A Facile Route to Bulladecin-Type Acetogenins – Total Synthesis of Asimilobin and Correction of the Configuration of Its Tetrahydrofuran Segment

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The most efficient method for the synthesis of the *trans/threo/trans*-bis(tetrahydrofuran) (THF) ring unit was established, and the first total synthesis of (–)-asimilobin and its diastereomer was then accomplished in twelve and fourteen steps, respectively, from *trans*-1,5,9-decatriene, by a convergent route with a Wittig reaction as the key step. By virtue of these synthetic results, the absolute configuration of the bis(THF) unit in naturally occurring asimilobin should be corrected.

Introduction

In the past few years, considerable attention was paid to the rapidly growing class of naturally occurring Annonaceous acetogenins, due to their broad spectrum of biological activities such as cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal, and immunosuppressive effects.[1] This class of polyketide-derived fatty acids was isolated from the *Annonaceae* family of tropical and subtropical trees. They are characterized by the presence of one to three THF rings in the center of a long hydrocarbon chain which has a butenolide moiety at the end. Their potent biological activity as well as their unique and diverse structures make Annonaceous acetogenins attractive targets for synthetic chemists.

Stereocontrolled construction of the THF units played a central role in the reported total syntheses of Annonaceous acetogenins.[2][3] Recently, several reports showed more convenient approaches to various THF units.[4] One of these reports, by Sinha, is on a very effective and useful synthetic method for the stereocontrolled construction of bis- or tris(THF) units by the oxidative cyclization of *trans*,*trans*,*trans*-trienol with $CF_3CO_2ReO_3$.[4h] Because we are interested in the stereocontrolled construction of such THF units, we successfully synthesized all the configurations of mono- and bis(THF) units[5] (Figure 1). One of these THF units was already used in the total synthesis of (+)-rolliniastatin (**1**) by Koert.[6] To explore more efficient routes, in order to establish large chemical libraries of Annonaceous acetogenins for comprehensive biological screening, the total syntheses by routine organic procedures of several other types of such interesting compounds are being carried out in our laboratory.

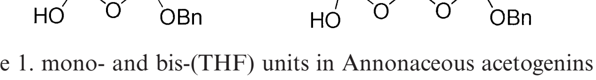
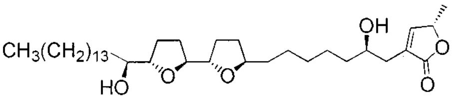


Figure 1. mono- and bis-(THF) units in Annonaceous acetogenins

Our first target compound is asimilobin, a relatively rare bulladecin-type acetogenin.[1b] Asimilobin was isolated by McLaughlin′s group, both from the seeds of *Asimina triloba*[7a] and from the bark of *Goniothalamus giganteus* (Annonaceae),[7b] and showed cytotoxicity values comparable with adriamycin against six human solid-tumor cell lines. The absolute configuration of asimilobin was determined to be **1a** (Figure 2) by spectroscopic analysis.[7a] The striking characteristic of this compound is the adjacent *trans*/*threo*/*trans*-bis(THF) ring core with only one *threo*-flanking hydroxy group at the α-position.



1a

Figure 2. Asimilobin

We have already reported the first total synthesis of (−)-asimilobin (**1a**) and (+)-asimilobin (**1b**), and the correction of the absolute configuration of naturally occurring asimilobin as a preliminary communication.[8] In this paper we will describe the full details of this total synthesis. As shown in Scheme 1, a convergent route to **1a** with a Wittig reaction as a key step was adopted. The two segments **2a** and **3**, can be synthesized from *trans*-1,5,9-decatriene (**5**) and L-glutamic acid, respectively.

Results and Discussion

In our earlier efforts towards the stereocontrolled construction of THF units, we developed a much more efficient synthetic method to the *trans*/*threo*/*trans*-bis(THF) ring building block **4a**, which had been synthesized previously with 80% de in fifteen steps by Wagner and Koert.[9] Compound **4a** could be synthesized according to our method in only two steps, in which metal-catalyzed asymmetric approaches were utilized (Scheme 2). Regioselective oxidation of the starting material **5** by the Sharpless asymmetric dihydroxylation (AD) reaction,[10] installed the two primitive

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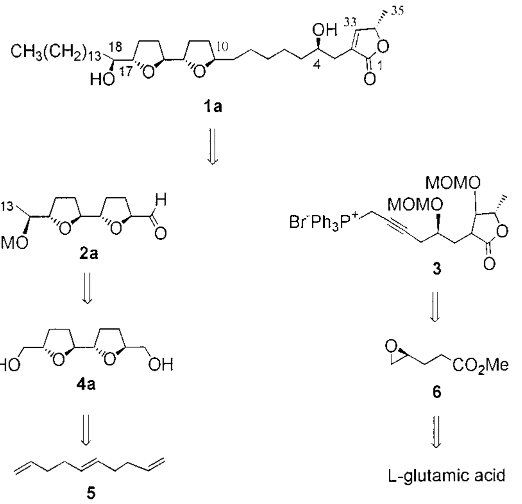
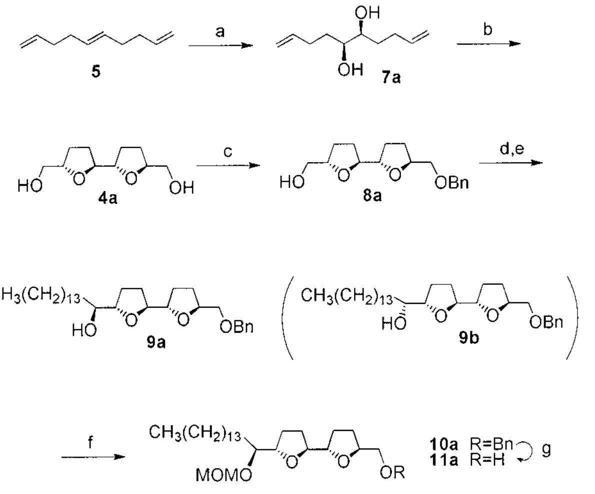


Scheme 1. Retrosynthesis of Asimilobin

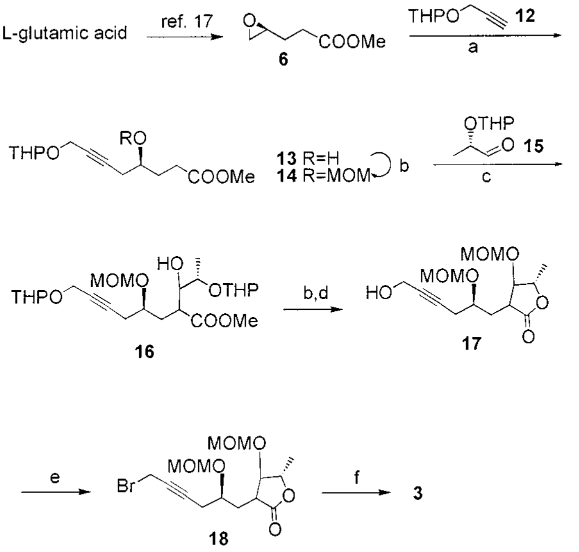
stereogenic centers in more than 94% ee[11] in the bis(THF) ring backbone. The resulting dienediol **7a** was smoothly oxidized and cyclized when Co(modp)$_2$ [bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II)][14] was used as a catalyst under oxygen, and the C_2-symmetric compound **4a**[12] was formed in 96% de,[13] as determined by GC/MS analysis of its dimethyl ether. To the best of our knowledge, this synthetic route is much shorter and more efficient than any other reported in the literature so far.[9]



