Total Synthesis of Asimicin and Bullatacin

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The efficient total synthesis of asimicin, **1**, and bullatacin, **2**, has demonstrated the advantages of three different strategies for the synthesis of the tricyclic intermediates **6** and **7**, which represent the key fragment of the bis-THF Annonaceous acetogenins. The naked carbon skeleton strategy is based on the production of all asymmetric centers by selective placement of the oxygen functions onto an unsaturated, nonfunctionalized carbon skeleton. Diversity in this approach arises from the relative timing of highly stereoselective reactions, such as the Sharpless asymmetric dihydroxylation (AD) reaction, the Kennedy oxidative cyclization (OC) with rhenium(VII) oxide, the Mitsunobu-type alcohol epimerization reaction, and the Williamson etherification reaction. The convergent strategy, which is based on the combinatorial coupling of two series of diastereomeric fragments, to produce intermediates such as **11** and **12**, enjoys the advantages of both efficiency and versatility. The third approach, which is based on partially functionalized intermediates, such as **13**, combines the advantages of both the linear and the convergent strategies—synthetic efficiency and diversity.

Introduction

Asimicin, **1**[1] and bullatacin, **2**,[2] are two diastereomeric members of the Annonaceous acetogenins, a rapidly growing family of natural products, that are known not only for their antitumor activity but also for being potent antimalarial, immunosuppressive, pesticidal, and antifeedant agents.[3] Compound **1** was isolated from the pawpaw tree, *Asimina triloba* Dunal, and **2** was discovered in *Annona bullata* using the brine shrimp lethality assay for activity-directed fractionation. High cytotoxicity was exhibited by **1** in cell lines of human nasophyraneal carcinoma (9KB, $ED_{50} < 10^{-5}$ μg/mL) and murine lymphocyte leukemia (9BS, $ED_{50} < 10^{-7}$ μg/mL). Similarly, **2** and its analogues have shown potential in vivo antitumor activity with normal mice bearing L1210 murine leukemia and with mice bearing A2780 conventional ovarian cancer xenografts.[4] The cytotoxicity of **2** was found to be higher than that of other chemotherapeutic agents in a variety of cancer cell lines,[5] particularly in HL-60 cells that are resistant to adriamycin.[6]

The structure of **1** and **2** was assigned mainly on the basis of ^{1}H and ^{13}C NMR and MS data. Their absolute configurations were determined using ^{1}H and ^{19}F NMR spectral data of both their (*R*) and (*S*) Mosher esters in comparison with model compounds.[1,2] These structures were confirmed via the total syntheses of both **1** and **2**, which were independently reported in our preliminary work[7] and by the Hoye,[8] Marshall,[9] and Sasaki groups.[10]

In designing the synthetic approach[11−13] to **1** and **2**, we viewed this task within the more general problem of the Annonaceous acetogenins diversity. More than 350 acetogenins have already been isolated from 37 species

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(1) (a) Rupprecht, J. K.; Chang, C.-J.; Cassady, M. J.; McLaughlin, J. L. *Heterocyclic* **1986**, *24*, 1197. (b) Lewis M. A.; Arnason, J. T.; Philogene, B. J. R.; Rupprecht, J. K.; Mclaughlin J. L. *Pesticide Biochem. Physiol.* **1993**, *45*, 15. (c) Zhao, G. X.; Miesbauer, L. R.; Smith, D. L.; Mclaughlin J. L. *J. Med. Chem.* **1994**, *37*, 1971.

(2) (a) Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463. (b) Li, X. H.; Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Wood, K. V.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 81. (c) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. J. *Am. Chem. Soc.* **1992**, *114*, 10203.

(3) For reviews, see: (a) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (b) Fang, X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27. (c) Gu, Z.-M.; Zhao, G.-X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. In *Recent Advances in Phytochemistry*; Arnason, J. T., Mata, R., Romeo, J. T., Eds.; Plenum Press: New York, 1995; Vol. 29, p 249. (d) Figadére, B. *Acc. Chem. Res.* **1995**, *28*, 359. (e) Koert, U. *Synthesis* **1995**, 115. (f) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat Prod. Rep.* **1996**, *13*, 275. (g) Cavé, Y.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the chemistry of organic natural products*; Herz, W., Kirby, G. W., Moore, R. E., Steglish, W., Tamm, C., Eds.; Springer-Verlag: New York, 1997; p 81. (h) Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem.* **1997**, *37*, 97. (i) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts* **1998**, *11*, 803. (j) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat Prod.* **1999**, *62*, 504 and references therein.

(4) Ahmadsahib K. I.; Hollingworth R. M.; McGovren J. P.; Hui Y.-H.; McLaughlin J. L. *Life Sci.* **1993**, *53*, 1113−1120.

(5) Chrestine, H.; Johnson, H. M.; Knox, R. M.; Rezai, A.; Ryan, W. J.; Montz F. J. *Cancer Chemother. Pharmacol.* **1994**, *34*, 166−170.

(6) Morre, D. J.; Cabo, R. D.; Farley, C.; Oberlies, H. N.; McLaughlin, J. L. *Life Sci.* **1995**, *56*, 343−348.

(7) For a preliminary version of this work, see: Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257.

(8) (a) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, 1981. (b) For the synthesis of (−)-bullatacin, see: Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043.

(9) For the synthesis of asimicin, see: Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.

(10) For the synthesis of bullatacin, see: Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419.

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in the Annonaceae, a family that is known to accommodate over 2300 species.[14] While most of these fatty acid derivatives exhibit remarkable structural diversity, they share very similar carbon skeletons, with the main variations being the relative and absolute configuration of the various stereogenic oxygen functions. For example, a dominant structural feature that appears in more than 40% of the Annonaceous acetogenins, including **1** and **2**, is a ten-carbon fragment containing two adjacent tetrahydrofuran rings flanked by two hydroxyl groups. With six stereogenic carbinol centers, this unit alone can have as many as 64 different stereoisomers, several of which have already been identified in the naturally occurring repertoire of acetogenins. Studies on the primary mode of action have established that such acetogenins are the most powerful inhibitors of complex I (NADH-ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems.[15] In addition, they are potent inhibitors of NADH oxidase, which is specifically active in the plasma membranes of tumors and is inactive in normal cells.[16]

The remarkable diversity and biological activity of the Annonaceous acetogenins suggest that chemical libraries of such structurally related compounds should be synthesized to allow systematic biological screenings and structure−activity relationship studies. We have already shown that this goal can be approached by several methods, based on either convergent or linear strategies.[11] In this report we demonstrate the advantages and versatility of three different approaches to the total synthesis of the bis-THF acetogenins **1** and **2**.[7] These approaches include the naked carbon skeleton strategy, the convergent approach, and a hybrid approach that combines the first two methods.

Results and Discussion

Our retrosynthetic analysis of both **1** and **2** (Scheme 1) dissects these target molecules into two major fragments, the butenolide moiety, **3**, and the bis-THF fragment, **4** or **5**. These epimeric fragments could be coupled to **3** using the Wittig olefination reaction. The phosphonium salts **4** and **5** could be prepared from the corresponding tricyclic intermediates **6** and **7**, respectively. The synthesis of the latter represents the most significant component in the entire synthesis, not only because these diastereomers contain six asymmetric centers but also because their stereoisomeric variability represents the origin of diversity in the bis-THF subgroup of the Annonaceous acetogenins. To meet this challenge we examined three general synthetic approaches: (a) the "naked" carbon skeleton strategy[17] using the nonfunctionalized skeletons **8**−**10**, (b) a convergent approach, which is based on the functionalized intermediates **11** and **12**, and (c) a hybrid strategy that combines the advantages of both (a) and (b) methodologies, using the partially functionalized intermediate **13**. All three approaches can be generally used for the synthesis of the title compounds **1** and **2**, as well as for synthesis of their diastereomers.

The "Naked" Carbon Skeleton Strategy. The key principle of this strategy is that all of the asymmetric centers are produced by selective placement of the oxygen functions onto an unsaturated nonfunctionalized carbon skeleton, such as **8**−**10**. We have already demonstrated the advantages of this strategy in the asymmetric total synthesis of other natural products as well.[17] The versatility of this approach stems from the flexible choice of the appropriate carbon skeleton, from induction of asymmetry using enantioselective transformations, such as the Sharpless asymmetric dihydroxylation (AD) reaction,[18] and from the relative timing of other reactions that are characterized by predictable relative stereochemistry, such as the Kennedy oxidative cyclization (OC) with rhenium(VII) oxide,[19,20] the Mitsunobu-type alcohol epimerization reaction,[21] and the Williamson etherification reaction.[22]

Carbon skeletons **8**, **9**, and **10** were prepared as shown in Scheme 2. Compound **8** was produced from **14**,[11e] which was easily prepared from undecanal. Aldehyde **14** was converted to the corresponding dibromoalkene **15** using

(11) (a) Reference 7. (b) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891. (c) Sinha, S. C.; Sinha, A.; Yazbak, Y.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640. (d) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *Pure. Appl. Chem.* **1997**, *69*, 423. (e) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863. (f) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (g) Sinha, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 2381. (h) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067.

(12) For the total or formal synthesis of adjacent bis-tetrahydrofuran acetogenins also see refs 8−10, 11c, 11e, 11g, and 11h. (a) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (b) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517. (c) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (d) Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632. (e) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996. (f) Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303. (g) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971. (h) Marshall, J. A.; Jiang, H. *J. Nat. Prod.* **1999**, *62*, 1123. (i) Ruan, Z.; Mooto, D. R. *Tetrahedron Lett.* **1999**, *40*, 49. (j) Emde, U.; Koert, U. *Tetrahedron Lett.* **1999**, *40*, 5979.

(13) For the various synthetic studies towards the synthesis of bis-tetrahydrofuran acetogenins, see: (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247. (b) Figadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428. (c) Zhang, H.; Seepersaud, M.; Seepersaud, S.; Mootoo, D. R. *J. Org. Chem.* **1998**, *63*, 2049. (d) Lee, S.; Lee, Y.-S.; Park, G.; Choi, S. R.; Yoon, S.-H. *Bull. Korean Chem. Soc.* **1998**, *19*, 115. (e) El Sukkari, H.; Renoux, B.; Bertrand, P.; Gesson, J.-P. *J. Chem. Res., Synop.* **1999**, 482 and 2157. (f) Tian, S.-K.; Wang, Z.-M.; Jiang, J.-K.; Shi, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2551. (g) Bertrand, P.; El Sukkari, H.; Gesson, J.-P.; Renoux, B. *Synthesis* **1999**, 330. (h) Jan, S.-T.; Li, K.; Vig, S.; Rudolph, A.; Uckun, F. M. *Tetrahedron Lett.* **1999**, *40*, 193. (i) Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi. G. *J. Org. Chem.* **2000** (ASAP).

(14) Leboeuf, M.; Cavé, A.; Bhunik, P. K.; Mukherjee, B.; Mukherjee, R. *Phytochemistry* **1982**, *21*, 2783.

(15) (a) Ahammadsahib, K. I.; Hollingworth, R. M.; McGovern, P. J.; Hui, Y.-H.; McLaughlin, J. L. *Life Sci.* **1993**, *53*, 1113. (b) Degli Esposti, M.; Ghelli, A.; Ratta, M.; Cortes, D. *Biochem. J.* **1994**, *301*, 161. (c) Hollingworth, R. M.; Ahammadsahib, K. I.; Gadelhak, G.; McLaughlin, J. L. *Biochem. Soc. Trans.* **1994**, *22*, 230.

(16) (a) Morré, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci.* **1995**, *56*, 343. (b) Wolvetang, E. J.; Johnson, K. L.; Krauer, K.; Ralph, S. J.; Linnane, A. W. *FEBS. Lett.* **1994**, *339*, 40.

(17) (a) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789. (b) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1994**, *59*, 949. (c) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1997**, *62*, 377.

(18) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

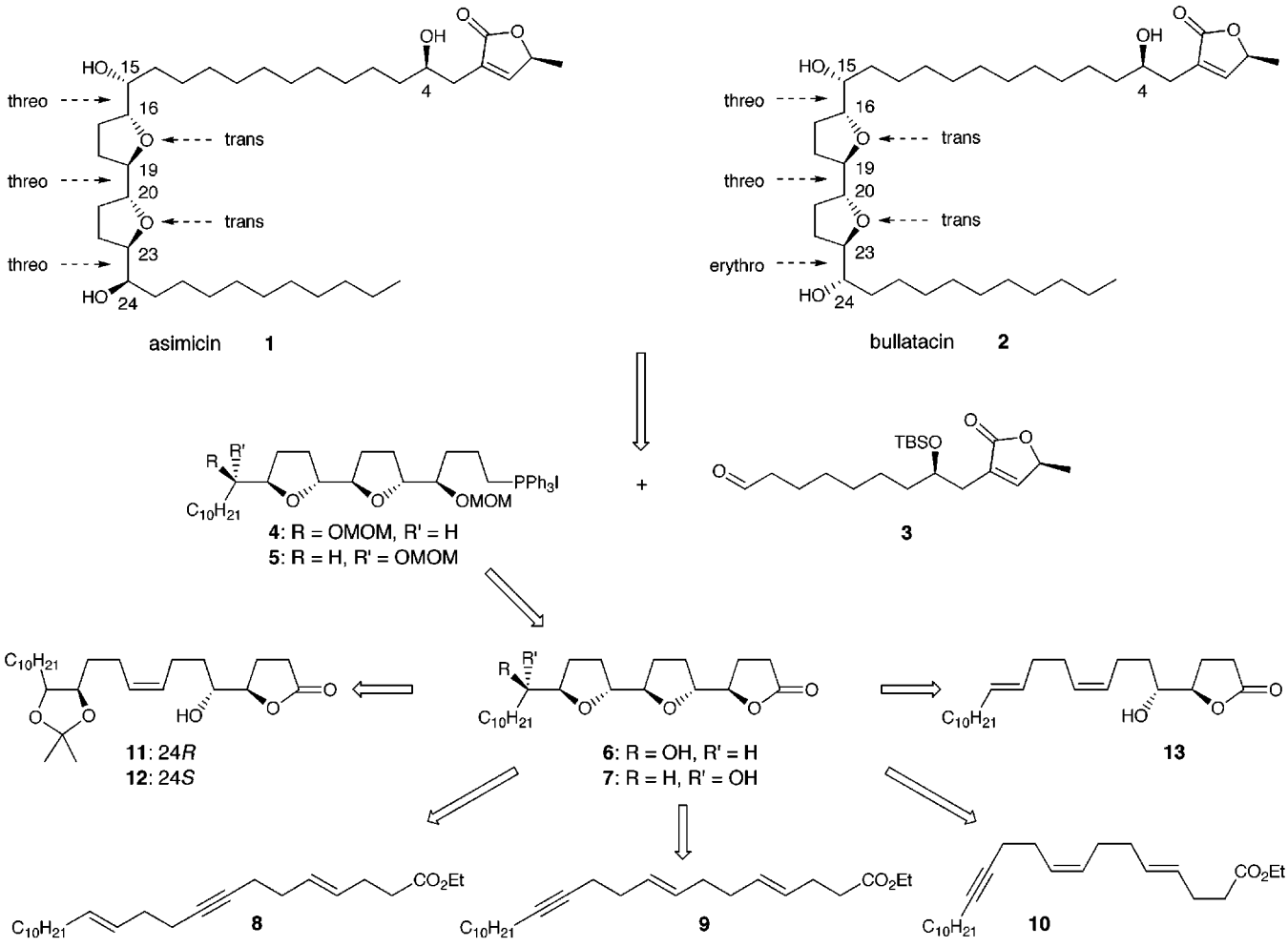
(19) (a) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 3729. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303. (d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133. (e) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750. (f) Towne, B. T.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022. (g) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633.

(20) (a) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447. (b) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014. (c) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017.

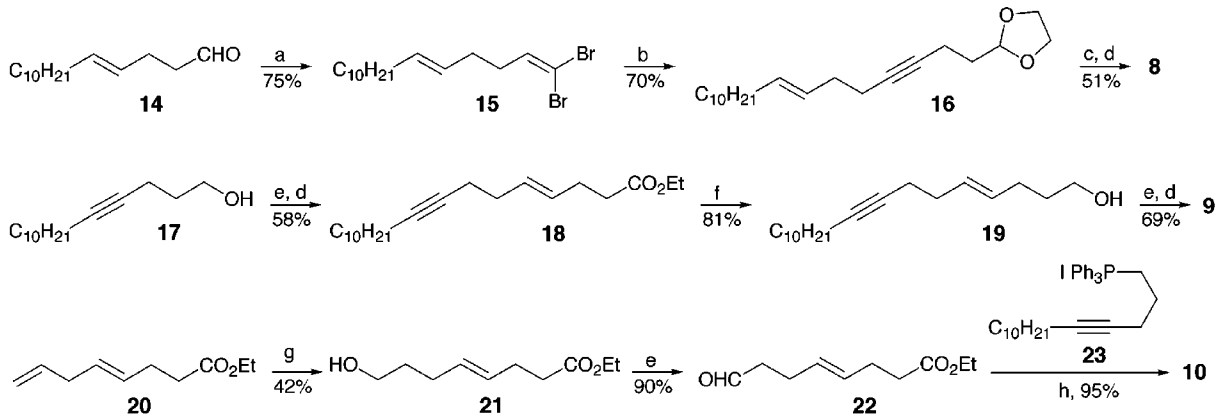
(21) Mitsunobu, O. *Synthesis* **1981**, 1.

(22) (a) Feuer, H.; Hooz, J. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; John Wiley & Sons: New York, 1967; pp 446−448. (b) Wagner, H.; Koert, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1873. (c) Koert, U.; Wagner, H.; Stein, M. *Chem. Eur. J.* **1997**, *3*, 1170.

Scheme 1. Retrosynthesis of Asimicin, 1, and Bullatacin, 2



Scheme 2. Synthesis of the "Naked" Carbon Skeletons[a]



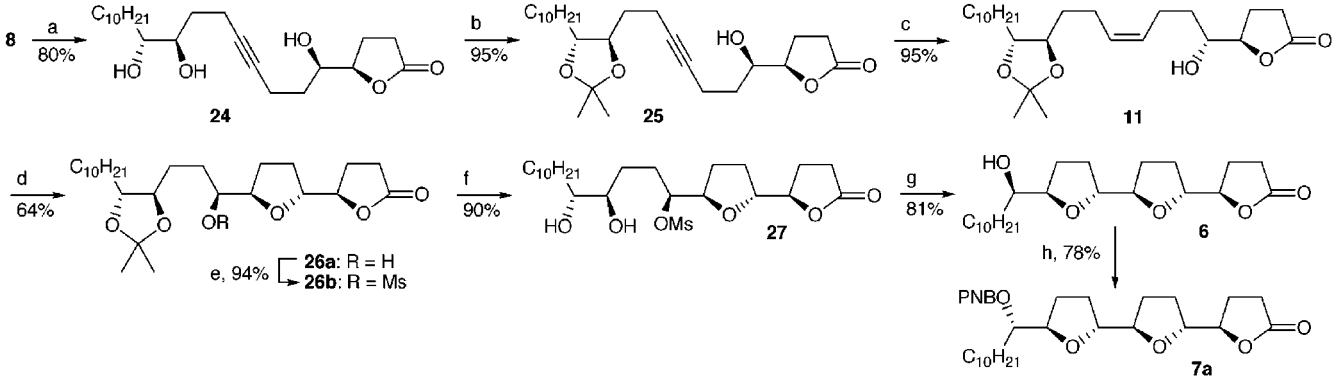
[a] Key: (a) CBr_4, PPh_3, 0 °C, 10 min; (b) BuLi, THF − HMPA, 2-(2-bromoethyl)-1,3-dioxolane, −78 °C to rt, 12 h; (c) AcOH − H_2O (3:2), 60 °C, 16 h; (d) i. vinylmagnesium bromide, THF, 0 °C, 1 h, ii. $(EtO)_3CCH_3$, $EtCO_2H$, reflux, 2 h; (e) PCC, Celite, CH_2Cl_2, rt, 1 h; (f) $LiAlH_4$, ether, 0 °C to rt, 1 h; (g) 9-BBN, THF, 0 °C to rt, 12 h, then H_2O_2 (30%), aqueous NaOH (3 N), 2 h; (h) **23**, $KN(SiMe_3)_2$, THF, HMPA, −78 °C, 2 h, then **22**, −78 °C to rt, 16 h.

carbon tetrabromide and triphenylphosphine. Reaction with *n*-butyllithium in THF−HMPA transformed **15** into a lithiated alkyne, which was then reacted with 2-(2-bromoethyl)-1,3-dioxolane to produce **16**. Acid-catalyzed hydrolysis of the dioxolane group afforded the corresponding aldehyde, which was then reacted with vinylmagnesium bromide to give an allylic alcohol. The latter was subjected to the Claisen−Johnson rearrangement procedure,[23] affording compound **8**.

