DOI: 10.1002/ejoc.200500850

First Total Synthesis of Longimicin D

Hiroaki Tominaga,[a] Naoyoshi Maezaki,*[a] Minori Yanai,[a] Naoto Kojima,[a] Daisuke Urabe,[a] Risa Ueki,[a] and Tetsuaki Tanaka*[a]

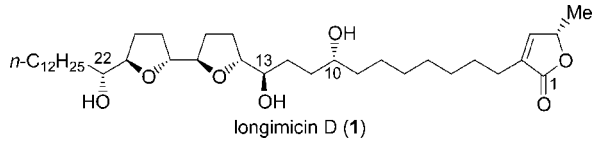
Keywords: Annonaceous acetogenins / Natural products / Total synthesis / Longimicin D

We have accomplished the first total synthesis of longimicin D (**1**), which displays potent cytotoxicity against human pancreatic carcinoma cells. The bis-THF core bearing congested stereocenters was constructed by our methodology for synthesis of poly-THF cores, which consists of asymmetric alkynylation with the C4 unit and stereodivergent THF ring formation. Although we had planned to join the C9–C34 bis-THF core segment **2** and the C1–C8 γ-lactone segment **3**, a model study revealed that the coupling was difficult. We resolved the problem by applying asymmetric alkynylation of bis-THF aldehyde **24** with functionalized alkyne **19** respresenting the polymethylene chain from the C3 to C12 position.

Introduction

Annonaceous acetogenins are polyketides containing one to three tetrahydrofuran (THF) ring(s) with various stereochemistries in the middle of a long hydrocarbon chain and a butenolide moiety at the end. More than 400 acetogenins have been isolated from nature so far.[1] They have attracted considerable attention, due to their various biological activities (antitumor, pesticidal, antimalarial, immunosuppressive, and antifeedant). Furthermore, it is known that some acetogenins inhibit multidrug-resistant cancer cells.[1] Their mode of action was suggested to be based on inhibitory activity against complex I (NADH-ubiquinone oxidoreductase) in the mammalian and insect mitochondrial electron transport system, and NADH oxidase, which is specifically active in the plasma membranes of tumors and is inactive in normal cells. Many workers are engaged in syntheses of members of the acetogenin family, due to their attractive biological activities.[2,3]

Longimicin D (**1**) is a structural isomer of asimicin, isolated by McLaughlin and co-workers from leaves and twigs of *Asimina longifolia* K. (*Annonaceae*) in 1996 (Scheme 1).[4] Longimicin D has a bis-THF ring moiety flanked by two hydroxy groups (*threo*/*trans*/*threo*/*trans*/*threo*-type) and also possesses an (*R*)-hydroxy group at the C10 position. Longimicin D exhibited selective cytotoxic activities against human lung carcinoma (A-549), human prostate adenocarcinoma (PC-3), and human pancreatic carcinoma (PaCa-2), with potency from 10^3 to 10^5 times that of adriamycin. There is no total synthesis of longimicin D, in spite of its high cytotoxicity. In a previous paper we have reported a systematic and stereoselective construction of the THF ring moiety for acetogenins, and a library of mono- and bis-THF ring moieties was synthesized by applying the methodology.[5] On the basis of the preliminary study, we next focused on a synthesis of longimicin D (**1**).



Scheme 1. Structure of longimicin D.

Here we describe the first total synthesis of longimicin D, with asymmetric alkynylation of an aldehyde neighboring a bis-THF core with a functionalized alkyne as a key step.

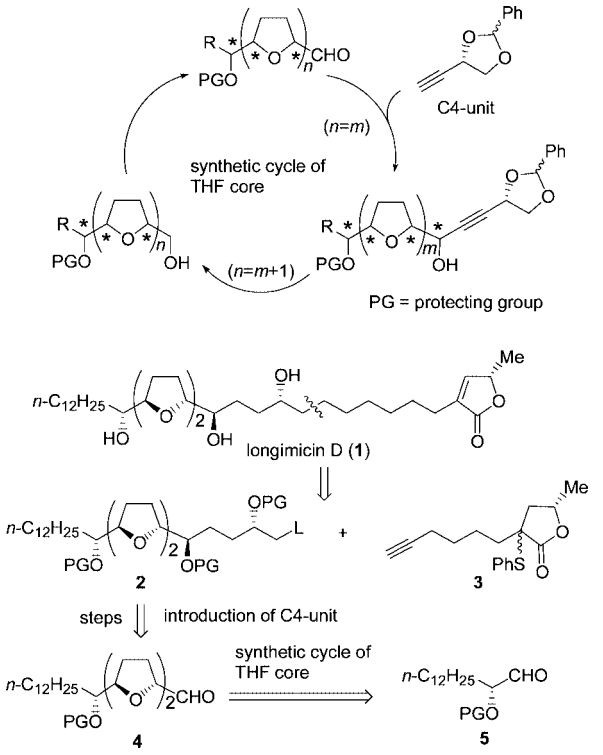
Results and Discussion

We planned to synthesize longimicin D (**1**) by applying a reiterative process based on asymmetric alkynylation of an α-oxyaldehyde with the C4 unit followed by stereodivergent THF ring formation as shown in Scheme 2.[5]

The reiterative process is advantageous in terms of economics (same reagents/solvents used) and technical effectiveness. In addition, since our methodology is stereodivergent in each step, a synthetic route for one stereoisomer will also apply to other stereoisomers.

We noted the presence of three latent C4 units in the C9–C20 THF core of the target molecule, and employed a synthetic route involving a triple introduction of the C4 unit for synthesis of the THF core. Longimicin D was thus disconnected into the THF core segment **2** and the γ-lactone

[a] Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan
Fax: +81-6-6879-8214
E-mail: maezaki@phs.osaka-u.ac.jp
t-tanaka@phs.osaka-u.ac.jp

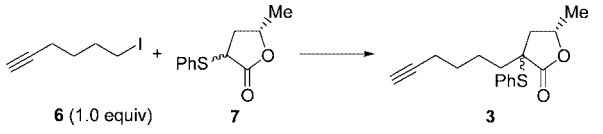


Scheme 2. Synthetic cycle for poly-THF cores and retrosynthetic analysis of longimicin D.

segment **3**. The segments **2** were to be synthesized from the previously reported bis-THF aldehyde **4**.[5a,5c]

The γ-lactone segment **3** was synthesized by alkylation of γ-lactone **7**[6] with alkyl iodide **6**, bearing a terminal alkyne.[7] The results are summarized in Table 1. Segment **3** was obtained in 48% yield when KHMDS was employed as a base (Entry 1), whilst addition of HMPA caused a decrease in the yield (Entries 2 and 3). Finally, we found that use of LDA at low temperature dramatically improved the yield (Entry 4), with the adduct **3** being obtained almost quantitatively.

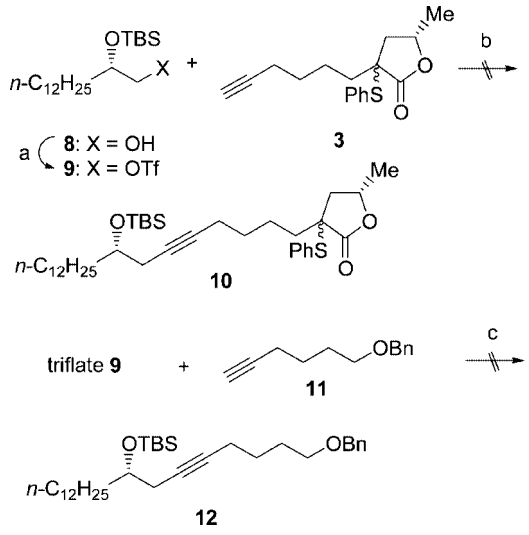
Table 1. Alkylation of γ-lactone **7** with **6**.



