Supporting Information – Part I

Stereoselective Synthesis of Unnatural (2*S*,3*S*)-6-Hydroxy-4-Sphingenine-Containing Sphingolipids

Daniel Leichnitz,[a] Sebastian Pflanze [a] and Christine Beemelmanns [a*]

* Corresponding author: christine.beemelmanns@hki-jena.de

[a] *Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Beutenbergstraße 11a, D-07745 Jena, Germany, Christine.beemelmanns@hki-jena.de*

Content

1. General Remarks

NMR measurements were performed on a Bruker AVANCE II 300 MHz, a Bruker AVANCE III 500 MHz and a Bruker AVANCE III 600 MHz spectrometer, equipped with a Bruker Cryoplatform. The chemical shifts are reported in parts per million (ppm) relative to the solvent residual peak of $CDCl_3$ (^{1}H: 7.26 ppm, singlet; ^{13}C: 77.16 ppm, triplett) DMSO-d_6 (^{1}H: 2.50 ppm, quintet; ^{13}C: 39.52 ppm, heptet) or benzene-d_6 (^{1}H: 7.16 ppm, singlet; ^{13}C: 128.06 ppm, triplett). The atom numbering is according to the longest linear carbon-chain.

LC-ESI-HRMS measurements were carried out on an Accela UPLC system (Thermo Scientific) coupled with an Accucore C18 column (100 x 2.1 mm, particle size 2.6 µm) combined with a Q-Exactive mass spectrometer (Thermo Scientific) equipped with an electrospray ion (ESI) source.

Chiral analytical HPLC was performed on a Knauer Smartline HPLC system using a Phenomenex Lux Cellulose-1 column (250 x 4.6 mm, particle size 5µm, pore diameter 1000 Å).

Flash chromatography was performed on Biotage Isolera™ Prime. Pre-coated silica gel 60 F254 plates (Merck) were used for TLC with detection via UV, $KMnO_4$, phosphomolybdic acid/$CeSO_4$ or anisaldehyde stains.

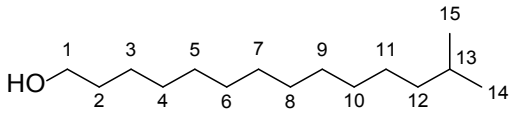
IR spectra were recorded on an FT/IR-4100 ATR spectrometer (JASCO).

Optical rotations were recorded in the respective solvent on a P-1020 polarimeter (JASCO).

Methanol (VWR, Germany); water (Millipore, Germany) for analytical and preparative HPLC, formic acid (Carl Roth, Germany); acetonitrile (VWR as LC-MS grade). Titanium isopropoxide was dried in high vacuum and dissolved in dry toluene prior to use. Dicyclohexylcarbodiimide (DCC) was purchased from Fluorochem and molten under vacuum prior to use. All other reagents and solvents for synthesis were purchased from Acros Organics, Alfa Aesar, Carbolution Chemicals, Carl Roth, Fluorochem, Sigma Aldrich, TCI, Th. Geyer and VWR and used without further purification.

2. Synthesis of Fatty Acids

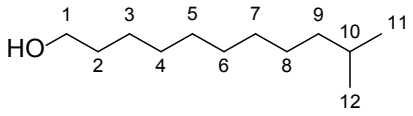
13-Methyltetradecanol (A)



To a solution of 11-bromoundecan-1-ol (2.50 g, 9.95 mmol) in THF (50 mL) at -78 °C was dropped a solution of *iso*-butyl magnesium bromide (12.5 mL, 2 M solution in Et_2O, 2.50 equiv.), stirred for 15 min and treated with a solution of Li_2CuCl_4 (0.1 M in THF, 5 mL, 0.05 equiv.). After stirring at -78 °C for 1 h the mixture was allowed to warm to r.t. overnight. The dark blue mixture was then cooled to 0 °C, *i*-PrOH and NH_4Cl-solution were added and extracted with TBME (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield alcohol **A** as a white wax (2.34 g, ca. quantitative), which was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (t, *J* = 6.7 Hz, 2H, 1-H), 1.61 – 1.45 (m, 3H, 2-H to 13-H), 1.36 – 1.20 (m, 19H, 3-H to 12-H), 1.16 – 1.08 (m, 2H, 12-H), 0.84 (d, *J* = 6.7 Hz, 6H, 14-H, 15-H) ppm.
The analytical data is consistent with literature reports.[1]

10-Methylundecanol (B)



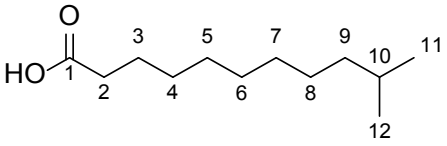
To iodine-activated Mg-turnings (15.3 g, 627 mmol, 4.00 equiv.) was added *iso*-propylbromide (36.8 mL, 392 mmol, 2.50 equiv.) in THF (500 mL) at once until the Mg-turnings were covered and an exothermic reaction could be monitored. The remaining bromide solution was added in a manner, that a slight reflux was sustained. Upon completed addition the flask was lowered into a pre-heated oil bath and refluxed for 5 d until titration vs. iodine in LiCl-solution (0.5 M in THF) confirmed the concentration of 0.8 M. The mixture was then cooled to r.t and additional THF (250 mL) was added. Cooling of the mixture to -78 °C and dropwise addition of 8-bromooctanol (35.0 g, 157 mmol) in THF (250 mL) were followed by stirring at -78 °C for 15 min and addition of Li_2CuCl_4 (16 mL, 0.1 M solution in THF, 16.0 mmol, 0.01 equiv.). Stirring was continued at -78 °C for 1 h followed by warming to r.t. over night. Cooling to 0 °C and careful addition of *i*-PrOH, NH_4Cl solution and 5 M aq. HCl resulted in a color change from blue to yellow. After complete consumption of remaining Mg-turnings the solvent was evaporated until ~300 mL remain, the residue was extracted with TBME (3x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* and filtered over a pad of silica to yield alcohol **B** as a brownish oil (30.0 g, ca. quantitative), which was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.6 Hz, 2H, 1-H), 1.70 – 1.37 (m, 3H, 2-H to 10-H), 1.39 – 1.16 (m, 14H, 3-H to 8-H), 1.23 – 1.04 (m, 2H, 9-H), 0.86 (d, *J* = 6.6 Hz, 6H, 11-H, 12-H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$) δ 63.3 (t, C-1), 39.2 (t, C-2), 33.0, 30.1, 29.8, 29.6 (4t, C-3 to C-9), 28.1 (d, C-10), 27.6, 25.9 (2t, C-3- to C-9), 22.8 (q, C-11, C-12) ppm.
The analytical data is consistent with literature reports.[2]

General procedure 1 (GP1) for oxidation of a primary alcohol to carboxylic acid

To a solution of alcohol (1.00 equiv.) in *t*-BuOH (2.3 mL/mmol) was added $KMnO_4$ (3.00 equiv.) Upon addition of an aqueous solution of NaOH (2 M, 4.50 equiv.) brown precipitate forms from the initial purple suspension. Stirring at r.t. for 16 h was followed by cooling to 0 °C and careful addition of sat. NaS_2O_5-solution. The brown precipitate was slowly filtered into 0 °C-cold conc. HCl using a pad of Celite, and thoroughly washed with water and TBME. The filtrate was extracted with TBME (3x), the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude carboxylic acid, which was used without further purification.

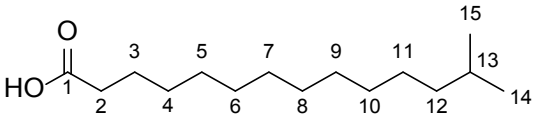
10-Methylundecanoic acid (13a)



According to **GP1**, reaction of 10-methylundecanol (15.0 g, 80.5 mmol) yielded **13a** as an off white wax (13.1 g, 81%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (broad s, 1H, $CO_2\underline{H}$), 2.34 (t, *J* = 7.5 Hz, 2H, 2-H), 1.72 – 1.54 (m, 2H, 3-H), 1.59 – 1.41 (m, 1H, 10-H), 1.40 – 1.20 (m, 14H, 4-H to 8-H), 1.20 – 1.10 (m, 2H, 9-H), 0.86 (d, *J* = 6.6 Hz, 6H, 11-H, 12-H) ppm.

The analytical data is consistent with the literature.[2]

13-Methyltetradecanoic acid (13b)

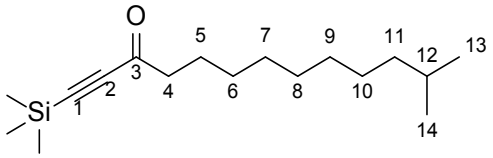


According to **GP1**, reaction of 13-methyltetradecanol (500 mg, 2.19 mmol) yielded **13b** as an off-white wax (498 mg, 94%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (t, *J* = 7.5 Hz, 2H, 2-H), 1.63 (h, *J* = 7.5 Hz, 2H, 3-H), 1.51 (hept, *J* = 6.7 Hz, 1H, 13-H), 1.40 – 1.19 (m, 16H, 4-H to 11-H), 1.19 – 1.10 (m, 2H, 12-H), 0.86 (d, *J* = 6.7 Hz, 6H, 14-H, 15-H) ppm.
The analytical data is consistent with the literature.[3]

General procedure 2 (GP2) for acid chloride formation and Friedel-Crafts-type acylation

The carboxylic acid (1.00 equiv.) was dissolved in $SOCl_2$ (7.00 equiv.) and stirred at r.t. for 16 h. Removal of the volatiles *in vacuo* at r.t. yielded the crude acid chloride, which was directly used in the next step. To a suspension of $AlCl_3$ (1.50 equiv.) in CH_2Cl_2 (1 mL/mmol) at 0 °C was added a solution of acyl chloride (1.00 equiv.) in CH_2Cl_2 (0.5 mL/mmol) and stirred for 15 min, after which bis(trimethylsilyl)acetylene (1.10 equiv.) was added portion wise. The mixture was allowed to warm to r.t., stirred for 3 h, poured into ice-cooled water and extracted with CH_2Cl_2 (3x). The combined organic phases were washed with sat. $NaHCO_3$ solution (careful! strong gas development!) and the aqueous phase thereof reextracted with CH_2Cl_2 and combined with the previous organic phase. Washing of the combined organic phases with brine, drying over $MgSO_4$, filtration and removal of the volatiles *in vacuo* yielded the crude alkynone, which was purified by flash-chromatography.

12-Methyl-1-(trimethylsilyl)tridec-1-yn-3-one (14a)

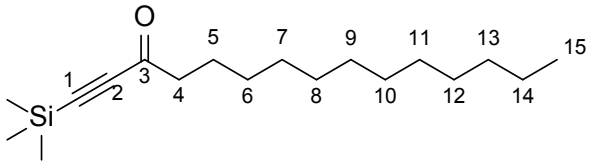


According to **GP2**, reaction of 10-Methylundecanoic acid (6.00 g, 30.0 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 20/1), **14a** as a brown liquid (6.58 g, 78%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (t, *J* = 7.4 Hz, 2H, 4-H), 1.63 (p, *J* = 7.3 Hz, 2H, 5-H), 1.49 (hept, *J* = 6.6 Hz, 1H, 12-H), 1.38 – 1.16 (m, 12H, 6-H to 10-H), 1.16 – 0.95 (m, 2H, 11-H), 0.83 (d, *J* = 6.7 Hz, 6H, 13-H, 14-H), 0.21 (s, 9H, $Si(C\underline{H}_3)_3$) ppm.

IR (ATR) ν_{max}: 2955, 2925, 2855, 1679, 1251, 1095, 842 cm^{-1}.

1-(Trimethylsilyl)pentadec-1-yn-3-one (14b)



According to **GP2**, reaction of tridecanoic acid (3.0 g, 14.0 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 10/1), **14b** as a brown oil (3.92 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (t, *J* = 7.4 Hz, 2H, 4-H), 1.64 (p, *J* = 7.2 Hz, 2H, 5-H), 1.43 – 1.13 (m, 18H, 6-H to 14-H), 0.94 – 0.75 (m, 3H, 15-H), 0.22 (s, 9H, $Si(C\underline{H}_3)_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1 (s, C-3), 102.2 (s, C-2), 97.5 (s, C-1), 45.4 (t, C-4), 32.0, 29.8, 29.74, 29.70, 29.5, 29.46, 29.4, 29.0 (8t, C-6 to C-14), 24.0 (t, C-5), 22.8 (t, C-6 to C-14), 14.2 (q, C-15), -0.7(q, Si($\underline{C}H_3$)$_3$) ppm.