Scheme 2. Conditions: a) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, *t*BuOH/H_2O (1:1), 0°C; 57%; b) Co(modp)$_2$, TBHP, O_2, *i*PrOH, 78%; c) NaH, BnBr, THF, 71%; d) Swern oxidation; e) $CH_3(CH_2)_{13}MgCl$, CuBr·SMe_2, Et_2O, −78 to 0°C; 49% (two steps); f) MOMCl, *i*Pr_2NEt, CH_2Cl_2; 87%; g) H_2, Pd/C, EtOH, 93%

Diol **4a** was monoprotected as the benzyl ether **8a**. Swern oxidation of the resulting alcohol **8a** gave an aldehyde, which was allowed to react with $CH_3(CH_2)_{13}MgCl$ in the presence of CuBr·SMe_2,[15] to give compound **9a**[16] (**9a** and **9b** were separated by column chromatography, **9a**/**9b** = 7.1:1). Protection of the secondary alcohol **9a** as a methoxymethyl ether, and subsequent removal of the benzyl group by catalytic hydrogenation over Pd/C, led to the bis(THF) ring segment **11a**.

The preparation of the other segment **3** is shown in Scheme 3. Epoxide **6**[17] was opened by lithium alkynylide, prepared from compound **12** in the presence of BF_3·OEt_2, and the resulting alcohol **13** was treated with MOMCl/*i*Pr_2NEt to give compound **14**. Aldol condensation of the enolate prepared from ester **14** with the aldehyde **15**[18] produced adduct **16** (mixture of diastereomers). Protection of the newly generated hydroxy group in compound **16** as a methoxymethyl ether and subsequent treatment with a 1:3 mixture of 9% aqueous H_2SO_4 and THF[18] afforded lactone **17**. Bromination of the propargyl alcohol **17** gave compound **18**, which was then treated with PPh_3 to afford the Wittig salt **3**.

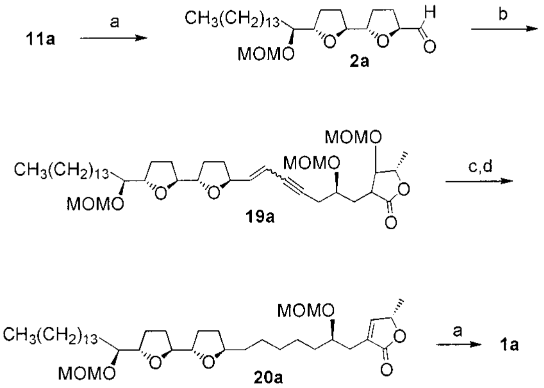


Scheme 3. Conditions: a) **12**, BuLi, THF, −78°C, then BF_3·OEt_2, then **6**, 83%; b) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 86%; c) LDA, THF, −78°C, then **15**, 80%; d) 9% H_2SO_4, THF, 65% (two steps); e) PPh_3, CBr_4, CH_2Cl_2, 89%; f) PPh_3, PhH, 87%

The coupling reaction between aldehyde **2a**, newly prepared from alcohol **11a**, and the ylide prepared from Wittig salt **3** in situ gave enyne **19a**[19] (Scheme 4). Compound **19a** was hydrogenated in the presence of Pd/C and then treated with DBU[18] to afford compound **20a**. Deprotection of **20a** with BF_3·OEt_2 gave the title compound **1a**. Thus, the total synthesis of **1a** was accomplished in twelve steps and in a total yield of 2.0% from *trans*-1,5,9-decatriene (**5**). This, to the best of our knowledge, is the shortest synthetic route for the total synthesis of naturally occurring Annonaceous acetogenins with one or two THF rings.[2][3]

The spectral data of the obtained target compound, (−)-asimilobin (**1a**), are consistent with those of naturally occurring asimilobin reported in the literature.[7] However, the specific rotation is discrepant: our synthetic sample of **1a**: $[\alpha]_D^{20} = -11.4$ (c = 0.70, $CHCl_3$), $[\alpha]_D^{20} = -11.9$ (c = 0.43, CH_2Cl_2); naturally occurring asimilobin: ref.[7a] $[\alpha]_D = +6.0$ (c = 0.05, $CHCl_3$); ref.[7b] $[\alpha]_D = +11.3$ (c = 1.00, CH_2Cl_2).

We are certain that the stereochemistry of our synthetic sample is that of (−)-asimilobin (**1a**), because the absolute



Scheme 4. Conditions: a) Swern oxidation; b) **3**, *t*BuOK, THF, −78 to 0°C, 32% (two steps); c) Pd/C, H_2, EtOH; d) DBU, THF, 56% (two steps); e) BF_3·OEt_2, DMS, 79%

configuration of dienediol **7a** was confirmed by an alternative preparation,[11] and both the stereogenic centers in the butenolide segment came from enantiomerically pure natural products. The consistency of the spectral data, and the large discrepancy in specific rotation suggest that the two compounds are enantiomers or diastereomers. The fact that the relative configurations of the two stereogenic regions [THF ring segment (C10−C18) and butenolide segment (C-4 and C-34)] in naturally occurring asimilobin are the same as those of our synthetic sample, and the fact that there is no interference in the ^1H and ^{13}C NMR spectral data between the two stereogenic regions (since they are separated by a five-carbon chain), allows us to conclude that only three isomers (**1b−d**, Figure 3) could have the same spectral data as those of compound **1a**. Only one of them, however, corresponds to the structure of naturally occurring asimilobin. Considering that the butenolides in Annonaceous acetogenins usually have the (4*R*,34*S*) configuration, which was further unambiguously confirmed by synthetic models,[7a] the THF ring segment of the naturally occurring asimilobin is more likely to have the absolute configuration opposite to that of compound **1a**. The more probable structure of naturally occurring asimilobin is therefore **1b**. To confirm this and to examine the feasibility of utilizing this route to synthesize the other diastereomers of compound **1a**, we carried out the total synthesis of compound **1b**.