The synthesis of carbon skeleton **9** (Scheme 2) started from pentadec-4-yn-1-ol, **17**, which was prepared by alkylation of 5-tetrahydropyranyloxypent-1-yne with 1-bro-

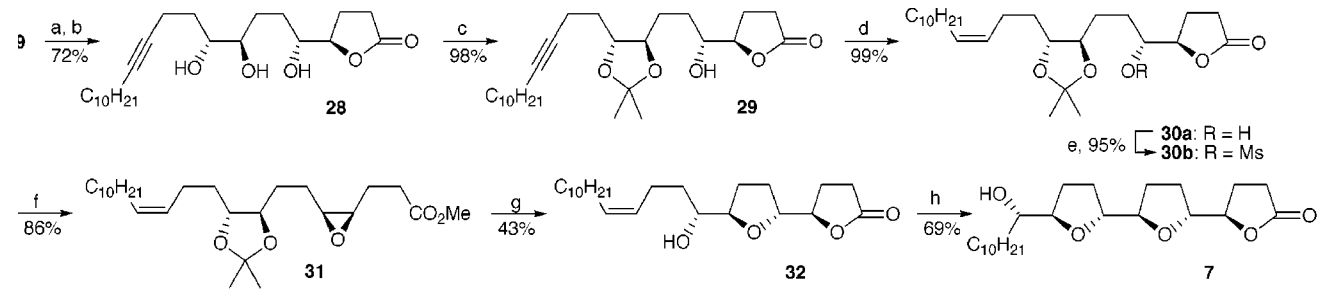
(23) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976.

Scheme 3. Synthesis of 6 and 7a by "Naked" Carbon Skeleton Approach[a]



[a] Key: (a) i. AD-mix-β, $MeSO_2NH_2$, *t*-BuOH−water (1:1), 0 °C, 16 h, ii. aqueous KOH, MeOH, 60 °C, 2 h, then HCl (3 N), iii. TsOH (5%), CH_2Cl_2, 0.5 h; (b) dimethoxypropane, acetone, TsOH (cat.), 0 to 25 °C, 0.5 h; (c) 5% Pd−$CaCO_3$−lead (10%, w/w), hexane−cyclohexene−Et_3N (2:2:1), −10 °C, 12 h; (d) Re_2O_7, lutidine, CH_2Cl_2, 2 h; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (f) TsOH (20% w/w), MeOH−H_2O (4:1), 60 °C, 16 h; (g) pyridine, 100 °C, 2 h; (h) DEAD, 4-nitrobenzoic acid, PPh_3, C_6H_6, 0 °C to rt, 12 h.

Scheme 4. First Synthesis of 7 by "Naked" Carbon Skeleton Approach[a]



[a] Key: (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH−water (1:1), 0 °C, 16 h; (b) i. aqueous KOH, MeOH, then HCl (3 N), ii. TsOH (5%), CH_2Cl_2, 0.5 h; (c) dimethoxypropane, acetone, TsOH (cat.), 0 to 25 °C, 0.5 h; (d) 5% Pd−$CaCO_3$−lead (10%, w/w), hexane−cyclohexene−Et_3N (2:2:1), −10 °C, 12 h; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (f) K_2CO_3, MeOH, 25 °C, 0.5 h; (g) i. $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C; (h) Re_2O_7, H_5IO_6, CH_2Cl_2, 1 h.

modecane followed by deprotection of the primary alcohol. PCC oxidation afforded the corresponding aldehyde, which was treated with vinylmagnesium bromide to produce an allylic alcohol. The latter was subjected to the Claisen−Johnson rearrangement procedure, affording compound **18**. Reduction of the ester function to primary alcohol **19**, oxidation to the corresponding aldehyde, and then repeating the reaction sequence with vinylmagnesium bromide followed by Claisen−Johnson rearrangement produced skeleton **9**.

For the synthesis of skeleton **10** (Scheme 2), we used ethyl octa-4,7-dienoate, **20**, which was obtained via the Claisen−Johnson rearrangement protocol with hexa-1,5-dien-3-ol and triethyl orthoacetate. Compound **20** was reacted with 9-BBN followed by oxidation with H_2O_2 under basic conditions to produce alcohol **21**. The latter was oxidized with PCC to give aldehyde **22**. The phosphonium salt **23** was obtained by converting alcohol **17** to the corresponding iodide followed by reaction with triphenylphosphine. Finally, Wittig coupling between **22** and **23** afforded compound **10**.

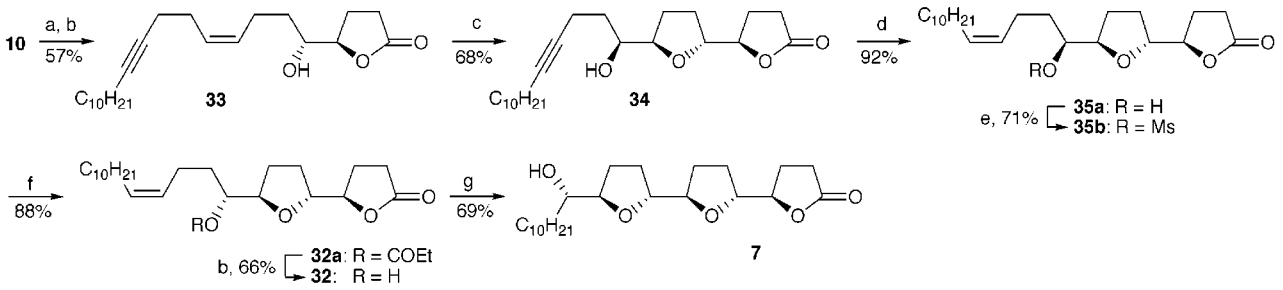
Carbon skeletons **8**−**10** were designed to produce the tricyclic intermediates **6** and **7** in fast and efficient pathways, demonstrating our modular use of the above-mentioned key reactions (AD, OC, Mitsunobu epimerization, and Williamson etherification reactions). For example, compound **6** could be obtained from skeleton **8** via the following reaction sequence: AD−OC−etherification (Scheme 3). The epimeric building block, **7**, could be obtained from skeleton **9** using a different sequence: AD−epimerization−etherification−OC (Scheme 4). Alternatively, intermediate **7** could also be obtained from skeleton **10** using another sequence of the same transformations: AD−OC−epimerization−OC (Scheme 5). In fact, Schemes 3−5 represent three alternative synthetic approaches to both **6** and **7** because these two epimers are interconvertible by the Mitsunobu epimerization reaction (see, for example, the conversion of **6** into **7a**, Scheme 3).

Thus, asymmetric dihydroxylation of **8** with AD-mix-β (Scheme 3) followed by base−acid treatment afforded the trihydroxylactone **24** as a solid powder from EtOAc. The vicinal diol was protected in the form of an acetonide, **25**, and the alkyne was partially hydrogenated to give the *cis*-olefin **11**.[24] Oxidative cyclization with dirhenium heptoxide and lutidine[11c] produced alcohol **26a**, which was converted to the corresponding mesylate, **26b**. Acid-catalyzed hydrolysis of the acetonide group to give **27** followed by treatment with pyridine effected a Williamson-type etherification to produce the tricyclic compound **6**.

Asymmetric dihydroxylation of **9** with AD-mix-β (Scheme 4) afforded the trihydroxylactone **28**. The vicinal diol in **28** was protected in the form of an acetonide, **29**, and the alkyne was partially hydrogenated to the *cis*-olefin **30a**. Conversion of the free alcohol in **30a** to the corresponding mesylate, **30b**, and treatment of the latter

(24) Compound **11** was also prepared by the Wittig reaction in our latter studies using convergent approach.

Scheme 5. Second Synthesis of 7 by "Naked" Carbon Skeleton Approach[a]



[a] Key: (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH−water (1:1), 0 °C, 16 h; (b) i. aqueous KOH, MeOH, then HCl (3 N), ii. TsOH (5%), CH_2Cl_2, 0.5 h; (c) Re_2O_7, lutidine, CH_2Cl_2, 2 h; (d) 5% Pd−$CaCO_3$−lead (10%, w/w), hexane−cyclohexene−Et_3N (2:2:1), −10 °C, 12 h; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (f) cesium propionate, DMF, 100 °C, 18 h; (g) Re_2O_7, H_5IO_6, CH_2Cl_2, 1 h.

with K_2CO_3 in methanol afforded the epoxyester **31**. Treatment of **31** with $BF_3{\cdot}Et_2O$ at low temperature effected ring closure to produce **32**. Finally, oxidative cyclization with dirhenium heptoxide and H_5IO_6 gave the bis-THF intermediate, **7**.

Asymmetric dihydroxylation of **10** with AD-mix-β (Scheme 5) afforded the hydroxylactone **33** in an enantiomerically pure form after crystallization from ether. Oxidative cyclization of **33** with dirhenium heptoxide and lutidine gave alcohol **34**. The triple bond was partially hydrogenated to produce the *cis*-olefin **35a**. The free alcohol configuration in **35a** was inverted in two steps, first mesylation to form **35b** and then reaction with cesium propionate to produce the propionate ester **32a**. Hydrolysis of the ester followed by lactonization afforded compound **32**, which was converted to **7** as has already been described in Scheme 4.

Several elements in the design and execution of the above-described synthetic sequences are noteworthy. (1) The significantly higher reactivity of AD reagents toward *E* alkenes relative to *Z* alkenes enables selective dihydroxylation of the former in the presence of the latter.[25] (2) The enantiomeric purity of a crude diol obtained from the AD reaction of a *trans* double bond, in substrates such as **8** and **9**, ranges above 95%. Considering 95−90% ee of each double bond, the diastereomeric purity of crude **24** and **28** may drop to 90 to 81%; however, the enantiomeric impurity due to *ent*-**24** and *ent*-**28** will still be below 0.25%. Thus, compounds **6** and **7** are obtained in essentially enantiomerically pure form. (3) Because of the relatively low reactivity of alkynes under conditions of olefin oxidation with either osmium or rhenium, the C−C triple bond may be considered to be a protected *Z*-olefin that can be easily "deprotected" via partial hydrogenation over a Lindlar catalyst. (4) Positioning of an ester function at the vicinity of a double bond undergoing AD reaction allows regioselective differentiation of the two resultant hydroxyl groups via formation of a stable lactone.[26] (5) Ring closure with overall inversion of the configuration at the carbon center can be carried out simply via activation of a hydroxyl group, e.g., by mesylation, followed by intramolecular substitution by another hydroxyl group, as exemplified by the sequence going from alcohol **26a** to mesylate **26b** and THF derivative **6**. Alternatively, with the help of an adjacent hydroxyl group, the same ring closure can be performed with overall retention of the configuration at carbon.[11b] This is done, for example, by converting mesylate **30b** to epoxide **31** followed by ring closure to give the THF derivative **7**. (6) Inversion of a carbinol configuration provides a pair of epimeric intermediates. This represents a useful branching point in synthetic schemes that start with a few "naked" skeletons and lead to diverse chemical libraries.

The Convergent Approach. The coupling of two fragments, each containing two asymmetric centers, enjoys the advantages of both efficiency and versatility. We have already shown that this approach, where the Wittig olefination reaction is used to form a *cis* alkene intermediate, could produce as many as 32 of the 64 possible stereoisomers of **6** and **7**.[11d] To that end, all possible stereoisomers of compounds **11** and **12** were synthesized from a complete pool of all diastereomeric building blocks.[11d] Here, in a similar way (Scheme 6) we prepared the two phosphonium salts, **38** and **41**, from lactone **36**, which was obtained from asymmetric dihydroxylation of ethyl (*E*)-pentadec-4-enoate.[26] LAH reduction of **36** afforded 1,4,5-trihydroxypentadecane. Protection of the vicinal diol in the form of an acetonide derivative, **37a**, was followed by conversion of the unprotected primary alcohol to iodide **37b**. The latter was reacted with triphenylphosphine to produce the phosphonium salt, **38**. Mitsunobu-type inversion of the hydroxyl configuration in **36** afforded the *p*-nitrobenzoate ester **39**. LAH reduction of the latter afforded the corresponding triol, which was converted to the acetonide derivative **40a** and then to iodide **40b** and finally to the phosphonium salt **41**, as described above.

Aldehyde **44** was obtained from ethyl (*E*)-8-benzyloxy-oct-4-enoate, **42**, which was prepared from 4-benzyloxy butanal[27] by Grignard reaction with vinylmagnesium bromide to produce an allylic alcohol, followed by the Johnson−Claisen rearrangement. Asymmetric dihydroxylation of **42** with AD-mix-β afforded hydroxylactone **43a** in more than 95% ee, which increased to essentially 100% ee in one crystallization. Protection of the free hydroxyl group as a *tert*-butyldiphenylsilyl ether, **43b**, and hydrogenolysis of the benzyl group afforded the primary alcohol **43c**. Finally, oxidation of the latter with PCC yielded the desired building block **44**.

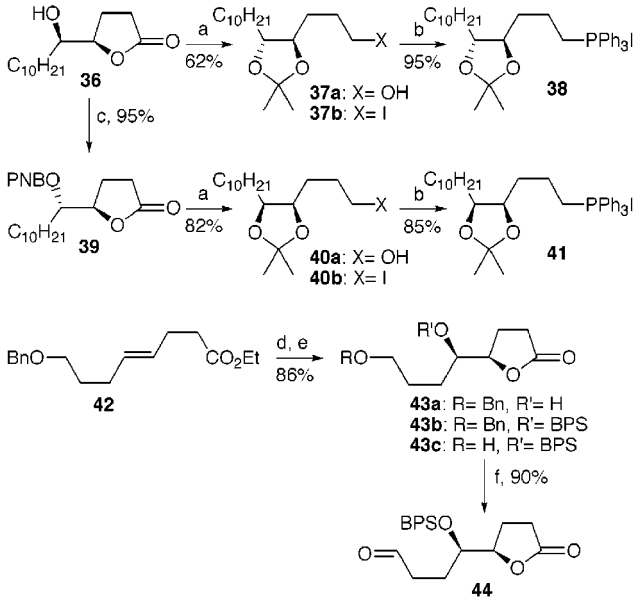
Wittig coupling of building blocks **38** and **44** produced the *cis* alkene **11a** (Scheme 7). The silyl ether was cleaved

(25) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345.

(26) Monoprotection of a vicinal diol in the form of a γ-lactone has been used in the synthesis of other natural products. See: (a) ref 16, 20. (b) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407. (c) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A.; Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6411. (d) Sinha-Bagchi, A.; Sinha, S. C.; Keinan, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2889.

(27) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 607.

Scheme 6. Synthesis of Chiral Building Blocks 38, 41, and 44[a]



[a]Key: (a) i. $LiAlH_4$, ether−THF, 0 °C−reflux, 2 h, ii. dimethoxypropane−acetone (1:1), TsOH (cat.), iii. I_2, imidazole, PPh_3, CH_2Cl_2, 1 h; (b) PPh_3, CH_3CN, reflux, 16 h; (c) DEAD, 4-nitrobenzoic acid, PPh_3, C_6H_6, 0 °C to rt, 2 h; (d) i. AD-mix-β, $MeSO_2NH_2$, *t*-BuOH−water (1:1), 0 °C, 16 h; ii. aqueous KOH, MeOH, then HCl (3 N), iii. TsOH (5%), CH_2Cl_2, 0.5 h; (e) i. BPSCl, imidazole, DMF, rt, 16 h, ii. Pd−C (10%), H_2, MeOH, $EtCO_2H$, rt, 24 h; (f) PCC, Celite, CH_2Cl_2, rt, 2 h.

by TBAF to produce the bis-homoallylic alcohol **11**. Oxidative cyclization of the latter using Re_2O_7 and lutidine afforded intermediate **26a**, whose conversion to **6** has already been described in Scheme 3. Similarly, Wittig coupling of building blocks **41** and **44** produced the *cis* alkene **12a**, which was deprotected to give the bis-homoallylic alcohol **12**. Compound **12** was reacted with Re_2O_7 and lutidine to produce compound **45a**, the free hydroxyl group was converted to the corresponding mesylate **45b**, and the acetonide was cleaved to produce the free diol **46**. Finally, heating in pyridine afforded compound **7**, which was identical with the product described in Schemes 4 and 5.

The Hybrid Synthetic Approach. This strategy combines the advantages of both approaches described above: the synthetic efficiency of the convergent approach and the diversity of the "naked" carbon skeleton approach. For example, the partially functionalized intermediate **13** (Scheme 8) offers a convenient entry not only to **6** but also to many of the stereoisomers of **6**. Yet, its construction from two fragments, **44** and **47**, facilitates the overall synthetic scheme. Furthermore, the use of diastereomers of **44** could lead to a complete chemical library of all stereoisomers of **6**.

The phosphonium salt **47** was easily obtained from pentadec-4-en-1-ol **17**, by converting it to the corresponding iodide followed by reaction with triphenylphosphine. Wittig coupling of **47** with aldehyde **44** afforded **13a**, and cleavage of the silyl ether produced intermediate **13**. This partially functionalized skeleton could be transformed into variety of stereoisomeric products. For example, compound **6** was synthesized from **13** in four steps: first oxidative cyclization with $CF_3CO_2ReO_3$ (TFAReO$_3$) and lutidine to produce the mono-THF derivative, **48a**, then mesylation to give **48b**, asymmetric dihydroxylation with AD-mix-β to give compound **27**, and, finally, heating in pyridine to produce **6** exclussively. No other diastereomers of **6**, if any formed, could be isolated.

Structure Verification. All samples of either **6** or **7** were found to be indistinguishable by ^1H and ^{13}C NMR, MS, and TLC, independent of the method used for their preparation. The final proof of the absolute configuration of **6** and **7** was obtained by the successful completion of the target natural products **1** and **2**. Yet, to avoid any mistake we verified their absolute stereochemistry by independent synthesis of authentic samples. The stereogenic centers C-4, C-5, C-12, and C-13 were always obtained by the Sharpless AD reaction, which is known to proceed with predictable stereoselectivity. Therefore, we determined the absolute configuration of these four centers with a high degree of confidence. However, the other two stereogenic centers, C-8 and C-9, were obtained by the oxidative cyclization reaction with rhenium(VII) oxide where the stereochemistry is known to be substrate-dependent.[28] Therefore, we examined the absolute configuration of our representative intermediate, **45a**, by comparison with authentic samples in which centers C-8 and C-9 were obtained by other methods.

For this comparison we prepared two diastereomeric reference compounds, **54** and **58** (Scheme 9). Following our previously described method,[11b] diene **51** was converted to the THF lactone, **52**,[8a] via the asymmetric dihydroxylation reaction. Deoxygenation of the free hydroxyl group at C-9 in **52** was carried out using the Barton two-step procedure:[29] first conversion to the corresponding thiocarbonate derivative, **53**, and then treatment with Bu_3SnH to produce compound **54**. The *cis*-THF diastereomer, **58**, was prepared from the bis-homoallylic alcohol **55** (Scheme 9). Vanadium(V) oxide-catalyzed epoxidation of **55** followed by in situ cyclization produced the *cis*-THF derivative **56**.[30] The latter was deoxygenated by using Barton's two-step procedure to produce the thiocarbonate intermediate **57** and then compound **58**.

Our synthetic intermediate **45a** was converted to the mono-THF derivative in six steps (Scheme 9). The free hydroxyl group was converted to thiocarbonate **45c**, which was then deoxygenated with Bu_3SnH to produce **59**. The acetonide function in the latter was hydrolyzed, and the resultant vicinal diol was cleaved using $Pb(OAc)_4$ to produce the corresponding aldehyde **60**. The latter underwent Wittig reaction with heptyltriphenylphosphorane followed by catalytic hydrogenation. The resultant product was found to be identical with **54** and different from **58** by ^1H and ^{13}C NMR spectra. This confirmed the correct absolute configuration of **45a** at position C-8 (and indirectly at C-9 on the basis of relative stereochemistry).

