Total Synthesis of (+)-Aspicilin. The Naked Carbon Skeleton Strategy vs the Bioorganic Approach

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The advantages of the "naked carbon skeleton" strategy in the total synthesis of polyoxygenated natural products are demonstrated in the total synthesis of the 18-membered macrolide (+)-aspicilin, **1**. This approach employs the easily prepared, nonfunctionalized carbon skeleton of the target molecule, hexadeca-1,3,15-triene, **2**. All the required stereogenic carbinol centers are then introduced onto this partially unsaturated hydrocarbon chain using the Sharpless asymmetric dihydroxylation (AD) reaction. Thus, asymmetric synthesis of **1** is achieved in 14 steps and 11% overall yield. Three stereogenic carbinol centers are introduced with very high regio- and enantioselectivity (epimeric excess of 96% at positions 3, 4, and 86% at position 15) by using AD-mix-β while the fourth is obtained using AD-mix-α. This approach is compared with an alternative synthesis of **1** (19 steps and 4.3% overall yield) using chiral building blocks derived from D-arabinose and from the enzymatic reduction of oct-7-yn-2-one, **34**, with *Thermoanaerobium brockii* alcohol-dehydrogenase (TBADH).

Introduction

A major challenge facing the contemporary synthesis of natural products involves the assembly of polyoxygenated carbon skeletons containing many asymmetric centers, as exhibited in macrolide antibiotics,[1] polyether antibiotics,[2] marine toxins,[3] and others. The commonly practiced bioorganic approach to the synthesis of such structures borrows the required asymmetric centers from naturally occurring compounds,[4] particularly from sugar molecules.[5] Recently developed methods for the enantioselective functionalization of simple olefins, such as the Sharpless asymmetric dihydroxylation (AD) reaction[6] and the Jacobsen asymmetric epoxidation reaction,[7] offer an alternative synthetic strategy. The easy preparation of the nonfunctionalized ("naked") carbon skeleton of the target molecule represents the first stage of this approach. All the required stereogenic carbinol centers are then introduced onto this partially unsaturated hydrocarbon chain. We have recently demonstrated the advantages of the "naked carbon skeleton" approach in the total synthesis of several natural products,[8] including various Annonaceous acetogenins.[9,10] Herein we compare both strategies by applying them to the total synthesis of the 18-membered lichen macrolide, (+)-aspicilin, **1**.[11−13]

Results and Discussion

The Naked Carbon Skeleton Approach. The introduction of the four chiral carbinol centers, with the correct absolute configuration, represents the crucial phase in any synthesis of aspicilin. We reasoned that hexahydroxylation of a simple, achiral hydrocarbon chain, such as the triene **2**, using the AD reaction might engender all four asymmetric centers with high enantiomeric purity. Retrosynthetic analysis indicates, however, that a single AD step cannot produce the 5*R*,6*S*,7*R*,18*S* configuration of **1**. Introduction of six oxygen functions into **2** with the appropriate absolute configuration requires a sequence of three regioselective AD reactions, using both AD-mix-β and AD-mix-α (Scheme 1). Thus, regio- and enantioselective dihydroxylation of

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Scheme 1

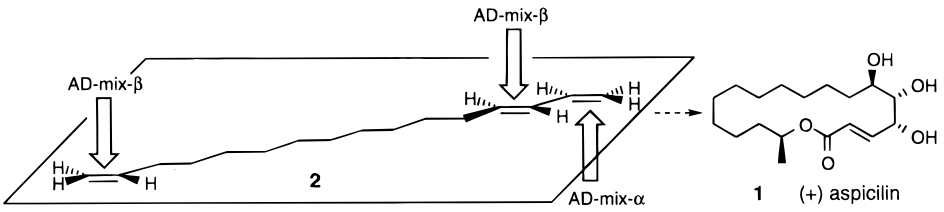
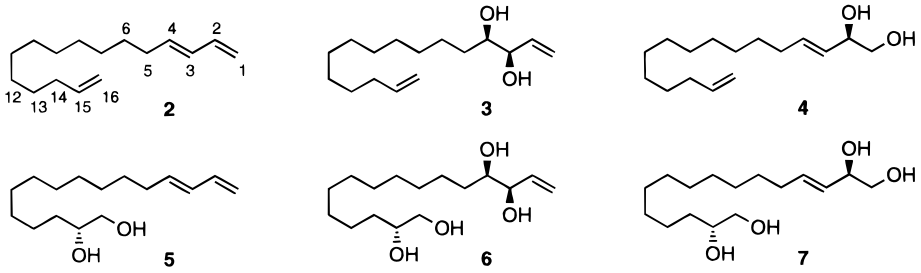


Table 1. Products Distribution in the AD Reaction of 2[a]



entry	AD-mix-β (equiv)[b]	**2** (%)	**3** (%)	**4** (%)	**5** (%)	**6** (%)[c]	**7** (%)	hexaols(%)
1[d]	1	64	26	3	5	2		
2	1[e]	3	52	3	6	36 (30)		
3	**2**		16	2	3	67 (63)	9	3
4	**2**[e,f]		<1			89 (80)	1	9
5	**3**		<2			83 (77)	6	9
6	**2**[e]					80		20

[a] All reactions were carried out with **2** (0.25 mmol) and AD-mix-β (containing either 0.2 or 0.5 mol % osmium) and methanesulfonamide (25 mg in entries 1,2; 50 mg in entries 3,4; and 75 mg in entry 5) in 1:1 *tert*-butyl alcohol:water (5 mL in entries 1,2; 10 mL in entries 3,4; and 15 mL in entry 5) at 0 °C for 18 h. The crude mixture of diols was converted to the corresponding acetonide derivatives by mixing with 1:1 acetone:dimethoxypropane (10 mL) and TsOH (10 mg), stirring at 60 °C for 1 h, and working up with aqueous sodium bicarbonate and CH_2Cl_2. Products ratio was determined by GC. In some cases this GC analysis was confirmed by ^{1}H NMR. [b] The amount of 1.4 g of AD-mix-β (usually employed for dihydroxylation of 1 mmol of alkene)[6] contains potassium osmate (0.002 mmol), $K_3Fe(CN)_6$ (3 mmol), K_2CO_3 (3 mmol), and 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine (0.01 mmol). Thus, 1 equiv represents here 0.35 g of AD-mix-β. [c] The numbers in parentheses represent the yield of isolated bis-acetonide, **8**. [d] This reaction was interrupted after 5 h at 0 °C. [e] Increased amounts of potassium osmate (0.005 instead of 0.002 mmol/equiv) were employed. [f] The reaction was interrupted after 8 h.

linear polyolefins[14] becomes the crucial issue that governs the entire synthesis.

(3*E*)-Hexadeca-1,3,15-triene, **2**, was prepared in 57% yield from tridec-12-enal in a sequence of four steps: Wittig−Horner reaction of tridec-12-enal with the sodium salt of triethyl phosphonoacetate followed by DIBAL-H reduction of the resultant ester afforded the corresponding primary alcohol. PCC oxidation of the latter produced penta-2,14-dienal that was then used in a second Wittig reaction with methylenetriphenylphosphorane to give **2**.

To examine the relative reactivity of the three double bonds in **2** toward AD-mix-β, we carried out the reaction with increasing amounts of the reagent (Table 1). The relative proportions of the diols **3**−**5** produced under conditions of low conversion (Table 1, entry 1) indicate that the disubstituted double bond is approximately five times more reactive than either of the two monosubstituted ones,[15] each of which exhibits comparable reactivity. As has already been observed in AD reactions with conjugated dienes,[8,16] dihydroxylation of one double bond strongly inhibits the reactivity of the remaining one toward further dihydroxylation, probably due to increased steric demands. Thus, further dihydroxylation of dienes **3** and **4** occur exclusively at the C-15 double bond, producing tetraols **6** and **7**, respectively (Table 1, entries 2−5). The relatively low proportions of **7** observed under increased concentration of oxidant reflect the high preference of **5** to produce **6** rather than **7**. Expectedly, further dihydroxylation of **6** and **7** to hexaols appears to be slow (9% after 8 h and 20% after 18 h) even with 0.5% catalyst (Table 1, entries 4 and 6). Thus, triene **2** was easily converted to the bis-acetonide **8** in 80% yield and 83% ee by treatment with 2 equiv of AD-mix-β followed by acid-catalyzed reaction with dimethoxypropane.

The enantiomeric purity of **8** was indirectly determined from the ^{1}H NMR spectra of the Mosher ester derivatives **9** and **10**.[17] The Mosher diester **9** was prepared in two steps from **8** by selective hydrolysis of the less sterically hindered acetonide to produce diol **25a** followed by double esterification with the Mosher's acyl chloride. The Mosher ester **10** was prepared from **8** in a sequence of four steps: (a) dihydroxylation of the terminal double bond using OsO_4 and quinuclidine; (b) sodium periodate degradation of the resultant diol to produce 2,3,14,15-bis(isopropylidenedioxy)pentadecanal; (c) $NaBH_4$ reduction of the latter to give the corresponding primary alcohol **24**; and (d) esterification with Mosher acyl chloride.

Because the two chiral portions in **8** are positioned far away from one another, there is no apparent interaction between them. In order to describe the local enantiomeric purity at each end of the molecule we propose a

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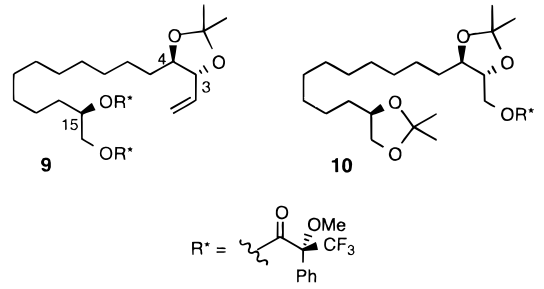


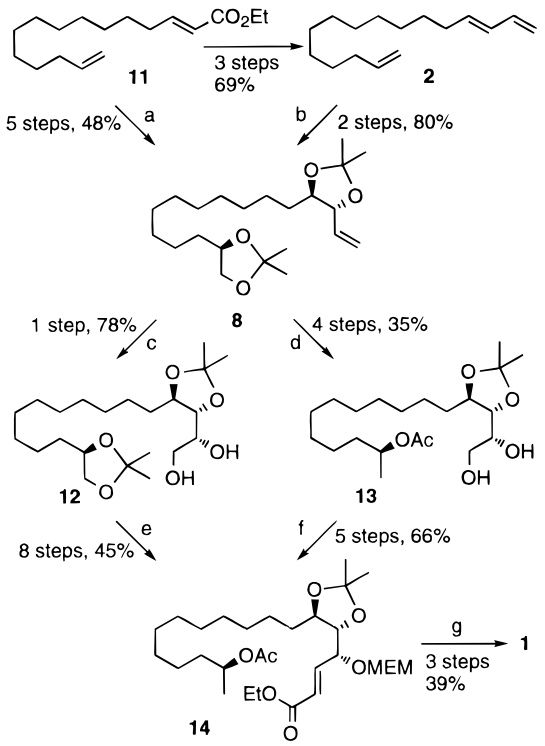
new term: *epimeric excess* (epe) which describes the "local enantiomeric excess" in a chiral molecule independent of the stereochemical purity of other asymmetric centers in the same molecule.[18] The ^{1}H NMR spectrum of **9**, for example, shows that the integration ratio between the two methoxy singlets at 3.48 and 3.40 ppm (representing the 15*R* epimer) and the two methoxy singlets at 3.44 and 3.42 ppm (representing the 15*S* epimer) was found to be 93:7. This indicates that the epimeric excess of **9**, as well as **8**, at position 15 is 86%.

