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Synthesis of the L-Acid (C1–C18) Fragment of Pamamycin-593 and De-*N*-methylpamamycin-579

Ayako Miura,[a] Shin-ya Takigawa,[a] Yukito Furuya,[a] Yusuke Yokoo,[a] Shigefumi Kuwahara,[a] and Hiromasa Kiyota*[a]

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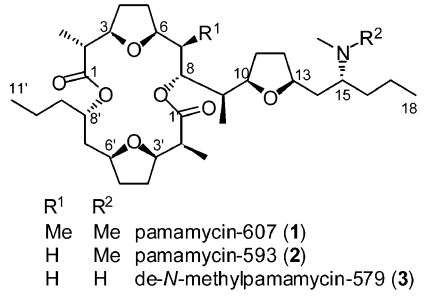
The L-acid (C1–C18) fragment of pamamycin-593 and de-*N*-methylpamamycin-579, strong aerial mycelium-inducers of *Streptomyces alboniger*, was synthesized using a *cis*-selective iodoetherification and a nucleophilic addition of a cerium acetylide to an aldehyde as the key steps.

Introduction

Pamamycins are a series of unique nitrogen-containing antibiotics isolated from *Streptomyces* sp.[1] Among them, pamamycin-607 (**1**) (Figure 1), isolated from *Streptomyces alboniger*, showed aerial mycelium-inducing activity in an aerial mycelium-less mutant of *S. alboniger*.[1b,1c] Recently, its new, low-molecular-weight derivatives, pamamycin-593 (**2**) and de-*N*-methylpamamycin 579 (**3**), showed stronger activity.[1c,2] The total synthesis of **1** was achieved by several groups.[3,4] The first was reported by Thomas' group.[4a]



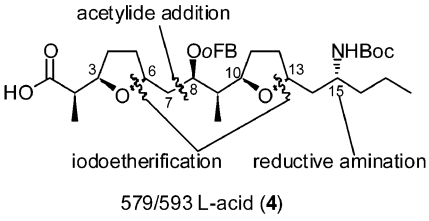


Figure 1. Structures of the pamamycins and our synthetic plan.

[a] Graduate School of Agricultural Sciences, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan
Fax: +81-22-717-8785
E-mail: kiyota@biochem.tohoku.ac.jp

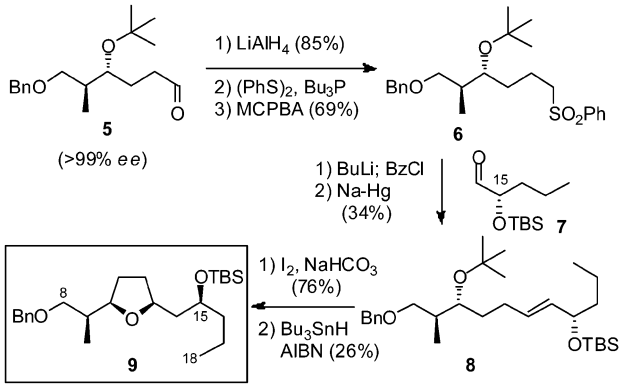
They used 5-*endo*-selenoetherification to construct the three THF rings. The total syntheses of **1** and its relatives were also achieved by Metz's,[4b,4c] Lee's,[4d] Kang's,[4e] and Hanquet's[4f] groups using a sulfone-guided cyclization, radical cyclization, iodoetherification, and hydrogenation, respectively, for the key THF ring formation. Synthetic approaches to the L-acid (L = large) fragments were also reported by Walkup's,[5a] Perlmutter's (oxymercuration),[5b] Bloch's (Michael cyclization),[5c] Solladié's,[5d] Hanquet's (hydrogenation),[4f] Nagumo's (phenonium ion cyclization),[5e] and our groups (iodoetherification).[6] Continuing our synthetic work of pamamycins,[6,7] we began the synthesis of these new compounds **2** and **3** for further biological studies. Here we describe an efficient and convergent synthesis of the L-acid fragment **4**.

Results and Discussion

In the previous paper, we prepared the C1–C18 portion of the L-acid (Scheme 1).[6] A Julia coupling of sulfone **6**, derived from **5**, with chiral aldehyde **7** afforded olefin **8**. *Cis*-selective iodoetherification followed by deiodination gave the C8–C18 fragment **9**.[6] However, the yields were low in the reductive desulfonylation and deiodination steps. Thus, we planned the new strategy in which the C15 amino group as to be introduced stereoselectively by the reductive amination of the corresponding keto group according to Lee's procedure.[4d]

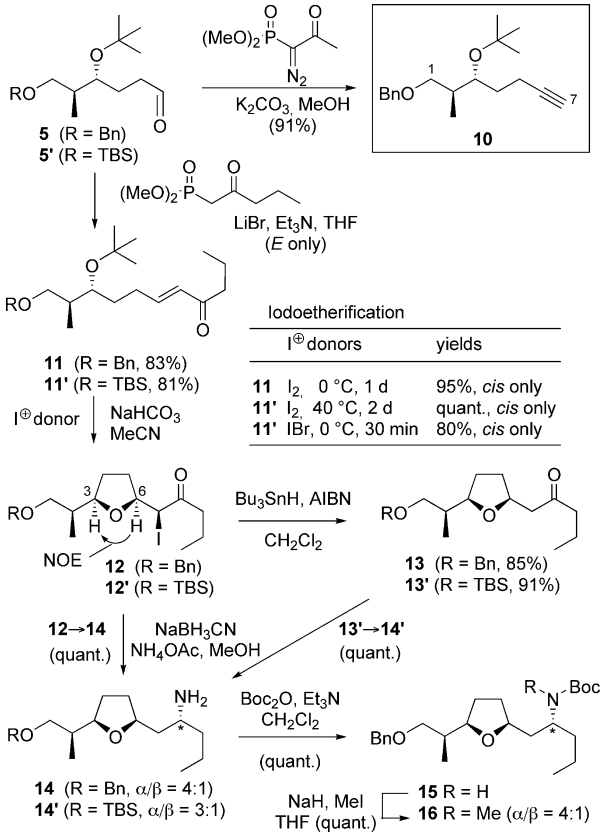
The key reaction in our new synthetic plan was also a *cis*-selective iodoetherification to construct both the *cis*-THF rings (Figure 1).[8] The whole carbon chain would be formed by a nucleophilic addition of an acetylide to an aldehyde to connect C7 and C8.

As shown in Scheme 2, our synthesis of the L-acid **4** began with the known aldehyde **5**, which was our common



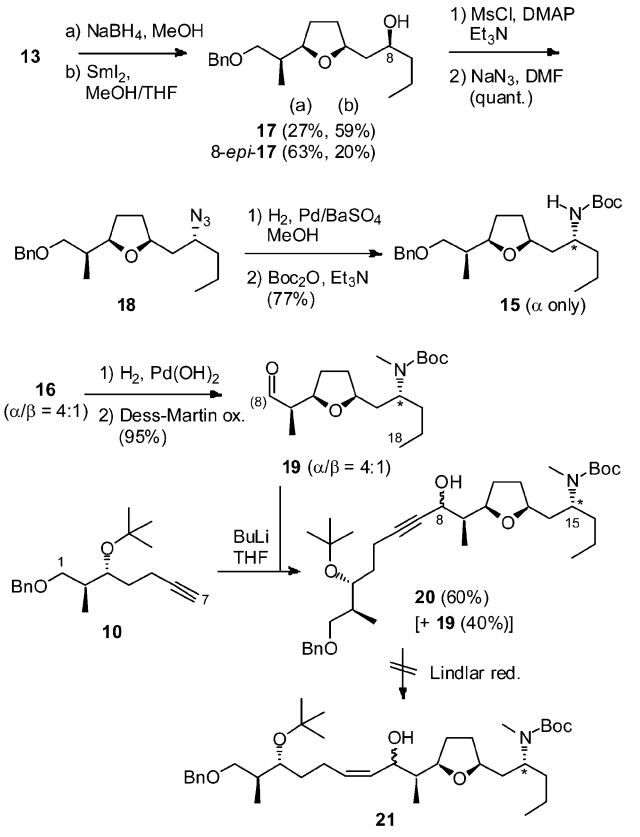
Scheme 1. Our previous synthesis of the C8–C18 fragment of the L-acid.

starting material for the synthetic studies of polynactin and the pamamycin series.[6,9] Treatment of **5** with the Ohira–Bestmann reagent[10] afforded alkyne **10** (C1–C7 fragment) in 91% yield. For the C8–C18 fragment, chain elongation of **5** by a Horner–Emmons reaction gave exclusively the **11** *E*-olefinic ketone with a benzyl protecting group. The corresponding TBS-protected compound was prepared in a similar way. The key iodoetherification[8] proceeded at 0 °C to give the *cis*-THF **12** in 95% yield. The use of IBr as a stronger iodonium ion donor shortened the reaction time but lowered the yield. The stereochemistry was confirmed



Scheme 2. Synthesis of the C1–C7 and C8–C18 fragments (reductive amination).

