Total Synthesis of the Annonaceous Acetogenin (+)-Asimicin. Development of a New Bidirectional Strategy

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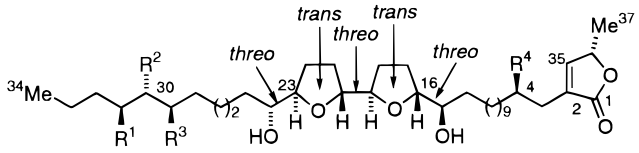
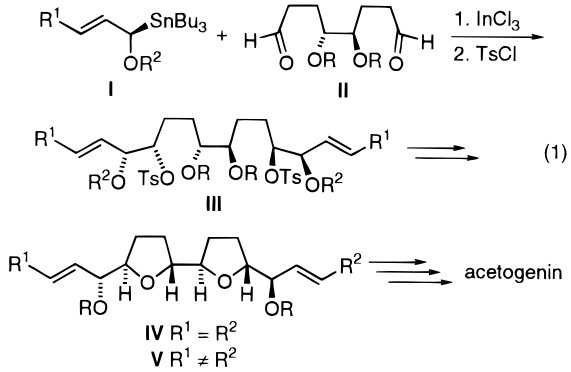
The total synthesis of the Annonaceous acetogenin (+)-asimicin is described. The approach employs the (*R*)-α-OSEM allylic stannane **7** of >95% ee and the dialdehyde **8** obtained from (*S,S*)-diethyl tartrate. Addition of **7** to **8** in the presence of $InCl_3$ afforded the bis-adduct **9** in 71% yield. Tosylation and treatment with TBAF led to the core bis-tetrahydrofuran intermediate, diol **11**, in 78% yield. Mono tosylation (*n*-BuLi, TsCl, THF−DMSO) and subsequent hydrogenolysis with $LiBEt_3H$ gave alcohol **14**. The iodide **15** was coupled with the higher-order vinylcyanocuprate to afford olefin **30**. This was converted to diol **31** of high ee by the Sharpless protocol. This diol yielded the epoxide **33** via the mono-trisylate **32**. Addition of (*R*)-lithio-2-(OTBS)-3-butyne in the presence of $BF_3{\cdot}OEt_2$ afforded the alcohol **34**. The SEM derivative **35** was treated with TBAF, and the resulting alcohol was converted to the butenolide **38** by a sequence involving treatment with $(CF_3CO)_2O$, then $Pd(PPh_3)_4$, CO, THF−H_2O, and finally $AgNO_3$/silica gel. Cleavage of the SEM protecting group with PPTS in ethanol afforded (+)-asimicin (**39**).

The past several years have witnessed an explosion of activity in the isolation and structure elucidation[1] and partial or total synthesis[2] of a growing family of acetogenins derived from the plant family Annonacea. The 30-some species examined thus far have yielded over 200 structurally related natural products, many of which show a range of impressive biological activities.[1] We have been interested in developing an efficient bidirectional approach to certain members possessing a C_2 symmetric *threo,trans,threo,trans,threo* bis-tetrahydrofuran central core (C15−C24), as illustrated by the asimicin subgroup.

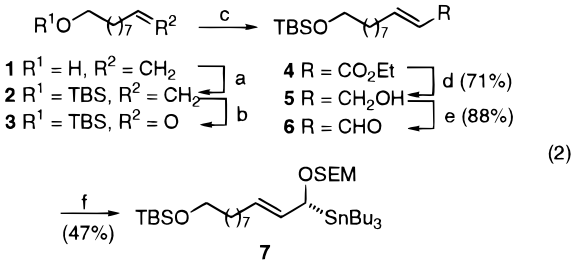


$R^1 = R^2 = R^3 = H,\ R^4 = OH$ Asimicin
$R^1 = R^2 = R^4 = H,\ R^3 = OH$ Asiminacin
$R^1 = R^3 = R^4 = H,\ R^2 = OH$ Asiminecin
$R^2 = R^3 = R^4 = H,\ R^1 = OH$ Asiminocin

The approach utilizes a nonracemic α-alkoxy allylic stannane (**I**) and a tartrate-derived dialdehyde (**II**) to construct the core bis-tetrahydrofuran unit *via* the bis-tosylate **III**. Subsequent desymmetrization (**IV** → **V**) and butenolide addition affords the targeted acetogenin (eq 1).[3] It should be noted that the R^1 chain must terminate in a functional group to enable attachment of the butenolide segment. This group could also be used to provide for the OH substituents on either the right- or left-hand chains, as required.



For our first application of this approach we chose asimicin as the target compound.[1c] For the R^1 group we selected $(CH_2)_8OTBS$, in part because of the ready availability of 9-decen-1-ol (**1**). The TBS ether **2** was subjected to ozonolysis and Horner−Emmons homologation to ester **4**, then reduction−oxidation to enal **6**, and application of our α-alkoxy allylic stannane methodology[4] to yield the SEM[5]-protected derivative **7** of >95% ee (eq 2).



a) TBSCl, DMF, Im b) O_3, EtOAc, -78°C; DMS c) NaH, $(EtO)_2POCH_2CO_2Et$, THF d) DIBAL-H, THF-toluene (71% for four steps) e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (88%) f) $LiSnBu_3$, THF; 1,1'-(azodicarbonyl)dipiperidine (ADD); *(S)*-BINAL-H; $TMSCH_2CH_2OCH_2Cl$, *i*-Pr_2NEt, THF

Addition of stannane **7** to dialdehyde **8**,[3] in the presence of $InCl_3$, yielded the bis-adduct **9**. The sterochem-

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

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(2) (a) Figadere, B. *Acc. Chem. Res.* **1995**, *28*, 359. (b) Koert, U. *Synthesis* **1995**, 115. (c) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801 and references therein.

(3) Model studies leading to IV (R = MOM, $R^1 = R^2$ = Me) and the other C_2 symmetric diastereomers of IV have been reported. Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247.

(4) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

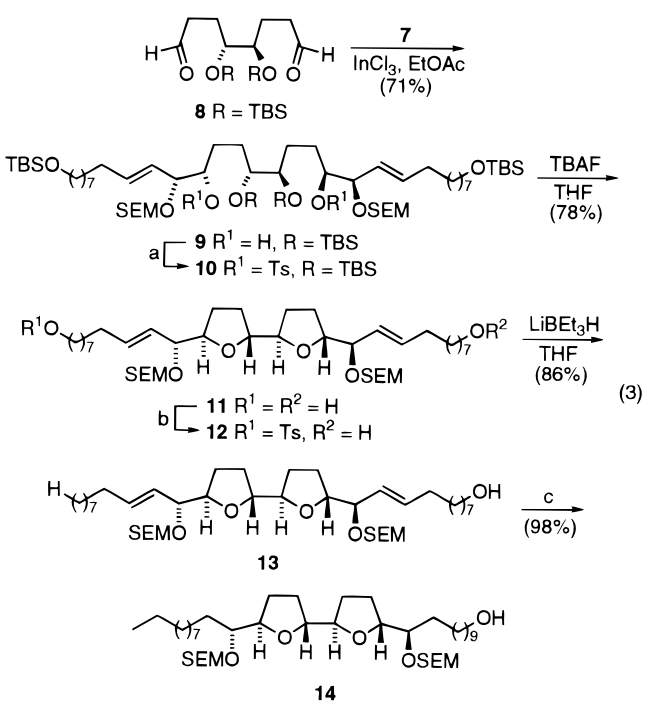
(5) SEM = $CH_2OCH_2CH_2TMS$. Lipshutz, B.; Miller, T. A. *Tetrahedron Lett.* **1989**, *30*, 7149.

