Total Synthesis of Trilobin

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The first total synthesis of (+)-trilobin (**1a**) was achieved in 22 steps and 2.74% yield by means of the "naked" carbon skeleton strategy, with all of the asymmetric centers in the bis-THF fragment of the molecules being produced by the Sharpless asymmetric dihydroxylation and the asymmetric epoxidation reactions. The synthetic scheme represents a general methodology for the preparation of *trans,cis*-bis-THF ring systems.

Introduction

Approximately 300 acetogenins have been isolated from various *Annonaceae* plants, many of which have shown remarkable cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant activities.[1] The past few years have witnessed an explosion of activity in the isolation, structural elucidation, and synthesis of these long-chain fatty acid derivatives.[2,3] Our synthetic approaches to the various classes of the Annonaceous acetogenins are based on either a convergent strategy or a linear scheme. The convergent synthesis, which employs asymmetric oxygenation reactions with chirality transfer methods, can provide access to libraries of bis-THF stereoisomers.[4] Alternatively, in the "naked" carbon skeleton strategy,[5] all oxygen functions are selectively placed onto a nonfunctionalized, unsaturated carbon skeleton.[6]

A dominant structural feature that appears in more than 40% of the Annonaceous acetogenins, particularly in those showing the highest antitumor activity, is a 10-carbon fragment containing two adjacent tetrahydrofuran rings flanked by two hydroxyl groups. Studies on the primary mode of action have established the role of such acetogenins as powerful, potent inhibitors of the NADH-ubiquinone oxidoreductase (complex I) of mammalian and insect mitochondrial electron-transport systems.[7] More recent studies have also demonstrated that these acetogenins are efficient inhibitors of the ubiquinone-linked NADH oxidase that is specifically active in the plasma membranes of tumor cells and is inactive in normal cells.[8] These combined actions may lead to programmed cell death (apoptosis) and could account for the observed high potencies of these compounds.[9] Two recently discovered members of this subgroup, trilobin (**1a**) and trilobacin (**1b**) (Figure 1) have attracted much interest as a result of their high biological activity.[10] Studies with human solid-tumor cell lines show that these acetogenins are cytotoxic agents over a billion times more potent than adriamycin. Interestingly, the corrected structures of both **1a** and **1b** exhibit two very unusual features: an

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(1) (a) 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, pp 249−310. (b) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. (c) Fang, X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J. L. *Phytochem. Anal.* **1993**, *4*, 27.

(2) For review articles, see: (a) Figadére, B. *Acc. Chem. Res.* **1995**, *28*, 359. (b) Koert, U. *Synthesis* **1995**, 115. (c) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447. (d) Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem.* **1997**, *37*, 97.

(3) For total synthesis of Annonaceous aceogenins and analogues by other groups, see: (a) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369. (b) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043. (c) Tam, V. T.; Chaboche, C.; Figadere, B.; Chappe, B.; Hieu, B. C.; Cavé, A. *Tetrahedron Lett.* **1994**, *35*, 883. (d) Trost, B. M.; Shi, Z. P. *J. Am. Chem. Soc.* **1994**, *116*, 7459. (e) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517. (f) Yao Z. J.; Wu, Y. L. *Tetrahedron Lett.* **1994**, *35*, 157. (g) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975. (h) Konno, H.; Makabe, H.; Tanaka, A.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 2355. (i) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981. (j) Yao Z. J.; Wu, Y. L. *J. Org. Chem.* **1995**, *60*, 1170. (k) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419. (l) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (m) Konno, H.; Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1996**, *37*, 5393. (n) Konno, H.; Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1996**, *52*, 9399. (o) Franck, X.; Figadere, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 1593. (p) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996. (q) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989. (r) Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632. (s) Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303. (t) Marshall, J. A.; Jiang, H. J. *Tetrahedron Lett.* **1998**, *39*, 1493.

(4) (a) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891. (b) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257. (c) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447. (d) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640. (e) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014. (f) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017. (g) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863. (h) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279.

(5) (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.

(6) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423.

(7) (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.

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

(9) Wolvetang, E. J.; Johnson, K. L.; Krauer, K.; Ralph, S. J.; Linnane, A. W. *FEBS Lett.* **1994**, *339*, 40.

(10) (a) Zhao, G.-X.; Hui, Y.-H.; Rupprecht, J. K.; McLaughlin J. L.; Wood, K. V. *J. Nat. Prod.* **1992**, *55*, 347. (b) Zhao, G.-X.; Gu, Z.-M.; Zeng, L.; Chao, J.-F.; Kozlowski, J. F.; Wood, K. V.; McLaughlin J. L. *Tetrahedron* **1995**, *51*, 7149 and references therein.

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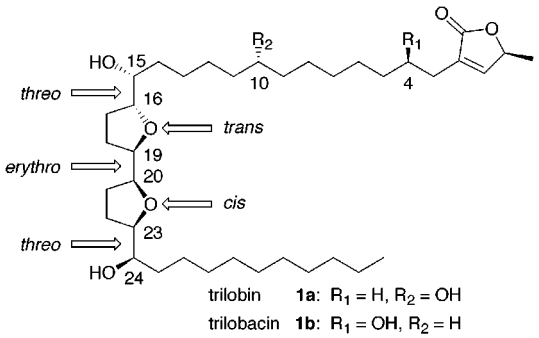


Figure 1. Structures of trilobin (**1a**) and trilobacin (**1b**).

erythro junction between the two adjacent THF rings and a *cis* stereochemistry in the B ring.[10b]

We have recently reported on the first total synthesis of (+)-trilobacin (**1b**) using the convergent synthetic approach.[4d] Here, we report on the first total synthesis of **1a** using the "naked" carbon skeleton strategy, with all of the asymmetric centers in the bis-THF fragment being produced by the Sharpless asymmetric dihydroxylation (AD)[11] and the asymmetric epoxidation (AE)[12] reactions.