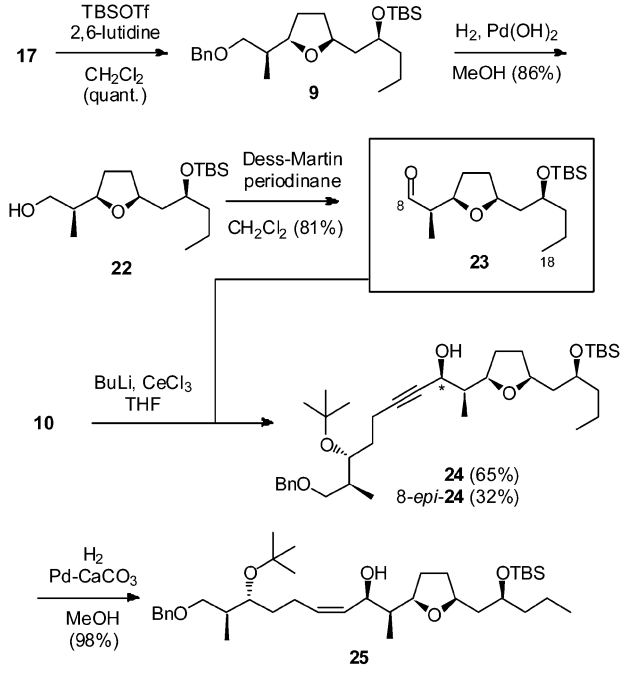
by an NOE experiment on **12′**. Reductive amination of the keto group of **12** using $NaBH_3CN$ simultaneously reduced the iodo group to give amine **14**.[4d] However, the α/β (*R*/*S*) ratio of the amino group was about 4:1. The reaction with the corresponding deiodo ketone **13'** gave **14'** as a 3:1 α/β mixture. Lee reported that the reductive amination of a similar keto group proceeded stereoselectively.[4d] These isomers were inseparable even after conversion to their *N*-Boc and *N*-Boc *N*-methyl derivatives **15** and **16**, respectively. Accordingly, the amino group was introduced by a stepwise sequence as shown in Scheme 3. Hydride reduction of ketone **13** afforded **17** (27%) and 8-*epi*-**17** (59%). The stereochemistry was assigned by comparison with previously reported data.[6,7b,9,11] All other hydride reagents tested gave mainly α-hydroxy compounds.[11] On the other hand, reduction by samarium(II) iodide gave predominantly **17**.[12] Compound **17** was converted to azide **18** with inversion of configuration and reduced to **15** as a single diastereomer. As a preliminary study, the *N*-methyl derivative **16** (α/β = 4:1) was subjected to the coupling reaction. Aldehyde **19**, prepared from **16**, was coupled with the lithium acetylide of **10** in 60% yield. However, the resulting mixture of four diastereomers were inseparable, and the next Lindlar reduction did not proceed. Thus, the amino group was introduced at a later stage of the synthesis.



Scheme 3. Coupling reaction of acetylide **10** with aldehyde **19**.

The hydroxy group of **17** was protected as a TBS ether (**9**),[6] and hydrogenolysis of the benzyl group afforded **22**. Oxidation of the newly formed hydroxy group led to the

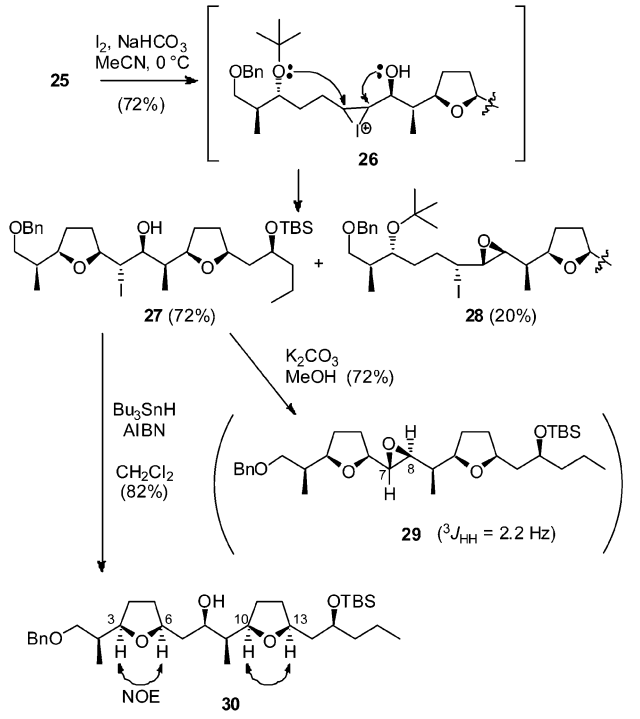
C8–C15 fragment, aldehyde **23**. Nucleophilic addition of the lithium acetylide derived from **10** to aldehyde **23** was successful using cerium trichloride, giving **24** and 8-*epi*-**24** in a ratio of about 2:1 (Scheme 4).[13] These isomers were separated by SiO_2 column chromatography. The yield was only 55% (with the same diastereomeric ratio) using the lithium acetylide. Partial reduction of the triple bond of **24** was successful, giving **25**.



Scheme 4. Coupling reaction of acetylide **10** with aldehyde **23**.

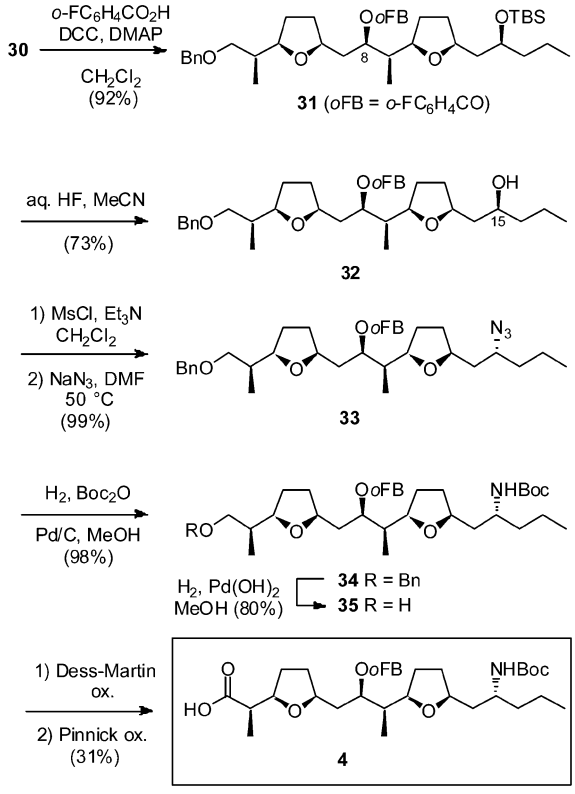
The second *cis*-selective iodoetherification afforded bis-THF compound **27** (Scheme 5). In this reaction, the undesired C7,8-epoxide **28** was formed in 20% via the iodonium cation intermediate **26**. The iodohydrin **27** was converted into the corresponding epoxide **29** to confirm the configuration of the 8β-hydroxy group. The *trans*-epoxy configuration was indicated by a vicinal coupling constant of 2.2 Hz between H7 and H8 in the ^1H NMR spectrum (ca. 5 Hz is typical of *cis*-epoxides). The iodo group of **27** was removed by Bu_3SnH to give **30**, and the stereochemistry of the iodoetherification was determined by observation of strong correlation between H3 and H6 in the NOESY spectrum.