S0022-3263(97)00423-4 CCC: $14.00

istry of this adduct follows from our previous model studies[3] and from its ultimate conversion to asimicin. Formation of the bis-tosylate **10** and then treatment with TBAF in THF at 40 °C led smoothly to the bis-tetrahydrofuran diol **11**.

We now faced the task of desymmetrization. This could be achieved by the method of McDougal[6] (TBSCl, NaH, THF; 83% yield, based on 40% recovered diol) or, more directly for our needs, by treatment of diol **11** with a slight excess of BuLi in THF−DMSO followed by addition of *p*-TsCl. In both instances, appreciable diol was recovered but only 5% or so of the bis-derivatized product was formed. As our main goal in the present study was to establish the overall feasibility of the approach, we did not attempt to optimize this step. The observed selectivity may stem from preferred internal hydrogen bonding of one of the terminal OH groups with the core system oxygens. In fact, molecular mechanics calculations[7] indicate that an appreciable number of the low-energy conformers exhibit such an arrangement, as illustrated in Figure 1.

The monotosylate **12** was reduced with Super-Hydride to afford alcohol **13**. The ^{1}H NMR spectrum of this intermediate showed only a single set of vinylic protons. Thus, perhaps not surprisingly, the terminal OH group does not disrupt the C_2 symmetry of the core unit, as perceived by the NMR probe. Hydrogenation of dienol **13** over Rh/Al_2O_3 afforded the tetrahydro product **14** (eq 3).[8]



(3)

a) *p*-TsCl, C_5H_5N (92%) b) *n*-BuLi, THF; *p*-TsCl (86%) c) H_2/Rh-Al_2O_3, EtOAc

We next turned our attention to introduction of the butenolide terminus and the associated C4 (*R*) hydroxyl substituent.

Our first attempt employed the aldehyde **17**, prepared from alcohol **14** by conversion to the iodide **15** and then displacement with NaCN in DMSO and reduction with DIBAL-H (eq 4). Our plan for the final phase of the synthesis was to add a chiral allenylstannane to aldehyde **17** to introduce the C4 alcohol and an appropriate

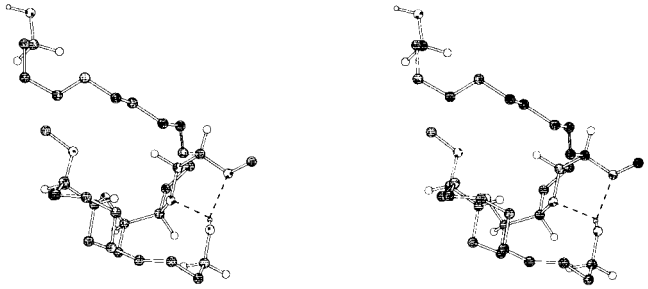
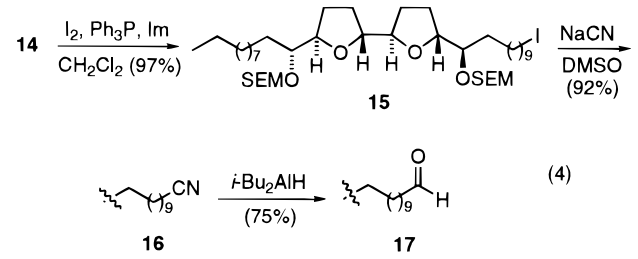
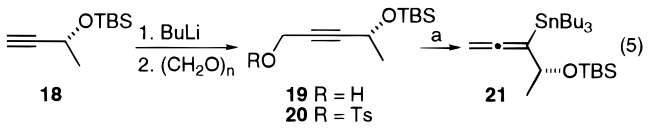


Figure 1. Stereoview of the lowest energy conformer of the methyl ether analogue of diol **16.4** showing H bonding of one terminal OH.



(4)

butenolide precursor.[9] The requisite stannane **21** was synthesized from the (*R*)-propargylic TBS ether **18**[10] by addition of formaldehyde and S_N2' displacement of the derived tosylate **20** with a Bu_3Sn cuprate reagent (eq 5).[11]



(5)

a) Bu_3SnLi, $CuBr{\bullet}SMe_2$

Although stannane **21** is nonracemic we would not expect the chirality at the carbinyl center to markedly affect the facial preference for attack at aldehyde **17**. We hoped to control this aspect of the addition through chiral catalysis.[12] In fact, model studies indicated that BINOL−Ti(O-*i*-Pr)$_4$-catalyzed reaction[12] of the racemic stannane **21** with heptanal afforded the (*R*)-alcohol adduct **22** of 95% ee, albeit in low yield, after prolonged reaction times (eq 6).

Unfortunately the analogous addition of the (*R*)-OTBS allenyl stannane **21** to aldehyde **17** could not be achieved. Only starting aldehyde was recovered after reaction times of up to 1 week with 0.5 equiv of the catalyst. This failure may be attributed to the oxygen substituents in

(6) McDougal, P. M.; Rico, J. G.; Oh, Y. I.; Condon, D. B. *J. Org. Chem.* **1986**, *51*, 3388.

(7) The program Macromodel V4.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through a 2000-step iteration. The ten lowest energy conformers, covering an energy range of 22 kJ, were examined. Of these, conformers 1 (86.4 kJ), 2 (90.3 kJ), 4(97.1 kJ), 7 (102.5 kJ), and 10 (108.4 kJ) showed hydrogen bonding between the core THF unit and one of the terminal OH groups. Conformer 5 (99.2 kJ) showed no H bonding, and conformers 8 (103.5 kJ) and 9 (103.9 kJ) showed H bonding between the two terminal OH groups.

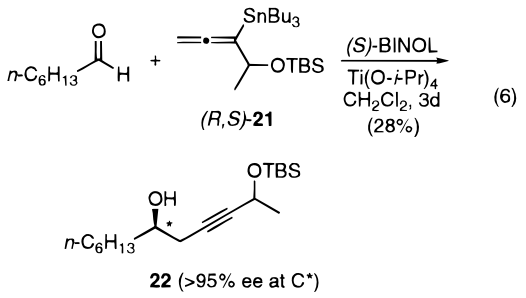
(8) Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883.

(9) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.

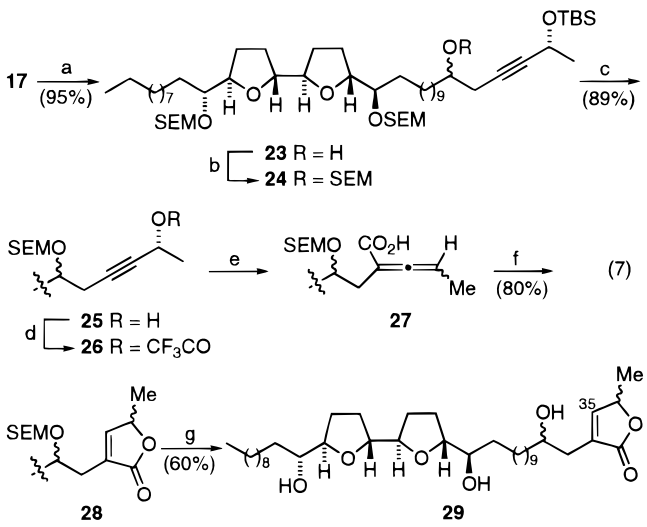
(10) Prepared from the TBS ether of (*R*)-lactaldehyde. Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230.