Similarly, examination of the ^{1}H NMR spectrum of **10** shows an integration ratio between the two sets of double doublets at 4.47 and 4.36 ppm (ascribed to the 3*R*,4*R* diastereomer in **8**) and the two sets at 4.42 and 4.39 ppm (ascribed to the 3*S*,4*S* diastereomer in **8**) was found to be >98:2, indicating that the epimeric excess of **8** at positions 3 and 4 is >96%. Overall, the enantiomeric purity of the entire molecule **8** is 83% ee (86% epe at position 15 and 96% epe at positions 3 and 4).

The high-yield conversion of **2** to **8** set the stage for a short and efficient synthesis of (+)-aspicilin (Schemes 2 and 3). Reaction of **8** with AD-mix-α produced an easily separable, 8:1 mixture of the desired (2*R*)-1,2-dihydroxy derivative, **12**, along with its 2*S* epimer. Having all the asymmetric centers in place, we turned to the next stage, i.e. the two-carbon extension of the molecular skeleton to form an α,*β*-unsaturated carboxylic ester. This transformation was achieved via a Wittig−Horner olefination of the appropriate aldehyde. To that end the diol **12** was monoprotected to give **17** in a three-step sequence: selective silylation of the primary alcohol, protection of the secondary alcohol as a MEM ether, **16**, and desilylation with tetrabutylammonium fluoride. The resultant alcohol **17** was oxidized with *N*-chlorosuccinimide, dimethyl sulfide, and triethylamine in toluene[19] to produce the corresponding aldehyde which was then reacted with triethyl phosphonoacetate−NaH to give the desired unsaturated ester, **18**.

Reductive deoxygenation at the *ω*-position to methyl carbinol was carried out according to our recently developed approach using a three-step sequence.[10] Thus, selective hydrolysis of the less sterically hindered acetonide to produce diol **19**, followed by conversion to 18-bromo-17-acetoxy derivative, **20**, and reductive debromination with tributyltin hydride afforded acetate **14**. Hydrolysis of the latter diester, followed by macrolactonization using the mixed anhydride approach,[10,20] produced lactone **21**. Finally, deprotection of **21** with $BF_3{\cdot}Et_2O$ and ethanedithiol followed by recrystallization from hexane/diethyl ether afforded (+)-aspicilin, **1**, in the form of colorless needles. Our synthetic **1** (recrystallized from diethyl ether) was found to be identical (by mp, $[\alpha]_D$, ^{1}H NMR, ^{13}C NMR, IR, and MS) to the naturally occurring compound.[11a]

Scheme 2. The Naked Carbon Skeleton Approach



Altogether, the above described asymmetric synthesis of **1**, starting from the achiral hydrocarbon **2**, has been achieved in 14 steps and 11% overall yield. Yet, in order to optimize the synthesis of **1** we have examined alternative synthetic routes as shown in the general synthetic plan (Scheme 2, pathways a,d,f). One such modification employs the unsaturated ester **11** instead of **2** as the substrate for the AD reaction. Thus, treatment of **11** with AD-mix-*β* afforded the tetraol **22** (Scheme 4) which was then protected in the form of a bis-acetonide, **23** (obtained with 83% ee). The latter was converted to **8** in three steps: LAH reduction to alcohol **24**, oxidation to the corresponding aldehyde, and Wittig reaction with methyltriphenylphosphonium bromide and *n*-BuLi in THF.

When comparing the two alternative pathways (a and b in Scheme 2), one should recall that triene **2** is obtained from ester **11** in three steps and 69% yield. Consequently, the actual comparison is between pathway b, including the conversion of **11** to **2** (five steps, 55%), and pathway a (conversion of **11** to **8**, five steps, 48%). Compound **8** was obtained by both routes in 83% ee. Although both routes are comparable in terms of number of steps, pathway b is advantageous over pathway a because it employs the asymmetric AD reagent on a later stage in the synthetic sequence and the overall yield is higher. Nevertheless, in future synthetic design of a target molecule that contains many stereogenic centers, one may consider using simpler substrates, as exemplified in pathway a.

Another decision to be made in the synthetic design involves the sequence of events on the way from **8** to **14**.

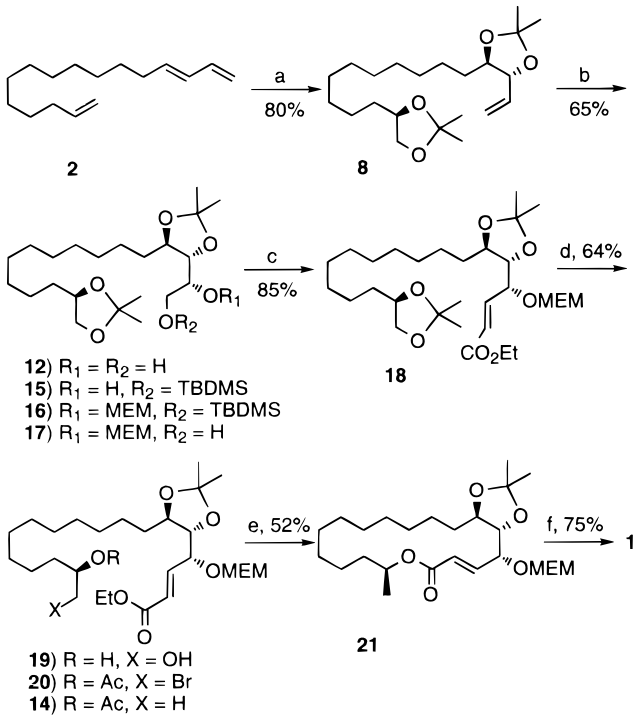
(18) Considering a simple case of a molecule containing only two asymmetric centers which have four possible stereoisomers: *RR*, *RS*, *SS*, and *SR*, the epimeric excess at one center is defined as:

$$\text{epe} = \frac{([RR]+[RS])-([SS]+[SR])}{[RR]+[RS]+[SS]+[SR]}$$

(19) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

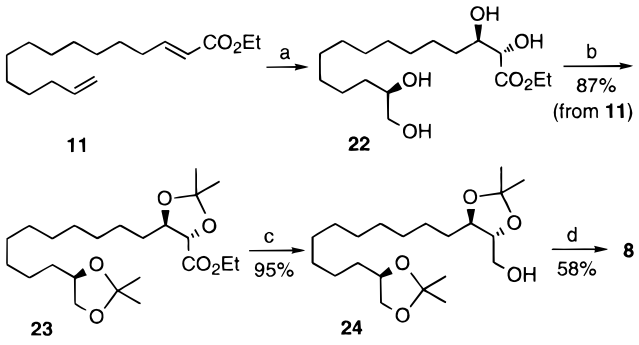
(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

Scheme 3. Synthesis of 1 via Pathways a, c, and e[a]



[a] Key: (a) (i) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH−H_2O, 0 °C, 18 h; (ii) dimethoxypropane (DMP), acetone, TsOH, 60 °C, 1 h. (b) (i) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH−H_2O, 0 °C, 48 h; (ii) TBDMSCl, Et_3N, DMAP, rt, 24 h; (iii) MEM chloride, *i*-Pr_2EtN, DMAP, rt, 18 h; (iv) TBAF, THF, rt, 1 h; (c) (i) Me_2S, NCS, toluene, −25 °C, 2 h, then Et_3N, rt, 15 min.; (ii) triethyl phosphonoacetate, NaH, THF, 0 °C, 20 min; (d) (i) AcOH, H_2O, rt; (ii) $(EtO)_3CMe$, Me_3SiBr, CH_2Cl_2, 0 °C, 1 h; iii. Bu_3SnH, AIBN, benzene, 80 °C, 2.5 h; (e) (i) LiOH, THF−H_2O, 40−50 °C, 12 h, then oxalic acid, 0 °C; (ii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 2 h then DMAP, toluene, 90 °C, 3.5 h; (f) $(CH_2SH)_2$, BF_3, CH_2Cl_2, 0 °C, 2 h.

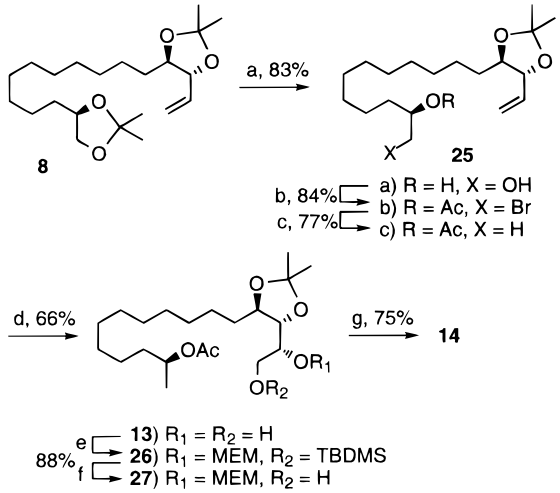
Scheme 4. Alternative Pathway b[a]



[a] Key: (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH−H_2O (1:1), 0 °C, 18 h; (b) DMP, acetone, TsOH, 60 °C, 1 h; (c) LAH, ether, 0 °C to reflux, 1 h; (d) (i) NCS, Me_2S, toluene, −25 °C, 2 h, then Et_3N. (ii) $MePPh_3Br$, BuLi, THF, 0 °C to rt, 1 h.

As described above in Scheme 2 (pathways c and e), dihydroxylation of the remaining double bond at position 1 was carried out before deoxygenation of the oxygen function at position 16. We have also examined the reversal of this sequence, where deoxygenation is performed prior to the AD reaction (Scheme 2, pathways d and f). This alternative route is described in detail in Scheme 5. Thus, the less hindered acetonide was first hydrolyzed to diol **25a** which was converted to the corresponding bromoacetate **25b**. Reductive debromination of the latter with Bu_3SnH produced **25c**. Dihydroxylation of **25c** with AD-mix-α produced diol **13** in 66% yield along with 8% of its epimer at position 2. Selective protection of the secondary alcohol in **13** was achieved in a three-step sequence: (1) silylation of the primary alcohol in the form of TBDMS ether using 1 equiv of TBDMSCl, (2) etherification of the secondary alcohol with MEMCl to form **26**, and (3) desilylation with TBAF to give alcohol **27**. The two-carbon homologation of the alcohol **27** to produce **14** was carried out in two steps as described above for alcohol **17**: first, oxidation to the corresponding aldehyde and then Wittig−Horner reaction with the sodium salt of triethyl phosphonoacetate.

Scheme 5. Alternative Pathways d and f[a]



[a] Key: (a) AcOH-H_2O (2:1), rt, 1 h; (b) $(EtO)_3CMe$, PPTS, CH_2Cl_2, 45 °C, 1 h, then TMSBr, CH_2Cl_2, 0 °C, 1 h, rt, 15 min; (c) Bu_3SnH, AIBN, benzene, reflux, 2 h; (d) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH−H_2O (1:1), 0 °C, 72 h; (e) TBDMSCl, *i*-Pr_2EtN, DMAP, rt, 16 h, then MEMCl, 24 h; (f) TBAF, THF, rt, 1 h; (g) (i) Me_2S, NCS, toluene, −25 °C, 2 h, then Et_3N, rt, 15 min; (ii) triethyl phosphonoacetate, NaH, THF, 0 °C, 20 min.