HRMS (ESI-TOF): calculated for $C_{18}H_{35}OSi$ $[M+H]^+$ 295.2452; found 295.2441.

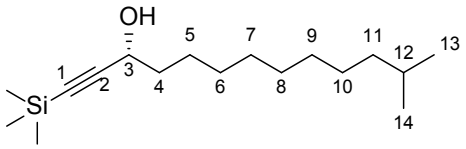
IR (ATR) ν_{max}: 2955, 2922, 2853, 1677, 1464, 1251, 842 cm^{-1}.

The analytical data is consistent with literature reports.[4]

General procedure 3 (GP3) for Noyori-type reduction

To a stirred solution of TMS-alkynone (1.00 equiv.) in *i*-PrOH (2.0 mL/mmol) were added RuCl[(*R*,*R*)-TsDPEN](mesitylene) (2.5 mol-%.) and an at 0 °C premixed solution of NEt_3 (6.00 equiv.) and formic acid (5.00 equiv.) in *i*-PrOH (2.0 mL/mmol). The dark brown solution was stirred at r.t. for 6 h, until complete consumption of the starting material on TLC was observed. The reaction was stopped by the addition of sat. NH_4Cl-solution, followed by TBME-extraction (3x). Washing of the combined organic phases with brine, drying over $MgSO_4$, filtration and removal of the volatiles *in vacuo* yielded the crude product, which was subjected to flash chromatography purification.

(*R*)-12-Methyl-1-(trimethylsilyl)tridec-1-yn-3-ol (C)



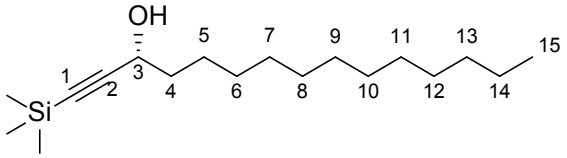
According to **GP3**, reaction of 12-methyl-1-(trimethylsilyl)tridec-1-yn-3-one (2.00 g, 7.13 mmol) yielded after flash chromatography (cyclohexane/ EtOAc 100/0 → 7/1) **C** as a brownish oil (1.40 g, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (t, *J* = 6.6 Hz, 1H, 3-H), 1.88 – 1.58 (m, 2H, 4-H), 1.62 – 1.00 (m, 15H, 5-H to 11-H), 0.88 (d, *J* = 6.7 Hz, 6H, 13-H, 14-H), 0.19 (s, 9H, Si($C\underline{H}_3$)$_3$) ppm.

HRMS (ESI-TOF): calculated for $C_{17}H_{34}NaOSi$ $[M+Na]^+$ 305.2271; found 305.2265.

IR (ATR) ν_{max}: 2954, 2924, 2854, 2170, 1249 cm^{-1}.

(*R*)-1-(Trimethylsilyl)pentadec-1-yn-3-ol (D)



According to **GP3**, reaction of 1-(trimethylsilyl)pentadec-1-yn-3-one (2.0 g, 6.79 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 7/1), **D** as a brown oil (1.72 g, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (t, *J* = 6.6 Hz, 1H, 3-H), 1.79 – 1.56 (m, 2H, 4-H), 1.50 – 1.37 (m, 2H, 5- to 14-H), 1.37 – 1.10 (m, 18H, 5- to 14-H), 0.87 (t, *J* = 6.9 Hz, 3H, 15-H), 0.16 (s, 9H $Si(C\underline{H}_3)_3$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 107.2 (s, C-2), 89.4 (s, C-1), 63.1 (d, C-3), 37.9 (t, C-4), 32.1, 29.83, 29.79, 29.69, 29.65, 29.5, 29.4, 25.3, 22.8 (9t, C-5 to C-14), 14.2 (q, C-15), 0.0 (q, $Si(\underline{C}H_3)_3$) ppm.

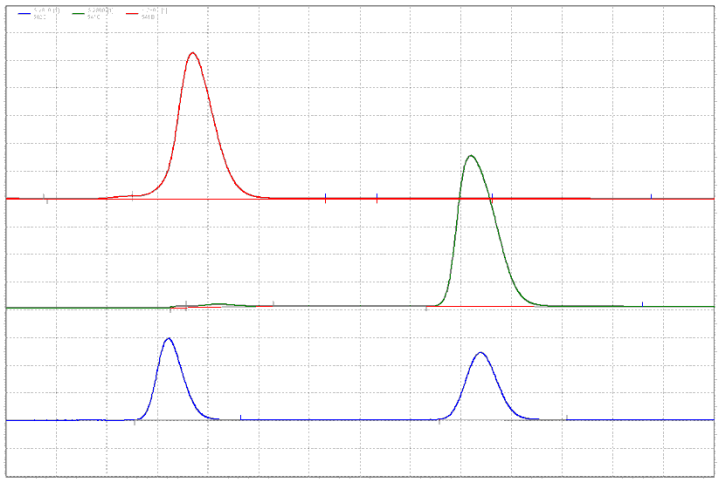
HRMS (ESI-TOF): calculated for $C_{18}H_{36}ONaSi$ $[M+Na]^+$ 319.2428; found 319.2421.

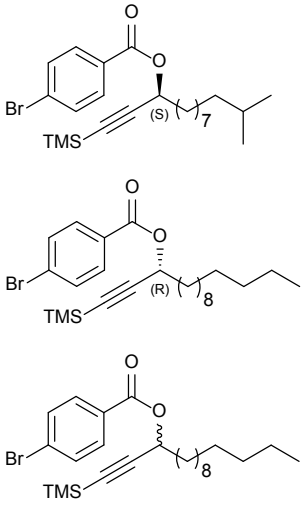
IR (ATR) ν_{max}: 2922, 2853, 1248, 1013 cm^{-1}.

$[\alpha]_D^{25}$: -1.86° (*c* = 1.0; $CHCl_3$)

Determination of enantiomeric excess of the Noyori-reduction

A sample of the alkynol (6.00 mg, 28.5 mmol) was converted into its 4-bromobenzoyl derivative (stirring with excess 4-bromobenzoyl chloride in pyridine at r.t. for 2 h, quenching with 1 M NaOH, cyclohexane extraction) and subjected to chiral HPLC using an isocratic gradient of A/B 80/20 (A = *n*Hex; B= *n*Hex/TBME 90/10).

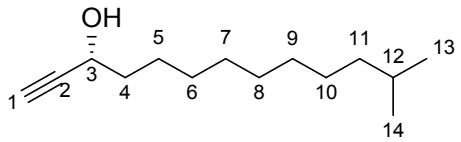




General procedure 4 (GP4) for TMS-deprotection

A solution of alkynol (1.00 equiv.) in DCM (1.0 mL/mmol) was added into a solution of KOH (4.00 equiv.) in $MeOH/H_2O$ (1/1, 5.0 mL/mmol) and stirred at r.t. After 16 h the mixture was acidified with 1 M HCl and extracted with TBME (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product which was used in the next step without further purification.

(*R*)-12-Methyl-1-tridec-1-yn-3-ol (E)



According to **GP4**, reaction of (*R*)-12-methyl-1-(trimethylsilyl)tridec-1-yn-3-ol (1.50 g, 5.31 mmol) yielded **E** as a yellow oil (1.12 g, ca quantitative).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (td, *J* = 6.6, 2.1 Hz, 1H, 3-H), 2.45 (d, *J* = 2.1 Hz, 1H, 1-H), 1.77 – 1.62 (m, 2H, 4-H), 1.59 – 1.38 (m, 2H, 5-H to 10-H, 12-H), 1.38 – 1.18 (m, 9H, 5-H to 10-H), 1.18 – 1.01 (m, 2H, 11-H), 0.86 (d, *J* = 6.7 Hz, 6H, 13-H, 14-H) ppm.

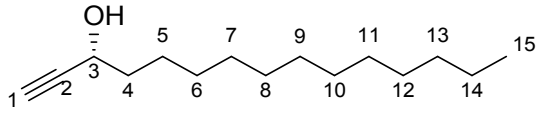
^{13}C NMR (151 MHz, $CDCl_3$) δ 85.2 (d, C-1), 72.9 (s, C-2), 62.4 (d, C-3), 39.2 (t, C-11), 37.7 (t, C-4), 30.0, 29.72, 29.65, 29.4 (4 t, C5 to C-10), 28.1 (d, C-12), 27.5, 25.2 (2 t, , C5 to C-10), 22.8 (q, C-13, C-14) ppm.

HRMS (ESI-TOF): calculated for $C_{14}H_{26}NaOSi$ $[M+Na]^+$ 233.1876; found 233.1868.

IR (ATR) ν_{max}: 2951, 2924, 2854, 2092, 1465 cm^{-1}.

$[\alpha]_D^{25}$: +3.44° (*c* = 1.0; $CHCl_3$)

(*R*)-Pentadec-1-yn-3-ol (F)



According to **GP4**, reaction of (*R*)-1-(trimethylsilyl)pentadec-1-yn-3-ol (1.10 g, 3.71 mmol) yielded **F** as a yellow wax (882 mg, ca quantitative).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (td, *J* = 6.6, 2.1 Hz, 1H, 3-H), 2.45 (d, *J* = 2.1 Hz, 1H, 1-H), 1.91 (broad s, 1H, O<u>H</u>), 1.77 – 1.63 (m, 2H, 4-H), 1.50 – 1.38 (m, 2H, 5- to 14-H), 1.37 – 1.18 (m, 18H, 5- to 14-H), 0.88 (t, *J* = 6.9 Hz, 3H, 15-H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 85.2 (C-2), 72.9 (C-1), 62.5 (C-3), 37.8 (C-4), 32.1, 29.81, 29.78, 29.70, 29.66, 29.5, 29.4, 25.2, 22.8 (9t, C-5 to C-14), 14.2 (q, C-15) ppm.

HRMS (ESI-TOF): calculated for $C_{15}H_{26}O$ $[M+Na]^+$ 319.2433; found 319.2421.

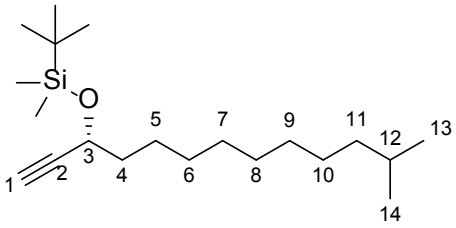
IR (ATR) ν_{max}: 3376, 3285, 2919, 2851, 1470, 1066 cm^{-1}.

General procedure 5 (GP5) for silyl protection

To a solution of alkynol (1.00 equiv.), DIPEA (1.70 equiv.) and 4-DMAP (0.10 equiv.) in DMF (1.0 mL/mmol) was added TBSCl (1.40 equiv.) in several portions and the mixture allowed to stir at r.t.. After 20 h the reaction was stopped by addition of citric acid-solution (10 wt-% in H_2O) and extracted with cyclohexane (3x). The combined organic phases were washed with sat. Na_2CO_3-

solution, brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product, which was used in the next step without further purification.

(*R*)-*tert*-Butyldimethyl((12-methyl-1-tridec-1-yn-3-yl)oxy)silane (11a)



According to **GP5**, reaction of (*R*)-12-methyl-1-tridec-1-yn-3-ol (600 mg, 2.85 mmol) yielded **11a** as a yellowish liquid (943 mg, ca. quantitative).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (td, *J* = 6.5, 2.1 Hz, 1H, 3-H), 2.36 (d, *J* = 2.1 Hz, 1H, 1-H), 1.76 – 1.61 (m, 2H, 4-H), 1.51 (hept, *J* = 6.7 Hz, 1H, 12-H), 1.46 – 1.36 (m, 2H, 5- to 10-H), 1.33 – 1.20 (m, 10H, 5-H to 10-H), 1.19 – 1.10 (m, 2H, 11-H), 0.91 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.86 (d, *J* = 6.7 Hz, 6H, 13-H, 14-H), 0.13, 0.11 (2s, each 3H, $Si(C\underline{H}_3)_2$) ppm.