(11) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 3211.

(12) Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett.* **1994**, *35*, 8323. For a review, see: Marshall, J. A. *Chemtracts: Organic Chemistry* **1996**, 280.



aldehyde **17** as the reaction also failed with 5-OSEM pentanal. The use of *i*-PrSSiMe$_3$ as a catalyst promoter was also unsuccessful.[13] Despite this lack of success, it was of interest to prepare the adduct of stannane **21** and aldehyde **17**, as a mixture of C4 epimers, in order to establish the feasibility of the butenolide construction. Accordingly, the addition was performed with BF_3·OEt_2 as the Lewis acid promoter[14] affording adduct **23** as a 1.2:1 mixture of diastereomers, favoring the (4*R*) adduct, according to ^{1}H NMR analysis of the *O*-methylmandelates.[15] The alcohol **23** was converted to the SEM ether **24**, and the TBS ether was cleaved with TBAF to afford alcohol **25** (eq 7).



a) *(R)*-**21**, BF_3•OEt_2, CH_2Cl_2 b) SEMCl, *i*-Pr_2NEt (99%) c) TBAF, THF
d) $(CF_3CO)_2O$, THF, 2,6-lutidine e) $Pd(PPh_3)_4$, CO, H_2O-THF
f) $AgNO_3$/silica gel g) PPTS, EtOH

Conversion of alcohol **25** to butenolide **28** was effected without isolation of intermediates by the following sequence.[16] First, the alcohol was treated with $(CF_3CO)_2O$ in THF−lutidine under an atmosphere of CO. Then, upon complete consumption of alcohol (TLC), 10 mol % of $Pd(PPh_3)_4$ and 20 equiv of H_2O were added. The allenic acid **27**, thus produced, was separated from solid byproducts, the solvent was replaced with hexanes, and 10% $AgNO_3$-on-silica gel was added to effect cyclization to the butenolide **28**.[9,17] The SEM ethers were cleaved by treatment with PPTS in ethanol at 50 °C.[18] Cleavage of the C4 ether was markedly slower than the two ethers adjacent to the bis-THF core unit.

Conversion of triol **29** to the tris-*O*-methyl mandelate was effected with DCC and *O*-methylmandelic acid.[15] This product showed four well-separated signals of nearly equal intensity for the C35 vinylic H in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum of triol **29** also showed a pair of nearly equal signals at 151.8/151.7 (C35) and 70.0/69.9 ppm (C4). The remaining signals in both spectra were sharp and well resolved. Evidently the sequence leading from alcohol **25** to butenolide **29** had caused epimerization of the butenolide carbinyl center.

The most likely origin of carbinyl epimerization was thought to be the carbonylation step leading to allenic acid **27**. We have previously shown that this type of conversion is best carried out with 1 mol % of the Pd(0) catalyst. Partial racemization was observed with as little as 5 mol %.[9] As these experiments were conducted on only 10 mg of alcohol **25** (MW 986), such small quantities could not be reliably introduced. Nonetheless, the foregoing sequence demonstrates the feasibility of effecting the final butenolide transformation, subject to control of catalyst stoichiometry. A more successful solution to the problem of stereocontrol at C4 was developed as outlined in eq 8 (Scheme 1), starting from iodide **15**.

Coupling with the higher order vinyl cyanocuprate[19] afforded the olefin **30**, and subsequent Sharpless asymmetric dihydroxylation yielded diol **31** of high ee.[20] When diol **31** was subjected to the Sharpless protocol for epoxide formation ($MeC(OMe)_3$, PPTS; MeCOBr; K_2CO_3, MeOH)[21] a complex mixture was produced consisting mainly of alcohol products derived from partial cleavage of the SEM ethers. Accordingly, a stepwise and milder approach to epoxide **33** was employed.

Treatment of diol **31** with 0.8 equiv of 2,4,6-triisopropylbenzenesulfonyl chloride in pyridine afforded the monotrisylate **32** along with recovered diol, which could be recycled. The monotrisylate **32** yielded the terminal epoxide **33** upon base treatment.[22] Subsequent addition of lithio-(*R*)-2-OTBS-3-butyne[10] in the presence of BF_3·OEt_2 led to alcohol **34** which was protected as the SEM ether **35**.[5] Cleavage of the TBS ether afforded alcohol **36**. This alcohol was subjected to the aforementioned sequential protocol, without isolation of intermediates, to effect its conversion to butenolide **38**. The SEM groups were removed through exposure to PPTS in EtOH at 50 °C. The ^{1}H and ^{13}C NMR spectra and optical rotation of the resulting triol were identical to those reported for (+)-asimicin **39**.[1c] Significantly, the ^{13}C NMR spectrum contained single peaks at 151.8 and 70.0 ppm.

The general strategy described herein should be applicable to a variety of Annonaceous acetogenins and various analogues. The present synthesis could benefit from introduction of a preassembled butenolide moiety. This could be achieved through initial utilization of a shorter chain stannane or by a convergent, but nonbidirectional, approach. These strategies will be examined

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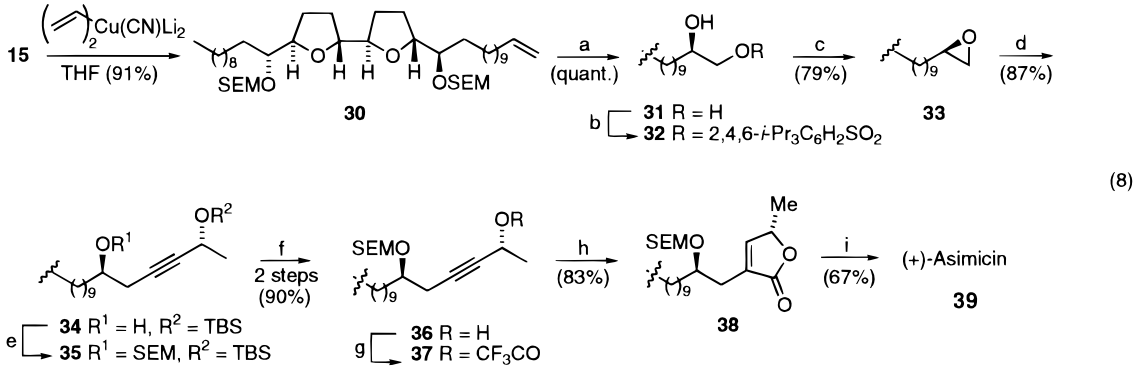
(14) Marshall, J. A.; Wolf, M. A.; Perkins, J. *J. Org. Chem.* **1995**, *60*, 5556.
(15) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.
(16) This procedure was developed by Clark A. Sehon in our laboratory. An earlier version can be found in ref 9.
(17) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.
(18) This procedure was first employed by Kevin Gill of our laboratory.
(19) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.
(20) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(21) Kolb, H. C.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *48*, 10515.
(22) *Cf.* Knapp, S.; Lal, G. S.; Sahai, D. *J. Org. Chem.* **1986**, *51*, 380.

