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Asymmetric Synthesis of *anti*-Aldol Segments via a Nonaldol Route: Synthetic Applications to Statines and (−)-Tetrahydrolipstatin

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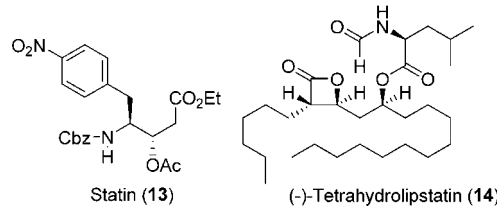

An asymmetric synthesis of *anti*-aldol segments via a nonaldol route is described. The strategy involves a highly diastereoselective synthesis of functionalized tetrahydrofuran derivatives from optically active 4-phenylbutyrolactone. Treatment of the tetrahydrofuran derivatives with a Lewis acid and acetic anhydride provided the corresponding ring-opened styrene derivatives. Oxidative cleavage of the styrene derivatives provided access to the *anti*-aldol segments. The utility of this methodology was demonstrated by the synthesis of statine derivatives and pancreatic lipase inhibitor, (−)-tetrahydrolipstatin.

Introduction

The *anti*-α-alkyl-*β*-hydroxycarbonyl motifs are prevalent in a wide variety of natural and unnatural bioactive organic molecules.[1] An asymmetric aldol addition of a suitable carbonyl derivative to an aldehyde stands out as the most straightforward approach to their synthesis. Consequently, a number of asymmetric methodologies have been developed over the years. Particularly, a number of chiral auxiliary-controlled highly diastereoselective *anti*-aldol additions have been reported.[2] However, issues related to limited reaction scope, functional group compatibility, ready availability of reagents and auxiliaries, and operation complexity continue to attract much interest for alternative approaches. One notable nonaldol process has been developed by Jung and co-workers.[3] Recently, in the context of the synthesis of cryptophycin 52, optically active phenylbutyrolactone **1** was efficiently converted to functionalized tetrahydrofuran derivative **2a** (Figure 1).[4] Both new stereogenic centers in **2a** were created based upon the chirality of 4-phenylbutyrolactone, which in turn was prepared on a multigram scale by using Corey−Bakshi−Shibata (CBS) reduction as the key step.[5] Opening of the tetrahydrofuran ring via an acyloxonium ion intermediate afforded functionalized *β*-hydroxy ester **3a**, which was converted to cryptophycin 52 (**4**). The overall process is practical and may provide convenient access to a variety of *γ*-substituted ester derivatives. Of particular interest, this functionalized hexenoate derivative can

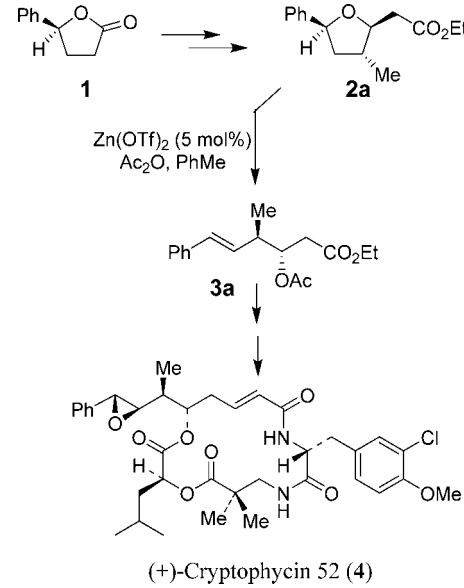

FIGURE 1. Nonaldol route to key *anti*-aldol precursor **3**.

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(1) (a) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (b) Hoffmann, R. W. *Angew Chem., Int. Ed.* **1987**, *26*, 489. (c) Heathcock, C. H. *Asymmetric Synthesis*. Morrison, J. D., Ed. Academic Press: New York, 1984; Vol. 3, p 111. (d) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1. (e) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, 317.

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SCHEME 1. Synthesis of *anti*-Aldol Segments

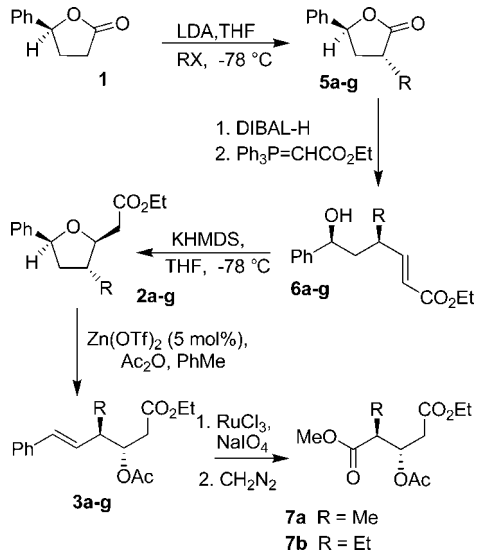
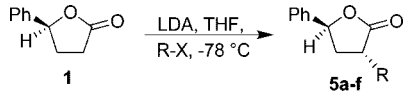


TABLE 1. The Alkylation of Lactone 1 with Various Electrophiles



entry	R	X	product	% yield	dr[a]
1	$-CH_3$	I	**5a**	75	16:1
2	$-CH_2CH_3$	I	**5b**	67	17:1
3	$-CH_2CN$	Br	**5c**	76	17:1
4	$-CH_2C_6H_5$	Br	**5d**	63	99:1
5	$-CH_2$-C_6H_5-*p*NO_2	Br	**5e**	71	99:1
6	$-CH_2CH_2CHCH_2$	Br	**5f**	32	20:1

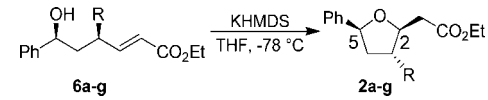
[a] The dr was determined by ^{1}H NMR of the crude reaction mixture.

serve as a useful *anti*-aldol surrogate since olefin cleavage would provide the *anti*-aldol product. Generation of such *anti*-aldol products would not be straightforward with the use of a direct aldol reaction. Encouraged by the good diastereoselectivity and overall efficiency of the route, we have now investigated the generality of this "nonaldol *anti*-aldol" strategy. We have applied this nonaldol strategy to the synthesis of statine derivatives which are widely utilized in the design and synthesis of aspartyl protease inhibitors. Also, we have demonstrated the utility of this method in the synthesis of (−)-tetrahydrolipstatin, a potent inhibitor of pancreatic lipase.

Results and Discussion

On the basis of our previous work, we decided to expand the scope and utility of functionalized tetrahydrofurans in synthesis.[4] In particular, we planned to study the opening of the tetrahydrofuran ring to unravel the cyclic stereochemistry into an acyclic form. As shown in Scheme 1, our synthesis utilized known lactone **1**, which was obtained in multigram quantities by employing CBS reduction as the key step.[5] Alkylation of lactone **1** with LDA, and a variety of electrophiles, provided substituted lactones **5a**−**f** in good diastereoselectivity (^{1}H NMR analysis) and excellent yields as shown in Table 1. Reduction of lactones **5a**−**f** and **1** by using DIBAL-H afforded the corresponding lactols. Wittig olefination of the resulting lactols gave rise to α,β-unsaturated esters **6a**−**g** with high *E*-selectivity as shown by ^{1}H NMR analysis. Treatment of the α,β-unsaturated esters **6a**−**g** with KHMDS in THF at −78 °C

TABLE 2. Synthesis of Substituted Tetrahydrofurans



entry	R	product	% yield	dr[a]
1	$-CH_3$	**2a**	70	11:1
2	$-CH_2CH_3$	**2b**	91	60:1
3	$-CH_2CN$	**2c**	82	11:1
4	$-CH_2$-C_6H_5	**2d**	91	49:1
5	$-CH_2$-C_6H_5-*p*NO_2	**2e**	70	14:1
6	$-CH_2CH_2CHCH_2$	**2f**	86	100:1
7	$-H$	**2g**	55	1:1

[a] The dr was determined by ^{1}H NMR of the crude reaction mixture.

furnished tetrahydrofuran derivatives **2a**−**g**. As shown in Table 2, these tetrahydrofuran derivatives were formed in excellent yield and diastereoselectivity.

Having made the requisite tetrahydrofurans **2a**−**g**, we then explored the key ring-opening reaction. Previously, we have carried out a ring-opening reaction of the methyl-substituted derivative **2a** by using a catalytic amount (6 mol %) of $ZnCl_2$ in the presence of acetic anhydride.[4,6] However, these conditions were not optimal for tetrahydrofuran derivatives containing electron-rich substituents at C-3. After surveying a number of Lewis acids, we found that a catalytic amount of $Zn(OTf)_2$ provided the best results. Thus, exposure of furans **2a**−**g** to $Zn(OTf)_2$ (5 mol %) and acetic anhydride in refluxing toluene gave rise to the *anti*-aldol precursors **3a**−**g** as shown in Table 3.

Initially, we explored the ring-opening reaction of unsubstituted tetrahydrofuran **2g** (R = H), which proceeded smoothly in the presence of a catalytic amount (5 mol %) of $Zn(OTf)_2$

(2) (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron.* **1984**, *40*, 2309. (b) Helmchen, G.; Leikauf, U.; Taufer-Knopfel, I. *Angew. Chem., Int. Ed.* **1985**, *24*, 874. (c) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (d) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (e) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (f) Meyers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672. (g) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (h) Braun, M.; Sacha, H. *Angew. Chem., Int. Ed.* **1991**, *30*, 1318. (i) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321. (j) Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1790. (k) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (l) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527. (m) Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171. (n) Kurosu, M.; Lorca, M. *J. Org. Chem.* **2001**, *66*, 1209. (o) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (p) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405. (q) Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2003**, *5*, 1063. (r) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591. (s) Fanjul, S.; Hulme, A. N.; White, J. W. *Org. Lett.* **2006**, *8*, 4219. (t) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899.

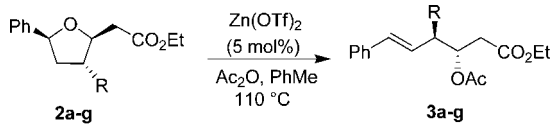
(3) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307. (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343. (g) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (h) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719. (i) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (j) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169. (k) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J. M. *Org. Lett.* **2003**, *5*, 3159. (l) Jung, M. E.; van den Heuvel, A.; Leach, A. G.; Houk, K. N. *Org. Lett.* **2003**, *5*, 3375. (m) Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4705. (n) Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543. (o) Jung, M. E.; Zhang, T. *Org. Lett.* **2008**, *10*, 137. (p) Jung, M. E.; Yoo, D. *Tetrahedron Lett.* **2008**, *49*, 816. (q) Jung, M. E.; Allen, D. A. *Org. Lett.* **2008**, *10*, 2039.

(4) Ghosh, A. K.; Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823.

(5) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(6) For the zinc-catalyzed ring expansion reaction see: (a) Hori, N.; Nagasawa, K.; Shimizu, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2145. (b) Nakata, T.; Nomura, S.; Matsukura, H. *Tetrahedron Lett.* **1996**, *37*, 213.