As shown in Scheme 6, the secondary hydroxy group of **30** was protected with the *o*-fluorobenzoyl group to give **31**. We chose this group because it is removable under mildly alkaline conditions. At first, the *m*-nitrobenzoyl group was used. However, the nitro group was not stable during the later hydrogenolysis step (azide to amine). The TBS group was removed (**32**), and the 15-hydroxy group was converted to an azido group (**33**). The azido group was then reduced, and the resulting amino group was simultaneously protected with the Boc group to form **34**. Hydrogenolysis of the benzyl group (**35**) and successive oxidations gave the L-acid with *N*,*O*-protecting groups **4**. The overall yield from



Scheme 5. Second iodoetherification to form *bis*-THF framework.

5 was 1.8% over 19 steps. We have already synthesized the S-acid[6,7] fragment (S = small), and studies towards the total synthesis are under way.



Scheme 6. Synthesis of the L-acid fragment of pamamycin-593 and de-*N*-methylpamamycin-579.

Conclusions

Synthesis of the L-acid (C1–C18) fragment of pamamycin-593 and de-*N*-methylpamamycin-579, strong aerial mycelium inducers of *Streptomyces alboniger*, was achieved using *cis*-selective iodoetherification and nucleophilic addition of a cerium acetylide (C1–C7) to an aldehyde (C8–C18) fragment as the key reaction.

Experimental Section

General: Optical rotation values were measured with a Horiba Sepa-300 polarimeter. FT-IR spectra were recorded as films with a Jasco 4100 spectrometer (ATR, Zn-Se). The IR spectrum was recorded as a film with a Jasco IR Report-100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Inova 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C), Inova 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C), and Gemini 2000 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded with a Jeol JMS–700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Merck silica gel 60 F_{254} (0.50 mm thickness) was used for preparative TLC.

(2*S*,3*R*)-3-*tert*-Butoxy-1-benzyloxy-2-methylhept-6-yne (10): To a solution of dimethyl 1-diazo-2-oxopropylphosphonate (0.79 g, 4.1 mmol) and aldehyde **5** (0.80 g, 2.7 mmol) in dry MeOH (11 mL) was added K_2CO_3 (0.76 g, 5.5 mmol) at 0 °C, and the mixture was stirred for 1 d while the temperature was gradually raised to room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave alkyne **10** (0.72 g, 2.5 mmol, 91%) as a pale yellow oil. R_f = 0.53 (hexane/EtOAc = 5:1). $[\alpha]_D^{24}$ = +28.1 (*c* = 1.05, Et_2O). FT-IR: $\tilde{\nu}$ = 3306 (w), 2972 (s), 2858 (w), 1455 (w), 1389 (w), 1362 (m), 1253 (w), 1190 (m), 1099 (m), 1068 (s), 1026 (w), 734 (m), 697 (m), 624 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.1 Hz, 3 H, 2-Me), 1.20 (s, 9 H, *t*Bu), 1.54–1.61 (m, 2 H), 1.92 (t, *J* = 2.6 Hz, 1 H, 7-H), 2.06 (m, 1 H), 2.21 (m, 2 H), 3.30 (dd, *J* = 9.3, 6.3 Hz, 1 H, 1-H), 3.37 (dd, *J* = 9.3, 6.8 Hz, 1 H, 1-H), 3.75 (dt, *J* = 6.3, 4.7 Hz, 1 H, 3-H), 4.47 (d, *J* = 11.8 Hz, 1 H, CHPh), 4.51 (d, *J* = 11.8 Hz, 1 H, CHPh), 7.27–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.8, 14.8, 29.0, 29.7, 38.1, 68.1, 70.4, 73.0, 73.2, 73.5, 85.0, 127.4, 127.4, 128.3, 138.7 ppm. HR-FABMAS (glycerol + MeOH) calcd. for $C_{19}H_{29}O_2$ $[M + H]^+$ 289.2168; found 289.2169.

(5*E*,9*R*,10*S*)-11-(Benzyloxy)-9-*tert*-butoxy-10-methylundec-5-en-4-one (11): To a suspension of LiBr (790 mg, 9.10 mmol) in dry THF (25 mL) was added dimethyl 2-oxopentylphosphonate (1.77 g, 9.10 mmol), Et_3N (0.70 mL, 5.00 mmol), and aldehyde **5** (1.3 g, 4.6 mmol) in dry THF (15 mL). After being stirred for 4 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl solution at 0 °C and extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (15:1) gave enone **11** (1.4 g, 3.8 mmol, 83%) as a pale yellow oil. R_f = 0.40 (hexane/EtOAc = 5:1). $[\alpha]_D^{24}$ = +17.4 (*c* = 0.60, Et_2O). FT-IR: $\tilde{\nu}$ = 2968 (s), 2874 (m), 1696 (m), 1671 (m), 1627 (m), 1455 (m), 1388 (m), 1362 (m), 1192 (m), 1063 (m), 1017 (m), 973 (m), 723 (m), 697 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.9 Hz, 3 H, 10-Me), 0.93 (t, *J* = 7.4 Hz, 3 H, 1-H), 1.19 (s, 9 H, *t*Bu), 1.45–1.53 (m, 2 H), 1.63 (m, 2 H), 2.04–2.31 (m, 3 H), 2.48 (t, *J* = 7.3 Hz, 2 H, 3-H), 3.32 (dd, *J* = 9.4, 6.3 Hz, 1 H, 11-H), 3.37 (dd, *J* = 9.4, 6.6 Hz, 1 H, 11-H), 3.66 (dt, *J* = 6.3, 5.2 Hz, 1 H, 9-H), 4.45 (d, *J* = 12.3 Hz, 1 H, CHPh), 4.52 (d, *J* = 12.3 Hz, 1 H, CHPh), 6.08 (dt, *J* = 15.9, 1.7 Hz, 1 H, 5-H) 6.83 (dt, *J* = 15.9, 6.9 Hz, 1 H, 6-H), 7.26–7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 12.0, 13.8, 17.7, 28.6, 29.0, 29.3, 38.0, 41.9, 71.1, 73.0, 73.0, 73.5, 127.4, 128.3, 130.1, 138.6, 147.6, 200.9 ppm. HR-FABMS (NOBA): calcd. for $C_{23}H_{37}O_3$ $[M + H]^+$ 361.2743; found 361.2749.

(5*S*,6*S*,9*R*,10*S*)-11-Benzyloxy-6,9-epoxy-5-iodo-10-methylundecan-4-one (12): After a suspension of I_2 (4.8 g, 19 mmol) and $NaHCO_3$ (3.1 g, 38 mmol) in dry MeCN (25 mL) was stirred at 0 °C for 15 min, a solution of **11** (1.4 g, 3.8 mmol) in dry MeCN (13 mL) was added, and the mixture was stirred for 1 d. The reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ solution at 0 °C and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **12** (1.5 g, 3.6 mmol, 95%) as a pale yellow oil. R_f = 0.45 (toluene/EtOAc = 19:1). $[\alpha]_D^{23}$ = –52 (*c* = 0.50, Et_2O). FT-IR: $\tilde{\nu}$ = 2962 (s), 2932 (s), 2873 (s), 1707 (m), 1454 (m), 1362 (m), 1053 (s), 734 (m), 697 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.4 Hz, 3 H, 1-H), 0.93 (d, *J* = 6.9 Hz, 3 H, 10-Me), 1.58–1.71 (m, 3 H), 1.82–1.97 (m, 3 H), 2.20 (m, 1 H), 2.66 (t, *J* = 7.1 Hz, 1 H, 3-H), 2.67 (t, *J* = 7.1 Hz, 1 H, 3-H), 3.32 (dd, *J* = 6.6, 9.1 Hz, 1 H, 11-H), 3.50 (dd, *J* = 4.7, 9.1 Hz, 1 H, 11-H), 3.84 (dt, *J* = 5.7, 8.0 Hz, 1 H, 9-H), 4.27 (m, 1 H, 5-H), 4.47 (s, 2 H, CH_2Ph), 7.28–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.5, 13.6, 17.4, 28.3, 31.2, 35.8, 39.2, 40.4, 72.7, 73.0, 79.3, 83.1, 127.4, 127.4, 128.3, 138.7, 204.2 ppm. HR-FABMS (NOBA): calcd. for $C_{19}H_{28}IO_3$ $[M + H]^+$ 431.1083; found 431.1082.