Scheme 1



a) $(DHQD)_2AQN$, $K_3Fe(CN)_6$, *t*-BuOH b) 2,4,6-*i*-$Pr_3C_6H_2SO_2Cl$, C_5H_5N (77%) c) NaH, THF d) *(R)*-LiC≡CCH(OTBS)CH_3, BF_3•OEt_2, THF e) SEMCl, *i*-Pr_2NEt, CH_2Cl_2 f) TBAF, THF g) $(CF_3CO)_2O$, 2,6-lutidine h) 1% $Pd(PPh_3)_4$, CO, THF, H_2O; $AgNO_3$/silica gel i) PPTS, EtOH

in connection with ongoing efforts directed toward the most biologically active members of this family and their relatives.[23]

Experimental Section

1-[(*tert*-Butyldimethylsilyl)oxy]-9-decen-1-ol (2). To a solution of 19.9 g (128 mmol) of 9-decen-1-ol **1** in 140 mL of THF−DMF (1:1) at rt were added 21.8 g (305 mmol) of imidazole and 22.9 g (153 mmol) of *tert*-butyldimethlysilyl chloride (TBSCl). The progress of the reaction was monitored by TLC. After 12 h the mixture was cooled to 0 °C, quenched with H_2O, and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product, silyl ether **2** (∼35 g), was carried on without further purification: ^{1}H NMR δ 5.82 (ddt, J = 10.0, 7.4, 6.9 Hz, 1H), 4.96 (dd, J = 17.3, 10.0 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 2.04 (q, J = 7.4 Hz, 2H), 1.56−1.46 (m, 2H), 1.41−1.25 (m, 8H), 0.90 (s, 9H), 0.04 (s, 6H).

9-[(*tert*-Butyldimethylsilyl)oxy]nonanal (3). A solution of 34.4 g (128 mmol) of silyl ether **2** in 30 mL of CH_2Cl_2 was cooled to −78 °C, and O_3 was bubbled through the solution. The reaction was judged to be complete upon the appearance of a faint blue color (approximately 3 h). After the solution was purged with N_2 and the faint blue color had disappeared, Me_2S was added at −78 °C. The reaction mixture was allowed to warm to rt and stir until the ozonide was completely consumed. The solvent was removed under reduced pressure, and the crude product, aldehyde **3** (∼35 g), was carried on without further purification: ^{1}H NMR δ 9.76 (t, J = 1.9 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 2.41 (td, J = 7.3, 1.9 Hz, 2H), 1.70−1.46 (m, 2H), 1.40−1.27 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H).

(*E*)-Ethyl-11-[(*tert*-Butyldimethylsilyl)oxy]-2-undecenoate (4). To solution of 47.2 g (191 mmol) of triethyl sodiophosphonoacetate in 200 mL of THF at 0 °C was added 34.6 g (128 mmol) of aldehyde **3** as a solution in THF (50 mL) over a period of 1 h. The progress of the reaction was monitored by TLC. After 1 h the mixture was cooled to 0 °C, quenched with H_2O, and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was filtered and removed under reduced pressure, and the crude product, ester **4** (∼44 g), was carried on without further purification: ^{1}H NMR δ 6.96 (dt, J = 15.8, 7.3 Hz, 1H), 5.80 (dt, J = 15.8, 1.5 Hz, 1H), 4.26−4.09 (m, 4H), 3.59 (t, J = 6.5 Hz, 2H), 2.19 (q, J = 7.3 Hz, 2H), 1.55−1.41 (m, 2H), 1.37−1.22 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H).

(*E*)-11-[(*tert*-Butyldimethylsilyl)oxy]-2-undecene-1,11-diol (5). To solution of 43.2 g (128 mmol) of ester **4** in 350 mL of THF at −78 °C was added 318 mL (318 mmol) of 1 M DIBAL-H in hexanes over a period of 2 h. The progress of the reaction was monitored by TLC. After 4 h the reaction was quenched with 100 mL of Rochelle's salt (dropwise over a period of 3 h) and stirred until the solution became clear (approximately 4 h). The reaction mixture was extracted with Et_2O and washed with brine. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 27.0 g (71% for four steps) of alcohol **5**: ^{1}H NMR δ 5.75−5.68 (m, 2H), 4.08 (d, J = 4.6 Hz, 1H), 3.59 (t, J = 6.5 Hz, 2H), 2.04 (q, J = 6.9 Hz, 2H), 1.55−1.44 (m, 2H), 1.41−1.23 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H).

(*E*)-11-[(*tert*-Butyldimethylsilyl)oxy]-2-undecenal (6). To solution of 2.41 mL (27.6 mmol) of $(COCl)_2$ in 100 mL of CH_2Cl_2 at −78 °C was added DMSO as a solution in CH_2Cl_2 (25 mL). After 10 min, 5.44 g (18.4 mmol) of alcohol **5** in 25 mL of CH_2Cl_2 was added and the mixture was allowed to stir for 1.5 h. Next 20.5 mL (148 mmol) of Et_3N was added and, after 5 min, the −78 °C bath was replaced with a 0 °C bath. After 2 h the reaction was quenched with H_2O, the organic phase was washed with brine, and the aqueous phase was extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 10% EtOAc−hexanes as eluant affording 4.74 g (88%) of aldehyde **6**: ^{1}H NMR δ 9.60 (dt, J = 8.1 Hz, 1H), 6.85 (dt, J = 15.8, 6.9 Hz, 1H), 5.80 (ddt, J = 15.8, 7.7, 1.5 Hz, 1H), 3.59 (t, J = 6.6 Hz, 2H), 2.33 (q, J = 6.9 Hz, 2H), 1.56−1.45 (m, 2H), 1.37−1.27 (m, 10H), 0.89 (s, 9H), 0.04 (s, 6H).

(*E,R*)-11-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2-(trimethylsilyl)ethoxy)methoxy]-1-(tri-*n*-butylstannyl)-2-undecene (7). An oven-dried flask was charged with 300 mL of THF followed by 5.0 mL (38.2 mmol) of diisopropylamine. The solution was cooled to 0 °C, and 15.3 mL (38.2 mmol) of 2.5 M butyllithium in hexanes was added. After 15 min, 10.3 mL (38.2 mmol) of tributyltin hydride was added and the mixture was stirred for 20 min. The solution was then cooled to −78 °C, and 8.65 g (29.4 mmol) of aldehyde **6** was added over a period of 10 min. After an additional 10 min, 11.1 g (44.1 mmol) of 1,1′-(azodicarbonyl)dipiperidine (ADD) was added. The resulting dark red reaction mixture was warmed to 0 °C and kept there for 1 h. The reaction was then quenched with 100 mL of dilute aqueous ammonium chloride solution (saturated aqueous NH_4Cl−H_2O 1:4) and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The concentrated reaction mixture was then diluted with 400 mL of hexanes causing a precipitate to form. Next the solution was cooled to 0 °C and quickly filtered through a pad of Celite with the aid of cold hexanes. The solvent was again removed under reduced pressure affording the crude acyl stannane. This oil was dissolved in 50 mL of THF and immediately subjected to reduction with BINAL-H (described below).