Entry	Conditions[a]	Yield (%)
1	A	48
2	B	23
3	C	32
4	D	97

[a] Conditions (values in parenthesis are equivalents of reagents.) A: **7** (1.0), KHMDS (1.0), 0 °C to room temp. B: **7** (1.0), KHMDS (1.0), HMPA (1.0), 0 °C to room temp. C: **7** (1.0), KHMDS (1.0), HMPA (5.0), 0 °C to room temp. D: **7** (1.1), LDA (1.1), HMPA (6.0), –78 to 0 °C.

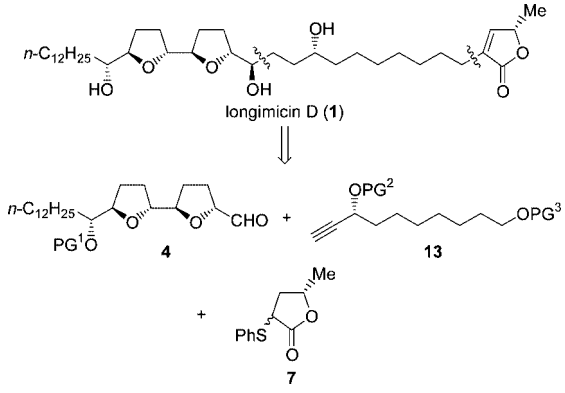
With the γ-lactone segment **3** to hand, we conducted a model study for the coupling reaction between the THF ring segment **2** and the triflate **9**, prepared from alcohol **8**.[5b] However, the reaction did not proceed and segment **3** decomposed under the reaction conditions (Scheme 3).



Scheme 3. Alkynylation of **9** with **3** or **11**: a) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, quant., b) *n*-BuLi, THF, –78 °C, c) *n*-BuLi, HMPA, THF, –78 °C to room temp.

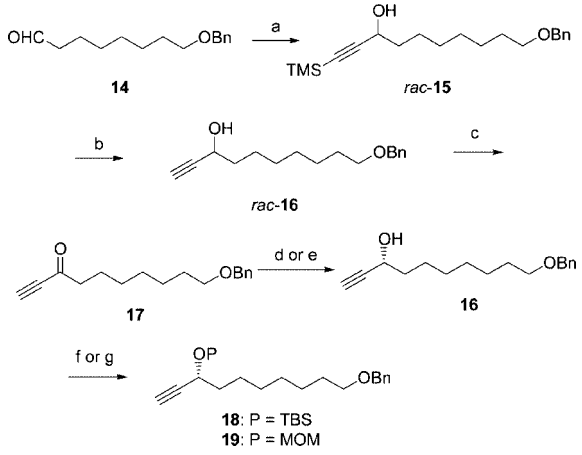
We assumed that the instability of **3** was a consequence of the labile γ-lactone, and so alkynylation of the triflate **9** with alkyne **11**, without the γ-lactone moiety,[8] was investigated, but again no reaction took place. Attempts involving the replacement of the alkylating agent with 2-(*tert*-butyldimethylsilyloxy)-1-iodotetradecane and 1,2-epoxytetradecane also failed.

Since all attempts to connect the polymethylene chain at the C9 position had been fruitless, we decided to try a new synthetic route, in which the polymethylene chain would be introduced by asymmetric alkynylation of the aldehyde **4** with alkyne **13** and the adduct coupled with the γ-lactone segment **7** (Scheme 4). This route is attractive, since the whole polymethylene chain might be introduced into the bis-THF core accompanied by stereocontrol over the C13 stereogenic center. At the same time, the route involved some risk of making the reaction sluggish, since alkynes with bulky substituents regularly show poor reactivity in Carreira's asymmetric alkynylation.[9]



Scheme 4. Alternate retrosynthetic analysis of longimicin D.

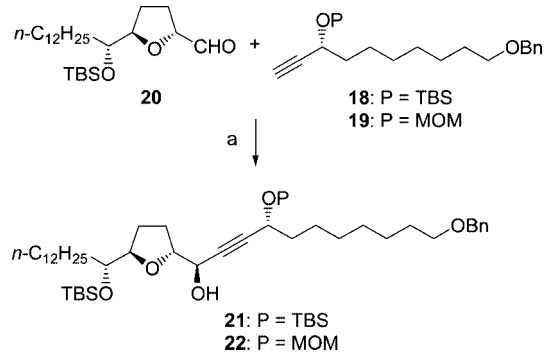
The synthesis of the alkynes **18** and **19** is depicted in Scheme 5. An attempted asymmetric alkynylation of 8-benzyloxyoctanal (**14**)[10] with (trimethylsilyl)acetylene under the conditions modified by Rein's group[3l] provided the alcohol **15** in moderate yield, albeit with unsatisfactory enantiomeric excess (*ee*) (58% yield and 89% *ee*). Alternatively, we examined asymmetric reduction of the ynone **17**, prepared by oxidation of racemic propargyl alcohol *rac*-**16** with Dess–Martin periodinane. Reduction with (*R*)-Me-CBS-oxazaborolidine[11] furnished (*R*)-alcohol **16** in 56% yield but with only 84% *ee*.[12] On the other hand, reduction with (*R*)-Alpine-Borane®[13] gave **16** in 60% yield and with 97% *ee*. The absolute configuration of **16** was confirmed as the desired (*R*) arrangement by the modified Mosher method.[14] Protection of the alcohol with *tert*-butyldimethylsilyl and methoxymethyl groups afforded alkynes **18** and **19** in 94 and 96% yields, respectively.



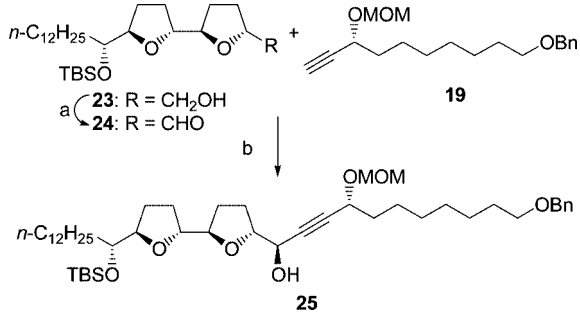
Scheme 5. Preparation of alkynes **18** and **19**: a) (trimethylsilyl)acetylene, *n*-BuLi, THF, –78 °C to room temp., b) K_2CO_3, MeOH, 0 °C to room temp., 93% in two steps, c) Dess–Martin periodinane, CH_2Cl_2, 0 °C to room temp., 98%, d) (*R*)-Me-CBS-oxazaborolidine, $BH_3{\cdot}SMe_2$, THF, 0 °C, 56%, 84% *ee*, e) (*R*)-Alpine-Borane®, room temp., 60%, 97% *ee*, f) TBSCl, imidazole, DMF, 0 °C to room temp., 94%, g) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 0 °C to room temp., 96%.