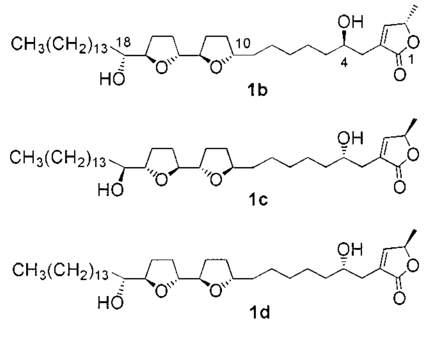
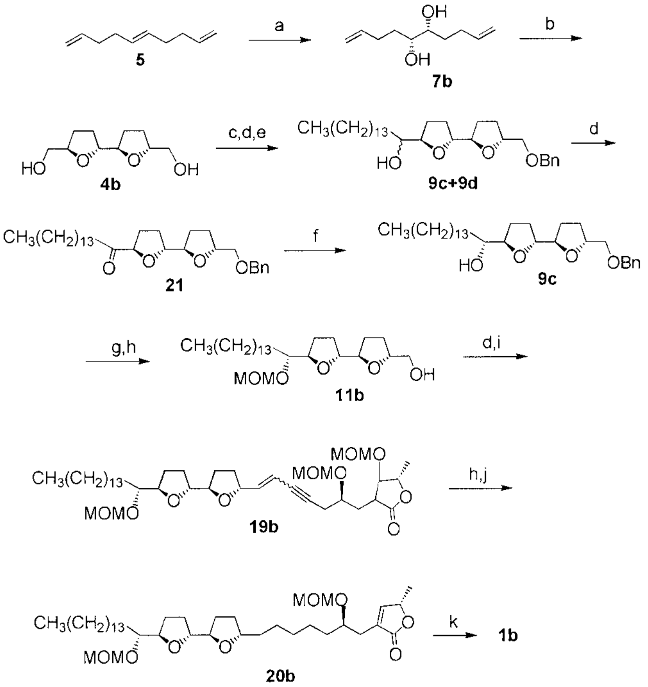


Figure 3. Possible structures of Asimilobin

The synthetic route to compound **1b** (Scheme 5) is similar to that of compound **1a**, but has two distinct differences. Firstly, we used the chiral ligand $(DHQD)_2$PHAL instead of $(DHQ)_2$PHAL to introduce the first two stereogenic centers by Sharpless AD reaction. Secondly, to improve the selectivity in the construction of C-18 stereogenic center, we selected to reduce ketone **21** with L-Selectride, to afford alcohol **9c** with much higher stereoselectivity (17:1). The total synthesis of **1b** was then accomplished in fourteen steps and in a total yield of 1.7% from *trans*-1,5,9-decatriene (**5**).



Scheme 5. Conditions: a) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $(DHQD)_2$PHAL, $K_2OsO_2(OH)_4$, *t*BuOH/H_2O (1:1), 0°C, 59%; b) $Co(modp)_2$, TBHP, O_2, *i*PrOH, 80%; c) NaH, BnBr, THF, 64%; d) Swern oxidation; e) $CH_3(CH_2)_{13}MgCl$, THF, −78 to 0°C, 72% (two steps); f) L-Selectride, THF, −78°C, 68% (two steps); g) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 83%; h) H_2, Pd/C, EtOH, 91%: i) **3**, *t*BuOK, THF, −78 to 0°C, 28% (two steps); j) DBU, THF, 63% (two steps); k) BF_3·OEt_2, DMS, 76%

We found that the obtained synthetic sample of (+)-asimilobin (**1b**)[20] {$[\alpha]_D^{24}$ = +6.4 (*c* = 0.36, $CHCl_3$); $[\alpha]_D^{24}$ = +7.0 (*c* = 0.10, CH_2Cl_2)},[8] had the same spectral data as those of compound **1a**, and a specific rotation which was very close to the specific rotation reported in the literature.[7a] It is well known that the optical rotation is dependent on solvent and concentration. We therefore carefully measured the specific rotation of **1b** again in the same concentration of chloroform and dichloromethane {$[\alpha]_D^{24}$ = +6.7 (*c* = 0.05, $CHCl_3$); $[\alpha]_D^{24}$ = +7.9 (*c* = 1.0, CH_2Cl_2)}. We are therefore convinced that the absolute configuration of the bis(THF) ring segment of naturally occurring asimilobin is opposite to that reported in the literature. Its correct absolute configuration should be that of **1b**.

Conclusion

We have developed: (i) an efficient synthetic method for the stereocontrolled construction of adjacent *trans*/*threo*/*trans*-bis(THF) ring units, (ii) a short and convenient route to couple this key intermediate with other building blocks, and (iii) the first total synthesis of (−)-asimilobin and (+)-asimilobin in twelve and fourteen steps, respectively, from the achiral starting materials **5**. To study the relationship between structure and biological activity, the syntheses of asimilobin analogs are in progress.

Experimental Section

General: Optical rotations were determined in solutions of either $CHCl_3$ or CH_2Cl_2, at room temperature, and with a Perkin−Elmer-241 MC digital polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. − ^{1}H NMR and ^{13}C NMR spectra were determined on solutions in $CDCl_3$, with tetramethylsilane (TMS) as internal standard, at 300 MHz and 75 MHz, respectively, with a Bruker AMX-300 spectrometer. − IR spectra were determined on neat samples, or on solutions in $CHCl_3$, with a Perkin−Elmer 983 spectrometer. − Mass spectra were recorded with an HP-5989 instrument. High-mass spectra were recorded with a Finnigan MA+ instrument. − Microanalyses were performed with a Carlo−Erba 1106 analyzer. − Organic solvents were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. − All reactions were monitored by TLC with Huanghai 60F$_{254}$ silica-gel-coated plates. − Flash column chromatography was carried out with 300−400-mesh silica gel.

(5*S*,6*S*)-1,9-Decadiene-5,6-diol (7a): To a well-stirred solution of $(DHQ)_2PHAL$ (1.09 g, 1.40 mmol), $K_2OsO_2(OH)_4$ (309 mg, 0.840 mmol), $K_3Fe(CN)_6$ (139 g, 421 mmol), K_2CO_3 (58.1 g, 421 mmol), and $MeSO_2NH_2$ (13.3 g, 140 mmol) in *t*BuOH/H_2O (1:1) (1400 mL) at 0°C was added triene **5** (19.1 g, 140 mmol). After stirring vigorously for 12 h, the reaction was quenched with Na_2SO_3 (140 g) and extracted with EtOAc. The organic layers were dried with $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether, 1:10) to give **7a** (13.6 g, 57%) as a colorless oil. − $[\alpha]_D^{20} = -21.3$ (c = 3.30, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.48−1.68 (m, 4 H), 2.10−2.39 (m, 4 H), 2.37 (br, s, 2 H), 3.42−3.53 (m, 2 H), 4.98 (dm, J = 10.0 Hz, 2 H), 5.04 (dm, J = 17.3 Hz, 2 H), 5.83 (ddt, J = 17.3, 10.0, 6.6 Hz, 2 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.87, 32.56, 73.82, 114.91, 138.23. − EI-MS; *m*/*z* (%):171 [MH$^+$] (14.5), 153 (100), 135 (50.0), 85 (14.3). − IR (neat) ṽ = 3402, 1639 cm^{-1}. − HRMS: calcd. for $C_{10}H_{18}O_2$ 170.1307; found 170.1309.

(2*S*,5*S*,6*S*,9*S*)-2,5;6,9-Diepoxydecane-1,10-diol (4a): To a solution of **7a** (1.70 g, 10.0 mmol) in *i*PrOH (250 mL) were added Co(modp)$_2$ (2.16 g, 4.00 mmol) and *t*BuOOH (1.80 g, 20.0 mmol); the reaction mixture was heated at 60°C under pure oxygen for 3 h, before it was cooled to room temperature. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added to the reaction mixture and the resulting solution was stirred for a further 10 min. *i*PrOH was evaporated under reduced pressure. The residue was extracted with EtOAc. The organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/petroleum ether, 1:10) to give **4a** (1.57 g 78%) as a colorless oil. − $[\alpha]_D^{18} = +18.5$ (c = 0.80, $CHCl_3$) {ref.[9]: $[\alpha]_D^{20} = +12.5$ (c = 0.80, $CHCl_3$)}. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.52−1.68 (m, 2 H), 1.70−1.85 (m, 2 H), 1.91−2.05 (m, 4 H), 2.49 (br, s, 2 H), 3.50 (dd, J = 11.8, 5.3 Hz, 2 H), 3.71 (dd, J = 11.8, 2.6 Hz, 2 H), 3.85−3.95 (m, 2 H), 4.10−4.21 (m, 2 H). − EI-MS; *m*/*z*: 171, 153, 101. − $C_{10}H_{18}O_4$ (202.2): calcd. C 59.39, H 8.97; found: C 59.32, H 8.94.