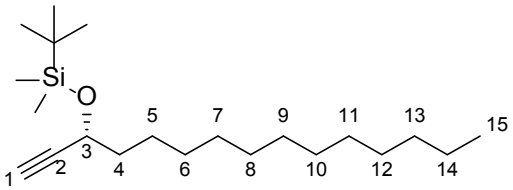
^{13}C NMR (151 MHz, $CDCl_3$) δ 86.0 (s, C-2), 72.0 (d, C-1), 62.9 (d, C-3), 39.2 (t, C-5 to C-11), 38.7 (t, C-4), 30.1, 29.8, 29.7, 29.4, 28.1, 27.6 (6t, C-5 to C-11), 25.9 (q, $SiC(\underline{C}H_3)_3$), 25.3 (d, C-12), 22.8 (q, C-13, C-14), 18.4 (s, $Si\underline{C}(CH_3)_3$, -4.4, -4.9 (2q, $Si(\underline{C}H_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{20}H_{40}NaOSi$ $[M+Na]^+$ 347.2741; found 347.2744.

IR (ATR) ν_{max}: 2928, 2856, 1643, 1537, 1460, 1250, 1126 cm^{-1}.

$[\alpha]_D^{25}$: +32.5° (*c* = 1.0; $CHCl_3$)

(*R*)-*tert*-Butyldimethyl(pentadec-1-yn-3-yloxy)silane (11b)



According to **GP5**, reaction of (*R*)-pentadec-1-yn-3-ol (700 mg, 3.12 mmol) yielded **11b** as a yellowish liquid (1.05 g, ca. quantitative).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (td, *J* = 6.5, 2.1 Hz, 1H, 3-H), 2.36 (d, *J* = 2.1 Hz, 1H, 1-H), 1.78 – 1.55 (m, 2H, 4-H), 1.50 – 1.35 (m, 2H, 5-H to 14-H), 1.36 – 1.18 (m, 18H, 5-H to 14-H), 0.91 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.88 (t, *J* = 6.9 Hz, 3H, 15-H), 0.14, 0.11 (2s, each 3H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 86.0 (s, C-2), 72.0 (d, C-1), 63.0 (d, C-3), 38.8 (t, C-4), 32.1, 29.9, 29.82, 29.76, 29.72, 29.5, 29.4 (7t, C-5 to C-14), 26.0 (q, $SiC(\underline{C}H_3)_3$), 25.3, 22.9 (2t, C-5 to C-14), 18.4 (s, $Si\underline{C}(CH_3)_3$), 14.3 (q, C-15), -4.4, -4.9 (2q, $Si(\underline{C}H_3)_2$) ppm.

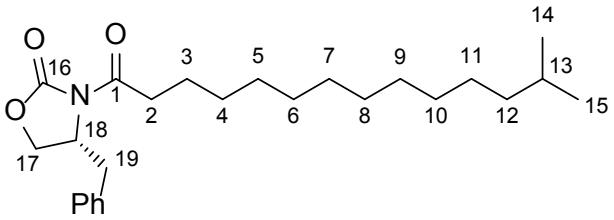
HRMS (ESI-TOF): calculated for $C_{21}H_{42}NaOSi$ $[M+Na]^+$ 361.2897; found 361.2906.

IR (ATR) ν_{max}: 2952, 2924, 2854, 1463, 1250 cm^{-1}.

$[\alpha]_D^{25}$: +28.2° (*c* = 1.0; $CHCl_3$)

The analytical data is consistent with literature reports.[5]

(*R*)-4-Benzyl-3-(13-methyltetradecanoyl)oxazolidin-2-one (15a)



13-Methytetradecanoic acid **13b** (2.50 g, 10.3 mmol, 1.00 equiv) was dissolved in thionyl chloride (4.00 mL, 55.1 mmol, 4.40 equiv.) and stirred for 16 h at r.t. After removal of the volaties *in vacuo* the acid chloride was dissolved in THF (10.0 mL).

A solution of (*R*)-4-benzyloxazolidinone[6] (1.84 g, 10.4 mmol, 1.00 equiv.), dissolved in THF (20.0 mL), was treated with *n*-BuLi (5.40 mL, 2.2 M in hexanes, 1.15 equiv.) at -78 °C and stirred at -78°C for 30 min. After adding the acid chloride in THF at -78 °C the highly viscous mixture was allowed to warm to r.t. and stirred for 16 h. The reaction was quenched by addition of sat. NH_4Cl solution and extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*. Flash chromatography (cHex/EtOAc 50/1 to 10/1, eluting at 10/1) yielded **15a** as a brownish solid (2.03 g, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 3H, Ph-H), 7.24 – 7.18 (m, 2H, Ph-H), 4.67 (ddt, *J* = 10.2, 6.8, 3.4 Hz, 1H, 18-H), 4.26 – 4.10 (m, 2H, 17-H), 3.30 (dd, *J* = 13.3, 3.3 Hz, 1H, 19-H), 3.08 – 2.69 (m, 3H, 19-H, 2-H), 1.81 – 1.60 (m, 2H, 3-H), 1.51 (dp, *J* = 13.1, 6.6 Hz, 1H, 13-H), 1.43 – 1.20 (m, 20H, 4-H to 11-H), 1.16 (dd, *J* = 8.0, 4.5 Hz, 2H, 12-H), 0.86 (d, *J* = 6.6 Hz, 7H, 14-H, 15-H) ppm.

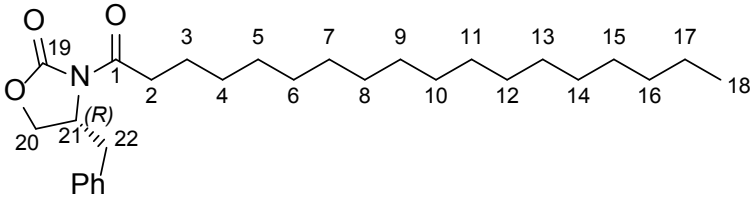
^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (s, C-1), 153.6 (s, C-16), 135.5 (s, Ph), 129.5, 129.1, 127.5 (3 d, Ph), 66.3 (t, C-17), 55.3 (d, C-18), 39.2, 38.1, 35.7, 30.1, 29.8, 29.8, 29.8, 29.6, 29.5, 29.3 (10 t, C-2 to C-12, C-19), 28.1 (d, C-13), 27.6, 24.4 (2 t, C-2 to C-12, C-19), 22.8 (q, C-14, C-15) ppm.

HRMS (ESI-TOF): calculated for $C_{25}H_{40}NO_3$ $[M+H]^+$ 402.3003; found 402.3003.

IR (ATR) ν_{max}: 2923, 2852, 1780, 1699 cm^{-1}.

$[\alpha]_D^{25}$: -39.9° (*c* = 0.85; $CHCl_3$).

(*R*)-4-Benzyl-3-stearoyloxazolidin-2-one (15b)



Stearic acid (1.69 g, 5.93 mmol, 1.05 equiv) was dissolved in thionyl chloride (1.80 mL, 24.8 mmol, 4.40 equiv.) and stirred at r.t for 16 h. After removal of the volaties *in vacuo* the acid chloride was dissolved in THF (12 mL).

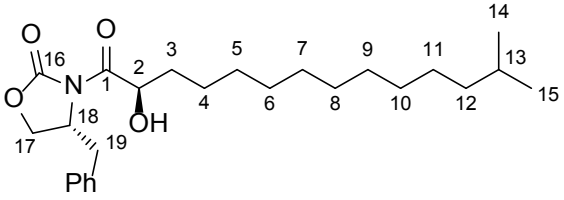
A solution of (*R*)-4-benzyloxazolidinone (1.00 g, 5.64 mmol, 1.00 equiv.), dissolved in THF (12 mL), was treated with *n*-BuLi (3.00 mL, 2.3 M in hexanes, 1.22 equiv.) at -78 °C and stirred at -78 °C for 30 min. After adding the acid chloride in THF at -78 °C the highly viscous mixture was allowed to warm to r.t. and stir for 3 h. Addition of 10% citric acid was followed by extraction with TBME (3x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*. Recrystallization from hot MeOH yielded **15b** as a colorless solid (1.36 g, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.13 (m, 5H, Ar-H), 4.70 (ddt, *J* = 10.4, 6.9, 3.4 Hz, 1H, 21-H), 4.28 – 4.13 (m, 2H, 20-H), 3.32 (dd, *J* = 13.4, 3.3 Hz, 1H, 22-H), 3.04 – 2.85 (m, 2H, 2-H), 2.79 (dd, *J* = 13.4, 9.6 Hz, 1H, 22-H), 1.82 – 1.61 (m, 2H, 3-H to 17-H), 1.46 – 1.19 (m, 32H, 3-H to 17-H), 0.99 – 0.80 (m, 3H, 18-H) ppm. The analytical data is consistent with the literature[7]

General procedure 6 (GP6) for Davis oxidation

To a solution of KHMDS (1.50 equiv., 0.7 M in toluene) in THF was dropped oxazolidinone (1.00 equiv.) in dry THF (3 mL/mmol) at -78 °C and the slurry was stirred for 30 min at the same temperature. Addition of a pre-cooled solution of Davis' oxaziridine (2.50 equiv.) in dry THF (10 mL/mmol) was followed by stirring at -78 °C for 2 h and the reaction was then stopped by addition of camphorsulfonic acid (4.00 equiv.) in dry THF (1 mL/mmol) at -78 °C followed by addition of NH_4Cl-solution. The mixture was extracted with TBME (3x), the combined organic phases were successively washed with Na_2CO_3-solution and brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product, which was purified using flash chromatography.

(*R*)-4-Benzyl-3-((*R*)-2-hydroxy-13-methyltetradecanoyl)oxazolidin-2-one (G)



According to **GP6**, reaction of oxazolidone **15a** (675 mg, 1.68 mmol) yielded, after flash chromatography (cHex/EtOAc 50/1 to 10/1, eluting at 10/1) **G** as a brownish solid (480 mg, 68%* as inseparable mixture with benzylidene-4-methylbenzenesulfonamide (3:1 ratio, product : side product).

^{1}H NMR (300 MHz, $CDCl_3$) δ7.42 – 7.27 (m, 3H, Ph-H), 7.24 – 7.13 (m, 2H, Ph-H), 5.08 – 4.93 (m, 1H, 2-H), 4.67 (ddt, *J* = 9.9, 6.6, 3.2 Hz, 1H, 18-H), 4.33 – 4.16 (m, 2H, 17-H), 3.45 (d, *J* = 7.9 Hz, 1H, O-H), 3.31 (dd, *J* = 13.5, 3.3 Hz, 1H, 19-H), 2.84 (dd, *J* = 13.5, 9.4 Hz, 1H, 19-H), 1.66 – 1.43 (m, 4H, 3-H to 13-H), 1.38 – 1.19 (m, 16H, 3-H to 13-H), 1.19 – 1.08 (m, 2H, 3-H to 13-H), 0.86 (d, *J* = 6.6 Hz, 6H, 14-H 15-H) ppm.

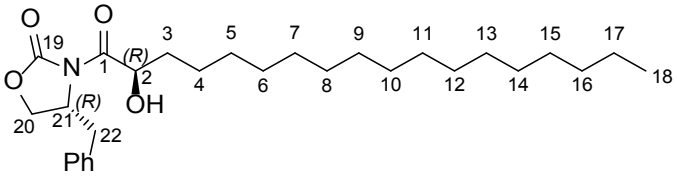
^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (s, C-1), 153.3 (C-16), 134.9 (s, Ph), 129.6, 129.2 (2 d, Ph), 127.6 (d, Ph), 71.0 (d, C-2), 67.0 (t, C-17), 55.7 (d, C-18), 39.2 (t, C-12), 37.6 (t, C-6), 34.4, 30.1, 29.82, 29.77, 29.7, 29.6, 29.4 (7 t, C-3 to C-11), 28.1 (d, C-13), 27.5, 25.4 (2t, C3 to C-12), 22.8 (q, C-14, C-15) ppm.

HRMS (ESI-TOF): calculated for $C_{25}H_{40}NO_4$ $[M+H]^+$ 418.2952; found 418.2952.

IR (ATR) ν_{max}: 3516(broad), 2924, 2853, 1783, 1698 cm^{-1}.

$[\alpha]_D^{25}$: -35.1° (*c* = 0.81; $CHCl_3$).