Results and Discussion

Our synthesis of **1a** (Scheme 1) starts with alcohol **2**, which was prepared by LAH reduction of the readily available ethyl pentadec-4-enoate.[4g,13] Alcohol **2** was oxidized with PCC to the corresponding aldehyde, the aldehyde was reacted with vinylmagnesium bromide, and the resultant allylic alcohol underwent the Johnson−Claisen rearrangement using triethyl orthoacetate in xylene to produce the desired "naked" carbon skeleton **3**. By means of our previously described strategy,[4a] diene **3** underwent double asymmetric dihydroxylation using AD-mix-β followed by base−acid treatment to produce the crystalline lactone **4**.[3i] Recrystallization of **4** from ethyl acetate afforded enantiomerically pure material. The vicinal diol was protected in the form of an acetonide **5a** using dimethoxypropane, and the remaining alcohol was converted to the corresponding mesylate **5b**. Acidic hydrolysis of the acetonide back to a vicinal diol was achieved with toluenesulfonic acid in aqueous methanol. Ring closure was achieved by heating in pyridine to give the THF derivative **6a**, which represents one of the key intermediates in the synthetic scheme. Compounds **6a** and its precursor **4** are >98% enantiomerically pure as judged by ^{1}H NMR spectra of the Mosher's esters of **6a**.

The alcohol function in **6a** was protected in the form of a *tert*-butyldiphenylsilyl ether (BPS) (**6b**), and the lactone was partially reduced to the corresponding lactol. Wittig−Horner olefination of the lactol using carbethoxymethyl triphenylphosphorane afforded the unsaturated ester **7**. Reduction of the ester with DIBAL-H at low temperature provided the allylic alcohol **8**. Asymmetric epoxidation of **8** was carried out in analogy to previous work with a similar skeleton.[3i] Only 50% epoxidation was achieved, followed by in situ ring closure to give **9**, when half of the stoichiometric amount of ligand and catalyst were used as reported.[3i] However, the epoxidation of **8** in the presence of a stoichiometric amount of the catalyst improved the yield to 75% of the bis-THF diol **9**. By means of a four-step sequence, the diol was converted into an epoxide with inversion of the configuration at the secondary carbinol function. Thus, the primary alcohol was first protected in the form of a TBDMS ether, the secondary alcohol was converted to the corresponding mesylate, and the TBDMS ether was cleaved by treatment with TsOH in methanol. Finally, reaction with K_2CO_3 in methanol affected the desired ring-closure reaction to produce epoxide **10**, another key intermediate in this synthesis.

Epoxide **10** was used for a new C−C bond forming reaction using trimethylsilylethynyllithium in the presence of $BF_3 \cdot Et_2O$ to produce alkyne **11**.[14] Cleavage of both silyl protecting groups in **11** afforded the terminal alkynediol **12**, which was then converted to the bis-MOM ether derivative **13**. This set the stage for completion of the carbon skeleton of the target molecule via coupling of alkyne **13** with the butenolide precursor **14**. Thus, the lithiated derivative of alkyne **13** was reacted with the known epoxide **14**[15] to produce intermediate **15** with the desired (10*R*) absolute configuration. Catalytic hydrogenation of the alkyne was achieved using Wilkinson's catalyst, affording **16**. Oxidation of sulfide to sulfoxide, followed by pyrolysis, produced the desired butenolide function in **17**. Finally, deprotection of the MOM ethers using $BF_3 \cdot Et_2O$ in dimethyl sulfide afforded **1a**. Synthetic trilobin **1a** and its *R*- and *S*-Mosher's esters showed ^{1}H NMR data identical to those of the naturally occurring trilobin and its *R*- and *S*-Mosher's ester derivatives.[10b]

In conclusion, the first total synthesis[16] of (+)-trilobin **1a** was achieved in 22 steps and 2.74% yield starting with the "naked" carbon skeleton **3**. The synthetic scheme represents a general methodology for the preparation of *trans*,*cis*-bis-THF ring systems. Because all steps are conveniently carried out on a millimole scale, this methodology is currently being used in our laboratories as a general approach for the preparation of chemical libraries of bis-THF acetogenin stereoisomers.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively, unless otherwise mentioned. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Optical rotations were measured in a 1-dm (1 mL) cell. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254). Column chromatographic separations (flash chromatography) were performed on silica gel (Merck, Kieselgel 60, 230−400 mesh). THF was dried by distillation over sodium−benzophenone ketyl. AD-mix-β was purchased from Aldrich (39276-6).

Pentadec-4-en-1-ol, 2. $LiAlH_4$ (2.6 g, 68 mmol) was slowly added to a solution of ethyl pentadec-4-enoate[13] (8.84 g, 33

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

(12) (a) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993; p 103. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

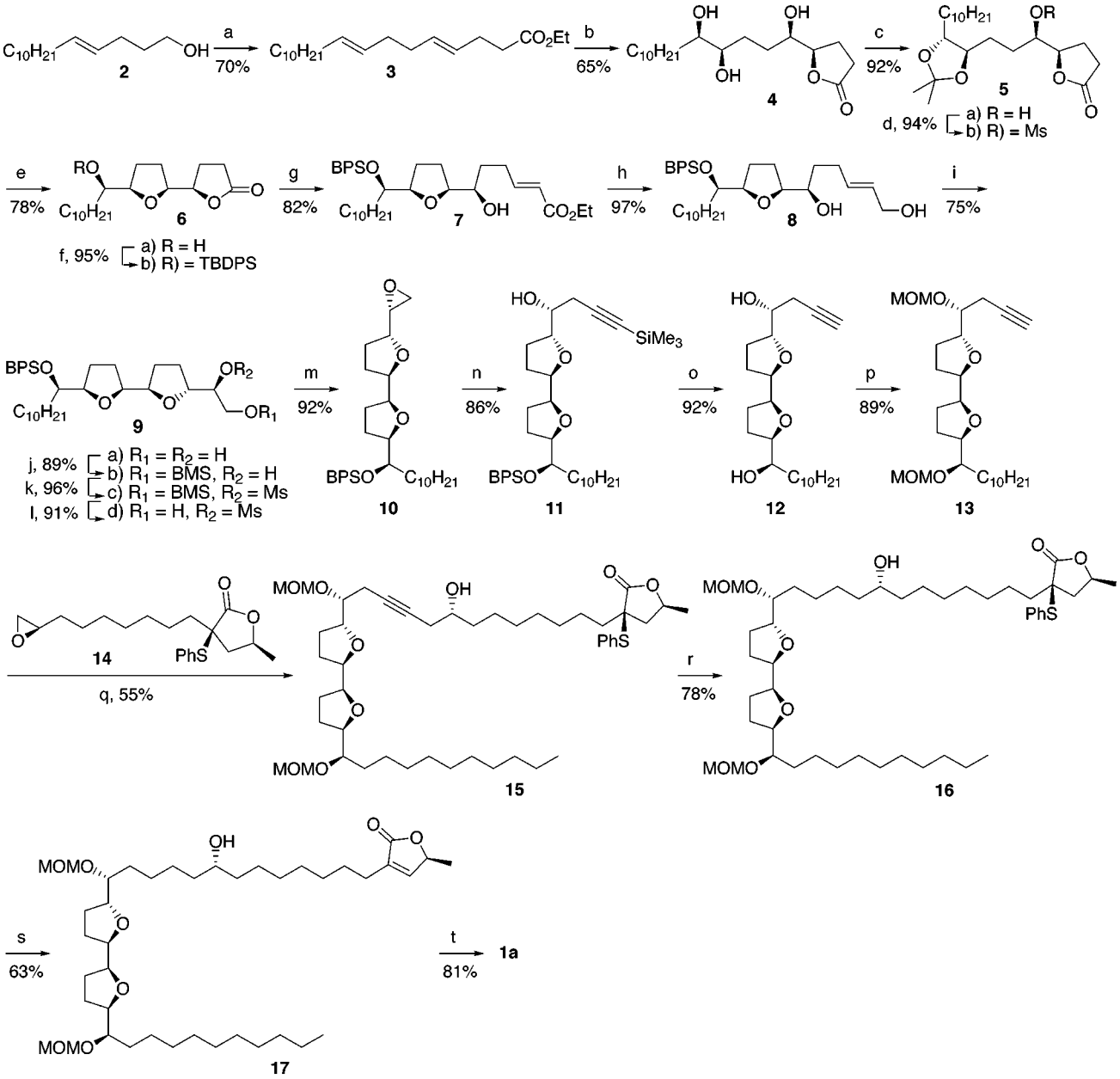
(13) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A.; Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; *Tetrahedron Lett.* **1992**, *33*, 6411.