(2*S*,5*S*,6*S*,9*S*)-1-Benzyloxy-2,5;6,9-diepoxy-1-decanol (8a): To a solution of diol **4a** (1.01 g, 5.00 mmol) in dry THF (50 mL) at 0°C was added NaH (120 mg, 5.00 mmol); the reaction mixture was stirred for 1 h, then a solution of benzyl bromide (855 mg, 0.596 mL, 5.00 mmol) in THF (2 mL) was added dropwise over 10 min. After stirring for 8 h, the solvent was removed under reduced pressure. To the obtained residue was added water and EtOAc. After separation, the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether, 2:3) to give **8a** (1.03 g, 71%) as a colorless oil. − $[\alpha]_D^{20} = -6.3$ (c = 1.00, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.55−1.81 (m, 4 H), 1.91−2.10 (m, 4 H), 3.46−3.57 (m, 3 H), 3.70 (dd, J = 11.7, 3.2 Hz, 1 H), 3.86−3.96 (m, 2 H), 4.09−4.17 (m, 1 H), 4.18−4.26 (m, 1 H), 4.56 (s, 2 H), 7.25−7.39 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 27.47, 28.44, 28.70, 28.79, 64.64, 72.79, 73.39, 78.48, 79.95, 82.20, 82.21, 127.62, 127.68, 128.36, 138.45. − EI-MS; *m*/*z* (%): 293 [MH$^+$] (11.0), 261 (3.21), 201 (26.6). − IR (neat): ṽ = 3426, 1601, 1495 cm^{-1}. − HRMS: calcd. for $C_{17}H_{24}O_4$ 292.1675; found 292.1678.

(2*S*,5*S*,6*S*,9*S*,10*S*)-1-Benzyloxy-2,5;6,9-diepoxy-10-tetracosanol (9a): To a solution of oxalyl chloride (125 mg, 0.086 mL, 0.98 mmol) in dry CH_2Cl_2 (10 mL) at −78°C under nitrogen was added DMSO (153 mg, 0.140 mL, 1.96 mmol) as a solution in CH_2Cl_2 (1 mL). After stirring for 10 min, a solution of **8a** (181 mg, 0.620 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred for 2 h. Triethylamine (0.50 mL) was then added and the mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine and dried with $MgSO_4$. After concentration under reduced pressure, the crude aldehyde was obtained. Freshly prepared $CH_3(CH_2)_{13}MgCl$ (0.20 M, 9.3 mL, 1.86 mmol) in ether was added to a solution of $CuBr{\cdot}SMe_2$ (382 mg, 1.86 mmol) in SMe_2 (4 mL) at −40°C under nitrogen. After stirring for 15 min, the reaction mixture was cooled to −78°C and added to a solution of the above-mentioned aldehyde in ether (2 mL). The reaction mixture was stirred for 1 h and allowed to warm to room temperature. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether. The organic layers were washed with saturated brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:15) to give **9a** (149 mg, 49%) and **9b** (21 mg, 6.9%), both as colorless oils. − **9a:** $[\alpha]_D^{13} = -11.4$ (c = 2.42, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.15−1.36 (m, 24 H), 1.36−1.45 (m, 2 H), 1.58−1.80 (m, 4 H), 1.90−2.11 (m, 4 H), 2.51 (br, s, 1 H), 3.34−3.43 (m, 1 H), 3.47 (dd, J = 10.0, 4.9 Hz, 1 H), 3.53 (dd, J = 10.0, 5.2 Hz, 1 H), 3.80−3.98 (m, 3 H), 4.19−4.24 (m, 1 H), 4.57 (s, 2 H), 7.27−7.39 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.19, 22.75, 25.72, 28.42, 28.50, 28.80, 28.91, 29.42, 29.73, 31.98, 33.49, 72.80, 73.37, 74.12, 78.57, 81.96, 81.97, 83.12, 127.57, 127.70, 128.37, 138.45. − EI-MS; *m*/*z* (%): 489 [MH$^+$] (2.44), 471 (11.0), 397 (9.03), 381 (18.8). − IR (neat): ṽ = 3466, 1495, 1466 cm^{-1}. − $C_{31}H_{52}O_4$ (488.7): calcd. C 76.18, H 10.72; found C 75.79, H 10.91. − **9b:** $[\alpha]_D^{13} = -9.8$ (c = 2.50, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.15−1.45 (m, 26 H), 1.58−1.67 (m, 2 H), 1.68−1.86 (m, 2 H), 1.86−2.11 (m, 4 H), 2.21 (br, s, 1 H), 3.48 (dd, *J* = 10.0, 5.1 Hz, 1 H), 3.55 (dd, *J* = 10.0, 4.9 Hz, 1 H), 3.85−3.96 (m, 4 H), 4.17−4.26 (m, 1 H), 4.56 (s, 2 H), 7.27−7.39 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.19, 22.75, 24.54, 26.11, 28.41, 28.85, 29.42, 29.62, 31.98, 32.46, 71.24, 72.77, 73.40, 78.49, 82.45, 82.63, 82.64, 127.57, 127.70, 128.37, 138.45. − EI-MS; *m/z* (%): 489 [MH^+] (3.19), 487 (2.19), 471 (16.6), 397 (14.0), 381 (30.0). − IR (neat): ṽ = 3466, 1495, 1466 cm^{-1}. − HRMS: calcd. for $C_{31}H_{52}O_4$ 488.3866; found 488.3879.

(2*S*,5*S*,6*S*,9*S*,10*S*)-1-Benzyloxy-2,5;6,9-diepoxy-10-(methoxymethoxy)tetracosane (10a): Ethyldiisopropylamine (221 mg, 0.300 mL, 1.71 mmol) was added to a solution of **9a** (355 mg, 0.686 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C, followed by the addition of chloromethyl methyl ether (110 mg, 0.100 mL, 1.37 mmol). The reaction mixture was stirred at room temperature for 1 d and was then quenched with water and extracted with CH_2Cl_2. The organic layers were washed with saturated brine and dried with $MgSO_4$. After concentration, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:20) to give **10a** (328 mg, 90%) as a colorless oil. − $[\alpha]_D^{13}$ = −25.0 (*c* = 1.17, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.20−1.35 (m, 24 H), 1.35−1.54 (m, 2 H), 1.61−1.81 (m, 4 H), 1.87−2.07 (m, 4 H), 3.39 (s, 3 H), 3.45 (dd, *J* = 10.0, 4.9 Hz, 1 H), 3.51 (dd, *J* = 10.0, 5.2 Hz, 1 H), 3.44−3.53 (m, 1 H), 3.88−3.99 (m, 2 H), 4.00−4.07 (m, 1 H), 4.18−4.23 (m, 1 H), 4.56 (s, 2 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 4.81 (d, *J* = 6.8 Hz, 1 H), 7.27−7.39 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.17, 22.76, 25.77, 28.28, 28.85, 29.43, 29.74, 29.91, 31.10, 32.00, 55.77, 72.98, 73.37, 78.53, 79.73, 81.63, 81.63, 81.71, 96.84, 127.55, 127.71, 128.38, 138.61. − EI-MS; *m/z* (%): 531 [M^+ − H] (5.42), 501 (25.8), 471 (46.7), 455 (37.4). − IR (neat): ṽ = 1495, 1466 cm^{-1}. − $C_{33}H_{56}O_5$ (532.8): calcd. C 74.39, H 10.59; found C 74.32, H 10.94.