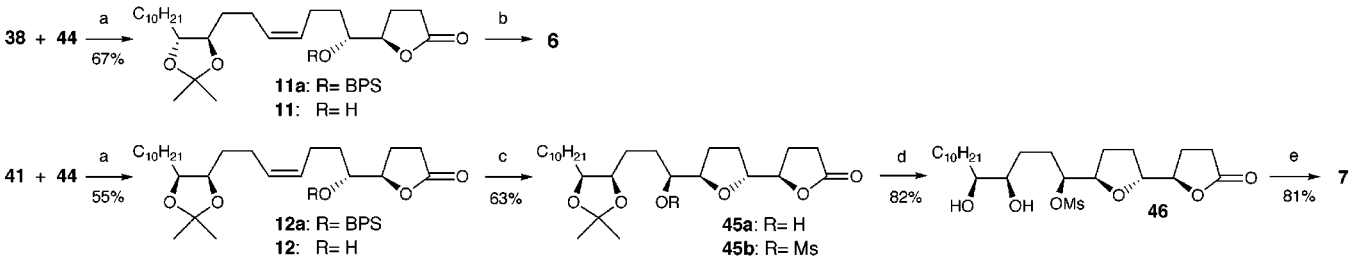
The Final Steps. The butenolide building block **3** was prepared from deca-1,9-diene **61** (Scheme 10). Dihy-

(28) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076.

(29) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609. (c) McCombie, S. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 4.2. (d) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413. (e) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: Boston, 1987; Chapter 5.

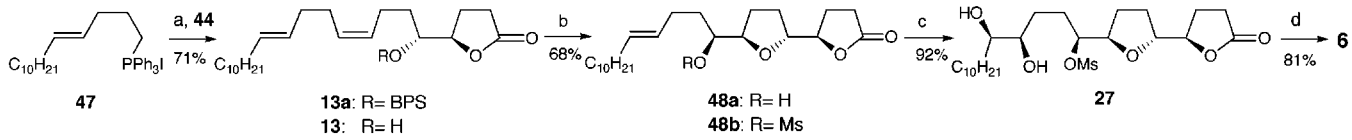
(30) Vanadium(V) oxide catalyzed epoxidation of (Z)-4-alkenol followed by acid-catalyzed cyclization is known to afford *cis*-THF compound as a major product, see: Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975.

Scheme 7. Synthesis of 6 and 7 by Convergent Approach[a]



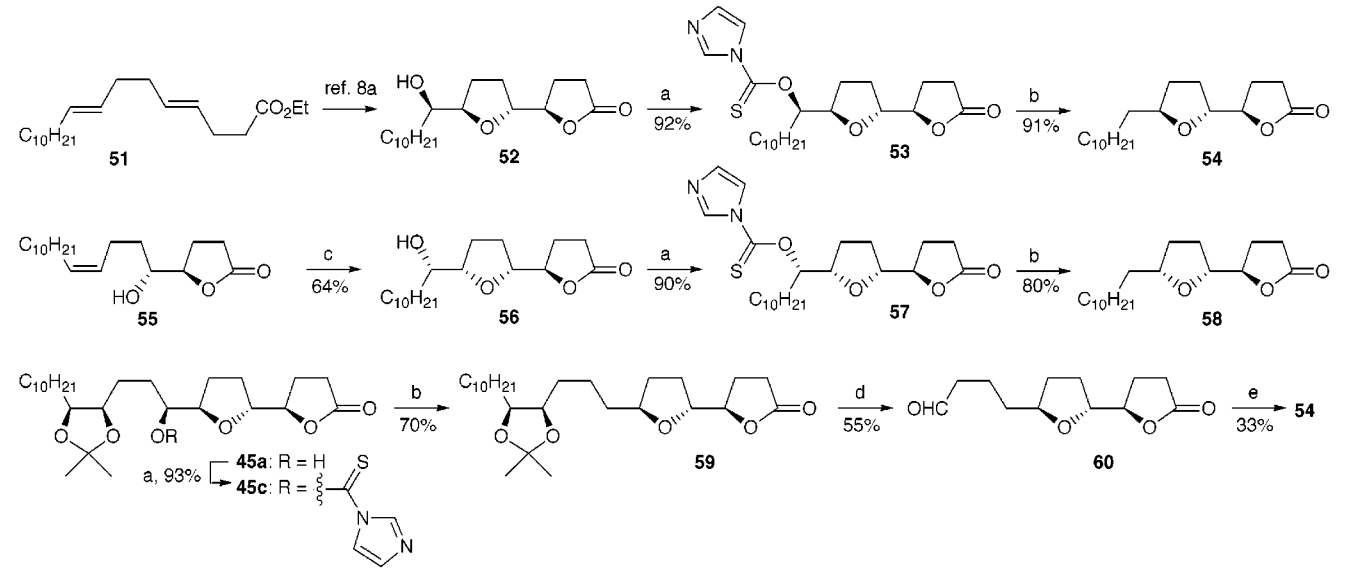
[a] Key: (a) i. $KN(SiMe_3)_2$, THF, HMPA, −78 °C, 2 h, then **44**, −78 °C to rt, 16 h, ii. TBAF, THF, rt, 2 h; (b) See Scheme 3; (c) i. Re_2O_7, lutidine, CH_2Cl_2, 2 h, ii. MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (d) TsOH (20% w/w), MeOH−H_2O (4:1), 60 °C, 16 h; (e) pyridine, 100 °C, 2 h.

Scheme 8. Synthesis of 6 by Hybrid Approach[a]



[a] Key: (a) i. $KN(SiMe_3)_2$, THF, HMPA, −78 °C, 2 h, then **44**, −78 °C to rt, 16 h, ii. TBAF, THF, rt, 2 h; (b) i. $TFAReO_3$, lutidine, CH_2Cl_2, 2 h, ii. MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (c) AD-mix-β, *t*-BuOH−water (2:1), 0 °C, 16 h, (d) pyridine, 100 °C, 2 h.

Scheme 9. Proof for Structure of 6 and 7[a]



[a] Key: (a) thiocarbonyldiimidazole, DMAP, CH_2Cl_2, rt, 12 h; (b) Bu_3SnH, AIBN, dry toluene, 90 °C, 2 h; (c) V_2O_5, TBHP, AcOH, CH_2Cl_2, rt, 5 h; (d) i. TsOH (20% w/w), MeOH−H_2O (4:1), 60 °C, 16 h, ii. $Pb(OAc)_4$, CH_2Cl_2, rt, 1 h; (e) i. $C_7H_{15}PPh_3I$, BuLi, THF, 0 °C, 0.5 h, then **60**, 0.5 h, ii. Pd−C (10%), H_2, EtOH, rt, 2 h.

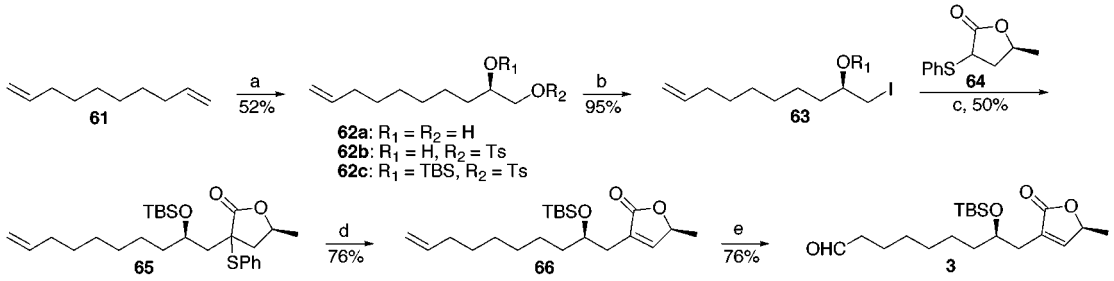
droxylation with AD-mix-β using pyrimidine ligand afforded diol **62a** in 82% ee. The primary hydroxyl was selectively converted to tosylate **62b**, and the secondary hydroxyl group was protected in the form of a silyl ether, **62c**, using TBSOTf at low temperature. The tosylate function was converted to iodide **63** using NaI in refluxing acetone. Lactone **64**[31] was reacted with LDA in THF−HMPA to produce the corresponding lithium enolate.[32] The latter was reacted with iodide **63** to produce intermediate **65**. The sulfide in **65** was oxidized with mCPBA, and the resultant sulfoxide was refluxed in toluene to produce the butenolide **66**. Dihydroxylation of the monosubstituted double bond with OsO_4 followed by oxidative cleavage with $NaIO_4$ produced the desired aldehyde **3**, which was contaminated with ca. 9% of another diastereomer as determined by ^1H NMR spectral analysis.

With all key components of **1** and **2** in hand, we completed the synthesis of these two acetogenins by attachment of the butenolide fragment **3** to either **6** or **7** (Scheme 11). Thus, LAH reduction of **6** produced the corresponding triol **67a**. The primary alcohol was protected as the *tert*-butyldimethylsilyl ether, and the two secondary alcohols were protected as methoxymethyl (MOM) ethers, **67b**. The primary alcohol was then deprotected with tetrabutylammonium fluoride to give alcohol **67c**, which was converted to iodide **67d** and then to the corresponding phosphonium salt **4**. The latter was converted to a Wittig reagent, which was reacted with aldehyde **3** to produce alkene **68**. Finally, homogeneous

(31) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242.

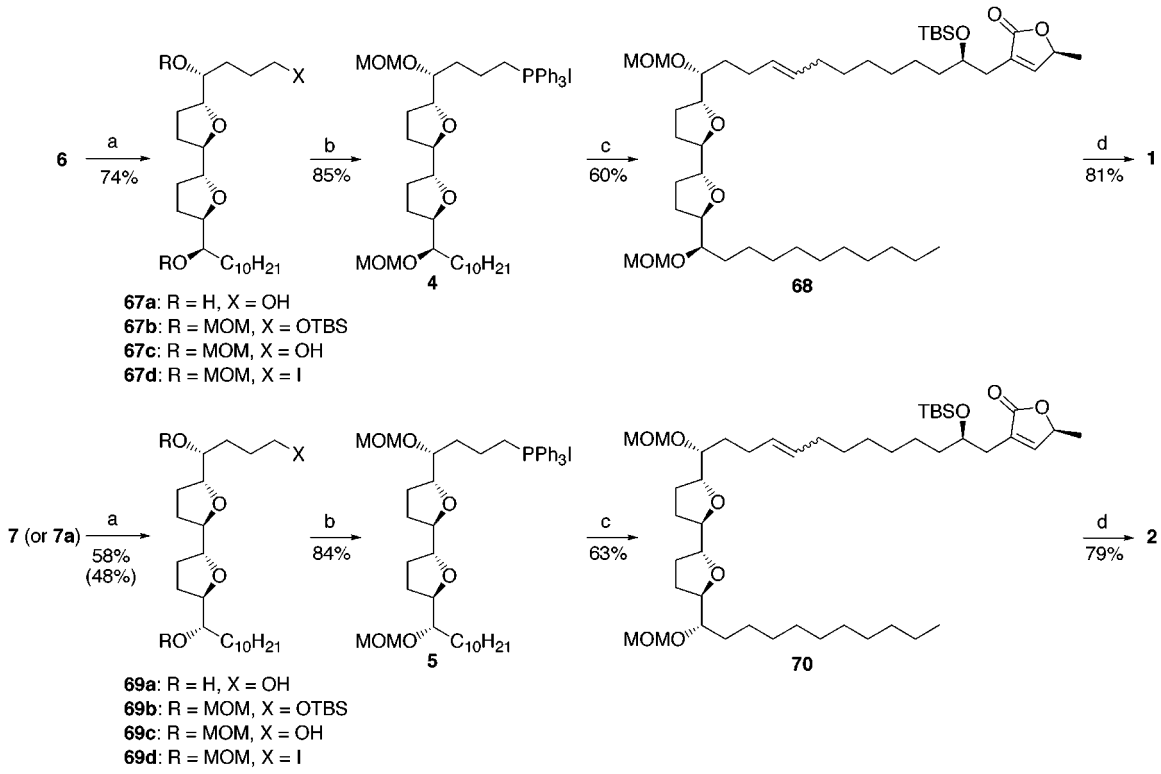
(32) Schaus, S. E.; Brnalt, J.; Jacobsen, E. N. *J. Org. Chem.*, **1998**, *63*, 4876.

Scheme 10. Synthesis of the Side Chain 3[a]



[a] Key: (a) i. AD-mix-β, *t*-BuOH−water (2:1), 0 °C, 16 h, ii. TsCl, collidine, 0 °C, 16 h, iii. TBSOTf, lutidine, CH_2Cl_2, −78 °C, 3 h; (b) NaI, $NaHCO_3$, acetone, reflux, 36 h; (c) LDA, THF, HMPA, compound **64**, −78 °C, then compound **63**, rt, 24 h; (d) i. *m*-CPBA, CH_2Cl_2, 0 °C, 10 min, ii. toluene, 90 °C, 2 h; (e) OsO_4, THF−H_2O, then $NaIO_4$, 2.5 h.

Scheme 11. The Final Steps[a]



[a] Key: (a) i. $LiAlH_4$, ether, 0 °C, then reflux, 2 h, ii. TBDMSCl, *i*-Pr_2EtN, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, then $ClCH_2OMe$, *i*-Pr_2EtN, 0 °C to rt, 12 h, iii. TBAF, THF, 0 °C to rt, 2 h, iv. I_2, PPh_3, imidazole, CH_2Cl_2, rt, 1 h; (b) PPh_3, $NaHCO_3$, CH_3CN, 40 °C, 36 h; (c) BuLi, THF, 0 °C, 15 min, then aldehyde **3**, 15 min; (d) i. $Rh(PPh_3)_3Cl$ (10%, w/w), benzene, EtOH, H_2, rt, 12 h, ii. 5% AcCl in MeOH, CH_2Cl_2, rt, 2 h.

hydrogenation over Wilkinson's catalyst followed by acidic cleavage of the silyl and MOM ethers produced asimicin **1**. Starting with **7** and following the same sequence through **69a**−**d**, **5**, and **70** afforded bullatacin, **2**. Pure asimicin, **1**, and bullatacin, **2**, were obtained by chromatography over silica gel. The spectral data (^1H and ^{13}C NMR) of both synthetic asimicin and bullatacin were identical to those of naturally occurring compounds.

Conclusions

The efficient total synthesis of asimicin, **1**, and bullatacin, **2**, have demonstrated the advantages of three different strategies for the synthesis of the bis-THF acetogenins. The naked carbon skeleton strategy is based on the production of all asymmetric centers by selective placement of the oxygen functions onto an unsaturated, nonfunctionalized carbon skeleton. Diversity in this approach arises from the relative timing of highly stereoselective reactions, such as the Sharpless asymmetric dihydroxylation (AD) reaction, the Kennedy oxidative cyclization (OC) with rhenium(VII) oxide, the Mitsunobu-type alcohol epimerization reaction, and the Williamson etherification reaction. The convergent strategy, which is based on the combinatorial coupling of two series of diastereomeric fragments, enjoys the advantages of both efficiency and versatility. The third approach, which is based on partially functionalized intermediates, combines the advantages of both the linear and the convergent strategies—synthetic efficiency and diversity. We are currently using these strategies for the synthesis of a complete library that contains all 64 stereoisomers of **1** and **2** at their C15−C24 fragment in order to screen them for antitumor, antimalarial, immunosuppressive, and pesticidal activity.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB-VSE double focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Negative mass spectra were obtained with Sciex API 100. Optical rotations were measured in a one-decimeter (1.3 mL) cell using an Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230−400 mesh, Art. 9385) under pressure. THF was dried and distilled over sodium ketyl. AD-mix-β (#39,276-6) was purchased from Aldrich. For the synthesis of **8**, **9**, and **10**, see the Supporting Information.

(4*R*,5*R*,12*R*,13*R*)-5,12,13-Trihydroxytricosa-8-yn-1,4-olide, 24. Compound **8** (1.78 g, 4.76 mmol) was added to a solution of AD-mix-β (13.3 g) and $MeSO_2NH_2$ (0.90 g, 9.4 mmol) in *t*-BuOH−water (1:1, 140 mL) at 0 °C. The mixture was stirred at this temperature for 16 h and then quenched by slow addition of $Na_2S_2O_5$ (14.3 g, 75.3 mmol). The mixture was stirred for 0.5 h, diluted with water, and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was heated in MeOH (10 mL) and aqueous KOH (15%, 10 mL) at 60 °C for 2 h. The reaction mixture was cooled with an ice bath, acidified with cold 3 N HCl, and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was stirred with TsOH (200 mg) in CH_2Cl_2 (20 mL) at rt for 1 h, then washed with saturated solution of $NaHCO_3$, and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was crystallized from EtOAc−MeOH to give **24** (1.5 g, 80%): mp 94−95 °C; $[\alpha]_D$ +20.2 (c = 1.38, MeOH); ^{1}H NMR δ 4.44 (td, J = 7.3, 4.4 Hz, 1H), 3.77 (dt, J = 8.6, 4.2 Hz, 1H), 3.55 (dt, J = 8.9, 5.0 Hz, 1H), 3.49 (s, 1H), 3.42 (m, 1H), 2.58 (m, 2H), 2.40−2.10 (m, 8H), 1.74−1.26 (m and br s, 22H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 178.8, 83.3, 80.5, 79.4, 74.1, 73.1, 71.6, 33.2, 32.4, 31.8, 29.6, 29.5, 29.2, 28.6, 25.6, 23.9, 22.6, 15.1, 14.9, 14.0 ppm; MS 419 (MNa^+).

(4*R*,5*R*,12*R*,13*R*)-5-Hydroxytricosa-12,13-isopropylidenedioxy-8-yn-1,4-olide, 25. TsOH (90 mg) was added to a mixture of **24** (0.61 g, 1.54 mmol) and acetone−2,2-dimethoxypropane (1:1, 10 mL). The mixture was stirred at rt for 0.5 h, diluted with CH_2Cl_2, washed with saturated solution of $NaHCO_3$, and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 9:1) to afford **25** (0.683 g, 95%); $[\alpha]_D$ +19.7 (c = 1.74, $CHCl_3$); ^{1}H NMR δ 4.43 (td, J = 7.3, 4.4 Hz, 1H), 3.74 (m, 1H), 3.62 (m, 2H), 2.68−2.46 (m, 2H), 2.41 (d, J = 5.9 Hz, 1H), 2.38−2.08 (m, 6H), 1.67 (m, 4H), 1.49 (m, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.40−1.22 (m, 15H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.2, 108.0, 82.8, 80.6, 80.5, 79.7, 79.2, 72.5, 32.9, 32.5, 31.9, 31.8, 29.7, 29.54, 29.47, 29.3, 28.6, 27.3, 27.2, 26.1, 24.0, 22.6, 15.6, 15.1, 14.1 ppm; MS 459 (MNa^+).