(14) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(15) Makabe, H.; Tanimoyo, H.; Tanaka, A.; Oritani, T. *Heterocycles* **1996**, *43*, 2229. Compound **14** thus prepared was enantiomerically impure, containing 10−15% of the C2 epimer. This fact, however, did not interfere with the synthesis, because the stereochemistry at C2 was irrelevant to the final product.

(16) Note added in proof: a total synthesis of **1** has also been reported simultaneously to this work. See: Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999**, *64*, 971.

Scheme 1. Total Synthesis of Trilobin[a]



[a] (a) i. PCC, celite, CH_2Cl_2, 2 h; ii. vinylmagnesium bromide, THF, −20 °C, 0.5 h; iii. triethyl orthoacetate, xylene, propionic acid (cat.), 2 h. (b) i. AD-mix-β, $MeSO_2NH_2$, *t*-butanol/water (1:1), 0 °C, 16 h; ii. 3 N aq KOH then HCl (3 N); iii. TsOH (cat.), CH_2Cl_2, rt, 0.5 h. (c) DMP, acetone, TsOH (cat.), 0 °C, 1 h. (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h. (e) i. MeOH/H_2O (9:1), TsOH, 16 h; ii. pyridine, 140 °C, 2 h. (f) TBDPSCl, imidazole, DMF, 16 h. (g) i. DIBAL-H, THF, −78 °C, 1.5 h; ii. carbethoxymethylene triphenylphosphorane, toluene, 80 °C, 16 h. (h) DIBAL-H, THF, −78 °C, 1 h. (i) i. TBHP, (+)-DET, Ti(O*i*-Pr)$_4$, CH_2Cl_2, −20 °C, 16 h. (j) TBDMSCl, diisopropylethylamine, DMAP, CH_2Cl_2, 16 h. (k) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h. (l) TsOH, MeOH, rt, 2 h. (m) MeOH, K_2CO_3, rt, 1 h. (n) trimethylethynylsilane, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 2 h. (o) TBAF, THF, 40 °C, 48 h. (p) MOMCl, diisopropylethylamine, CH_2Cl_2, 0 °C to rt, 16 h. (q) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, then **14**, 2 h. (r) $RhCl(PPh_3)_3$, benzene, H_2, rt, 16 h. (s) i. *m*-CPBA, CH_2Cl_2, 0 °C, 20 min; ii. toluene, 90 °C, 1 h. (t) $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, 0 °C, 10 min.

mmol) in dry ether (100 mL) at 0 °C. The mixture was allowed to warm to room temperature over 1 h, and then worked up by slow addition of wet ether and water. The resultant crude **2** was found to be pure by TLC and was taken to the next step without further purification. ^{1}H NMR: δ 5.42 (m, 2H), 3.64 (t, J = 6.5 Hz, 2H), 2.06 (q, J = 7.2 Hz, 2H), 1.96 (q, J = 5.5 Hz, 2H) 1.64 (m, 2H), 1.38−1.22 (m and br s, 16H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 131.3, 129.3, 62.6, 32.5, 32.4, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 22.7, 14.1. MS: 249 (MNa^+).

Ethyl Nonadeca-4,8-dienoate, 3. Celite (14 g) and PCC (14 g, 65 mmol) were added to a solution of **2** (7.5 g, 33 mmol) in CH_2Cl_2 (150 mL), and the mixture was stirred for 2 h. Filtration over silica gel afforded the corresponding aldehyde (6.57 g, 89%). A solution of vinylmagnesium bromide (1 M in THF, 35 mL, 35 mmol) was added to the solution of the crude aldehyde in dry THF at 0 °C, and the mixture was stirred for 0.5 h. Workup with saturated aqueous NH_4Cl and ether produced heptadeca-1,6-dien-3-ol (7.28 g), which was taken to next step without further purification.^{1}H NMR: δ 5.86 (ddd, J = 16.9, 10.5, 6.2 Hz, 1H), 5.42 (m, 2H), 5.22 (dt, J = 16.9, 1.5 Hz, 1H), 5.10 (dt, J = 10.5, 1.5 Hz, 1H), 4.12 (q, J = 6.3 Hz, 1H), 2.06 (q, J = 7.2 Hz, 2H), 1.96 (q, J = 5.5 Hz, 2H), 1.64 (m, 3H), 1.38−1.22 (m and br s, 16H), 0.87 (t, J = 7.1 Hz, 3H).