In order to evaluate which of the two alkynes, **18** or **19**, was more appropriate for asymmetric alkynylation of the α-tetrahydrofurancarbaldehyde, we conducted asymmetric alkynylations of mono-THF aldehyde **20**[5b] with alkynes **18** or **19** in a model study (Scheme 6), and found that the alkyne **19**, bearing a small MOM group, was better than the TBS-protected alkyne **18**, with high steric demand. Whilst no product was obtained from **18**, the alkyne **19** afforded adduct **22** in good yield and with excellent stereoselectivity.[15]

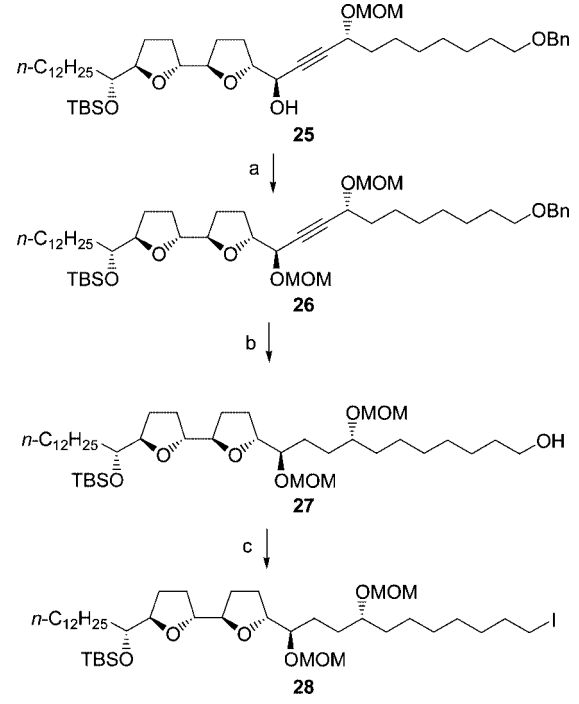
On the basis of this model study, the asymmetric alkynylation of bis-THF aldehyde **24** with the alkyne **19** was carried out (Scheme 7). The bis-THF alcohol **23** prepared by our reiterative THF ring formation[5a] was oxidized by DMSO oxidation with SO_3·pyridine to give aldehyde **24** in 90% yield. Introduction of the alkyne **19** into the bis-THF core **24** proceeded successfully, exclusively giving the desired propargyl alcohol **25** in 65% yield.[16]



Scheme 6. Asymmetric alkynylation of alkynes **18** and **19**: a) $Zn(OTf)_2$, Et_3N, (1*R*,2*S*)-(–)-*N*-methylephedrine, toluene, room temp., **21** (0%), **22** (89%, β-OH/α-OH > 97:3).



Scheme 7. Asymmetric alkynylation of aldehyde **24** with alkyne **19**: a) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C to room temp., 90%, b) $Zn(OTf)_2$, Et_3N, (1*R*,2*S*)-(–)-*N*-methylephedrine, toluene, room temp., 65%, β-OH/α-OH > 97:3.

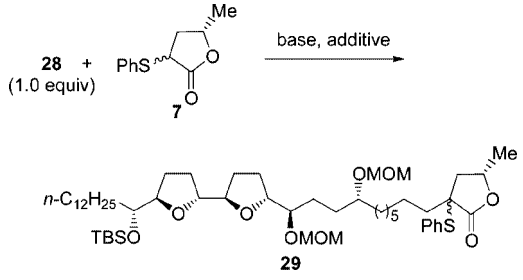


Scheme 8. Preparation of bis-THF ring segment **28**: a) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 0 °C to room temp., 94%, b) H_2, 10% Pd/C, EtOAc, room temp., 73%, c) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to room temp., 82%.

After MOM protection of the secondary alcohol **25** in 94% yield, the resulting compound **26** was hydrogenated on 10% Pd/C to give alcohol **27** in 73% yield. The alcohol **27** was converted into iodide **28** in 82% yield (Scheme 8).

The coupling of the bis-THF core **28** and the γ-lactone **7** is summarized in Table 2. When a small excess of the base was used, very little of the coupling product **29** was obtained and 85% of the iodide **28** was recovered (Entry 1). Although addition of 1.1 equivalents of HMPA slightly improved the yield (Entry 2), the yield of **29** was not increased by further additional HMPA (Entry 3). Eventually we obtained **29** in 76% yield by use of two equivalents of **7**, LDA, and HMPA (Entry 4).

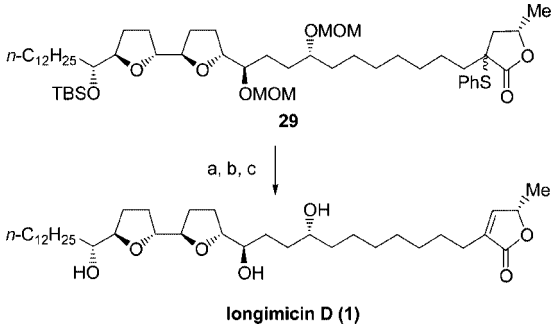
Table 2. Coupling reaction between iodide **28** and γ-lactone **7**.



Entry	Conditions[a]	Yield (%)	
		29	**28**
1	A	trace	85
2	B	31	64
3	C	38	45
4	D	76	19

[a] Conditions (values in parenthesis are equivalents of reagents). A: **7** (1.1), LDA (1.1). B: **7** (1.1), LDA (1.1), HMPA (1.1). C: **7** (1.1), LDA (1.1), HMPA (6.0). D: **7** (2.0), LDA (2.0), HMPA (2.0).

The total synthesis of longimicin D (**1**) (Scheme 9) was accomplished from **29** by subsequent reactions – (1) oxidation of the sulfide, (2) thermolytic elimination of the sulfoxide, and (3) global deprotection with acidic MeOH – to give **1** in excellent yield.



Scheme 9. Synthesis of longimicin D: a) *m*-CPBA, CH_2Cl_2, 0 °C, b) toluene, reflux, c) AcCl, MeOH, CH_2Cl_2, room temp., 71% in three steps.

The spectroscopic and physical data of synthetic **1** (^{1}H NMR, ^{13}C NMR, IR, MS) were in good agreement with those reported, while the specific rotation of synthetic **1** {$[\alpha]_D^{25}$ = +23.2 (*c* = 0.48 in EtOH)} was higher than that reported in the literature {$[\alpha]_D$ = +14 (*c* = 0.1 in EtOH)}.[3,17]

Conclusion

We have accomplished the first total synthesis of longimicin D by employing our systematic synthesis of the poly-THF core of annonaceous acetogenins, with asymmetric alkynylation of the bis-THF aldehyde bearing congested stereogenic centers with a functionalized alkyne as a key step.

Experimental Section

Optical rotations were measured with a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-GX-500 spectrometer (500 MHz). ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a JEOL JNM-AL300 spectrometer (75 MHz). All signals are expressed as δ values in ppm downfield from the internal standard (tetramethylsilane). The following abbreviations are used: broad = br., singlet = s, doublet = d, triplet = t, quadruplet = q, quintet = qn, sextet = sext, and multiplet = m. IR absorption spectra (FT = diffuse reflectance spectroscopy) were recorded in KBr powder with a Horiba FT-210 IR spectrophotometer, and only noteworthy absorptions (in cm^{-1}) are listed. Mass spectra were obtained with JEOL JMS-600H and JEOL JMS-700 mass spectrometers. Column chromatography was carried out on Kanto Chemical silica gel 60N (spherical, neutral, 63–210 μm) and flash column chromatography was carried out on Merck silica gel 60 (0.040–0.063 mm). All air- or moisture-sensitive reactions were carried out in flame-dried glassware under Ar or N_2. All solvents were dried and distilled by standard procedures. All organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure on a rotary evaporator.