(*R*)-4-Benzyl-3-((*R*)-2-hydroxyoctadecanoyl)oxazolidin-2-one (H)



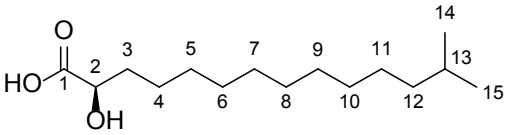
According to **GP6**, reaction of oxazolidinone **15b** (400 mg, 901µmol) yielded **H** after flash chromatography (cHex/EtOAc 100/0 to 50/50, eluting at 75/25) as a yellowish oil (128 mg, 31%* as inseparable mixture with benzylidene-4-methylbenzenesulfonamide (1:3 ratio, product : side product).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 3H, Ar-H), 7.23 – 7.19 (m, 2H, Ar-H), 5.03 (dd, *J* = 8.0, 3.5 Hz, 1H, 2 -H), 4.67 (ddt, *J* = 9.8, 6.6, 3.3 Hz, 1H, 21-H), 4.27 – 4.24 (m, 2H, 20-H), 3.32 (dd, *J* = 13.4, 3.3 Hz, 1H, 22-H), 2.84 (dd, *J* = 13.5, 9.4 Hz, 1H, 22-H), 1.75 – 1.45 (m, 2H, 3-H TO 17-H), 1.38 – 1.17 (m, 28H, 3-H TO 17-H), 0.95 – 0.80 (m, 3H, 18-H) ppm.

General procedure 3 (GP7) for removal of auxiliary

To a solution of oxazolidinone in BHT-stabilized THF (6.00 ml/mmol) at 0 °C was added a solution of LiOH (3.0 equiv.) and H_2O_2 (6.00 equiv.) in H_2O (1.00 ml/mmol LiOH) and the mixture stirred at 0 °C for 16 h. The reaction was stopped by addition of sat. NaS_2O_3-solution and EtOAc, the mixture centrifuged, the organic phase collected and the process repeated two more times. Subsequent acidifying with 1 M HCl followed by EtOAc-extraction (3x), combination of the acidic organic phases, washing with brine, drying over $MgSO_4$, filtration and removal of the volatiles *in vacuo* yielded the crude fatty acid, which was purified by flash chromatography.

(*R*)-2-Hydroxy-13-methyltetradecanoic acid (16a)



According to **GP7**, reaction of oxazolidinone **G** (30.0 mg. 71.8 µmol) yielded **16a** after flash chromatography (Hex/EtOAc + 0.1% AcOH 100/0 to 50/50, eluting at 60/40) as an off-white wax (12 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 7.5, 4.3 Hz, 1H, 2-H), 1.94 – 1.78, 1.78 – 1.60 (2 m, each 1H, 3-H), 1.58 – 1.41 (m, 3H, 4-H to 11-H, 13-H), 1.40 – 1.20 (m, 14H, 4-H to 11-H), 1.20 – 1.07 (m, 2H, 12-H), 0.86 (d, *J* = 6.6 Hz, 6H, 14-H, 15-H) ppm.

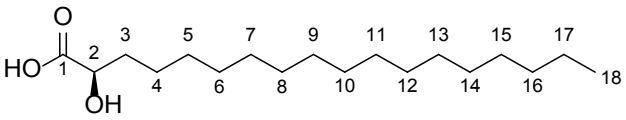
^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0 (s, C-1), 70.4 (d, C-2), 39.2 (t, C-3), 34.4, 30.08, 30.06, 29.84, 29.79, 29.7, 29.6, 29.4 (8 t, C-5 to C-12), 28.1(d, C-13), 27.6, 24.9 (2 t, C-4 to C-12), 22.8 (q, C-14, C-15) ppm.

HRMS (ESI-TOF): calculated for $C_{15}H_{29}O_3$ $[M-H]^-$ 257.2122; found 257.2120.

IR (ATR) ν_{max}: 3516(broad), 2924, 2853, 1783, 1698 cm^{-1}.

$[\alpha]_D^{25}$: -35.1° (*c* = 0.81; $CHCl_3$).

(*R*)-2-Hydroxyoctadecanoic acid (16b)



According to **GP7**, reaction of oxazolidinone **H** (11.6 mg, 25.1 µmol) yielded **16b** after flash chromatography (cHex/EtOAc 100/0 to 50/50, eluting at 60/40) as a colorless solid (1.08 mg, 15%).

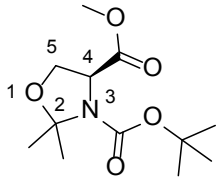
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 7.5, 4.1 Hz, 1H, 2-H), 1.85 – 1.75, 1.69 – 1.59 (2 m, each 1H, 3-H), 1.49 – 1.35 (m, 2H 4-H to 17-H), 1.32 – 1.20 (m, 26H, 4-H to 17-H), 0.87 (t, *J* = 7.0 Hz, 3H, 18-H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6 (s, C-1), 70.3 (d, C-2), 34.4 (t, C-3), 32.0, 29.82, 29.80, 29.78, 29.7, 29.6, 29.5, 29.5, 25.0, 22.8 (10 t, C-4 to C-17), 14.2 (q, C-18) ppm.

HRMS (ESI-TOF): calculated for $C_{18}H_{35}O_3$ $[M-H]^-$ 299.2581; found 299.2580.

3. Synthesis of Capine Base

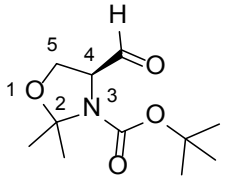
3-(*tert*-Butyl) 4-methyl (*S*)-2,2-dimethyloxazolidine-3,4-dicarboxylate (I)



N-Boc-L-serine methyl ester (25.8 g, 114 mmol, 1.00 equiv.) was dissolved in toluene (350 mL) and toluenesulfonic acid (980 mg, 5.63 mmol, 0.05 equiv) in toluene (10 mL) and 2,2-dimethoxypropane (63.6 mL, 513 mmol, 4.50 equiv.) were added. The mixture was refluxed using a Dean-Stark apparatus for 24 h. The solvent was reduced *in vacuo* and the remains mixed with sat. $NaHCO_3$ solution (60 mL) and extracted with EtOAc (3x 80 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield a brown oil, which was purified via column chromatography (cyclohexane/EtOAc 50/1 → 6/1) to yield **I** as a brownish oil (23.5 g, 77%). The analytical data is consistent with the literature.[8]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (dd, *J* = 6.7, 2.7 Hz, 1H, 4-H)*, 4.35 (dd, *J* = 7.0, 3.1 Hz, 1H, 4-H), 4.12 (dt, *J* = 9.2, 6.6 Hz), 4.01 (ddd, *J* = 9.3, 7.1, 2.9 Hz, each 1H, 5-H), 3.73 (s, 3H, OC$\underline{H_3}$), 1.65 (s, 2H), 1.61 (s, 1H)*, 1.51 (s, 2H, each C(C$\underline{H_3}$)$_2$), 1.47 (s, 5H, C(C$\underline{H_3}$)$_2$, Boc-C$\underline{H_3}$)*, 1.39 (s, 5H, Boc-C$\underline{H_3}$) ppm (* minor rotamer)

Garner's aldehyde (3)



To a -78 °C cooled solution of **I** (23.5 g, 90.8 mmol, 1.00 equiv) in CH_2Cl_2 (200 mL) was slowly added a pre-cooled solution of DIBAL-H (130 mL, 1.2 M in toluene, 1.70 equiv.) over 150 min. The reaction was stirred at -78 °C for 16 h and treated with additional DIBAL-H-solution (20 mL, 0.26 equiv.) and stirring continued for 3 h. After complete consumption of the starting material MeOH (5 mL) was slowly added at -78 °C and the mixture warmed to r.t., poured into saturated Na/K-tartrate solution and stirred until phase separation became visible (~2 h) followed by extraction with CH_2Cl_2 (3x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and submitted to vacuum distillation (70-75 °C, 1.0 mbar) to yield **3** as a colorless oil (14.6 g, 70%), which was stored in the freezer for several months.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (dd, *J* = 16.8, 2.2 Hz, 1H, C<u>H</u>O), 4.31 (dt, *J* = 5.6, 2.5 Hz, 1H, 4-H)*, 4.16 (dt, *J* = 6.4, 3.2 Hz, 1H, 4-H), 4.12 – 3.98 (m, 2H, 5-H), 1.61 (s, 2H), 1.56 (s, 1H)*, 1.52 (s, 2H, each C(C<u>H</u>$_3$)$_2$), 1.48 (s, 4H, C(C<u>H</u>$_3$)$_2$, Boc-CH_3)*, 1.40 (s, 6H, Boc-CH_3) ppm (* minor rotamer). The analytical data is consistent with the literature.[9]

General procedure 8 (GP8) for the hydrometalation

To a solution of alkyne **11a** (100 mg, 295 µmol, 1.05 equiv.) in the respective solvent was added M-H (1.10 equiv.) at the given temperature and stirred for the given time.

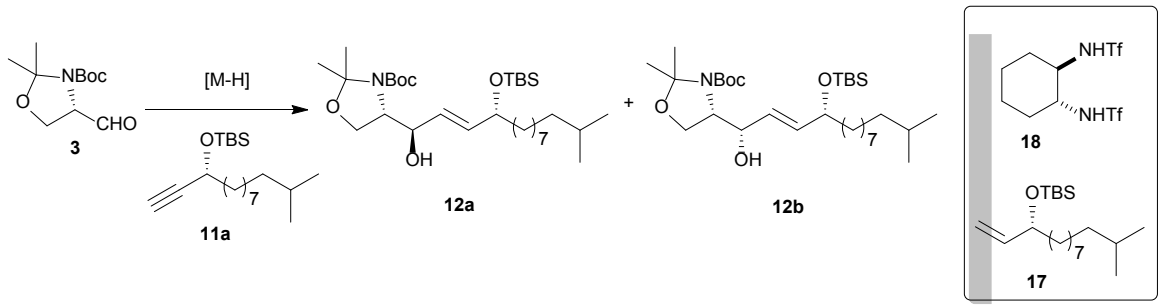
When Et_2Zn was used, the mixture was then cooled to -40 °C and treated with Et_2Zn (380 µL, 0.9 M in hexanes, 342 µmol, 1.21 equiv.) followed by Garner's aldehyde **3** (65 mg, 283 µmol, 1.00 equiv.).

After stirring for a given time aqueous work up was performed using sat. NH_4Cl-solution or sat. Na/K-tartrate-solution; extraction with TBME, washing with brine, drying over $MgSO_4$, filtration and removal of the volatiles *in vacuo* yielded a sticky oil, which was directly dissolved in MeOH/THF (3/1, 1 mL) and treated with $NaBH_4$ (3 mg, 81.0 µmol, 0.29 equiv.) at 0 °C. After stirring at r.t. for 30 min, AcOH (5 µL, 87 µmol) was added, the volatiles removed *in vacuo*, the residue filtered over a silica pad and washed with EtOAc. Removal of the volatiles *in vacuo* yielded the crude product, which was purified via flash chromatography.

General procedure 9 (GP9) for the hydrozirconation

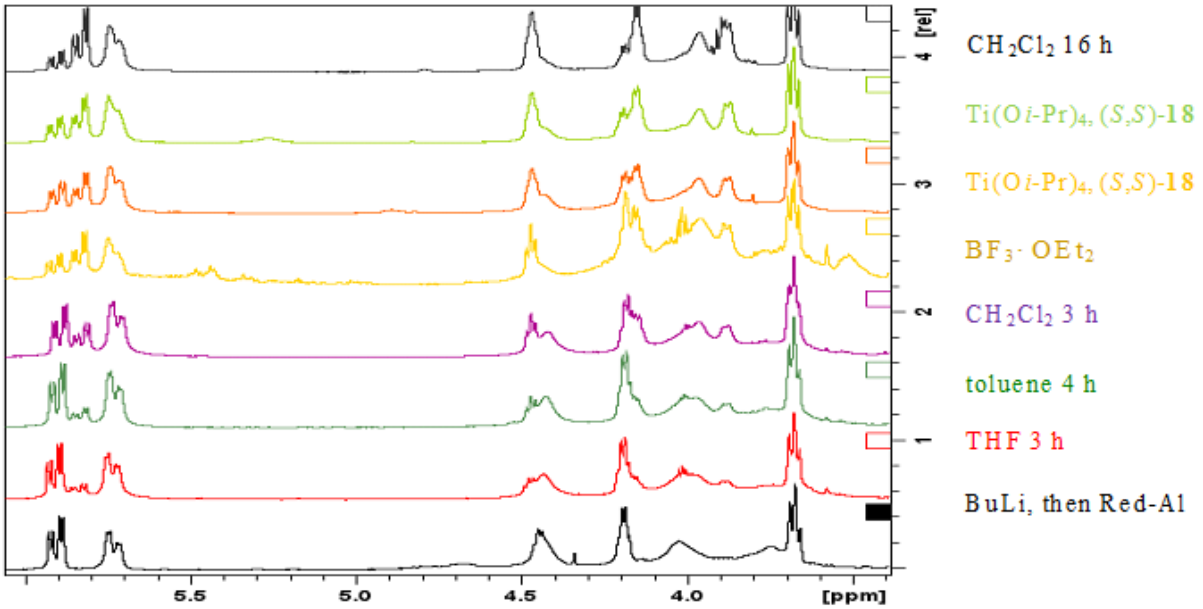
To a suspension of Schwartz's reagent (1.10 equiv.) in CH_2Cl_2 (1.0 mL/mmol) at 0 °C was dropped TBS-alkynol (1.10 equiv.) and the initially off-white suspension stirred at r.t. to turn into a yellowish solution. After 3 h the mixture was cooled to the temperature indicated and Et_2Zn (1.20 equiv., 0.9 M solution in hexanes) as well as the additives were added dropwise. Then Garner's aldehyde (1.00 equiv.) dissolved in CH_2Cl_2 (1.0 mL/mmol) was added. Further stirring for the time indicated was followed by carefully stopping the reaction by addition of Na/K-tartrate solution. The milky suspension was filtered through a pad of Celite and thoroughly washed with H_2O and EtOAc. The filtrate was extracted with EtOAc (3x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product which was purified by flash chromatography.