(2*S*,5*S*,6*S*,9*S*,10*S*)-2,5;6,9-Diepoxy-10-(methoxymethoxy)-1-tetracosanol (11a): To a solution of **10a** (176 mg, 0.331 mmol) in EtOH (5 mL) was added 10% Pd/C (30 mg); the mixture was hydrogenated under 1 atm pressure at 40 °C for 10 h. After filtration and concentration, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:3) to give **11a** (136 mg, 93%) as a colorless oil. − $[\alpha]_D^{14}$ = −11.9 (*c* = 2.35, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.20−1.35 (m, 24 H), 1.35−1.54 (m, 2 H), 1.61−1.82 (m, 4 H), 1.87−2.08 (m, 4 H), 3.40 (s, 3 H), 3.43−3.57 (m, 2 H), 3.63−3.74 (m, 1 H), 3.88−3.98 (m, 2 H), 4.00−4.10 (m, 1 H), 4.10−4.25 (m, 1 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 4.81 (d, *J* = 6.8 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.18, 22.76, 25.77, 27.54, 28.12, 28.53, 28.78, 29.44, 29.74, 31.05, 32.01, 55.79, 64.84, 79.78, 79.98, 81.84, 81.85, 96.90, period − EI-MS; *m/z* (%): 411 (12.5), 381 (26.0), 365 (10.4), 309 (16.9). − IR(neat): ṽ = 3426 cm^{-1}. − $C_{26}H_{50}O_5$ (442.7): calcd. C 70.54, H 11.38; found C 70.40, H 11.50.

Methyl (4*S*)-4-Hydroxy-8-*O*-(tetrahydropyran-2-yl)-6-octynoate (13): To a solution of **12** (6.72 g, 48.0 mmol) in dry THF (95 mL) was added a solution of *n*BuLi (2.5 M in hexane, 19.2 mL, 48.0 mmol) at −78 °C under nitrogen. The mixture was stirred for 20 min and BF_3·OEt_2 (6.0 mL, 48.0 mmol) was added. After stirring for a further 15 min, a solution of epoxide **6** (5.21 g, 40.0 mmol) in THF (20 mL) was added dropwise. The reaction mixture was stirred for 30 min and quenched with aqueous ammonium chloride solution. After warming to room temperature, the mixture was extracted with EtOAc. The organic layers were washed with saturated brine and dried with $MgSO_4$. After concentration, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:10), to give **13** (8.94 g, 83%) as a colorless oil. − $[\alpha]_D^{20}$ = −5.4 (*c* = 1.25, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.49−1.69 (m, 3 H), 1.69−1.97 (m, 5 H), 2.35−2.59 (m, 4 H), 3.48−3.58 (m, 1 H), 3.67 (s, 3 H), 3.68−3.89 (m, 2 H), 4.17−4.34 (m, 2 H), 4.79 (t, *J* = 3.1 Hz, 1 H), period − EI-MS; *m/z* (%): 271 [MH^+] (1.0), 253 (0.3), 239 (1. 8), 201 (0.2). − IR (neat): ṽ = 3440, 2232, 1734 cm^{-1}. − HRMS: calcd. for $C_{13}H_{18}O_4$ [M − CH_3OH] 238.1205; found 238.1192.

Methyl (4*S*)-4-(Methoxymethoxy)-8-*O*-(tetrahydropyran-2-yl)-6-octynoate (14): This compound was prepared by the same procedure as that used for the preparation of **10a**. Ether **14** was obtained as a colorless oil (8.94 g, 86%). − $[\alpha]_D^{20}$ = −33.6 (*c* = 1.92, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.49−1.64 (m, 4 H), 1.64−2.08 (m, 4 H), 2.37−2.55 (m, 4 H), 3.37 (s, 3 H), 3.48−3.56 (m, 1 H), 3.66 (s, 3 H), 3.65−3.74 (m, 1 H), 3.76−3.87 (m, 1 H), 4.15−4.31 (m, 2 H), 4.62 (d, *J* = 7.0 Hz, 1 H), 4.69 (d, *J* = 7.0 Hz, 1 H), 4.78 (t, *J* = 3.2 Hz, 1 H), period − EI-MS; *m/z* (%): 315 [MH^+], 283 (0.6), 253 (0.7), 231 (7.4). − IR (neat): ṽ = 2239, 1736 cm^{-1}. − HRMS: calcd. for $C_{16}H_{26}O_6$ 314.1729; found 314.1762.

Methyl (2*RS*,4*S*)-2-{[(1*RS*,2*S*)-1-Hydroxy-2-*O*-(tetrahydropyran-2-yl)]propyl}-4-(methoxymethoxy)-8-*O*-(tetrahydropyran-2-yl)-6-octynoate (16): To a solution of diisopropylamine (1.28 g, 1.77 mL, 12.7 mmol) in dry THF (40 mL) was added a solution of *n*BuLi (2.5 M, 4.25 mL, 10.6 mmol) at −78 °C under nitrogen. The mixture was stirred for 15 min and a solution of **14** (2.78 g, 8.85 mmol) in THF (5 mL) was added. After stirring for 30 min, a solution of newly prepared aldehyde **15** (1.67 g, 10.6 mmol) in THF (5 mL) was added to the reaction solution. The reaction mixture was stirred for 30 min and quenched with aqueous ammonium chloride solution. After warming to room temperature, the mixture was extracted with EtOAc. The organic layer was washed with saturated brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:5) to give **16** (3.36 g, 80%) as a colorless oil. − $[\alpha]_D^{20}$ = −3.2 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.25 (d, *J* = 6.4 Hz, 3 H), 1.49−1.64 (m, 8 H), 1.64−1.87 (m, 4 H), 1.98−2.11 (m, 1 H), 2.13−2.28 (m, 1 H), 2.49−2.58 (m, 2 H), 2.88−2.97 (m, 1 H), 3.38 (s, 3 H), 3.48−3.56 (m, 2 H), 3.68 (s, 3 H), 3.65−3.74 (m, 2 H), 3.75−3.97 (m, 3 H), 4.15−4.31 (m, 2 H), 4.60−4.70 (m, 3 H), 4.80−4.85 (m, 1 H). − EI-MS: *m/z* 389 (3.4), 357 (5.4), 305 (1.5), 273 (4.5). − IR (neat): ṽ = 3462, 2223, 1734 cm^{-1}. − $C_{24}H_{40}O_9$ (472.6): calcd. C 61.00, H 8.53; found C 61.12, H 8.61.