(*cis*,4*R*,5*R*,12*R*,13*R*)-5-Hydroxy-12,13-isopropylidenedioxytricosa-8-en-1,4-olide, 11. Lindlar catalyst (64 mg) was added to a solution of **25** (0.64 g, 1.46 mmol) in a mixture of hexanes−cyclohexene−Et_3N (2:2:1, 20 mL). The mixture was stirred under an H_2 atmosphere at °C for 12 h and then filtered through Celite, solvents were removed, and the crude product was purified by column chromatography (silica gel, hexanes−EtOAc, 9:1) to give **11** (0.60 g, 95%): $[\alpha]_D$ −1.9 (c = 2.1, $CHCl_3$); ^{1}H NMR δ 5.41 (m, 2H), 4.42 (td, J = 7.4, 4.6 Hz, 1H), 3.60 (m, 3H), 2.67−2.48 (m, 2H), 2.30−2.05 (m, 7H), 1.64−1.44 (m, 8H), 1.39 (s, 3H), 1.38 (s, 3H), 1.36−1.22 (m and br s, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.2, 130.2, 129.0, 107.8, 83.0, 80.9, 80.3, 72.7, 32.9, 32.5, 31.8, 29.7, 29.53, 29.45, 29.3, 28.6, 27.3, 26.1, 24.0, 23.9, 23.0, 22.6, 14.1 ppm; HRMS ($C_{26}H_{46}O_5Na$ = 461.3243) found 461.3229 (MNa^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-9-Hydroxy-12,13-isopropylidenedioxy-5,8-oxidotricosa-1,4-olide, 26a. Re_2O_7 (3.3 g, 6.81 mmol) was added in portions to a solution of compound **11** (1.0 g, 2.7 mmol) and 2,6-lutidine (2.4 mL, 20.4 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred overnight at rt and then quenched by dropwise addition of saturated solution of $NaHCO_3$ (8 mL) and H_2O_2 (35% in water, 8 mL). After stirring for 20 min, the mixture was extracted with CH_2Cl_2, the organic layer was washed with water and dried over $MgSO_4$, solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 3:1) to give **26a** (0.654 g, 64%) in the form of a colorless oil: $[\alpha]_D$ +9.7 (c = 0.65, $CHCl_3$); ^{1}H NMR δ 4.47 (ddd J = 8.2, 5.5, 3.0 Hz, 1H), 4.09 (ddd J = 10.3, 7.4, 3.0 Hz, 1H), 3.89 (m, 1H), 3.79 (m, 1H), 3.59 (m, 2H), 2.68 (ddd, J = 17.6, 10.0, 6.8 Hz, 1H), 2.46 (ddd, J = 17.6, 10.0, 6.6 Hz, 1H), 2.40 (br d, J = 2.9 Hz, 1H), 2.35−2.12 (m, 2H), 2.08 (m, 1H), 1.87 (m, 4H), 1.70−1.40 (m, 7H), 1.38 (s, 6H), 1.36−1.22 (m and br s, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.5, 108.0, 83.2, 81.5, 81.1, 81.06, 81.0, 71.7, 32.7, 31.9, 29.8, 29.6, 29.4, 29.3, 29.25, 28.2, 28.0, 27.3, 27.2, 26.1, 25.4, 24.6, 22.6, 14.1 ppm; HRMS ($C_{26}H_{46}O_6Cs$ = 587.2349) found 587.2373 (MCs^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-12,13-Isopropylidinedioxy-9-mesyloxy-5,8-oxidotricosa-1,4-olide, 26b. MsCl (0.15 mL, 1.8 mmol) was added to a solution of **26a** (0.412 g, 0.9 mmol) and Et_3N (0.5 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) at −30 °C. The mixture was stirred at this temperature for 0.5 h, then quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 7:3) to yield **26b** (0.45 g, 94%) in the form of a colorless oil: $[\alpha]_D$ +13.6 (c = 1.60, $CHCl_3$); ^{1}H NMR δ 4.78 (dt, J = 8.7, 3.5 Hz, 1H), 4.44 (ddd, J = 8.2, 5.6, 2.8 Hz, 1H), 4.06 (m, 2H), 3.57 (m, 1H), 3.49 (td, J = 8.9, 2.6 Hz, 1H), 3.03 (s, 3H), 2.63 (ddd, J = 16.7, 10.0, 6.6 Hz, 1H), 2.45 (ddd, J = 16.7, 10.0, 6.8 Hz, 1H), 2.28 (m, 1H), 2.20−1.55 (m, 9H), 1.47 (m, 4H), 1.35 (s, 3H), 1.34 (s, 3H), 1.40−1.22 (m and br s, 14H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.3, 108.0, 83.7, 81.1, 81.0, 80.9, 80.8, 80.6, 38.5, 32.7, 31.8, 29.7, 29.6, 29.5, 29.2, 28.9, 28.5, 28.1, 27.7, 27.24, 27.2, 26.0, 24.6, 22.6, 14.1 ppm; HRMS ($C_{27}H_{48}O_8SCs$ = 665.2124) found 665.2150 (MCs^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-12,13-Dihydroxy-9-mesyloxy-5,8-oxidotricosa-1,4-olide, 27. TsOH (0.3 g) was added to a solution of **26b** (0.48 g, 0.92 mmol) in MeOH−water (9:1, 5 mL). The mixture was stirred at rt for 16 h, diluted with a saturated solution of $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to give **27** (0.40 g, 90%) in the form of a colorless oil: ^{1}H NMR δ 4.79 (dt, J = 7.8, 4.0 Hz, 1H), 4.44 (ddd, J = 8.2, 5.7, 2.9 Hz, 1H), 4.05 (m, 2H), 3.36 (m, 2H), 3.03 (s, 3H), 2.63 (br s, 2H), 2.59 (m, 1H), 2.45 (ddd, J = 17.1, 10.0, 6.8 Hz, 1H), 2.27 (m, 1H), 2.15−1.75 (m, 5H), 1.66 (m, 2H), 1.42 (m, 3H), 1.35−1.20 (m and br s, 17H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.5, 84.1, 81.1, 80.6, 74.3, 74.1, 38.4, 33.4, 31.8, 29.6, 29.5, 29.2, 28.1, 28.0, 27.7, 26.1, 25.6, 24.5, 22.6, 14.0 ppm; HRMS ($C_{24}H_{44}O_8SCs$ = 625.1811) found 625.1840 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-13-Hydroxy-5,8:9,12-dioxidotricosa-1,4-olide, 6. Compound **27** (0.714 g, 1.45 mmol) was dissolved in pyridine (20 mL), and the mixture was heated at reflux for 3 h, cooled to rt, diluted with water, and extracted with EtOAc. The organic layer was first washed with a cold 3 N HCl and then with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to give **6** (0.46 g, 81%): mp 108−109 °C; $[\alpha]_D$ +4.0 (c = 0.25, $CHCl_3$); ^{1}H NMR δ 4.46 (ddd, J = 8.2, 5.8, 2.6 Hz, 1H), 4.09 (td, J = 7.2, 2.6 Hz, 1H), 3.88 (m, 2H), 3.78 (dt, J = 8.1, 6.2 Hz, 1H), 3.37 (m, 1H), 2.69 (ddd, 17.4, 9.4, 7.8 Hz, 1H), 2.44 (m, 2H), 2.25 (m, 2H), 2.10−1.85 (m, 5H), 1.78−1.54 (m, 3H), 1.52−1.22 (m and br s, 18H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.7, 83.0, 82.5, 81.45, 81.41, 81.0, 74.0, 33.5, 31.9,

29.7, 29.6, 29.3, 28.8, 28.5, 28.3, 28.26, 27.7, 25.6, 24.7, 22.6, 14.1 ppm; HRMS ($C_{23}H_{40}O_5Cs$ = 529.1930) found 529.1954 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-13-(4-Nitrobenzyloxy)-5,8:9,12-dioxidotricosa-1,4-olide, 7a, from 6. DEAD (0.57 mL, 3.6 mmol) was added dropwise to a solution of **6** (470 mg, 1.2 mmol), PPh_3 (944 mg, 3.6 mmol), and 4-nitrobenzoic acid (602 mg, 3.6 mmol) in dry benzene (10 mL). The mixture was stirred at rt for 16 h and then was worked up by passing it through a double layer column of alumina over silica gel to give the nitrobenzoate ester **7a** (510 mg, 78%): ^{1}H NMR δ 8.26 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H), 5.21 (dt, J = 7.7, 5.2 Hz, 1H), 4.43 (ddd, J = 8.1, 5.9, 2.6 Hz, 1H), 4.10 (q, J = 7.3 Hz, 1H), 4.03 (td, J = 6.9, 2.2 Hz, 1H), 3.84 (m, 2H), 2.65 (ddd, J = 17.3, 9.9, 7.4 Hz, 1H), 2.41 (ddd, J = 17.3, 9.2, 7.0 Hz, 1H), 2.21 (m, 2H), 2.03−1.67 (m, 8H), 1.35−1.20 (m and br s, 18H), 0.84 (t, J = 7.0 Hz, 3H); MS 568 (MNa^+).

(4*R*,5*R*,8*R*,9*R*)-5,8,9-Trihydroxytricosa-12-yne-1,4-olide, 28. Using the above-described procedure for the conversion of **8** to **24**, compound **9** (3.94 g, 10.5 mmol) was dihydroxylated using AD-mix-β (29.4 g) and $MeSO_2NH_2$ (2.0 g, 21 mmol). Acid−base treatments of the crude product as above afforded **28** (3.0 g, 72%) in the form of white crystals from EtOAc: mp 76−78 °C; $[\alpha]_D$ +4.4 (c = 1.65, MeOH); ^{1}H NMR δ 4.44 (td, J = 7.0, 4.0 Hz, 1H), 4.12 (br s, 1H), 3.79 (br s, 1H), 3.61 (m, 1H), 3.54 (m, 1H), 3.45 (m, 1H), 3.18 (br s, 1H), 2.62 (ddd, J = 18.0, 10.0, 5.5 Hz, 1H), 2.49 (ddd, J = 18.0, 9.8, 8.2 Hz, 1H), 2.35−2.08 (m, 6H), 1.67 (m, 6H), 1.45 (m, 2H), 1.40−1.20 (m and br s, 14H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 178.1, 83.3, 81.1, 79.4, 74.1, 73.6, 71.4, 32.7, 31.9, 29.8, 29.6, 29.5, 29.3, 29.14, 29.08, 28.9, 28.6, 24.0, 22.6, 18.7, 15.3, 14.1 ppm; MS 419 (MNa^+).

(4*R*,5*R*,8*R*,9*R*)-5-Hydroxytricosa-8,9-isoproylidenedioxy-12-yne-1,4-olide, 29. Compound **28** (2.37 g, 6.3 mmol) was allowed to react with acetone (12 mL), 2,2-dimethoxypropane (12 mL), and TsOH (30 mg), as described above for the conversion of the **24** to **25**. Purification by column chromatography (silica gel, hexanes−EtOAc, 4:1) afforded **29** (2.57 g, 98%) in the form of oil: $[\alpha]_D$ +9.8 (c = 3.72, $CHCl_3$); ^{1}H NMR δ 4.44 (td, J = 7.0, 4.0 Hz, 1H), 3.75 (dt, J = 8.2, 5.8 Hz, 1H), 3.70−3.60 (m, 2H), 3.05 (d, J = 4.5 Hz, 1H), 2.64 (ddd, J = 18.0, 10.0, 5.5 Hz, 1H), 2.50 (ddd, J = 18.0, 9.9, 8.2 Hz, 1H), 2.40−2.10 (m, 6H), 1.90−1.60 (m, 6H), 1.47 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H), 1.40−1.22 (m, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.4, 108.3, 82.9, 80.8, 80.3, 79.5, 78.9, 73.2, 32.2, 31.8, 29.8, 29.49, 29.47, 29.2, 29.1, 29.0, 28.96, 28.8, 28.5, 27.14, 27.13, 23.9, 22.5, 18.6, 15.5, 14.1 ppm; MS 437 (MH^+), 459 (MNa^+).

(*cis*,4*R*,5*R*,8*R*,9*R*)-5-Trihydroxytricosa-8,9-isoproylidenedioxy-12-en-1,4-olide, 30a. Lindlar catalyst (257 mg) was added to a solution of **29** (2.57 g, 6.17 mmol) in hexane−cyclohexene−Et_3N (2:2:1, 50 mL), and the mixture was stirred under an H_2 atmosphere at temperatures between −10 and −4 °C for 16 h and then filtered through Celite. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 4:1) to give **30a** (2.56 g, 99%) in the form of oil: $[\alpha]_D$ +2.6 (c = 2.48, $CHCl_3$); ^{1}H NMR δ 5.37 (m, 2H), 4.45 (td, J = 7.0, 4.0 Hz, 1H), 3.64 (m, 3H), 3.15 (d, J = 4.6 Hz, 1H), 2.65 (ddd, J = 17.9, 10.0, 5.6 Hz, 1H), 2.51 (ddd, J = 17.9, 10.0, 8.2 Hz, 1H), 2.30−2.10 (m, 4H), 2.03 (q, J = 6.8 Hz, 2H), 1.77−1.52 (m, 6H),1.39 (s, 3H), 1.38 (s, 3H), 1.40−1.22 (m and br s, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.4, 131.0, 128.4, 108.2, 82.9, 80.6, 80.3, 73.3, 32.6, 31.9, 29.9, 29.64, 29.6, 29.5, 29.3, 29.2, 28.5, 27.3, 27.19, 27.15, 24.0, 23.7, 22.6, 14.1 ppm; MS 439 (MH^+), 461 (MNa^+).

(*cis*,4*R*,5*R*,8*R*,9*R*)-5-Mesyloxytricosa-8,9-isoproylidenedioxy-12-en-1,4-olide, 30b. MsCl (1.2 mL, 9 mmol) was added to a cold (−10 °C) solution of **30a** (2.61 g, 5.95 mmol) and Et_3N (3 mL, 21.5 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at this temperature for 2 h, then quenched with water, and extracted with CH_2Cl_2, and the organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 7:3) to give **30b** (2.82 g, 95%) in the form of oil: ^{1}H NMR δ 5.38 (m, 2H), 4.78 (dt, J = 7.6, 5.6 Hz, 1H), 4.64 (td, J = 7.6, 5.6 Hz, 1H), 3.62 (m, 2H), 3.13 (s, 3H), 2.60 (m, 2H), 2.35 (m, 1H), 2.16 (m, 3H), 2.02 (m, 2H), 1.93 (m, 2H), 1.80−1.50 (m, 4H), 1.38 (s, 3H), 1.36 (s, 3H), 1.40−1.22 (m and br s, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 175.9, 131.0, 128.4, 108.2, 82.8, 80.2, 79.7, 79.5, 39.1, 32.6, 31.9, 29.7, 29.6, 29.5, 29.3, 28.0, 27.7, 27.6, 27.3, 27.24, 27.2, 24.2, 23.7, 22.6, 14.1 ppm; MS 649 (MCs^+).

(4*R*,5*S*,8*R*,9*R*)-Methyl 4,5-epoxytricosa-8,9-isopropylinedioxy-12-enoate, 31. K_2CO_3 (1.5 g, 11.3 mmol) was added to a solution of **30b** (2.8 g, 5.68 mmol) in MeOH (15 mL). The mixture was stirred at rt for 0.5 h and then worked up with CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 4:1) to afford **31** (2.17 g, 86%) in the form of oil: $[\alpha]_D$ +31.1 (c = 1.98, $CHCl_3$); ^{1}H NMR δ 5.34 (m, 2H), 3.66 (s, 3H), 3.58 (m, 2H), 2.95 (m, 2H), 2.47 (m, 2H), 2.16 (m, 2H), 2.01 (q, J = 6.8 Hz, 2H), 1.90 (m, 1H), 1.76 (m, 3H), 1.56 (m, 4H), 1.35 (s, 3H), 1.34 (s, 3H), 1.40−1.22 (m and br s, 16H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 173.2, 130.9, 128.5, 108.1, 80.6, 80.3, 57.2, 56.1, 51.6, 32.8, 31.9, 30.9, 30.0, 29.7, 29.6, 29.5, 29.3, 27.3, 27.24, 27.2, 24.9, 23.8, 23.3, 22.6, 14.1 ppm; MS 585 (MCs^+).

(*cis*,4*R*,5*R*,8*R*,9*R*)-9-Hydroxy-5,8-oxidotricosa-12-en-1,4-olide, 32. $BF_3{\cdot}Et_2O$ (0.31 g, 2.24 mmol) was added dropwise to a cold (−78 °C) solution of **31** (1.02 g, 2.36 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at this temperature for 5 h, then worked up with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−EtOAc, 7:3) to yield **32** (372 mg, 43%): $[\alpha]_D$ −7.3 (c = 2.06, $CHCl_3$); ^{1}H NMR δ 5.37 (m, 2H), 4.48 (ddd, J = 8.2, 5.4, 2.9 Hz, 1H), 4.06 (td, J = 7.6, 2.8 Hz, 1H), 3.84 (dt, J = 8.2, 5.7 Hz, 1H), 3.39 (m, 1H), 2.64 (ddd, J = 17.6, 10.0, 7.0 Hz, 1H), 2.44 (ddd, J = 17.6, 10.0, 6.5 Hz, 1H), 2.30−1.90 (m, 10H), 1.70 (m, 1H), 1.45 (m, 2H), 1.40−1.23 (m and br s, 16H), 0.85 (t, J = 6.8 Hz, 3H); HRMS ($C_{23}H_{40}O_4Na$ = 403.2820) found 403.2816 (MNa^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-13-Hydroxy-5,8:9,12-dioxidotricosa-1,4-olide, 7. Re_2O_7 (0.265 g, 0.54 mmol) was added to a mixture of **32** (65 mg, 0.17 mmol) and periodic acid (50.6 mg, 0.22 mmol) in dry CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 1 h. A saturated solution of $NaHCO_3$ was added followed by H_2O_2 (1 mL), the mixture was extracted with CH_2Cl_2, the organic layer was washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to give **7** (47 mg, 69%) in the form of crystals: mp: 97−98 °C; $[\alpha]_D$ −4.3 (c = 2.20, $CHCl_3$); ^{1}H NMR δ 4.48 (ddd, J = 7.9, 6.0, 2.4 Hz, 1H), 4.12 (td, J = 7.0, 2.5 Hz, 1H), 3.93−3.80 (m, 4H), 2.70 (ddd, J = 17.6, 9.6, 8.1 Hz, 1H), 2.44 (ddd, J = 17.6, 9.4, 7.0 Hz, 1H), 2.25 (m, 2H), 2.10−1.72 (m, 8H), 1.66 (m, 2H), 1.46 (m, 1H), 1.40−1.24 (m and br s, 16H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 177.7, 83.0, 82.6, 82.0, 81.6, 80.8, 71.3, 32.5, 31.9, 29.7, 29.6, 29.5, 29.3, 28.8, 28.34, 28.3, 27.7, 26.0, 24.5, 22.6, 14.1 ppm; HRMS ($C_{23}H_{40}O_5Na$ = 419.2773) found 419.2785 (MNa^+).

(*cis*,4*R*,5*R*)-5-Hydroxytricosa-8-en-12-yn-1,4-olide, 33. Using the above-described procedure for the conversion of **8** to **24**, compound **10** (3.86 g, 10.3 mmol) was dihydroxylated with AD-mix β (14.03 g) and $MeSO_2NH_2$ (0.95 g, 10 mmol) in *t*-BuOH−water (1:1, 100 mL). Acid−base treatment of the crude product as above afforded **33** (2.12 g, 5.87 mmol, 57%) in the form of crystals from EtOAc: mp 38−39 °C; $[\alpha]_D$ −18.7 (c = 1.00, MeOH); ^{1}H NMR δ 5.45 (m, 2H), 4.41 (td, J = 7.4, 5.0 Hz, 1H), 3.60 (m, 1H), 2.56 (m, 2H), 2.30−2.05 (m, 11H), 2.70−1.20 (m and br s, 18H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 129.6, 129.4, 83.0, 80.7, 79.5, 73.0, 32.6, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.6, 27.0, 24.1, 23.2, 22.7, 19.1, 18.7, 14.1 ppm; MS 385 (MNa^+).

(4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-5,8-oxidotricosa-12-yne-1,4-olide, 34. Compound **33** (0.35 g, 0.96 mmol) was added to a mixture of Re_2O_7 (1.4 g, 2.89 mmol) and 2,6-lutidine (0.41 g,

3.84 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at rt for 8 h and then worked up with a saturated solution of $NaHCO_3$ (10 mL) and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and purified by column chromatography (silica gel, hexanes− EtOAc, 1:1) to afford **34** (0.25 g, 68%): mp 58−59 °C; $[\alpha]_D$ −16.6 (c = 1.00, $CHCl_3$); ^{1}H NMR δ 4.46 (ddd, J = 8.2, 5.5, 3.0 Hz, 1H), 4.05 (m, 1H), 3.88 (m, 2H), 2.64 (m, 1H), 2.47 (m, 1H), 2.35−1.80 (m, 11H), 1.65−1.40 (m, 4H), 1.38−1.22 (m and br s, 14H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 83.2, 81.4, 81.2, 81.1, 79.2, 71.1, 31.9, 31.8, 29.6, 29.5, 29.3, 29.1, 29.1, 28.9, 28.2, 28.0, 25.3, 24.7, 22.7, 18.7, 15.5, 14.1 ppm; MS 379 (MH^+), 401 (MNa^+).

(4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-5,8-oxidotricosa-12-en-1,4-olide, 35a. Lindlar catalyst (50 mg) was added to a solution of **33** (0.25 g, 0.66 mmol) in hexane−cyclohexene−Et_3N (2:2:1, 3 mL) under an H_2 atmosphere. The mixture was stirred at temperatures between −10 and −4 °C for 16 h and filtered through Celite, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to give **35a** (0.235 g, 92%): ^{1}H NMR δ 5.37 (M, 2H), 4.45 (m, 1H), 4.08 (m, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 2.70−2.60 (m, 1H), 2.50−2.38 (m, 1H), 2.34−1.84 (m, 12H), 1.68 (br s, 1H), 1.41 (q, J = 7.7 Hz, 2H), 1.38−1.22 (m and br s, 14H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 130.9, 128.7, 83.4, 81.4, 81.1, 71.2, 32.5, 31.9, 29.7, 29.6, 29.5, 29.3, 28.2, 28.0, 27.2, 24.9, 24.7, 23.7, 22.7, 14.1 ppm; HRMS ($C_{23}H_{40}O_4Na$ = 403.2824) found 403.2835 (MNa^+).