(6*S*,9*R*,10*S*)-11-Benzyloxy-6,9-epoxy-10-methylundecan-4-one (13): A solution of **12** (200 mg, 0.47 mmol), AIBN (15 mg, 0.093 mmol), and Bu_3SnH (270 mg, 0.93 mmol) in dry CH_2Cl_2 (4.5 mL) was stirred at 0 °C for 2 h. Then KF (200 mg) was added, and the mixture was filtered through a Celite pad. The filtrate was concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1 to 5:1) gave **13** (120 mg, 0.40 mmol, 85%) as a pale yellow oil. R_f = 0.40 (hexane/EtOAc = 4:1). $[\alpha]_D^{25}$ = –4.0 (*c* = 0.50, Et_2O). FT-IR: $\tilde{\nu}$ = 2961 (s), 2874 (s), 1710 (s), 1454 (m), 1363 (m), 1199 (w), 1073 (s), 735 (m), 697 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H, 1-H), 0.94 (d, *J* = 6.9 Hz, 3 H, 10-Me), 1.45 (m, 1 H, 7-H), 1.55–1.64 (m, 4 H, 2-H, 8-H), 1.84–1.95 (m, 2 H, 8-H, 10-H), 2.05 (m, 1 H, 7-H), 2.43 (dt, *J* = 1.5, 7.4 Hz, 2 H, 3-H), 2.64 (dd, *J* = 6.3, 15.4 Hz, 1 H, 5-H), 2.72 (dd, *J* = 6.6, 15.4 Hz, 1 H, 5-H), 3.34 (dd, *J* = 7.4, 9.1 Hz, 1 H, 11-H), 3.57 (dd, *J* = 4.4, 9.1 Hz, 1 H, 11-H), 3.70 (q, *J* = 7.1 Hz, 1 H, 9-H), 4.20 (quint, *J* = 6.3 Hz, 1 H, 6-H), 4.50 (s, 2 H, CH_2Ph), 7.25–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.6, 13.7, 17.0, 28.4, 31.2, 39.0, 45.6, 49.1, 73.0, 73.1, 75.1, 81.0, 127.4, 127.5, 128.3, 138.8, 209.7 ppm. HR-FABMAS (NOBA): calcd. for $C_{19}H_{29}O_3$ $[M + H]^+$ 305.2217; found 305.2121.

(4*S*,6*S*,9*R*,10*S*)-11-Benzyloxy-6,9-epoxy-10-methylundecan-4-ol (17)

a) $NaBH_3$ Reduction: A solution of **13** (100 mg, 0.33 mmol) and $NaBH_4$ (15 mg, 0.40 mmol) in MeOH (20 mL) was stirred at 0 °C for 30 min. The mixture was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated. en vacuo. Chromatography afforded **17** (27 mg, 0.088 mmol, 27%) and 8-*epi*-**17** (63 mg, 0.21 mmol, 63%) as colorless oils.

b) SmI_2 Reduction: To a solution of **13** (29 mg, 0.095 mmol) in dry MeOH (0.5 mL) was added SmI_2 (0.1 M in THF, 5.0 mL, 0.50 mmol) at 45 °C, and the mixture was stirred for 4.5 h under argon. The reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (5:1) gave **17** (17 mg, 0.055 mmol, 59%) and 8-*epi*-**17** (6.0 mg, 0.020 mmol, 21%) as pale yellow oils. **17**: R_f = 0.20 (hexane/EtOAc = 4:1). $[\alpha]_D^{23}$ = –6.15 (*c* = 1.00, Et_2O). FT-IR: $\tilde{\nu}$ = 3432 (br., m), 2958 (s), 2932 (s), 1870 (s), 1454 (m), 1364 (m), 1072 (s), 1027 (m), 734 (m), 697 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.927 (t, *J* = 7.1 Hz, 3 H, 1-H), 0.934 (d, *J* = 6.9 Hz, 3 H, 10-Me), 1.29–1.79 (m, 8 H), 1.86–1.99 (m, 3 H), 3.38 (dd, *J* = 6.7, 9.1 Hz, 1 H, 11-H), 3.55 (dd, *J* = 4.8, 9.1 Hz, 1 H, 11-H), 3.72 (dt, *J* = 6.3, 7.4 Hz, 1 H, 4-H), 3.84 (m, 1 H, 9-H), 4.12 (q, *J* = 7.1 Hz, 1 H, 6-H), 4.50 (s, 2 H, CH_2Ph), 7.23–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.7, 14.2, 19.0, 28.7, 30.6, 38.9, 39.4, 40.8, 68.9, 73.0, 73.1, 76.9, 81.4, 127.4, 127.5, 128.3, 138.7 ppm. HR-FABMS (NOBA): calcd. for $C_{19}H_{31}O_3$ $[M + H]^+$ 307.2273; found 307.2271. HR-EIMS: calcd. for $C_{19}H_{30}O_3$ $[M]^+$ 306.2195; found 306.2197. 8-*Epi*-**17**: R_f = 0.29 (hexane/EtOAc = 4:1). IR: $\tilde{\nu}$ = 3500 (br., m), 2950 (s), 1450 (s), 1360 (s), 1280 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.925 (t, *J* = 7.1 Hz, 3 H, 1-H), 0.93 (d, *J* = 6.9 Hz, 3 H, 10-Me), 1.30–1.73 (m, 8 H), 1.82–2.06 (m, 3 H), 3.38 (dd, *J* = 6.7, 9.1 Hz, 1 H, 11-H), 3.53 (dd, *J* = 4.7, 9.1 Hz, 1 H, 11-H), 3.72 (q, *J* = 6.3 Hz, 1 H, 4-H), 3.84 (br. s, 1 H, OH), 4.01 (ddt, *J* = 7.1, 3.0, 6.8 Hz, 1 H, 6-H), 4.50 (s, 2 H, CH_2Ph), 7.23–7.34 (m, 5 H, Ph) ppm. HR-EIMS: calcd. for $C_{19}H_{30}O_3$ $[M]^+$ 306.2195; found 306.2196.

(2*S*,3*R*,6*S*,8*R*)-8-Azido-1-benzyloxy-3,6-epoxyundecane (18): To a solution of **17** (23 mg, 0.073 mmol) and Et_3N (0.050 mL, 0.37 mmol) in dry CH_2Cl_2 (0.5 mL) was added MsCl (0.030 mL, 0.37 mmol). After being stirred for 30 min, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated en vacuo. The residue was used in the next step without further purification. A mixture of the crude mesylate and NaN_3 (24 mg, 0.37 mmol) in DMF (4.0 mL) was stirred for 2 d at 50 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated. en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **18** (24.5 mg, 0.074 mmol, quant.) as a pale yellow oil. $[\alpha]_D^{26}$ = –11 (*c* = 0.30, Et_2O). R_f = 0.73 (toluene/EtOAc = 5:1). FT-IR: $\tilde{\nu}$ = 2960 (m), 2933 (m), 2872 (m), 2098 (s), 1415 (w), 1254 (w), 1094 (m), 1070 (m), 734 (m), 697 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.9 Hz, 3 H, 11-Me), 0.95 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.37–1.65 (m, 8 H), 1.79–2.05 (m, 3 H), 3.32–3.40 (m, 2 H), 3.60 (dd, *J* = 4.4, 9.1 Hz, 1 H), 3.72 (q, *J* = 7.4 Hz, 1 H), 3.92 (quint, *J* = 6.9 Hz, 1 H), 4.51 (s, 2 H, CH_2Ph), 7.25–7.34 (m, 5 H, Ph) ppm. HR-FABMS (NOBA): calcd. for $C_{19}H_{30}N_3O_2$ $[M + H]^+$ 332.2338; found 332.2341.