An oven-dried flask was charged with a suspension of 3.35 g (88.2 mmol) of $LiAlH_4$ powder in 250 mL of THF. The

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resulting slurry was cooled to 0 °C, and 4.06 g (88.2 mmol) of EtOH (freshly distilled) was added dropwise over a period of 15 min. After 20 min, 25.3 g (88.2 mmol) of (*S*)-1,1′-bi-2-naphthol in THF (80 mL) was added over 30 min by means of a cannula. The resulting cloudy, milky solution was refluxed for 2 h. The solution was then cooled to −78 °C, and the acylstannane in THF (described above) was added over 45 min by means of a cannula. The reaction mixture was stirred until the reduction was judged to be complete by TLC (approximately 2 h). The reaction was quenched by the careful addition of dilute aqueous ammonium chloride solution (saturated aqueous NH_4Cl-H_2O 1:4) and extracted with Et_2O. The layers were separated, and the aqueous layer was acidified by the addition of 200 mL of 1.0 M HCl and extracted with Et_2O. The organic layers were combined, dried over magnesium sulfate, and filtered, and the solvent was removed under reduced pressure. Hexane (400 mL) was then added causing the formation of a precipitate that was allowed to settle. The solid yellow residue (recovered BINOL) was triturated and filtered with hexanes. Solvent was removed from the filtrate under reduced pressure, and the yellow oil was again triturated with 200 mL of hexane and filtered (occasionally a third trituration and filtration are required). Solvent was again removed under reduced pressure to afford crude hydroxystannane as a yellow oil. The crude hydroxystannane was dissolved in 50 mL of CH_2Cl_2 and cooled to 0 °C. To the solution was added 19.2 mL (117 mmol) of diisopropylethylamine followed by 7.32 g (44.1 mmol) of (2-(trimethylsilyl)ethoxy)-methyl chloride (SEMCl). After 12 h the reaction was quenched with 100 mL of a saturated aqueous NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 1% EtOAc−hexanes as eluant affording 9.97 g (47%) of stannane **7**: $[\alpha]_D$ 42.0 (*c* 1.9, $CHCl_3$); ^1H NMR δ 5.54 (dt, J = 15.4, 7.3 Hz, 1H), 5.38 (dd, J = 15.4, 6.5 Hz, 2H), 4.68, 4.58 (ABq, J = 6.5 Hz, 2H), 4.58 (d, J = 7.4 Hz, 1H), 3.67, 3.50 (ABdt, J = 10.0, 7.7 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 2.00 (q, J = 6.6 Hz, 2H), 1.56−1.44 (m, 2H), 1.38−1.21 (m, 10H), 0.93−0.86 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H), 0.02 (s, 9H); ^{13}C NMR δ −5.3, −4.1, 9.1, 13.7, 18.1, 25.8, 26.0, 27.4, 29.1, 29.2, 29.4, 29.6, 23.9, 63.3, 65.0, 72.3, 93.3, 125.4, 131.3.

(9*E*,21*E*,11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-1,11,20,30-Tetrakis-[*tert*-butyldimethylsilyl)oxy]-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]-9,21-triacontadiene-12,19-diol (9). A solution of 1.23 g (5.6 mmol) of $InCl_3$ in 135 mL of EtOAc was placed in a sonication bath at rt for 15 min to dissolve the $InCl_3$. The solution was removed from the bath, and 1.13 g (2.80 mmol) of aldehyde **8** was added with stirring. The solution was cooled to −78 °C followed by addition of 5.96 g (8.30 mmol) of stannane (*R*)-**7**. The reaction mixture was allowed to slowly warm to rt as its progress was monitored by TLC. When the aldehyde was no longer present the reaction was quenched with cold 1 M HCl and extracted with Et_2O. The organic extracts were dried over $MgSO_4$, and Et_3N (approximately 2 equiv) was added to remove tin byproducts. The solvent was distilled under reduced pressure and the product purified by column chromatography on silica gel with 10% EtOAc−hexanes as eluant to afford 2.53 g (71%) of adduct **9**: $[\alpha]_D$ −27.6 (*c* 1.5, $CHCl_3$); IR (film) 3501 cm^{-1}; ^1H NMR δ 5.71 (dq, J = 15.4, 6.9 Hz, 2H), 5.40 (dd, J = 15.4, 8.1 Hz, 2H), 4.72, 4.65 (ABq, J = 6.9 Hz, 4H), 3.94 (dd, J = 8.1, 3.1 Hz, 2H), 3.77−3.47 (m, 12H), 2.20 (bs, 2H), 1.93−1.81 (m, 2H), 1.68−1.17 (m, 30H), 0.92−0.89 (m, 4H), 0.89 (s, 18H), 0.87 (s, 18H), 0.03 (s, 12H), 0.03−0.02 (m, 18H), 0.02 (s, 12H); ^{13}C NMR δ −5.2, −4.6, −4.0, −1.4, 18.0, 18.1, 25.8, 25.9, 26.0, 26.8, 29.1, 29.3, 29.4, 29.5, 29.9, 32.5, 32.9, 63.3, 65.3, 74.3, 75.9, 80.6, 92.1, 125.0, 137.1. Anal. Calcd for $C_{66}H_{142}O_{10}Si_6$: C, 62.70; H, 11.32. Found: C, 62.75; H, 11.29.

(9*E*,21*E*,11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-1,11,20,30-Tetrakis-[(*tert*-butyldimethylsilyl)oxy]-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]-9,21-triacontadiene-12,19-diol Bis-*p*-toluenesulfonate (10). To a solution of 2.65 g (2.10 mmol) of diol **9** in 8 mL of pyridine was added 2.40 g (12.6 mmol) of *p*-toluenesulfonyl chloride. The progress of the reaction was monitored by TLC. After 12 h, when the diol was no longer present, the reaction was quenched at rt with H_2O and saturated aqueous $CuSO_4$ and then extracted with Et_2O. The extracts were dried over $MgSO_4$, the solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel. Elution with 10% EtOAc−hexanes afforded 3.04 g (92%) of tosylate **10**: IR (film) 1605 cm^{-1}; ^1H NMR δ 7.78 (d, J = 8.1 Hz, 4H), 7.30 (d, J = 8.1 Hz, 4H), 5.71 (dq, J = 15.4, 6.2 Hz, 2H), 5.40 (dd, J = 15.4, 7.7 Hz, 2H), 4.60, 4.51 (ABq, J = 6.9 Hz, 4H), 4.49−4.44 (m, 2H), 4.23 (dd, J = 8.1, 2.4 Hz, 2H), 3.72−3.41 (m, 4H), 3.60 (t, J = 6.5 Hz, 4H), 3.33 (bd, J = 9.3 Hz, 4H), 2.42 (s, 6H), 2.01 (dt, J = 6.9, 5.8 Hz, 4H), 1.80−1.66 (m, 2H), 1.58−1.20 (m, 30H), 0.91−0.88 (m, 4H), 0.89 (s, 18H), 0.84 (s, 18H), 0.04 (s, 12H), 0.02 (s, 18H), −0.02 (s, 12H); ^{13}C NMR δ −5.3, −4.7, −4.1, −1.4, 17.9, 18.3, 21.6, 25.8, 26.0, 26.4, 27.0, 29.0, 29.3, 29.4, 29.5, 32.4, 32.9, 63.3, 65.1, 75.3, 77.9, 86.0, 92.1, 124.9, 127.9, 129.5, 134.8, 137.1, 143.0.