(3*RS*,5*S*)-3-(Hex-5-ynyl)-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (3): (Table 1, Entry 4). *n*-BuLi (1.58 M in hexane, 3.35 mL, 5.29 mmol) was added to a solution of iPr_2NH (0.741 mL, 5.29 mmol) in THF (8.8 mL) with stirring at –78 °C. After the mixture had been stirred for 15 min, a solution of **7** (1.10 g, 5.29 mmol) in THF (8.8 mL) was added with stirring at –78 °C. After this mixture had been stirred for 15 min, a solution of **6** (1.00 g, 4.81 mmol) in HMPA (5.02 mL, 28.8 mmol) was added with stirring at –78 °C for 1 h. After stirring at 0 °C for 30 min, the reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 20:1) yielded **3** (1.35 g, 97%, 9:1 diastereomeric mixture) as a colorless oil. $[\alpha]_D^{25}$ = –48.1 (*c* = 1.04 in $CHCl_3$). ^{1}H NMR: δ = 1.23 (d, *J* = 6.1 Hz, 2.7 H), 1.39 (d, *J* = 6.1 Hz, 0.3 H), 1.47–1.58 (m, 3.1 H), 1.71–1.82 (m, 2.9 H), 1.96 (t, *J* = 2.7 Hz, 1 H), 1.98 (dd, *J* = 14.0, 6.7 Hz, 1 H), 2.19–2.22 (m, 2 H), 2.35 (dd, *J* = 14.0, 5.5 Hz, 0.1 H), 2.54 (dd, *J* = 14.0, 7.3 Hz, 0.9 H), 4.51 (m, 0.9 H), 4.65 (m, 0.1 H), 7.34–7.42 (m, 3 H), 7.53–7.57 ppm (m, 2 H). ^{13}C NMR: δ = 17.7, 20.3 (0.1 C), 21.1 (0.9 C), 22.9 (0.1 C), 23.2 (0.9 C), 27.8, 33.5 (0.1 C), 35.2 (0.9 C), 39.6 (0.9 C), 41.9 (0.1 C), 55.4 (0.1 C), 55.5 (0.9 C), 68.5 (0.1 C), 68.6 (0.9 C), 72.9 (0.9 C), 73.3 (0.1 C), 83.5 (0.9 C), 83.6 (0.1 C), 128.6 (2 C), 128.8 (0.1

C), 129.4 (0.9 C), 129.6 (0.1 C), 129.9 (0.9 C), 136.4 (1.8 C), 136.7 (0.2 C), 174.9 (0.1 C), 176.5 ppm (0.9 C). IR (KBr): $\tilde{\nu}$ = 3294, 3074, 3060, 2978, 2943, 2864, 2116, 1763, 1190 cm^{-1}. MS (FAB): *m*/*z* = 289 [*M* + H]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{17}H_{21}O_2S$: 289.1262; found: 289.1292 [*M* + H]$^+$.

(2*S*)-2-(*tert*-Butyldimethylsilyloxy)tetradecanyl Trifluoromethanesulfonate (9): 2,6-Lutidine (0.0823 mL, 0.725 mmol) was added to a solution of **8** (50.0 mg, 0.145 mmol) in CH_2Cl_2 (1.3 mL) with stirring at room temp. After 5 min, trifluoromethanesulfonic anhydride (0.0488 mL, 0.290 mmol) was added to the reaction mixture with stirring at 0 °C and the stirring was continued for 25 min. Water (0.1 mL) was added to the reaction mixture with stirring at 0 °C. After the mixture had been stirred at room temp. for 5 min, saturated $NaHCO_3$ was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography on silica gel (hexane/EtOAc, 50:1) yielded **9** (69.5 mg, quant.) as a colorless oil. This compound was immediately used in the next reaction because of its instability.

***rac*-10-(Benzyloxy)dec-1-yn-3-ol (*rac*-16):** *n*-BuLi (1.60 M in hexane, 13.7 mL, 21.9 mmol) was added with stirring at –78 °C to a solution of (trimethylsilyl)acetylene (3.03 mL, 21.9 mmol) in THF (28 mL). After 15 min, a solution of **14** (3.42 g, 14.6 mmol) in THF (28 mL) was added to the reaction mixture. After 15 min at the same temperature, the whole was stirred for 1.75 h at room temp. The reaction was quenched with saturated NH_4Cl at 0 °C and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. K_2CO_3 (4.64 g, 33.6 mmol) was added to a solution of the residue in MeOH (30 mL) with stirring at room temp. After 3.5 h, water was added to the reaction mixture, which was then extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 6:1) yielded *rac*-**16** (3.53 g, 93% in two steps) as a pale yellow oil. ^{1}H NMR: δ = 1.32–1.50 (m, 8 H), 1.59–1.76 (m, 4 H), 1.84 (br. d, *J* = 4.3 Hz, 1 H), 2.46 (d, *J* = 1.8 Hz, 1 H), 3.46 (t, *J* = 6.7 Hz, 2 H), 4.33–4.38 (m, 1 H), 4.50 (s, 2 H), 7.26–7.31 (m, 1 H), 7.33–7.35 ppm (m, 4 H). ^{13}C NMR: δ = 24.8, 25.8, 29.0, 29.1, 29.4, 37.4, 61.8, 70.2, 72.5, 72.6, 85.1, 127.3, 127.5 (2 C), 128.1 (2 C), 138.3 ppm. IR (KBr): $\tilde{\nu}$ = 3404, 3303, 3087, 3064, 3030, 1454 cm^{-1}. MS (FAB): *m*/*z* = 283 [*M* + Na]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{17}H_{24}NaO_2$: 283.1674; found: 283.1659 [*M* + Na]$^+$.

10-(Benzyloxy)dec-1-yn-3-one (17): Dess–Martin periodinane (3.05 g, 7.19 mmol) was added with stirring at 0 °C to a solution of *rac*-**16** (624 mg, 2.40 mmol) in CH_2Cl_2 (24 mL). After the mixture had been stirred for 2 h at room temp., further Dess–Martin periodinane (1.02 g, 2.40 mmol) was added with stirring at 0 °C. After additional stirring for 1 h, the reaction mixture was filtered through silica gel and the filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (hexane/EtOAc, 10:1) yielded **17** (604 mg, 98%) as a colorless oil. ^{1}H NMR: δ = 1.31–1.41 (m, 6 H), 1.61 (qn, *J* = 6.7 Hz, 2 H), 1.65–1.71 (m, 2 H), 2.58 (t, *J* = 7.3 Hz, 2 H), 3.19 (s, 1 H), 3.46 (t, *J* = 6.7 Hz, 2 H), 4.50 (s, 2 H), 7.26–7.30 (m, 1 H), 7.32–7.36 ppm (m, 4 H). ^{13}C NMR: δ = 23.4, 25.7, 28.6, 28.9, 29.4, 45.1, 70.1, 72.6, 78.4, 81.2, 127.2, 127.4 (2 C), 128.1 (2 C), 138.4, 187.2 ppm. IR (KBr): $\tilde{\nu}$ = 3263, 3087, 3062, 3030, 2029, 1684, 1454 cm^{-1}. MS (FAB): *m*/*z* = 259 [*M* + H]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{17}H_{23}O_2$: 259.1698; found: 259.1696 [*M* + H]$^+$.

(3*R*)-10-(Benzyloxy)dec-1-yn-3-ol (16): The ketone **17** (922 mg, 3.57 mmol) was added to neat (*R*)-Alpine-Borane®, prepared by concentration of the commercially available 0.5 M THF solution (7.13 mmol, 14.3 mL). The resulting mixture was stirred at room temp. for 6 h. After completion of the reaction, the mixture was cooled to 0 °C and acetaldehyde (0.399 mL, 7.13 mmol) was added to destroy the excess reagent (1 h reaction time). The mixture was concentrated under reduced pressure and the residue was dissolved in anhydrous ethyl ether (9.5 mL). The solution was cooled to 0 °C and *N*-methylaminoethanol (0.573 mL, 7.13 mmol) was added to remove 9-BBN. After 15 min, the 9-BBN-ethanolamine adduct was filtered through a sintered glass funnel. The precipitated was washed (2 × 5 mL) with cold ether. The combined filtrate and washings were dried and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/Et_2O, 4:1) yielded **16** (555 mg, 60%, 97% *ee*) as a colorless oil. $[\alpha]_D^{25}$ = +1.7 (*c* = 1.07 in $CHCl_3$). The spectroscopic data were identical to those for *rac*-**16**.