A solution of the crude alcohol (7.28 g), triethylorthoacetate (11 mL, 60 mmol), and propionic acid (37 mg, 0.5 mmol) in xylene (11 mL) was heated at reflux for 2 h. Removal of the

solvent under high vaccum followed by column chromatography (silica gel, hexanes/ethyl acetate 49:1−19:1) afforded **3** (7.5 g, 70% from **2**). ^{1}H NMR: δ 5.50−5.30 (m, 4H), 4.11 (q, J = 7.2 Hz, 2H), 2.37−2.23 (m, 4H), 2.05−1.90 (m, 6H), 1.35−1.22 (m and br s, 16H), 1.23 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 173.2, 131.1, 130.8, 129.4, 128.2, 60.2, 34.4, 32.6, 31.9, 29.6, 29.5, 29.3, 29.1, 27.9, 22.7, 14.2, 14.1.

(4*R*,5*R*,8*R*,9*R*)-5,8,9-Trihydroxynonadecan-1,4-olide, 4. Methanesulfonamide (3.6 g, 40 mmol) and **3** (6.44 g, 20 mmol) were added to a two-phase homogeneous mixture of AD-mix-β (56 g, Os content 0.4%) in *tert*-butyl alcohol/water (1:1, 600 mL). The mixture was stirred at 0 °C for 16 h and then worked up by slow addition of sodium metabisulfite (60 g). The crude lactone thus obtained was mixed with methanol (40 mL) and aqueous NaOH (3N, 20 mL), and the mixture was stirred at 60 °C for 2 h, cooled, acidified with aqueous HCl (3 N, 25 mL), and extracted with ethyl acetate. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL). The mixture was stirred with TsOH (0.5 g) for 1 h and washed with saturated aqueous $NaHCO_3$. Solvent was removed again, and the residue was crystallized from ethyl acetate to give lactone **4** (4.48 g, 65%). Mp: 94−97 °C. $[\alpha]_D$: + 7.32° (*c* 1.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 4.39 (td, J = 6.9, 4.0 Hz, 1H), 3.52 (dt, J = 4.5, 4.0 Hz, 1H), 3.31 (m, 2H), 2.80 (br s, 3H), 2.58 (ddd, J = 17.9, 10.0, 5.5 Hz, 1H), 2.46 (ddd, J = 17.9, 9.9 Hz, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.70−1.18 (m and br s, 22H), 0.82 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 178.4, 83.5, 77.4, 73.9, 73.0, 33.3, 31.8, 29.6, 29.5 (two signals), 29.2, 29.1, 28.6, 25.6, 23.9, 22.6, 14.0. MS: 345 (MH^+), 377 (MNa^+).

(4*R*,5*R*,8*R*,9*R*)-5-Hydroxy-8,9-isopropylidenedioxynonadecan-1,4-olide, 5a. Compound **4** (4.40 g, 12.8 mmol) and TsOH (0.5 g) were dissolved in a 1:1 mixture of dimethoxypropane and acetone (50 mL), and the mixture was stirred at room temperature for 0.5 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. Filtration through a short bed of silica gel afforded acetonide **5a** (4.53 g, 92%) in the form of a colorless oil. ^{1}H NMR: δ 4.43 (td, J = 7.5, 4.0 Hz, 1H), 3.59 (m, 3H), 2.63 (ddd, J = 17.8, 9.9, 5.6 Hz, 1H), 2.50 (ddd, J = 17.8, 9.9, 8.1 Hz, 1H), 2.30−2.10 (m, 2H), 1.80−1.22 (m and br s, 23H), 1.36 (s, 6H), 0.86 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 177.5, 108.0, 82.9, 80.9, 80.6, 73.2, 32.6, 31.8, 29.8, 29.7, 29.5, 29.4, 29.2, 29.1, 28.5, 27.2, 27.1, 26.0, 23.9, 22.6, 14.0. MS: 407 (MNa^+).

(4*R*,5*R*,8*R*,9*R*)-5-Mesyloxy-8,9-isopropylidenedioxynonadecan-1,4-olide, 5b. Methanesulfonyl chloride (1.8 mL, 23.2 mmol) was added dropwise to a solution of **5a** (4.50 g, 11.7 mmol) and triethylamine (5 mL) in CH_2Cl_2 (20 mL) at −30 °C, and the mixture was stirred at between −30 and 0 °C for 2 h. Workup with water and methylene chloride and filtration through a short bed of silica gel afforded mesylate **5b** (5.08 g, 94%), which was taken to the next step without further purification. ^{1}H NMR: δ 4.75 (m, 1H), 4.61 (m, 1H), 3.59 (m, 2H), 3.12 (s, 3H), 2.60 (m, 2H), 2.35 (m, 1H), 2.10 (m, 1H), 1.88 (m, 2H), 1.76−1.18 (m and br s, 20H), 1.34 (s, 3H), 1.33 (s, 3H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 175.9, 108.1, 82.9, 80.9, 79.8, 79.5, 39.0, 32.6, 31.8, 31.5, 29.7, 29.5, 29.4, 29.3, 28.0, 27.8, 27.6, 27.3, 27.2, 26.0, 24.2, 22.6, 14.1. MS: 485 (MNa^+).

(4*R*,5*S*,8*R*,9*R*)-9-Hydroxy-5,8-oxidononadecan-1,4-olide, 6a. Compound **5b** (5.08 g, 11 mmol) and TsOH (200 mg) were dissolved in methanol/water (4:1, 20 mL), and the mixture was stirred at room temperature for 16 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. Solvent was removed under reduced pressure, and the residue was dissolved in pyridine (20 mL) and refluxed for 2 h. Workup with CH_2Cl_2 water followed by column chromatography (silica gel, hexanes/ethyl acetate 1:1) afforded **6a** (2.80 g, 78%). $[\alpha]_D$: − 7.38° (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 4.42 (td, J = 7.2, 5.6 Hz, 1H), 3.97 (q, J = 6.3 Hz, 1H), 3.75 (q, J = 6.9 Hz, 1H), 3.38 (m, 1H), 2.58−2.42 (m, 2H), 2.30 (m, 1H), 2.18−1.60 (m, 5H), 1.50−1.18 (m and br s, 19H), 0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 176.9, 83.3, 81.1, 80.0, 74.2, 33.6, 31.8, 29.6, 29.5, 29.2, 28.1, 27.5, 27.3, 25.5, 23.9, 22.6, 14.0. HRMS: calcd for $C_{29}H_{34}O_4Na$ 349.2355, found 349.2366 (MNa^+).