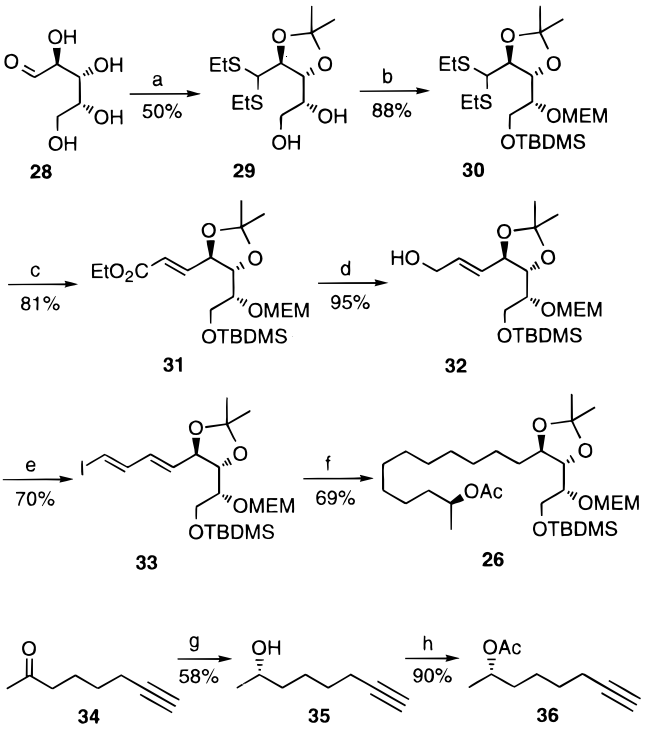
Although both alternative routes (pathways c,e vs pathways d,f in Scheme 2) involve nine steps each, the first route produces compound **14** from **8** in 35% yield while in the second route the yield is 23%. Overall, our preferred synthesis of **1** is outlined by pathways b, c, and e, although all the routes involve convenient procedures and easy purification of most intermediates.

The Bioorganic Approach

The commonly practiced synthetic approach to molecules containing many stereogenic centers employs enantiomerically pure chiral building blocks that are derived from the chiral pool of natural products in general, and from sugar molecules in particular.[5] In fact, the Quinkert group has already employed mannose and (*S*)-propylene oxide in their efficient synthesis of (+)-aspicilin.[12a] We have also examined this alternative approach, where the three stereogenic centers at positions 5, 6, and 7 of **1** are obtained from D-arabinose, **28**, while the stereochemistry at position 18 originates from an enzyme-catalyzed reaction (Scheme 6). Thus, **28** was converted to **29** as described earlier by Armstrong.[21] Selective silylation of the primary alcohol using 1 equiv of TBDMSCl followed by protection of the secondary one in the form of a MEM ether was carried out in one pot to

(21) Armstrong, R. W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 915.

Scheme 6. Synthesis of Aspicilin Based on the Chiral Pool and Enzymatic Approach[a]



[a] Key: (a) Reference 22; (b) TBDMSCl, *i*-Pr_2EtN, DMAP, rt, 12 h, then MEMCl, 24 h. (c) (i) $HgCl_2$, HgO, MeCN-H_2O (4:1), 50 °C, 2 h; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (d) DIBAL-H, THF, −30 °C, 1 h; (e) (i) PCC, CH_2Cl_2, 1 h; (ii) CHI_3, $CrCl_2$, THF, 0 °C, 2 h; (f) (i) **36**, $Pd(PPh_3)_4$, CuI, Et_3N, 0 °C to rt, 1 h; (ii) Rh−Al_2O_3 (5%), THF, H_2; (g) TBADH, NADP, mercaptoethanol, i-PrOH (ref 22); (h) Ac_2O, pyridine, rt, 24 h.

give **30**. Deprotection of the thioacetal followed by Wittig−Horner reaction of the resultant aldehyde using the sodium salt of triethyl phosphonoacetate produced **31**. DIBAL-H reduction of the ethyl ester afforded the alcohol **32**. Oxidation of the latter to the corresponding aldehyde followed by treatment with iodoform in presence of chromium(II) chloride afforded the iododiene **33**.

In this convergent approach the other chiral building block, acetoxyalkyne **36**, was prepared in two steps from alkynone **34**. Thus, the enzymatic reduction of **34** with *Thermoanaerobium brockii* alcoholdehydrogenase (TBADH), according to our previously described procedure,[22] produced the alkynol **35** which was acetylated to give **36**. Cross coupling of the two building blocks, **33** and **36**, catalyzed by both $Pd(PPh_3)_4$ and CuI produced a mixture of isomeric ynediene products, which was subjected to catalytic hydrogenation over Rh−Al_2O_3 to give the intermediate **26**. The identity of this compound was verified by desilylation to give the alcohol **27** which was found to be identical by ^1H NMR, ^{13}C NMR, HRMS, and optical rotation to the compound described above.

In conclusion, asymmetric total synthesis of (+)-aspicilin, **1**, has been achieved in 14 steps and 11% overall yield (8.8% after recrystallization) starting from the achiral hydrocarbon **2**. Following our bioorganic approach, the synthesis of **1** was achieved in 20 steps and 4.3% overall yield.[23] Although this is a convergent synthesis, it is slightly longer and less efficient than the one based on the naked carbon skeleton approach, where all asymmetric centers have been introduced in two synthetic steps of asymmetric dihydroxylation reactions with very high regio- and enantioselectivity. From a more general perspective, the naked carbon skeleton approach is not dependent on the availability of naturally occurring starting materials with the appropriate stereogenic centers. This work has demonstrated the advantages of this synthetic methodology in the preparation of natural products comprising polyoxygenated carbon skeletons.

(22) Keinan, E.; Seth, K. K.; Lamed, R.; Ghirlando, R.; Singh, S. P. *Biocatalysis* **1990**, *3*, 57.

(23) In comparison, the Quinkert synthesis of (+)-aspicilin from D-mannose (reference 12a) was achieved in 13% overall yield.

Experimental Section

General Methods. ^1H 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. Infrared spectra were measured with a Perkin-Elmer 1600 (FTIR) spectrometer. Optical rotations were measured in a one decimeter (1 mL) cell using 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, 70−230 mesh, Art. 9385) at atmospheric pressure. THF was dried by distillation over sodium benzophenone ketyl. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) was purchased from Aldrich. AD-mix-α (Aldrich no. 39275-8), AD-mix-*β* (Aldrich no. 39276-6). TBADH (Sigma no. A-9287, 40 units/mg), NADP (Sigma no. N-3886).

Hexadeca-1,3,15-triene, 2. Triethyl phosphonoacetate (4.49 g, 20 mmol) was added dropwise to a heterogeneous mixture of NaH (60% in oil, 800 mg, 20 mmol) in dry THF (50 mL) at 0 °C. The mixture was stirred for 10 min, a solution of tridec-12-enal (2.78 g, 14.2 mmol) in dry THF (5 mL) was added dropwise, and stirring was continued for 20 min. Saturated aqueous NH_4Cl was added, and the mixture was extracted with ether−hexane (1:1). Solvents were removed under reduced pressure, and the residue was filtered over silica gel (hexane:ethyl acetate, 19:1) yielding ethyl pentadeca-2,-14-dienoate, **11** (3.13 g, 83%), in the form of a colorless oil.

DIBAL-H (35 mL, 1 M in hexane, 35 mmol) was added dropwise to a solution of the above mentioned ester **11** (3.13 g, 11.8 mmol) in dry THF (20 mL) at −30 °C and stirred for 1 h at same temperature. The reaction mixture was diluted with ether (40 mL), a saturated aqueous solution of NH_4Cl (10 mL) was added dropwise, and the mixture was stirred at rt for 1 h and then was filtered through a short bed of Celite. The filtrate was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the corresponding alcohol (2.77 g) which was used in the next step without further purification. ^1H NMR: 5.81 (ddt, J = 17.2, 10.2, 6.7 Hz, 1H), 5.66 (m, 2H), 4.99 (dq, J = 17.2, 1.6 Hz, 1H), 4.93 (m, 1H), 4.08 (d, J = 5.2 Hz, 2H), 2.04 (m, 4H), 1.37 (br s, 5H), 1.27 (br s, 16H) ppm. ^{13}C NMR: 139.24, 133.57, 128.79, 114.08, 63.83, 33.80, 32.24, 29.57, 29.48, 29.17, 29.13, 28.93 ppm.

Pyridinium chlorochromate (PCC, 3.8 g, 17.7 mmol) and Celite (3.8 g) were added to a solution of the above mentioned crude alcohol (2.77 g) in CH_2Cl_2 (50 mL), and the mixture was stirred for 1 h and then filtered through silica gel (hexane: ethyl acetate, 9:1) to afford pentadeca-2,14-dienal (2.4 g) in the form of a colorless oil. ^1H NMR: 9.49 (d, J = 8.0 Hz, 1H), 6.86 (dt, J = 15.7, 6.8 Hz, 1H), 6.12 (ddt, J = 15.7, 6.8, 1.5 Hz, 1H) 5.82 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 4.99 (dq, J = 17.0, 1.9 Hz, 1H), 4.93 (m, 1H), 2.34 (qd, J = 7.0, 1.4 Hz, 2H), 2.04 (qt, J = 7.1, 2.6 Hz, 2H), 1.49 (m, 2H), 1.42−1.23 (m and br s, 14H) ppm.

n-BuLi (2.5 M in hexane, 6.0 mL, 15 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (5.36 g, 15 mmol) in dry THF (30 mL) at 0 °C, and the mixture was stirred at rt for 30 min. A solution of the above

mentioned aldehyde (2.4 g) in dry THF (10 mL) was added dropwise, the mixture was stirred at 60 °C for 1 h and then worked-up by addition of saturated aqueous solution of NH_4Cl and extraction with ether. Column chromatography (silica gel, hexane:ethyl acetate, 19:1) afforded the hexadeca-1,3,15-triene, **2** (1.8 g, 69% yield from the ester) in the form of an oil. ^{1}H NMR: 6.31 (dt, J = 17.0, 10.2 Hz, 1H), 6.04 (dd, J = 15.2, 10.4 Hz, 1H), 5.81 (m, 1H), 5.70 (dt, J = 15.2, 7.0 Hz, 1H), 5.08 (dd, J = 17.0, 1.2 Hz, 1H), 4.99 (dq, J = 17.2, 1.9 Hz, 1H), 4.94 (m, 2H), 2.06 (m, 4H), 1.37 (br s, 4H), 1.26 (br s, 12H) ppm. ^{13}C NMR: 139.25, 137.36, 135.64, 130.81, 114.54, 114.07, 33.81, 32.55, 29.57, 29.48, 29.19, 29.14, 28.94 ppm.