(3*R*)-10-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)dec-1-yne (18): Imidazole (52.3 mg, 0.768 mmol) was added with stirring at 0 °C to a solution of **16** (100 mg, 0.384 mmol) in DMF (0.3 mL). After 5 min, TBSCl (116 mg, 0.768 mmol) was added to the mixture with stirring at 0 °C. After 2 h at room temp., the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 20:1) yielded **18** (136 mg, 94%) as a colorless oil. $[\alpha]_D^{28}$ = +24.4 (*c* = 1.31 in $CHCl_3$). ^{1}H NMR: δ = 0.11 (s, 3 H), 0.13 (s, 3 H), 0.90 (s, 9 H), 1.29–1.45 (m, 8 H), 1.61 (qn, *J* = 6.7 Hz, 2 H), 1.64–1.69 (m, 2 H), 2.36 (d, *J* = 1.8 Hz, 1 H), 3.46 (t, *J* = 6.7 Hz, 2 H), 4.33 (td, *J* = 6.7, 1.8 Hz, 1 H), 4.50 (s, 2 H), 7.26–7.34 ppm (m, 5 H). ^{13}C NMR: δ = –5.1, –4.6, 18.2, 25.0, 25.7 (3 C), 26.1, 29.1, 29.3, 29.7, 38.5, 62.7, 70.4, 71.9, 72.8, 85.7, 127.4, 127.5 (2 C), 128.3 (2 C), 138.7 ppm. IR (KBr): $\tilde{\nu}$ = 3307, 3087, 3068, 3030, 2113, 1471 cm^{-1}. MS (FAB): *m*/*z* = 375 [*M* + H]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{23}H_{39}O_2Si$: 375.2719; found: 375.2692 [*M* + H]$^+$.

(3*R*)-10-(Benzyloxy)-3-(methoxymethoxy)dec-1-yne (19): MOMCl (0.233 mL, 3.07 mmol) and *i*Pr_2NEt (0.527 mL, 3.07 mmol) were added with stirring at 0 °C to a solution of **16** (400 mg, 1.54 mmol) in CH_2Cl_2 (3.1 mL). After stirring for 2 h at room temp., the reaction mixture was diluted with EtOAc and washed with water, saturated NH_4Cl, and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 8:1) yielded **19** (448 mg, 96%) as a colorless oil. $[\alpha]_D^{27}$ = +88.0 (*c* = 2.30 in $CHCl_3$). ^{1}H NMR: δ = 1.31–1.52 (m, 8 H), 1.61 (qn, *J* = 6.7 Hz, 2 H), 1.68–1.79 (m, 2 H), 2.40 (d, *J* = 1.8 Hz, 1 H), 3.38 (s, 3 H), 3.46 (t, *J* = 6.7 Hz, 2 H), 4.31 (td, *J* = 6.7, 1.8 Hz, 1 H), 4.50 (s, 2 H), 4.60 (d, *J* = 6.7 Hz, 1 H), 4.94 (d, *J* = 6.7 Hz, 1 H), 7.26–7.30 (m, 1 H), 7.31–7.37 ppm (m, 4 H). ^{13}C NMR: δ = 24.9, 25.9, 29.0, 29.1, 29.6, 35.4, 55.4, 65.2, 70.2, 72.6, 73.3, 82.5, 93.9, 127.2, 127.4 (2 C), 128.1 (2 C), 138.5 ppm. IR (KBr): $\tilde{\nu}$ = 3291, 3087, 3064, 3031, 2111, 1454 cm^{-1}. MS (FAB): *m*/*z* = 327 [*M* + Na]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{19}H_{28}NaO_3$: 327.1936; found: 327.1939 [*M* + Na]$^+$.

(1*R*,4*R*)-11-(Benzyloxy)-1-[(1*R*,4*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-1,4-epoxyheptadecanyl]-4-(methoxymethoxy)undec-2-yn-1-ol (22): A flask was charged with $Zn(OTf)_2$ (262 mg, 0.720 mmol). Vacuum (8 Torr) was applied and the flask was heated to 125 °C for 8 h. The flask was allowed to cool to room temp. and the vacuum was then released. (1*R*,2*S*)-(–)-*N*-Methylephedrine (141 mg, 0.785 mmol) and toluene (0.7 mL) and Et_3N (0.110 mL, 0.785 mmol) were added to the flask with stirring at room temp. A solution of **19** (199 mg, 0.654 mmol) in toluene (0.35 mL) was

added to the mixture with stirring at room temp. After 0.25 h, a solution of **20** (135 mg, 0.327 mmol) in toluene (0.35 mL) was added to the mixture with stirring at room temp. After stirring for 6 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 20:1) yielded **22** (208 mg, 89%, β-OH/α-OH > 97:3) as a colorless oil. $[\alpha]_D^{26}$ = +53.3 (c = 1.55 in $CHCl_3$). ^{1}H NMR: δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.86–0.91 (m, 12 H), 1.26–1.79 (m, 36 H), 1.88–1.94 (m, 1 H), 2.02–2.08 (m, 1 H), 2.49 (br. s, 1 H), 3.36 (s, 3 H), 3.46 (t, J = 6.4 Hz, 2 H), 3.57 (td, J = 6.1, 3.7 Hz, 1 H), 3.91 (dt, J = 7.9, 6.1 Hz, 1 H), 4.03 (q, J = 6.7 Hz, 1 H), 4.21 (dd, J = 6.7, 1.2 Hz, 1 H), 4.34 (td, J = 6.7, 1.2 Hz, 1 H), 4.50 (s, 2 H), 4.57 (d, J = 6.7 Hz, 1 H), 4.91 (d, J = 6.7 Hz, 1 H), 7.27–7.31 (m, 1 H), 7.32–7.34 ppm (m, 4 H). ^{13}C NMR: δ = –4.6, –4.2, 14.1, 18.2, 22.6, 25.2, 25.5, 25.9 (3 C), 26.1, 27.6, 28.3, 29.2, 29.3, 29.55 (2 C), 29.59 (3 C), 29.63, 29.7, 29.8, 31.9, 32.9, 35.6, 55.5, 65.3, 65.5, 70.4, 72.8, 74.8, 82.1, 82.7, 83.5, 84.2, 94.0, 127.4, 127.5 (2 C), 128.3 (2 C), 138.6 ppm. IR (KBr): $\tilde{\nu}$ = 3427, 3089, 3064, 3027, 1462 cm^{-1}. MS (FAB): m/z = 740 $[M + Na]^+$. HRMS (FAB): m/z calcd. for $C_{43}H_{76}NaO_6Si$: 739.5309; found: 739.5309 $[M + Na]^+$.