(2*S*,3*R*,6*S*,8*R*)-1-Benzyloxy-8-*tert*-butoxycarbonylamino-3,6-epoxyundecane (15): A suspension of **18** (20 mg, 0.060 mmol) and Pd/$BaSO_4$ (30 mg) in dry MeOH (1.0 mL) was stirred for 10 h under hydrogen (1 atm). The reaction mixture was filtered, and the filtrate was concentrated en vacuo. The residue was used in the next step without further purification. A solution of the crude amine, Et_3N (0.025 mL, 0.18 mmol), and Boc_2O (52 mg, 0.24 mmol) in CH_2Cl_2 (2.0 mL) was stirred at 20 °C for 1 d. The reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **15** (18 mg, 0.046 mmol, 77%) as a pale yellow oil, $[\alpha]_D^{23}$ = –36 (*c* = 0.10, Et_2O). FT-IR $\tilde{\nu}$ = 3357 (w), 2959 (s), 2931 (s), 2871 (s), 1711 (s), 1499 (m), 1454 (m), 1364 (s), 1249 (m), 1169 (s), 1067 (s), 735 (m), 697 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.9 Hz, 3 H, 11-H), 0.95 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.26–1.63 (m, 8 H), 1.42 (s, 9 H, *t*Bu), 1.82–1.93 (m, 2 H), 2.02 (m, 1 H), 3.37 (dd, *J* = 7.4, 9.1 Hz, 1 H, 1-H), 3.37 (m, 1 H), 3.61 (dd, *J* = 4.4, 9.1 Hz, 1 H, 1-H), 3.65 (q, *J* = 7.4 Hz, 1 H), 3.86 (quint, *J* = 6.3 Hz, 1 H), 4.51 (s, 2 H, CH_2Ph), 4.56 (br. d, *J* = 7.4 Hz, 1 H, NH), 7.28–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.7, 14.0, 18.9, 28.4, 28.5, 31.4, 38.3, 39.0, 41.3, 49.0, 73.0, 73.2, 78.7, 81.0, 127.3, 127.5, 128.3, 138.8, 155.7 ppm. HR-FABMAS (NOBA): calcd. for $C_{24}H_{40}NO_4$ $[M + H]^+$ 406.2957; found 406.2961.

(4*S*,6*S*,9*R*,10*S*)-11-Benzyloxy-4-*tert*-butyldimethylsilyloxy-6,9-epoxyundecane (9): A solution of **17** (15 mg, 0.048 mmol), 2,6-lutidine (0.022 mL, 0.19 mmol), and TBSOTf (0.022 mL, 0.095 mmol) in dry CH_2Cl_2 (1.0 mL) was stirred at 0 °C for 12 h, while the temperature was gradually raised to room temperature. The reaction mixture was then poured into brine and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **9** (20 mg, 0.048 mmol, quant) as a pale yellow oil. R_f = 0.66 (hexane/EtOAc = 4:1). $[\alpha]_D^{24}$ = +8.9 (*c* = 1.2, $CHCl_3$).[6] FT-IR: $\tilde{\nu}$ = 2955 (s), 2930 (s), 2855 (m), 1461 (w), 1376 (w), 1252 (w), 1066 (m), 1005 (w), 944 (w), 834 (m), 808 (w), 773 (m), 732 (w), 696 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.037 (s, 3 H, SiMe), 0.043 (s, 3 H, SiMe), 0.88 (s, 9 H, *t*Bu), 0.90 (t, *J* = 7.1 Hz, 3 H, 11-H), 0.95 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.25–1.58 (m, 8 H), 1.82–1.98 (m, 3 H), 3.34 (dd, *J* = 7.4, 9.1 Hz, 1 H, 1-H), 3.59 (pseudo q, *J* = 8.0 Hz, 1 H), 3.64 (dd, *J* = 4.4, 9.1 Hz, 1 H, 1-H), 3.80–3.90 (m, 2 H), 4.50 (s, 2 H, CH_2Ph), 7.25–7.36 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 14.4, 18.1, 18.2, 25.7, 26.0, 28.9, 31.5, 40.5, 43.5, 69.7, 73.0, 73.4, 75.7, 80.6, 127.4, 127.5, 128.3, 138.9 ppm. HR-FABMS (NOBA + NaCl): calcd. for $C_{25}H_{44}O_3SiNa$ $[M + Na]^+$ 443.2957; found 443.2959.

(2*S*,3*R*,6*S*,8*S*)-8-*tert*-Butyldimethylsilyloxy-3,6-epoxy-2-methylundecan-1-ol (22): A suspension of **9** (50 mg, 0.12 mmol) and 10% Pd/C (25 mg) in dry MeOH (8 mL) was stirred for 15 min under hydrogen (1 atm). The reaction mixture was filtered, and the filtrate was concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave alcohol **22** (36 mg, 0.11 mmol, 0.067 mmol, 92%) as a pale yellow oil. R_f = 0.43 (hexane/EtOAc = 4:1). $[\alpha]_D^{24}$ = +44.9 (*c* = 1.05, Et_2O). FT-IR: $\tilde{\nu}$ = 3461 (w), 2956 (s), 2930 (s), 2856 (m), 1462 (w), 1377 (w), 1253 (w), 1039 (m), 939 (w), 834 (m), 807 (w), 773 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, $SiMe_2$), 0.82 (d, *J* = 6.9 Hz, 3 H, 11-H), 0.89 (s, 9 H, *t*Bu), 0.86–0.92 (m, 3 H), 1.27–1.63 (m, 9 H), 1.72 (m, 1 H), 1.88–2.07 (m, 2 H), 3.52–3.63 (m, 4 H), 3.80 (m, 1 H), 3.97 (pseudo quint, *J* = 7.4 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.7, 14.3, 18.0, 18.1, 25.9, 30.6, 30.8, 40.6, 41.0, 43.2, 68.8, 69.5, 76.6, 85.8 ppm. HR-FABMS (NOBA): calcd. for $C_{18}H_{39}O_3Si$ $[M + H]^+$ 331.2667; found 331.2669.

(2*R*,3*R*,6*S*,8*S*)-8-*tert*-Butyldimethylsilyloxy-3,6-epoxy-2-methylundecanal (23): A suspension of **22** (22 mg, 0.060 mmol), Dess–Martin periodinane (40 mg, 0.094 mmol), and $NaHCO_3$ (20 mg, 0.24 mmol) in dry Et_2O (2.5 mL) was stirred at 0 °C for 30 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined extracts were

washed with saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave aldehyde **23** (17 mg, 0.053 mmol, 88%) as a pale yellow oil. R_f = 0.43 (hexane/EtOAc = 4:1). FT-IR (film): $\tilde{\nu}$ = 2950 (s), 2700 (m, H–CO), 1725 (s, C=O), 1460 (s), 1370 (s), 1250 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.037 (s, 3 H, SiMe), 0.043 (s, 3 H, SiMe), 0.88 (s, 9 H, *t*Bu), 0.89 (t, J = 7.4 Hz, 3 H, 11-H), 1.06 (d, J = 7.1 Hz, 3 H, 2-Me), 1.23–1.66 (m, 8 H), 1.92–2.07 (m, 2 H), 2.43 (pseudo quint, J = 7.1 Hz, 1 H), 3.80–3.98 (m, 3 H), 9.77 (d, J = 2.5 Hz, 1 H, 1-H) ppm. HR-FABMS (glycerol): calcd. for $C_{18}H_{37}O_3Si$ $[M + H]^+$ 329.2512; found 329.2514.