(4*R*,5*R*,8*R*,9*S*)-9-Mesyloxy-5,8-oxidotricosa-12-en-1,4-olide, **35b.** Following the above-described procedure for the conversion of **26a** to **26b**, compound **35a** (0.268 g, 0.69 mmol) was treated with MsCl (0.33 mL, 2.3 mmol) and Et_3N (3 mL, 21.5 mmol) in CH_2Cl_2 (2 mL) at 0 °C. Purification by column chromatography (silica gel, hexanes−EtOAc, 7:3) afforded **35b** (0.22 g, 71%) in the form of oil: ^{1}H NMR δ 5.42 (m, 1H), 5.31 (m, 1H), 4.80 (ddd, J = 8.2, 4.5, 3.4 Hz, 1H), 4.46 (ddd, J = 8.0, 5.5, 2.6 Hz, 1H), 4.07 (m, 2H), 3.04 (s, 3H), 2.66 (ddd, J = 16.8, 10.0, 6.7 Hz, 1H), 2.47 (ddd, J = 16.8, 10.0, 6.7 Hz, 1H), 2.30−1.86 (m, 12H), 1.63 (m, 2H), 1.40−1.22 (m and br s, 14H), 0.88 (t, J = 7.2 Hz, 3H); HRMS ($C_{24}H_{42}O_6SCs$ = 591.1776) found 591.1778 (MCs^+).

(*cis*,4*R*,5*R*,8*R*,9*R*)-9-Hydroxy-5,8-oxidotricosa-12-en-1,4-olide, **32.** Cesium propionate (0.69 g, 2.47 mmol) was added to the solution of **35b** (0.22 g, 0.49 mmol) and 18-crown-6 (100 mg) in DMF (1 mL), and the mixture was heated at 100 °C for 24 h. Workup with water and CH_2Cl_2 followed by purification by column chromatography (silica gel, hexanes−EtOAc, 7:3) gave the corresponding propionate ester **32a** (0.191 g, 88%) in the form of oil: $[\alpha]_D$ −7.3 (c = 2.06, $CHCl_3$).

A mixture of **32a** (0.191 g, 0.43 mmol) in aqueous KOH (15%, 1 mL) and THF (1 mL) was stirred at rt for 16 h, then cooled, acidified with 3 N HCl, and extracted with EtOAc. Solvents were removed under reduced pressure, the residue was dissolved with TsOH (20 mg) in CH_2Cl_2, and the mixture was stirred at rt for 2 h and then worked up with a saturated solution of $NaHCO_3$ and CH_2Cl_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 7:3) to give **32** (0.109 g, 66%): $[\alpha]_D$ −7.3 (c = 2.06, $CHCl_3$). ^{1}H NMR and ^{13}C NMR spectra were found to be identical with those of the above-described **32** which was obtained from **31**.

(4*R*,5*R*)-4,5-Isopropylidenedioxypentadecanol, 37a. $LiAlH_4$ (2.88 g, 7.6 mmol) was added in portions to a solution of **36**[11e] (6.5 g, 25.0 mmol) in dry ether (50 mL) at 0 °C. The mixture was stirred at 0 °C, then refluxed for another 2 h and cooled, diluted with ether, and worked up by dropwise addition of water. After all inorganic material was precipitated, the solid was filtered through Celite and the filtrate was evaporated to give crude corresponding triol (6.3 g, 98%): mp 81 °C; $[\alpha]_D$ +20.0 (c = 0.73, MeOH); ^{1}H NMR δ 3.70−3.56 (m, 2H), 3.81 (m, 2H), 1.98 (m, 5H), 1.71−1.20 (m and br s, 20H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 74.1, 73.9, 62.1, 33.1, 31.7, 29.9, 29.5, 29.4, 29.1, 28.6, 25.6, 22.5, 13.8 ppm; HRMS ($C_{15}H_{33}O$ = 261.2430) found 261.2436 (MH^+).

The above-mentioned triol (4.5 g, 17.2 mmol) and TsOH (0.46 g, 2.4 mmol) were dissolved in a mixture of acetone−hexanes 1:2 (140 mL), and the solution was refluxed for 6 h with azeotrope distillation. The reaction mixture was worked up by addition of a saturated solution of $NaHCO_3$ and extraction with ether. Solvents were removed, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 7:3) to give **37a** (3.61 g, 70%): $[\alpha]_D$ +21.5 (c = 5.3, $CHCl_3$); ^{1}H NMR δ 3.63−3.50 (m, 4H), 2.28 (br s, 1H), 1.68−1.18 (m, 25H), 0.81 (t, J = 6.8 Hz, 3H);^{13}C NMR δ 107.9, 81.1, 80.6, 62.3, 32.7, 31.7, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 27.2, 27.1, 25.9, 22.6, 14.1; HRMS ($C_{18}H_{37}O$ = 301.2743) found 301.2735 (MH^+).

(4*R*,5*R*)-1-Iodo-4,5-isopropylidenedioxypentadecane, 37b. I_2 (5.24 g, 20.6 mmol) was added to a solution of **37a** (5.18 g, 17.2 mmol), PPh_3 (6.76 g, 25.8 mmol), and imidazole (1.75 g, 25.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The mixture was stirred at rt for 2 h, and a saturated solution of $NaHCO_3$ was added followed by I_2 until the color started appearing. The reaction mixture was worked up with hexanes and water, and the organic phase was washed with a 10% aqueous $Na_2S_2O_3$ solution. Solvents were removed under vacuum, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 19:1) to give **37b** (6.35 g, 90%): ^{1}H NMR δ 3.53 (m, 2H), 3.17 (t, J = 6.6 Hz, 2H), 1.97−1.85 (m, 2H), 1.62−1.21 (m and br s, 25H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 108.0, 80.9, 79.9, 33.6, 32.9, 31.9, 30.1, 29.9, 29.7, 29.6, 29.5, 27.3, 27.2, 26.2, 22.7, 14.1, 6.9; MS 409 $(M - H)^-$.

(4*R*,5*R*)-4,5-Isopropylidendioxypentadecan-1-yltriphenyphosphoniumiodide, 38. A mixture of iodide **37b** (5.0 g, 12.2 mmol), PPh_3 (6.47 g, 24.7 mmol), and $NaHCO_3$ (2.07 g, 24.7 mmol) in CH_3CN (150 mL) was heated at reflux for 16 h. Solvents were evaporated, and the residue was redissolved in CH_2Cl_2. Inorganic material was removed by filtration, solvents were removed, and the residue was triturated with ether to afford **38** (8.17 g, 95%) as thick syrup: ^{1}H NMR δ 7.75 (m, 10H), 7.68 (m, 5H), 3.67 (m, 2H), 3.49 (m, 2H), 1.82−1.16 (m and br s, 28H), 0.79 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 135.1, 133.8, 133.7, 130.5, 130.4, 118.5, 117.7, 108.0, 81.2, 80.2, 32.6, 29.7, 29.6, 29.5, 29.3, 27.4, 27.3, 26.2, 22.7, 19.9, 19.8, 14.1 ppm; HRMS 545.3535 $(M - I)^+$.

(4*R*,5*S*)-1-Iodo-4,5-isopropylidenedioxypentadecane, 40b. Alcohol **40a** (3.22 g, 10.7 mmol), which was produced from **36** as in ref 11e, was converted to **40b** using PPh_3 (4.19 g, 16.0 mmol), imidazole (1.09 g, 16.0 mmol), and I_2 ((3.24 g, 12.8 mmol) in CH_2Cl_2 (70 mL). Workup and purification by silica gel (hexanes−EtOAc, 4:1) as above for compound **37b** afforded pure **40b** as an oil (3.73 g, 92%): $[\alpha]_D$ +16.6 (c = 0.98, $CHCl_3$); ^{1}H NMR δ 4.06−3.98 (m, 2H), 3.24 (t, J = 6.8 Hz, 2H), 1.86−1.98 (m, 2H), 1.64−1.25 (m and br s, 25H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR δ 107.5, 78.0, 77.3, 31.9, 30.6, 30.1, 29.7, 29.6, 29.5, 29.3, 28.6, 26.3, 26.0, 22.7, 14.1, 7.1 ppm; MS 409 $(M - H)^-$.

(4*R*,5*S*)-4,5-Isopropyldiendioxypentadecan-1-yltriphenylphosphoniumiodide, 41. Iodide **40b** (3.2 g, 7.8 mmol) was converted to compound **41** (4.46 g, 85%) using PPh_3 (4.14 g, 15.8 mmol) and $NaHCO_3$ (2.07 g, 24.7 mmol) in CH_3CN (85 mL) as above for compound **38**: $[\alpha]_D$ +15.3 (c = 1.38, $CHCl_3$); ^{1}H NMR δ 7.78 (m, 10H), 7.68 (m, 5H), 4.10 (m, 1H), 4.02 (m, 1H), 3.91−3.79 (m, 1H), 3.59−3.49 (m, 1H), 1.89−1.19 (m and br s, 28H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 135.3, 133.9, 133.8, 130.6, 130.3, 118.7, 117.8, 107.6, 78.2, 77.7, 32.0, 30.3, 30.2, 29.7, 29.5, 28.7, 26.6, 26.1, 23.0, 22.8, 22.5, 19.7, 14.3 ppm; MS 546 $(M - I)^-$.

Ethyl 8-Benzyloxy-4-*en*-octenoate, 42. 4-Benzyloxy-1-butanal[27] (13.7 g, 76.9 mmol) was reacted with vinylmagnesium bromide (1 M solution in THF, 84 mL, 84 mmol) in dry THF (137 mL) at 0 °C (0.5 h) to afford the corresponding allylic alcohol (11.44 g, 73%) as an oil after purification by column chromatography (silica gel, hexanes−EtOAc, 4:1): ^{1}H NMR δ 7.32 (m, 5H), 5.85 (ddd, J = 10.4, 6.2, 0.8 Hz, 1H), 5.22 (dt, J = 17.2, 0.8 Hz, 1H), 5.03 (dt, J = 11.2, 1.2 Hz, 1H), 4.50 (s, 2H), 4.01 (td, J = 7.2 Hz, 1H), 3.50 (t, J = 6.0 Hz, 2H), 1.73−1.43 (m, 3H); ^{13}C NMR δ 141.1, 138.2, 128.5, 127.8, 127.7, 127.6, 114.4, 73.0, 72.6, 70.3, 34.2, 25.8 ppm.

The above-mentioned alcohol (11.44 g, 56.6 mmol) was transformed to ester **42** (12.96 g, 83%) as an oil, by being

refluxed (2.5 h) with triethyl orthoacetate (19.32 g, 119 mmol) and propionic acid (0.41 g, 5.6 mmol) in xylenes (50 mL) and then isolated by distillation under reduced pressure (130 °C, 0.5 mmHg): ^{1}H NMR δ 7.33 (m, 5H), 5.48−5.36 (m, 2H), 4.48 (s, 2H), 4.12 (q, J = 7.12 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 2.33 (m, 3H), 2.05 (q, J = 6.4 Hz, 2H), 1.23 (t, J = 7.2 Hz, 2H); ^{13}C NMR δ 173.2, 138.6, 130.9, 128.6, 128.3, 127.6, 127.5, 72.8, 69.6, 60.2, 34.3, 29.4, 29.0, 27.9, 14.2 ppm; MS 277 (MH^+).

(4*R*,5*R*)-8-Benzyloxy-5-hydroxyoctane-1,4-olide, 43a. Compound **42** (15.2 g, 55 mmol) was converted to lactone **43a** by reaction with AD-mix-β (77.0 g) and $MeSO_2NH_2$ (5.23 g, 55 mmol) in *t*-BuOH−water (1:1, 550 mL) at 0 °C (16 h). The reaction was quenched with $Na_2S_2O_5$ (82.5 g), and the solution was extracted with EtOAc. Base−acid treatment (first with 50 mL 3 N aqueous KOH in 75 mL MeOH at 60 °C for 2 h, then acidification with 3 N HCl and extraction with EtOAc and finally lactonization with 1.5 g of TsOH in 100 mL CH_2Cl_2) afforded **43a** (13.51 g, 93%) after purification (silica gel, hexanes−EtOAc, 1:1−0:1) as white crystals from ether: mp 81 °C; $[\alpha]_D$ −16.5 (c = 2.2, $CHCl_3$); ^{1}H NMR δ 7.36−7.26 (m, 5H), 4.50 (s, 2H), 4.40 (td, J = 11.2, 4.0 Hz, 1H), 3.57 (m, 1H), 3.50 (m, 1H), 2.80 (d, J = 4.8 Hz, 1H), 2.61 (ddd, J = 17.6, 10.0, 2.8 Hz, 1H), 2.48 (ddd, J = 18.0, 10.0, 8.4 Hz, 1H), 2.21 (m, 1H), 2.13 (m, 1H), 1.80−1.59 (m, 4H); ^{13}C NMR δ 128.4, 127.8, 82.9, 73.3, 73.1, 70.1, 30.4, 28.6, 26.0, 24.0 ppm; MS 265 (MH^+).

(4*R*,5*R*)-8-Benzyloxy-5-(*tert*-butyldiphenylsilyloxy)octan-1,4-olide, 43b. BPSCl (6.2 mL, 23.8 mmol) was added to a solution of compound **43a** (4.5 g, 17.0 mmol) and imidazole (2.72 g, 40 mmol) in DMF (6 mL), and the mixture was stirred at rt for 16 h. The reaction mixture was worked up (water−ether), solvents were removed, and the residue was purified by chromatography over silica gel (hexanes−EtOAc, 9:1) to afford the BPS ether **43b** (8.0 g, 94%): $[\alpha]_D$ −31.9 (c = 2.1, $CHCl_3$); ^{1}H NMR δ 7.68 (m, 4H), 7.44−7.22 (m, 11H), 4.52 (td, J = 7.2, 3.6 Hz, 1H), 4.32 (s, 2H), 3.75 (m, 1H), 3.25 (dt, J = 9.2, 2.4 Hz, 1H), 3.13 (dt, J = 9.2, 6.8 Hz, 1H), 2.55 (m, 1H), 2.44 (m, 1H), 2.1 (m, 1H), 1.66 (m, 1H), 1.47 (m, 3H), 1.04 (s, 9H); ^{13}C NMR δ 177.3, 135.9, 135.86, 129.9, 129.84, 128.3, 127.7, 127.6, 127.5, 127.48, 81.0, 74.6, 72.7, 69.9, 29.5, 27.0, 25.3, 19.5, 14.2 ppm; MS 503 (MH^+), 525 (MNa^+).

(4*R*,5*R*)-8-Hydroxy-5-(*tert*-butyldiphenylsilyloxy)octan-1,4-olide, 43c. A 10% Pd−C mixture (2.0 g) was added to **43b** (3.4 g, 8.55 mmol) and propionic acid (2 mL) in MeOH (20 mL). The mixture was stirred under an H_2 atmosphere for 16 h, and then it was filtered through Celite. Solvents were removed, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to give alcohol **43c** (3.46 g, 98%): $[\alpha]_D$ −21.6 (c = 0.93, $CHCl_3$); ^{1}H NMR δ 7.66 (m, 4H), 7.35 (m, 6H), 4.51 (ddd, J = 9.2, 6.8, 4.0 Hz, 1H), 3.83 (td, J = 8.6, 4.8 Hz, 1H), 3.31 (m, 2H), 2.48 (m, 2H), 2.12 (m, 2H), 1.61 (m, 1H), 1.39 (m, 3H), 1.03 (s, 9H); ^{13}C NMR δ 177.5, 135.9, 135.7, 130.0, 129.8, 127.7, 127.6, 81.15, 74.6, 62.2, 29.0, 28.5, 28.9, 27.1, 23.2, 14.1 ppm; MS 413 (MH^+), 435 (MNa^+).

(4*R*,5*R*)-*tert*-Butyldiphenylsilyloxyoctan-1-al-5,8-olide, 44. Compound **43c** (6.47 g, 15 mmol) was converted to aldehyde **44** (5.54 g, 90%) by stirring with a mixture of PCC (6.46 g, 0.03 mol) and Celite (6.46 g) in CH_2Cl_2 (75 mL) at rt (2 h). Aldehyde **44** was purified by column chromatography (silica gel, hexanes−EtOAc, 7:3): ^{1}H NMR δ 9.44 (t, J = 1.6 Hz, 1H), 7.66 (m, 4H), 7.35 (m, 6H), 4.43 (td, J = 10.8, 4.0 Hz, 1H), 3.79 (q, J = 5.6 Hz, 1H), 3.70 (m, 1H), 2.63 (d, J = 5.2 Hz, 1H), 2.56−2.30 (m, 4H), 2.11 (m, 2H), 1.84 (m, 2H), 1.72 (m, 1H), 1.24 (m, 1H), 1.06 (m, 7H); ^{13}C NMR δ 201.2, 176.9, 135.9, 135.9, 133.3, 132.8, 130.1, 130.0, 127.8, 81.2, 73.4, 39.4, 28.4, 27.0, 24.9, 23.2, 19.5; MS 433 (MNa^+).

(*cis*,4*R*,5*R*,12*R*,13*R*)-5-*tert*-Butyldiphenylsilyloxytricosa-12,13-isoproylidenedioxy-8-en-1,4-olide, 11a. Compound **11a** was synthesized from Wittig salt **38** (1.5 g, 2.2 mmol), NaHMDS (1.0 M in toluene, 4.44 mL), HMPA (1.15 mL, 6.66 mmol), and aldehyde **44** (762 mg, 1.85 mmol) in dry THF (15 mL) by using the procedure for the synthesis of **10** (see Supporting Information). Workup (saturated solution of NH_4Cl and ether) and purification by flash chromatography (silica gel, hexanes−EtOAc, 4:1) afforded compound **11a** (0.95 g, 76%) in the form of an oil: $[\alpha]_D$ −13.4 (c = 1.35, $CHCl_3$); ^{1}H NMR δ 7.67 (m, 4H), 7.29 (m, 6H), 5.16 (m, 1H), 4.95 (m, 1H), 4.46 (ddd, J = 6.6, 3.6 Hz, 1H), 3.68 (m, 1H), 3.49 (m, 2H), 2.48 (ddd, J = 9.8, 6.6 Hz, 1H), 2.42 (ddd, J = 9.5, 8.0 Hz, 1H), 2.11−1.30 (m and br s, 34H), 1.03 (s, 9H), 0.82 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 177.2, 135.9, 135.8, 133.7, 133.1, 129.9, 129.8, 129.5, 129.1, 127.7, 127.5, 80.9, 80.7, 80.3, 74.5, 33.0, 32.8, 32.3, 31.9, 29.8, 29.7, 29.7, 29.5, 29.3, 27.4, 27.0, 26.2, 23.8, 23.3, 22.7, 22.6, 19.5, 14.1 ppm; MS 809 (MCs^+).

Conversion of Compound 11a to 11. TBAF (1 M in THF, 3 mL, 3.0 mmol) was added to a solution of compound **11a** (1.35 g, 2.0 mmol) in dry THF (20 mL) at 0 °C, and the mixture was stirred for 2 h at rt. Workup (ether−water) followed by purification (silica gel, hexanes−EtOAc, 1:1) afforded **11** (0.77 g, 88%) as an oil: $[\alpha]_D$ −1.6 (c = 1.37, $CHCl_3$). All spectral data were identical to those obtained from compound **11**, which was prepared from compound **25**.