(1*R*,4*R*)-11-(Benzyloxy)-1-[(1*R*,4*R*,5*R*,8*R*,9*R*)-9-(*tert*-butyldimethylsilyloxy)-1,4;5,8-diepoxyhenicosanyl]-4-(methoxymethoxy)undec-2-yn-1-ol (25): DMSO (0.234 mL, 3.30 mmol) and Et_3N (0.690 mL, 4.95 mmol) were added to a solution of **23** (200 mg, 0.413 mmol) in CH_2Cl_2 (1.24 mL) with stirring at room temp., and then SO_3·pyridine (263 mg, 1.65 mmol) was added to the mixture with stirring at 0 °C. The whole mixture was stirred at 0 °C for 10 min and at room temp. for 1 h, quenched with water, and extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 5:1 → 1:1) yielded **24** (180 mg, 90%). This aldehyde was immediately used in the next reaction, due to its instability. The asymmetric alkynylation procedure was the same as that used for the preparation of **22**. Compound **25** (188 mg, 65%, β-OH/α-OH > 97:3) was prepared from **24** (177 mg, 0.367 mmol) and **19** (224 mg, 0.734 mmol) as a colorless oil. $[\alpha]_D^{23}$ = +44.6 (c = 1.01 in $CHCl_3$). ^{1}H NMR: δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.85–0.91 (m, 12 H), 1.22–1.47 (m, 30 H), 1.58–2.03 (m, 11 H), 2.06–2.11 (m, 1 H), 2.72 (s, 1 H), 3.35 (s, 3 H), 3.45 (t, J = 6.8 Hz, 2 H), 3.58–3.61 (m, 1 H), 3.84–3.95 (m, 3 H), 4.07 (q, J = 7.0, Hz, 1 H), 4.24 (d, J = 7.0 Hz, 1 H), 4.33 (t, J = 6.5 Hz, 1 H), 4.49 (s, 2 H), 4.56 (d, J = 6.5 Hz, 1 H), 4.91 (d, J = 6.5 Hz, 1 H), 7.25–7.33 ppm (m, 5 H). ^{13}C NMR: δ = –4.7, –4.3, 14.1, 18.2, 22.6, 25.2, 25.7, 25.9 (3 C), 26.1, 27.3, 28.1, 28.2, 28.5, 29.2, 29.3 (2 C), 29.58 (2 C), 29.59 (2 C), 29.64, 29.7, 29.8, 31.9, 32.5, 35.6, 55.6, 65.5 (2 C), 70.4, 72.8, 74.8, 81.4, 82.1, 82.4 (2 C), 83.4, 84.2, 94.0, 127.4, 127.5 (2 C), 128.3 (2 C), 138.6 ppm. IR (KBr): $\tilde{\nu}$ = 3425, 2058, 1101, 1066, 1032 cm^{-1}. MS (FAB): m/z = 810 $[M + Na]^+$. HRMS (FAB): m/z calcd. for $C_{47}H_{82}NaO_7Si$: 809.5727; found: 809.5760 $[M + Na]^+$.

(8*R*,11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-1-(Benzyloxy)-20-(*tert*-butyldimethylsilyloxy)-12,15;16,19-diepoxy-8,11-bis(methoxymethoxy)-dotriacont-9-yne (26): *i*Pr_2NEt (0.194 mL, 1.11 mmol) and MOMCl (0.051 mL, 0.667 mmol) were added with stirring at 0 °C to a solution of **25** (175 mg, 0.222 mmol) in CH_2Cl_2 (2.2 mL). The whole mixture was stirred at 0 °C for 10 min and at room temp. for 30.5 h. MOMCl (0.017 mL, 0.222 mmol) was added to the reaction mixture at 0 °C, with additional stirring at room temp. for 2 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel (hexane/EtOAc, 5:1) yielded **26** (174 mg, 94%) as a colorless oil. $[\alpha]_D^{28}$ = +23.6 (c = 0.96 in $CHCl_3$). ^{1}H NMR: δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.85–0.89 (m, 12 H), 1.26–1.48 (m, 30 H), 1.61 (tt, J = 7.6, 6.7 Hz, 2 H), 1.65–1.78 (m, 5 H), 1.86–1.99 (m, 4 H), 2.07–2.13 (m, 1 H), 3.36 (s, 3 H), 3.37 (s, 3 H), 3.48 (t, J = 6.7 Hz, 2 H), 3.59–3.62 (m, 1 H), 3.87–4.00 (m, 3 H), 4.17 (td, J = 6.7, 6.7 Hz, 1 H), 4.34 (td, J = 6.7, 1.8 Hz, 1 H), 4.42 (dd, J = 6.7, 1.8 Hz, 1 H), 4.49 (s, 2 H), 4.56 (d, J = 6.7 Hz, 1 H), 4.63 (d, J = 6.7 Hz, 1 H), 4.88 (d, J = 6.7 Hz, 1 H), 4.91 (d, J = 6.7 Hz, 1 H), 7.25–7.34 ppm (m, 5 H). ^{13}C NMR: δ = –4.7, –4.3, 14.1, 18.2, 22.6, 25.2, 25.8, 25.9 (3 C), 26.1, 27.2, 28.0, 28.1, 28.3, 29.2, 29.30, 29.32, 29.56 (2 C), 29.58 (2 C), 29.62, 29.7, 29.8, 31.9, 32.4, 35.6, 55.46, 55.52, 65.5, 68.5, 70.4, 72.8, 74.7, 80.5, 81.2, 81.9, 82.0, 82.3, 85.0, 94.0, 94.2, 127.4, 127.5 (2 C), 128.3 (2 C), 138.6 ppm. IR (KBr): $\tilde{\nu}$ = 2067, 2035, 1101, 1032 cm^{-1}. MS (FAB): m/z = 854 $[M + Na]^+$. HRMS (FAB): m/z calcd. for $C_{49}H_{86}NaO_8Si$: 853.5990; found: 853.5981 $[M + Na]^+$.

(8*R*,11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-20-(*tert*-Butyldimethylsilyloxy)-12,15;16,19-diepoxy-8,11-bis(methoxymethoxy)dotriacontan-1-ol (27): A solution of **26** (218 mg, 0.262 mmol) in EtOAc (2.6 mL) was hydrogenated on 10% Pd/C (10.9 mg) with stirring at room temp. for 11 h. The Pd/C was filtered off and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/EtOAc, 3:1) yielded **27** (142 mg, 73%) as a colorless oil. $[\alpha]_D^{27}$ = +24.9 (c = 0.98 in $CHCl_3$). ^{1}H NMR: δ = 0.049 (s, 3 H), 0.051 (s, 3 H), 0.85–0.87 (m, 12 H), 1.24–1.94 (m, 46 H), 3.35 (s, 3 H), 3.37 (s, 3 H), 3.34–3.56 (m, 3 H), 3.60 (t, J = 6.7 Hz, 2 H), 3.84–3.90 (m, 3 H), 3.99 (dt, J = 8.5, 6.1 Hz, 1 H), 4.64–4.61 (m, 2 H), 4.65 (d, J = 6.7 Hz, 1 H), 4.81 ppm (d, J = 6.7 Hz, 1 H). ^{13}C NMR: δ = –4.7, –4.2, 14.1, 18.2, 22.6, 25.2, 25.6, 25.7, 25.9 (3 C), 26.7, 27.5, 28.1, 28.2, 28.4, 29.3 (2 C), 29.56 (2 C), 29.58 (2 C), 29.62, 29.7, 29.8, 30.2, 31.9, 32.6, 32.7, 34.2, 55.4, 55.7, 62.9, 75.0, 77.5, 79.7, 81.3 (2 C), 81.7, 82.5, 95.2, 96.7 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 2854, 1464, 1147, 1099 cm^{-1}. MS (FAB): m/z = 768 $[M + Na]^+$. HRMS (FAB): m/z calcd. for $C_{42}H_{84}NaO_8Si$: 767.5833; found: 767.5852 $[M + Na]^+$.