(9*E*,21*E*,11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-12,15:16,19-Diepoxy-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]-9,21-triacontadiene-1,30-diol (11). To solution of 3.01 g (1.90 mmol) of bis-TBS ether **10** in 19 mL of THF at 40 °C was added 19.3 mL (19.3 mmol) of 1 M TBAF in THF. The progress of the reaction was monitored by TLC. During 6 h, a more polar spot appeared which was gradually replaced with a less polar one. The mixture was cooled to rt, quenched with H_2O, and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 60% EtOAc−hexanes as eluant affording 1.17 g (78%) of bis-tetrahydrofuran diol **11**: $[\alpha]_D$ −59.4 (*c* 1.4, $CHCl_3$); IR (film) 3441, 1666 cm^{-1}; ^1H NMR δ 5.68 (dq, J = 15.4, 7.0 Hz, 2H), 5.33 (dd, J = 15.4, 7.7 Hz, 2H), 4.71, 4.67 (ABq, J = 6.9 Hz, 4H), 4.07−3.92 (m, 6H), 3.74, 3.52 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.63 (t, J = 7.0 Hz, 4H), 2.20 (bs, 2H), 2.03 (dt, J = 7.0, 6.5 Hz, 4H), 1.97−1.65 (m, 8H), 1.61−1.13 (m, 24H), 0.92 (ABq (appt t), J = 8.8 Hz, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.5, 18.0, 25.6, 27.8, 27.9, 28.9, 29.0, 29.3, 32.3, 62.8, 64.8, 76.6, 78.5, 81.2, 81.5, 91.8, 126.6, 135.6. Anal. Calcd for $C_{42}H_{82}O_8Si_2$: C, 65.41; H, 10.72. Found: C, 65.12; H, 10.58.

(9*E*,21*E*,11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-12,15:16,19-Diepoxy-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]-9,21-triacontadiene-1,30-diol Mono-*p*-toluenesulfonate (12). To a solution of 304 mg (0.40 mmol) of diol **11** in 1.5 mL of THF at rt was added 0.20 mL (0.20 mmol) of 2.5 M butyllithium in hexanes. The solution was heated to 40 °C for 10 min, and 0.25 mL of DMSO was added. After an additional 30 min at 40 °C, the reaction mixture was allowed to cool to rt and 75 mg (0.40 mmol) of *p*-toluenesulfonyl chloride was added as a solution in THF (0.25 mL). After 1 h the reaction was quenched with H_2O and the solution extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 35% EtOAc−hexanes as eluant affording 185 mg (51%) of monotosylate **12** (86% based on 126 mg of recovered diol): $[\alpha]_D$ −38.8 (*c* 1.9, $CHCl_3$); IR (film) 3493, 1675, 1606 cm^{-1}; ^1H NMR δ 7.79 (d, J = 8.1 Hz, 4H), 7.34 (d, J = 8.1 Hz, 4H), 5.74−5.61 (m, 2H), 5.32 (dd, J = 15.4, 7.8 Hz, 2H), 4.73−4.65 (m, 4H), 4.07−3.92 (m, 8H), 3.74, 3.52 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.63 (t, J = 7.0 Hz, 4H), 2.45 (s, 3H), 2.10 (vbs, 1H), 2.07−1.98 (m, 2H), 1.95−1.45 (m, 18H), 1.40−1.17 (m, 16H), 0.92 (ABq (appt t), J = 8.8 Hz, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.4, 18.1, 21.6, 25.3, 25.7, 27.8, 27.9, 28.8, 28.9, 29.0, 29.1, 29.2, 29.3, 32.3, 32.8, 63.0, 64.8, 70.6, 78.6, 81.3, 81.5, 91.9, 126.6, 127.8, 129.8, 135.6, 135.6. Anal. Calcd for $C_{49}H_{88}O_{10}SSi_2$: C, 63.59; H, 9.58. Found: C, 63.34; H, 9.49.

(9*E*,21*E*,11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-12,15:16,19-Diepoxy-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]-9,21-triacontadien-1-ol (13). To solution of 180 mg (0.19 mmol) of monotosylate **12** in 0.3 mL of THF at 0 °C was added 1.94 mL (1.94 mmol) of 1 M Super-Hydride in THF. The progress of the reaction was monitored by TLC. After 12 h the reaction mixture was cooled to 0 °C, quenched with H_2O, and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The

solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 125 mg (86%) of alcohol **13**: $[\alpha]_D$ −50.9 (*c* 1.4, $CHCl_3$); IR (film) 3484, 1675 cm^{-1}; ^1H NMR δ 5.68 (dt, J = 15.4, 6.5 Hz, 2H), 5.32 (dd, J = 15.4, 7.7 Hz, 2H), 4.71, 4.67 (ABq, J = 6.6 Hz, 4H), 4.07−3.92 (m, 6H), 3.74, 3.52 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.63 (t, J = 7.0 Hz, 4H), 2.20 (vbs, 1H), 2.03 (dt, J = 6.9, 5.8 Hz, 4H), 1.95−1.63 (m, 12H), 1.60−1.17 (m, 23H), 0.96−0.84 (m, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.4, 14.1, 18.0, 22.6, 25.7, 27.9, 29.0, 29.0, 29.1, 29.2, 29.3, 29.4, 31.8, 32.3, 32.3, 32.8, 62.9, 64.8, 78.6, 81.3, 81.5, 91.9, 126.5, 126.6, 135.6, 135.7. Anal. Calcd for $C_{42}H_{82}O_7Si_2$: C, 66.79; H, 10.94. Found: C, 66.88; H, 10.85.

(11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-12,15:16,19-Diepoxy-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]triacontan-1-ol (14). To solution of 100 mg (0.13 mmol) of alcohol **13** in 0.3 mL of EtOAc at rt was added 272 mg of 5% $Rh-Al_2O_3$. The mixture was placed under a balloon filled with H_2. After 12 h, the mixture was filtered through a pad of Celite with EtOAc. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 98 mg (98%) of alcohol **14**: $[\alpha]_D$ 42.5 (*c* 1.4, $CHCl_3$); IR (film) 3475, cm^{-1}; ^1H NMR δ 4.85, 4.71 (ABq, J = 7.3 Hz, 4H), 4.04−3.95 (m, 2H), 3.95−3.87 (m, 2H), 3.75−3.53 (m, 6H), 3.52−3.45 (m, 2H), 2.20 (vbs, 1H), 1.99−1.74 (m, 8H), 1.70−1.20 (m, 39H), 0.98−0.85 (m, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.5, 14.1, 18.1, 22.7, 25.7, 28.2, 29.3, 29.4, 29.5, 29.6, 29.8, 31.2, 31.9, 32.8, 63.0, 65.2, 79.3, 81.2, 81.7, 94.8. Anal. Calcd for $C_{42}H_{86}O_7Si_2$: C, 66.44; H, 11.42. Found: C, 66.31; H, 11.43.