Table 1. Optimization of hydrozirconation reaction.

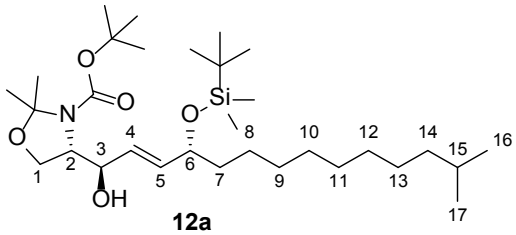


[M-H]	additive	temperature	time [h]	solvent	yield	12a : 12b
DIBAL[a)]	---	r.t. → 60 °C	1	toluene	---	---
Red-Al[a)]	---	-15 °C → r.t. then 60 °C	72	THF	---	---
catecholborane[a)]	Et_2Zn	r.t. → 60 °C	48	CH_2Cl_2	---	---
dicyclohexylborane[a)]	Et_2Zn	0 °C → r.t. then 60 °C	48 then 1	CH_2Cl_2	---	---
Cp_2ZrHCl[a)]	---	0 °C to r.t.	3	CH_2Cl_2	--	---
Cp_2ZrHCl[b)]	Et_2Zn	-40 °C → r.t.	4	CH_2Cl_2	33%	1.3 : 1.0
Cp_2ZrHCl[b)]	Et_2Zn	-40 °C → r.t.	16	CH_2Cl_2	29%	1.3 : 1.0
Cp_2ZrHCl[b)]	Et_2Zn	-40 °C → r.t.	16	CH_2Cl_2	50%	1.0 : 1.4
Cp_2ZrHCl[b)]	Et_2Zn, $BF_3 \cdot OEt_2$	-78 °C→ 0 °C	6	CH_2Cl_2	<12%	1.0 : 1.7
Cp_2ZrHCl[b)]	Et_2Zn	-40 °C → r.t.	3	THF	15%	2.7 : 1.0
Cp_2ZrHCl[b)c)]	$ZnBr_2$	0 °C → r.t.	16	THF	18%	n.d.
Cp_2ZrHCl[b)]	Et_2Zn	-40 °C → r.t.	4	toluene	24%	2.4 : 1.0
Cp_2ZrHCl[b)]	Et_2Zn, 0.5 eq. Ti(O*i*-Pr)$_4$, 8 mol-% (*R*,*R*)-**18**	-78 °C → -20 °C	16	toluene	39%	1.0 : 1.3
Cp_2ZrHCl[b)]	Et_2Zn, 0.5 eq. Ti(O*i*-Pr)$_4$, 8 mol-% (*S*,*S*)-**18**	-78 °C → -20 °C	16	toluene	65%	1.0 : 2.4

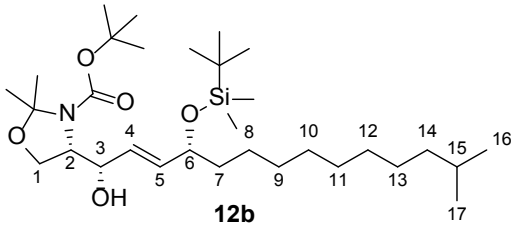
a) Reaction performed according to **GP8**. b) Reaction performed according to **GP9**, c) alkynol **11b** was used.



***tert*-Butyl (*S*)-4-((1*R*,4*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (12a)**



12a



12b

To a solution of silyl ether **11a** (200 mg, 616 µmol, 1.00 equiv.) in THF (1.23 mL) at -78 °C was dropped a solution of *n*-BuLi in hexanes (308 µL, 2.20 M, 1.10 equiv.) and the resulting mixture was stirred for 30 min, after which a solution of HMPA (441 mg, 2.46 mmol, 4.00 equiv.) in THF (1.23 mL) and Garner's aldehyde **3** (169 mg, 739 mmol, 1.20 equiv.) in THF (1.48 mL) were added slowly at -78 °C. After stirring for 45 min at the same temperature, the mixture was allowed to warm to r.t. and stirred for further 3 h at r.t.. Addition of sat. NH_4Cl-solution was followed by CH_2Cl_2 extraction (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product which was purified via flash chromatography (cHex/EtOAc 100/0 to 50/50, eluting at 85/15) to yield a yellowish oil (242 mg), which was directly used in the next step.

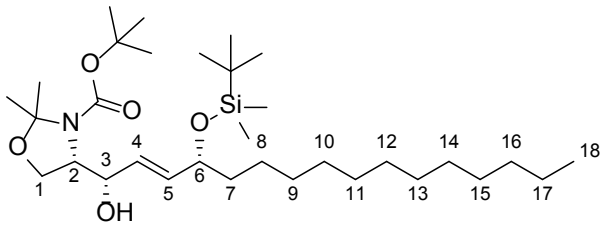
To a solution of the alkyne (50.0 mg, 90.3 µmol) in THF (1.81 mL) at -10 °C was dropped a solution of Red-Al in toluene (63 µL, 3.6 M, 2.50 equiv.) with observable gas evolution. The mixture was warmed to 0 °C over 90 min after which saturated Na/K-tartrate solution was added. The mixture was extracted with TBME (3x) and the combined organic phases washed with brine, dried over $MgSO_4$ and the volatiles removed *in vacuo* to yield **12a** as a colorless oil (49.9 mg, 70% over two steps).

^{1}H NMR (500 MHz, C_6D_6, 320 K) δ 5.91 (dd, *J* = 15.4, 5.9 Hz, 1H, 5-H), 5.74 (dd, *J* = 15.5, 5.2 Hz, 1H, 4-H), 4.47 – 4.39 (m, 1H, 3-H), 4.28 – 4.15 (m, 1H, 6-H), 4.12 – 3.92 (m, 1H, 2-H), 3.68 (t, *J* = 7.9 Hz, 2H, 1-H), 1.86 – 1.22 (m, 30H, C($C\underline{H}_3$)$_2$, Boc-C$\underline{H}_3$, 7-H to 15-H), 1.22 – 1.10 (m, 2H, 7-H to 14-H), 1.02 (s, 9H,SiC($C\underline{H}_3$)$_3$), 0.90 (d, *J* = 6.5 Hz, 6H, 16-H, 17-H), 0.12 (s, 6H, Si($C\underline{H}_3$)$_2$) ppm.
^{13}C NMR (126 MHz, C_6D_6) δ 136.1 (d, C-5), 129.0 (d, C-4), 94.8 (s, ($\underline{C}CH_3$)$_2$), 80.4 (s, Boc-$\underline{C}$(CH_3)$_3$), 73.4 (d, C-6), 73.3 (d, C-3), 64.7 (t, C-1), 62.7 (d, C-2), 39.9 (t, C-7), 33.0, 30.23, 30.21, 30.1, 29.8 (5 t, C-8 to C-14), 28.5 (q,Boc-C($\underline{C}H_3$)$_3$), 26.3 (t, C-8 to C-14), 26.1 (d, C-15) 25.6 (s, C($\underline{C}H_3$)$_2$), 22.9 (q, C-16, C-17), 18.5 (s, Si$\underline{C}$(CH_3)$_3$), -3.9, -4.4 (2 q, Si($\underline{C}H_3$)$_2$) ppm. Boc-C=O missing; expected around 154 ppm.

***tert*-Butyl (*S*)-4-((1*S*,4*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (12b)**

^{1}H NMR (500 MHz, C_6D_6) δ 5.83 (dd, *J* = 15.4, 5.9 Hz, 1H, 5-H), 5.73 (dd, *J* = 15.4, 5.7 Hz, 1H, 4-H), 4.53 – 4.30 (m, 1H, 3-H), 4.25 – 4.10 (m, 2H, 6-H), 4.08 – 3.93 (m, 1H, 2-H), 3.93 – 3.83 (m, 1H, 1-H), 3.74 – 3.60 (m, 1H, 1-H), 1.70 – 1.57 (m, 4H, 7-H to 14-H), 1.57 – 1.23 (m, 28H, C($C\underline{H}_3$)$_2$, Boc-C$\underline{H}_3$, 7-H to 15-H), 1.01 (s, 9H, SiC($\underline{C}H_3$)$_3$), 0.90 (d, *J* = 6.6 Hz, 6H, 16-H, 17-H), 0.12 (s, 6H, Si($C\underline{H}_3$)$_2$) ppm.
^{13}C NMR (126 MHz, C_6D_6, 320 K) δ 136.8 (d, C-5), 129.6 (d, C-4), 94.6 (s, ($\underline{C}CH_3$)$_2$), 80.5 (s, Boc-$\underline{C}$(CH_3)$_3$), 73.4 (d, C-6), 73.2 (d, C-3), 64.7 (t, C-1), 62.7 (d, C-2), 39.9 (t, C-7), 33.0, 30.23, 30.21, 30.1, 29.8 (5 t, C-8 to C-14), 28.5 (q,Boc-C($\underline{C}H_3$)$_3$), 26.3 (t, C-8 to C-14), 26.1 (d, C-15) 25.6 (s, C($\underline{C}H_3$)$_2$), 22.9 (q, C-16, C-17), 18.5 (s, Si$\underline{C}$(CH_3)$_3$), -3.8, -4.4 (2 q, Si($\underline{C}H_3$)$_2$) ppm. Boc-C=O missing; expected around 154 ppm.
HRMS (ESI-TOF): calculated for $C_{31}H_{61}NNaO_5Si$ $[M+Na]^+$ 578.4211; found 578.4223.
IR (ATR) ν_{max}: 2926, 2854, 1698, 1375, 1364, 1251 cm^{-1}.
$[\alpha]_D^{25}$: -28.6° (*c* = 1.1; $CHCl_3$).

***tert*-Butyl (*S*)-4-((1*S*,4*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyhexadec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (19b)**

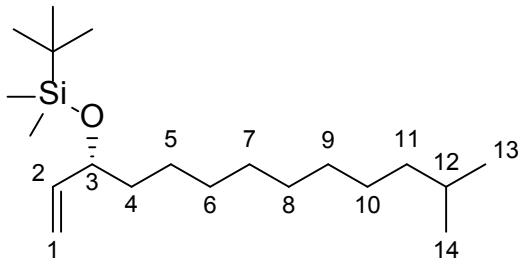


According to **GP9**, reaction of silyl ether **11b** (200 mg, 872 µmol) yielded after flash chromatography (cHex/ EtOAc 100/0 → 50/50, eluting at 75/25) **19b** as a yellowish oil (61%, 1:3.3 d.r.).

^{1}H NMR (500 MHz, C_6D_6) δ 5.84 (dd, *J* = 15.4, 6.0 Hz, 1H, 5-H), 5.73 (dd, *J* = 15.5, 5.8 Hz, 1H, 4-H), 4.54 – 4.43 (m, 1H, 3-H), 4.23 – 4.13 (m, 1H, 6-H), 4.04 – 3.95 (m, 1H, 2-H), 3.95 – 3.84, 3.76 – 3.60 (2 m, each 1H, 1-H), 1.79 – 1.58 (m, 4H, 7-H to 17-H), 1.48 – 1.23 (m, 33H, Boc-C(C$\underline{H}_3)_3$, C(C$\underline{H}_3)_2$, 7-H to 17-H), 1.02 (s, 9H, SiC(C$\underline{H}_3)_3$), 0.96 – 0.86 (m, 3H, 18-H), 0.13 (s, 6H, Si(C$\underline{H}_3)_2$) ppm.

