090, 1070, 730, 700. MS (high resolution): *m/z* M^+ + H ($C_{24}H_{41}O_4$) calcd 393.3006, found 393.3041.

Phenyl (3*S*,5*R*)-5-(Benzyloxy)-3-hydroxydecanethioate (25). To a stirred solution of aldehyde **11** (610 mg, 1.92 mmol) in dry CH_2Cl_2 (24 mL) cooled at −78 °C was added freshly distilled TiC_4 (0.21 mL, 1.92 mmol) dropwise via syringe. The resulting light yellow suspension was stirred briefly for 10 min followed by the addition of the 1-(*tert*-butyldimethylsiloxy)-1-(phenylthio)ethene (0.591 mL, 2.1 mmol). The reaction mixture was stirred for 45 min at −78 °C, water (30 mL) was added, and the mixture was partitioned between ether (150 mL) and water (10 mL). The aqueous layer was extracted with ether (3 × 40 mL), and the combined organic layers were washed once with water (10 mL) and brine (10 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography (hexane–ethyl acetate (7:1 → 4.7:1)) afforded the minor diastereomeric thioester (29 mg) and **25** (606 mg, 79% based on recovered starting material (69 mg) as colorless oils.

For **25** $[\alpha]_D$ −14.28° (*c* 2.97, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 5H, SPh-*H*'s), 7.27–7.36 (m, 5H, Ph-*H*'s), 4.60 (d, *J* = 11.25, 1H, OCH_APh), 4.50 (d, *J* = 11.25, 1H, OCH_BPh), 4.34–4.46 (m, 1H, C*H*OBn), 3.68–3.80 (m, 1H, C*H*OH), 3.23 (d, *J* = 3.66, 1H, O*H*), 2.86 (dd, J_1 = 7.14, J_2 = 15.75, $CH_AC(=O)$SPh), 2.80 (dd, J_1 = 5.20, J_2 = 15.68, $CH_BC(=O)$SPh), 1.45–1.80 (m, 4H, CH_2's), 1.26 (bs, 18H, CH_2's), 0.88 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.04, 138.18, 134.36, 129.43, 129.11, 128.34, 127.84, 127.62, 127.17, 76.24, 71.23, 65.67, 50.56, 39.72, 39.39, 31.79, 29.65, 29.46, 29.23, 25.09, 22.57, 14.02. IR (film): 3460 (bs), 2940, 2860, 1710, 1480, 1470, 1460, 1440, 1090, 1070, 1030, 750, 700, 690. MS (high resolution): *m/z* M^+ + H ($C_{29}H_{43}O_3S$) calcd 471.2935, found 471.2913. For the minor diastereomer, $[\alpha]_D$ −36.07° (*c* 1.68, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 5H, SPh-*H*'s), 7.24–7.40 (m, 5H, Ph-*H*'s), 4.63 (d, *J* = 11.17, 1H, OCH_APh), 4.44 (d, *J* = 11.35, 1H, OCH_BPh), 4.30 (m, 1H, C*H*OBn), 3.77 (bs, 1H, O*H*), 3.70 (m, 1H, C*H*OH), 2.87 (dd, J_1 = 7.15, J_2 = 15.38, $CH_AC(=O)$SPh), 2.76 (dd, J_1 = 5.20, J_2 = 15.45, $CH_BC(=O)$SPh), 1.52–1.86 (m, 4H, CH_2's), 1.27 (bs, 18H, CH_2's), 0.89 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.38, 137.83, 134.35, 129.39, 129.09, 128.42, 127.79, 127.71, 127.35, 78.89, 77.10, 70.47, 68.12, 50.61, 40.13, 33.15, 31.81, 29.72, 29.55, 29.52, 29.49, 29.24, 24.48, 22.59, 14.03 IR (film): 3460 (bs), 3020, 2930, 2860, 2400, 1700, 1520, 1425, 1220, 1105, 1050, 930. MS (high resolution): *m/z* M^+ + H ($C_{29}H_{43}O_3S$) calcd 471.2935, found 471.2936.