(2*S*,3*R*,8*S*,9*S*,10*R*,13*S*,*15S*)-1-Benzyloxy-3-*tert*-butoxy-15-*tert*-butyldimethylsilyloxy-10,13-epoxy-2,9-dimethyloctadec-6-yn-8-ol (24): To a solution of alkyne **10** (260 mg, 0.90 mmol) in dry THF (5.0 mL) was added BuLi (1.6 M in hexane, 0.53 mL) at –70 °C, and the mixture was stirred for 1 h at –78 °C under argon. This mixture was then added to a suspension of dry $CeCl_3$ (240 mg, 0.91 mmol) in dry THF (2.0 mL), and the mixture was stirred for an additional 1 h at –78 °C. To this mixture was added aldehyde **23** (110 mg, 0.33 mmol) in dry THF (3.0 mL), and the mixture was stirred for 6 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (15:1) gave **24** (134 mg, 0.217 mmol, 65%) and 8-*epi*-**24** (66 mg, 0.107 mmol, 32%) as pale yellow oils. **24**: R_f = 0.31 (hexane/Et_2O = 3:1). $[\alpha]_D^{24}$ = +38 (c = 0.20, Et_2O). FT-IR: $\tilde{\nu}$ = 3488 (w), 2958 (s), 2360 (s), 2337 (m), 1461 (w), 1363 (w), 1254 (w), 1193 (w), 1069 (m), 835 (m), 775 (w), 698 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.062 (s, 3 H, SiMe), 0.078 (s, 3 H, SiMe), 0.88 (s, 9 H, *t*Bu), 0.86–0.92 (m, 9 H), 1.20 (s, 9 H), 1.26–1.63 (m, 10 H), 1.81 (m, 1 H), 1.91–2.00 (m, 2 H), 2.08 (m, 1 H), 2.17–2.39 (m, 2 H), 3.29 (dd, J = 6.6, 9.1 Hz, 1 H, 1-H), 3.39 (dd, J = 6.6, 9.1 Hz, 1 H, 1-H), 3.68–3.70 (m, 2 H), 3.75–3.83 (m, 2 H), 3.91–4.04 (m, 2 H), 4.34 (s, 2 H), 4.49 (s, 2 H), 7.29–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.6, –4.4, 12.0, 13.8, 14.3, 15.3, 18.0, 18.1, 26.0, 29.0, 30.2, 30.4, 30.7, 38.1, 40.5, 43.3, 43.9, 67.6, 69.5, 70.7, 73.0, 73.2, 73.4, 79.0, 82.1, 86.4, 127.4, 127.4, 128.3, 138.7 ppm. HR-FABMS (NOBA + NaCl): calcd. for $C_{37}H_{64}O_5SiNa$ $[M + Na]^+$ 639.4421; found 639.4423. 8-*epi*-**24**: R_f = 0.23 (hexane/Et_2O = 3:1). FT-IR: $\tilde{\nu}$ = 3438 (w), 2957 (s), 2360 (s), 2339 (m), 1456 (m), 1362 (m), 1253 (m), 1193 (m), 1066 (s), 835 (m), 775 (w), 697 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.88 (s, 9 H), 0.86–0.94 (m, 9 H), 1.19 (s, 9 H), 1.26–1.72 (m, 10 H), 1.87–2.12 (m, 3 H), 2.17–2.38 (m, 2 H), 3.28 (dd, J = 6.6, 9.3 Hz, 1 H, 1-H), 3.38 (dd, J = 6.9, 9.3 Hz, 1 H, 1-H), 3.60 (m, 1 H), 3.670 (m, 1 H), 3.79 (m, 1 H), 3.99 (m, 1 H), 4.19 (s, 1 H), 4.39 (d, J = 8.2 Hz, 1 H), 4.48 (s, 2 H), 7.29–7.35 (m, 5 H, Ph) ppm.

(2*S*,3*R*,6*Z*,8*S*,9*S*,10*R*,13*S*,*15S*)-1-Benzyloxy-3-*tert*-butoxy-15-*tert*-butyldimethylsilyloxy-10,13-epoxy-2,9-dimethyloctadec-6-en-8-ol (25): A suspension of **24** (25 mg, 0.040 mmol) and Lindlar catalyst (42 mg) in dry MeOH (0.5 mL) was stirred for 15 min under hydrogen (1 atm). The reaction mixture was filtered, and the filtrate was concentrated en vacuo. The residue was chromatographed on silica gel. Elution with toluene/EtOAc (20:1) gave **25** (24 mg, 0.039 mmol, 98%) as a pale yellow oil. R_f = 0.34 (hexane/EtOAc = 5:1). $[\alpha]_D^{23}$ = +34 (c = 0.50, Et_2O). FT-IR: $\tilde{\nu}$ = 3516 (w), 2958 (s), 2934 (s), 2856 (m), 1461 (w), 1362 (w), 1253 (m), 1194 (w), 1071 (m), 946 (w), 835 (m), 774 (m), 734 (w), 697 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 9 H), 0.81–0.92 (m, 9 H), 1.19 (s, 9 H), 1.26–1.63 (m, 12 H), 1.80–2.16 (m, 4 H), 3.30 (dd, J = 6.6, 9.1 Hz, 1 H), 3.39 (dd, J = 6.3, 9.1 Hz, 1 H), 3.61 (q, J = 5.5 Hz, 1 H), 3.72–3.84 (m, 2 H), 3.92–4.01 (m, 2 H), 4.44–4.53 (m, 3 H), 5.49–5.52 (m, 2 H), 7.28–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.7, –4.3, 12.3, 13.6, 14.1, 14.4, 18.0, 18.1, 22.7, 24.7, 24.1, 25.9, 29.0, 30.6, 31.0, 31.2, 31.6, 38.2, 40.6, 43.3, 44.2, 69.5, 71.0, 71.5, 73.0, 73.3, 73.4, 76.6, 82.2, 127.4, 127.5, 128.3, 129.6, 132.1, 138.7 ppm. HR-FABMS (NOBA): calcd. for $C_{37}H_{67}O_5Si$ $[M + H]^+$ 619.4758; found 619.4761.

(2*S*,3*R*,6*S*,7*S*,8*S*,9*R*,10*R*,13*S*,15*S*)-1-Benzyloxy-15-*tert*-butyldimethylsilyloxy-3,6:10,13-diepoxy-7-iodo-2,9-dimethyloctadecan-8-ol (27): To a suspension of I_2 (57 mg, 0.23 mmol) and $NaHCO_3$ (38 mg, 0.45 mmol) in dry MeCN (1.0 mL) was added **26** (28 mg, 0.045 mmol) in dry MeCN (1.0 mL) at 0 °C, and the mixture was stirred for 20 min at 0 °C. Then the reaction mixture was poured into saturated aqueous $Na_2S_2O_3$ solution and extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **27** (22 mg, 0.032 mmol, 72%) as a pale yellow oil. R_f = 0.29 (hexane/EtOAc = 5:1). $[\alpha]_D^{23}$ = +26 (c = 0.35, Et_2O). FT-IR: $\tilde{\nu}$ = 3411 (w), 2956 (s), 2928 (s), 2855 (s), 1461 (m), 1377 (w), 1254 (m), 1066 (m), 952 (w), 835 (m), 807 (w), 774 (m), 733 (w) and 697 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiMe_2$), 0.86–0.91 (m, 3 H), 0.88 (s, 9 H, *t*Bu), 0.96 (d, J = 6.9 Hz, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 1.26–1.59 (m, 8 H), 1.64–2.18 (m, 8 H), 3.41 (dd, J = 6.9, 9.3 Hz, 1 H), 3.61 (dd, J = 4.9, 9.3 Hz, 1 H), 3.71–3.93 (m, 6 H), 4.21 (pseudo dt, J = 8.8, 3.3 Hz, 1 H), 4.38 (pseudo dd, J = 8.8, 2.2 Hz, 1 H), 4.51 (s, 2 H,CH_2 Ph), 7.28–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –4.5, 10.9, 13.6, 14.3, 17.9, 18.0, 25.8, 28.0, 29.0, 31.3, 31.9, 38.2, 40.5, 41.6, 43.2, 44.5, 69.6, 73.0, 73.1, 73.8, 76.1, 77.6, 81.8, 82.6, 127.4, 127.6, 128.4 ppm. HR-FABMS (NOBA + NaCl): calcd. for $C_{33}H_{57}O_5SiNaI$ $[M + Na]^+$ 711.2918; found 711.2917.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*S*)-1-Benzyloxy-15-*tert*-butyldimethylsilyloxy-3,6:7,8:10,13-triepoxy-2,9-dimethyloctadecane (29): A suspension of **27** (6.1 mg, 0.0087 mmol) and K_2CO_3 (12 mg, 0.087 mmol) in dry MeOH (0.6 mL) was stirred at 20 °C for 2 h, and the reaction mixture was poured into water and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **29** (3.5 mg, 0.0062 mmol, 72%) as a pale yellow oil. R_f = 0.31 (hexane/EtOAc = 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, SiMe), 0.87–0.91 (m, 3 H), 0.88 (s, 9 H, *t*Bu), 0.96 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.0 Hz, 3 H), 1.26–1.36 (m, 4 H), 1.39 (m, 4 H), 1.52–1.64 (m, 4 H), 1.80–1.98 (m, 4 H), 2.77 (dd, J = 2.2, 7.1 Hz, 1 H), 2.91 (dd, J = 2.2, 3.6 Hz, 1 H), 3.39 (dd, J = 7.1, 9.1 Hz, 1 H), 3.47 (dd, J = 4.4, 9.1 Hz, 1 H), 3.67 (m, 1 H), 3.72–3.91 (m, 3 H), 3.97 (m, 1 H), 4.51 (s, 2 H), 7.28–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.6, –4.4, 13.2, 13.5, 14.4, 18.1, 18.1, 25.9, 26.8, 28.6, 29.0, 31.5, 38.8, 40.5, 41.1, 43.4, 59.1, 56.0, 69.7, 73.0, 73.2, 75.9, 77.8, 80.9, 81.4, 127.4, 127.5, 128.3, 138.8 ppm. HR-FABMS (NOBA): calcd. for $C_{33}H_{57}O_5Si$ $[M + H]^+$ 561.3975; found 561.3981.