(*cis*,4*R*,5*R*,12*R*,13*S*)-5-*tert*-Butyldiphenylsilyloxytricosa-8,9-isoproylidenedioxy-8-en-1,4-olide, 12a. Compound **12a** (7.85 g, 71%) was synthesized from Wittig salts **41** (11.0 g, 16.37 mmol), KHMDS (0.5 M in toluene, 32 mL, 16 mmol), HMPA (5.9 mL, 33 mmol), and aldehyde **44** (5.75 g, 14.0 mmol) in dry THF (60 mL) as above for the synthesis of **10** or **11a** and obtained after purification (silica gel, hexanes−EtOAc, 7:3) in the form of oil: $[\alpha]_D$ −58.8 (c = 0.82, $CHCl_3$); ^{1}H NMR δ 7.67 (m, 4H), 7.38 (m, 6H), 5.22 (m, 1H), 4.98 (m, 1H), 4.50 (dt, J = 10.4, 3.6 Hz, 1H), 3.98 (m, 1H), 3.91 (ddd, J = 9.6, 5.6, 3.6 Hz, 1H), 3.72 (ddd, J = 5.2, 3.6, 1.6 Hz, 1H), 2.56−2.42 (m, 2H), 2.12 (m, 2H), 1.90 (m, 2H), 1.68 (m, 1H), 1.45 (m, 3H), 1.39 (s, 3H), 1.33 (m, 3H), 1.32−1.21 (m, 9H), 1.05 (s, 9H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 177.2, 135.9, 135.8, 129.9, 129.7, 129.5, 129.1, 127.7, 127.6, 107.3, 80.7, 78.0, 77.3, 74.5, 32.3, 31.8, 29.7, 27.6, 29.5, 29.3, 28.7, 28.5, 27.0, 26.3, 26.0, 23,9, 23.7, 22.9, 22.6, 14.1 ppm; MS 678 (MH^+), 700 (MNa^+).

(4*R*,5*R*,12*R*,13*S*)-5-Hydroxytricosa-8,9-isoproylidenedioxy-8-en-1,4-olide, 12. Compound **12a** (7.85 g, 11.61 mmol) was deprotected with TBAF in dry THF (70 mL) to afford **12** (3.94 g, 77.5%) after purification (silica gel, hexanes−EtOAc, 1:1) as above for the conversion of **11a** to **11**: ^{1}H NMR δ 5.38 (q, J = 5.2 Hz, 2H), 4.38 (dt, J = 11.6, 4.4 Hz, 1H), 3.99 (m, 2H), 3.55 (m, 1H), 2.58−2.49 (m, 2H), 2.26−2.11 (m, 6H), 1.59−1.45 (m, 4H), 1.40 (s, 3H), 1.30 (s, 3H), 1.30−1.21 (m and br s, 19H), 0.85 (t, J = 6.4 Hz, 3H); ^{13}C NMR δ 130.2, 129.2, 83.0, 78.0, 77.2, 72.8, 32.8, 31.7, 29.7, 29.6, 29.5, 29.3, 26.2, 26.0, 24.0, 23.7, 23.1, 22.6, 14.0 ppm; MS 439 (MH^+), 461 (MNa^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*S*)-9-Hydroxy-12,13-isopropylidenedioxy-5,8-oxidotricosa-1,4-olide, 45a. Compound **12** was (2.0 g, 4.56 mmol) converted to compound **45a** by reaction with Re_2O_7 (5.0 g, 10.33 mmol) and 2,6-lutidine (1.22 g, 11.4 mmol) in dry CH_2Cl_2 (40 mL) at rt (overnight) as above for the conversion of compound **11** to **26a**. Workup (saturated solution of $NaHCO_3$, 8 mL, and hydrogen peroxide, 35% in water, 8 mL, stirring for 20 min, and extraction with CH_2Cl_2) and column chromatography (silica gel, hexanes−EtOAc, 3:1) afforded **45a** (0.654 g, 64%) in the form of a colorless oil: $[\alpha]_D$ +9.7 (c = 0.65, $CHCl_3$); ^{1}H NMR δ 4.41 (ddd J = 8.8, 5.6, 3.2 Hz, 1H), 4.02 (m, 3H), 3.89 (m, 1H), 3.75 (m, 1H), 2.60 (ddd, J = 16.4, 10.0, 6.4 Hz, 1H), 2.42 (ddd, J = 16.8, 10.0, 6.8 Hz, 1H), 2.24 (m, 2H), 2.14 (m, 1H), 2.01 (br d, J = 1.2 Hz, 1H), 1.86 (m, 3H), 1.62−1.41 (m, 5H), 1.38 (s, 3H), 1.29 (s, 3H), 1.25−1.20 (m, 17H), 0.84 (t, J = 6.0 Hz, 3H); ^{13}C NMR δ 177.4, 107.4, 83.3, 81.4, 81.1, 78.3, 78.1, 71.7, 29.64, 29.6, 29.55, 29.5, 29.3, 28.6, 28.2, 28.0, 26.5, 26.3, 25.1, 24.7, 22.6, 14.1 ppm; MS 587 (MCs^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*S*)-12,13-Isopropylidinedioxy-9-mesyloxy-5,8-oxidotricosa-1,4-olide, 45b. Compound **45a** (0.3 g, 0.66 mmol) was mesylated using MsCl (0.15 mL, 1.8 mmol) and Et_3N (0.5 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) at −30 °C in 0.5 h, as above for the conversion of the compound **26a** to **26b**. Workup (water−CH_2Cl_2) and purification by column chromatography (silica gel, hexanes−EtOAc, 7:3) afforded **45b** (0.35 g, 99%) in the form of a colorless oil: $[\alpha]_D$ +13.6 (c = 1.60, $CHCl_3$); ^{1}H NMR δ 4.73 (dt, J = 8.0, 4.0 Hz, 1H), 4.40 (ddd, J = 8.4, 5.6, 2.8 Hz, 1H), 3.98 (m, 2H), 3.93 (ddd, J =

10.0, 6.0, 3.2 Hz, 1H), 2.98 (s, 3H), 2.56 (ddd, J = 17.6, 10.8, 7.6 Hz, 1H), 2.41 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 2.28 (m, 1H), 2.20−1.83 (m, 7H), 1.47 (m, 6H), 1.35 (s, 3H), 1.26 (s, 3H), 1.23−1.15 (m and br s, 14H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 177.3, 107.5, 83.8, 81.1, 81.0, 81.8, 80.6, 77.9, 77.7, 31.8, 29.6, 29.51, 29.3, 28.6, 28.1, 27.7, 26.3, 26.1, 26.0, 25.8, 24.6, 22.6, 14.0 ppm; HRMS ($C_{27}H_{48}O_8SCs$ = 665.2124) found 665.2144 (MCs^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*S*)-12,13-Dihydroxy-9-mesyloxy-5,8-oxidotricosa-1,4-olide, 46. Compound **45b** (0.35 g, 0.65 mmol) was stirred with TsOH (50 mg) in MeOH−water (4:1, 2 mL) for 16 h as above for the conversion of **26b** to **27**. Workup (saturated solution of $NaHCO_3$−EtOAc) afforded the crude diol (292 mg, 82%): $[\alpha]_D$ −4.2 (c = 0.79, $CHCl_3$); ^{1}H NMR δ 4.82 (dt, J = 7.9, 4.0 Hz, 1H), 4.44 (ddd, J = 8.1, 5.6, 2.8 Hz, 1H), 4.12−4.02 (m, 2H), 3.59−3.52 (m, 2H), 3.03 (s, 3H), 2.64 (ddd, J = 17.6, 10.1, 6.6 Hz, 1H), 2.46 (ddd, J = 16.9, 10.1, 6.7 Hz, 1H), 2.32−2.22 (m, 1H), 2.05 (m, 5H), 1.98−1.84 (m, 3H), 1.72−1.61 (m, 2H), 1.53−1.40 (m, 4H), 1.24 (br s, 15H), 0.87−0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 177.5, 84.0, 81.2, 81.0, 80.7, 74.7, 74.1, 38.6, 31.9, 31.6, 29.6, 29.3, 28.4, 28.1, 27.8, 26.7, 26.3, 26.0, 24.6, 22.7, 14.1 ppm; MS ($C_{24}H_{44}O_8S$ = 625.1811) found 625.1839 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-13-Hydroxy-5,8:9,12-dioxidotricosa-1,4-olide, 7. Compound **46** (292 mg) was refluxed in pyridine (20 mL) for 3 h as above for the conversion of compound **27** to **6** to afford compound **7** (0.17 g, 81%, 65% from **46b**) after purification by column chromatography (silica gel, hexanes−EtOAc, 1:1). All physical data were identical to those obtained for compound **32**.

Pentadec-4-en-1-yl triphenylphosphonium Iodide, 47. Compound **47** was prepared from *trans*-1-iodopentadec-4-en-1-ol[11g] via the corresponding iodide (for process, see preparation of **23**). The iodide was prepared using *trans*-pentadec-4-en-1-ol (1 g, 4.4 mmol), iodine (1.34 g, 5.28 mmol), PPh_3 (1.78 g, 6.8 mmol), and imidazole (0.42 g, 6.2 mmol) in CH_2Cl_2 (10 mL) to afford the former (1.28 g, 86%) after column chromatography (silica gel, hexanes−EtOAc, 19:1): ^{1}H NMR δ 5.47 (m, 1H), 5.30 (m, 1H), 3.16 (t, J = 7.2 Hz, 2H), 2.70 (q, J = 6.8 Hz, 2H), 1.95 (q, J = 6.4 Hz, 2H), 1.85 (m, 2H), 1.24 (m, 17H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR δ 132.3, 127.6, 33.1, 32.6, 31.9, 29.6, 29.55, 29.5, 29.3, 29.2, 22.7, 14.1, 6.7 ppm.

Compound **47** (2.1 g, 92%) was obtained by refluxing iodide (1.28 g, 3.8 mmol) and PPh_3 (1.99 g, 7.6 mmol) in CH_3CN (12 mL): ^{1}H NMR δ 7.61 (m, 10H), 5.42 (dt, J = 15.4, 6.7 Hz, 1H), 5.21 (dt, J = 15.4, 6.7 Hz, 1H), 3.53 (m, 2H), 2.28 (q, J = 6.8 Hz, 2H), 1.88 (q, J = 6.8 Hz, 2H), 1.66 (m, 2H), 1.15 (m, 17H), 0.81 (t, J = 6.4 Hz, 3H).

(*cis*,*trans*,4*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxytricosa-8,12-dien-1,4-olide, 13a. Compound **13a** was prepared from Wittig salt **47** (9.4 g, 15.7 mmol), KHMDS (0.5 M in toluene, 31.6 mL, 15.7 mmol), HMPA (5.6 mL, 31 mmol), and aldehyde **44** (5.68 g, 13.6 mmol) as above for compound **10**. Purification by flash chromatography (silica gel, hexanes−EtOAc, 4:1) afforded compound **13a** (6.48 g, 79%) in the form of an oil: ^{1}H NMR δ 7.68 (m, 4H), 7.39 (m, 6H), 5.33 (m, 2H), 5.22 (m, 1H), 4.97 (m, 1H), 4.51 (td, J = 6.7, 3.5 Hz, 1H), 3.73 (m, 1H), 2.58 (m, 1H), 2.46 (m, 1H), 2.14 (q, J = 7.3 Hz, 2H), 1.96−1.78 (m, 8H), 1.75−1.18 (m and br s, 18H), 1.04 (s, 9H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 177.3, 135.9, 135.8, 133.7, 133.0, 130.9, 129.9, 129.7, 129.3, 128.4, 127.7, 127.6, 80.7, 74.5, 32.6, 32.3, 31.9, 31.5, 29.6, 29.5, 29.3, 27.2, 27.0, 23.2, 23.0, 22.6, 19.5, 14.1; MS 625 (MNa^+).

(*cis*,*trans*,4*R*,5*R*)-5- Hydroxytricosa-8,12-dien-1,4-olide, 13. Compound **13a** (6.4 g, 10.6 mmol) was deprotected with TBAF (1 M in THF, 12 mL, 12 mmol) in dry THF (20 mL) at 0 °C to rt (2 h) as above for the conversion of **11a** to **11** to afford **13** (3.44 g, 90%) after purification (silica gel, hexanes−EtOAc, 1:1): $[\alpha]_D$ +17.8 (c = 1.12, $CHCl_3$); ^{1}H NMR (500 MHz): δ 5.38 (m, 4H), 4.40 (td, J = 7.4, 4.8 Hz, 1H), 3.57 (dt, J = 8.8, 4.4 Hz, 1H), 2.59 (m, 1H), 2.50 (dd, J = 18.0, 9.2 Hz, 1H), 2.22 (m, 3H), 2.08 (m, 3H), 2.08−1.82 (br, 1H), 2.02 (q, J = 6.6 Hz, 2H), 1.94 (q, J = 6.6 Hz, 2H), 1.58 (m, 2H), 1.35−1.18 (m and br s, 16H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.1, 131.1, 130.7, 129.3, 128.5, 83.0, 73.1, 32.7, 32.6, 31.9, 29.6, 29.5, 29.2, 28.6, 27.4, 24.1, 23.2, 22.7, 14.1 ppm; MS 387 (MNa^+).

(*trans*,4*R*,5*R*,8*R*,9*S*)-9-Hydroxy-5,8-oxidotricos-12-en-1,4-olide, 48a. Compound **13** (1.4 g, 3.85 mmol) was added to a mixture of trifluoroacetylrhenium(VII) oxide (prepared from Re_2O_7 (5 g, 10.3 mmol) and TFAA (2.0 mL, 13.4 mmol) in dry THF (50 mL) at 0 °C) and 2,6-lutidine (3.6 mL, 31 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at 0 °C to rt for 8 h and then worked up with a saturated solution of $NaHCO_3$ (10 mL), H_2O_2 (2.0 mL), and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to afford **48a** (1.1 g, 75%): $[\alpha]_D$ −7.0 (c = 1.0, $CHCl_3$); ^{1}H NMR δ 5.41 (m, 2H), 4.43 (m, 1H), 4.05 (m, 1H), 3.85 (m, 1H), 3.76 (m, 1H), 2.62 (m, 1H), 2.46 (m, 1H), 2.23 (m, 1H), 2.15 (m, 2H), 2.05−1.83 (m, 8H), 1.38 (q, J = 7.4 Hz, 2H), 1.23 (m and br s, 16H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.5, 131.4, 129.2, 83.3, 81.4, 81.0, 71.0, 32.5, 32.4, 31.9, 29.6, 29.5, 29.3, 29.1, 28.9, 28.2, 28.0, 24.9, 24.6, 22.6, 14.1 ppm; MS 403 (MNa^+).

(*trans*,4*R*,5*R*,8*R*,9*S*)-9-Mesyloxy-5,8-oxidotricos-12-en-1,4-olide, 48b. Mesylate **48b** (1.22 g, 90%) was obtained by reacting compound **48a** (1.1 g, 2.9 mmol) with MsCl (0.45 mL, 5.8 mmol) and Et_3N (2 mL) in CH_2Cl_2 (10 mL) as above in the synthesis of **26b**, followed by purification (silica gel, hexanes−EtOAc, 7:3) in the form of a colorless oil: ^{1}H NMR δ 5.46 (dt, J = 15.4, 6.6 Hz, 1H), 5.34 (dt, J = 15.4, 6.2 Hz, 1H), 4.77 (quintet, J = 4.5 Hz, 1H), 4.44 (ddd, J = 8.1, 5.5, 2.6 Hz, 1H), 4.05 (m, 2H), 3.01 (s, 3H), 2.65 (ddd, J = 17.6, 10.2, 7.0 Hz, 1H), 2.45 (ddd, J = 17.6, 10.3, 6.6 Hz, 1H), 2.26 (m, 1H), 2.16 (m, 2H), 2.06 (m, 3H), 1.95 (m, 4H), 1.71 (m, 1H), 1.58 (m, 1H), 1.35−1.20 (m and br s, 16H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR 177.5, 131.4, 129.3, 83.9, 81.1, 80.6, 74.3, 74.0, 60.3, 43.2, 38.5, 33.4, 31.8, 31.5, 29.5, 29.2, 28.1, 27.7, 26.1, 25.6, 24.6, 22.6, 21.0, 14.1 ppm; MS 481 (MNa^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-12,13-Dihydroxy-9-mesyloxy-5,8-oxidotricosan-1,4-olide, 27. Compound **48b** (1.21 g, 2.64 mmol) was dihydroxylated using AD-mix-β (3.70 g) and $MeSO_2NH_2$ (251 mg, 2.64 mmol) in *t*-BuOH−water (1:1, mL) at 0 °C (for process, see first stage of three-step process in the conversion of **8** to **24**) to afford compound **27** (1.1 g, 92%): ^{1}H NMR δ 5.18 (br s, 1H), 4.80 (m, 1H), 4.44 (m, 1H), 4.04 (m, 2H), 3.36 (m, 2H), 3.02 (s, 3H), 2.62 (m, 1H), 2.45 (m, 1H), 2.26 (m, 1H), 2.16−2.02 (m, 4H), 1.95−1.80 (m, 2H), 1.72−1.62 (m, 2H), 1.54−1.37 (m, 3H), 1.33−1.15 (m and br s, 17H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 177.6, 83.9, 81.2, 80.6, 74.4, 74.1, 60.4, 43.3, 38.5, 33.5, 31.8, 31.6, 29.6, 29.3, 28.2, 27.7, 26.2, 25.6, 24.6, 22.1, 21.0, 14.1 ppm; MS 515 (MNa^+).

(4*R*,5*R*,8*R*,9*R*)-9-Imidazolylthiocarbonyloxy-5,8-oxidononadecan-1,4-olide, 53. A solution of compound **52**[8a] (163 mg, 0.5 mmol), thiocarbonyldiimidazole (268 mg, 1.5 mmol), and DMAP (10 mg) in CH_2Cl_2 (8 mL) was stirred at rt for 16 h. The crude product was chromatographed over silica gel (hexanes−EtOAc, 3:2) to afford **53** (200 mg, 92%) as a colorless oil: ^{1}H NMR (300 MHz) δ 8.33 (s, 1H), 7.60 (s, 1H), 7.01 (s, 1H), 5.59 (dt, J = 7.4, 6.1 Hz, 1H), 4.45 (ddd, J = 7.9, 4.4, 1.8 Hz, 1H), 4.15 (dt, J = 7.9, 5.7 Hz, 1H), 4.01 (td, J = 7.0, 1.8 Hz, 1H), 2.58−1.95 (m, 6H), 1.82−1.18 (m and brs, 20H), 0.83 (t, J = 6.6 Hz); MS 459 (MNa^+).

(4*R*,5*R*,8*R*)-5,8-Oxidononadecan-1,4-olide, 54. Tributyltinhydride (0.25 mL, 0.91 mmol) was added dropwise to a solution of compound **53** (200 mg, 0.46 mmol) and AIBN (10 mg) in dry toluene at 90 °C, and the mixture was stirred at that temperature for 3 h. The crude product was chromatographed over silica gel (hexanes−EtOAc, 7:3) to afford **54** (130 mg, 91%) as a colorless oil: ^{1}H NMR (500 MHz) δ 4.44 (ddd, J = 7.7, 5.1, 2.6 Hz, 1H), 4.02 (td, J = 7.3, 2.6 Hz, 1H), 3.88 (m, 1H), 2.67 (ddd, J = 16.1, 10.0, 7.3 Hz, 1H), 2.43 (ddd, J = 16.1, 10.0, 5.8 Hz, 1H), 2.24 (m, 2H), 2.05−1.92 (m, 3H), 1.58−1.20 (m and brs, 21H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125.75 MHz): δ 177.7, 81.5, 80.8, 80.1, 35.7, 32.1, 31.1, 29.7, 29.5, 29.3, 28.2, 27.9, 26.2, 24.8, 22.7, 14.1 ppm; MS 311 (MH^+).

(4*R*,5*R*,8*S*,9*S*)-9-Hydroxy-5,8-oxidononadecan-1,4-olide, 56. Dry TBHP (5−6 M solution in nonane, 0.5 mL, 2.5−

3.0 mmol) was added dropwise to a solution of **55**[33] and V_2O_5 (28 mg, 0.11 mmol) in dry CH_2Cl_2 (10 mL), and the mixture was stirred at rt for 16 h. The reaction mixture was worked up (water and CH_2Cl_2), solvents were removed under vacuum, and the residue was purified by column chromatography over silica gel (hexanes−EtOAc, 1:1) to afford **56** (155 mg, 64%): ^{1}H NMR (500 MHz) δ 4.46 (m, 1H), 3.98 (m, 1H), 3.77 (quintet, J = 7.0 Hz, 1H), 3.36 (m, 1H), 2.58 (m, 1H), 2.44 (m, 1H), 2.26−2.13 (m, 3H), 1.99−1.85 (m, 3H), 1.71 (m, 1H), 1.43 (br, 1H), 1.36 (m, 2H), 1.21 (s, 15H), 0.82 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz) δ 177.5, 83.6, 81.0, 80.7, 74.2, 33.6, 31.8, 29.6, 29.5, 29.2, 28.2, 27.8, 27.6, 25.5, 24.4, 22.6, 14.1 ppm; MS 349 (MNa^+).