^{13}C NMR (126 MHz, C_6D_6) δ 136.9 (d, C-5), 129.0 (d, C-4), 94.6 (s, $\underline{C}(CH_3)_2$), 80.6 (s, Boc-$\underline{C}(CH_3)_3$)), 73.4 (d, C-6), 73.3 (C-3), 64.7 (t, C-1), 62.7 (d, C-2), 38.8 (t, C-7), 32.4, 30.2, 30.16, 30.13, 29.8 (5 t, C-8 to C-16), 28.4 (q,Boc-C($\underline{C}H_3)_3$), 26.3 (t, C-8 to C-16), 25.6 (q, C($\underline{C}H_3)_2$), 23.1 (t, C-17), 18.5 (s, Si$\underline{C}(CH_3)_3$), 14.3 (q, C-18), -3.8, -4.4 (2 q, Si($\underline{C}H_3)_2$) ppm. Boc-C=O missing; expected around 154 ppm.

(*R*)-*tert*-Butyldimethyl((12-methyltridec-1-en-3-yl)oxy)silane (17)



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 16.7, 10.3, 6.0 Hz, 1H, 2-H), 5.12 (dt, *J* = 17.2, 1.6 Hz, 1H, 1-H), 5.00 (dt, *J* = 10.3, 1.5 Hz, 1H, 1-H), 4.14 – 3.96 (m, 1H, 3-H), 1.54 – 1.37 (m, 4H, 4-H to 12-H), 1.39 – 1.13 (m, 14H, 4-H to 12-H), 1.20 – 0.97 (m, 2H, 4-H to 12-H), 0.89 (s, 9H, SiC(C$\underline{H}_3)_3$), 0.86 (d, *J* = 6.7 Hz, 6H, 13-H, 14-H), 0.05, 0.03 (2 s, each 3H,Si(C$\underline{H}_3)_2$) ppm.

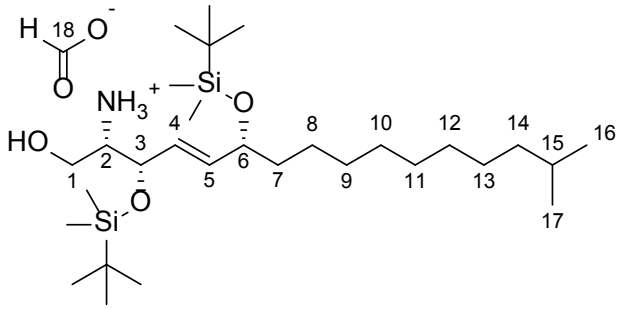
IR (ATR) ν_{max}: 2949, 2923, 2852, 1645, 1457, 1250, 1027 cm^{-1}.

$[\alpha]_D^{25}$: -0.37° (*c* = 1.0; $CHCl_3$)

General procedure 10 (GP10) for Boc-deprotection

To a solution of oxazolidine (1.00 equiv.) and 2,6-lutidine (3.50 equiv.) in CH_2Cl_2 (3.0 mL/mmol) at 0 °C was slowly added TBSOTf (1.10 equiv.) and the mixture stirred at 0 °C for 30 min. After consumption of the starting material TMSOTf (2.00 equiv.) was added dropwise into the solution and stirring was continued at 0 °C for further 60 min. The reaction was quenched by addition of Na_2CO_3-solution and the reaction mixture extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product, which was purified by reverse-phase flash chromatography.

(2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-ammonium formate (22)



According to **GP10**, reaction of oxazolidinone **12b** (800 mg, 1.44 mmol) yielded **22** after RP-flash chromatography (H_2O/MeOH +0.1% formic acid 15/85 to 0/100, eluting at 10/90) as yellowish oil (352 mg, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H, 18-H), 5.81 (dd, *J* = 15.4, 4.8 Hz, 1H, 4-H), 5.52 (dd, *J* = 15.5, 7.5 Hz, 1H, 5-H), 4.29 (t, *J* = 7.6 Hz, 1H, 3-H), 4.16 – 4.12 (m, 1H, 6-H), 3.78 (dd, *J* = 12.1, 3.4 Hz, 1H, 1-H), 3.71 – 3.60 (m, 1H, 1-H), 3.10 – 3.02 (m, 1H, 2-H), 1.63 – 1.41 (m, 4H, 7-H to 13-H), 1.41 – 1.21 (m, 15H, 7-H to 13-H, 15-H), 1.21 – 1.11 (m, 2H, 14-H), 0.91 (s, 18H, 2 SiC($\underline{CH_3}$)$_3$), 0.88 (d, *J* = 6.6 Hz, 6H, 16-H, 17-H), 0.12, 0.08, 0.06, 0.03 (4s, each 3H, 2 Si($\underline{CH_3}$)$_2$) ppm.

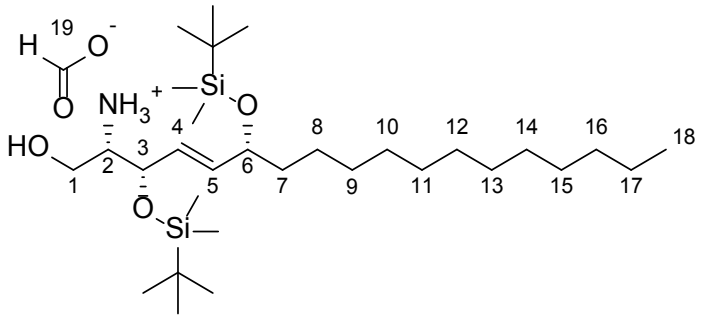
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2 (d, C-18), 138.8 (d, C-5), 126.9 (C-4), 71.9 (d, C-3), 71.8 (d, C-6), 59.3 (t, C-1), 58.1 (d, C-2), 39.0, 38.1, 29.9, 29.8, 29.6, 29.6, 29.6 (7t, C-7 to C-14), 27.9 (d, C-15), 27.4, 25.8 (s, SiC($\underline{CH_3}$)$_3$), 25.2(t, C-7 to C-14), 22.6 (C-16, C-17), 18.1, 18.0 (2 s, Si$\underline{C}$(CH_3)$_3$), -3.7, -4.3, -4.62, -4.66 (4 q, Si($\underline{C}H_3$)$_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{29}H_{64}NO_3Si_2$ $[M+H]^+$ 530.4419; found 530.4427.

IR (ATR) ν_{max}: 2952, 2926, 2855, 1576, 1252 cm^{-1}.

$[\alpha]_D^{25}$: +2.26° (*c* = 1.0; $CHCl_3$)

(2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctadec-4-en-2-ammonium formate (23)



According to **GP10,** reaction of oxazolidinine **19b** (200 mg, 350 µmol) yielded after RP-flash chromatography (H_2O/MeOH +0.1%formic acid 15/85 to 0/100, eluting at 10/90) **23** as a colorless oil (162 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H, 19-H), 5.77 (dd, *J* = 15.5, 5.1 Hz, 1H, 5 -H), 5.51 (dd, *J* = 15.5, 7.4 Hz, 1H, 4-H), 4.24 (t, *J* = 7.4 Hz, 1H, 3-H), 4.11 (d, *J* = 5.9 Hz, 1H, 6-H), 3.84 – 3.65, 3.63 – 3.50 (2 m, each 1H, 1-H), 3.03 – 2.87 (m, 1H, 2-H), 1.54 – 1.39 (m, 2H, 7-H to 17-H), 1.35 – 1.17 (m, 20H, 7-H to 17-H), 0.91 – 0.84 (m, 21H, $SiC(C\underline{H_3})_3$, 18-H), 0.10, 0.06, 0.04, 0.01 (4 s, each 3H, $Si(C\underline{H_3})_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6 (d, C-5), 127.4 (d, C-4), 72.6 (d, C-6), 72.0 (d, C-3), 60.3 (t, C-1), 58.3 (d, C-2), 38.3 (t, C-7), 32.1, 29.85, 29.80, 29.76, 29.5 (5 t, C-8 to C-16), 26.02, 26.00 (2 q, $SiC(\underline{C}H_3)_3$) , 25.4 (t, C-8 to C-16), 22.8 (t, C-17), 18.3, 18.2 (2 s, $Si\underline{C}(CH_3)_3$), 14.3 (q, C-18), -3.7, -4.3, -4.55, -4.61 (4 q, $Si(\underline{C}H_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{30}H_{66}NO_3Si_2$ $[M+H]^+$ 544.4579; found 544.4555

IR (ATR) ν_{max}: 2952, 2926, 2855, 1652, 1463, 1253, 1218 cm^{-1}.

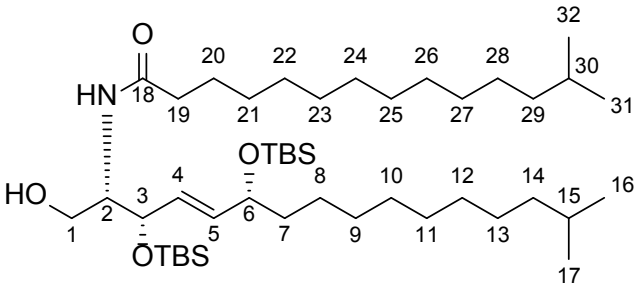
4. Synthesis of Sphingolipids

General procedure 11 (GP11) for amide bond formation

Method A) Carboxylic acid (1.10 equiv.) and HBTU were dissolved in DMF (20 mL/mmol) at 0 °C and stirred for 5 min. A solution of ammonium salt (1.00 equiv) and DIPEA (2.50 equiv.) in DMF (20 ml/mmol) was added and the mixture was stirred at r.t. until complete consumption of the ammonium salt was detected by TLC (~2 h). The mixture was quenched by addition of sat. Na_2CO_3-solution and extracted with EtOAC (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product, which was purified by flash chromatography.

Method B) Carboxylic acid (1.10 equiv.) and freshly dried DCC (1.20 equiv.) were dissolved in CH_2Cl_2, (1 mL/mmol) at 0 °C and stirred for 15 min. A solution of ammonium salt (1.00 equiv) and DIPEA (2.50 equiv.) in CH_2Cl_2 (20 ml/mmol) was added and the mixture was stirred at r.t. for 3 h. The mixture was quenched by addition of sat. Na_2CO_3-solution, filtered over a pad of Celite and extracted with EtOAC (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product, which was purified by flash chromatography.

N-((2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-13-methyltetradecanamide (24)



According to **GP11a**, reaction of compound **22** (40 mg; 69.4 µmol) yielded after flash chromatography (cHex/EtOAc 100/0 to 0/100, eluting at 55/45) **24** as a yellowish oil (18.6 mg, 35% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (d, *J* = 7.4 Hz, 1H, N-H), 5.68 (dd, *J* = 15.5, 5.3 Hz, 1H, 5-H), 5.59 (dd, *J* = 15.5, 5.9 Hz, 1H, 4-H), 4.43 – 4.35 (m, 1H, 3-H), 4.09 (q, *J* = 5.9 Hz, 1H, 6-H), 3.94 – 3.83 (m, 1H, 2-H), 3.78 – 3.54 (m, 2H, 1-H), 2.19 (t, *J* = 7.7 Hz, 2H, 19-H), 1.74 – 1.56 (m, 6H, 7-H to 14-H, 20-H to 29-H), 1.55 – 1.37 (m, 5H, 15-H, 30-H, 7-H to 14-H, 20-H to 29-H), 1.32 – 1.19 (m, 22H, 7-H to 14-H, 20-H to 29-H), 1.19 – 1.09 (m, 5H, 7-H to 14-H, 20-H to 29-H), 0.91, 0.89 (2 s, each 9H, $SiC(\underline{CH_3})_3$), 0.86 (d, *J* = 6.6 Hz, 12H, 16-H, 17-H, 31-H, 32-H), 0.09, 0.06, 0.03, 0.00 (4 s, each 3H, 2 $Si(\underline{CH_3})_2$) ppm.