(4*R*,5*S*,8*R*,9*R*)-9-*tert*-Butyldiphenylsilyloxy-5,8-oxidononadecan-1,4-olide, 6b. Compound **6a** (1.37 g, 4.2 mmol) and imidazole (571 mg, 8.4 mmol) were dissolved in dry DMF (3 mL), TBDPSCl (1.76 g, 6.4 mmol) was added, and the mixture was stirred at room temperature for 16 h. Workup with water and ether followed by column chromatography (silica gel, hexane/ethyl acetate 9:1−4:1) afforded **6b** (2.30 g, 95%) in the form of a colorless oil. ^{1}H NMR: δ 7.68 (m, 4H), 7.38 (m, 6H), 4.24 (dt, J = 7.3, 6.1 Hz, 1H), 3.90 (td, J = 7.3, 5.5 Hz, 1H), 3.80 (q, J = 6.3 Hz, 1H), 3.67 (q, J = 5.5 Hz, 1H), 2.47 (ddd, J = 17.7, 9.8, 6.6 Hz, 1H), 2.39 (ddd, J = 17.7, 9.5, 7.4 Hz, 1H), 2.11 (m, 1H), 1.96 (m, 2H), 1.82 (m, 1H), 1.74 (m, 2H), 1.48 (m, 1H), 1.40−1.08 (m and br s, 17H), 1.03 (s, 3H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 177.3, 135.9, 135.8, 134.5, 134.2, 129.4, 127.3, 82.0, 81.6, 79.5, 75.2, 33.5, 31.9, 29.6, 29.5, 29.4, 29.3, 28.2, 28.1, 27.0, 26.6, 25.0, 23.8, 21.7, 19.6, 14.1. MS: 697 (MCs^+).

(*E*,6*R*,7*S*,10*R*,11*R*)-Ethyl 11-*tert*-Butyldiphenylsilyloxy-6-hydroxy-7,10-oxidoheneicosa-2-enoate, 7. Compound **6b** (2.50 g, 4.4 mmol) was dissolved in dry THF (10 mL), DIBAL-H (1 M in toluene, 6.0 mL, 6.0 mmol) was added at −78 °C, and the mixture was stirred at the same temperature for 1.5 h. Water (2 mL), Celite (2 g), and ether (10 mL) were added, and the mixture was stirred at 0 °C for 0.5 h. Filtration over Celite and removal of the solvent under reduced pressure afforded the corresponding lactol (2.21 g), which was taken to next step without purification. ^{1}H NMR: δ 7.70 (m, 4H), 7.36 (m, 6H), 5.49 and 5.41 (t, J = 3.2 Hz, and ddd, J = 8.6, 5.5, 1.6 Hz, together 1H), 4.20−3.95 (m, 2H), 3.89 (m, 1H), 3.74−3.66 (m, 2H), 2.20−1.12 (m, 26H), 1.04 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H).

The crude lactol (2.21 g) and ethoxycarbonylmethyltriphenylphosphorane (2.09 g, 5.7 mmol) were dissolved in dry toluene (20 mL), and the mixture was stirred at 80 °C for 16 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 9:1) to give **7** (2.31 g, 82% from **6b**). ^{1}H NMR: δ 7.70 (m, 4H), 7.38 (m, 6H), 6.94 (dt, J = 14.7, 6.4 Hz, 1H), 5.82 (dt, J = 14.7, 1.5 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.82 (m, 1H), 3.68−3.56 (m, 3H), 2.35 (m, 1H), 2.20 (m, 1H), 1.94 (d, J = 3.4 Hz, 1H), 1.82−1.12 (m, 24H), 1.28 (t, J = 7.2 Hz, 3H), 1.04 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 166.6, 148.7, 135.8, 134.6, 134.2, 129.4, 127.5, 127.4, 121.5, 81.7, 81.2, 75.8, 71.0, 60.1, 33.7, 31.9, 30.6, 29.6, 29.5, 29.4, 29.3, 28.6, 27.6, 27.0, 25.1, 24.2, 22.7, 19.5, 14.3, 14.1. MS: 659 (MNa^+).

***(E*,6*R*,7*S*,10*R*,11*R*)-11-*tert*-Butyldiphenylsilyloxy-7,10-oxidoheneicos-2-en-1,6-diol, 8.** Compound **7** (2.31 g, 3.63 mmol) was dissolved in dry THF (15 mL), DIBAL-H (1 M in toluene, 14.5 mL, 14.5 mmol) was added at −78 °C, and the mixture was stirred at the same temperature for 1h. Water (5 mL), Celite (5 g), and ether (25 mL) were added, and the mixture was stirred at 0 °C for 0.5 h. Filtration over Celite, removal of the solvent, and column chromatography (silica gel, hexanes/ethyl acetate 4:1) produced allylic alcohol **8** (2.10 g, 97%) in the form of a colorless oil. ^{1}H NMR: δ 7.66 (m, 4H), 7.44 (m, 6H), 5.65 (m, 2H), 4.01 (d, J = 6.7 Hz, 2H), 3.83 (q, J = 5.2 Hz, 1H), 3.66 (m, 1H), 3.60 (m, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.80−1.12 (m and br s, 26H), 1.03 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 135.9, 132.7, 129.4, 127.4, 127.3, 81.8, 81.1, 75.7, 71.1, 63.7, 33.6, 31.9, 31.8, 29.6, 29.5, 29.4, 29.3, 28.6, 27.6, 27.0, 25.1, 24.1, 22.7, 14.1. MS: 595 (MH^+).