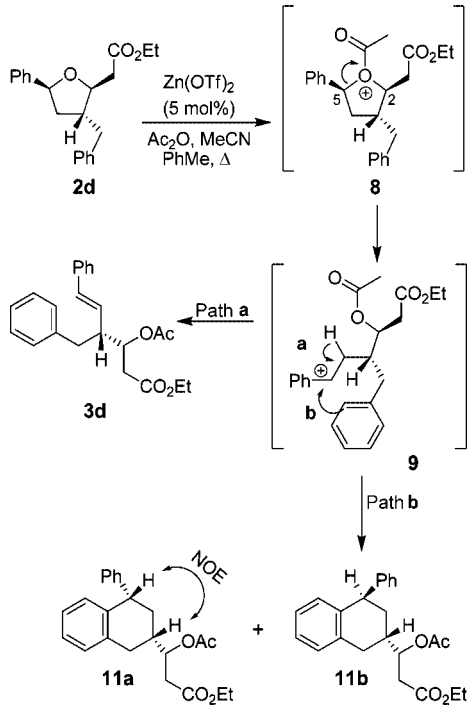
TABLE 3. Synthesis of Substituted β-Acetoxy Ester



entry	R	product	% yield
1	$-CH_3$	**3a**	76
2	$-CH_2CH_3$	**3b**	60
3	$-CH_2CN$	**3c**	53
4	$-CH_2$-C_6H_5[a]	**3d**	
5	$-CH_2$-C_6H_5-pNO_2	**3e**	90
6	$-CH_2CH_2CHCH_2$	**3f**	86
7	$-H$	**3g**	78

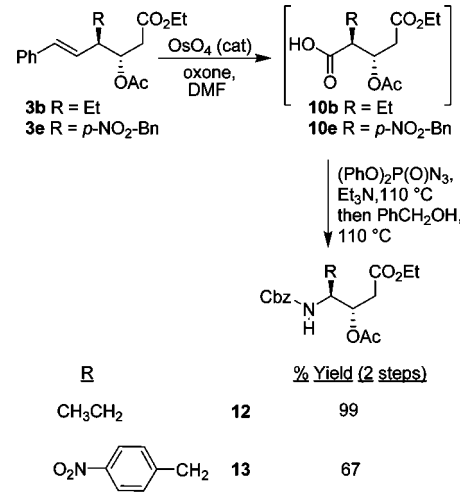
[a] See Scheme 2 for benzyl example.

SCHEME 2. Lewis Acid Catalyzed Ring-Opening of Benzyl Derivative 2d



and excess acetic anhydride to furnish the styrene **3g** in 78% yield. The reactions with methyl- and ethyl-substituted derivatives **2a** and **2b** also gave the respective styrene derivatives **3a** and **3b** in good yield (Table 3, entries 1 and 2). The ring-opening reaction of nitrile-substituted derivative **2c** failed to furnish any appreciable amount of the corresponding styrene derivative, probably due to the strong coordination of the nitrile group with $Zn(OTf)_2$. When the reaction was carried out in the presence of 3 equiv of $Zn(OTf)_2$, the desired styrene derivative **3c** was obtained in 53% yield. We then explored the ring-opening reaction with benzyl- and allyl-substituted tetrahydrofurans. The ring-opening reaction of the allyl-substituted tetrahydrofuran provided a complex mixture of products due to cation−olefin cyclization. The ring-opening reaction with homoallyl derivative **2f** (Table 3, entry 6) proceeded smoothly to afford styrene derivative **3f** in 86% yield. Our attempts to open **2d** with $Zn(OTf)_2$ under a variety of reaction conditions provided a complex mixture of opened ring products as well as substituted tetraline derivatives. As shown in Scheme 2, exposure of **2d** to 5 mol % of $Zn(OTf)_2$ resulted in a 1:4 mixture of styrene

SCHEME 3. Oxidative Cleavage and Synthesis of Statines



derivative **3d** with a diastereomeric mixture (3:1) of tetraline derivatives **11a** and **11b**. This mixture was separated by HPLC and the identity of products **11a** and **11b** was confirmed by extensive NMR studies.

The rationale for the ring-opening reaction and the formation of tetraline derivatives **11a** and **11b** is shown in Scheme 2. Activation of acetic anhydride by $Zn(OTf)_2$ leads to the formation of acyloxonium ion **8**. The ring-opening by cleavage of the C−O bond at C-5 would give rise to a more stable benzylic carbonium ion **9**. Cleavage of the C−O bond at C-2, on the other hand, would provide a less stable carbonium ion. Also, elimination of an α-proton of the ester followed by cleavage of the C−O bond may lead to the formation of an α,β-unsaturated ester derivative. However, no product corresponding to the cleavage of the C−O bond at C-2 was isolated. The formation of products **3d**, **11a**, and **11b** can be rationalized through the formation of benzylic carbonium ion **9**. The loss of a proton from **9** (path a) presumably resulted in the styrene derivative **3d**. The tetraline derivatives **11a** and **11b** were formed due to a competing intramolecular trapping of the benzylic carbonium ion intermediate **9** as shown in path b. The observed ratio of tetralines **11a** and **11b** can be rationalized on the basis of proposed transition states **TS-11a** and **TS-11b** shown in Figure 2. The transition state **TS-11a** is preferred over **TS-11b** because of the developing 1,3-diaxial interaction in **TS-11b**.

Upon the basis of this insight, we speculated that an electron-withdrawing group on the aromatic ring would slow down the

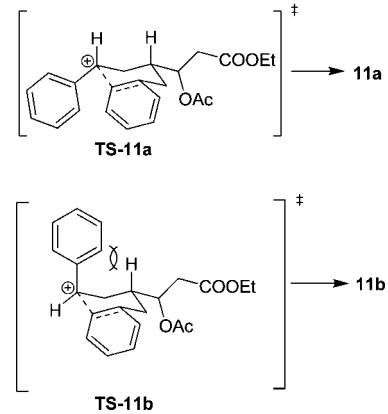
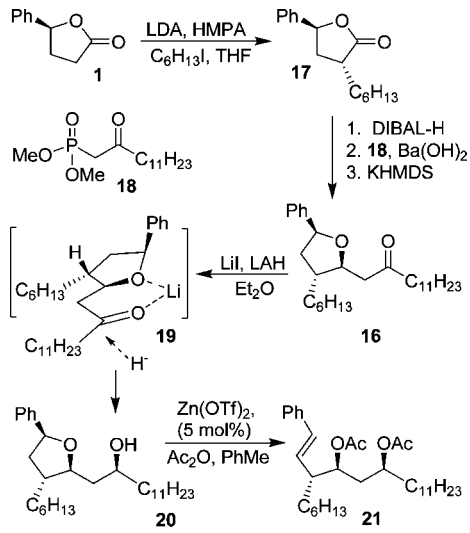


FIGURE 2. Proposed transition state for the intramolecular trapping of the benzylic carbonium ion.

SCHEME 4. Synthesis of Styrene Derivative 21



competing intramolecular trapping of the benzylic carbonium ion and would favor the formation of the desired styrene opening product through pathway a in Scheme 2. Indeed, Lewis acid-catalyzed reaction with *p*-NO_2 benzyl derivative **2e** furnished styrene derivative **3e** in 90% yield.

Various styrene derivatives resulting from the Lewis acid-catalyzed ring opening are suitable precursors of the *anti*-aldol segments. As shown in Scheme 1, oxidative cleavage of styrenes **3a** and **3b** with $RuCl_3/NaIO_4$ gave rise to the corresponding acids which were subsequently converted to the methyl esters **7a** and **7b** by treatment with diazomethane. However, better yields for the cleavage of styrenes were obtained by using OsO_4 and oxone in DMF.[7] Accordingly, styrenes **3b** and **3e** were converted to their respective acids **10b** and **10e** and then subjected to Curtius rearrangement.[8] The resulting acids without further purification were exposed to 2.2 equiv of diphenyl phosphorazidate and 2.2 equiv of triethylamine in toluene at reflux. Benzyl alcohol was added and the resulting mixture was heated at reflux for 12 h to provide Cbz derivatives **12** and **13** in 99% and 67% yields, respectively, over two steps (Scheme 4). These statine derivatives have been extensively utilized in the design of aspartyl protease inhibitors, particularly for renin and HIV-1 protease inhibitors.[9−11] The present methodology will provide access to substituted statine derivatives in optically active form.

We have utilized this methodology in the total synthesis of (−)-tetrahydrolipstatin (**14**). This natural product was isolated from *Streptomyces toxytricini* in 1987, and was approved by

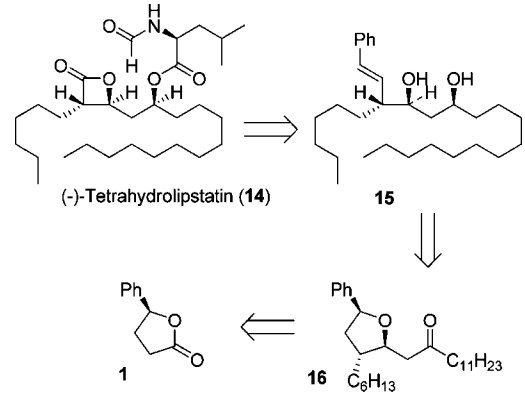


FIGURE 3. Retrosynthetic analysis for (−)-tetrahydrolipstatin.

the FDA under the trade name Orlistat in 2006, for the treatment of obesity.[12] The β-lactone moiety present in Orlistat inhibits gastric and pancreatic lipases, thus slowing the hydrolysis of triglycerides into free fatty acids and reducing their absorption in the gut.[13] Futhermore, tetrahydrolipstatin was recently shown to be a potent fatty acid synthase (FAS) inhibitor. FAS is an enzyme responsible for the synthesis of fatty acids in many human carcinomas and is required for tumor cell survival, making FAS inhibitor a promising drug for the treatment of cancer.[14] Tetrahydrolipstatin and its analogues have been of great interest in the past years, as they have shown many interesting biological activities. This has provided immense interest in the chemistry and biology of tetrahydrolipstatin.[15]

As shown in Figure 3, the structural element of the β-lactone functionality can be derived from the styrene derivative **15** by oxidative cleavage to provide the *anti*-aldol unit with appropriate stereochemistry. Styrene derivative **15** can be obtained from the tetrahydrofuran derivative **16** by a stereoselective reduction followed by a Lewis acid-catalyzed, acyloxonium ion-mediated ring-opening reaction. Stereochemically defined tetrahydrofuran derivative **16** would be derived from optically active lactone **1** by the sequence of reaction steps described above.

The synthesis of styrene **21** is shown in Scheme 4. Alkylation of lactone **1** with iodohexane using LDA in the presence of

(7) Travis, R. B.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824.

(8) Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1996**, *61*, 6175.

(9) (a) Baxter, E. W.; Reitz, A. B. *Annu. Rep. Med. Chem.* **2005**, *40*, 35. (b) Baeck, M.; Nyhlen, J.; Kvarnstroem, I.; Appelgren, S.; Borkakoti, N.; Jansson, K.; Lindberg, J.; Nystroem, S.; Hallberg, A.; Rosenquist, A.; Samuelsson, B. *Bioorg. Med. Chem.* **2008**, *16*, 9471. (c) Barazza, A.; Gotz, M.; Cadamuro, S. A.; Goettig, P.; Willem, M.; Steuber, H.; Kohler, T.; Jestel, A.; Reinemer, P.; Renner, C.; Bode, W.; Moroder, L. *ChemBioChem.* **2007**, *8*, 2078.

(10) (a) Billich, A.; Fricker, G.; Mueller, I.; Donatsch, P.; Ettmayer, P.; Gstach, H.; Lehr, P.; Peichl, P.; Scholz, D.; Rosenwirth, B. *Antimicrob. Agents Chemother.* **1995**, *39*, 1406. (b) Sakurai, M.; Sugano, M.; Handa, H.; Komai, T.; Yagi, R.; Nishigaki, T.; Yabe, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1369.

(11) (a) Jones, M. D.; Sueiras-Diaz, J.; Szelke, M.; Leckie, B. J.; Beattie, S. R.; Morton, J.; Neidle, S.; Kuroda, R. *J. Pept. Res.* **1997**, *50*, 109. (b) Hom, R. K.; Fang, L. Y.; Mamo, S.; Tung, J. S.; Guinn, A. C.; Walker, D. E.; Davis, D. L.; Gailunas, A. F.; Thorsett, E. D.; Sinha, S.; Knops, J. E.; Jewett, N. E.; Anderson, J. P.; Varghese, J. *J. Med. Chem.* **2003**, *46*, 1799.