(2*S*,3*R*,6*S*,8*R*,9*S*,10*R*,13*S*,15*S*)-1-Benzyloxy-15-*tert*-butyldimethylsilyloxy-3,6:10,13-diepoxy-2,9-dimethyloctadecan-8-ol (30): A solution of **27** (70 mg, 0.10 mmol), AIBN (8.3 mg, 0.051 mmol), and Bu_3SnH (0.054 mL, 0.20 mmol) in dry CH_2Cl_2 (1.2 mL) was stirred at 0 °C. for 2 h. KF (70 mg) was then added, and the mixture was extracted with Et_2O. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **30** (49 mg, 0.083 mmol, 82%) as a pale yellow oil. R_f =

0.43 (hexane/EtOAc = 3:1). $[\alpha]_D^{22}$ = +25 (*c* = 0.45, Et_2O). FT-IR: $\tilde{\nu}$ = 3502 (w), 2956 (s), 2932 (s), 2855 (m), 1460 (w), 1375 (w), 1252 (w), 1065 (m), 943 (w), 835 (m), 808 (w), 774 (m), 733 (w), 697 (w) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, SiMe), 0.87 (d, *J* = 8.4 Hz, 3 H, 9-Me), 0.88 (t, *J* = 7.2 Hz, 3 H, 18-H), 0.88 (s, 9 H, *t*Bu), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.26–1.34 (m, 3 H, 17-H), 1.42 (m, 2 H, 16-H), 1.47 (m, 1 H), 1.52–1.70 (m, 8 H, 14-H), 1.73 (m, 1 H), 1.89 (m, 1 H, 2-H), 1.91–2.02 (m, 2 H), 3.34 (dd, *J* = 7.7, 9.1 Hz, 1 H, 1-H), 3.50 (br. s, OH), 3.62 (dd, *J* = 4.4, 9.1 Hz, 1 H, 1-H), 3.71 (q, *J* = 7.8 Hz, 1 H, 3-H), 3.73 (dd, *J* = 8.4, 6.6 Hz, 1 H, 10-H), 3.80 (quint, *J* = 6.3 Hz, 1 H, 15-H), 3.91 (m, 1 H, 8-H), 3.92 (m, 1 H, 13-H), 4.06 (dq, *J* = 8.4, 6.6 Hz, 1 H, 6-H), 4.50 (s, 2 H, CH_2Ph), 7.27–7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = –4.7, –4.4, 13.0, 13.7, 14.4, 18.0, 18.1, 25.9, 28.7, 30.1, 31.2, 31.5, 39.1, 39.2, 40.6, 43.1, 43.3, 69.5, 71.3, 73.0, 73.3, 76.3, 76.9, 80.7, 82.5, 127.4, 127.5, 128.3, 138.9 ppm. HR-FABMS (NOBA): calcd. for $C_{33}H_{59}O_5Si$ $[M + H]^+$ 563.4132; found 563.4133.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*S*)-1-Benzyloxy-15-*tert*-butyldimethylsilyloxy-3,6:10,13-diepoxy-2,9-dimethyloctadecan-8-yl *o*-Fluorobenzoate (31): To a solution of **30** (7.5 mg, 0.013 mmol), *o*-fluorobenzoic acid (18 mg, 0.13 mmol), and DMAP (15 mg, 0.13 mmol) in dry CH_2Cl_2 (1 mL) was added DCC (52 mg, 0.25 mmol) at 0 °C, and the mixture was stirred at room temperature for 8 h. The reaction mixture was filtered, and the filtrate was washed with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution, and brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **31** (8.0 mg, 0.012 mmol, 92%) as a pale yellow oil. R_f = 0.51 (hexane/EtOAc = 4:1). $[\alpha]_D^{25}$ = +10 (*c* = 0.57, Et_2O). FT-IR: $\tilde{\nu}$ = 2956 (s), 2931 (s), 2855 (s), 1715 (s), 1613 (m), 1456 (m), 1299 (s), 1249 (s), 1127 (m), 1076 (s), 836 (m), 775 (m), 757 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, SiMe), 0.87 (s, 9 H, *t*Bu), 0.91 (t, *J* = 7.1 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.29–1.66 (m, 12 H), 1.84–2.00 (m, 6 H), 3.38 (dd, *J* = 7.4, 9.3 Hz, 1 H), 3.63 (dd, *J* = 4.7, 6.9 Hz, 1 H), 3.67–3.74 (m, 2 H), 3.81–3.95 (m, 3 H), 4.53 (s, 2 H, CH_2Ph), 5.54 (m, 1 H, 8-H), 7.12–7.25 (m, 6 H), 7.37 (d, *J* = 4.4 Hz, 1 H), 7.54 (m, 1 H), 7.97 (dt, *J* = 1.9, 7.7 Hz, 1 H) ppm. HR-EIMS: calcd. for $C_{40}H_{61}FO_6Si$ $[M]^+$ 684.4221; found 684.4222.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*S*)-1-Benzyloxy-3,6:10,13-diepoxy-15-hydroxy-2,9-dimethyloctadecan-8-yl *o*-Fluorobenzoate (32): A 15 mL Falcon tube equipped with a magnetic stir bar was charged with **31** (8.0 mg, 0.013 mmol) in dry MeCN (1 mL). To the solution was added HF (40% aqueous HF/MeCN = 1:19, 0.050 mL) at 0 °C, and the mixture was stirred at room temperature for 15 h. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (3:1) gave **32** (5.3 mg, 0.0093 mmol, 73%) as a pale yellow oil. R_f = 0.54 (hexane/EtOAc = 1:1). $[\alpha]_D^{26}$ = –6.0 (*c* = 0.37, Et_2O). FT-IR: $\tilde{\nu}$ = 3525 (w), 2961 (s), 2871 (s), 1714 (s), 1613 (m), 1488 (m), 1455 (m), 1378 (w), 1299 (s), 1250 (m), 1128 (m), 1079 (m), 758 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.8 Hz, 3 H, 18-H), 0.93 (d, *J* = 7.3 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.30–1.71 (m, 12 H), 1.85–1.96 (m, 6 H), 2.82 (br. s, 1 H), 3.34 (t, *J* = 8.8 Hz, 1 H), 3.60 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.66 (quint, *J* = 7.3 Hz, 2 H), 3.83 (br. s, 1 H), 3.87 (quint, *J* = 6.3 Hz, 1 H), 4.03 (m, 1 H), 4.50 (s, 2 H, CH_2Ph), 5.56 (t, *J* = 6.3 Hz, 1 H, 8-H), 7.12 (dd, *J* = 8.8, 10.3 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 7.20–7.40 (m, 4 H), 7.33 (d, *J* = 4.4 Hz, 1 H), 7.50 (m, 1 H), 7.94 (t, *J* = 7.8 Hz, 1 H) ppm. HR-FABMS (NOBA): calcd. for $C_{34}H_{48}FO_6$ $[M + H]^+$ 571.3435; found 571.3442.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*R*)-15-Azido-1-benzyloxy-3,6:10,13-diepoxy-2,9-dimethyloctadecan-8-yl *o*-Fluorobenzoate (33): To a solution of **32** (11 mg, 0.018 mmol) and Et_3N (0.051 mL, 0.37 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added MsCl (0.014 mL, 0.18 mmol), and the mixture was stirred for 13 h. The mixture was then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated en vacuo. The residual crude mesylate was used in the next step without further purification. A solution of the crude mesylate and NaN_3 (15 mg, 0.23 mmol) in DMF (2 mL) was stirred at 50 °C for 2 d. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **33** (11 mg, 0.018 mmol, 99%) as a pale yellow oil. R_f = 0.54 (hexane/EtOAc = 3:1). $[\alpha]_D^{21}$ = –4.4 (*c* = 0.64, Et_2O). FT-IR: $\tilde{\nu}$ = 2962 (m), 2872 (m), 2359 (s), 2101 (s), 1717 (m), 1613 (w), 1488 (w), 1455 (w), 1298 (m), 1250 (w), 1078 (w) and 758 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.9 Hz, 3 H, 18-H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 7.1 Hz, 3 H), 1.34–1.61 (m, 12 H), 1.76–2.02 (m, 6 H), 3.37 (dd, *J* = 7.4, 9.1 Hz, 2 H, 1 H), 3.38 (m, 1 H), 3.60 (dd, *J* = 4.4, 9.1 Hz, 1 H), 3.63–3.76 (m, 2 H), 3.82–3.94 (m, 2 H), 4.50 (s, 2 H, CH_2Ph), 5.53 (dt, *J* = 2.7, 6.8 Hz, 1 H, 8-H), 7.13 (m, 1 H), 7.19 (m, 1 H), 7.33 (d, *J* = 4.4 Hz, 1 H), 7.47–7.54 (m, 5 H), 7.94 (m, 1 H) ppm. HR-FABMS (NOBA): calcd. for $C_{34}H_{47}FN_3O_5$ $[M + H]^+$ 596.3500; found 596.3496.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*R*)-1-Benzyloxy-15-*tert*-butoxycarbonylamino-3,6:10,13-diepoxy-2,9-dimethyloctadecan-8-yl *o*-Fluorobenzoate (34): A suspension of **33** (13 mg, 0.021 mmol), 10% Pd/C (22 mg), and Boc_2O (9.1 mg, 0.042 mmol) in dry MeOH (1.0 mL) was stirred for 2 h under hydrogen (1 atm). The reaction mixture was filtered, and the filtrate was concentrated en vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (5:1) gave **34** (14 mg, 0.021 mmol, 98%) as a pale yellow oil. R_f = 0.37 (hexane/EtOAc = 3:1). $[\alpha]_D^{27}$ = –4.7 (*c* = 0.36, Et_2O). FT-IR: $\tilde{\nu}$ = 3388 (w), 2963 (m), 2872 (m), 1709 (s), 1613 (m), 1488 (w), 1455 (w), 1364 (m), 1298 (m), 1249 (m), 1078 (m), 805 (m), 757 (m), 697 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H, 18-H), 0.93 (d, *J* = 6.3 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.25–1.62 (m, 10 H), 1.41 (s, 9 H, *t*Bu), 1.81–2.05 (m, 8 H), 3.34 (dd, *J* = 7.3, 8.7 Hz, 1 H), 3.56 (m, 1 H), 3.60 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.64–3.71 (m, 2 H), 3.82 (quint, *J* = 6.3 Hz, 1 H), 3.90 (quint, *J* = 6.3 Hz, 1 H), 4.49 (s, 2 H), 4.51 (br. s, 1 H), 5.53 (m, 1 H, 8-H), 7.12 (dd, *J* = 8.3, 10.3 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.26 (s, 2 H), 7.33 (d, *J* = 4.4 Hz, 3 H), 7.49 (m, 1 H), 7.94 (m, 1 H) ppm. HR-FABMS (NOBA): calcd. for $C_{39}H_{57}FNO_7$ $[M + H]^+$ 670.4119; found 670.4121.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*R*)-15-*tert*-Butoxycarbonylamino-3,6:10,13-diepoxy-1-hydroxy-2,9-dimethyloctadecan-8-yl *o*-Fluorobenzoate (35): A suspension of **34** (6.1 mg, 0.0091 mmol) and $Pd(OH)_2$ (5.0 mg) in dry MeOH (0.50 mL) was stirred overnight under hydrogen (1 atm). The reaction mixture was filtered, and the filtrate was concentrated en vacuo to give alcohol **35** (4.2 mg, 0.0072 mmol, 80%) as a pale yellow oil. R_f = 0.31 (hexane/EtOAc = 1:1). $[\alpha]_D^{20}$ = +3.8 (*c* = 0.20, Et_2O). FT-IR: $\tilde{\nu}$ = 3391 (w), 2961 (s), 1711 (s), 1613 (w), 1507 (w), 1488 (w), 1456 (m), 1365 (w), 1298 (m), 1250 (m), 1172 (w), 1080 (w) and 758 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.9 Hz, 3 H 18-H), 0.90 (t, *J* = 7.1 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 1.23–1.65 (m, 10 H), 1.42