Asymmetric Dihydroxylation of 2. A solution of **2** (55 mg, 0.25 mmol) and AD-mix-β (0.35 g, OsO_4 content 0.2%) in *tert*-butyl alcohol/water (1:1, 5 mL) was stirred at 0 °C for 18 h. Sodium metabisulfite (0.38 g) was added, and the mixture was extracted with ethyl acetate. Removal of solvents under reduced pressure afforded a mixture of the products **3**−**7** along with unreacted **2**. This mixture was mixed with dimethoxypropane−acetone (1:1, 2 mL) and TsOH (10 mg), stirred at 60 °C for 1 h, diluted with diethyl ether, and washed with saturated aqueous $NaHCO_3$, the organic layer was then dried over sodium sulfate, the solvents were removed under reduced pressure, and the residue was filtered through silica gel using CH_2Cl_2 as eluent. The resultant solution was concentrated, and the product ratio was obtained by GC analysis using authentic samples of the acetonide derivatives of **3**−**7** as references. ^{1}H NMR of the acetonides: Acetonides of **3** and **4** (isolated as a 9:1 mixture): acetonide of **3**: 5.79 (m, 2H), 5.35 (br d, J = 16.0 Hz, 1H), 5.23 (br d, J = 11.2 Hz, 1H), 4.97 (br d, J = 16.0 Hz, 1H), 4.91 (br d, J = 11.2 Hz, 1H), 3.96 (t, J = 7.6 Hz, 1H), 3.65 (m, 1H), 2.05 (q, J = 7.2 Hz, 2H), 1.60−1.20 (m and br s, 18H), 1.41 (s, 3H), 1.40 (s, 3H) ppm. Acetonide of **4** (partial spectrum): 5.40 (dd, 1H), 4.45 (q, 1H), 4.05 (m, 1H) and 3.55 (t, 1H) ppm. Diacetonide of **6**: vide infra. Acetonide of **7**: 5.79 (dt, J = 15.3, 6.7 Hz, 1H), 5.42 (ddt, J = 15.3, 7.8, 1.4 Hz, 1H), 4.46 (td, J = 8.0, 6.2 Hz, 1H), 4.05 (m, 3H), 3.55 (t, J = 8.1 Hz, 1H), 3.50 (t, J = 7.2 Hz, 1H), 2.04 (m, 2H), 1.72−1.22 (m and br s, 18H), 1.43 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H) ppm.

(3*R*,4*R*,15*R*)-3,4:15,16-Bis(isopropylidenedioxy)hexadec-1-ene, 8. Compound **2** (1.45 g, 6.6 mmol) was added to a solution of AD-mix-β (18.4 g, OsO_4 content 0.5%) and sulfonamide (630 mg 6.6 mmol) in *tert*-butyl alcohol/water (1:1, 130 mL) at 0 °C, and the mixture was stirred vigorously for 8 h at the same temperature. Sodium metabisulfite (19.8 g) was added slowly, and the mixture was extracted with ethyl acetate to give crude tetraol, **7**. The latter was treated with acetone/dimethoxypropane (1:1, 50 mL) and TsOH (100 mg) at 60 °C for 1 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 and chromatographed over silica gel (hexane:ethyl acetate, 9:1) to give **8** (1.94 g, 80% from **2**). $[\alpha]_D$ −10.0° (c = 2.50, $CHCl_3$). ^{1}H NMR: 5.81 (ddd, J = 17.4, 10.3, 7.4 Hz, 1H), 5.36 (ddd, J = 17.4, 1.5, 1.1 Hz, 1H), 5.24 (ddd, J = 10.3, 1.5, 0.8 Hz, 1H), 4.03 (m, 3H), 3.67 (dt, J = 8.3, 5.7 Hz, 1H), 3.50 (t, J = 7.2 Hz, 1H), 1.68−1.20 (m and br s, 20H), 1.42 (s, 3H), 1.41 (s, 6H), 1.36 (s, 3H) ppm. ^{13}C NMR: 135.55, 118.70, 108.42, 82.74, 80.67, 76.14, 69.51, 33.57, 31.86, 29.67, 29.63, 29.47, 27.28, 26.94, 26.90, 26.02, 25.74 ppm. IR: 2984.4, 2928.2, 2854.8, 1456.4, 1368.7. HRMS: calcd for $C_{22}H_{40}O_4Na$ (MNa^+) 391.2824, found 391.2835.

Determination of the Epimeric Excess of 8 at C-15. A solution of **8** (18 mg, 0.05 mmol) in AcOH−water (1:1, 1 mL) was stirred at rt for 2 h. Solvents were removed under reduced pressure, and the residue was filtered through a short bed of silica gel to give the dihydroxy derivative, **25a** (8 mg). This diol (3 mg) and DMAP (30 mg) were dissolved in CH_2Cl_2 (0.5 mL). (*S*)-Mosher acyl chloride (20 μL) (prepared from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid) was added, and the mixture was stirred for 18 h and then filtered through a double bed of silica gel and neutral activated alumina using CH_2Cl_2 as an eluent affording the bis Mosher ester **9**. Assignment of the ^{1}H NMR signals was achieved by comparison of the spectra of **9** obtained in three different dihydroxylation reactions: (a) with AD-mix-β, (b) with AD-mix-α, and (c) with OsO_4 and quinuclidine. Thus, the two methoxy singlets at δ 3.48 and 3.40 correspond to the 15*R* configuration and those at δ 3.44 and 3.42 correspond to the 15*S* configuration. The ratio between these two sets of signals in **9** obtained from the reaction with AD-mix-β was found to be 93:7.

Determination of the Epimeric Excess of 8 at C-3 and C−4. A solution of **8** (18 mg, 0.05 mmol) was dihydroxylated with OsO_4, quinuclidine, and NMO in acetone to give the crude 1,2-dihydroxy derivative (20 mg). Treatment with $NaIO_4$ (42 mg, 0.2 mmol) and water (0.1 mL) in CH_2Cl_2 (2 mL) and workup with water and CH_2Cl_2, drying over Na_2SO_4, and filtration over silica gel produced the crude aldehyde. The latter was dissolved in methanol, cooled to 0 °C, and treated with $NaBH_4$ (19 mg, 0.5 mmol). Workup with diethyl ether and water and filtration of the organic layer over silica gel (hexane:ethyl acetate 9:1) afforded the corresponding alcohol **24**. A solution of **24** (5 mg), (*S*)-Mosher acyl chloride (20 μL) and DMAP (30 mg) in CH_2Cl_2 was stirred for 18 h, and filtered through a double bed of silica gel and neutral activated alumina using CH_2Cl_2 to give **10**. Assignment of the ^{1}H NMR signals was achieved by comparison of the spectra of **10** obtained in three different dihydroxylation reactions: (a) with AD-mix-β, (b) with AD-mix-α, and (c) with OsO_4 and quinuclidine. ^{1}H NMR of **10** from reaction a corresponds to the (3*R*,4*R*) configuration in **8**: δ 4.47 (dd, J = 11.9, 3.6 Hz, 1H) and 4.36 (dd, J = 11.9, 4.4 Hz, 1H) ppm. ^{1}H NMR of **10** from reaction b corresponds to the (3*S*,4*S*) configuration in **8**: δ 4.42 (dd, J = 11.7, 4.9 Hz, 1H) and 4.39 (dd, J = 11.7, 4.0 Hz, 1H) ppm. The ratio between these two sets of signals in **10** obtained from the reaction with AD-mix-β was found to be >49:1.

(2*R*,3*S*,4*R*,15*R*)-3,4:15,16-Bis(isopropylidenedioxy)-hexadecane-1,2-diol, 12. A solution of **8** (915 mg, 2.49 mmol), AD-mix-α (3.49 g, OsO_4 content 0.5%), and sulfonamide (240 mg) in *tert*-butyl alcohol−water (1:1, 50 mL) was stirred at 0 °C for 48 h. Workup and purification over silica gel (hexane:ethyl acetate, 3:2) afforded a mixture (893 mg, 89%) containing **12** (78%) and its 2*S* epimer (11%). This crude mixture was taken to next step without purification. An analytical sample of **12** was obtained by chromatography over silica gel. ^{1}H NMR: 4.05 (m, 2H), 3.97 (td, J = 7.8, 3.2 Hz, 1H), 3.72 (m, 4H), 3.50 (t, J = 7.2 Hz, 1H), 2.60 (br s, 2H), 1.72−1.24 (m and br s, 20H), 1.41 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR: 108.68, 108.54, 81.23, 79.20, 76.13, 72.45, 69.47, 63.75, 34.07, 33.53, 29.59, 29.45, 29.42, 27.31, 27.03, 26.90, 26.14, 25.70 ppm. HRMS: calcd for $C_{22}H_{42}O_6Na$ (MNa^+) 425.2879, found 425.2883.

(2*R*,3*S*,4*R*,15*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3,4:15,16-bis(isopropylidenedioxy)hexadecan-2-ol, 15. TBDMSCl (369 mg, 2.44 mmol) and DMAP (20 mg) were added to a solution of **3** (893 mg, 2.22 mmol) in CH_2Cl_2 (5 mL) and triethylamine (0.4 mL), and the mixture was stirred at rt for 24 h. Workup and filtration over silica gel afforded **15** (974 mg, 85%) along with the 2*S* epimer of **15** (138 mg, 12%). Physical data of **15**: $[\alpha]_D$ +6.6° (c = 3.08, $CHCl_3$). ^{1}H NMR: 4.03 (m, 3H), 3.79 (dd, J = 9.5, 3.1 Hz, 1H), 3.66 (t, J = 5.8 Hz, 1H), 3.62 (m, 1H), 3.56 (t, J = 7.3 Hz, 1H), 3.50 (t, J = 7.3 Hz, 1H), 2.55 (d, J = 4.5 Hz, 1H), 1.78−1.24 (m and br s, 20H), 1.41 (s, 3H), 1.40 (s, 3H), 1.39 (s, 6H), 0.91 (s, 9H), 0.09 (s, 6H) ppm. ^{13}C NMR: 108.53, 108.47, 80.08, 79.90, 76.16, 73.06, 69.56, 64.26, 34.21, 33.58, 29.70, 29.65, 29.54, 29.51, 29.49, 27.39, 27.06, 26.94, 26.19, 25.84, 25.76, 18.25, −5.38, −5.45 ppm. IR: 3490.0, 2985.0, 2927.7, 2855.7, 1462.8, 1368.6. HRMS: calcd for $C_{28}H_{56}O_6SiNa$ (MNa^+) 539.3744, found 539.3760.

(2*R*,3*S*,4*R*,15*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3,4:15,16-bis(isopropylidenedioxy)-2-[(2′-methoxyethoxy)-methoxy]hexadecane, 16. MEM chloride (1 mL) was added to a solution of alcohol **15** (974 mg, 1.89 mmol), diisopropylethylamine (2 mL), and DMAP (20 mg) in CH_2Cl_2 (2 mL) at 0 °C ,and the mixture was stirred at rt for 16 h. Workup with CH_2Cl_2 and water followed by filtration through a short bed of silica gel afforded **16** (1.0 g, 88%). $[\alpha]_D$ −5.6° (c = 2.57, $CHCl_3$). ^{1}H NMR: 4.90 (d, J = 6.9 Hz, 1H), 4.76 (d, J = 6.9 Hz, 1H), 4.01 (m, 3H), 3.81 (dd, J = 9.2, 2.5 Hz, 1H), 3.74 (m, 5H), 3.53 (t, J = 4.6 Hz, 1H), 3.47 (t, J = 7.2 Hz, 1H), 3.36 (s, 3H), 1.70−1.20 (m and br s, 20H), 1.38 (s, 3H), 1.36 (s, 3H),

1.34 (s, 3H), 1.33 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H) ppm. ^{13}C NMR: 108.49, 108.39, 95.53, 79.97, 78.51, 78.18, 76.11, 71.66, 69.48, 67.17, 63.15, 58.98, 34.19, 33.59, 29.72, 29.62, 29.50, 29.46, 27.36, 26.95, 26.91, 26.17, 25.83, 25.72, 18.20, −5.49, −5.53 ppm. IR: 2984.3, 2928.2, 2855.6, 1462.3, 1377.9. HRMS: calcd for $C_{32}H_{64}O_8SiNa$ (MNa^+) 627.4268, found 627.4285.