(11*R*,12*S*,15*R*,16*R*,19*S*,20*R*)-1-Iodo-12,15:16,18-diepoxy-11,20-bis[(2-(trimethylsilyl)ethoxy)methoxy]triacontane (15). To a solution of 215 mg (0.82 mmol) of triphenylphosphine in 4.0 mL of CH_2Cl_2 was added 112 mg (1.60 mmol) of imidazole with stirring. Next 208 mg (0.82 mmol) of iodine was added as a solution in 3.0 mL of benzene. After 15 min 415 mg of alcohol **14** was added as a solution in 2.0 mL of CH_2Cl_2. The progress of the reaction was monitored by TLC. After 1 h the reaction was quenched with Na_2SO_3 (approximately 2 equiv) as a solution in saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 10% EtOAc−hexanes as eluant affording 460 mg (97%) of iodide **15**: $[\alpha]_D$ 32.9 (*c* 1.5, $CHCl_3$); ^1H NMR δ 4.85, 4.71 (ABq, J = 6.9 Hz, 4H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.88 (m, 2H), 3.74, 3.52 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.52−3.45 (m, 2H), 3.19 (t, J = 7.3 Hz, 2H), 1.97−1.78 (m, 6H), 1.71−1.20 (m, 41H), 0.97−0.85 (m, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.5, 7.2, 14.1, 18.1, 22.7, 25.8, 28.2, 28.5, 29.3, 29.4, 29.5, 29.6, 29.9, 30.5, 31.2, 31.9, 33.6, 65.2, 79.3, 81.2, 81.7, 94.9.

(13*R*,14*S*,17*R*,18*R*,21*S*,22*R*)-14,17:18,21-Diepoxy-13,22-bis[(2-(trimethylsilyl)ethoxy)methoxy]-1-dotriacontene (30). An oven-dried flask was charged with 978 mg (11.0 mmol) of CuCN and then evacuated and flushed with argon three times. The CuCN was dissolved in THF, and the solution was cooled to −78 °C with stirring. To the resulting slurry was added 10.9 mL (21.9 mmol) of 2 M vinyllithium in THF, and the mixture was allowed to stir for 10 min. The mixture was warmed to 0 °C for 20 min and was subsequently recooled to −78 °C. Next, iodide **15** was added neat and the reaction mixture was slowly warmed to 0 °C and kept there for 12 h. The reaction was quenched by being poured into a solution of saturated aqueous NH_4Cl-NH_4OH (9:1) and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 365 mg (91%) of adduct **30**: $[\alpha]_D$ 38.7 (*c* 1.3, $CHCl_3$); ^1H NMR δ 5.88−5.74 (m, 1H), 4.96 (ddt, J = 22.7, 17.3, 3.5 Hz, 2H), 4.85, 4.71 (ABq, J = 6.9 Hz, 4H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.80 (m, 2H), 3.69, 3.59 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.52−3.45 (m, 2H), 2.08−1.99 (m, 2H), 1.97−1.73 (m, 6H), 1.70−1.18 (m, 41H), 0.97−0.84 (m, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.4, 14.1, 18.1, 22.7, 25.8, 28.2, 28.9, 29.1, 29.3, 29.4, 29.6, 29.9, 31.2, 31.9, 33.8, 65.2, 79.3, 81.2, 81.7, 94.8, 114.1, 139.2. Anal. Calcd for $C_{44}H_{88}O_6Si_2$: C, 68.69; H, 11.53. Found: C, 68.78; H, 11.50.

(2*R*,13*R*,14*S*,17*R*,18*R*,21*S*,22*R*)-14,17:18,21-Diepoxy-13,22-bis[(2-(trimethylsilyl)ethoxy)methoxy]dotriacontane-1,2-diol (31). To solution of 7 mg (8.0 μmol) of $(DHQD)_2AQN$, 724 mg (2.4 mmol) of $K_2Fe_3(CN)_6$, 331 mg (2.4 mmol) of K_2CO_3, and 1 mg (3.0 μmol) of $K_2OsO_2(OH)_4$ in 1.0 mL of *tert*-BuOH−H_2O at 0 °C was added 35 mg (46 μmol) of olefin **30**. The progress of the reaction was monitored by TLC. After 12 h, when the reaction was judged to be complete, it was quenched with Na_2SO_3 (approximately 1.5 equiv) and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 50% EtOAc−hexanes as eluant affording 36 mg (100%) of diol **31**: $[\alpha]_D$ 38.3 (*c* 1.4, $CHCl_3$); IR (film) 3439 cm^{-1}; ^1H NMR δ 4.85, 4.71 (ABq, J = 7.0 Hz, 4H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.80 (m, 2H), 3.75−3.53 (m, 5H), 3.51−3.39 (m, 4H), 2.10 (vbs, 2H), 1.97−1.58 (m, 6H), 1.49−1.19 (m, 41H), 0.97−0.84 (m, 4H), 0.01 (s, 18H); ^{13}C NMR δ −1.4, 14.1, 18.1, 22.6, 25.5, 28.2, 29.3, 29.5, 29.6, 29.8, 29.9, 31.1, 31.9, 33.2, 65.2, 66.8, 72.2, 79.3, 81.2, 81.7, 94.8. Anal. Calcd for $C_{44}H_{90}O_8Si_2$: C, 65.78; H, 11.29. Found: C, 65.88; H, 11.31.

(2*R*,13*R*,14*S*,17*R*,18*R*,21*S*,22*R*)-14,17:18,21-Diepoxy-13,22-bis[(2-(trimethylsilyl)ethoxy)methoxy]dotriacontane-1,2-diol 1-(2,4,6-Triisopropylbenzenesulfonate) (32). To a solution of 40 mg (0.05 mmol) of diol **31** in 0.1 mL of pyridine at rt was added 13 mg (0.04 mmol) of 2,4,6-triisopropylbenzenesulfonyl chloride. After 10 h the mixture was cooled to 0 °C, quenched with H_2O and saturated aqueous $CuSO_4$, and then extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 10 mg (19%) of alcohol **32** (77% based on 30 mg of recovered diol): IR (film) 3447 cm^{-1}; ^1H NMR δ 7.19 (s, 2H), 4.85, 4.77 (ABq, J = 7.0 Hz, 4H), 4.18−3.86 (m, 7H), 3.69, 3.59 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.52−3.44 (m, 2H), 2.96−2.86 (m, 3H), 2.20 (vbs, 1H), 1.95−1.59 (m, 6H), 1.50−1.18 (m, 41H), 0.97−0.84 (m, 4H), 0.01 (s, 18H).

This diol could be recycled by the foregoing procedure with comparable results.

(2*R*,13*R*,14*S*,17*R*,18*R*,21*S*,22*R*)-1,2:14,17:18,21-Triepoxy-13,22-bis[(2-(trimethylsilyl)ethoxy)methoxy]dotriacontane (33). To solution of 45 mg (0.04 mmol) of sulfonate **32** in 0.1 mL of THF at rt was added 10 mg (0.42 mmol) of NaH. The progress of the reaction was monitored by TLC. After 2 h the mixture was cooled to 0 °C, quenched with H_2O, and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 26 mg (79%) of epoxide **33**: ^1H NMR δ 4.85, 4.71 (ABq, J = 6.9 Hz, 4H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.80 (m, 2H), 3.69, 3.59 (ABdt, J = 10.0, 7.7 Hz, 4H), 3.52−3.45 (m, 2H), 2.94−2.87 (m, 1H), 2.74 (t, J = 4.6 Hz, 1H), 2.46 (dd, J = 5.0, 2.7 Hz, 1H), 1.98−1.74 (m, 6H), 1.70−1.18 (m, 43H), 0.97−0.84 (m, 4H), 0.01 (s, 18H).