(s, 9 H, *t*Bu), 1.72 (m, 1 H), 1.81–2.02 (m, 7 H), 3.36 (br. s, 1 H), 3.59–3.72 (m, 5 H), 3.82 (quint, J = 6.9 Hz, 1 H), 3.96 (quint, J = 6.9 Hz, 1 H), 4.59 (m, 1 H), 5.57 (m, 1 H, 8-H), 7.12 (m, 1 H), 7.20 (m, 1 H), 7.48 (m, 1 H), 7.96 (dt, J = 1.9, 7.7 Hz, 1 H) ppm. HR-FABMS (NOBA): calcd. for $C_{32}H_{51}FNO_7$ $[M + H]^+$ 580.3650; found 580.3647.

(2*S*,3*R*,6*S*,7*S*,8*R*,9*R*,10*R*,13*S*,15*R*)-1-Benzyloxy-15-*tert*-butoxycarbonylamino-3,6:10,13-diepoxy-8-*o*-fluorobenzoyloxy-2,9-dimethyloctadecanoic Acid (4): A mixture of **35** (8.7 mg, 0.015 mmol) and Dess–Martin periodinane (9.5 mg, 0.023 mmol) in dry CH_2Cl_2 (1.5 mL) was stirred at 0 °C for 12 h. The reaction mixture was then filtered, and the filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution and brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was used in the next step without further purification. A mixture of the crude aldehyde, 2-methylbut-2-ene (7.0 mg, 0.10 mmol), 80% $NaClO_2$ (6.0 mg, 0.053 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (5.5 mg, 0.035 mmol) in *t*BuOH/H_2O (4:1, 0.15 mL) was stirred at room temperature for 1.5 h. The mixture was then diluted with EtOAc, washed with saturated aqueous NH_4Cl solution and brine, dried with $MgSO_4$, and concentrated en vacuo. The residue was chromatographed on a TLC plate. Development with hexane/EtOAc (1:1) gave **4** (2.8 mg, 0.0047 mmol, 31%) as a pale yellow oil. FT-IR: $\tilde{\nu}$ = 3327 (w), 2961 (s), 1711 (s), 1613 (w), 1488 (w), 1456 (m), 1366 (w), 1299 (m), 1250 (m), 1170 (w), 1128 (w), 1080 (w) and 758 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 3 H, 18-H), 1.01 (d, J = 6.9 Hz, 3 H), 1.18 (d, J = 6.9 Hz, 3 H), 1.23–1.65 (m, 10 H), 1.42 (s, 9 H, *t*Bu), 1.81–2.10 (m, 7 H), 2.43 (m, 1 H), 3.63 (br. s, 2 H), 3.81 (m, 1 H), 3.95 (m, 1 H), 4.08 (m, 1 H), 4.50 (br. s, 1 H), 5.60 (br. s, 1 H), 7.12 (m, 1 H), 7.20 (m, 1 H), 7.51 (m, 1 H), 7.96 (dt, J = 1.9, 7.7 Hz, 1 H) ppm. HR-FABMS (NOBA): calcd. for $C_{32}H_{49}FNO_8$ $[M + H]^+$ 594, 3442; found 594.3448.

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