(2*R*,3*S*,4*R*,15*R*)-3,4:15,16-Bis(isopropylidenedioxy)-2-[(2′-methoxyethoxy)methoxy]hexadecan-1-ol, 17. A solution of tetrabutylammonium fluoride (1 M in THF, 2 mL) was added to a solution of **16** (1.0 g, 1.66 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred at rt for 1 h. Workup with ether and water followed by filtration through silica gel afforded **17** (786 mg, Yield 97%). $[\alpha]_D$ +33.6° (c = 3.30, $CHCl_3$). ^{1}H NMR: 4.84 (d, J = 7.2 Hz, 1H), 4.76 (d, J = 7.2 Hz, 1H), 4.03 (m, 2H), 3.93 (td, J = 6.4, 2.9 Hz, 1H), 3.83 (m, 2H), 3.65 (m, 4H), 3.55 (t, J = 4.5 Hz, 2H), 3.47 (t, J = 7.2 Hz, 1H), 3.38 (m, 1H), 3.37 (s, 3H), 1.68−1.22 (m and br s, 20H), 1.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H) ppm. ^{13}C NMR: 108.78, 108.52, 95.99, 82.59, 80.03, 79.35, 76.16, 71.55, 69.48, 67.60, 62.62, 58.94, 34.16, 33.56, 29.62, 29.49, 29.46, 27.39, 26.95, 26.88, 26.08, 25.72 ppm. IR: 3481.7, 2984.3, 2927.5, 2855.2, 1456.3. HRMS: calcd for $C_{26}H_{50}O_8Na$ (MNa^+) 513.3403, found 513.3420.

(4*R*,5*S*,6*R*,17*R*)-(*E*)-Ethyl 5,6:17,18-Bis(isopropylidenedioxy)-4-[(2′-methoxyethoxy)methoxy]octadec-2-enoate, 18. Methyl sulfide (204 mg, 3.29 mmol) was added dropwise to a solution of NCS (320 mg, 2.4 mmol) in toluene (10 mL) at 0 °C, the mixture was stirred for 10 min and then cooled to −25 °C, and alcohol **17** (786 mg, 1.6 mmol) in toluene (2 mL) was added dropwise. The mixture was stirred at same temperature for 2 h, and then triethylamine (0.27 mL) was added dropwise. Warming to rt followed by workup with diethyl ether and brine and removal of solvents under reduced pressure afforded crude aldehyde which was taken to the next step without purification.

Triethyl phosphonoacetate (897 mg, 4 mmol) was added dropwise to a heterogeneous mixture of NaH (60% in oil, 160 mg, 4 mmol) in dry THF (10 mL) at 0 °C, and the mixture was stirred for 10 min. A solution of the above mentioned aldehyde (680 mg) in dry THF (2 mL) was added dropwise, and the mixture was stirred for additional 20 min at same temperature. Aqueous workup with diethyl ether and brine and purification over silica gel (hexane/ethyl acetate; 19:1) afforded **18** (761 mg, 85% from **17**). $[\alpha]_D$ −26.9° (c = 5.09, $CHCl_3$). ^{1}H NMR: 6.88 (dd, J = 15.8, 6.6 Hz, 1H), 6.05 (dd, J = 15.8, 1.2 Hz, 1H), 4.75 (s, 2H), 4.33 (ddd, J = 6.3, 4.9, 1.2 Hz, 1H), 4.21 (qq, J = 7.2, 2.0 Hz, 2H), 4.06 (m, 2H), 3.90 (td, J = 7.8, 3.7 Hz, 1H), 3.77 (m, 2H), 3.65 (dt, J = 11.2, 4.4 Hz, 1H), 3.55 (t, J = 4.5 Hz, 2H), 3.50 (t, J = 7.2 Hz, 1H), 3.39 (s, 3H), 1.70−1.22 (m and br s, 20H), 1.41 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR: 165.71, 143.68, 124.27, 109.12, 108.54, 93.75, 82.01, 78.37, 76.14, 75.54, 71.61, 69.51, 67.39, 60.56, 59.02, 33.93, 33.58, 29.64, 29.49, 27.43, 26.94, 26.77, 26.06, 25.75, 14.19 ppm. IR: 2984.0, 2929.2, 2855.4, 1723.0, 1659.4, 1456.3, 1368.6. HRMS: calcd for $C_{30}H_{54}O_9Na$ (MNa^+) 581.3666, found 581.3650.

(4*R*,5*S*,6*R*,17*R*)-(*E*)-Ethyl 17,18-Dihydroxy-5,6-(isopropylidenedioxy)-4-[(2′-methoxyethoxy)methoxy]octadec-2-enoate, 19. A solution of **18** (761 mg, 1.36 mmol) in AcOH−water (1:1, 20 mL) was stirred for 2 h at rt. Solvents were removed under reduced pressure, and the residue was filtered through silica gel to give diol **19** (620 mg, 88%). $[\alpha]_D$ −22.9° (c = 3.08, $CHCl_3$). ^{1}H NMR: 6.87 (dd, J = 15.8, 6.6 Hz, 1H), 6.04 (dd, J = 15.8, 1.2 Hz, 1H), 4.73 (s, 2H), 4.32 (ddd, J = 6.3, 4.9, 1.2 Hz, 1H), 4.19 (qq, J = 7.2, 1.9 Hz, 2H), 3.89 (td, J = 7.8, 3.8 Hz, 1H), 3.75 (m, 2H), 3.64 (m, 3H), 3.53 (t, J = 4.6 Hz, 2H), 3.41 (m, 1H), 3.37 (s, 3H), 2.59 (br s, 2H), 1.65−1.22 (m and br s, 20H), 1.39 (s, 3H), 1.35 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR: 165.77, 143.72, 124.24, 109.13, 93.74, 81.99, 78.28, 75.53, 72.25, 71.59, 67.33, 66.77, 60.58, 59.00, 33.89, 33.12, 29.58, 29.48, 29.43, 27.41, 26.76, 26.00, 25.51, 14.17 ppm. IR: 3428.3, 2984.0, 2926.3, 2854.6, 1722.2, 1659.3, 1456.2, 1369.3. HRMS: calcd for $C_{27}H_{50}O_9Na$ (MNa^+) 541.3353; found 541.3365.

(4*R*,5*S*,6*R*,17*R*)-(*E*)-Ethyl 17-Acetoxy-18-bromo-5,6-(isopropylidenedioxy)-4-[(2′-methoxyethoxy)methoxy]octadec-2-enoate, 20. A solution of diol **19** (620 mg, 1.2 mmol), triethyl orthoacetate (1.5 mmol), and TMSBr (229 mg, 1.5 mmol) was stirred at 0 °C for 1 h. More methylene chloride was added, washed with saturated solution of sodium bicarbonate, and filtered through silica gel to yield **20** (630 mg, 84%) as colorless oil. ^{1}H NMR: 6.88 (dd, J = 15.8, 6.6 Hz, 1H), 6.05 (dd, J = 15.8, 1.2 Hz, 1H), 4.99 (m, 1H), 4.75 (s, 2H), 4.33 (ddd, J = 6.3, 4.9, 1.1 Hz, 1H), 4.21 (qq, J = 7.1, 2.0 Hz, 2H), 3.90 (td, J = 7.9, 3.8 Hz, 1H), 3.77 (m, 2H), 3.65 (dt, J = 11.2, 4.4 Hz, 1H), 3.54 (t, J = 4.6 Hz, 2H), 3.51 (dd, J = 10.8, 4.6 Hz, 1H), 3.43 (dd, J = 10.8, 5.4 Hz, 1H), 3.38 (s, 3H), 2.09 (s, 3H), 1.70−1.22 (m and br s, 20H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR: 170.46, 165.72, 143.69, 124.27, 109.13, 93.77, 82.02, 78.31, 75.54, 72.44, 71.62, 67.36, 60.56, 59.03, 34.24, 33.93, 32.48, 29.64, 29.51, 29.48, 29.39, 29.28, 27.43, 26.78, 26.06, 25.03, 21.02, 14.20 ppm. IR: 2983.7, 2926.8, 2854.9, 1742.6, 1722.2, 1659.5. HRMS: calcd for $C_{29}H_{51}O_9BrCs$ (MCs^+) 755.1771, found 755.1780.

(4*R*,5*S*,6*R*,17*S*)-(*E*)-Ethyl 17-Acetoxy-5,6-(isopropylidenedioxy)-4-[(2′-methoxyethoxy)methoxy]octadec-2-enoate, 14. Bu_3SnH (0.6 mL, 2.23 mmol) was added dropwise over 30 min to a solution of **20** (630 mg, 1.01 mmol) and AIBN (20 mg) in benzene at reflux temperature. Refluxing was continued for additional 2 h, solvent was removed under reduced pressure, and the residue was chromatographed over silica gel (using first CH_2Cl_2 to remove organotin compounds and then hexane:ethyl acetate 4:1) to give **14** (475 mg, 86%). $[\alpha]_D$ −21.0° (c = 2.68, $CHCl_3$). ^{1}H NMR: 6.89 (dd, J = 15.8, 6.6 Hz, 1H), 6.05 (dd, J = 15.8, 1.2 Hz, 1H), 4.88 (m, 1H), 4.75 (s, 2H), 4.33 (ddd, J = 6.3, 4.9, 1.2 Hz, 1H), 4.21 (qq, J = 7.1, 2.0 Hz, 2H), 3.90 (td, J = 7.9, 3.7 Hz, 1H), 3.77 (m, 2H), 3.65 (dt, J = 11.2, 4.4 Hz, 1H), 3.55 (t, J = 4.5 Hz, 2H), 3.39 (s, 3H), 2.03 (s, 3H), 1.64−1.22 (m and br s, 20H), 1.40 (s, 3H), 1.37 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR: 170.78, 165.70, 143.67, 124.27, 109.11, 93.74, 82.00, 78.30, 75.52, 71.60, 71.04, 67.34, 60.54, 59.01, 35.88, 33.91, 29.64, 29.52, 29.49, 29.42, 27.42, 26.78, 26.05, 25.38, 21.37, 19.93, 14.18 ppm. IR: 2982.9, 2928.4, 2855.3, 1726.9, 1659.5. HRMS: calcd for $C_{29}H_{52}O_9Cs$ (MCs^+) 677.2666, found 677.2675.