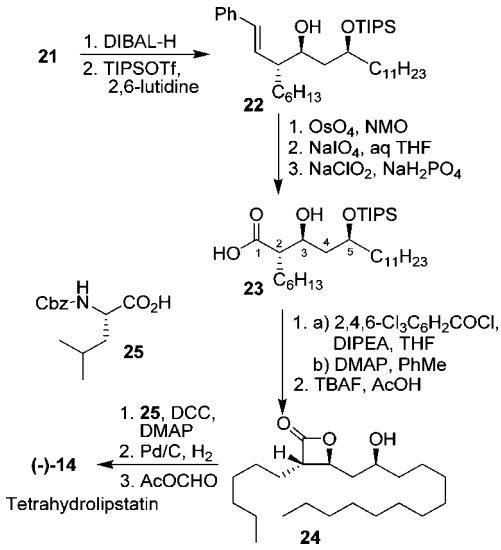
(12) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081.

(13) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadel, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086.

(14) (a) Richardson, R. D.; Yatsandra Oyola, G.; Zancanella, M.; Knowles, L. M.; Cieplak, P.; Romo, D.; Jeffrey, W.; Smith, J. W. *J. Med. Chem.* **2008**, *51*, 5285. (b) Ortar, G.; Bisogno, T.; Ligresti, A.; Morera, E.; Nalli, M.; Di Marzo, V. *J. Med. Chem.* **2008**, *51*, 6970, and references cited therein.

(15) (a) Kumaraswamy, G.; Markondaiah, B. *Tetraherdon Lett.* **2008**, *49*, 327. (b) Yadav, J. S.; Rao, K. V.; Prasad, A. R. *Synthesis* **2006**, 3888. (c) Polkowska, J.; Lukaszewicz, E.; Kiegiel, J.; Jurczak, J. *Tetrahedron Lett.* **2004**, *45*, 3873. (d) Yadav, J. S.; Vishweahwar Rao, K.; Sridhar Reddy, M.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4393. (e) Yadav, J.; Sridhar Reddy, M.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995. (f) Thadani, A. N.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 8051. (g) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Aust. J. Chem.* **2003**, *56*, 795. (h) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Tetrahedron Lett.* **2003**, *44*, 2869. (i) Ghosh, A. K.; Fidanze, S. *Org. Lett.* **2000**, *2*, 2405. (j) Dirat, O.; Kouklovsky, C.; Langlois, Y. *Org. Lett.* **1999**, *1*, 753. (k) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743. (l) Paterson, I.; Doughty, V. A. *Tetrahedron Lett.* **1999**, *40*, 393. (m) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1.* **1998**, 2679. (n) Giese, B.; Roth, M. J. *J. Braz. Chem. Soc.* **1996**, *7*, 243. (o) Pommier, A.; Pons, J. M.; Kocienski, P. J.; Wong, L. *Synthesis* **1994**, 1294. (p) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768. (q) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 781. (r) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714. (s) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1990**, *31*, 3645. (t) Pons, J.-M.; Kocienski, P. *Tetrahedron Lett.* **1989**, *30*, 1833. (u) Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218. (v) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412. (w) Barbier, P.; Schneider, F. *Helv. Chim. Acta* **1987**, *70*, 196.

SCHEME 5. Synthesis of (−)-Tetrahydrolipstatin 14



HMPA furnished the requisite lactone **17** in 84% yield with an excellent diastereomeric ratio (99:1 by ^{1}H NMR). DIBAL-H reduction of lactone **17** afforded the corresponding lactol in quantitative yield. A Horner−Wadsworth−Emmons reaction of the resulting lactol with phosphonate **18** in the presence of $Ba(OH)_2$ resulted in the formation of tetrahydrofuran derivative **16** in 83% yield with an excellent diastereomeric ratio (33:1 by ^{1}H NMR).[16,17]

At this point, our attempt at the ring-opening reaction of substituted tetrahydrofuran **16** was unsuccessful resulting in recovery of the starting material. This was possibly due to the sequestering of the Lewis acid through the formation of a stable six-membered complex with the ketone. We therefore planned to reduce the ketone stereoselectively and then carry out the ring-opening reaction. For the stereoselective reduction of the ketone, we elected to carry out a chelation-controlled reduction described by us previously.[18] Thus, reduction of ketone **16** with LAH in the presence of LiI resulted in the formation of alcohol **20** in 88% yield with excellent diastereoselectivity (17:1 *dr*). The high degree of diastereoselectivity can be explained by formation of a chelated rigid intermediate **19**. Hydride attack presumably proceeded from the less hindered bottom face, providing the *syn*-alcohol **20** selectively. Subsequent ring-opening reaction of alcohol **20** with 5 mol % of $Zn(OTf)_2$ and an excess of Ac_2O in refluxing toluene proceeded smoothly, providing diacetoxy styrene derivative **21** in 85% yield.

The completion of the total synthesis of tetrahydrolipstatin is shown in Scheme 5. Treatment of diacetate **21** with DIBAL-H at −78 °C gave the corresponding diol. Selective protection of this diol with TIPSOTf in the presence of 2,6-lutidine at −78 °C gave silyl ether **22**.[15i] Oxidative cleavage of the styrene moiety with OsO_4 and $NaIO_4$ resulted in an aldehyde that was oxidized to the acid by using sodium chlorite in 50% yield over three steps. For the formation of the β-lactone, we planned to utilize conditions reported by Adam and co-workers ($PhSO_2Cl$/pyridine, p-NO_2PhSO_2Cl/pyridine).[19] Our many attempts to form the β-lactone using acid **23** under the same conditions resulted in low yields (10−15%). Ortar and co-workers have reported a similar poor yield during their synthesis of tetrahydrolipstatin.[14b] Interestingly, in an earlier synthesis of (−)-tetrahydrolipstatin from our laboratory, we employed the above Adam's conditions to the C-5 epimer of acid **23** and obtained the corresponding C-5 epimeric β-lactone in 74% yield.[15i] Presumably, the steric hindrance of the TIPS-protected *syn*-diol **23** is responsible for the sluggish reaction and poor yield of the corresponding β-lactone under Adam's conditions. We then utilized Yamaguchi conditions and formed the desired β-lactone in 55% yield.[20]

Removal of the TIPS protecting group was achieved by using TBAF and acetic acid to give alcohol **24** in 62% yield. To complete the synthesis, we attempted the esterification of **24** with *N*-formyl leucine in the presence of DCC/DMAP. These conditions resulted in substantial epimerization of tetrahydrolipstatin (1:1 ratio). Reduction of DMAP concentration to 0.2 equiv suppressed the formation of the epimer to 1.4:1. To circumvent this problem, we carried out a three-step procedure as described by Uskokovic and co-workers.[21] This involved (1) esterification with Cbz-Leu-OH **25**, using DCC and DMAP,[22] (2) removal of the Cbz protection by hydrogenolysis, and (3) formylation of the amine by using the mixed anhydride at 23 °C to provide (−)-tetrahydrolipstatin (**14**, $[\alpha]^{20}_D$ −32 (*c* 0.05, $CHCl_3$); lit.[15v] ($[\alpha]^{23}_D$ −33 (*c* 0.36, $CHCl_3$)) in 48% yield over 2 steps. Spectral data (^{1}H and ^{13}C NMR) of synthetic (−)-tetrahydrolipstatin are identical with those reported for the natural product.

In conclusion, we have developed an alternative strategy to the formation of *anti*-aldol segments in optically active form via a nonaldol route. The strategy utilizes optically active 4-phenylbutyrolactone as the key starting material. Both stereogenic centers of the *anti*-aldol segments are derived from the 4-phenyltetrahydrofuran. The scope and utility of this methodology was demonstrated by the asymmetric synthesis of statine derivatives which are important scaffolds for aspartyl protease inhibitors. Furthermore, the methodology was utilized in the stereoselective synthesis of (−)-tetrahydrolipstatin. The key steps involved a highly diastereoselective chelation-controlled *syn*-reduction of a ketone, a catalytic asymmetric ring-opening reaction, and the formation of the β-lactone under Yamaguchi conditions. Further application of this methodology is in progress.

Experimental Section

General Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance ARX- 400 and DRX-500 spectrometers. IR spectra were recorded on a Mattason Genesis II FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. Anhydrous solvents were obtained as follows: THF and diethyl ether by distillation from sodium and benzophenone; pyridine and dichloromethane from CaH_2. All other solvents were reagent grade. All moisture-sensitive reactions were carried out in a flame-dried flask under argon atmosphere. Column

(16) (a) Grimes, K. D.; Lu, Y.-J.; Zhang, Y.-M.; Luna, V. A.; Hurdle, J. G.; Carson, E. I.; Qi, J.; Kudrimoti, S.; Rock, C. O.; Lee, R. E. *ChemMedChem.* **2008**, *3*, 1936. (b) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K. *J. Org. Chem.* **2007**, *72*, 6591–6594.

(17) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774.

(18) (a) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783. (b) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419. (c) Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423.

(19) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(21) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714.

(22) Frelek, J.; Fryszkowska, A.; Kwit, M.; Ostaszewski, R. *Tetrahedron: Asymmetry* **2006**, *17*, 2469.

chromatography was performed with Whatman 240−400 mesh silica gel under a low pressure of 3−5 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. HPLC data were collected using a system composed of an Agilent 1100 series degasser, quaternary pump, thermostatable column compartment, variable wavelength detector, and Agilent 1200 series auto sampler and fraction collector controlled by Chemstation software. All chromatographic reagents used were HPLC grade.

(3*R*,5*S*)-3-Methyl-5-phenyldihydrofuran-2(3*H*)-one (5a). To a stirring solution of THF (5 mL) and diisopropylamine (490 μL, 3.7 mmol) at 0 °C under argon was added *n*-BuLi (2.1 mL, 1.6 M solution in hexanes, 3.39 mmol) dropwise; the mixture was then stirred for 15 min and cooled to −78 °C. Then lactone **1** (500 mg, 3.08 mmol) was dissolved in 15 mL of THF and added dropwise over a 0.5 h period. The reaction mixture was stirred for an additional 0.5 h at −78 °C. Iodomethane (210 μL, 3.4 mmol) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature, then the aqueous layer was extracted with EtOAc (3×) and the organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The residue was chromatographed on silica gel (85:15 hexanes/EtOAc) to give **5a** (407 mg, 75% yield) as an oil; dr (16:1), $[\alpha]^{20}_D$ −19.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.18 (m, 5H), 5.55 (dd, *J* = 8, 5 Hz, 1H), 2.71 (m, 1H), 2.46−2.31 (m, 2H), 1.33 (d, *J* = 4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 139.8, 128.6, 128.0, 124.9, 78.2, 38.2, 33.5, 15.3; IR (NaCl) 3066, 1773, 1450, and 1171 cm^{-1}.

(3*R*,5*S*)-3-Ethyl-5-phenyldihydrofuran-2(3*H*)-one (5b). To a stirring solution of THF (5 mL) and diisopropylamine (450 μL, 3.39 mmol) at 0 °C under argon was added *n*-BuLi (2 mL, 1.6 M solution in hexanes, 3.24 mmol) dropwise, the mixture was stirred for 15 min, then DMPU (3 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. Lactone **1** (500 mg, 3.08 mmol) was dissolved in 15 mL of THF and added dropwise over a 0.5 h period. The reaction mixture was stirred for an additional 0.5 h at −78 °C. Then iodoethane (370 μL, 4.62 mmol) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The residue was chromatographed on silica gel (80:20 hexanes/EtOAc) to give **5b** (393 mg, 67% yield) as an oil; dr (17:1); $[\alpha]^{20}_D$ −28.5 (*c* 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 5.55 (t, *J* = 4 Hz, 1H), 2.64−2.56 (m, 1H), 2.45−2.34 (m, 2H), 1.95−1.87 (m, 1H), 1.64−1.55 (m, 1H), 1.03 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 139.9, 128.6, 128.1, 124.9, 78.5, 40.1, 35.9, 23.5, 11.6; IR (NaCl) 2955, 2872, 1773, 1453, and 1171 cm^{-1}; CI-HRMS (*m*/*z*) calcd for $C_{12}H_{14}O_2$ ($[M]^+$) 190.0994, found 190.0992.