(8*R*,11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-20-(*tert*-Butyldimethylsilyloxy)-12,15;16,19-diepoxy-1-iodo-8,11-bis(methoxymethoxy)dotriacontane (28): Imidazole (27.4 mg, 0.403 mmol) and iodine (40.9 mg, 0.161 mmol) were added with stirring (0.5 h) at 0 °C to a solution of Ph_3P (38.7 mg, 0.148 mmol) in CH_2Cl_2 (2.1 mL). A solution of **27** (100 mg, 0.135 mmol) in CH_2Cl_2 (0.29 mL) was added to the reaction mixture with stirring at 0 °C. After the mixture had been stirred at room temp. for 2 h, Ph_3P (35.1 mg, 0.135 mmol) and iodine (34.0 mg, 0.135 mmol) were added with stirring at 0 °C. After additional stirring at room temp. for 0.5 h, saturated $Na_2S_2O_3$ was added to the reaction mixture with stirring until the brown color of the solution had vanished. The mixture was extracted with Et_2O and the combined organic layers were washed with brine prior to drying and solvent evaporation. Purification by flash column chromatography on silica gel (hexane/EtOAc, 10:1) yielded **28** (94.6 mg, 82%) as a colorless oil. $[\alpha]_D^{25}$ = +23.1 (c = 0.97 in $CHCl_3$). ^{1}H NMR: δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.85–0.89 (m, 12 H), 1.26–1.94 (m, 46 H), 3.18 (t, J = 6.7 Hz, 2 H), 3.37 (s, 3 H), 3.39 (s, 3 H), 3.46–3.58 (m, 3 H), 3.85–3.92 (m, 3 H), 4.01 (dt, J = 8.5, 6.1 Hz, 1 H), 4.03–4.66 (m, 2 H), 4.67 (d, J = 7.3 Hz, 1 H), 4.83 ppm (d, J = 7.3 Hz, 1 H). ^{13}C NMR: δ = –4.7, –4.2, 7.11, 14.1, 18.2, 22.6, 25.2, 25.7, 25.9 (3 C), 26.7, 27.6, 28.1, 28.2, 28.4, 28.5, 29.3, 29.5, 29.57 (2 C), 29.59 (2 C), 29.64, 29.8, 30.2, 30.4, 31.9, 32.6, 33.5, 34.2, 55.5, 55.7, 75.0, 77.4, 79.7, 81.3 (2 C), 81.6, 82.5, 95.3, 96.7 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 2856, 1464, 1250, 1147 cm^{-1}.

MS (FAB): *m*/*z* = 877 [*M* + Na]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{42}H_{83}INaO_7Si$: 877.4850; found: 877.4841 [*M* + Na]$^+$.

(3*RS*,5*S*)-3-[(8*R*,11*R*,12*R*,15*R*,16*R*,19*R*,20*R*)-20-(*tert*-Butyldimethylsilyloxy)-12,15;16,19-diepoxy-8,11-bis(methoxymethoxy)dotriacontanyl]-5-methyl-3-(phenylsulfenyl)tetrahydrofuran-2-one (29): (Table 2, Entry 4). *n*-BuLi (1.56 M in hexane, 0.120 mL, 0.187 mmol) was added to a solution of *i*Pr$_2$NH (0.0263 mL, 0.187 mmol) in THF (0.30 mL) with stirring at –78 °C for 15 min. A solution of **7** (39.0 mg, 0.187 mmol) in THF (0.30 mL) was added to the reaction mixture with stirring at –78 °C. After the mixture had been stirred for 15 min, a solution of **28** (80.1 mg, 0.0937 mmol) and HMPA (0.0326 mL, 0.187 mmol) in THF (0.34 mL) was added with stirring at –78 °C for 1 h. After stirring at 0 °C for 4 h, the mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were washed with saturated NH_4Cl, water, and brine prior to drying and solvent evaporation. After removal of excess **7** by column chromatography on silica gel (CH_2Cl_2), purification by column chromatography on silica gel (hexane/EtOAc, 4:1) yielded **29** (66.4 mg, 76%) as a colorless oil along with recovered **28** (15.3 mg, 19%). $[\alpha]_D^{25}$ = +5.91 (*c* = 0.95 in $CHCl_3$). ^{1}H NMR: δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.87–0.89 (m, 12 H), 1.19 (d, *J* = 6.7 Hz, 3 H), 1.25–1.82 (m, 44 H), 1.85–2.01 (m, 4 H), 1.96 (dd, *J* = 14.0, 6.7 Hz, 1 H), 2.51 (dd, *J* = 14.0, 6.7 Hz, 1 H), 3.37 (s, 3 H), 3.39 (s, 3 H), 3.46–3.58 (m, 3 H), 3.85–3.92 (m, 3 H), 4.01 (dt, *J* = 9.2, 6.1 Hz, 1 H), 4.49 (sext, *J* = 6.7 Hz, 1 H), 4.63 (d, *J* = 6.7 Hz, 1 H), 4.65 (d, *J* = 6.7 Hz, 1 H), 4.67 (d, *J* = 6.7 Hz, 1 H), 4.84 (d, *J* = 6.7 Hz, 1 H), 7.33–7.41 (m, 3 H), 7.51–7.56 ppm (m, 2 H). ^{13}C NMR: δ = –4.7, –4.2, 14.1, 18.2, 21.5, 22.7, 24.6, 25.3, 25.7, 26.0 (3 C), 26.8, 27.6, 28.2, 28.3, 28.4, 29.3 (2 C), 29.3, 29.5, 29.6 (3 C), 29.7 (2 C), 29.8, 30.2, 31.9, 32.6, 34.3, 36.5, 40.1, 55.5, 55.7, 56.2, 73.2, 75.0, 77.5, 79.8, 81.3 (2 C), 81.7, 82.5, 95.3, 96.8, 129.0 (2 C), 129.7, 130.4, 136.8 (2 C), 175.5 ppm. IR (KBr): $\tilde{\nu}$ = 3073, 3060, 2925, 2854, 1768, 1720, 1464, 1441, 1250 cm^{-1}. MS (FAB): *m*/*z* = 957 [*M* + Na]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{53}H_{94}NaO_9SSi$: 957.6285; found: 957.6306 [*M* + Na]$^+$

Longimicin D (1): A solution of *m*-CPBA (75% in water, 13.7 mg, 0.0597 mmol) in CH_2Cl_2 (0.49 mL) was added to a solution of **29** (46.5 mg, 0.0497 mmol) in CH_2Cl_2 (0.49 mL) with stirring at 0 °C for 1.5 h. The reaction mixture was diluted with EtOAc and washed with saturated $Na_2S_2O_3$, water, and brine prior to drying and solvent evaporation. The residue was diluted with toluene (1.50 mL) and the solution was stirred under reflux for 2 h. After the solvent evaporation, a low polar byproduct was removed by column chromatography on silica gel (hexane/EtOAc, 4:1 → 1:1). After the solvent evaporation, a solution of 5% AcCl in MeOH (1.0 mL) was added to a solution of the residue in CH_2Cl_2 (0.80 mL) with stirring at room temp. for 6 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine prior to drying and solvent evaporation. Purification by column chromatography on silica gel ($CHCl_3$/MeOH, 50:1) yielded longimicin D (22.0 mg, 71% in three steps) as a colorless, waxy solid. $[\alpha]_D^{25}$ = +23.2 (*c* = 0.48 in EtOH). ^{1}H NMR: δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.25–1.46 (m, 36 H), 1.41 (d, *J* = 6.7 Hz, 3 H), 1.49–1.56 (m, 2 H), 1.60–1.74 (m, 4 H), 1.97–2.00 (m, 4 H), 2.26 (t, *J* = 7.9 Hz, 2 H), 2.45 (br., 3 H), 3.37–3.41 (m, 1 H), 3.45 (br., 1 H), 3.62 (br., 1 H), 3.83–3.88 (m, 4 H), 5.00 (br. q, *J* = 6.7 Hz, 1 H), 6.99 ppm (br. s, 1 H). ^{13}C NMR: δ = 14.1, 19.2, 22.7, 25.1, 25.66, 25.70, 27.4, 28.4, 28.9, 29.0, 29.1, 29.25, 29.34, 29.5, 29.55, 29.61, 29.63 (3 C), 29.66 (2 C), 29.71, 31.9, 33.4, 33.6, 37.5, 71.7, 74.0, 74.2, 77.4, 81.7, 81.9, 82.9, 83.2, 134.3, 148.9, 173.9 ppm. IR (KBr): $\tilde{\nu}$ = 3375, 2927, 2854, 1755, 1653, 1466, 1319, 1198, 1068, 953, 874 cm^{-1}. MS (FAB): *m*/*z* = 623 [*M* + H]$^+$. HRMS (FAB): *m*/*z* calcd. for $C_{37}H_{67}O_7$: 623.4887; found: 623.4940 [*M* + H]$^+$.