(4*R*,5*S*,6*R*,17*S*)-(*E*)-5,6-(Isopropylidenedioxy)-4-[(2′-methoxyethoxy)methoxy]octadec-2-ene-17-olide, 21. A mixture of **14** (457 mg, 0.84 mmol) in THF (10 mL) and aqueous LiOH (0.3 M, 10 mL) was stirred at 40−50 °C for 12 h. Ethyl acetate (10 mL) was added, and the mixture was cooled to 0 °C and then acidified with 10% solution of oxalic acid. Workup and removal of solvents followed by filtration through a short bed of silica gel (hexane:ethyl acetate, 2:3) afforded a hydroxy acid which was taken to the next step without further purification.

2,4,6-Trichlorobenzoyl chloride (0.4 mL) was added to a solution of the above mentioned hydroxy acid and triethylamine (0.6 mL) in THF (3 mL) and stirred at rt for 2 h. The mixture was diluted with toluene, filtered, and added dropwise over 2.5 h to a solution of DMAP (1.1 g) in toluene (120 mL) at reflux temperature. Removal of solvents under reduced pressure and filtration through silica gel yielded **21** (200 mg, 52% from **14**). $[\alpha]_D$ −21.9° (c = 2.68, $CHCl_3$). ^{1}H NMR: 6.90 (dd, J = 15.8, 7.8 Hz, 1H), 6.04 (dd, J = 15.8, 1.0 Hz, 1H), 5.03 (m, 1H), 4.79 (q, J = 7.1 Hz, 2H), 4.42 (d, J = 7.8 Hz, 1H), 3.81 (m, 3H), 3.67 (td, J = 11.0, 4.5 Hz, 1H), 3.55 (t, J = 4.7 Hz, 2H), 3.39 (s, 3H), 1.60−1.18 (m and br s, 20H), 1.42 (s, 3H), 1.39 (s, 3H), 1.25 (d, J = 6.2 Hz, 3H) ppm. ^{13}C NMR: 165.01, 142.21, 125.82, 108.74, 93.73, 81.85, 74.86, 73.89, 71.56, 71.08, 67.16, 58.95, 35.25, 31.59,27.91, 27.66, 27.43, 27.34, 27.11, 26.81, 26.47, 26.08, 24.64, 23.45, 20.48 ppm. IR: 2982.9, 2930.5, 2857.9, 1717.8, 1654.4. HRMS: calcd for $C_{25}H_{44}O_7Na$, (MNa^+) 479.2985, found 479.2980.

(+)-Aspicilin, 1. $BF_3{\cdot}Et_2O$ (50 μL) was added to a solution of **21** (100 mg, mmol) and ethanedithiol (70 μl) in CH_2Cl_2 (2 mL), and the mixture was stirred at 0 °C for 2 h. Workup and purification over silica gel afforded **1** (54 mg, 75%). This material was recrystallized from diethyl ether. Mp 154−156 °C, lit.[12c] 154−156 °C, lit.[11b] 153−154 °C $[\alpha]_D$ = +38.5° (c =

1.05, $CHCl_3$), lit.[12c] +39.4° (c = 0.868, $CHCl_3$), lit.[11b] +32° (c = 2.31, $CHCl_3$). ^{1}H NMR: 6.91 (dd, J = 15.8, 5.0 Hz, 1H), 6.12 (dd, J = 15.8, 1.8 Hz, 1H), 5.05 (m, 1H), 4.58 (m, 1H), 3.77 (m, 1H), 3.60 (m, 2H), 3.33 (m, 1H), 2.81 (br s, 1H), 1.55 (q, J = 6.4 Hz, 4H), 1.50−1.20 (m, 16H), 1.25 (d, J = 6.3 Hz, 3H) ppm.

(2*S*,3*R*,14*R*)-Ethyl 2,3,14,15-Tetrahydroxypentadecanoate, **22.** Ethyl pentadeca-2,14-dienoate, **11** (1.27 g, 4.77 mmol), was added to a solution of AD-mix-β (13.4 g, OsO_4 content 0.5%) and sulfonamide (453 mg) in *tert*-butyl alcohol/water (1:1, 200 mL) at 0 °C, and the mixture was stirred vigorously for 18 h at same temperature. Sodium metabisulfite (14.3 g) was added slowly, and the mixture was extracted with ethyl acetate to give crude **22** (1.79 g) which was used in the next step without further purification. An analytical sample of **22** was obtained by recrystallization from ethyl acetate. $[\alpha]_D$ +13.2° (c = 2.1, $CHCl_3$). ^{1}H NMR (CD_3OD): 4.12 (qq, J = 7.2, 1.6 Hz, 2H), 3.95 (d, J = 2.8 Hz, 1H), 3.73 (td, J = 6.7, 2.7 Hz, 1H), 3.45 (m, 1H), 3.36 (dd, J = 11.1, 4.4 Hz, 1H), 3.31 (dd, J = 11.1, 6.6 Hz, 1H), 1.50−1.22 (m and br s, 20H), 1.20 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (CD_3OD): 174.75, 74.81, 73.67, 73.23, 67.37, 62.16, 34.42, 34.21, 30.85, 30.69, 26.91, 26.70, 14.51 ppm. HRMS: calcd for $C_{17}H_{34}O_6Cs$ (MCs^+) 467.1410, found 467.1388.

(2*S*,3*R*,14*R*)-Ethyl 2,3:14,15-Bis(isopropylidenedioxy)-pentadecanoate, 23. A solution of crude **22** (1.79 g) in acetone-dimethoxypropane (1:1, 30 mL) was stirred with TsOH (50 mg) at 60 °C for 1 h. Saturated solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 and chromatographed over silica gel to give the bis-acetonide, **23** (1.72 g, 87% from **11**). $[\alpha]_D$ +2.6° (c = 2.8, $CHCl_3$). ^{1}H NMR: 4.24 (qq, J = 7.2, 2.3 Hz, 2H), 4.14−4.00 (m, 4H), 3.49 (t, J = 7.1 Hz, 1H), 1.80−1.22 (m and br s, 20H), 1.46 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR: 170.97, 110.65, 108.50, 79.18, 79.10, 76.11, 69.48, 61.23, 33.56, 33.49, 29.61, 29.46, 29.41, 27.14, 26.91, 25.72, 25.62, 25.58, 14.17 ppm. IR: 2985.1, 2928.4, 2854.9, 1760.6. HRMS: calcd for $C_{23}H_{43}O_6$ (MH^+) 415.3060, found 415.3075.

(2*R*,3*R*,14*R*)-2,3:14,15-Bis(isopropylidenedioxy)pentadecan-1-ol, **24.** LAH (190 mg, 5 mmol) was added to a solution of **23** (1.16 g, 2.8 mmol) in dry ether (15 mL) at 0 °C. The mixture was stirred at this temperature for 30 min and then refluxed for 1 h and worked-up with ether and water. Purification over silica gel (hexane:ethyl acetate; 9:1) afforded **24** (990 mg, 95%). $[\alpha]_D$ +5.2° (c = 2.52, $CHCl_3$). ^{1}H NMR: 4.07 (m, 1H), 4.03 (t, J = 5.9 Hz, 1H), 3.88 (td, J = 8.2, 4.4 Hz, 1H), 3.80 (ddd, J = 11.9, 5.2, 3.0 Hz, 1H), 3.73 (ddd, J = 7.5, 4.4 3.0 Hz, 1H), 3.60 (ddd, J = 11.9, 7.5, 4.4 Hz, 1H), 3.50 (t, J = 7.2 Hz, 1H), 2.04 (dd, J = 7.3, 5.2 Hz, 1H), 1.70−1.22 (m and br s, 20H), 1.42 (s, 3H), 1.41 (s, 6H), 1.36 (s, 3H) ppm. ^{13}C NMR: 108.52, 81.46, 76.85, 76.14, 69.50, 62.04, 33.56, 33.06, 29.65, 29.62, 29.46, 29.44, 27.36, 27.01, 26.93, 25.95, 25.73 ppm. IR: 3478.8, 2984.9, 2926.7, 2854.9, 1455.6. HRMS: calcd for $C_{21}H_{40}O_5Na$ (MNa^+) 395.2773, found 395.2760.

(3*R*,4*R*,15*R*)-3,4;15,16-Bis(isopropylidenedioxy)hexadec-1-ene, **8 (from 24).** Methyl sulfide (306 mg, 4.94 mmol) was added dropwise to a mixture of NCS (480 mg, 3.6 mmol) in toluene (10 mL) at 0 °C, the mixture was stirred for 10 min and then cooled to −25 °C, and alcohol **24** (893 mg, 2.4 mmol) in toluene (2 mL) was added dropwise. The mixture was stirred at the same temperature for 2 h, triethylamine (0.41 mL) was added dropwise, and the mixture was warmed to rt and worked up with diethyl ether and brine. Solvents were removed under reduced pressure to give a crude aldehyde which was taken to next step without purification.

n-BuLi (2.5 M in hexane, 1.4 mL, 3.5 mmol) was added to a solution of methyltriphenylphosphonium bromide (1.29 g, 3.6 mmol) in dry THF (10 mL) at 0 °C, the mixture was stirred at rt for 0.5 h, cooled to 0 °C and a THF solution of the above mentioned aldehyde was added and stirred at rt for 1 h. Workup with saturated aqueous NH_4Cl and diethyl ether followed by purification over silica gel afforded alkene **8** (514 mg, 58% from **24**). This product was found to be identical by ^{1}H NMR, ^{13}C NMR, IR and HRMS to the above described **8** that has been obtained from **2**.

(3*R*,4*R*,15*R*)-3,4-(Isopropylidenedioxy)hexadec-1-ene-15,16-diol, **25a.** A solution of **8** (1.2 g, 3.3 mmol) in AcOH-H_2O (2:1, 30 mL) was stirred at rt for 1 h. Solvents were removed under reduced pressure, and the residue was filtered through a short bed of silica gel, affording pure diol, **25a** (900 mg, 83%). $[\alpha]_D$ −0.5° (c = 2.48, $CHCl_3$). ^{1}H NMR: 5.80 (ddd, J = 17.2, 10.3, 7.4 Hz, 1H), 5.36 (ddd, J = 17.2, 1.5, 1.0 Hz, 1H), 5.24 (ddd, J = 10.3, 1.6, 0.8 Hz, 1H), 3.98 (dd, J = 8.3, 6.6 Hz, 1H), 3.68 (m, 3H), 3.44 (dd, J = 10.9, 7.6 Hz, 1H), 2.05 (br s, 1H), 1,92 (br s, 1H), 1.55 (m, 2H), 1.50−1.22 (m and br s, 18H), 1.42 (s, 3H), 1.41 (s, 3H) ppm. ^{13}C NMR: 135.51, 118.77, 108.44, 82.74, 80.66, 72.29, 66.76, 33.11, 31.85, 29.67, 29.60, 29.49, 29.43, 27.27, 26.89, 26.01, 25.52. IR: 3387.3, 2984.9, 2922.3, 2853.7, 1645.4. HRMS: calcd for $C_{19}H_{36}O_4Cs$ (MCs^+) 461.1668, found 461.1654.