2-((3*R*,5*S*)-2-Oxo-5-phenyltetrahydrofuran-3-yl)acetonitrile (5c). The title compound was prepared from **1** following the same procedure that was used for the synthesis of **5a**, using bromoacetonitrile. Purification by flash chromatography (80:20 hexanes/EtOAc) afforded **5c** as an oil (471 mg, 76% yield); dr (17:1); $[\alpha]^{20}_D$ +2.60 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 5H), 5.73 (dd, *J* = 7, 4 Hz, 1H), 3.04−2.97 (m, 1H), 2.87 (dd, *J* = 17, 5 Hz, 1H), 2.73−2.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 138.5, 128.9, 128.6, 124.6, 116.7, 78.3, 35.2, 35.2, 18.4; IR (NaCl) 3032, 2925, 2854, 2251, 1777, 1451, and 1171 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{12}H_{11}NO_2$ ($[M + H]^+$) 202.9888, found 202.0866.

(3*R*,5*S*)-3-Benzyl-5-phenyldihydrofuran-2(3*H*)-one (5d). The title compound was prepared from γ-lactone **1** following the same procedure that was used for the synthesis of **5a**, using benzyl bromide. Purification by flash chromatography (90:10, hexanes/EtOAc) afforded **5d** (116 mg, 63% yield) as an oil; dr (99:1); $[\alpha]^{20}_D$ +135.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 400 MHz) δ 7.38−7.16 (m, 10H), 5.39 (dd, *J* = 7.8, 4.7 Hz, 1H), 3.25 (dd, *J* = 13.6, 4.3 Hz, 1H), 3.02−2.95 (m, 1H), 2.90−2.85 (m, 1H), 2.50−2.43 (m, 1H), 2.31−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 139.6, 138.0, 128.8, 128.6, 128.6, 128.1, 126.8, 124.8, 78.6, 40.4, 36.1, 35.5; IR (NaCl) 3033, 2926, 1764, 1495, 1451, 1132, and 1011 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{17}H_{16}O_2$ ($[M]^+$) 252.1150, found 252.1147.

(3*S*,5*S*)-3-(4-Nitrophenyl)-5-phenyldihydrofuran-2(3*H*)-one (5e). The title compound was prepared from γ-lactone **1** following the same procedure that was used for the synthesis of **5a**, using *p*-nitrobenzyl bromide. Purification by flash chromatography (95:5 toluene/MeOH) afforded **5e** (917 mg, 71% yield) as an oil; dr (99:1); $[\alpha]^{20}_D$ +29.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8 Hz, 2H), 7.41−7.31 (m, 5H), 7.26−7.24 (m, 2H), 5.50 (dd, *J* = 12, 5 Hz, 1H), 3.32 (m, 1H), 3.04−2.95 (m, 2H), 2.48−2.41 (m, 1H), 2.35−2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 146.9, 145.7, 139.2, 129.8, 128.8, 128.3, 124.7, 123.9, 78.3, 39.7, 35.8, 35.4; IR (NaCl) 2998, 2885, 2837, 2362, 1776, 1602, 1516, and 1346 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{17}H_{15}NO_4$ ($[M]^+$) 297.1001, found 297.1004.

(3*R*,5*S*)-3-(But-3-enyl)-5-phenyldihydrofuran-2(3*H*)-one (5f). To a stirring solution of THF (5 mL) and diisopropylamine (485 μL, 3.71 mmol) at 0 °C under argon was added *n*-BuLi (2.2 mL, 1.6 M solution in hexanes, 3.54 mmol) dropwise; the mixture was stirred for 15 min, then HMPA (3 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. Then lactone **1** (546 mg, 3.37 mmol) was dissolved in 15 mL of THF and added dropwise over a 0.5 h period. The reaction mixture was stirred for another 0.5 h at −78 °C. Then a catalytic amount of TBAI (190 mg, 0.51 mmol) was added in one portion, and then 1-bromo-3-butene (380 μL, 3.71 mmol) was added dropwise; next the reaction mixture was stirred for 1 h at −78 °C and then warmed to 0 °C and stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The residue was chromatographed on silca gel (90:10 hexanes/EtOAc) to give **5f** (233 mg, 32% yield) as an oil; dr (20:1); $[\alpha]^{20}_D$ −11.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (m, 5H), 5.84−5.74 (m, 1H), 5.56 (t, *J* = 6 Hz, 1H), 5.08−4.99 (m, 2H), 2.71−2.63 (m, 1H) 2.41−2.38 (m, 2H), 2.25−2.13 (m, 2H), 2.05−1.96 (m, 1H), 1.68−1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 139.7, 136.9, 128.6, 128.1, 124.8, 115.7, 78.5, 38.0, 36.5, 31.2, 29.5; IR (NaCl) 2969, 1775, and 1167 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{14}H_{16}O_2$ ($[M]^+$) 216.1150, found 216.1152.

(*E*,*S*)-Ethyl 6-Hydroxy-6-phenylhex-2-enoate (6g). To a solution of **1** (307 mg, 1.89 mmol) in 15 mL of CH_2Cl_2 under argon at −78 °C was added DIBAL-H (2.3 mL, 1 M solution in CH_2Cl_2, 2.28 mmol) dropwise. The reaction was stirred for 0.5 h at −78 °C and then quenched with 2 mL of methanol then warmed to room temperature, 15 mL of K−Na tartrate was added, and once the emulsion had separated, the aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Without further purification the crude oil was dissolved in 20 mL of CH_2Cl_2 then Ph_3PCHCO_2Et (835 mg, 2.39 mmol) was added and the reaction mixture was refluxed for 12 h at 40 °C. The reaction mixture was then concentrated and chromatographed (90:10 hexanes/EtOAc) to give **6g** (393 mg, 89% yield over two steps) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 6.98−6.94 (m, 1H), 5.82 (d, *J* = 15 Hz, 1H), 4.70−4.66 (m, 1H), 4.18 (q, *J* = 7 Hz, 2H), 2.30−2.25 (m, 2H), 2.06 (s, 1H), 1.96−1.84 (m, 2H), 1.27 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 148.4, 144.1, 128.5, 127.7, 125.8, 121.6, 73.6, 60.1, 37.0, 28.4, 14.2; IR (NaCl) 3300, 2982, 1716, 1652, 1451, and 1193 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{14}H_{18}O_3$ ($[M]^+$) 234.1256, found 234.1255.

(4*R*,6*S*,*E*)-Ethyl 6-Hydroxy-4-methyl-6-phenylhex-2-enoate (6a). The title compound was prepared from γ-lactone **5a** following

the same procedure that was used for the synthesis of **6g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **6a** (502 mg, 94% yield over two steps) as a single diastereomer; $[\alpha]^{20}_D$ −21.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 5H), 6.86 (dd, J = 16, 8 Hz, 1H), 5.86 (d, J = 16 Hz, 1H), 4.64−4.61 (m, 1H), 4.18 (q, J = 7 Hz, 2H), 2.63−2.60 (m, 1H), 2.03 (s, 1H), 1.89−1.82 (m, 1H), 1.70−1.63 (m, 1H), 1.29 (t, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 153.4, 144.6, 128.5, 127.6, 125.6, 120.4, 72.1, 60.2, 45.3, 33.4, 20.1, 14.2; IR (NaCl) 3300, 2958, 1717, 1652, 1455, and 1272 cm^{-1}.

(4*R*,6*S*,*E*)-Ethyl 4-Ethyl-6-hydroxy-6-phenylhex-2-enoate (6b). The title compound was prepared from γ-lactone **5b** following the same procedure that was used for the synthesis of **6g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **6b** (482 mg, 89% yield over two steps) as a single diastereomer; $[\alpha]^{20}_D$ −6.6 (*c* 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 6.75 (dd, J = 16, 10 Hz, 1H), 5.88 (d, J = 16 Hz, 1H), 4.59−4.55 (m, 1H), 4.18 (q, J = 7 Hz, 2H), 2.49−2.44 (m, 1H), 2.25 (s, 1H), 1.92−1.85 (m, 1H), 1.63−1.56 (m, 1H), 1.51−1.46 (m, 1H), 1.41−1.36 (m, 3H), 1.30 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 152.3, 144.9, 128.4, 128.2, 127.4, 125.5, 122.1, 60.2, 43.6, 40.9, 27.7, 14.1, 11.5; IR (NaCl) 3136, 2961, 1719, 1649, 1452, and 1199 cm^{-1}; CI-HRMS (*m*/*z*) calcd for $C_{16}H_{22}O_3$ ($[M]^+$) 262.1569, found 262.1570.

(4*R*,6*S*,*E*)-Ethyl 4-(Cyanomethyl)-6-hydroxy-6-phenylhex-2-enoate (6c). The title compound was prepared from γ-lactone **5c** following the same procedure that was used for the synthesis of **6g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **6c** (110 mg, 83% yield over two steps) as a single diastereomer; $[\alpha]^{20}_D$ −25.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 6.81 (dd, J = 16, 9 Hz, 1H), 6.03 (d, J = 16 Hz, 1H), 4.65−4.62 (m, 1H), 4.21 (q, J = 7 Hz, 2H,), 3.03−2.97 (m, 1H), 2.52−2.49 (m, 2H), 2.19 (s, 1H), 2.03−1.95 (m, 1H), 1.81−1.74 (m, 1H), 1.31 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 146.7, 143.9, 128.6, 127.9, 125.5, 124.1, 117.5, 71.5, 60.6, 42.5, 35.8, 22.8, 14.1; IR (NaCl) 3146, 3053, 2249, 1712, 1657, 1451, 1306, and 1223 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{16}H_{19}NO_3$ ($[M]^+$) 273.1365, found 273.1370.

(4*R*,6*S*,*E*)-Ethyl 4-Benzyl-6-hydroxy-6-phenylhex-2-enoate (6d). The title compound was prepared from γ-lactone **5d** following the same procedure that was used for the synthesis of **6g**. Purification by flash chromatography (80:20 hexanes:EtOAc) afforded **6d** (944 mg, 84% yield over two steps) as a single diastereomer; oil; $[\alpha]^{20}_D$ +13.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.11 (m, 10H), 6.84 (dd, J = 15.5, 9.4 Hz, 1H), 5.79 (d, J = 15.7 Hz, 1H), 4.61 (dd, J = 10.3, 3.1 Hz, 1H), 4.21−4.14 (m, 2H), 2.96−2.87 (m, 1H), 2.75−2.72 (m, 2H), 1.99−1.87 (m, 2H), 1.69−1.62 (m, 1H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.3, 144.7, 138.9, 129.1, 128.4, 128.2, 127.5, 126.1, 125.5, 122.2, 71.7, 60.2, 43.1, 41.3, 40.8, 14.1; IR (NaCl) 3447, 3062, 1716, 1651, 1494, 1453, 1370, 1305, 1217, and 1030 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{21}H_{24}O_3$ ($[M]^+$) 324.1725, found 324.1728.