(3*RS*,4*RS*,5*S*)-3-[(2*S*)-6-Hydroxy-2-(methoxymethoxy)-4-hexynyl]-4-(methoxymethoxy)-5-methyldihydrofuran-2(3*H*,4*H*,5*H*)-one (17): The newly generated hydroxy group in **16** (3.24 g, 6.86 mmol) was protected by an MOM ether, in a similar manner to that used for the preparation of **10a**. The obtained product was dissolved in THF (50 mL), and 9% sulfuric acid (18 mL) was added. The reaction mixture was stirred at room temperature for 16 h and extracted with EtOAc. The organic layer was washed with saturated brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:3) to give **17** (1.42 g, 65%) as a colorless oil. − $[\alpha]_D^{20}$ = −32.5 (*c* = 1.10, $CHCl_3$). − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.48 (d, *J* = 6.4 Hz, 3 H), 1.83−2.08 (m, 1 H), 2.20−2.33 (m, 1 H), 2.55−2.60 (m, 2 H), 2.85−2.92 (m, 1 H), 3.38 (s, 3 H), 3.41 (s, 3 H), 3.88−4.00 (m, 2 H), 4.20−4.28 (m, 2 H), 4.30−4.35 (m, 1 H), 4.65−4.78 (m, 4 H). − EI-MS: *m/z* 255 (0.43), 247 (5.92), 217 (4.57). − IR (neat): ṽ = 3434, 2225, 1772 cm^{-1}. − HRMS: calcd. for $C_{11}H_{19}O_6$ [M − $CH_2C{\equiv}CCH_2OH$] 247.1182; found 247.1180. − $C_{15}H_{24}O_7$ (316.4): calcd. C 56.95, H 7.65; found C 56.72, H 7.56.

(3*RS*,4*RS*,5*S*)-3-[(2*S*)-6-Bromo-2-(methoxymethoxy)-4-hexynyl]-4-(methoxymethoxy)-5-methyldihydrofuran-2(3*H*,4*H*,5*H*)-one (18): To a solution of **17** (432 mg, 1.37 mmol) in dry CH_2Cl_2 (5 mL) was added CBr_4 (684 mg, 2.06 mmol) and PPh_3 (431 mg, 1.64 mmol) at 0°C. After being stirred for 5 min, the mixture was purified by flash chromatography (EtOAc/petroleum ether, 1:6) to give **18** (461 mg, 89%) as a colorless oil. − $[\alpha]_D^{20} = -41.9$ (c = 0.80, $CHCl_3$). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.48 (d, J = 6.4 Hz, 3 H), 1.86−2.03 (m, less than 1 H), 2.18−2.27 (m, more than 1 H), 2.59−2.65 (m, 2 H), 2.85−2.92 (m, 1 H), 3.38 (s, 3 H), 3.41 (s, 3 H), 3.85−3.98 (m, 2 H), 3.92 (t, J = 1.2 Hz, 2 H), 4.33−4.40 (m, 1 H), 4.66−4.76 (m, 4 H). − EI-MS; m/z (%): 379 [MH^+] (0.872), 348 (0.94), 346 (0.93), 247 (4.02), 217 (3.81). − IR (neat): $\tilde{\nu}$ = 2233, 1771 cm^{-1}. − HRMS: calcd. for $C_{11}H_{19}O_6$ [$M - CH_2C{\equiv}CCH_2Br$]: 247.1182; found 247.1167.

Preparation of Phosphonium Salt 3: To a solution of **18** (276 mg, 0.728 mmol) in dry benzene (2 mL) was added PPh_3 (197 mg, 0.750 mmol) and the reaction mixture was stirred at room temperature for 14 h, ether (30 mL) was then added to the reaction mixture which was then stirred for 5 min. The precipitate was isolated by filtration and dried in vacuum to give **3** as a yellowish powder.

(3*RS*,4*RS*,5*S*)-3-[(2*S*,8*S*,11*S*,12*S*,15*S*,16*S*)-8,11;12,15-Diepoxy-2,16-bis(methoxymethoxy)tricosa-4-yn-6-enyl]-4-(methoxymethoxy)-5-methyldihydrofuran-2(3*H*,4*H*,5H)-one (19a): The above-mentioned salt **3** was added to dry THF (8 mL) and cooled to −78°C under argon. After adding *t*BuOK (72 mg, 0.64 mmol), the mixture was allowed to warm to −50°C, stirred for 15 min, and then cooled again to −78°C. Freshly prepared aldehyde **2a** [from **11a** (111 mg, 0.25 mmol) by Swern oxidation] was added as a solution in THF (1 mL), and the reaction mixture was further stirred for another 1 h. After warming to room temperature, the reaction was quenched with water and extracted with EtOAc. The organic layer was washed with saturated brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:3) to give **19a** (57 mg, 32%) as a colorless oil. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.20−1.36 (m, 24 H), 1.36−1.54 (m, 2 H), 1.48 (d, J = 6.4 Hz, 3 H), 1.58−1.80 (m, 3 H), 1.88−2.07 (m, 5 H), 2.16−2.27 (m, 2 H), 2.61−2.70 (m, 2 H), 2.86−2.94 (m, 1 H), 3.37−3.45 (m, 9 H), 3.48−3.57 (m, 1 H), 3.86−3.99 (m, 4 H), 4.00−4.10 (m, 1 H), 4.31−4.40 (m, 1 H), 4.67−4.78 (m, 5 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.88−4.98 (m, 1 H), 5.45−5.53 (m, 1 H), 5.84−5.96 (m, 1 H). − EI-MS; m/z (%): 723 [MH^+] (2.17), 691 (4.12), 661 (3.43), 646 (6.72), 631 (7.31), 616 (8.12). − IR (neat): $\tilde{\nu}$ = 1774 cm^{-1}. − $C_{41}H_{70}O_{10}$ (723.0): calcd. C 68.11, H 9.76; found C 68.07, H 9.50.

(5*S*)-3-[(2*R*,8*R*,11*S*,12*S*,15*S*,16*S*)-8,11;12,15-Diepoxy-2,16-bis(methoxymethoxy)tricosyl]-5-methylfuran-2(5*H*)-one (20a): To a solution of **19a** (41 mg, 0.057 mmol) in EtOH (2 mL) was added 10% Pd/C (10 mg); the reaction mixture was stirred under 1 atm pressure of hydrogen at room temperature for 7 h. After filtration and concentration, the residue was dissolved in THF (5 mL), and DBU (50 mg) was added. The reaction mixture was stirred overnight at room temperature. After removal of the solvent, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:3) to give **20a** (21 mg, 56%) as a colorless oil. − $[\alpha]_D^{20} = -24.1$ (c = 1.00, $CHCl_3$). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.9 Hz, 3 H), 1.20−1.36 (m, 30 H), 1.36−1.54 (m, 8 H), 1.43 (d, J = 7.0 Hz, 3 H), 1.58−1.75 (m, 3 H), 1.90−2.07 (m, 3 H), 2.51 (d, J = 5.8 Hz, 2 H), 3.35−3.42 (m, 6 H), 3.47−3.56 (m, 1 H), 3.75−3.97 (m, 4 H), 3.98−4.07 (m, 1 H), 4.67−4.78 (m, 3 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.98−5.08 (m, 1 H), 7.18−7.21 (m, 1 H). − EI-MS; m/z: 591, 531, 449. − IR (neat): $\tilde{\nu}$ = 1757 cm^{-1}. − for $C_{39}H_{70}O_8$ (667.0): calcd. C 70.23, H 10.58; found C 70.34, H 10.35.