(3*R*,4*R*,15*R*)-15-Acetoxy-16-bromo-3,4-(isopropylidenedioxy)hexadec-1-ene, 25b. A solution of diol **25a** (900 mg, 2.74 mmol), triethyl orthoacetate (894 mg, 5.48 mmol), and PPTS (5 mg) in CH_2Cl_2 (5 mL) was heated at 45 °C for 1 h. Solvents were removed under vacuum, the residue was redissolved in CH_2Cl_2 and cooled to 0 °C, and bromotrimethylsilane (503 mg, 3.3 mmol) was added. The mixture was stirred at same temperature for 1 h and then at rt for 15 min, solvents were removed under reduced pressure, and the residue was filtered through a short bed of silica gel, affording bromo acetate **25b** (1.0 g, 84%). ^{1}H NMR: 5.78 (ddd, J = 17.2, 10.3, 7.4 Hz, 1H), 5.33 (ddd, J = 17.2, 1.4, 1.0 Hz, 1H), 5.21 (ddd, J = 10.3, 1.5, 0.8 Hz, 1H), 4.96 (m, 1H), 3.95 (dd, J = 8.3, 7.4 Hz, 1H), 3.64 (dt, J = 8.3, 5.7 Hz, 1H), 3.48 (dd, J = 10.8, 4.6 Hz, 1H), 3.40 (dd, J = 10.8, 5.4 Hz, 1H), 2.06 (s, 3H), 1.64 (q, J = 7.2 Hz, 2H), 1.51 (m, 2H), 1.43−1.20 (m and br s, 16H), 1.39 (s, 3H), 1.38 (s, 3H) ppm. ^{13}C NMR: 170.37, 135.54, 118.65, 108.37, 82.71, 80.63, 72.42, 34.20, 32.44, 31.83, 29.64, 29.44, 29.40, 29.34, 29.23, 27.27, 26.88, 26.00, 24.99, 20.99 ppm. IR: 2984.7, 2927.2, 2854.6, 1743.8, 1460.6, 1428.1. HRMS: calcd for $C_{21}H_{37}O_4BrCs$ (MCs^+), 565.0930 (567), found 565.0945.

(3*R*,4*R*,15*S*)-15-Acetoxy-3,4-(isopropylidenedioxy)hexadec-1-ene, **25c.** A solution of tributyltin hydride (1.5 mL, 5.58 mmol) in benzene (2 mL) was added dropwise over 1 h to a solution of **25b** (1.0 g, 2.31 mmol) and AIBN (25 mg) in benzene (10 mL) at reflux temperature. The mixture was refluxed for an additional h, solvents were removed under reduced pressure, and the residue was redissolved in CH_2Cl_2 and treated with saturated aqueous sodium bicarbonate and solid iodine (20 mg). The mixture was extracted with CH_2Cl_2, washed with aqueous sodium thiosulfate, and chromatographed over silica gel (hexane:ethyl acetate, 4:1) to yield **25c** (627 mg, 77%) as colorless oil. ^{1}H NMR: 5.80 (ddd, J = 17.2, 10.2, 7.4 Hz, 1H), 5.36 (ddd, J = 17.2, 2.5, 1.0 Hz, 1H), 5.24 (ddd, J = 10.2, 1.5, 0.7 Hz, 1H), 4.88 (m, 1H), 3.98 (t, J = 7.5 Hz, 1H), 3.67 (dt, J = 8.3, 6.1 Hz, 1H), 2.03 (s, 3H), 1.66−1.22 (m and br s, 20H), 1.42 (s, 3H), 1.41 (s, 3H), 1.20 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR: 170.80, 135.54, 118.73, 108.42, 82.75, 80.70, 71.04, 35.92, 31.85, 29.68, 29.49, 29.43, 27.27, 26.90, 26.03, 25.38, 21.38, 19.94 ppm. IR: 2984.0, 2928.9, 2854.9, 1737.0, 1460.8. HRMS: calcd for $C_{21}H_{39}O_4$ (MH^+) 355.2848, found 355.2860.

(2*R*,3*S*,4*R*,15*S*)-15-Acetoxy-3,4-(isopropylidenedioxy)-hexadecane-1,2-diol, 13. Compound **25c** (587 mg, 1.66 mmol) was added to a solution of AD-mix-α (2.32 g, OsO_4 content 0.5%) and methanesulfonamide (158 mg) in *tert*-butyl alcohol−water (1:1, 33 mL), and the mixture was stirred at 0 °C for 72 h. Workup and purification over silica gel (hexane: ethyl acetate, 3:2) afforded pure **13** (422 mg, 66%) and its (2*S*) epimer (58 mg, 8%). $[\alpha]_D$ +16.7° (c = 3.58, $CHCl_3$). ^{1}H NMR: 4.89 (m, 1H), 3.96 (td, J = 8.0, 3.3 Hz, 1H), 3.82−3.64 (m, 4H), 2.48 (d, J = 5.1 Hz, 1H), 2.12 (t, J = 5.6 Hz, 1H), 2.03 (s, 3H), 1.72−1.22 (m and br s, 20H), 1.40 (s, 3H), 1.38 (s, 3H), 1.20 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR: 171.01, 108.67, 81.04, 79.38, 72.70, 71.16, 63.83, 35.84, 34.14, 29.62, 29.47, 29.44, 29.37, 27.33, 27.02, 26.12, 25.33, 21.37, 19.90 ppm. IR: 3434.1, 2983.2, 2926.2, 1737.0. HRMS: calcd for $C_{21}H_{40}O_6Na$ (MNa^+) 411.2733, found 411.2715.

(2*R*,3*S*,4*R*,15*S*)-15-Acetoxy-1-[(*tert*-butyldimethylsilyl)-oxy]-3,4-(isopropylidenedioxy)-2-[(2′-methoxyethoxy)-methoxy]hexadecane, **26.** A solution of **25c** (422 mg, 1.09 mmol), diisopropylethylamine (1 mL), DMAP (20 mg) and TBDMSCl (181 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was stirred

at rt for 16 h. MEM chloride (0.5 mL) was added, and the mixture was stirred for 24 h. Workup with water and CH_2Cl_2 and filtration over a short bed of silica gel afforded crude **26** (658 mg) which was taken to next step without further purification. ^{1}H NMR: 4.93 (d, J = 6.9 Hz, 1H), 4.88 (m, 1H), 4.79 (d, J = 6.9 Hz, 1H), 4.01 (m, 1H), 3.83 (dd, J = 9.1, 2.6 Hz, 1H), 3.72 (m, 5H), 3.55 (t, J = 4.8 Hz, 2H), 2.02 (s, 3H), 1.70−1.20 (m and br s, 20H), 1.39 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm. ^{13}C NMR: 170.64, 108.36, 95.50, 79.93, 78.49, 78.15, 71.67, 70.94, 67.11, 63.12, 58.96, 35.85, 34.17, 29.70, 29.48, 29.38, 27.33, 26.92, 26.15, 25.81, 25.34, 21.30, 19.89, 18.17, −5.52, −5.56 ppm. IR: 2982.6, 2926.6, 2855.5, 1737.8, 1462.6. HRMS: calcd for $C_{31}H_{62}O_8SiCs$ (MCs^+) 723.3268, found 723.3279.

(2*R*,3*S*,4*R*,15*S*)-15-Acetoxy-3,4-(isopropylidenedioxy)-2-[(2′-methoxyethoxy)methoxy]hexadecan-1-ol, **27.** A solution of tetrabutylammonium fluoride (1 M in THF, 0.9 mL) was added to a solution of **26** (483 mg, 0.82 mmol) in THF (2 mL), and the mixture was stirred at rt for 1 h. Workup with ether and water and filtration over silica gel afforded the MEM ether **27** (337 mg, 88% from **13**). $[\alpha]_D$ +43.8° (c = 2.50, $CHCl_3$). ^{1}H NMR: 4.88 (m, 1H), 4.87 (d, J = 7.3 Hz, 1H), 4.78 (d, J = 7.3 Hz, 1H), 3.86 (td, J = 7.9, 3.3 Hz, 1H), 3.89−3.79 (m, 2H), 3.76−3.60 (m, 4H), 3.57 (dd, J = 4.9, 3.4 Hz, 2H), 3.42 (br s, 1H), 3.39 (s, 3H), 2.03 (s, 3H), 1.68−1.20 (m and br s, 20H), 1.39 (s, 3H), 1.36 (s, 3H), 1.20 (d, J = 6.2 Hz, 3H) ppm. ^{13}C NMR: 170.68, 108.69, 95.91, 82.47, 79.60, 79.31, 71.51, 70.95, 67.54, 62.54, 58.89, 35.82, 34.12, 29.58, 29.45, 29.35, 27.35, 26.95, 26.05, 25.32, 21.30, 19.88 ppm. IR: 3477.2, 2983.1, 2925.9, 2855.0, 1737.3. HRMS: calcd for $C_{25}H_{48}O_8Cs$ (MCs^+) 609.2404, found 609.2400.

(4*R*,5*S*,6*R*,17*S*)-(*E*)-Ethyl-17 Acetoxy-5,6-(isopropylidenedioxy)-4-[(2′-methoxyethoxy)methoxy]octadec-2-enoate, 14. Methyl sulfide (190 mg, 1.42 mmol) was added dropwise to a solution of NCS (142 mg, 1.07 mmol) in toluene (5 mL) at 0 °C, the mixture was stirred for 10 min and cooled to −25 °C, and then alcohol **27** (337 mg, 0.71 mmol) in toluene (2 mL) was added dropwise. The mixture was stirred at same temperature for 2 h, triethylamine (0.12 mL) was added dropwise, the mixture was warmed to rt and worked up with ether and brine, and solvents were removed under reduced pressure to give a crude aldehyde which was taken to next step without purification.

Triethyl phosphonoacetate (450 mg, 2 mmol) was added dropwise to a heterogeneous mixture of NaH (60% in mineral oil, 80 mg, 2 mmol) in dry THF (5 mL) at 0 °C, and the mixture was stirred for 10 min. The above mentioned aldehyde (330 mg) in dry THF (2 mL) was added dropwise, and the mixture was stirred for 20 min at same temperature and then worked-up with ether and saturated aqueous NH_4Cl. Purification over silica gel (hexane-ethyl acetate, 9:1) afforded **14** (291 mg, 75% from **27**). $[\alpha]_D$ −23.9° (c = 2.02, $CHCl_3$). This product was found to be identical by ^{1}H NMR, ^{13}C NMR, IR, and HRMS to an authentic sample of **14** that was obtained from **20** by reduction with tributyltin hydride (vide supra).

5-[(*tert*-Butyldimethylsilyl)oxy]-4-[(2′-methoxyethoxy)-methoxy]-2,3-*O*-isopropylidene-D-arabinose Diethyl Dithioacetal, 30. TBDMSCl (886 mg, 5.87 mmol) was added to a solution of **29**[21] (1.58 g, 5.34 mmol) and DMAP (30 mg) in CH_2Cl_2 and ethyldiisopropylamine (1:1, 10 mL), and the mixture was stirred for 12 h. Upon disappearance of the starting material (by TLC), MEMCl (1.5 mL) was added, the mixture was stirred for additional 24 h and then worked-up with ether and water and purified over silica gel (hexane:ethyl acetate, 19:1) to give **30** in the form of a colorless oil (2.35 g, 88%). $[\alpha]_D$ +28.6° (c = 2.09, $CHCl_3$).^{1}H NMR: 4.95 (d, J = 6.8 Hz, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.40 (dd, J = 7.4, 3.3 Hz, 1H), 4.24 (t, J = 6.4 Hz, 1H), 3.97 (d, J = 3.3 Hz, 1H), 3.91 (dd, J = 10.8, 3.9 Hz, 1H), 3.79 (m, 2H), 3.72 (m, 2H), 3.57 (m, 2H), 3.39 (s, 3H), 2.73 (m, 4H), 1.46 (s, 3H), 1.39 (s, 3H), 1.26 (td, J = 7.6, 5.6 Hz, 6H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm. ^{13}C NMR: 109.97, 95.27, 82.85, 78.49, 78.14, 71.77, 67.35, 63.02, 59.03, 53.63, 27.20, 27.07, 25.86, 25.35, 24.73, 14.39, 14.35, −5.5 ppm. IR: 2928.4, 2883.8, 1379.3, 1252.4. HRMS: calcd for $C_{22}H_{46}O_6S_2SiCs$ (MCs^+) 631.1559, found 631.1531.