(4*R*,6*S*,*E*)-Ethyl 6-Hydroxy-4-(4-nitrobenzyl)-6-phenylhex-2-enoate (6e). The title compound was prepared from γ-lactone **5e** following the same procedure that was used for the synthesis of **6g**. Purification by flash chromatography (80:20 hexanes/EtOAc) afforded **6e** (531 mg, 96% yield over two steps) as a single diastereomer; $[\alpha]^{20}_D$ +21.04 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9 Hz, 2H), 7.34−7.24 (m, 7H), 6.76 (dd, J = 16, 10 Hz, 1H), 5.75 (d, J = 16 Hz, 1H), 4.62−4.59 (m, 1H), 4.18−4.12 (m, 2H), 2.99−2.94 (m, 1H), 2.89−2.84 (m, 1H), 2.79−2.74 (m, 1H), 2.20−2.19 (m, 1H), 1.96−1.89 (m, 1H), 1.69−1.63 (m, 1H), 1.26 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 149.9, 146.9, 146.4, 144.5, 129.8, 128.5, 127.7, 125.4, 123.5, 122.9, 71.5, 60.4, 43.3, 41.1, 40.7, 14.1; IR (NaCl) 2900, 1709, 1516, and 1345 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{21}H_{23}NO_5$ ($[M + H]^+$) 370.1654, found 370.1657.

(*R*,*E*)-Ethyl 4-((*S*)-2-Hydroxy-2-phenylethyl)octa-2,7-dienoate (6f). The title compound was prepared from γ-lactone **5f** following the same procedure that was used for the synthesis of **6g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **6f** (95 mg, quantitative yield over two steps) as a single diastereomer; $[\alpha]^{20}_D$ +1.6 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.23 (m, 5H), 6.74 (dd, J = 16, 10 Hz, 1H), 5.89 (d, J = 16 Hz, 1H), 5.81−5.71 (m, 1H), 5.01−4.90 (m, 2H), 4.59−4.55 (m, 1H), 4.18 (q, J = 7 Hz, 2H), 2.64−2.55 (m, 1H), 2.25 (s, 1H), 2.07−1.93 (m, 2H), 1.91−1.85 (m, 1H), 1.64−1.57 (m, 1H), 1.55−1.42 (m, 1H), 1.30 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 152.0, 144.9, 138.0, 128.4, 127.4, 125.5, 122.2, 114.8, 71.7, 60.3, 43.9, 38.8, 33.9, 31.2, 14.1; IR (NaCl) 3265, 2852, 1709, 1641, 1303, and 1161 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{18}H_{24}O_3$ ($[M]^+$) 287.1725, found 288.1722.

Ethyl 2-((5*S*)-5-Phenyltetrahydrofuran-2-yl)acetate (2g). To a stirred solution of KHMDS (4.0 mL, 0.5 M solution in toluene, 2.01 mmol) in THF (5 mL) was added **6g** (392 mg, 1.67 mmol) in THF (15 mL) at −78 °C dropwise over a 30 min period and the mixture was then stirred at −78 °C for an additional 1 h. Then the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (3×), then the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated and chromatographed (90:10 hexanes/EtOAc) to give **2g** as a mixture of diastereomers (216 mg, 55% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.22 (m, 10H), 5.04 (t, J = 7 Hz, 1H), 4.92 (t, J = 7 Hz, 1H), 4.65−4.59 (m, 1H), 4.51−4.44 (m, 1H), 4.21−4.14 (m, 4H), 2.81−2.71 (m, 2H), 2.62−2.52 (m, 2H), 2.42−2.09 (m, 4H), 1.95−1.72 (m, 4H), 1.28 (t, J = 7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 143.3, 142.8, 128.2, 128.2, 127.1, 125.6, 125.4, 81.1, 80.3, 75.9, 75.8, 60.4, 41.0, 40.9, 35.0, 34.2, 32.0, 31.1, 14.1; IR (NaCl) 2977, 1734, and 1188 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{14}H_{18}O_3$ ($[M]^+$) 234.1256, found 234.1254.

Ethyl 2-((2*S*,3*R*,5*S*)-3-Methyl-5-phenyltetrahydrofuran-2-yl)acetate (2a). The title compound was prepared from alcohol **6a** following the same procedure that was used for the synthesis of **2g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **2a** (354 mg, 70% yield) as an oil; dr (11:1); $[\alpha]^{20}_D$ +53.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.22 (m, 5H), 5.03 (t, J = 7 Hz, 1H), 4.22−4.16 (m, 2H), 4.05−4.00 (m, 1H), 2.72−2.61 (m, 2H), 2.09−1.99 (m, 3H), 1.29 (t, J = 7 Hz, 3H), 1.10 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 143.4, 128.1, 126.9, 125.1, 82.5, 79.3, 60.4, 42.6, 39.8, 38.1, 17.1, 14.1; IR (NaCl) 2961, 1736, 1029, and 699 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{15}H_{20}O_3Na$ ($[M + Na]^+$) 271.1310, found 271.1303.

Ethyl 2-((2*S*,3*R*,5*S*)-3-Ethyl-5-phenyltetrahydrofuran-2-yl)acetate (2b). The title compound was prepared from alcohol **6b** following the same procedure that was used for the synthesis of **2g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **2b** (379 mg, 91% yield) as an oil; dr (60:1); $[\alpha]^{20}_D$ −39.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.22 (m, 5H), 5.55 (t, J = 7 Hz, 1H), 4.23−4.15 (m, 2H), 4.14−4.10 (m, 1H), 2.72−2.62 (m, 2H), 2.10−2.00 (m, 2H), 1.96−1.87 (m, 1H), 1.61−1.53 (m, 1H), 1.44−1.33 (m, 1H), 1.29 (t, J = 7 Hz, 3H), 0.96 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 143.3, 128.0, 126.9, 125.5, 81.0, 79.6, 60.3, 45.5, 40.3, 40.3, 25.4, 14.0, 12.4; IR (NaCl) 3011, 1736, and 1274 cm^{-1}; CI-HRMS (*m*/*z*) calcd for $C_{16}H_{22}O_3$ ($[M]^+$) 262.1569, found 262.1568.

Ethyl 2-((2*S*,3*R*,5*S*)-3-(Cyanomethyl)-5-phenyltetrahydrofuran-2-yl)acetate (2c). The title compound was prepared from alcohol **6c** following the same procedure that was used for the synthesis of **2g**. Purification by flash chromatography (80:20 hexanes/EtOAc) afforded **2c** (62 mg, 82% yield) as an oil; dr (11:1); $[\alpha]^{20}_D$ −36.9 (*c* 3.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 5.02 (t, J = 7 Hz, 1H), 4.21−4.14 (m, 3H), 2.84−2.40 (m, 6H), 2.29−2.13 (m, 2H), 1.28 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 141.4, 128.3, 127.5, 125.5, 118.2, 79.8, 79.4, 60.7, 40.2, 39.9, 39.6, 20.4, 14.0; IR (NaCl) 2872,

2400, 1729, and 1240 cm^{-1}; EI-HRMS (*m/z*) calcd for $C_{16}H_{19}NO_3$ ($[M]^+$) 273.1365, found 273.1369.

Ethyl 2-((2*S*,3*R*,5*S*)-3-Benzyl-5-phenyltetrahydrofuran-2-yl)acetate (2d). The title compound was prepared from alcohol **6d** following the same procedure that was used for the synthesis of **2g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **2d** (435 mg, 91% yield) as an oil; dr (49:1); $[\alpha]^{20}_D$ −32.7 (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.20 (m, 10H) 5.08 (t, J = 7.2 Hz, 1H), 4.28−4.22 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.87 (dd, J = 13.7, 6.3 Hz, 1H), 2.76−2.62 (m, 2H), 2.53 (dd, J = 15.1, 4.9 Hz, 1H), 2.40−2.34 (m, 1H), 2.21−2.14 (m, 1H), 2.03−1.96 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 143.1, 139.8, 128.7, 128.4, 128.1,127.1, 126.2, 125.5, 81.0, 79.5, 60.5, 45.3, 40.3, 40.3, 38.8, 14.1; IR (NaCl) 3027, 2978, 2928, 1734, 1603, 1494, 1453, 1368, 1304, 1158, and 1029 cm^{-1}; ESI-HRMS (*m/z*) calcd for $C_{21}H_{24}O_3$ ($[M]^+$) 324.1725, found 324.1724.

Ethyl 2-((2*S*,3*R*,5*S*)-3-(4-Nitrobenzyl)-5-phenyltetrahydrofuran-2-yl)acetate (2e). The title compound was prepared from alcohol **6e** following the same procedure that was used for the synthesis of **2g**. Purification by flash chromatography (80:20 hexanes/EtOAc) afforded **2e** (344 mg, 70% yield) as an oil; dr (14:1); $[\alpha]^{20}_D$ −20.1 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8 Hz, 2H), 7.37−7.17 (m, 7H), 5.06 (t, J = 7 Hz, 1H), 4.24−4.13 (m, 3H), 3.01−2.96 (m, 1H), 2.82−2.77 (m,1H), 2.71−2.65 (m, 1H), 2.58−2.53 (m, 1H), 2.42−2.37 (m, 1H), 2.14−2.08 (m, 1H), 2.04−1.92 (m, 1H), 1.27 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 170.9, 147.7, 146.5, 142.5, 129.5, 128.2, 127.2, 125.4, 125.0, 123.7, 80.7, 79.4, 60.6, 44.9, 40.0, 38.6, 14.1; IR (NaCl) 2926, 1727, 1517, and 1346 cm^{-1}; EI-HRMS (*m/z*) calcd for $C_{21}H_{23}NO_5$ ($[M]^+$) 369.1576, found 369.1573.

Ethyl 2-((2*S*,3*R*,5*S*)-3-(But-3-enyl)-5-phenyltetrahydrofuran-2-yl)acetate (2f). The title compound was prepared from alcohol **6f** following the same procedure that was used for the synthesis of **2g**. Purification by flash chromatography (80:20 hexanes/EtOAc) afforded **2f** (63 mg, 86% yield) as an oil; dr (100:1); $[\alpha]^{20}_D$ −51.2 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.22 (m, 5H), 5.88−5.74 (m, 1H), 5.05−4.97 (m, 3H), 4.23−4.10 (m, 3H), 2.68−2.65 (m, 2H), 2.15−1.99 (m, 6H), 1.67−1.61 (m, 1H), 1.50−1.45 (m, 1H), 1.30−1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 143.2,138.0, 128.1, 127.0, 125.5, 114.8, 81.2, 79.7, 60.5, 43.4, 40.5, 40.3, 32.1, 31.9, 14.1; IR (NaCl) 2898, 1736, 1658, 1549, and 1449 cm^{-1}; EI-HRMS (*m/z*) calcd for $C_{18}H_{24}O_3$ ($[M]^+$) 288.1725, found 288.1725.

(*R*,*E*)-Ethyl 3-Acetoxy-6-phenylhex-5-enoate (3g). To a stirred suspension of $Zn(OTf)_2$ (15 mg, 0.042 mmol) in toluene (2 mL) under argon was added **2g** (197 mg, 0.84 mmol) dissolved in toluene (10 mL). Then Ac_2O (1.58 mL, 16.7 mmol) was added and the reaction mixture was refluxed for 4 h until TLC indicated complete consumption of the starting material. The reaction was then cooled to room temperature and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated and chromatographed (90:10 hexane/EtOAc) to give **3g** (181 mg, 78% yield) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 6.45 (d, J = 16 Hz, 1H), 6.17−6.09 (m, 1H), 5.38−5.35 (m, 1H), 4.12 (q, J = 7 Hz, 2H), 2.61 (d, J = 7 Hz, 2H), 2.56−2.53 (m, 2H), 2.03 (s, 3H), 1.24 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.1, 136.9, 133.5, 128.4, 127.3, 126.0, 124.1, 69.7, 60.5, 38.5, 37.5, 21.0, 14.0; IR (NaCl) 2933, 2857, 1739, 1455, 1372, 1237, and 1030 cm^{-1}; CI-HRMS (*m/z*) calcd for $C_{16}H_{21}O_4$ ($[M + H]^+$) 277.1440, found 277.1442.