Methyl (3*S*,5*R*)-5-(Benzyloxy)-3-hydroxydecanoate (24). From 25. To a stirred solution of thioester **25** (0.96 g, 2.04 mmol) in MeOH–CH_2Cl_2 (1:1, 20 mL) at room temperature was added CF_3SO_3Ag (1.57 g, 6.12 mmol). The resulting mixture was stirred for 2 h and diluted with ether (100 mL). The white precipitate was removed by filtration through a small pad of SiO_2, and the pad was washed with ether (3 × 50 mL). The filtrate was concentrated *in vacuo* to afford a colorless oily residue, which after flash chromatography (hexane–ethyl acetate (6:1 → 4.5:1), yielded 0.781 g (97%) of methyl ester **24** as a colorless oil, $[\alpha]_D$ −19.02° (*c*, 2.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.38 (m, 5H, Ph-*H*'s), 4.60 (d, *J* = 11.26, 1H, OCH_APh), 4.51 (d, *J* = 11.36, 1H, OCH_BPh), 4.27–4.36 (m, 1H, C*H*OBn), 3.71 (s, 1H, CO_2CH_3), 3.68–3.80 (m, 1H, C*H*OH), 2.53–2.80 (br, 1H, O*H*), 2.48 (d, *J* = 6.27, 2H, $CH_2CO_2CH_3$), 1.46–1.82 (m, 4H, CH_2's), 0.88 (t-like, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.87, 138.31, 128.30, 127.57, 76.34, 71.30, 65.06, 51.59, 41.54, 39.94, 33.52, 31.80, 29.68, 29.48, 29.24, 25.12, 22.58, 14.02. IR (film): 3480 (bs), 2920, 2850, 1740, 1450, 1435, 1200, 1170, 1090, 1070, 730, 700. MS (high resolution): *m/z* M^+ + H ($C_{24}H_{41}O_4$) calcd 393.3006, found 393.3041.

Methyl (2*S*,3*S*,5*R*)-5-(Benzyloxy)-2-hexyl-3-hydroxyhexadecanoate (32). To a stirred solution (~50 °C) of 2.9 mmol of LDA in 2.0 mL of THF (2.1 mL of 1.4 M MeLi in ether and 0.41 mL of diisopropylamine) was quickly added a solution of methyl ester **24** (0.474 g, 1.21 mmol) in THF (4.5 mL). The reaction mixture was stirred at −50 °C for 40 min, warmed to −30 °C, stirred at −30 °C for 40 min, and finally recooled to −50 °C. *n*-Hexyl iodide (0.534 mL, 3.62 mmol) in HMPA (0.6 mL) was then added dropwise. The resulting mixture was stirred at −50 °C for 1 h, warmed to −20 °C, and stirred at −20 °C for 1 h. *n*-Hexyl iodide (0.18 mL, 1.21 mmol) was added and the mixture stirred further at −20 °C for 1 h, warmed to 0 °C, and stirred at 0 °C for 1 h. The yellow reaction mixture was diluted with ether (75 mL) and poured into saturated aqueous NH_4Cl (40 mL). The aqueous layer was extracted with ether (3 × 50 mL), the combined organic layers were washed once with water (10 mL) and brine (15 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash chromatography (hexane–ethyl acetate (16:1 →

7:1)) afforded the minor diastereomeric hydroxy ester (9.8 mg) and **32** (0.396 g, 85% based on recovered **24**, 0.09 g) as a colorless oils.