(4*R*,5*R*,6*R*)-(*E*)-Ethyl 7-[(*tert*-Butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-6-[(2′-methoxyethoxy)methoxy]-hept-2-enoate, **31.** $HgCl_2$ (2.51 g, 9.24 mmol) and HgO (2.0 g, 9.24 mmol) were added to a solution of thioacetal **30** (2.3 g, 4.62 mmol) in acetonitrile−water (4:1, 20 mL) at rt, the mixture was stirred at 50 °C for 2 h and filtered through Celite, and the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, washed three times with 1 M aqueous KI and with water, and filtered through a short bed of silica gel (hexane:ethyl acetate, 3:1) to give an aldehyde in the form of an oil (1.55 g, 86%). This was taken to the next step without further purification.

Triethyl phosphonoacetate (900 mg, 4 mmol) was added dropwise to a heterogeneous mixture of NaH (60% in oil, 160 mg, 4 mmol) in dry THF (10 mL) at 0 °C ,and the mixture was stirred for 10 min. A solution of above mentioned aldehyde (718 mg, 1.83 mmol) in dry THF (2 mL) was added dropwise, and stirring was continued for 20 min. Saturated aqueous NH_4Cl was added, and the mixture was extracted with ether. Removal of solvents and filtration through silica gel (hexane:ethyl acetate, 9:1) afforded **31** (794 mg, 94%, 81% from **30**). $[\alpha]_D$ +6.4° (c = 6.94, $CHCl_3$). ^{1}H NMR: 6.98 (dd, J = 15.6, 4.8 Hz, 1H), 6.15 (dd, J = 15.6, 1.6 Hz, 1H), 4.92 (d, J = 6.9 Hz, 1H), 4.82 (d, J = 6.9 Hz, 1H), 4.68 (ddd, J = 7.8, 4.8, 1.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.96 (dd, J = 7.8, 5.0 Hz, 1H), 3.85 (q, J = 5.0 Hz, 1H), 3.81−3.70 (m, 4H), 3.55 (m, 2H), 3.39 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR: 166.19, 145.21, 121.71, 110.08, 95.97, 82.62, 79.33, 78.08, 71.47, 67.70, 62.35, 60.47, 58.88, 26.85, 26.60, 25.77, 14.16, −5.20. IR: 2985.2, 2932.6, 1722.3, 1462.0. HRMS: calcd for $C_{22}H_{42}O_8SiCs$ (MCs^+) 595.1703, found 595.1677.

(4*R*,5*R*,6*R*)-(*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)-6-[(2′-methoxyethoxy)methoxy]hept-2-enol, **32.** DIBAL-H (5.2 mL, 1 M in hexane, 5.2 mmol) was added dropwise to a solution of ester **31** (794 mg, 1.72 mmol) in dry THF (10 mL) at −30 °C, the mixture was stirred at the same temperature for 1 h and diluted with ether (10 mL), and saturated aqueous NH_4Cl (2 mL) was added dropwise. Stirring was continued for an additional 1 h, the mixture was filtered through celite and dried over Na_2SO_4, solvents were removed under vacuum, and the residue was filtered through silica gel (hexane:ethyl acetate, 3:1) to give **32** (685 mg, 95%). $[\alpha]_D$ −2.7° (c = 2.46, $CHCl_3$). ^{1}H NMR: 6.01 (dtd, J = 15.5, 5.2, 0.9 Hz, 1H), 5.77 (ddt, J = 15.5, 7.0, 1.6 Hz, 1H), 4.89 (d, J = 6.8 Hz, 1H), 4.82 (d, J = 6.8 Hz, 1H), 4.51 (t, J = 7.4 Hz, 1H), 4.17 (t, J = 4.5 Hz, 2H), 3.91 (dd, J = 8.1, 4.4 Hz, 1H), 3.83 (q, J = 5.6 Hz, 1H), 3.79−3.67 (m, 4H), 3.56 (t, J = 4.8 Hz, 2H), 3.39 (s, 3H), 1.66 (t, J = 5.9 Hz, 1H), 1.41 (s, 6H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm. ^{13}C NMR: 133.42, 128.94, 108.94, 95.64, 80.29, 77.86, 77.20, 71.72, 67.18, 62.82, 59.02, 26.94, 26.85, 25.83, −5.48, −5.54 ppm. HRMS: calcd for $C_{20}H_{40}O_7SiCs$ (MCs^+) 553.1598, found 553.1624.

(5*R*,6*R*,7*R*)-1-Iodo-8-[(*tert*-butyldimethylsilyl)oxy]-5,6-(isopropylidenedioxy)-7-[(2′-methoxyethoxy)methoxy]-octa-1,3-diene, 33. PCC (350 mg, 1.63 mmol) and Celite (350 mg) were added to a solution of alcohol **32** (469 mg) in CH_2Cl_2 (5 mL), and the mixture was stirred for 1 h. Filtration through silica gel (hexane:ethyl acetate, 4:1) afforded the corresponding aldehyde (420 mg) which was taken to the next step without further purification.

CHI_3 (788 mg, 2 mmol) and $CrCl_2$ (740 mg, 6 mmol) were added to a solution of above mentioned aldehyde (420 mg) in dry THF (5 mL) at 0 °C, and the mixture was stirred at same temperature for 2 h. Workup with ether and water and filtration through silica gel (hexane:ethyl acetate, 9:1) afforded **33** (425 mg, 70% from **32**) as a mixture of two geometrical isomers in a ratio of 5:1, which was taken to next step without further purification. ^{1}H NMR: 7.03 and 6.74 (dd, J = 14.4, 10.7 Hz and dd, J = 9.8, 7.6 Hz, together 1H), 6.54 and 6.28 (dd, J = 15.2, 10.0 Hz and dd, J = 15.4, 10.8 Hz, together 1H), 6.38 and 6.33 (d, J = 14.4 Hz and d, J = 7.6 Hz, together 1H), 5.99 and 5.75 (dd, J = 15.4, 7.1 Hz and dd, J = 15.4, 6.6 Hz, together 1H), 4.91 and 4.89 (d, J = 6.9 Hz and d, J = 6.9 Hz, together 1H), 4.82 and 4.80 (d, J = 6.9 Hz and d, J = 6.9 Hz, together 1H), 4.61 and 4.50 (t, J = 7.4 Hz and t, J = 7.6 Hz,

together 1H), 3.98−3.81 (m, 2H), 3.80−3.66 (m, 4H), 3.59−3.54 (m, 2H), 3.40 and 3.39 (s each, together 3H), 1.43, 1.41 and 1.40 (s each, together 6H), 0.89 (s, 9H), 0.06 and 0.05 (s each, together 6H) ppm.

(2*R*,3*S*,4*R*,15*S*)-15-Acetoxy-1-[(*tert*-butyldimethylsilyl)-oxy]-3,4-(isopropylidenedioxy)-2-[(2′-methoxyethoxy)-methoxy]hexadecane, **26.** $Pd(PPh_3)_4$ (90 mg, 0.078 mmol) was added to a mixture of **36** (131 mg, 0.78 mmol), **33** (425 mg, 0.78 mmol), and CuI (31 mg, 0.16 mmol) in triethylamine (2 mL) under argon at 0 °C, and the mixture was stirred at rt for 1 h. Solvents were removed under reduced pressure, and the residue was filtered through a short bed of silica gel (hexane:ethyl acetate, 9:1) to give corresponding coupled product ynediene (356 mg) which was taken to next step without further purification.

A mixture of above mentioned crude ynediene (356 mg) and Rh/Al_2O_3 (5%, 89 mg) in THF (10 mL) was stirred under hydrogen atmosphere (>1 atm) at rt for 24 h. Filtration through Celite, removal of solvents, and filtration through silica gel (hexane:ethyl acetate, 9:1) afforded **26** (316 mg, 69% from **33**). Desilylation of the latter (vide supra) produced alcohol **27** which was found to be identical by $[\alpha]_D$, ^{1}H NMR, ^{13}C NMR, IR, and HRMS to an authentic sample of **27** (vide supra).

(2*S*)-Oct-7-yn-2-ol, **35.** Following the procedure described in ref 22. A mixture of oct-7-yn-2-one, **34** (800 mg, 6.5 mmol), TBADH (5 mg, 200 units), NADP (10 mg, 0.012 mmol), and mercaptoethanol (5 mg) in 2-propanol (10 mL) and aqueous phosphate buffer (50 mM, 40 mL) was stirred at rt for 24 h. The mixture was extracted with CH_2Cl_2, and the organic phase was subjected to column chromatography (silica gel, hexane:ethyl acetate 9:1), affording recovered ketone **34** (100 mg) and alcohol **35** (400 mg, 58%). $[\alpha]_D$ +11.0° (c = 2.62, $CHCl_3$). ^{1}H NMR: 3.76 (m, 1H), 2.17 (m, 2H), 1.92 (t, J = 2.6 Hz, 1H), 1.80 (br, 1H), 1.58−1.35 (m, 6H), 1.16 (d, J = 6.2 Hz, 3H) ppm. ^{13}C NMR: 84.42, 68.31, 67.81, 38.64, 28.36, 24.84, 23.42, 18.31. IR: 3374.4, 3302.1, 2965.4, 2861.9, 2115.9.

(2*S*)-2-Acetoxyoct-7-yne, **36.** A solution of alcohol **35** (400 mg, 3.17 mmol), pyridine (2 mL), and acetic anhydride (1 mL) was stirred at rt for 24 h and then worked-up by addition of ether and washing with 2 N HCl and with brine. Filtration through silica gel (hexane:ethyl acetate; 19:1) afforded acetate **36**. $[\alpha]_D$ +2.5° (c = 2.00, $CHCl_3$). ^{1}H NMR: 4.90 (m, 1H), 2.20 (td, J = 6.8, 2.6 Hz, 2H), 2.03 (s, 3H), 1.95 (t, J = 2.6 Hz, 1H), 1.66−1.34 (m, 6H), 1.21 (d, J = 6.2 Hz, 3H) ppm. ^{13}C NMR: 170.71, 84.18, 70.70, 68.33, 35.26, 28.12, 24.41, 21.30, 19.83, 18.23 ppm. IR: 3297.8, 2977.2, 2940.0, 2359.3, 1735.4.

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **1, 2, 8, 10, 12**−**24**, **25a**−**c**, **26**, **27**, **30**−**33**, **35**, and **36** and ^{13}C NMR spectra of compounds **2, 8, 12**−**24**, **25a**−**c**, **26**, **27**, **30**−**32**, **35**, and **36** (53 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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