(3*S*,4*R*,*E*)-Ethyl 3-Acetoxy-4-methyl-6-phenylhex-5-enoate (3a). The title compound was prepared from furan **2a** following the same procedure that was used for the synthesis of **3g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **3a** (323 mg, 76% yield) as an oil; $[\alpha]^{20}_D$ +27.3 (*c* 1.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 6.44 (d, J = 16 Hz, 1H), 6.09 (dd, J = 16, 8 Hz, 1H), 5.36−5.32 (m, 1H), 4.14−4.08 (m, 2H), 2.68−2.56 (m, 3H), 2.04 (s, 3H), 1.23 (t, J = 7 Hz, 3H), 1.12 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 137.0, 131.4, 130.1, 128.4, 127.3, 126.1, 73.0, 60.6, 40.8, 36.9, 20.9, 16.0, 14.0; IR (NaCl) 2949, 2875, 1740, 1371, 1237, 1179, and 1028 cm^{-1}; CI-HRMS (*m/z*) calcd for $C_{17}H_{22}O_4$ ($[M - H]^+$) 289.1440, found 289.1437.

(3*S*,4*R*,*E*)-Ethyl 3-Acetoxy-4-ethyl-6-phenylhex-5-enoate (3b). The title compound was prepared from furan **2b** following the same procedure that was used for the synthesis of **3g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **3b** (251 mg, 60% yield) as an oil; $[\alpha]^{20}_D$ −19.4 (*c* 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$ 400 MHz) δ 7.37−7.19 (m, 5H), 6.41 (d, J = 16 Hz, 1H), 6.00 (dd, J = 16, 9 Hz, 1H), 5.42−5.38 (m, 1H), 4.15−4.05 (m, 2H), 2.63−2.52 (m, 2H), 2.34−2.28 (m, 1H), 2.03 (m, 3H), 1.61−1.55 (m, 1H), 1.40−1.36 (m, 1H) 1.23 (t, J = 7 Hz, 3H), 0.91 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 136.9, 133.1, 128.5, 128.3, 127.2, 126.0, 72.0, 60.4, 48.9, 37.5, 24.0, 20.8, 13.9, 11.7; IR (NaCl) 3097, 1742, 1640, 1370, 1236, and 1028 cm^{-1}; ESI-HRMS (*m/z*) calcd for $C_{18}H_{24}O_4$ ($[M + Na]^+$) 327.1572, found 327.1569.

(3*S*,4*R*,*E*)-Ethyl 3-Acetoxy-4-(cyanomethyl)-6-phenylhex-5-enoate (3c). The title compound was prepared from furan **2c** following the same procedure that was used for the synthesis of **3g**, using 3 equiv of $Zn(OTf)_2$. Purification by flash chromatography (85:15 hexanes/EtOAc) afforded **3c** (116 mg, 53% yield) as an oil; $[\alpha]^{20}_D$ −24.6 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 5H), 6.60 (d, J = 16 Hz, 1H), 6.10 (dd, J = 16, 9 Hz, 1H), 5.47−5.43 (m, 1H), 4.20−4.06 (m, 2H), 2.68−2.49 (m, 5H), 2.12 (s, 3H), 1.30−1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.7, 135.9, 128.6, 128.2, 126.5, 123.5, 117.7, 71.1, 60.9, 43.0, 37.0, 29.6, 20.9, 20.7, 14.0; IR (NaCl) 2876, 2130, 1544, 1370, and 1231 cm^{-1}; CI-HRMS (*m/z*) calcd for $C_{18}H_{22}NO_4$ ($[M + H]^+$) 316.1549, found 316.1544.

(3*S*,4*R*,*E*)-Ethyl 3-Acetoxy-4-benzyl-6-phenylhex-5-enoate (3d). To a stirred suspension of $Zn(OTf)_2$ (3 mg, 0.008 mmol), **2d** (50 mg, 0.15 mmol), and CH_3CN (400 μL, 7.71 mmol) in toluene (3 mL) under argon was added Ac_2O (730 μL, 7.71 mmol) then the reaction mixture was refluxed for 4 h. The reaction was then cooled to room temperature and saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed with saturated solution $NaHCO_3$ brine and dried over Na_2SO_4. The organic layer was then concentrated and chromatographed (90:10 hexanes/EtOAc) to give **3d**, **11a**, and **11b** (55.8 mg) as a complex mixture. The following mixture was separated by HPLC by using the following conditions: column, YMC-Pack ODS-A 250 × 10 mm, 5 μm coupled to Luna C_{18} 250 × 10 mm, 5 μm; flow rate, 2.75 mL/min; solvents, isocratic 80:20 MeOH:H_2O; UV, 210 nm; temperature, 25 °C. The yield was 9 mg (16% yield). $[\alpha]^{20}_D$ −102.28 (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.16 (m, 10H), 6.28 (d, J = 16 Hz, 1H), 6.13 (dd, J = 16, 9.1 Hz, 1H), 5.43 (m, 1H), 4.14 (m, 2H), 2.92 (dd, J = 13, 5.2 Hz, 1H), 2.84−2.78 (m, 1H), 2.76−2.57 (m, 3H), 2.12 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.2, 139.2, 137.0, 133.6, 129.2, 128.4, 128.2, 127.7, 127.4, 126.2, 126.1, 72.0, 60.6, 48.6, 37.9, 37.5, 29.7, 21.0, 14.1; IR (NaCl) 3026, 2929, 2956, 1741, 1601, 1495, 1453, 1370, 1235, 1179, and 1029 cm^{-1}; ESI-HRMS (*m/z*) calcd for $C_{23}H_{26}O_4$ ($[M + H]^+$) 367.1909, found 367.1913.

(*R*)-Ethyl 3-Acetoxy-3-((2*S*,4*S*)-4-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (11a). The title compound was obtained in 47% yield (26 mg); $[\alpha]^{20}_D$ −25.7 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.04 (m, 8H), 6.79 (d, J = 7.8 Hz, 1H), 5.35 (dt, J = 7.3, 5.8 Hz, 1H), 4.21−4.15 (m, 2H), 4.09 (dd, J = 12.2, 5.5 Hz, 1H), 2.97−2.91 (m, 1H), 2.86−2.78 (m, 1H), 2.72−2.70 (m, 2H), 2.35−2.21 (m, 2H), 2.09 (s, 3H), 1.66 (dd, J = 25.3, 12.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.3, 146.4, 139.5, 135.6, 129.4,

128.9, 128.7, 128.5, 126,4, 126.0, 125.9, 73.0, 60.7, 46.8, 38.1, 36.7, 35.6, 32.5, 20.9, 14.1; IR (NaCl) 3061, 1735, 1599, 1493, 1371, 1178, and 1028 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{23}H_{26}O_4$ ($[M]^+$) 366.1831, found 366.1833.

(*R*)-Ethyl 3-Acetoxy-3-((2*S*,4*R*)-4-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (11b). The title compound was obtained in 20% yield (11 mg); $[\alpha]^{20}_D$ −60.9 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.12 (m, 6H), 7.02−6.98 (m, 3H), 5.32 (dt, *J* = 5.6, 3.7 Hz, 1H), 4.37 (t, *J* = 4.3 Hz, 1H), 4.10−4.03(m, 2H), 2.96 (dd, *J* = 16.1, 5.1 Hz, 1H), 2.72−2.50 (m, 3H), 2.12−2.06 (m, 1H), 2.04 (s, 3H), 2.04−2.00 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.3, 146.7, 137.6, 136.1, 130.3, 129.0, 128.5, 128.1, 126.3, 126.1, 125.9, 72.6, 60.6, 43.7, 37.1, 32.8, 32.7, 31.9, 20.9, 14.0; IR (NaCl) 3059, 1741, 1601, 1493, 1448, 1370, 1236, 1176, and 1028 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{23}H_{26}O_4$ ($[M + H]^+$) 367.1909, found 367.1904.

(3*S*,4*R*,*E*)-Ethyl 3-Acetoxy-4-(4-nitrobenzyl)-6-phenylhex-5-enoate (3e). The title compound was prepared from furan **2e** following the same procedure that was used for the synthesis of **3g**. Purification by flash chromatography (90:10 hexanes/EtOAc) afforded **3e** in 90% yield; $[\alpha]^{20}_D$ −142.8 (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9 Hz, 2H), 7.31−7.21 (m, 7H), 6.22 (d, *J* = 16 Hz, 1H), 6.06 (dd, *J* = 16, 9 Hz, 1H), 5.49−5.32 (m, 1H), 4.15−4.04 (m, 2H), 3.05−2.98 (m, 1H), 2.85−2.79 (m, 2H), 2.69−2.55 (m, 2H), 2.11 (s, 3H), 1.22 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 170.1, 147.2, 146.4, 136.3, 134.4, 129.9, 128.5, 127.7, 126.3, 126.1, 123.5, 71.8, 60.7, 48.4, 37.9, 37.3, 20.9, 14.0; IR (NaCl) 2918, 1740, 1600, 1345, and 1235 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{23}H_{25}NO_6Na$ ($[M + Na]^+$) 434.1580, found 434.1577.

(3*S*,4*R*)-Ethyl 3-Acetoxy-4-styryloct-7-enoate (3f). The title compound was prepared from furan **2f** following the same procedure that was used for the synthesis of **3g**. Purification by flash chromatography (95:5 hexanes/EtOAc) afforded **3f** in 86% yield; dr (50:1); $[\alpha]^{20}_D$ −37.8 (*c* 2.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 6.41 (d, *J* = 16 Hz, 1H), 6.00 (dd, *J* = 16, 9 Hz, 1H), 5.83−5.73 (m, 1H), 5.41−5.37 (m, 1H), 5.03−4.96 (m, 2H), 4.18−4.06 (m, 2H), 2.63−2.52 (m, 2H), 2.51−2.43 (m, 1H), 2.17−2.11 (m, 1H), 2.06−1.98 (m, 4H), 1.65−159 (m, 1H), 1.54−1.45 (m, 1H), 1.24 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 138.0, 136.9, 133.4, 128.4, 128.3, 127.3, 126.1, 114.9, 72.3, 60.5, 46.4, 37.6, 31.2, 30.2, 20.9, 14.0; IR (NaCl) 3039, 2884, 1742, 1597,1449, 1369, and 1234 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{20}H_{27}O_4$ ($[M + H]^+$) 331.1909, found 331.1906.

(2*S*,3*S*)-5-Ethyl 1-Methyl 3-acetoxy-2-methylpentanedioate (7a). To a stirring solution of **3a** (113 mg, 0.62 mmol) in a mixture of CH_3CN:CCl_4:H_2O (1:1:1.5, 3.5 mL) was added $RuCl_3 \cdot H_2O$ (13 mg, 0.062 mmol) followed by $NaIO_4$ (663 mg, 3.1 mmol). The resulting solution was allowed to stir overnight; after this time the solvents were evaporated under reduced pressure and saturated aqueous $NaHCO_3$ was added and the mixture was washed with Et_2O (2×). The layers were then separated and the aqueous layer was acidified with 1 N HCl to pH 3. The aqueous layer was then extracted with EtOAc (3×) and the combined organic layers were dried on anhydrous Na_2SO_4 and concentrated under reduced pressure to give a mixture of acids.

To the above crude mixture of acids in ether was added CH_2N_2 in Et_2O until a yellow color persisted. The excess CH_2N_2 was quenched with AcOH until the solution turned colorless. The solvents were then evaporated under reduced pressure and the residue was purified by column chromatography (1:4 EtOAc/hexanes) to give ester **7a** (99 mg, 64% yield over 2 steps) as colorless oil; $[\alpha]^{20}_D$ +13.4 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.37−5.43 (m, 1H), 4.02−4.12 (m, 2H), 3.64 (s, 3H), 2.81−2.90 (m, 1H), 2.50−2.66 (m, 2H), 1.97 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 169.7, 169.5, 100.9, 70.5, 60.4, 51.6, 42.1, 35.9, 20.5, 13.8, 12.1; IR (NaCl) 1739, 1463, 1373, and 1200 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{11}H_{18}O_6$ ($[M + H]^+$) 247.1182, found 247.1185.