(4*R*,5*R*,8*S*,9*S*)-9-Imidazolylthiocarbonyloxy-5,8-oxidononadecan-1,4-olide, 57. Compound **56** (150 mg, 0.46 mmol) was converted to **57** using thiocarbonyldiimidazole (250 mg, 0.91 mmol) and DMAP (10 mg) in CH_2Cl_2 (8 mL) as above for the conversion of compound **52** to **53** (rt, 16 h). Pure compound **57** (180 mg, 90%) was obtained by chromatography of the crude product over silica gel (hexanes−EtOAc, 3:2) as a colorless oil: ^{1}H NMR (500 MHz) δ 8.40 (s, 1H), 7.72 (s, 1H), 7.00 (s, 1H), 5.70 (m, 1H), 4.46 (m, 1H), 4.16 (m, 1H), 3.94 (m, 1H), 2.60 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H), 1.94 (m, 3H), 1.72 (m, 3H), 1.20 (s, 16H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125.75 MHz) δ 184.6, 177.4, 137.4, 130.7, 85.7, 80.8, 80.1, 31.9, 29.5, 29.3, 29.2, 28.2, 27.7, 24.9, 24.4, 22.6, 14.1 ppm; MS 459 (MNa^+).

(4*R*,5*R*,8*S*)-5,8-Oxidononadecan-1,4-olide, 58. Compound **57** (66 mg, 0.15 mmol) was converted to **58** using tributyltinhydride (0.086 mL, 0.3 mmol) and AIBN (5 mg) in dry toluene (90 °C, 3 h) as above for the conversion of **53** to **54**. Pure **58** (38 mg, 80%) was obtained by chromatography of the crude product over silica gel (hexanes−EtOAc, 7:3) as a colorless oil: ^{1}H NMR (500 MHz) δ 4.46 (ddd, J = 7.7, 4.4, 2.6 Hz, 1H), 3.96 (td, J = 5.5, 2.6 Hz, 1H), 3.85 (quintet, J = 6.2 Hz, 1H), 2.66 (ddd, J = 17.9, 9.9, 7.7 Hz, 1H), 2.40 (m, 1H), 2.20 (m, 2H), 1.92 (m, 2H), 1.51 (m, 3H), 1.23 (s, 19H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125.75 MHz) δ 177. 8, 81.1, 80.7, 80.4, 35.4, 31.9, 31.1, 29.6, 29.3, 28.9, 27.6, 26.3, 24.5, 22.6, 14.1 ppm; MS 333 (MNa^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*S*)-9-Imidazolylthiocarbonyloxy-12,13-isoproylidenedioxy-5,8-oxidotricosan-1,4-olide, 45c. Compound **45a** (60 mg, 0.14 mmol) was converted to **45c** using 1,1-thiocarbonyldiimidazole (75 mg, 0.43 mmol) and DMAP (10 mg) in CH_2Cl_2 (8 mL) as above for the conversion of compound **52** to **53** (rt, 36 h). Pure compound **46c** (70 mg, 93%) was obtained by chromatography of the crude product over silica gel (hexanes−EtOAc, 2:3) as a colorless oil: ^{1}H NMR (500 MHz) δ 8.28 (s, 1H), 7.58 (s, 1H), 7.00 (s, 1H), 5.73 (quintet, J = 4.4 Hz, 1H), 4.40 (ddd, J = 7.3, 3.3, 1.8 Hz, 1H), 4.20 (m, 1H), 4.00−3.91 (m, 3H), 2.59 (m, 1H), 2.40 (m, 1H), 2.22−2.00 (m and brs, 25H), 0.84 (t, J = 6.6 Hz); MS 587 (MNa^+).

(4*R*,5*R*,8*R*,12*R*,13*S*)-12,13-Isoproylidenedioxy-5,8-oxidotricosan-1,4-olide, 59. Compound **46c** (70 mg, 0.127 mmol) was converted to **59** using tributyltinhydride (0.081 mL, 0.3 mmol) and AIBN (10 mg) in dry toluene (90 °C, 3 h) as above for the conversion of **53** to **54**. Pure **59** (39 mg, 70%) was obtained by chromatography of the crude product over silica gel (hexanes−EtOAc, 7:3) as a colorless oil: ^{1}H NMR (500 MHz) δ 4.42 (ddd, J = 7.7, 5.1, 2.6 Hz, 1H), 3.99 (m, 2H), 3.88 (m, 1H), 2.62 (m, 1H), 2.40 (m, 1H), 2.26−2.15 (m, 2H), 2.04−1.88 (m, 3H), 1.69 (s, 3H), 1.55−1.22 (m and br s, 29H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 177.6, 107.2, 81.4, 80.4, 80.1, 78.0, 77.8, 35.6, 32.0, 31.8, 29.6, 29.5, 29.3, 28.6, 28.2, 27.8, 26.2, 26.0, 25.1, 24.7, 22.6, 14.1 ppm; MS 461 (MNa^+).

(4*R*,5*R*,8*R*)-5,8-Oxido-12-oxotricosan-1,4-olide, 60. A solution of compound **59** (39 mg, 0.097 mmol) and TsOH (10 mg) in MeOH−water (9:1, mL) was stirred at rt for 24 h. The reaction mixture was worked up (aqueous $NaHCO_3$ and EtOAc), solvents were removed under vacuum, and the corresponding diol was taken to the next step without purification: ^{1}H NMR (400 MHz) δ 4.43 (m, 1H), 4.00 (td, J = 7.6, 2.4 Hz, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.54 (br, 2H), 2.81−1.29 (m and br s, 32H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz) δ 178.0, 81.6, 80.5, 80.2, 74.6, 74.5, 35.3, 32.1, 29.6, 29.3, 28.2, 27.9, 26.0, 25.1, 24.8, 22.6, 14.1 ppm; MS 421 (MNa^+).

Lead(IV) acetate (85 mg, 0.19 mmol) was added to a solution of the above-mentioned crude diol (37 mg) in CH_2Cl_2 (5 mL), and the mixture was stirred at rt for 1 h. Pure aldehyde (11 mg, 54%) was obtained by filtration of the reaction mixture over silica gel (hexanes−EtOAc, 7:3): ^{1}H NMR (300 MHz) δ 9.70 (s, 1H), 4.43 (m, 1H), 3.87−3.64 (m, 4H), 2.70−1.20 (m, 12 H).

(4*R*,5*R*,8*R*)-5,8-Oxidononadecan-1,4-olide, 54, from 60. BuLi (1.6 M in hexane, 0.087 mL, 0.139 mmol) was added to a stirring mixture of *n*-heptyltriphenylphosphonium bromide (61 mg, 0.139 mmol) in dry THF (2 mL) at 0 °C. After 0.5 h, a solution of compound **60** (11 mg, 0.048 mmol) in dry THF (1 mL) was added dropwise and the mixture was stirred for an additional 0.5 h. Workup (NH_4Cl solution−ether) and purification over silica gel (hexanes−EtOAc, 7:3) afforded the pure Wittig product: ^{1}H NMR (400 MHz) δ 5.34 (m, 2H), 4.45 (ddd, J = 7.6, 5.3, 3.0 Hz, 1H), 4.03 (td, J = 7.6, 2.4 Hz, 1H), 3.87 (m, 1H), 2.66 (ddd, J = 17.3, 10.0, 7.3 Hz, 1H), 2.42 (ddd, J = 17.3, 9.7, 5.9 Hz, 1H), 2.22 (m, 2H), 2.01 (m, 7H), 1.57−1.24 (m and br s, 13H), 0.86 (t, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 130.3, 129.3, 81.5, 80.6, 80.1, 35.3, 32.1, 31.7, 28.9, 28.2, 27.8, 27.2, 26.3, 24.8, 22.6, 14.1 ppm.

A mixture of the above-mentioned compound (5 mg, 0.0162 mmol) and Pd−C (10%, 2 mg) in ethanol was stirred under an H_2 atmosphere at rt for 4 h. The reaction mixture was filtered over Celite, solvents were removed under vacuum, and the crude product was passed through a short bed of silica gel to afford **54**.

(2*R*)-Dec-9-ene-1,2-diol, 62a. AD-mix-β (37.8 g) was added to a mixture of 1,9-decadiene, **61** (3.7 g, 27 mmol), in *t*-BuOH−water (2:1, 540 mL) at 0 °C, and the mixture was stirred at this temperature for 24 h. $Na_2S_2O_5$ (40 g) was added to the mixture (slow addition), stirred for 0.5 h, diluted with water, and extracted with EtOAc. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−EtOAc, 1:1) to give **62a** (3.5 g, 75%) in the form of a colorless oil: ^{1}H NMR δ 5.79 (m, 1H), 4.97 (m, 1H), 4.91 (m, 1H), 3.67 (m, 1H), 3.62 (d, J = 11.3 Hz, 1H), 3.39 (dd, J = 10.6, 8.1 Hz, 1H), 2.76 (br s, 2H), 2.02 (q, J = 6.7 Hz, 2H), 1.45−1.25 (m and br s, 10 H); ^{13}C NMR δ 139.1, 114.2, 72.3, 66.7, 33.7, 33.1, 29.5, 29.0, 28.8, 25.5 ppm; HRMS ($C_{10}H_{20}O_2Na$ = 195.1361) found 195.1367 (MNa^+).

(2*R*)-1-Tosyloxydec-9-en-2-ol, 62b. TsCl (155 mg, 0.81 mmol) was added to a solution of **62a** (0.1 g, 0.58 mmol), in dry collidine (5 mL) at 0 °C. The mixture was stirred between 0 °C and rt for 16 h and then diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with dilute HCl and then with water and dried over anhydrous $MgSO_4$. Solvents were evaporated under vacuum, and the resultant residue was purified by column chromatography (silica gel, benzene−EtOAc, 9:1), affording **62b** (0.132 g, 70%) in the form of a colorless oil: $[\alpha]_D$ −6.3 (c = 0.975, $CHCl_3$); ^{1}H NMR δ 7.79 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 5.78 (m, 1H), 4.97 (m, 1H), 4.91 (m, 1H), 4.02 (dd, J = 9.6, 2.5 Hz, 1H), 3.86 (dd, J = 9.6, 7.1 Hz, 1H), 3.82 (m, 1H), 2.44 (s, 3H), 2.06−1.98 (m, 3H), 1.39−1.16 (m and br s, 10H); ^{13}C NMR δ 145.1, 139.0, 129.9, 128.0, 114.3, 74.0, 69.5, 33.7, 32.6, 29.2, 28.9, 28.7, 25.1, 21.7 ppm; HRMS ($C_{17}H_{27}O_4S$ = 327.1630) found 327.1639 (MH^+).

(2*R*)-1-Tosyloxy-2-*tert*-butyldimethylsilyloxydec-9-ene, 62c. TBSOTf (3 mL, 12.9 mmol) was added to a solution of **62b** (3.53 g, 10.8 mmol) and 2,6-lutidine (1.9 mL, 16.2 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C. The mixture was stirred at the same temperature for 1 h and then worked up with water and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−EtOAc) to give **62c** (4.7 g, 99%) in the form of a colorless oil: $[\alpha]_D$ +2.8 (c = 1.20, $CHCl_3$); ^{1}H NMR δ 7.77 (d, J = 8.3 Hz, 2H), 7.33 (d, J =

(33) For the synthesis of **55** see: Supporting Informations.

8.3 Hz, 2H), 5.78 (m, 1H), 4.97 (m, 1H), 4.92 (m, 1H), 3.83 (m, 3H), 2.43 (s, 3H), 2.01 (m, 2H), 1.35−1.22 (m and br s, 10H), 0.82 (s, 9H), 0.004 (s, 3H), −0.01 (s, 3H); ^{13}C NMR δ 144.7, 139.0, 132.9, 129.8, 127.9, 114.2, 73.2, 69.9, 34.0, 33.7, 29.4, 28.9, 28.7, 25.7, 24.7, 21.6, 18.0, −4.6, −4.8 ppm; MS 441 (MH^+).

(2*R*)-2-*tert*-Butyldimethylsilyloxy-1-iododec-9-ene, 63. A mixture of **62c** (4.57 g, 10.3 mmol), NaI (15.43 g, 0.103 mol), and $NaHCO_3$ (0.865 g, 10.3 mmol) in dry acetone (100 mL) was stirred at reflux temperature for 36 h. Solvent was removed under reduced pressure, and the residue was dissolved in water and extracted with EtOAc. The organic layer was washed with aqueous $Na_2S_2O_3$ and then with brine, dried over $MgSO_4$,and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−EtOAc) to afford **63** (3.88 g, 95%) in the form of a colorless oil: $[\alpha]_D$ +8.0 (c = 1.04, $CHCl_3$); ^{1}H NMR δ 5.80 (m, 1H), 4.98 (m, 1H), 4.93 (m, 1H), 3.52 (m, 1H), 3.17 (d, J = 5.1 Hz, 2H), 2.03 (q, J = 6.8 Hz, 2H), 1.52−1.28 (m, 10H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ 139.1, 114.2, 71.4, 36.9, 33.7, 29.4, 29.0, 28.8, 25.8, 24.9, 18.1, 14.1, −4.4, −4.6 ppm; HRMS ($C_{16}H_{33}OSi$ = 269.2301) found 269.2299 $(M-I)^+$.

(2*RS*,4*S*,2′*R*)-2′-*tert*-Butyldimethylsilyloxydec-9-en-1-yl-2-(phenylsulfanyl)pentan-1,4-olide, 65. Lactone **64** (1 g, 4.8 mmol) in dry THF (5 mL) was added dropwise to an ice-cold solution of LDA (5.3 mmol, prepared from 5.3 mmol of BuLi and 5.8 mmol of diisopropylamine in 15 mL of dry THF). The mixture was stirred for 30 min, iodide **63** (2.28 g, 5.76 mmol) and HMPA (2.6 mL) in THF (5 mL) were added, and the mixture was stirred at rt for 16 h. The mixture was worked up with saturated aqueous NH_4Cl and ether, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ether, 1:0−9:1) to give **65** (1.14 g, 50%) in the form of a colorless oil (mixture of two diastereomers in a 4:1 ratio): ^{1}H NMR of the major product, δ 7.54 (m, 2H), 7.35 (m, 3H), 5.79 (m, 1H), 4.98 (m, 1H), 4.92 (m, 1H), 4.51 (m, 1H), 4.24 (m, 1H), 3.04 (dd, J = 14.0, 7.6 Hz, 1H), 2.05−1.82 (m, 5H), 1.36−1.20 (m and br s, 10H), 1.23 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); HRMS ($C_{27}H_{45}O_3SSi$ = 477.2859), found 477.2874 (MH^+).

(4*S*,2′*R*)-2′-*tert*-Butyldimethylsilyloxydec-9-en-1-ylpent-2-en-1,4-olide, 66. *m*-CPBA (0.54 g, 3.14 mmol) was added in portions to a solution of **65** (1 g, 2.09 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at this temperature for 20 min and then worked up with a saturated solution of $NaHCO_3$ and CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was dissolved in toluene (30 mL) and heated at the reflux temperature for 2 h, solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes−ether, 9:1−7:3) to give **66** (0.58 g, 76%) in the form of a colorless oil: ^{1}H NMR δ 7.11 (d, J = 1.4 Hz, 1H), 5.79 (m, 1H), 4.99 (m, 1H), 4.96 (m, 1H), 4.91 (m, 1H), 3.93 (m, 1H), 2.41 (dt, J = 5.7, 1.3 Hz, 2H), 2.02 (q, J = 6.8 Hz, 2H), 1.40 (d, J = 6.8 Hz, 3H), 1.45−1.24 (m and br s, 10H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); MS 367 (MH^+), 389 (MNa^+).

(4*S*,2′*R*)-2′-*tert*-Butyldimethylsilyloxynonan-9-al-1-ylpent-2-en-1,4-olide, 3. OsO_4 (0.77 g, 3.06 mmol) was added to a solution of **66** (0.865 g, 2.35 mmol) in THF−water (4:1, 30 mL) under argon. The mixture was stirred for 5 min, and sodium metaperiodate (2.51 g, 11.7 mmol) was added over 10 min in three portions. The mixture was stirred for 2.5 h and then diluted with ether (50 mL) and distilled water (40 mL). The aqueous phase was extracted with additional ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−ether, 7:3−3:7) to provide **3** (0.65 g, 76%) in the form of a colorless oil: $[\alpha]_D$ +18.2 (c = 0.72, $CHCl_3$); ^{1}H NMR δ 9.73 (t, J = 1.6 Hz, 1H), 7.10 (s, 1H), 4.99 (q, J = 6.8 Hz, 1H), 3.92 (m, 1H), 2.39 (m, 4H), 1.60 (m, 2H), 1.39 (d, J = 6.8 Hz, 3H), 1.35−1.24 (m, 8H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 202.9, 174.0, 151.6, 130.7, 77.5, 70.0, 43.8, 36.8, 32.7, 29.4, 29.1, 25.8, 24.9, 21.9, 18.9, 18.0, −4.5 ppm; HRMS ($C_{20}H_{37}O_4Si$ = 369.2461), found 369.2456 (MH^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1,4,13-Triydroxy-5,8:9,12-dioxidotricosane, 67a. $LiAlH_4$ (71 mg, 1.88 mmol) was added in portions to a stirred solution of **6** (372 mg, 0.94 mmol) in dry ether at 0 °C, and the mixture was allowed to warm to rt, then refluxed for 2 h, cooled back to rt, diluted with ether, and worked up by dropwise addition of water. The inorganic material was filtered off and washed with EtOAc, and the combined organic solution was collected. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, EtOAc−MeOH, 1:0−19:1) to give **67a** (375 mg, 100%) in the form of a colorless oil: $[\alpha]_D$ +10.2 (c = 2.08, $CHCl_3$); ^{1}H NMR δ 3.86−3.77 (m, 4H), 3.65−3.61 (m, 2H), 3.57 (br s, 1H), 3.42 (m, 1H), 3.33 (m, 1H), 3.21 (br s, 1H), 2.99 (br s, 1H), 1.94 (m, 4H), 1.76−1.22 (m and br s, 26H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 83.2, 83.0, 81.9, 81.8, 73.85, 73.82, 62.6, 33.3, 31.8, 30.2, 29.6, 29.5, 29.3, 29.1, 29.0, 28.3, 28.26, 25.6, 22.6, 14.1 ppm; HRMS ($C_{23}H_{44}O_5Na$ = 423.3086), found 423.3072 (MNa^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1- *tert*-Butyldimethylsilyloxy-4,13-di(methoxymethoxy)-5,8:9,12-dioxidotricosane, 67b. TBSCl (155 mg, 1.03 mmol) was added to a stirred solution of **67a** (375 mg, 0.936 mmol), diisopropylethylamine (0.5 mL, 2.81 mmol), and DMAP (46 mg, 0.374 mmol) in dry CH_2Cl_2 (15 mL), and the solution was stirred for 6 h at rt. Upon completion of the reaction (by TLC), the mixture was cooled to 0 °C; diisopropylethylamine (1.95 mL, 11.2 mmol) and MOMCl (1.0 g, 12.54 mmol) were added sequentially. The mixture was stirred for another 12 h and then worked up with water and CH_2Cl_2, the combined organic layer was washed with water and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane−EtOAc, 4:1) to give **67b** (508 mg, 90%) in the form of a colorless oil: ^{1}H NMR δ 4.80 (d, J = 6.8 Hz, 2H), 4.64 (d, J = 6.8 Hz, 2H), 3.97 (m, 2H) 3.89 (m, 2H), 3.59 (m, 2H), 3.45 (m, 2H), 3.37 (s, 6H), 1.89 (m, 4H), 1.80−1.20 (m and br s, 26H), 0.87 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR δ 96.6, 81.76, 81.71, 81.17, 81.13, 79.41, 79.3, 63.1, 55.7, 31.9, 31.1, 29.8, 29.6, 29.3, 28.9, 28.3, 28.2, 27.5, 25.9, 25.6, 22.7, 18.3, 14.1, −5.3 ppm; HRMS ($C_{33}H_{66}O_7SiNa$ = 625.4476), found 625.4460 (MNa^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1-Hydroxy-4,13-di(methoxymethoxy)-5,8:9,12-dioxidotricosane, 67c. TBAF (1 M in THF, 1.1 mL, 1.1 mmol) was added to a solution of compound **67b** (0.508 g, 0.84 mmol) in dry THF (10 mL) at 0 °C. After stirring for 2 h at rt, the reaction mixture was worked up with water and ether. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes−EtOAc, 1:1) to yield compound **67c** (0.39 g, 95%) in the form of a colorless oil: $[\alpha]_D$ +41.3 (c = 5.70, $CHCl_3$); ^{1}H NMR δ 4.82 (d, J = 6.8 Hz, 1H), 4.82 (d, J = 6.8 Hz, 1H), 4.67 (d, J = 6.8 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.01 (m, 2H), 3.92 (m, 2H), 3.64 (m, 2H), 3.54 (m, 1H), 3.46 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 2.32 (br s, 1H), 1.93 (m, 4H), 1.80−1.56 (m, 7H), 1.54−1.22 (m and br s, 19H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 96.6, 96.5, 81.7, 81.5, 81.2, 79.4, 79.2, 62.6, 55.7, 55.6, 31.8, 31.0, 29.7, 29.5, 29.2, 28.6, 28.2, 28.1, 27.3, 25.5, 22.6, 14.0 ppm; HRMS ($C_{27}H_{52}O_7Cs$ = 621.2767) found 621.2782 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1-Iodo-4,13-di(methoxymethoxy)-5,8:9,12-dioxidotricosane, 67d. I_2 (0.254 g, 1.0 mmol) was added in portions to a cold (0 °C) solution of **67c** (0.39 g, 0.8 mmol), PPh_3 (0.31 g, 1.2 mmol), and imidazole (71 mg, 1.04 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred at rt for 1 h, and a saturated solution of $NaHCO_3$ was added followed by I_2 in portions until the color persisted. The mixture was worked up with water and CH_2Cl_2, and the organic layer was washed with a 10% solution of $Na_2S_2O_3$ and then with water. The combined solution was dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes−EtOAc, 4:1) to give **67d** (0.41 g, 86%) in the form of a colorless oil: ^{1}H NMR δ 4.82 (d, J = 6.8 Hz, 1H), 4.80 (d, J