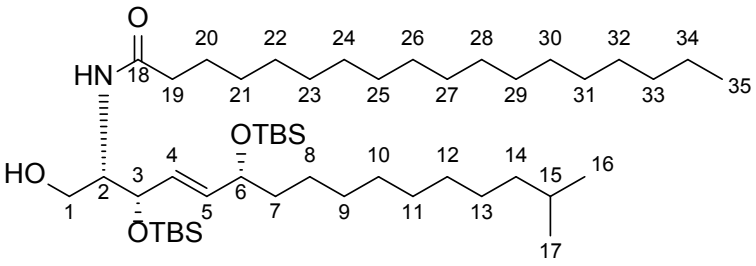
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (s, C-18), 136.0 (d, C-5), 128.9 (d, C-4), 72.4 (d, C-6), 71.7 (C-3), 64.1 (t, C-1), 56.5 (d, C-2), 39.2, 38.5 (2 t, C-7 to C-14, C-20 to C-29), 36.9 (t, C-19), 30.11, 30.07, 29.9, 29.81, 29.78, 29.7, 29.6, 29.5, 29.5, 29.4 (10 t, C-7 to C-14, C-20 to C-29), 28.1 (d, C-15, C-30), 27.6 (t, C-8 to C-14, C-20 to C-29), 26.0 (q, $SiC(\underline{CH_3})_3$), 25.8, 25.4 (2 t, C-8 to C-14, C-20 to C-29), 22.8 (q, C-16, C-17, C-31, C-32), 18.3, 18.2 (2 s, $Si\underline{C}(CH_3)_3$), -4.0, -4.2, -4.7, -4.9 (4 q, $Si(\underline{CH_3})_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{44}H_{91}NNaO_4Si_2$ $[M+Na]^+$ 776.6379; found 776.6397.

IR (ATR) ν_{max}: 2926, 2855, 1652, 1507 cm^{-1}.

$[\alpha]_D^{25}$: -0.99° (*c* = 1.0; $CHCl_3$)

N-((2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)stearamide (26)



According to **GP11**, reaction of compound **22** (40 mg; 69.4 µmol) yielded after flash chromatography (cHex/EtOAc 100/0 to 0/100, eluting at 55/45) **26** as a yellowish oil (16.2 mg, 30% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (d, *J* = 7.5 Hz, 1H, N-H), 5.68 (dd, *J* = 15.5, 5.0 Hz, 1H, 5-H), 5.58 (dd, *J* = 15.3, 5.8 Hz, 1H, 4-H), 4.39 (dd, *J* = 6.0, 3.1 Hz, 1H, 3-H), 4.14 – 4.05 (m, 1H, 6-H),

3.95 – 3.82 (m, 1H, 2-H), 3.79 – 3.52 (m, 2H, 1-H), 2.18 (dd, *J* = 9.1, 6.3 Hz, 2H, 19-H), 1.80 – 1.57 (m, 5H, 7-H to 14-H, 20-H to 34-H), 1.56 – 1.36 (m, 3H, 15-H; 7-H to 14-H, 20-H to 34-H), 1.36 – 1.16 (m, 64H, 7-H to 14-H, 20-H to 34-H), 1.17 – 1.11 (m, 2H, 7-H to 14-H, 20-H to 34-H), 0.91, 0.88 (2 s, each 9H, 2 SiC($\underline{CH_3}$)$_3$), 0.87 – 0.79 (m, 9H, 16-H, 17-H, 35-H), 0.09, 0.05, 0.03, -0.00 (4 s, each 3H, Si($\underline{CH_3}$)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (s, C-18), 136.0 (d, C-5), 128.9 (d, C-4), 72.4 (C-6), 71.6 (d, C-3), 64.1 (t, C-1), 56.5 (d, C-2), 39.2 (t, C-8 to C-14, C-20 to C-34), 38.5 (t, C-7), 36.9 (t, C-19), 32.1, 30.1, 29.9, 29.81, 29.78, 29.7, 29.7, 29.5, 29.4 (9 t, C-8 to C-14, C-20 to C-34), 28.1 (d, C-15), 27.6 (t, C-8 to C-14, C-20 to C-34), 26.0 (s, SiC($\underline{CH_3}$)$_3$), 25.8, 25.4, 22.8 (C-16, C-17), 18.3, 18.2 (2 s, Si$\underline{C}$(CH$_3$)$_3$), 14.3 (q, C-35), -4.0, -4.2, -4.7, -4.9 (4 q, Si($\underline{CH_3}$)$_2$) ppm.

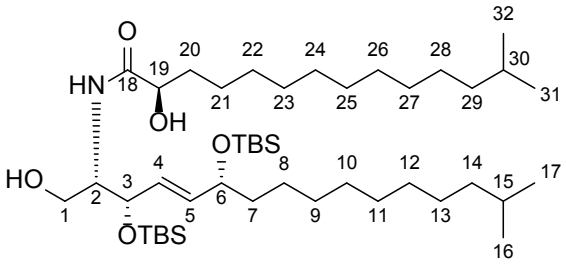
HRMS (ESI-TOF): calculated for $C_{47}H_{97}NaO_4Si_2$ $[M+Na]^+$ 818.6848; found 818.6871.

IR (ATR) ν_{max}: 2951, 2924, 2853, 1652, 1507, 1083 cm^{-1}.

$[\alpha]_D^{25}$: -3.00° (*c* = 1.0; $CHCl_3$)

HRMS (ESI-TOF): calculated for $C_{42}H_{84}NO_3Si$ $[M\text{-OTBS}]^+$ 678.6215; found 678.6209.

(*R*)-*N*-((2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-2-hydroxy-13-methyltetradecanamide (27)



According to **GP11**, reaction of compound **22** (10.0 mg, 17.4 µmol) yielded, after flash chromatography (cHex/EtOAc 100/0 to 0/100, eluting at 50/50) **27** as a colorless oil (6.4 mg, 47%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, *J* = 7.6 Hz, 1H, N-H), 5.70 (dd, *J* = 15.6, 5.1 Hz, 1H, 5-H), 5.58 (dd, *J* = 15.6, 6.0 Hz, 1H, 4-H), 4.40 (dd, *J* = 6.1, 3.1 Hz, 1H, 3-H), 4.10 (dd, *J* = 7.7, 4.1 Hz, 2H, 6-H, 19-H), 3.88 (dtd, *J* = 8.9, 5.9, 3.0 Hz, 1H, 2-H), 3.70 (dd, *J* = 5.9, 4.7 Hz, 2H, 1-H), 1.89 – 1.75 (m, 1H, 20-H), 1.74 – 1.36 (m, 9H, 7-H to 15-H, 20-H to 30-H), 1.36 – 1.19 (m, 26H, 7-H to 14-H, 21-H to 29-H), 1.19 – 1.01 (m, 2H, 7-H to 14-H, 21-H to 29-H), 0.91, 0.89 (2 s, each 9H, SiC($\underline{CH_3}$)$_3$), 0.86 (d, *J* = 6.6 Hz, 12H, 16-H, 17-H, 31-H, 32-H), 0.10, 0.06, 0.04, 0.01 (4s, each 3H, 2 Si($\underline{CH_3}$)$_2$) ppm.

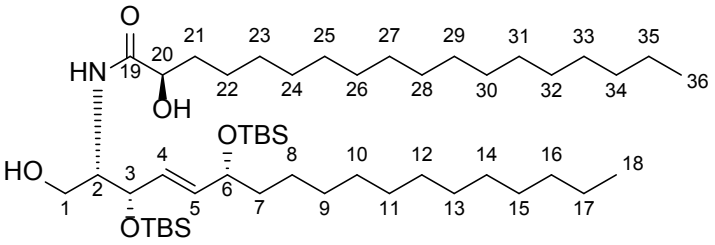
^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (s, C-18), 136.3 (d, C-5), 128.6 (d, C-4), 72.4 (C-6), 72.3 (d, C-19), 71.8 (d, C-3), 63.7 (t, C-1), 56.4 (d, C-2), 39.2 (t, C-7), 38.5, 35.1, 32.0, 30.1, 29.9, 29.82, 29.78, 29.72, 29.69, 29.55, 29.51, 29.46 (12 t, C-8 to C-14, C-20 to C-29), 28.1 (d, C-15, C-30), 27.6 (t, C-8 to C-14, C-20 to C-29), 26.02, 25.96 (2q, SiC($\underline{CH_3}$)$_3$), 25.4, 25.3 (2 t, C-8 to C-14, C-20 to C-29), 22.8 (q, C-16, C-17, C-31, C-32), 18.4, 18.2 (2 s, Si$\underline{C}$(CH$_3$)$_3$), -3.9, -4.2, -4.6, -4.9 (4 q, Si($\underline{CH_3}$)$_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{42}H_{84}NO_4Si$ $[M\text{-}OTBS]^+$ 694.6164; found 694.6134.

IR (ATR) ν_{max}: 2954, 2924, 2853, 1652, 1464, 1252, 1082 cm^{-1}.

$[\alpha]_D^{25}$: +8.65° (*c* = 0.6; $CHCl_3$).

(*R*)-*N*-((2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctadec-4-en-2-yl)-2-hydroxyoctadecanamide (29)



According to **GP11**, reaction of compound **23** (15.0 mg, 25.4 µmol) yielded, after flash chromatography (cHex/EtOAc 100/0 to 0/100, eluting at 50/50) **29** as a colorless oil (5.2 mg, 25% yield).

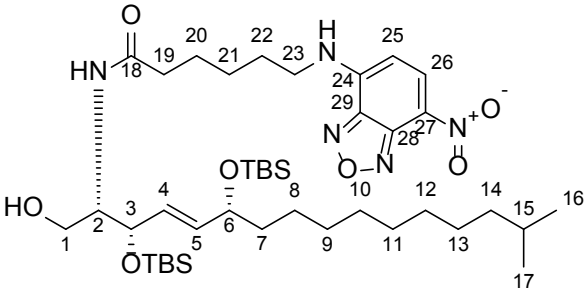
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 7.6 Hz, 1H, N-H), 5.70 (dd, *J* = 15.6, 5.1 Hz, 1H, 5-H), 5.59 (dd, *J* = 15.6, 5.8 Hz, 1H, 4-H), 4.40 (dd, *J* = 6.1, 3.0 Hz, 1H, 3-H), 4.17 – 4.05 (m, 2H, 6-H, 20-H), 3.92 – 3.83 (m, 1H, 2-H), 3.81 – 3.63 (m, 2H, 1-H), 1.92 – 1.75 (m, 1H, 21-H), 1.75 – 1.37 (m, 6 H, 7-H to 17-H, 22-H to 35-H), 1.37 – 1.14 (m, 45H, 7-H to 17-H, 22-H to 35-H), 0.91 (s, 9H, $SiC(\underline{CH_3})_3$), 0.90 – 0.83 (m, 15H, 18-H, 36-H, $SiC(\underline{CH_3})_3$), 0.10, 0.06, 0.04, 0.01 (4 s, each 3H, $Si(\underline{CH_3})_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{44}H_{91}NNaO_5Si_2$ $[M+Na]^+$ 792.6328; found 792.6397.

IR (ATR) ν_{max}: 2953, 2923, 2854, 1653, 1464, 1253, 1083 cm^{-1}.

$[\alpha]_D^{25}$: +8.22° (*c* = 0.6; $CHCl_3$).

***N*-((2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-6-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)hexanamide (31)**



According to **GP11**, reaction of compound **22** (20.0 mg, 34.7 µmol) and DCC (9.31 mg, 45.1 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 to 0/100, eluting at 60/40), **31** as orange solid (14.1 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.6 Hz, 1H, 26-H), 6.67 (broad s, 1H, DCU-NH) 6.16 (d, *J* = 8.6 Hz, 1H, 25-H), 5.94 (d, *J* = 7.6 Hz, 1H, NH), 5.70 (dd, *J* = 15.6, 5.0 Hz, 1H, 5-H), 5.60 (dd, *J* = 15.8, 5.9 Hz, 1H, 4-H), 4.40 (dd, *J* = 6.0, 2.8 Hz, 1H, 3-H), 4.10 (q, *J* = 5.7 Hz, 1H, 6-H), 4.01 – 3.87 (m, 1H, 2-H), 3.80 – 3.61 (m, 2H, 1-H), 3.61 – 3.37 (m, 4H, 23-H, DCU), 2.26 (dtt, *J* = 22.3, 14.9, 7.1 Hz, 2H, 19-H), 2.02 – 1.87 (m, 4H, 22-H, DCU), 1.81 (dt, *J* = 14.5, 7.3 Hz, 4H, DCU), 1.78 – 1.64 (m, 6H, DCU-H), 1.64 – 1.56 (m, 2H, DCU-H), 1.56 – 1.48 (m, 2H, 7-H to 14-H, 20-H to 22-H), 1.48 – 1.39 (m, 1H, 15-H), 1.38 – 1.30 (m, 2H, 7-H to 14-H, 20-H to 22-H), 1.30 – 1.19 (m, 16H, 7-H to 14-H, 20-H to 22-H), 1.18 – 1.06 (m, 6H, 7-H to 14-H, 20-H to 22-H), 0.90, 0.88 (s, each 9H, $SiC(\underline{CH_3})_3$), 0.85 (d, *J* = 6.6 Hz, 7H, 16-H, 17-H), 0.09, 0.06, 0.03, -0.01 (4 s, 3H, $Si(\underline{CH_3})_2$) ppm.