(2*S*,3*S*)-5-Ethyl 1-Methyl 3-acetoxy-2-ethylpentanedioate (7b). The title compound was obtained from **3b** (216 mg, 0.71 mmol) as described for **7a** after flash chromatography (1:4 EtOAc/hexanes) as a colorless oil (144 mg, 87% yield over 2 steps); $[\alpha]^{20}_D$ +1.4 (*c* 2.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.37−5.43 (m, 1H), 4.06−4.12 (m, 2H), 3.65 (s, 3H), 2.63−2.69 (m, 2H), 2.55 (dd, *J* = 15.8, 7.7 Hz, 1H), 1.98 (s, 3H), 1.51−1.68 (m, 2H), 1.20 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.9, 169.7, 70.0, 60.7, 51.6, 50.3, 36.6, 20.9, 20.7, 14.0, 11.7; IR (NaCl) 1743, 1370, 1233, and 1177 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{12}H_{20}O_6$ ($[M + H]^+$) 261.1338, found 261.1339.

(3*S*,4*S*)-Ethyl 3-Acetoxy-4 (benzyloxycarbonylamino)-5-(4-nitrophenyl)pentanoate (13). To a stirred solution of **3e** (50 mg, 0.12 mmol) in DMF (0.6 mL) was added OsO_4 in 2.5% *tert*-butyl alcohol (1 μL) and the mixture was stirred for 5 min. Then Oxone (300 mg, 0.48 mmol) was added and the reaction mixture was stirred for 3 h. After 3 h, Na_2SO_3 was added and the reaction was stirred until the mixture turned brown, then 1 M HCl was added, the aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with 1 M HCl (3×) and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a mixture of the crude acid and benzoic acid.

To a stirred solution of the crude and benzoic acid (58 mg, 0.12 mmol) in PhMe (2.5 mL) under argon was added Et_3N (38 μL, 0.27 mmol) and diphenylphosphoryl azide (59 μL, 0.27 mmol). The resulting mixture was heated at reflux for 3 h and then benzyl alcohol (51 μL, 0.49 mmol) was added. Stirring and refluxing were continued for an additional 12 h. After this period the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed (70:30 hexanes/EtOAc) to give protected amine **13** (37 mg, 67% yield over 2 steps) as an oil; $[\alpha]^{20}_D$ −47.2 (*c* 6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.34−7.21 (m, 7H), 5.35−5.31 (m, 1H), 5.10−4.93 (m, 3H), 4.26−4.20 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.90 (dd, *J* = 6.2, 14 Hz, 1H), 2.78 (dd, *J* = 8.6, 13.9 Hz, 1H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.07 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.6, 155.8, 146.6, 144.7, 135.9, 129.9, 128.4, 128.2, 128.0, 123.5, 70.5, 66.8, 60.8, 54.0, 38.7, 36.45, 20.7, 13.9; IR (NaCl) 3344, 3034, 3066, 2981, 1740, 1604, 1520, 1347, 1228, and 1045 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{23}H_{26}N_2O_8$ ($[M + H]^+$) 459.1767, found 459.1765.

(3*S*,4*S*)-Ethyl 3-Acetoxy-4-(benzyloxycarbonylamino)hexanoate (12). The title compound was prepared from styrene **3b** following the same procedure that was used for the synthesis of **13**. Purification by flash chromatography (80:20 to 70:30 hexanes/EtOAc) afforded protected amine **12** (48 mg, 99% yield over 2 steps) as an oil; $[\alpha]^{20}_D$ −22.6 (*c* 2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 5.37 (dt, *J* = 8.8, 2.5 Hz, 2H), 5.11 (s, 2H), 4.80 (d, *J* = 10.1 Hz, 1H), 4.15−4.09 (m, 2H), 3.82−3.74 (m, 1H), 2.62−2.59 (m, 2H), 2.02 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.8, 156.3, 136.2, 128.5, 128.2, 128.1, 70.9, 66.9, 60.7, 55.0, 36.8, 25.7, 20.7, 14.0, 10.3; IR (NaCl) 3347, 1732, 1531, 1456, 1372, 1229, 1183, 1054, and 1028 cm^{-1}; EI-HRMS (*m*/*z*) calcd for $C_{18}H_{25}NO_6$ ($[M]^+$) 351.1682, found 351.1682.

(3*R*,5*S*)-3-Hexyl-5-phenyldihydrofuran-2(3*H*)-one (17). To a stirring solution of THF (7 mL) and diisopropylamine (0.9 mL, 6.78 mmol) at 0 °C under argon was added *n*-BuLi (4.1 mL, 1.6 M solution in hexanes, 6.48 mmol) dropwise; the mixture was then stirred for 15 min, HMPA (4 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. Then lactone **1** (1.0 g, 6.17 mmol) in THF (15 mL) was added dropwise over a 0.5 h period. The reaction mixture was stirred

for an additional 0.5 h at −78 °C. Then iodohexane (2.7 mL, 7.41 mmol) was added dropwise and the reaction mixture was stirred for 6 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (95:5 to 90:10 hexanes/EtOAc) to give **17** (1.21 g, 84% yield) as an amorphous solid; $[\alpha]^{20}_D$ −11.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.29 (m, 5H), 5.55 (t, J = 6.3 Hz, 1H), 2.64−2.60 (m, 1H), 2.41−2.37 (m, 2H), 1.92−1.85 (m, 1H), 1.58−1.49 (m, 1H), 1.42−1.23 (m, 9H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 139.9, 128.6, 128.1, 124.9, 78.6, 38.8, 36.4, 31.5, 30.4, 28.9, 27.2, 22.5, 14.0; IR (NaCl) 2947, 2855, 1865, 1649, 1454, and 1166 cm^{-1}; CI-HRMS (*m*/*z*) calcd for $C_{16}H_{22}O_2$ ([M]$^+$) 246.1620, found 246.1617.

1-((2*S*,3*R*,5*S*)-3-Hexyl-5-phenyltetrahydrofuran-2-yl)tridecan-2-one (16). To a stirring solution of CH_2Cl_2 (35 mL) and **17** (1.04 g, 4.22 mmol) at −78 °C under argon was added DIBAL-H (5.10 mL, 1 M solution in dichloromethane, 5.07 mmol) dropwise. The solution was stirred for a 0.5 h at −78 °C and then quenched with a saturated solution of Na−K tartrate and allowed to warm to room temperature. Once the emulsion had separated the aqueous layer was then extracted with CH_2Cl_2 (3×), then the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Without further purification the crude lactol was used in the next reaction.

To a stirring suspension of THF (5 mL) and $Ba(OH)_2$ (1.07 g, 3.38 mmol) at room temperature under argon was added **18** (9.05 g, 29.6 mmol) dissolved in THF (20 mL) dropwise and the mixture was stirred for 15 min. Then the crude lactol in THF (40 mL) was added dropwise and the mixture was stirred for 72 h. The reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (95:5 hexanes/EtOAc) to give **16** (1.5 g, 83% yield over two steps) as an oil; dr (33:1); $[\alpha]^{20}_D$ −45.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (m, 5H), 4.97 (t, J = 7 Hz, 1H), 4.08−4.03 (m, 1H), 2.79 (dd, J = 15, 8 Hz, 1H), 2.65 (dd, J = 15, 4 Hz, 1H), 2.54−2.51 (m, 2H), 2.02 (t, J = 7 Hz, 2H), 1.94−1.86 (m, 1H), 1.60 (t, J = 7 Hz, 2H,), 1.50−1.47 (m, 1H), 1.40−1.11 (m, 30H), 0.89 (t, J = 7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 143.5, 128.1, 127.0, 125.5, 125.2, 81.2, 79.5, 48.0, 44.2, 43.8, 40.6, 32.6, 31.8, 31.7, 29.5, 29.4, 29.3, 29.1, 28.1, 23.5, 22.6, 22.5, 14.0, 14.0; IR (NaCl) 2924, 2853, 1715, 1651, and 1457 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{29}H_{48}O_2Na$ ([M + Na]$^+$) 451.3552, found 451.3554.

(*S*)-1-((2*S*,3*R*,5*S*)-3-Hexyl-5-phenyltetrahydrofuran-2-yl)tridecan-2-ol (20). To a stirring solution of ether (25 mL) and **16** (530 mg, 1.24 mmol) at −40 °C under argon was added LiI (1.66 g, 12.4 mmol). The reaction was stirred for 20 min at −40 °C and then cooled to −78 °C, then $LiAlH_4$ (469 mg, 12.4 mmol) was added in three portions and the reaction was then stirred for 30 min. The reaction was quenched with Na−K tartrate and allowed to warm to room temperature. Once the emulsion had separated the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel (95:5 hexanes/EtOAc) to give **20** (464 mg, 88% yield) as an oil; dr (17:1); $[\alpha]^{20}_D$ −52.4(*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 5H), 5.01 (t, J = 7 Hz, 1H), 3.91−3.84 (m, 2H), 3.77−3.71 (m, 1H), 2.05−1.96 (m, 2H), 1.89−1.82 (m, 2H), 1.69−1.61 (m, 2H), 1.46−1.37 (m, 3H), 1.10−1.40 (m, 30H), 0.88 (t, J = 7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 128.2, 127.1, 125.5, 86.3, 80.1, 72.1, 44.9, 41.5, 40.6, 37.5, 32.5, 31.9, 31.7, 29.7, 29.6, 29.4, 29.3, 28.2, 25.5, 22.6, 22.5, 14.1, 14.0; IR (NaCl) 3148, 2924, 2853, 1643, 1457, and 1092 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{29}H_{51}O_2$ ([M + H]$^+$) 431.3889, found 431.3892.

(7*R*,8*S*,10*S*)-7-Styrylhenicosane-8,10-diyl Diacetate (21). To a stirring suspension of $Zn(OTf)_2$ (19.5 mg, 0.054 mmol) in toluene (3 mL) under argon was added furan **20** (462 mg, 1.1 mmol) dissolved in toluene (10 mL). Then Ac_2O (2.03 mL, 21.5 mmol) was added and the reaction mixture was refluxed for 4 h. The reaction was quenched with a saturated solution of aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2×) and brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated and chromatographed (95:5 hexanes/EtOAc) to give **21** (460 mg, 85% yield) as an oil; $[\alpha]^{20}_D$ −19.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.20 (m, 5H), 6.40 (d, J = 16 Hz, 1H), 6.00 (dd, J = 16, 10 Hz, 1H), 5.04−5.00 (m, 1H), 4.95−4.85 (m, 1H), 2.39−2.32 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.83−1.79 (m, 2H), 1.52−1.41 (m, 3H), 1.31−1.19 (m, 31H), 0.88 (t, J = 7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 137.2, 132.6, 129.4, 128.5, 127.2, 126.1, 73.1, 71.3, 47.0, 36.7, 34.0, 31.8, 31.7, 31.2, 29.5, 29.5, 29.3, 29.3, 29.2, 27.2, 22.6, 22.6, 21.2, 21.1, 14.1, 14.0; IR (NaCl) 2923, 2853, 1737, and 1238 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{33}H_{54}O_4Na$ ([M + Na]$^+$) 537.3920, found 537.3921.