Acknowledgments

We acknowledge financial support in the forms of a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (No. 16590006), and a Grant-in-Aid for Scientific Research on a Priority Area from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 17035052). We also thank the Research Foundation for Pharmaceutical Sciences and the Suntory Institute for Bioorganic Research for financial support. N.K. and H.T. are grateful for a Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists.

[1] For reviews for annonaceous acetogenins: a) A. Bermejo, B. Figadère, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269–303; b) F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540; c) M.-C. Zafra-Polo, B. Figadère, T. Gallardo, J. R. Tormo, D. Cortes, *Phytochemistry* **1998**, *48*, 1087–1117; d) "Acetogenins from *Annonaceae*": A. Cavé, B. Figadère, A. Laurens, D. Cortes, in: *Progress in the Chemistry of Organic Natural Products*, *Vol. 70* (Ed.: W. Hertz), Springer-Verlag, New York, **1997**, pp. 81–288; e) L. Zeng, Q. Ye, N. H. Oberlies, G. Shi, Z.-M. Gu, K. He, J. L. McLaughlin, *Nat. Prod. Rep.* **1996**, *13*, 275–306; f) M. C. Zafra-Polo, M. C. González, E. Estornell, S. Sahpaz, D. Cortes, *Phytochemistry* **1996**, *42*, 253–271; g) "*Annaceous Acetogenins*", Z.-M. Gu, G.-X. Zhao, N. H. Oberlies, L. Zeng, J. L. McLaughlin, in: *Recent Advances in Phytochemistry*, *Vol. 29* (Eds.: J. T. Arnason, R. Mata, J. T. Romeo), Plenum Press, New York, **1995**, pp. 249–310; h) X.-P. Fang, M. J. Rieser, Z.-M. Gu, G.-X. Zhao, J. L. McLaughlin, *Phytochem. Anal.* **1993**, *4*, 27–67; i) J. K. Rupprecht, Y.-H. Hui, J. L. McLaughlin, *J. Nat. Prod.* **1990**, *53*, 237–278.

[2] For reviews of synthesis of annonaceous acetogenins: a) G. Casiraghi, F. Zanardi, L. Battistini, G. Rassu, *Chemtracts*, *Organic Chemistry* **1998**, *11*, 803–827; b) M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175–4200; c) B. Figadère, *Acc. Chem. Res.* **1995**, *28*, 359–365; d) R. Hoppe, H.-D. Scharf, *Synthesis* **1995**, 1447–1464; e) U. Koert, *Synthesis* **1995**, 115–132.

[3] Recent reports of syntheses of annonaceous acetogenins: a) Y.-T. He, S. Xue, T.-S. Hu, Z.-J. Yao, *Tetrahedron Lett.* **2005**, *46*, 5393–5397; b) J. M. Tinsley, E. Mertz, P. Y. Chong, R.-A. F. Rarig, W. R. Roush, *Org. Lett.* **2005**, *7*, 4245–4248; c) N. Maezaki, H. Tominaga, N. Kojima, M. Yanai, D. Urabe, R. Ueki, T. Tanaka, T. Yamori, *Chem. Eur. J.* **2005**, *11*, 6237–6245; d) S. Hanessian, S. Giroux, M. Buffat, *Org. Lett.* **2005**, *7*, 3989–3992; e) J. M. Tinsley, W. R. Roush, *J. Am. Chem. Soc.* **2005**, *127*, 10818–10819; f) G. Keum, C. H. Hwang, S. B. Kang, Y. Kim, E. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 10396–10399; g) S. Takahashi, N. Ogawa, H. Koshino, T. Nakata, *Org. Lett.* **2005**, *7*, 2783–2786; h) D. Strand, T. Rein, *Org. Lett.* **2005**, *7*, 2779–2781; i) L. Zhu, D. R. Mootoo, *Org. Biomol. Chem.* **2005**, *3*, 2750–2754; j) K. J. Quinn, A. K. Isaacs, B. A. DeChristopher, S. C. Szklarz, R. A. Arvary, *Org. Lett.* **2005**, *7*, 1243–1245; k) G. L. Nattrass, E. Díez, M. M. McLachlan, D. J. Dixon, S. V. Ley, *Angew. Chem. Int. Ed.* **2005**, *44*, 580–584; l) D. Strand, T. Rein, *Org. Lett.* **2005**, *7*, 199–202.

[4] Q. Ye, K. He, N. H. Oberlies, L. Zeng, G. Shi, D. Evert, J. L. McLaughlin, *J. Med. Chem.* **1996**, *39*, 1790–1796.

[5] a) N. Kojima, N. Maezaki, H. Tominaga, M. Yanai, D. Urabe, T. Tanaka, *Chem. Eur. J.* **2004**, *10*, 672–680; b) N. Kojima, N. Maezaki, H. Tominaga, M. Asai, M. Yanai, T. Tanaka, *Chem. Eur. J.* **2003**, *9*, 4980–4990; c) N. Maezaki, N. Kojima, H. Tominaga, M. Yanai, T. Tanaka, *Org. Lett.* **2003**, *5*, 1411–1414; d)

N. Maezaki, N. Kojima, M. Asai, H. Tominaga, T. Tanaka, *Org. Lett.* **2002**, *4*, 2977–2980.
[6] J. D. White, T. C. Somers, G. N. Reddy, *J. Org. Chem.* **1992**, *57*, 4991–4998.
[7] I. Mancini, M. Cavazza, G. Guella, F. Pietra, *J. Chem. Soc., Perkin Trans. 1* **1994**, *15*, 2181–2186.
[8] K. Lee, Y.-H. Kim, S. B. Han, H. Kang, S. Park, W. S. Seo, J. T. Park, B. Kim, S. Chang, *J. Am. Chem. Soc.* **2003**, *125*, 6844–6845.
[9] a) E. El-Sayed, N. K. Anand, E. M. Carreira, *Org. Lett.* **2001**, *3*, 3017–3020; b) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; c) H. Sasaki, D. Boyall, E. M. Carreira, *Helv. Chim. Acta* **2001**, *84*, 964–971; d) D. Boyall, F. López, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233–4236; e) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373–381; f) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
[10] K. Ishihara, N. Hanaki, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 10695–10704.
[11] J. Bach, R. Berenguer, J. Garcia, T. Loscertales, J. Vilarrasa, *J. Org. Chem.* **1996**, *61*, 9021–9025.
[12] *ee* was determined by HPLC analysis (CHIRALCEL OB, hexane/*i*PrOH, 9:1) .
[13] F. Babudri, V. Fiandanese, O. Hassan, A. Punzi, F. Naso, *Tetrahedron* **1998**, *54*, 4327–4336.
[14] a) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096; b) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; c) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549.
[15] The stereochemistry of **22** was confirmed by comparison of ^{1}H and ^{13}C NMR spectra with the model compounds, which we have synthesized previously; see ref.[5b].
[16] The stereochemistry of **25** was tentatively assumed from the previous results and finally confirmed by total synthesis of longimicin D.
[17] The optical rotations of natural acetogenins are sometimes smaller than those of synthetic samples when they were measured at low concentrations, presumably owing to experimental error or the presence of impurities; see: a) N. Maezaki, N. Kojima, A. Sakamoto, H. Tominaga, C. Iwata, T. Tanaka, M. Monden, B. Damdinsuren, S. Nakamori, *Chem. Eur. J.* **2003**, *9*, 389–399; b) T.-S. Hu, Y.-L. Wu, Y. Wu, *Org. Lett.* **2000**, *2*, 887–889; c) Q. Yu, Y. Wu, H. Ding, Y.-L. Wu, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1183–1188; d) S. C. Sinha, S. C. Sinha, E. Keinan, *J. Org. Chem.* **1999**, *64*, 7067–7073.

Received: October 31, 2005
Published Online: January 17, 2006