(2*S*,3*R*,6*R*,7*S*,10*R*,11*R*)-11-*tert*-Butyldiphenylsilyloxy-3,6:7,10-dioxidoheneicosane-1,2-diol, 9a. A mixture of **8** (1.74 g, 2.92 mmol), activated molecular sieves (4A, 0.3 g), (+)-diethyl tartrate (0.71 g, 3.44 mmol), and Ti(*i*-OPr)$_4$ (823 mg, 2.9 mmol) in dry CH_2Cl_2 was stirred at −20 °C for 0.5 h. *tert*-Butyl hydroperoxide (TBHP, 5−6 M in isooctane, 2.9 mL) was added dropwise, and the mixture was stirred at the same temperature for 16 h. Workup with water, aqueous NaOH, and ether followed by column chromatography (silica gel, hexanes/ethyl acetate 1:4) afforded **9a** (1.34 g, 75%, 88% on the basis of recovered starting material) in the form of a colorless oil. $[\alpha]_D$: −3.5° (*c* 5.56, $CHCl_3$). ^{1}H NMR: δ 7.69 (m, 4H), 7.38 (m, 6H), 3.95−3.84 (m, 2H), 3.83 (q, J = 6.0 Hz, 1H), 3.78−3.57 (m, 5H), 2.46 (d, J = 3.6 Hz, 1H), 2.37 (m, 1H), 1.98−1.02 (m

and br s, 26H), 1.03 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 136.0, 135.9, 134.4, 134.3, 129.3, 127.3, 81.7, 81.4, 80.9, 80.4, 75.3, 73.0, 64.0, 32.9, 31.9, 29.6, 29.5, 29.4, 29.3, 28.4, 28.0, 27.2, 27.0, 20.5, 25.1, 22.7, 19.5, 14.1. MS: 633 (MNa^+).

(2*S*,3*R*,6*R*,7*S*,10*R*,11*R*)-1-*tert*-Butyldimethylsilyloxy-11-*tert*-butyldiphenylsilyloxy-3,6:7,10-dioxidoheneicosan-2-ol, 9b. Compound **9a** (1.34 g, 2.2 mmol), diisopropylethylamine (2 mL), and DMAP (15 mg) were dissolved in dry CH_2Cl_2 (10 mL). TBDMSCl (365 mg, 2.4 mmol) was added, and the mixture was stirred at room temperature for 16 h. Workup with water and CH_2Cl_2 and purification by column chromatography (silica gel, hexanes/ethyl acetate 1:1) afforded **9b** (1.41 g, 89%) in the form of a colorless oil. ^{1}H NMR: δ 7.70 (m, 4H), 7.35 (m, 6H), 3.89 (m, 1H), 3.85 (q, J = 6.6 Hz, 1H), 3.78 (q, J = 6.5 Hz, 1H), 3.74−3.66 (m, 3H), 3.65−3.52 (m, 2H), 2.43 (d, J = 4.2 Hz, 1H), 2.05−1.02 (m and br s, 26H), 1.04 (s, 9H), 0.89 (s, 9H), 0.88 (t, J = 7.0 Hz, 3H), 0.06 (s, 6H). ^{13}C NMR: δ 136.0, 134.6, 134.3, 129.3, 127.5, 127.3, 127.1, 81.7, 81.4, 81.2, 81.0, 79.1, 75.2, 73.2, 64.4, 32.8, 31.9, 29.6, 29.5, 29.4, 29.3, 28.5, 27.5, 27.0, 26.4, 25.8, 25.6, 25.1, 22.6, 19.5, 14.1. MS: 723 (MH^-).

(2*S*,3*R*,6*R*,7*S*,10*R*,11*R*)-1-*tert*-Butyldimethylsilyloxy-11-*tert*-butyldiphenylsilyloxy-2-mesyloxy-3,6:7,10-dioxidoheneicosane, 9c. Methanesulfonyl chloride (0.5 mL, 6.5 mmol) was added dropwise to a solution of **9b** (1.41 g, 1.96 mmol) and triethylamine (2 mL) in CH_2Cl_2 (10 mL) at −30 °C, and the mixture was stirred at between −30 and 0 °C for 2 h. Workup with water and CH_2Cl_2 followed by filtration through a short bed of silica gel afforded **9c** (1.50 g, 96%), which was taken to next step without further purification. $[\alpha]_D$: −3.71° (*c* 5.81, $CHCl_3$). ^{1}H NMR: δ 7.68 (m, 4H), 7.36 (m, 6H), 4.59 (dt, J = 6.3, 4.9 Hz, 1H), 4.06 (q, J = 6.3 Hz, 1H), 3.90−3.70 (m, 6H), 3.03 (s, 3H), 2.05−1.02 (m, 26H), 1.03 (s, 9H), 0.88 (s, 9H), 0.87 (t, J = 7.1 Hz, 3H), 0.06 (s, 6H).^{13}C NMR: δ 136.0, 135.9, 134.7, 134.4, 129.3, 127.3, 127.2, 84.1, 81.8, 80.7, 77.4, 75.3, 63.1, 38.3, 33.1, 31.8, 29.6, 29.5, 29.4, 29.2, 28.5, 27.9, 27.0, 26.4, 25.8, 25.1, 22.6, 19.5, 14.0, −5.5. MS: 801 (MH^-).

(2*S*,3*R*,6*R*,7*S*,10*R*,11*R*)-11-*tert*-Butyldiphenylsilyloxy-2-mesyloxy-3,6:7,10-dioxidoheneicosan-1-ol, 9d. Compound **9c** (1.50 g, 1.87 mmol) and TsOH (200 mg) were dissolved in methanol/water (4:1, 20 mL), and the mixture was stirred at room temperature for 16 h. Saturated aqueous $NaHCO_3$ was added, the mixture was extracted with CH_2Cl_2, and the organic extract was filtered through a short bed of silica gel. Removal of solvents under reduced pressure afforded **9d** (1.17 g, 91%) in the form of a colorless oil. ^{1}H NMR: δ 7.67 (m, 4H), 7.33 (m, 6H), 4.62 (dt, J = 6.5, 3.5 Hz, 1H), 4.03 (q, J = 7 Hz, 1H), 3.89−3.64 (m, 5H), 3.05 (s, 3H), 2.00−1.05 (m and bs, 26H), 0.87 (t, J = 7 Hz, 3H).^{13}C NMR: δ 136.0, 135.9, 134.6, 134.4, 129.4, 127.3, 127.2, 83.8, 81.8, 80.6, 77.8, 75.3, 62.6, 38.3, 33.1, 31.8, 29.6, 29.4, 29.2, 28.4, 27.6, 27.0, 26.9, 25.0, 22.6, 20.9, 19.5, 14.0. MS: 711 (MNa^+).