(7*R*,8*S*,10*S*)-7-Styryl-10-(triisopropylsilyloxy)henicosan-8-ol (22). To a stirring solution of CH_2Cl_2 (12 mL) and diacetate **21** (448 mg, 0.87 mmol) at −78 °C under argon was added DIBAL-H (1.83 mL, 1 M in CH_2Cl_2, 1.82 mmol) dropwise and then the reaction mixture was stirred for 0.5 h. The reaction was then quenched with Na−K tartrate and allowed to warm to room temperature. Once the emulsion had separated the aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine and dried over Na_2SO_4. The organic layer was then concentrated and chromatographed (85:15 hexanes/EtOAc) to give the diol (303 mg, 81% yield) as an oil; $[\alpha]^{20}_D$ −7.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.19 (m, 5H), 6.42 (d, J = 16 Hz, 1H), 6.07 (dd, J = 16, 9 Hz, 1H), 3.84−3.81 (m, 2H), 3.13 (s, 1H), 2.93 (s, 1H), 2.24−2.11 (m, 1H), 1.66−1.36 (m, 6H), 1.33−1.19 (m, 29H), 0.90−0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 132.8, 130.3, 128.5, 127.2, 126.1, 75.5, 73.0, 50.5, 40.7, 38.1, 31.8, 31.7, 31.0, 29.6, 29.3, 27.4, 25.4, 22.6, 22.6, 14.1, 14.0; IR (NaCl) 3018, 2925, and 1215 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{29}H_{50}O_2Na$ ([M + Na]$^+$) 453.3709, found 453.3706.

To a stirring solution of CH_2Cl_2 (5 mL) and the diol (138 mg, 0.321 mmol) at −78 °C under argon were added 2,6-lutidine (75 μL, 0.64 mmol) and TIPSOTf (91 μL, 0.34 mmol) dropwise, then the reaction mixture was stirred at −78 °C for 1 h. The reaction was then quenched with H_2O and allowed to warm to room temperature, the aqueous layer was extracted with CH_2Cl_2 (3×), then the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated and chromatographed (98:2 hexanes/EtOAc) to give **22** (131 mg, 70% yield) as an oil; $[\alpha]^{20}_D$ +4.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.19 (m, 5H), 6.39 (d, J = 15 Hz, 1H), 6.15 (dd, J = 15, 9 Hz, 1H), 4.08−4.05 (m, 1H), 3.83−3.80 (m, 1H), 2.99 (s, 1H), 2.17−2.10 (m, 1H), 1.67−1.45 (m, 7H), 1.30−1.02 (m, 33H), 1.19−1.04 (m, 20H), 0.90−0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 131.9, 131.0, 128.4, 126.9, 126.1, 73.5, 50.1, 41.0, 37.9, 31.9, 31.8, 31.2, 29.8, 29.6, 29.4, 29.3, 27.5, 24.9, 22.6, 18.3, 18.1, 14.1, 12.9; IR (NaCl) 3018, 2927, and 1215 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{38}H_{71}O_2Si$ ([M + H]$^+$) 587.5223, found 587.5228.

(2*S*,3*S*,5*S*)-2-Hexyl-3-hydroxy-5-(triisopropylsilyloxy)hexadecanoic Acid (23). To a stirring solution of **22** (1.13 g, 1.92 mmol) in acetone:H_2O (24 mL:3 mL) were added OsO_4 (1.21 mL, 2.5% in *tert* -butyl alcohol, 0.095 mmol) and NMO (451 mg, 3.84 mmol) at room temperature, then the reaction was stirred for 48 h. Then Na_2SO_3 (500 mg) was added and once the reaction mixture turned brown H_2O (20 mL) was added. The aqueous layer was extracted with EtOAc (3×), then the combined organic layers were washed

with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to give the crude triol.

To a solution of the crude triol in THF:H_2O (16 mL:2 mL) was added $NaIO_4$ (617 mg, 2.88 mmol) at room temperature and the reaction mixture was stirred for 24 h. Water was added and the aqueous layer was extracted with EtOAc (3×), then the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo to give the crude aldehyde.

To a solution of the crude aldehyde in *tert*-butyl alcohol:H_2O (10 mL:10 mL) was added $NaClO_2$ (1.74 g, 19.2 mmol), NaH_2PO_4 (2.65 g, 19.2 mmol), and 2-methyl-2-butene (3 mL, 28.8 mmol) at room temperature and then the reaction was stirred for 12 h. Then 10 mL of H_2O was added and the reaction mixture was acidified with 1 M HCl to pH 3. The aqueous layer was extracted with EtOAc (3×) then the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated and chromatographed (90:10 to 80:20 hexanes/EtOAc) to give acid **23** (507 mg, 50% yield over three steps) as an oil; $[\alpha]^{20}_D$ +3.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14−4.08 (m, 1H), 4.00−3.97 (m, 1H), 2.42−2.38 (m, 1H), 1.79−1.72 (m, 2H), 1.64−1.52 (m, 4H), 1.36−1.16 (m, 33H), 1.12−1.01 (m, 20H), 0.89−0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 74.1, 71.5, 51.7, 40.4, 37.9, 31.8, 31.5, 29.7, 29.5, 29.5, 29.3, 29.0, 27.2, 24.9, 22.6, 22.5, 18.1, 18.0, 14.0, 14.0, 12.9; IR (NaCl) 3565, 2924, 1713, 1463, and 1090 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{31}H_{64}O_4SiNa$ ([M + Na]$^+$) 551.4472, found 551.4478.

(3*S*,4*S*)-3-Hexyl-4-((*S*)-2-hydroxytridecyl)oxetan-2-one (24). To a solution of acid **23** (69 mg, 0.13 mmol) and diisopropylethylamine (57 μL, 0.32 mmol) in THF (2 mL) was added 2,4,6-trichlorobenzoyl chloride (31 μL, 0.19 mmol) at room temperature, then the mixture was stirred for 3 h. Then THF was removed under vacuum and the reaction mixture was dissolved in toluene (2 mL) and added dropwise over a period of 3 h to a solution of DMAP in toluene (2 mL) with stirring for 36 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (98:2 hexanes/EtOAc) to give the lactone (37 mg, 55% yield) as an oil; $[\alpha]^{20}_D$ −15.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (dt, J = 6.2, 4.3 Hz, 1H), 3.99−3.97 (m, 1H), 3.29−3.24 (m, 1H), 2.10−2.04 (m, 1H), 1.99−1.94 (m, 1H), 1.80−1.72 (m, 2H), 1.58−1.54 (m, 4H), 1.37−1.19 (m, 36H), 1.08−0.99 (m, 26H), 0.93−0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 74.7, 69.5, 56.7, 40.5, 36.2, 31.8, 31.4, 29.7, 29.6, 29.5, 29.3, 29.0, 27.7, 26.6, 25.1, 22.6, 22.4, 18.1, 18.1, 14.1, 14.0, 12.5; IR (NaCl) 2924, 2855, 1827, 1464, 1116, and 1062 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{31}H_{63}O_3Si$ ([M + H]$^+$) 511.4547, found 511.4540.

To a solution of lactone (12 mg, 0.024 mmol) and AcOH (10 μL, 0.19 mmol) in THF (2 mL) at 0 °C under argon was added TBAF (0.26 mL, 1 M in THF, 0.26 mmol) and the resulting mixture was stirred for 4 h at 0 °C. The reaction was quenched with pH 7 buffer and the aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated and chromatographed (85:15 hexanes/EtOAc) to give β-lactone **24** (5 mg, 62% yield) as an oil; $[\alpha]^{20}_D$ −10.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48−4.44 (m, 1H), 3.82−3.76 (m, 1H), 3.33−3.29 (m, 1H), 2.05−1.98 (m, 1H), 1.93−1.86 (m, 1H), 1.85−1.79 (m, 1H), 1.78−1.70 (m, 1H), 1.54−1.49 (m, 2H), 1.47−1.38 (m, 2H), 1.35−1.21 (m, 27H), 0.90−0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 76.2, 69.3, 56.8, 56.8, 41.2, 37.6, 31.9, 31.5, 29.6, 29.5, 29.3, 28.6, 27.7, 26.8, 25.4, 22.6, 22.5, 14.1, 14.0; IR (NaCl) 3325, 2925, 2854, 1817, 1704,1526, 1467, and 1263 cm^{-1}; CI-HRMS (*m*/*z*) calcd for $C_{22}H_{43}O_3$ ([M + H]$^+$) 355.3212, found 355.3207.

(−)-Tetrahydrolipstatin (14). To a stirred solution of Cbz-Leu-OH **25** (48 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon was added DCC (38 mg, 0.18 mmol). The reaction mixture was stirred for 20 min at 0 °C, then the solvent was removed under vacuum and the reaction mixture was dissolved in DMF (1 mL). Then the reaction mixture was added dropwise to a solution of β-lactone **24** (32 mg, 0.1 mmol) and DMAP (0.13 mg, 0.01 mmol) in DMF (1 mL) and was stirred for 12 h at room temperature. The reaction was quenched with H_2O (3 mL), the aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with H_2O and brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and chromatographed (95:5 to 90:10 hexanes/EtOAc) to give the ester (35 mg, 63% yield) as an oil; $[\alpha]^{20}_D$ −20 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 5H), 5.17−5.06 (m, 3H), 5.02−4.97 (m, 1H), 4.37−4.26 (m, 2H), 3.22−3.18 (m, 1H), 2.17−2.11 (m, 1H), 1.99−1.94 (m, 1H), 1.77−1.44 (m, 10H), 1.36−1.15 (m, 33H), 1.01−0.94 (m, 6H), 0.89−0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.8, 155.9, 136.1, 128.5, 128.1, 128.0, 74.5, 72.2, 66.9, 56.9, 52.7, 41.5, 38.6, 34.0, 31.8, 31.5, 31.4, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 27.6, 26.6, 25.0, 24.7, 24.6, 22.9, 22.8, 22.6, 22.4, 21.6, 14.1, 14.0; IR (NaCl) 3363, 2926, 1824, 1727, 1522, 1467, 1261, and 1048 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{36}H_{59}NO_6Na$ ([M + Na]$^+$) 624.4240, found 624.4244.

A stirred solution of the ester (93 mg, 0.15 mmol) in ethanol (1.5 mL) was hydrogenated in the presence of 10% Pd/C (20 mg) at room temperature and atmospheric pressure for 4 h. The suspension was filtered through a short pad of Celite and the filtrate was evaporated under reduced pressure to give the crude amine, which was used without further purification in the next reaction.

A solution of crude amine was stirred in THF (1 mL) then freshly generated formic acetic anhydride was added (0.14 mL, 1.85 mmol) dropwise and the reaction was stirred for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with H_2O, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and chromatographed (7:3 to 1:1 pentanes/ether) to give (−)-tetrahydrolipstatin (37 mg, 48% yield over two steps) as an oil; $[\alpha]^{20}_D$ −32 (*c* 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 5.91 (d, J = 8.1 Hz, 1H), 5.05−5.0 (m, 1H), 4.71−4.66 (m, 1H), 4.29 (dt, J = 7.3, 4.7 Hz, 1H), 3.22 (dt, J = 7.1, 3.2 Hz, 1H), 2.15−2.10 (m, 1H), 2.08−2.00 (m, 1H), 1.85−1.51 (m, 7H), 1.41−1.15 (m, 26H), 0.96 (t, J = 6.3 Hz, 6H), 0.89 (t, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.7, 160.5, 74.7, 72.7, 57.0, 49.6, 41.5, 38.7, 34.0, 31.8, 31.4, 29.6, 29.4, 29.3, 28.9, 27.6, 26.6, 25.8, 25.0, 24.8, 22.8, 22.6, 22.5, 21.7, 14.1, 14.0; IR (NaCl) 3328, 2925, 2854, 1825, 1717, 1708, 1457, 1377, 1258, and 1186 cm^{-1}; ESI-HRMS (*m*/*z*) calcd for $C_{29}H_{53}NO_5Na$ ([M + Na]$^+$) 518.3821, found 518.3824.

Formic Acetic Anhydride. To a solution of formic acid 88% (1 mL) at 0 °C was added acetic anhydride (2 mL) dropwise. The reaction was then refluxed at 60 °C for 1 h. The resulting solution was then directly used in the synthesis of **14**.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of selected compounds and HPLC chromatograms for **3d**, **11a**, and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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