= 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 3.97 (m, 2H), 3.89 (m, 2H), 3.49 (m, 2H), 3.37 (s, 6H), 3.21 (m, 2H), 1.92 (m, 6H), 1.76 (m, 2H), 1.62 (m, 3H), 1.55−1.22 (m and br s, 17H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR *δ* 96.7, 96.6, 81.72, 81.67, 81.3, 81.1, 79.4, 78.3, 55.8, 55.7, 32.0, 31.9, 31.1, 29.8, 29.6, 29.5, 29.3, 28.3, 28.25, 28.2, 25.6, 22.7, 14.1, 7.1 ppm; HRMS ($C_{27}H_{51}IO_6Cs$ = 731.1785), found 731.1757 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-4,13-Di(methoxymethoxy)-5,8:9,12-dioxidotricosane-1-triphenylphosphonium Iodide, 4. A mixture of **67d** (0.39 g, 0.65 mmol), $NaHCO_3$ (0.27 g, 3.25 mmol), and PPh_3 (1.2 g, 4.55 mmol) in dry CH_3CN (15 mL) was stirred at 40 °C for 36 h. The solvent was removed under reduced pressure. The residue was dissolved in dry CH_2Cl_2 and filtered to remove inorganic materials, the solvent were removed under reduced pressure, and the residue was triturated with dry ether−hexanes (1:1) several times to remove unreacted PPh_3. The residue was then mixed with benzene, the solvent was removed under reduced pressure (3 ×), and the residue was dried under high vacuum for 16 h to afford **4** (0.476 g, 85%): ^{1}H NMR *δ* 7.78 (m, 9H), 7.68 (m, 6H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 3.94 (m, 1H), 3.89 (m, 1H), 3.83 (m, 2H), 3.76 (m, 1H), 3.72 (m, 1H), 3.51 (m, 1H), 3.42 (m, 1H), 3.35 (s, 3H), 3.07 (s, 3H), 2.10−1.54 (m, 12H), 1.46−1.22 (m and br s, 18H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR *δ* 135.0, 133.8, 133.7, 130.5, 130.4, 118.6, 117.7, 97.2, 96.7, 82.2, 81.7, 81.4, 81.3, 79.6, 79.2, 55.7, 55.6, 31.9, 31.4, 31.3, 31.0, 29.8, 29.6, 29.3, 28.5, 28.4, 28.2, 25.6, 22.9, 22.6, 22.4, 18.8, 14.1 ppm; HRMS ($C_{45}H_{66}IO_6PCs$ = 993.2696), found 993.2653 (MCs^+).

11,12-Dehydroasimcin-4-*tert*-butyldimethylsilyl-13,22-dimethoxymethyl-*tris*-ether, 68. BuLi (1.6 M solution in hexane, 0.11 mL, 0.174 mmol) was added dropwise to an ice-cold stirred solution of **4** (0.150 g, 0.174 mmol) in dry THF (4 mL) under argon, and the mixture was stirred for 15 min. A solution of **3** (0.064 g, 0.174 mol) in dry THF (2 mL) was added dropwise, and the mixture was stirred for 15 min and then quenched with a saturated solution of NH_4Cl and extracted with ether. The combined organic layer was dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (silica gel, benzene−EtOAc, 9:1−1:1) to provide **68** (85 mg, 60%) in the form of a colorless oil: ^{1}H NMR *δ* 7.10 (q, *J* = 1.2 Hz, 1H), 5.33 (m, 2H), 4.99 (qq, *J* = 6.8, 1.4 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 2H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.02−3.87 (m, 5H), 3.49−3.43 (m, 2H), 3.38 (s, 3H), 3.37 (s, 3H), 2.40 (d, *J* = 5.6 Hz, 2H), 2.20−1.23 (m and br s, 42H), 1.39 (d, *J* = 6.8 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR *δ* 174.0, 151.5, 130.8, 130.3, 129.2, 96.7, 96.6, 81.7, 81.6, 81.23, 81.18, 79.5, 79.3, 77.5, 70.1, 55.73, 55.68, 37.9, 32.7, 31.9, 31.2, 31.1, 29.8, 29.7, 29.6, 29.3, 28.2, 27.2, 25.8, 25.6, 25.1, 23.4, 22.7, 18.9, 18.0, 14.1, −4.5 ppm; HRMS ($C_{47}H_{86}O_9SiCs$ = 955.5095), found 955.5132 (MCs^+).

Asimicin, 1. Chlorotris(triphenylphosphine)rhodium(I) (8.4 mg, 9.1 *μ*mol) was added to a degassed solution of **68** (50 mg, 60.7 *μ*mol) in a mixture of benzene−EtOH (1:1, 2 mL), and the mixture was stirred under an H_2 atmosphere for 12 h. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, benzene−EtOAc, 7:3−1:1) to provide corresponding 11,12-dihydrogenated product (49 mg, 98%) in the form of a colorless oil: $[\alpha]_D$ +27.0 (*c* = 2.10, $CHCl_3$); ^{1}H NMR *δ* 7.09 (br s, 1H), 4.97 (q, *J* = 5.8 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 2H), 4.63 (d, *J* = 6.8 Hz, 2H), 3.99−3.85 (m, 5H), 3.45−3.41 (m, 2H), 3.35 (s, 6H), 2.39 (d, *J* = 5.6 Hz, 2H), 1.93−1.21 (m and br s, 44H), 1.38 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3 H), 0.83 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR *δ* 174.0, 151.5, 130.8, 96.6, 81.7, 81.2, 79.4, 77.4, 70.1, 55.6, 36.9, 32.7, 31.9, 31.1, 29.8, 29.7, 29.6, 29.3, 28.2, 25.8, 25.6, 25.1, 22.6, 18.9, 14.1 ppm; HRMS ($C_{47}H_{88}O_9SiCs$ = 957.5252), found 957.5226 (MCs^+).

AcCl was dissolved in MeOH (5%, 1 mL) and added to a solution of the above-mentioned dihydrogenated product (20 mg, 24.2 *μ*mol) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 2 h, diluted with CH_2Cl_2, and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (silica gel, benzene−EtOAc, 1:1−0:1) to provide **1** (12.5 mg, 83%) in the form of a colorless oil: $[\alpha]_D$ +14.4 (*c* = 0.62, chloroform), lit.[8a] +14.7 (*c* = 0.31, $CHCl_3$); ^{1}H NMR *δ* 7.17 (s, 1H), 5.06−5.01 (q, *J* = 6.64 Hz, 1H), 3.84−3.80 (m, 5H), 3.40−3.34 (m, 2H), 2.52−2.48 (d, *J* = Hz, 1H), 2.40−2.34 (d, *J* = Hz, 1H), 1.96−1.94 (m, 4H), 1.75−1.23 (m and br s, 48H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR *δ* 174.63, 151.81, 131.14, 83.14, 81.77, 77.97, 74.03, 69.94, 37.36, 33.38, 33.28, 31.88, 29.69, 29.59, 29.48, 29.31, 28.96, 28.34, 25.62, 25.54, 22.66, 19.08, 14.10 ppm; HRMS ($C_{37}H_{66}O_7Cs$ = 755.3863), found 755.3841 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-1,4,13-Trihydroxy-5,8:9,12-dioxidotricosane, 69a, from 7. Using the above-described procedure for the conversion of **6** to **67a**, compound **7** (0.15 g, 0.378 mmol) was treated with $LiAlH_4$ (28 mg, 0.75 mmol) in dry ether (10 mL) followed by column chromatography (silica gel, EtOAc−MeOH, 1:0−19:1) to give **69a** (0.15 g, 99%): $[\alpha]_D$ +5.2 (*c* = 0.68, $CHCl_3$); ^{1}H NMR *δ* 4.28 (br s, 1H), 3.93−3.75 (m, 5H), 3.70−3.40 (m, 5H), 1.96 (m, 4H), 1.78 (m, 1H), 1.73 (m, 2H), 1.68−1.35 (m, 7H), 1.26 (m and br s, 16H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR *δ* 83.1, 82.8, 82.5, 82.2, 74.1, 71.1, 62.6, 32.2, 31.8, 29.9, 29.6, 29.54, 29.48, 29.23, 29.19, 29.0, 28.4, 26.0, 24.2, 22.6, 14.0 ppm; MS 423 (MNa^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-1,4,13-Trihydroxy-5,8:9,12-dioxidotricosane, 69a, from 7a. Compound **7a** (510 mg, 0.93 mmol) was reduced with $LiAlH_4$ (114 mg, 3 mmol) in dry ether (20 mL) at reflux (2 h) in a manner similar to that for the conversion of **6** to **67a**. The crude product was purified by column chromatography using silica gel (EtOAc−MeOH, 1:0−19:1) to afford **69a** (300 mg, 81%).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-1-*tert*-Butyldimethylsilyloxy-4,13-di(methoxymethoxy)-5,8:9,12-dioxidotricosane, 69b. Following the above-described procedure for the conversion of **67a** to **67b**, compound **69a** (0.150 g, 0.37 mmol) was reacted with TBSCl (84 mg, 0.55 mmol), diisopropylethylamine (0.143 g, 1.1 mmol), and DMAP (20 mg, 0.16 mmol) in dry CH_2Cl_2 (5 mL) and then with MOMCl (0.4 g, 4.9 mmol) and diisopropylethylamine (0.57 mL, 4.4 mmol). Purification by column chromatography (silica gel, hexanes−EtOAc, 4:1) afforded **69b** (0.2 g, 91%) in the form of an oil: ^{1}H NMR *δ* 4.81 (d, *J* = 6.8 Hz, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.8, Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 3.98 (m, 2H), 3.88 (m, 2H), 3.68 (m, 1H), 3.60 (m, 2H), 3.50 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 1.95−1.55 (m, 10H), 1.42 (m, 4H), 1.40−1.22 (m and br s, 16H), 0.87 (s, 9H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR *δ* 96.7, 96.6, 81.7, 81.6, 81.3, 81.2, 79.3, 78.6, 63.0, 55.5, 31.8, 31.78, 29.6, 29.5, 29.46, 29.2, 28.8, 28.4, 28.2, 28.1, 27.2, 26.3, 25.8, 25.5, 22.6,18.2, 14.0, −5.43, −5.47 ppm; MS 735 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-1-Hydroxy-4,13-bis(methoxymethoxy)-5,8:9,12-dioxidotricosane, 69c. Following the above-described procedure for deprotection of **67b** to give **67c**, compound **69b** (0.2 g, 0.33 mmol) was treated with TBAF (1 M in THF, 0.4 mL, 0.4 mmol) in dry THF (10 mL) at 0 °C. Purification by column chromatography (silica gel, hexanes−EtOAc, 1:1) afforded **69c** (0.145 g, 90%) in the form of an oil: $[\alpha]_D$ +14.5 (*c* = 0.93, $CHCl_3$); ^{1}H NMR *δ* 4.84 (d, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.08−3.97 (m, 2H), 3.90 (m, 2H), 3.69 (m, 3H), 3.57 (m, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.04 (br s, 1H), 1.93 (m, 4H), 1.72 (m, 6H), 1.60−1.45 (m, 4H), 1.40−1.22 (m and br s, 16H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR *δ* 96.8, 96.7, 81.8, 81.44, 81.41, 79.4, 78.7, 62.8, 55.8, 55.6, 31.9, 31.8, 29.7, 29.6, 29.3, 28.7, 28.5, 28.2, 28.0, 27.3, 26.3, 25.6, 22.6, 14.1 ppm; MS 621 (MCs^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-1-Iodo-4,13-di(methoxymethoxy)-5,8:9,12-dioxidotricosane, 69d. Using the above-described procedure for the conversion of **67c** to **67d**, alcohol **69c** (0.140 g, 0.287 mmol) was reacted with I_2 (91 mg, 0.36 mmol), PPh_3 (0.113 g, 0.43 mmol), and imidazole (25 mg, 0.37 mmol) in dry CH_2Cl_2 (5 mL) to give iodide **69d** (0.124 g, 72%): $[\alpha]_D$ +15.8 (*c* = 0.74, $CHCl_3$); ^{1}H NMR *δ* 4.81 (d, *J* = 6.8 Hz, 1H), 4.78 (d,

J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.89 (m, 2H), 3.68 (m, 1H), 3.53 (m, 1H), 3.39 (s, 6H), 3.22 (m, 2H), 2.05−1.40 (m, 14H), 1.38−1.22 (m and br s, 16H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 96.7, 81.8, 81.6, 81.4, 78.7, 78.4, 55.8, 55.6, 31.9, 31.85, 31.82, 29.7, 29.56, 29.53, 29.3, 28.5, 28.2, 28.1, 26.3, 25.6, 22.6, 14.1, 7.0 ppm; MS 621 (MNa^+).

(4*R*,5*R*,8*R*,9*R*,12*R*,13*S*)-4,13-Bis(methoxymethoxy)-5,8:9,12-dioxidotricos-1-yl Triphenylphosphonium Iodide, 5. Using the above-described procedure for the conversion of **67d** to **4**, iodide **69d** (70 mg, 0.11 mmol) was reacted with PPh_3 (0.144 g, 0.55 mmol) in the presence of $NaHCO_3$ (37 mg, 0.44 mmol) in dry CH_3CN (5 mL) to afford the Wittig salt **5** (80 mg, 84%): ^{1}H NMR δ 7.79 (m, 9H), 7.68 (m, 6H), 4.73 (d, J = 6.4 Hz, 2H), 4.59 (d, J = 6.4 Hz, 1H), 4.55 (d, J = 6.4 Hz, 1H), 3.90 (m, 2H), 3.80 (m, 2H), 3.70 (m, 2H), 3.62 (m, 1H), 3.51 (m, 1H), 3.33 (s, 3H), 3.06 (s, 3H), 2.15−1.50 (m, 14H), 1.40−1.20 (m and br s, 16H), 0.84 (t, J = 6.4 Hz, 3H); ^{13}C NMR δ 135.0, 133.7, 133.6, 130.5, 130.4, 118.5, 117.6, 97.1, 96.7, 82.0, 81.7, 81.5, 79.2, 78.6, 55.5, 31.9, 31.8, 31.3, 31.2, 29.7, 29.5, 29.2, 28.5, 28.3, 28.2, 26.2, 25.6, 22.9, 22.6, 22.4, 18.8, 14.0 ppm; HRMS ($C_{45}H_{66}IO_6PCs$ = 993.2696) found 993.2653 (MCs^+).

11,12-Dehydrobullatacin-4-*tert*-butyldimethylsilyl-13,-22-dimethoxymethyl-*tris*-ether, 70. Using the above-described procedure for the conversion of **4** to **68**, BuLi (1.6 M solution in hexane, 20.7 μL, 0.03 mmol) was reacted with **5** (26 mg, 0.03 mmol) in dry THF (4 mL) under argon, and the resultant Wittig reagent was reacted with aldehyde **3** (14 mg, 0.03 mmol) to give **70** (17 mg, 63%) in the form of a colorless oil: ^{1}H NMR δ 7.10 (br s, 1H), 5.39−5.27 (m, 2H), 4.98 (q, J = 6.8 Hz, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.6 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.02−3.89 (m, 3H), 3.86 (m, 2H), 3.66 (m, 1H), 3.49 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.40 (d, J = 5.6 Hz, 2H), 2.20−1.50 (m, 12H), 1.45−1.20 (m and br s, 30H), 1.39 (d, J = 6.8 Hz, 3H), 0.85 (s, 9H), 0.85 (t, J = 6.4 Hz, 3H), 0.02 (s, 3H), −0.01 (s, 3H); HRMS ($C_{47}H_{86}O_9SiCs$ = 955.5095) found 955.5131 (MCs^+).

Bullatacin, 2. Compound **70** (20 mg, 24.3 μmol) was hydrogenated using catalytic chlorotris(triphenylphosphine)-rhodium(I) (3.8 mg, 4.13 μmol) and H_2 to give the corresponding 11,12 dihydrogenated product (20 mg, 99%) in the form of a colorless oil: $[\alpha]_D$ +14.4 (c = 1.06, $CHCl_3$); ^{1}H NMR δ 7.10 (d, J = 1.3 Hz, 1H), 4.99 (dq, J = 6.8, 1.3 Hz 1H), 4.80 (d, J = 6.8 Hz, 1H), 4.77 (d, J = 6.6 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 3.95 (m, 3H), 3.86 (m, 2H), 3.67 (m, 1H), 3.46 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.40 (d, J = 5.6 Hz, 2H), 1.90 (m, 4H), 1.85−1.20 (m and br s, 42H), 1.39 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 6.4 Hz, 3H), 0.85 (s, 9 H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 174.0, 151.5, 130.8, 96.8, 96.7, 81.8, 81.6, 81.5, 81.3, 79.5, 78.7, 77.5, 70.1, 55.7, 36.9, 32.7, 31.9, 31.0, 29.6, 29.3, 28.5, 28.3, 28.1, 26.4, 25.9, 25.7, 25.1, 22.7, 18.9, 18.0, 14.1, −4.5 ppm; HRMS ($C_{47}H_{88}O_9SiCs$ = 957.5252), found 957.5224 (MCs^+).

Following the above-described procedure for the preparation of asimicin **1**, a solution of the above-mentioned dihydrogenated product (20 mg, 24.2 μmol) in CH_2Cl_2 was reacted with a solution of acetyl chloride (4% in MeOH) to produce **2** (12 mg, 80%): $[\alpha]_D$ +13.9 (c = 0.57, $CHCl_3$); lit.[3a] +13.0 (c = 0.004, $CHCl_3$), lit.[8a] +12.8 (c = 0.26, $CHCl_3$); ^{1}H NMR δ 7.17 (d, J = 1.4 Hz, 1H), 5.04 (qq, J = 6.8, 1.4 Hz 1H), 3.95−3.80 (m, 6H), 3.38 (m, 1H), 2.73 (br, 1H), 2.60−2.28 (br, 2H), 2.50 (m, 1H), 2.38 (m, 1H), 2.06−1.20 (m and br s, 51H), 1.41 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 174.4, 151.5, 131.4, 83.2, 82.9, 82.4, 82.1, 77.8, 74.0, 71.7, 70.0, 37.5, 33.5, 33.4, 32.6, 31.9, 29.7, 29.6, 29.5, 29.3, 28.8, 28.4, 26.5, 25.6, 25.55, 24.8, 22.6, 19.1, 14.0 ppm; HRMS ($C_{37}H_{66}O_7Cs$ = 755.3863), found 755.3853 (MCs^+).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for selected compounds and experimental for compounds **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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