(2*R*,6*R*,17*R*,18*S*,21*R*,22*R*,25*S*,26*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-18,21:22,25-diepoxy-17,26-bis[(2-(trimethylsilyl)ethoxy)methoxy]-3-hextriacontyn-6-ol (34). To solution of 51 mg (0.28 mmol) of alkyne **18** in 0.2 mL of THF at −78 °C was added 0.12 mL (0.28 mmol) of 2.5 M butyllithium in hexanes. After 10 min 34 μL (0.28 mmol) of $BF_3 \cdot Et_2O$ was added followed, after 10 min, by 13 mg (0.01 mmol) of epoxide **33** as a solution in THF (0.1 mL). The progress of the reaction was monitored by TLC. After 20 min the reaction was quenched with H_2O and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 14 mg (87%) of alcohol **34**: IR (film) 3472, 2366 cm^{-1}; ^1H NMR δ 4.85, 4.72 (ABq, J = 6.9 Hz, 4H), 4.52 (qt, J = 6.6, 1.9 Hz, 1H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.88 (m, 2H), 3.74−3.54 (m, 5H), 3.52−3.45 (m,

2H), 2.37 (ABqdd, J = 13.8, 4.6, 1.9 Hz, 2H), 1.99−1.75 (m, 6H), 1.71−1.17 (m, 44H), 0.97−0.84 (m, 4H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.01 (s, 18H).

(2*R*,6*R*,17*R*,18*S*,21*R*,22*R*,25*S*,26*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-18,21:22,25-diepoxy-6,17,26-tris[(2-(trimethylsilyl)ethoxy)methoxy]-3-hextriacontyne (35). To a solution of 21 mg (0.02 mmol) of alcohol **34** in 0.1 mL of CH_2Cl_2 at 0 °C was added 21 μL (0.13 mmol) of Hunig's base followed by 12 μL (0.06 mmol) of SEMCl. The progress of the reaction was monitored by TLC. The reaction mixture was warmed to rt, and after 12 h it was quenched with H_2O and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 10% EtOAc−hexanes as eluant affording 30 mg of silyl ether **35** (containing an inseparable impurity of identical R_f, from the SEMCl): IR (film) 2242 cm^{-1}; ^{1}H NMR δ 4.89−4.65 (m, 6H), 4.54−4.45 (m, 1H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.88 (m, 2H), 3.74−3.54 (m, 7H), 3.52−3.45 (m, 2H), 2.42 (ABqd, J = 13.8, 4.6 Hz, 2H), 1.98−1.74 (m, 6H), 1.37 (d, J = 6.2 Hz, 3H), 1.71−1.19 (m, 43H), 0.98−0.91 (m, 6H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.01 (s, 27H).

(2*R*,6*R*,17*R*,18*S*,21*R*,22*R*,25*S*,26*R*)-18,21:22,25-Diepoxy-6,17,26-tris[(2-(trimethylsilyl)ethoxy)methoxy]-3-hextriacontyn-2-ol (36). To solution of 23 mg (0.02 mmol) of silyl ether **35** in 0.1 mL of THF at 40 °C was added 31 μL (0.03 mmol) of 1 M TBAF in THF. The progress of the reaction was monitored by TLC. After 6 h the reaction was quenched with H_2O and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% EtOAc−hexanes as eluant affording 19 mg (90% for two steps) of propargylic alcohol **36**: IR (film) 3439 cm^{-1}; ^{1}H NMR δ 4.85, 4.72 (ABq, J = 6.9 Hz, 4H), 4.78, 4.69 (ABq, J = 7.7 Hz, 4H), 4.51 (qt, J = 6.1, 1.9 Hz, 2H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.88 (m, 2H), 3.74−3.54 (m, 7H), 3.52−3.45 (m, 2H), 2.44 (d, J = 5.0 Hz, 2H), 1.99−1.73 (m, 6H), 1.42 (d, J = 6.5 Hz, 3H), 1.71−1.21 (m, 44H), 0.97−0.84 (m, 6H), 0.01 (s, 27H).

4,15,24-Tris[(2-(trimethylsilyl)ethoxy)methoxy]asimicin (Annonaceous acetogenin numbering system) (38). To solution of 18 mg (18.0 μmol) of propargylic alcohol **36** in 326 μL of THF at rt was added 8 μL (72.0 μmol) of 2,6-lutidine followed by 5 μL (36.0 μmol) of trifluoroacetic anhydride under a carbon monoxide atmosphere (balloon). The progress of the reaction was monitored by TLC. After complete consumption of the starting alcohol (approximately 20 min) 0.5 mg (0.02 μmol) of $Pd(PPh_3)_4$ and 13 μL (730 μmol) of H_2O were added. After 1.7 h the reaction mixture was diluted with Et_2O, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the crude product was taken up in 200 μL of hexanes and 20 μL of CH_2Cl_2 under a nitrogen atmosphere. The flask was then protected from light, and 6 mg (36 μmol) of 10% $AgNO_3$ on silica gel was added to the solution. After 2 h the reaction was judged to be complete and the crude reaction mixture was filtered through a pad of Celite with the aid of Et_2O. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 2% acetone−CH_2Cl_2 as eluant affording 15 mg (83%) of SEM-protected asimicin **38**: IR (film) 1772 cm^{-1}; ^{1}H NMR δ 7.15 (s, 1H), 5.05−4.97 (m, 1H), 4.85, 4.72 (ABq, J = 6.9 Hz, 4H), 4.70−4.65 (m, 2H), 4.00 (dt, J = 7.7, 5.7 Hz, 2H), 3.94−3.88 (m, 2H), 3.85−3.79 (m, 1H), 3.74−3.54 (m, 7H), 3.52−3.45 (m, 2H), 2.49 (d, J = 5.0 Hz, 2H), 1.97−1.74 (m, 6H), 1.40 (dt, J = 6.9, 1.5 Hz, 3H), 1.71−1.21 (m, 44H), 0.97−0.84 (m, 6H), 0.01 (s, 27H).

(+)-Asimicin (39). To solution of 15 mg (15 μmol) of SEM-protected asimicin **38** in 0.3 mL of EtOH at 40 °C was added 1 mg (4.0 μmol) of PPTS. The progress of the reaction was monitored by TLC. After 16 h the reaction was quenched with H_2O and extracted with Et_2O. The organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product was purified by column chromatography on silica gel with 20% acetone−CH_2Cl_2 as eluant affording 6 mg (67%) of (+)-asimicin (**39**): $[\alpha]_D$ 15.0 (c 0.2, $CHCl_3$) reported[1c] $[\alpha]_D$ 14.7 (c 0.3 $CHCl_3$); IR (film) 3441, 1666 cm^{-1}; ^{1}H NMR δ 7.18 (bs, 1H), 5.06 (q, J = 7.7 Hz, 1H), 3.91−3.79 (m, 5H), 3.39 (q, J = 5.0 Hz, 1H), 2.54 (d, J = 15.0 Hz, 1H), 2.45−2.34 (m, 1H), 2.11 (vbs, 3H), 2.04−1.91 (m, 2H), 1.74−1.59 (m, 4H), 1.43 (q, J = 6.9 Hz, 1H), 1.53−1.19 (m, 41H), 0.88 (t, J = 6.9 Hz, 1H); ^{13}C NMR δ 14.1, 19.1, 22.7, 25.6, 28.4, 29.0, 29.3, 29.5, 29.6, 31.9, 33.3, 33.4, 37.4, 70.0, 74.1, 77.9, 81.8, 83.1, 151.7.

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Supporting Information Available: Experimental procedures for **16**, **17**, and **20**−**23** and ^{1}H NMR and ^{13}C NMR spectra for selected compounds (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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