For **32**, $[\alpha]_D$ −22.37 (*c* 2.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.38 (m, 5H, Ph-*H*'s), 4.59 (d, *J* = 11.39, 1H, OC*H*APh), 4.51 (d, *J* = 11.36, 1H, OCH_BPh), 4.00 (bs, 1H, C*H*OBn), 3.71 (s, 1H, CO_2CH_3), 3.66–3.78 (m, 1H, C*H*OH), 3.13 (bs, O*H*), 2.36–2.47 (m, 1H, C*H*CO_2CH_3), 1.41–1.74 (m, 4H, CH_2's), 1.26 (m, 28H, CH_2's), 0.76–0.93 (m, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.54, 137.98, 127.98, 127.48, 127.25, 76.79, 76.30, 75.84, 71.02, 69.00, 51.36, 51.11, 38.16, 33.16, 31.50, 31.20, 29.36, 29.22, 29.18, 28.94, 28.81, 28.74, 26.96, 24.91, 22.28, 22.14, 13.72, 13.64. IR (film): 3500, 2920, 2850, 1740, 1715, 1465, 1450, 1375, 1195, 1160, 1090, 1065, 730, 695. MS (high resolution): *m/z* M^+ + H ($C_{30}H_{53}O_4$) calcd 477.3946, found 477.3893.

For the minor diastereomer, $[\alpha]_D$ −15.62° (*c* 1.21, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.24-7.40 (m, 5H, Ph-*H*'s), 4.58 (d, *J* = 11.53, 1H, OCH_APh), 4.50 (d, *J* = 11.49, 1H, OCH_BPh), 4.03 (m, 1H, C*H*OBn), 3.69 (s, 1H, CO_2CH_3), 3.64–3.80 (m, 1H, C*H*OH), 3.30 (d, 1H, O*H*), 2.45 (dd, J_1 = 6.7, J_2 = 14.1, 1H, C*H*CO_2CH_3), 1.43–1.80 (m, 4H, CH_2's), 1.26 (m, 28H, CH_2's), 0.82–0.94 (m, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.46, 138.17, 128.32, 127.77, 127.61, 77.10, 71.11, 69.15, 51.68, 51.39, 36.98, 33.24, 31.81, 31.55, 29.64, 29.55, 29.53, 29.49, 29.25, 29.13, 27.98, 27.52, 25.27, 22.59, 22.47, 14.03, 13.96. IR (film): 3480, 3030, 2940, 2860, 2400, 1730, 1520, 1435, 1220, 1050, 925. MS (high resolution): *m/z* M^+ + H ($C_{30}H_{53}O_4$) calcd 477.3946, found 477.3934.

(2*S*,3*S*,5*R*)-5-(Benzyloxy)-2-hexyl-3-hydroxyhexadecanoic Acid (18). To a stirred solution of hydroxy ester **32** (40 mg, 0.0839 mmol) in EtOH (0.96 mL) was added 1 N KOH (252 μL, 0.252 mmol). The reaction mixture was heated at 50 °C for 4 h, cooled, and concentrated *in vacuo*. The residue was diluted was water (0.7 mL), acidified in cold with 1 N HCl, and extracted with ethyl acetate (4 × 20 mL). The combined organic extract washed with water (2 mL) and brine (2 mL) and dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography ($CHCl_3$–EtOH (49:1 → 19:1)) afforded 38.5 mg (quantitative) of hydroxy acid **18** as a colorless oil, $[\alpha]_D$ −25.88° (*c* 1.53, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.44 (m, 5H, Ph-*H*'s), 4.59 (d, *J* = 11.4, 1H, OCH_APh), 4.52 (d, *J* = 11.5, 1H, OCH_BPh), 4.04–4.41 (m, 1H, C*H*OBn), 3.68–3.79 (m, 1H, C*H*OH), 2.32–2.43 (m, 1H, C*H*CO_2H), 1.44–1.94 (m, 4H, CH_2's), 1.26 (m, 28H, CH_2's), 0.72–0.95 (m, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, C_6D_6): δ 137.98, 128.34, 127.85, 127.68, 76.75, 71.32, 69.12, 51.65, 37.90, 33.30, 31.80, 31.50, 29.67, 29.53, 29.24, 29.09, 27.13, 25.27, 22.58, 22.49, 14.01, 13.94. IR (film): 3420 (bs), 2930, 2860, 1720, 1470, 1460, 1200, 1060, 900, 830, 730, 690. MS (high resolution): *m/z* M^+ ($C_{29}H_{50}O_4$) calcd 462.3711, found 462.3718.