(2*R*,3*R*,6*R*,7*S*,10*R*,11*R*)-11-*tert*-Butyldiphenylsilyloxy-1,2:3,6:7,10-trioxidoheneicosane, 10. Compound **9d** (1.17 g, 1.70 mmol) was dissolved in methanol (10 mL), K_2CO_3 (828 mg, 6 mmol) was added, and the mixture was stirred at room temperature for 1 h. Workup with water and CH_2Cl_2 followed by column chromatography (silica gel, hexane/ethyl acetate 8:2) afforded epoxide **10** (930 mg, 92%) in the form of a colorless oil. $[\alpha]_D$: −5.6° (*c* 3.0, $CHCl_3$). ^{1}H NMR: δ 7.69 (m, 4H), 7.36 (m, 6H), 3.94−3.78 (m, 3H), 3.68 (m, 2H), 2.92 (m, 1H), 2.72 (dd, J = 5.2, 4.2 Hz, 1H), 2.66 (dd, J = 5.2, 2.7 Hz, 1H), 2.05−1.02 (m, 26H), 1.03 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 136.0, 135.9, 129.3, 127.2, 82.1, 81.9, 81.0, 78.9, 75.3, 32.9, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 28.7, 28.6, 28.0, 27.0, 26.4, 25.1, 22.7, 14.1. MS: 615 (M^+Na^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-1-Trimethylsilyl-13-*tert*-butyldiphenylsilyloxy-5,8:9,12-dioxidotricos-1-yn-4-ol, 11. *n*-BuLi (1.6 M, 1.9 mL, 3.04 mmol) was added to a solution of trimethylsilylacetylene (295 mg, 3 mmol) in dry THF (5 mL) at −30 °C, and the mixture was stirred at the same temperature for 1 h. $BF_3{\cdot}Et_2O$ (0.37 mL, 3 mmol) was added dropwise, the mixture was stirred for 10 min, epoxide **10** (575 mg, 0.97 mmol) in dry THF (2 mL) was added dropwise, and the mixture was stirred at the same temperature for 1 h. Workup with saturated aqueous NH_4Cl and ether followed by column chromatography (silica gel, hexanes/ethyl acetate 6:4) afforded **11** (575 mg, 86%) in the form of a colorless oil. $[\alpha]_D$: −12.6° (*c* 3.58, $CHCl_3$). ^{1}H NMR: δ 7.68 (m, 4H), 7.36 (m, 6H), 3.89 (m, 2H), 3.77 (m, 1H), 3.69 (m, 2H), 3.52 (m, 1H), 2.41 (m, 3H), 2.02−1.12 (m, 26H), 1.02 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H), 0.13 (s, 6H). ^{13}C NMR: δ 135.9, 134.6, 134.3, 129.2, 127.2, 103.0, 86.7, 81.7, 81.3, 81.1, 80.9, 75.2, 71.9, 71.1, 32.8, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 28.7, 28.4, 28.0, 27.0, 26.4, 25.2, 25.1, 22.6, 19.5, 14.0, −0.1. MS: 713 (MNa^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-5,8:9,12-Dioxidotricos-1-yne-4,-13-diol, 12. Compound **11** (279 mg, 0.40 mmol) was dissolved in dry THF (5 mL). TBAF (1 M in THF, 1.5 mL, 1.5 mmol) was added at 0 °C, and the mixture was stirred at 40 °C for 48 h. Workup with water and ether and filtration through a short bed of silica gel afforded **12** (140 mg, 92%) in the form of a colorless oil. $[\alpha]_D$: −11.4° (*c* 4.2, $CHCl_3$). ^{1}H NMR: δ 4.08−3.97 (m, 2H), 3.94 (q, J = 4.8 Hz, 1H), 3.7 (q, J = 6.4 Hz, 1H), 3.58 (br, 1H), 3.34 (br, 1H), 2.75 (br, 1H), 2.62 (br, 1H), 2.64 (dd, J = 6.2, 2.6 Hz, 2H), 2.03−1.68 (m, 11H), 1.41−1.22 (m, bs, 16H), 0.84 (t, J = 6.4 Hz, 3H). ^{13}C NMR δ 82.6, 81.5, 81.4, 81.2, 80.5, 74.4, 71.8, 70.2, 34.1, 31.8, 29.7, 29.6, 29.2, 28.8, 28.1, 28.0, 26.9, 25.7, 23.9, 22.6, 14.1. MS: 403 (MNa^+).

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-4,13-Di(methoxymethoxy)-5,8:9,12-dioxidotricos-1-yne, 13. Diol **12** (140 mg, 0.37 mmol) and di-*iso*-propylethylamine (0.26 mL, 1.5 mmol) were dissolved in CH_2Cl_2 (2 mL). MOMCl (0.11 mL, 1.4 mmol) was added at 0 °C, and the mixture was stirred at between 0 °C and room temperature for 16 h. Workup with water and CH_2Cl_2 and filtration through a short bed of silica gel followed by removal of solvent under reduced pressure afforded **13** (155 mg, 89%) in the form of a colorless oil. ^{1}H NMR: δ 4.83 (d, J = 6.8 Hz, 1H), 4.77 (s, 2H), 4.65 (d, J = 6.8 Hz, 1H), 4.13 (m, 1H), 3.90−3.78 (m, 3H), 3.63 (m, 1H), 3.44 (m, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.57−2.36 (m, 2H), 2.08−1.22 (m and br s, 27H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR: δ 96.5, 96.4, 82.4, 81.4, 81.3, 80.4, 79.9, 77.3, 55.7, 55.6, 31.8, 31.3, 29.7, 29.5, 29.3, 28.9, 28.4, 28.0, 27.5, 25.3, 22.6, 21.6, 14.1. HRMS: calcd for $C_{27}H_{48}O_6Cs$ 601.2505, found, 601.2528 (MCs^+).

(2*RS*)-2-Thiophenoxy-2,35:12,13:12,13-hexadehydrotrilobin-bis(methoxymethoxy) Ether, 15. *n*-BuLi (1.6 M, 0.2 mL, 0.32 mmol) was added at −78 °C to a solution of **13** (153 mg, 0.32 mmol) in dry THF (2 mL), and the mixture was stirred at the same temperature for 1 h. $BF_3{\cdot}Et_2O$ (45 μL, 0.36 mmol) was added, and the mixture was stirred for 20 min. A solution of epoxide **14** (130 mg, 0.37 mmol) in dry THF (1 mL) was added dropwise at −78 °C, and the mixture was stirred at the same temperature for 1 h. Workup with saturated aqueous NH_4Cl and ether and filtration through a short bed of silica gel afforded **15** (143 mg, 55%) in the form of a colorless oil. ^{1}H NMR: δ 7.52 (m, 2H), 7.34 (m, 3H), 4.80 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.45 (m, 1H), 4.08 (m, 1H), 3.86−3.72 (m, 3H), 3.63 (m, 1H), 3.56 (q, J = 5.6 Hz, 1H), 3.41 (m, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.47 (dd, J = 14.0, 7.6 Hz, 2H), 2.40−2.16 (m, 4H), 2.08−1.62 (m, 10H), 1.58−1.16 (m and br s, 30H), 1.15 (d, J = 6.3 Hz, 3H), 0.84 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 177.0, 136.7, 130.4, 129.6, 128.9, 96.5, 96.3, 82.4, 81.4, 81.3, 80.6, 79.9, 79.4, 77.9, 73.1, 70.0, 55.6, 40.0, 36.4, 36.2, 31.8, 31.3, 29.7, 29.5, 29.4, 29.3, 29.2, 28.9, 28.4, 27.9, 27.8, 27.4, 25.5, 25.3, 24.5, 22.6, 21.8, 21.4, 14.0.