(−)-Asimilobin (1a): To a solution of **20a** (16 mg, 0.024 mmol) in SMe_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (0.20 mL) at 0°C. The reaction mixture was stirred at room temperature for 30 min, quenched with water, and extracted with EtOAc. The organic layer was washed with saturated brine and dried with $MgSO_4$. After concentration under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:1) to give **1** (11 mg, 79%) as a white waxy solid. − $[\alpha]_D^{20} = -11.4$ (c = 0.70, $CHCl_3$); $[\alpha]_D^{20} = -11.9$ (c = 0.43, CH_2Cl_2); ref.[7a]: $[\alpha]_D = +6.0$ (c = 0.05, $CHCl_3$); ref.[7b]: $[\alpha]_D = +11.3$ (c = 1.00, CH_2Cl_2). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 7.0 Hz, 3 H), 1.20−1.36 (m, 30 H), 1.36−1.54 (m, 6 H), 1.43 (d, J = 7.0 Hz, 3 H), 1.54−1.72 (m, 5 H), 1.89−2.06 (m, 3 H), 2.34−2.45 (m, 1 H), 2.53 (dm, J = 15.0 Hz, 1 H), 3.34−3.44 (m, 1 H), 3.76−3.90 (m, 4 H), 3.90−3.98 (m, 1 H), 5.06 (q, J = 7.0 Hz, 1 H), 7.18−7.21 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.19, 19.16, 22.77, 25.56, 25.63, 25.69, 25.75, 26.11, 28.49, 28.79, 28.83, 28.99, 29.43, 29.53, 29.76, 32.01, 32.14, 33.46, 33.57, 35.74, 37.39, 69.97, 74.25, 78.04, 79.98, 81.33, 82.12, 83.20, 131.20, 151.90, 174.65. − EI-MS; m/z (%): 579 [MH^+] (14.4), 561 [M − OH] (15.7), 543 (19.7), 527 (13.1), 525 (13.9). − IR ($CHCl_3$): $\tilde{\nu}$ = 3422, 1747 cm^{-1}. − UV: λ_{max} = 209 nm (EtOH); ref.[7b]: λ_{max} = 209 nm (EtOH). − HRMS: calcd. for $C_{35}H_{62}O_6$ 578.4546; found 578.4502. − $C_{35}H_{62}O_6$ (578.9): calcd. C 72.62, H 10.80; found C 72.47, H 10.54.

(5*R*,6*R*)-1,9-Decadiene-5,6-diol (7b): The procedure was the same as that used for the preparation of **7a**, except that chiral ligand $(DHQD)_2PHAL$ was added instead of $(DHQ)_2PHAL$. To a well-stirred solution of $(DHQD)_2PHAL$ (218 mg, 0.28 mmol), $K_2OsO_2(OH)_4$ (62 mg, 0.17 mmol), $K_3Fe(CN)_6$ (27.7 g, 83.90 mmol), K_2CO_3 (11.6 g, 84.1 mmol), and $MeSO_2NH_2$ (2.66 g, 28.0 mmol) in tBuOH/H_2O (1:1) (280 mL) at 0°C was added triene **5** (3.82 g, 28.10 mmol). After being stirred vigorously for 12 h, the reaction was quenched with Na_2SO_3 (60 g) and extracted with EtOAc. The organic layers were dried with $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether, 1:10) to give **7b** (2.82 g, 59%) as a colorless oil. − $[\alpha]_D^{20} = +22.0$ (c = 4.00, $CHCl_3$). − The spectral data are the same as those of **7a**.

(2*R*,5*R*,6*R*,9*R*)-2,5;6,9-Diepoxydecane-1,10-diol (4b): This compound was synthesized from **7b** by the same procedure as that used for the preparation of **4a**. − $[\alpha]_D^{20} = -20.1$ (c = 1.20, $CHCl_3$). − The spectral data are the same as those of **4a**.

Diastereomers 9c and 9d: These were synthesized from **4b** by a procedure similar to that used for the preparation of **9a** and **9b**, except that $CuBr{\cdot}SMe_2$ was not added during the Grignard reaction step. To a solution of oxalyl chloride (61 mg, 0.042 mL, 0.48 mmol) in dry CH_2Cl_2 (5 mL) at −78°C under nitrogen was added DMSO (75 mg, 0.067 mL, 0.96 mmol) as a solution in CH_2Cl_2 (1 mL). After being stirred for 10 min, a solution of the monobenzyl ether of **4b** (70 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred for 2 h. Triethylamine (1.0 mL) was then added and the mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine and dried with $MgSO_4$. After being concentrated under reduced pressure, the crude aldehyde was obtained. Freshly prepared $CH_3(CH_2)_{13}MgCl$ (0.48 M, 2.0 mL, 0.96 mmol) in ether was cooled to −78°C under nitrogen and the solution was added to a solution of the above-mentioned aldehyde in THF (2 mL). The reaction mixture was stirred for 1 h and allowed to warm to room temperature. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether. The organic layers were washed with saturated brine and dried with $MgSO_4$. After being concentrated under reduced pressure, the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:15), which gave **9c** and **9d** as a colorless oil. They were immediately used for the next reaction.

(2*R*,5*R*,6*R*,9*R*,10*R*)-1-Benzyloxy-2,5;6,9-diepoxy-10-tetracosanol (9c): A pair of diastereomers (**9c** + **9d**) (484 mg, 0.992 mmol) was oxidized by the Swern method to give ketone **21**. To a solution of **21** in THF (5 mL) was slowly added a solution of L-Selectride (1.0 M, 2.0 mL, 2.0 mmol) at −78 °C under argon. After the reaction mixture was stirred for 1 h, MeOH (2 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and it was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether, 1:15) to give **9c** (328 mg, 68%) and **9d** (19 mg, 4%), both as colorless oils. − **9c:** $[\alpha]_D^{20} = +14.7$ ($c = 2.10$, $CHCl_3$). − Its spectral data are the same as those of **9a**.

(2*R*,5*R*,6*R*,9*R*,10*R*)-2,5;6,9-Diepoxy-10-(methoxymethoxy)-1-tetracosanol (11b): This compound was synthesized from **9c** according to the same procedure as that used for the preparation of **11a**. − $[\alpha]_D^{20} = +12.8$ ($c = 2.40$, $CHCl_3$). − Its spectral data are the same as those of **11a**.

(3*RS*,4*RS*,5*S*)-3-[(2*S*,8*R*,11*R*,12*R*,15*R*,16*R*)-8,11;12,15-Diepoxy-2,16-bis(methoxymethoxy)tricosa-4-yn-6-enyl]-4-(methoxymethoxy)-5-methyldihydrofuran-2(3*H*,4*H*,5*H*)-one (19b): The procedure used was the same as that used for the preparation of **19a**. − ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, $J = 6.9$ Hz, 3 H), 1.20−1.36 (m, 24 H), 1.36−1.54 (m, 2 H), 1.48 (d, $J = 6.4$ Hz, 3 H), 1.58−1.80 (m, 3 H), 1.88−2.07 (m, 5 H), 2.16−2.27 (m, 2 H), 2.61−2.70 (m, 2 H), 2.86−2.94 (m, 1 H), 3.37−3.45 (m, 9 H), 3.48−3.57 (m, 1 H), 3.86−3.99 (m, 4 H), 4.00−4.10 (m, 1 H), 4.31−4.40 (m, 1 H), 4.67−4.78 (m, 5 H), 4.82 (d, $J = 6.9$ Hz, 1 H), 4.88−4.98 (m, 1 H), 5.45−5.53 (m, 1 H), 5.84−5.96 (m, 1 H). − EI-MS; *m/z*: 723 [MH^+]. − IR (neat): $\tilde{\nu} = 1774\ cm^{-1}$. − $C_{41}H_{70}O_{10}$ (723.0): calcd. C 68.11, H 9.76; found C 68.32, H 9.61.

(5*S*)-3-[(2*R*,8*S*,11*R*,12*R*,15*R*,16*R*)-8,11;12,15-Diepoxy-2,16-bis(methoxymethoxy)tricosyl]-5-methylfuran-2(5*H*)-one (20b): The procedure was the same as that used for the preparation of **20a**. − $[\alpha]_D^{26} = +2.7$ ($c = 0.55$, $CHCl_3$). − ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, $J = 6.9$ Hz, 3 H), 1.20−1.36 (m, 30 H), 1.36−1.54 (m, 8 H), 1.43 (d, $J = 7.0$ Hz, 3 H), 1.58−1.75 (m, 3 H), 1.90−2.07 (m, 3 H), 2.51 (d, $J = 5.8$ Hz, 2 H), 3.35−3.42 (m, 6 H), 3.47−3.56 (m, 1 H), 3.75−3.97 (m, 4 H), 3.98−4.07 (m, 1 H), 4.67−4.78 (m, 3 H), 4.82 (d, $J = 6.9$ Hz, 1 H), 4.98−5.08 (m, 1 H), 7.18−7.21 (m, 1 H). − EI-MS; *m/z*: 591, 531, 449. − IR (neat): $\tilde{\nu} = 1757\ cm^{-1}$. − $C_{39}H_{70}O_8$ (667.0): calcd. C 70.23, H 10.58; found C 70.42, H 10.68.

(+)-Asimilobin (1b): The procedure was the same as that used for the preparation of **1a**. − $[\alpha]_D^{24} = +6.4$ ($c = 0.36$, $CHCl_3$); $[\alpha]_D^{24} = +7.0$ ($c = 0.10$, CH_2Cl_2); $[\alpha]_D^{24} = +6.7$ ($c = 0.05$, $CHCl_3$); $[\alpha]_D^{24} = +7.9$ ($c = 1.0$, CH_2Cl_2). − ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3 H), 1.20−1.36 (m, 30 H), 1.36−1.54 (m, 6 H), 1.43 (d, $J = 7.0$ Hz, 3 H), 1.54−1.72 (m, 5 H), 1.89−2.06 (m, 3 H), 2.34−2.45 (m, 1 H), 2.53 (dm, $J = 15.0$ Hz, 1 H), 3.34−3.44 (m, 1 H), 3.76−3.90 (m, 4 H), 3.90−3.98 (m, 1 H), 5.06 (q, $J = 7.0$ Hz, 1 H), 7.18−7.21 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 300 MHz): $\delta = 14.19$, 19.20, 22.77, 25.56, 25.64, 25.69, 25.76, 26.12, 28.49, 28.78, 28.82, 28.98, 29.44, 29.53, 29.77, 32.01, 32.15, 33.48, 33.60, 35.75, 37.41, 69.98, 74.25, 78.03, 79.98, 81.31, 82.13, 83.20, 131.27, 151.87, 174.65. − FABMS; *m/z*: 602 [MH + Na], 600 [MNa − H], 580 [M + 2 H], 578 [M^+], 560 [M − H_2O], 544 [M − H − Na], 528. − IR ($CHCl_3$): $\tilde{\nu} = 3430$, $1750\ cm^{-1}$. − HRMS: calcd. for $C_{35}H_{62}O_6$ 578.4546; found 578.4528. − $C_{35}H_{62}O_6$ (578.9): calcd. C 72.62, H 10.80; found C 72.38, H 10.64.

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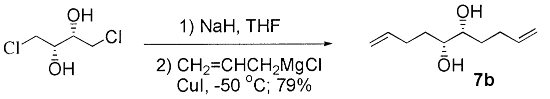


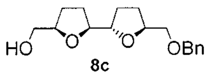
7b

ee: 94%

$[\alpha]_D^{16}$ +20.2 (c 4.13, $CHCl_3$)

[12] The ^{1}H NMR spectral data and the sign of optical rotation of compound **4a** are the same as those reported in the literature (see ref.[9]).

[13] The ^{1}H and ^{13}C NMR spectra of compound **8a**, the monobenzyl ether of diol **4a**, were compared to those of all its possible diastereomers, **8c**, **8d**,[5] and **8e** (U. Koert, M. Stein, H. Wagner, *Liebigs Ann*. **1995**, 1415–1426), and no other diastereomer was detected. **8c:** ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.69–1.85 (m, 3 H), 1.85–1.97 (m, 3 H), 1.97–2.10 (m, 2 H), 3.46–3.57 (m, 3 H), 3.77 (dd, J = 11.7, 2.8 Hz, 1 H), 3.86–3.94 (m, 1 H), 3.95–4.03 (m, 1 H), 4.08–4.16 (m, 1 H), 4.19–4.28 (m, 1 H), 4.56 (s, 2 H), 7.25–7.39 (m, 5 H). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 27.35, 28.79, 28.79, 28.80, 65.68, 72.57, 73.38, 78.76, 80.16, 81.67, 81.98, 127.67, 127.67, 128.39, 138.42. – **8d:** ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.55–1.77 (m, 3 H), 1.77–1.90 (m, 2 H), 1.90–2.04 (m, 3 H), 3.42–3.57 (m, 3 H), 3.68 (dd, J = 11.7, 3.1 Hz, 1 H), 3.78–3.87 (m, 1 H), 3.88–3.98 (m, 1 H), 4.06–4.22 (m, 2 H), 4.56 (s, 2 H), 7.25–7.39 (m, 5 H). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 27.50, 27.69, 28.33, 28.89, 64.66, 72.81, 73.39, 78.60, 80.05, 82.13, 82.66, 127.70, 127.71, 128.39, 138.47. – **8e:** ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.73–1.84 (m, 3 H), 1.84–2.02 (m, 5 H), 3.41–3.56 (m, 3 H), 3.74 (dd, J = 11.7, 2.8 Hz, 1 H), 3.84–3.96 (m, 2 H), 4.05–4.18 (m, 2 H), 4.56 (s, 2 H), 7.25–7.39 (m, 5 H). – ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 27.32, 27.97, 28.18, 28.70, 65.43, 72.50, 73.36, 78.48, 80.06, 81.59, 81.89, 127.60, 127.77, 128.38, 138.24.



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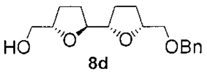

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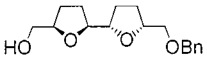

8e

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[20] The ee of **7b** (over 94%) and the de of **4b** (over 95%) were confirmed by the same methods as used before.[11][13]

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