(2*RS*)-2-Thiophenoxy-2,35-didehydrotrilobin-bis-(methoxymethoxy) Ether, 16. Compound **15** (143 mg, 0.18 mmol) and chlorotriphenylphosphine rhodium(I) (40 mg) were dissolved in benzene (2 mL), and the mixture was stirred under a H_2 atmosphere for 16 h and then filtered over Celite. Solvent was removed under reduced pressure, and the residue was filtered through a short bed of silica gel to give **16** (116 mg, 78%) in the form of a colorless oil. ^{1}H NMR: δ 7.52 (d, J = 8.0

Hz, 2H), 7.34 (m, 3H), 4.82 (d, J = 6.5 Hz, 1H), 4.79 (d, J = 7.0 Hz, 1H), 4.64 (d, J = 6.5 Hz, 1H), 4.63 (d, J = 7.0 Hz, 1H), 4.46 (m, 1H), 3.95 (dt, J = 8.5, 6.5 Hz, 1H), 3.85 (dt, J = 8.5, 7.0 Hz, 1H), 3.78 (m, 2H), 3.54 (m, 1H), 3.42 (m, 2H), 3.37 (s, 6H), 2.48 (dd, J = 14.0, 8.0 Hz, 1H), 2.05−1.18 (m and br s, 48H), 1.15 (d, J = 6.5 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 177.1, 136.8, 130.4, 129.7, 129.0, 96.7, 82.5, 81.7, 81.5, 81.1, 80.0, 79.6, 73.2, 71.8, 56.3, 55.7, 40.1, 37.4, 36.5, 31.9, 31.3, 31.1, 29.8, 29.6, 29.5, 29.3, 29.1, 28.5, 28.3, 27.5, 25.8, 25.6, 25.5, 24.6, 22.7, 21.5, 14.1. HRMS: calcd for $C_{47}H_{80}O_9$-SCs 953.4577, found 953.4544 (MCs^+).

Trilobin-bis(methoxymethoxy) Ether, 17. Compound **16** (116 mg, 0.14 mmol) was dissolved in CH_2Cl_2, *m*-CPBA (50−60%, 60 mg, 0.17 mmol) was added at 0 °C, and the mixture was stirred at the same temperature for 20 min and then worked up with saturated aqueous $NaHCO_3$ and CH_2Cl_2. The crude product was dissolved in toluene (8 mL) and heated at 90 °C for 1 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate 1:3) to give **17** (63 mg, 63%) in the form of a colorless oil. ^{1}H NMR: δ 7.52 (d, J = 8.0 Hz, 2H), 6.96 (q, J = 1.4 Hz, 1H), 4.97 (qq, J = 7.1, 1.4 Hz, 1H), 4.81 (d, J = 6.8 Hz, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 3.95 (dt, J = 8.2, 6.3 Hz, 1H), 3.85 (dt, J = 8.2, 6.3 Hz, 1H), 3.79 (m, 2H), 3.55 (m, 1H), 3.43 (m, 2H), 3.36 (s, 6H), 2.23 (tt, J = 8.0, 1.4 Hz, 1H), 2.05−1.18 (m and br s, 46H), 1.37 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 148.9, 134.2, 96.6, 82.5, 81.7, 81.5, 81.1, 80.0, 79.6, 77.4, 71.8, 55.7, 40.1, 37.4, 31.9, 31.3, 31.1, 29.8, 29.6, 29.5, 29.3, 29.2, 29.1, 29.0, 28.5, 28.3, 27.5, 27.3, 25.8, 25.6, 25.5, 25.3, 25.1, 22.6, 19.2, 14.1. HRMS: calcd for $C_{41}H_{74}O_9Cs$ 843.4387, found 843.4416 (MCs^+).

Trilobin, 1a. $BF_3{\cdot}Et_2O$ (0.4 mL, 0.25 mmol) was added at 0 °C to a solution of **17** (63 mg, 0.089 mmol) and Me_2S (1 mL) in CH_2Cl_2 (1 mL), and the mixture was stirred for 10 min. Workup with saturated aqueous $NaHCO_3$ and CH_2Cl_2 followed by filtration through a short bed of silica gel afforded **1a** (45 mg, 81%) in the form of a white powder (recrystallized from diethyl ether). Mp: 65−67 °C. $[\alpha]_D$: +20.0° (*c* 0.20, MeOH), [lit.[10b] +33.3° (*c* 0.00015 g/mL, MeOH)]. ^{1}H NMR: δ 6.96 (q, J = 1.4 Hz, 1H), 4.96 (qq, J = 7.0, 1.4 Hz, 1H), 4.01 (m, 1H), 3.93 (q, J = 6.2 Hz, 1H), 3.80 (m, 2H), 3.55 (m, 1H), 3.43 (m, 2H), 3.36 (m, 2H), 2.80 (br s, 1H), 2.35 (br s, 1H), 2.23 (t, J = 7.2 Hz, 2H), 2.20−1.18 (m and br s, 47H), 1.38 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ 148.9, 134.2, 83.2, 82.6, 81.6, 80.9, 77.4, 74.5, 73.7, 71.8, 37.4, 37.3, 34.2, 33.5, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 28.8, 28.2, 28.1, 27.3, 26.9, 25.8, 25.7, 25.6, 25.1, 22.7, 19.2, 14.1. MS: 623 (MH^+).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1a**, **4**, **5a**, **5b**, **6a**, **6b**, **7**, **8**, **9a**, **10**, **11**, **13**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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