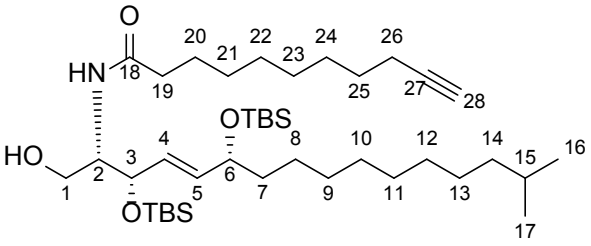
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6 (s, C-18), 157.0 (DCU), 144.4 (s, C-29), 144.1 (s, C-28), 136.6 (d, C-26), 136.1 (d, C-5), 128.7 (d, C-4), 123.9, (s, C-27) 98.7 (d, C-25), 72.3 (d, C-6), 71.7 (d, C-3), 64.1 (t, C-1), 56.4 (d, C-2), 49.5 (t, C-23), 39.2 (t, C-7), 38.5 (DCU), 36.1 (t, C-19), 34.0 (DCU), 30.1, 29.9, 29.83, 29.80, 29.77 (5 t, C-7 to C-14), 28.13 (C-20 to C-22, DCU?), 28.07 (C-15), 27.6 ((t, C-8 to C-14), 26.4 (t, C-20 to C-22, DCU?), 26.0 (q, $SiC(\underline{CH_3})_3$), 25.7 (t, DCU), 25.4 (t, C-8 to 14, C-20 to 22, DCU), 25.1 (t, DCU), 24.7 (t, C-8 to 14, C-20 to 22, DCU), 22.8 (q, C-16,17), 18.4, 18.2 (2 s, 2 s, $Si\underline{C}(CH_3)_3$), -4.0, -4.3, -4.6, -4.8 (4 q, $Si(\underline{CH_3})_2$) ppm (C-24 cannot be assigned unambiguously).

HRMS (ESI-TOF): calculated for $C_{41}H_{75}N5NaO_7Si_2$ $[M+Na]^+$ 828.5097; found 828.5093.

IR (ATR) ν_{max}: 3283 (broad), 2927, 2855,1646, 1584, 1300, 1256 cm^{-1}.

$[\alpha]_D^{25}$: -2.82° (*c* = 1.0; $CHCl_3$)

***N*-((2*S*,3*S*,6*R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)undec-10-ynamide (32)**



According to **GP11**, reaction of compound **22** (20.0 mg, 34.7 µmol) with undec-10-ynoic acid (6.96 mg, 38.2 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 to 0/100, eluting at 50/50), **32** as yellowish oil (11.2 mg, 46%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (d, *J* = 7.4 Hz, 1H, N-H), 5.68 (dd, *J* = 15.5, 5.3 Hz, 1H, 5-H), 5.62 – 5.54 (m, 1H, 4-H), 4.39 (dd, *J* = 6.1, 3.0 Hz, 1H, 3-H), 4.09 (q, *J* = 5.8 Hz, 1H, 6-H), 3.88 (dt, *J* = 13.1, 4.8 Hz, 1H, 2-H), 3.71 (dd, *J* = 10.9, 6.1 Hz, 1H, 1-H), 3.63 (dd, *J* = 10.9, 5.5 Hz, 1H, 1-H), 2.18 (qd, *J* = 7.3, 2.3 Hz, 4H, 19-H, 26-H), 1.93 (t, *J* = 2.7 Hz, 1H, 28-H), 1.68 – 1.55 (m, 2H, 7-H to

14-H, 20-H to 25-H), 1.56 – 1.46 (m, 3H, 7-H to 15-H, 20-H to 25-H), 1.48 – 1.34 (m, 4H, -H), 1.36 – 1.21 (m, 20H, 7-H to 14-H, 20-H to 25-H), 1.14 (q, *J* = 6.7 Hz, 2H, 7-H to 14-H, 20-H to 25-H), 0.91 (s, 9H, -H), 0.88 (2 s, each 9H, SiC(C$\underline{H}_3$)$_3$), 0.86 (d, *J* = 6.6 Hz, 6H, 16-H, 17-H), 0.09, 0.06, 0.03 - 0.00 (4 s, each 3H, Si(C$\underline{H}_3$)$_2$) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (s, C-18), 136.0 (d, C-5), 128.9 (d, C-4), 84.9 (d, C-28), 72.4 (d, C-6), 71.6 (d, C-3), 68.3 (s, C-27), 64.1 (t, C-1), 56.6 (d, C-2), 39.2, 38.5, 36.9, 30.1, 29.84, 29.80, 29.77, 29.74, 29.4, 29.1, 28.8, 28.6 (12 t, C-7 to C-14, C-19 to C-25), 28.1 (d, C-15), 27.6 (t, C-7 to C-14, C-19 to C-25), 26.0 (s, SiC($\underline{C}H_3$)$_3$), 25.8, 25.4 (2 t, C-7 to C-14, C-19 to C-25), 22.8 (q, C-16, C-17), 18.5 (t, C-26), 18.3, 18.2 (2 s, Si$\underline{C}$(CH$_3$)$_3$), -4.0, -4.2, -4.6, -4.8 (4 q, Si($\underline{C}H_3$)$_2$) ppm.

HRMS (ESI-TOF): calculated for $C_{34}H_{64}NO_3$ $[M\text{-}OTBS]^+$ 562.4650; found 562.4648

IR (ATR) ν_{max}: 2952, 2926, 2855, 1652, 1463, 1253, 1218 cm^{-1}.

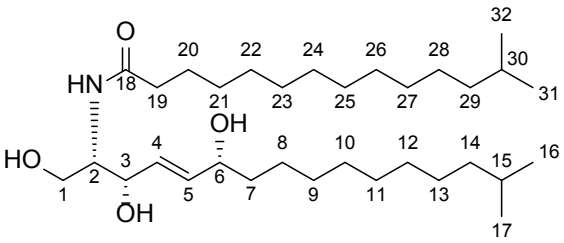
$[\alpha]_D^{25}$: -3.25° (*c* = 1.1; $CHCl_3$)

General procedure 12 (GP12) for silyl deprotection

Method A: To a solution of the Silylether (1.00 equiv.) in THF (10 mL/mmol) was added TBAF (2.50 equiv, 1 M solution in THF) and the mixture stirred at r.t. until no starting material was observed on TLC. The mixture was diluted with MeOH and the volatiles were removed *in vacuo* to yield the crude product, which was purified by flash chromatography.

Method B: To a solution of the silylether (1.00 equiv.) in THF (20 mL/mmol) at 0°C were added pyridine (10.0 equiv.) and HF·pyridine complex (40.0 equiv.) and the mixture was stirred at r.t. for 16. h. Addition of sat. $NaCO_3$-solution was followed by EtOAc-extraction. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the volatiles removed in vacuo to yield the crude product which was purified by preparative RP-TLC (H_2O/MeCN 5/95).

13-Methyl-*N*-((2*S*,3*S*,6*R*,*E*)-1,3,6-trihydroxy-15-methylhexadec-4-en-2-yl)tetradecanamide (25)



According to **GP11a**, reaction of amide **24** (16.7 mg, 22.1 µmol) yielded, after flash chromatography (cHex/EtOAc 100/0 to 0/100, eluting at 0/100) **25** as a colorless solid (2.6 mg, 22%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.16 (d, *J* = 8.0 Hz, 1H, N-H), 5.80 (dd, *J* = 15.5, 5.9 Hz, 1H, 5-H), 5.71 (dd, *J* = 15.5, 5.6 Hz, 1H, 4-H), 4.50 – 4.46 (m, 1H, 3-H), 4.11 (q, *J* = 6.3 Hz, 1H, 6-H), 3.97 – 3.91 (m, 1H, 2-H), 3.86 (dd, *J* = 11.1, 4.0 Hz, 1H, 1-H), 3.80 (dd, *J* = 11.1, 4.6 Hz, 1H, 1-H), 2.22 (t, *J*

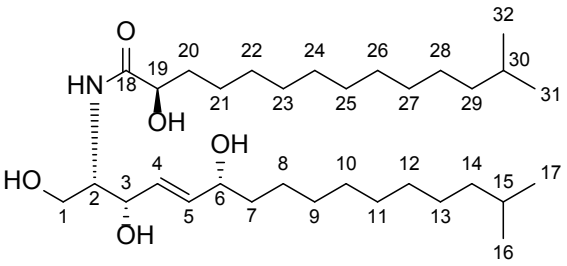
= 7.7 Hz, 2H, 19-H), 1.80 – 1.55 (m, 18H, -H), 1.51 (hept, *J* = 6.9 Hz, 2H, 15-H, 29-H), 1.26 (d, *J* = 9.5 Hz, 55H, -H), 1.18 – 1.08 (m, 4H, -H), 0.86 (d, *J* = 6.6 Hz, 12H, 16-H, 17-H, 31-H, 32-H) ppm.

HRMS (ESI-TOF): calculated for $C_{32}H_{63}NNaO_4$ $[M+Na]^+$ 548.4649 found 548.4627

IR (ATR) ν_{max}: 2917, 2848, 1698, 1540, 1219 cm^{-1}.

$[\alpha]_D^{25}$: -8.52° (*c* = 0.1; $CHCl_3$)

(*R*)-2-Hydroxy-13-methyl-*N*-((2*S*,3*S*,6*R*,*E*)-1,3,6-trihydroxy-15-methylhexadec-4-en-2-yl)tetradecanamide (28)



According to **GP11b,** reaction of amide **27** (5.4 mg, 7.01 µmol) yielded, after preparative RP-TLC (H_2O/MeCN 5/95, R_f = 0.5) **28** as a colorless solid (0.4 mg, 11% yield).

^{1}H NMR (600 MHz, DMSO) δ 7.11 (d, *J* = 8.8 Hz, 1H, N-H), 5.59 (broad s, 1H, O-H), 5.53 (dd, *J* = 15.7, 5.7 Hz, 1H, 5-H), 5.46 (dd, *J* = 15.6, 5.7 Hz, 1H, 5-H), 5.12 (broad s, 1H, O-H), 4.71 (broad s, 1H, O-H), 4.56 (broad s, 1H, O-H), 4.32 – 4.22 (m, 1H, 19-H), 3.86 – 3.75 (m, 2H, 3-H, 6-H), 3.65 (tdd, *J* = 8.1, 5.3, 2.5 Hz, 1H, 2-H), 1.64 – 1.53 (m, 2H, 7-H to 14-H, 20-H to 29-H), 1.53 – 1.38 (m, 4H, 7-H to 15-H, 20-H to 30-H), 1.38 – 1.16 (m, 40H, 7-H to 14-H, 20-H to 29-H), 1.16 – 1.03 (m, 3H, 7-H to 14-H, 20-H to 29-H), 0.84 (d, *J* = 6.6 Hz, 12H, 16-H, 17-H, 31-H, 32-H) ppm.

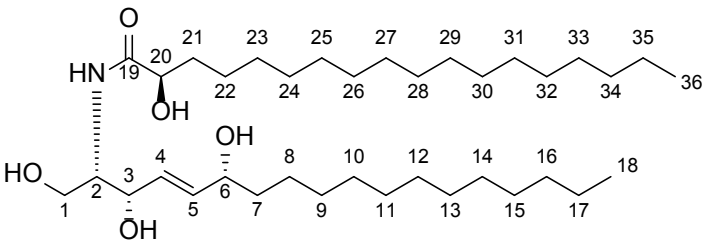
Not visible in 1H due to water peak: 3.42, 3.32 (1-H) ppm.

^{13}C NMR (151 MHz, DMSO) δ 173.6 (s, C-18), 134.4 (d, C-5), 129.8 (d, C-4), 71.0 (d, C-3), 70.4 (d, C-6), 67.9 (d, C-19), 60.1 (t, C-1), 54.3 (d C-2), 38.5, 37.4, 34.4, 31.4, 29.4, 29.3, 29.20, 29.17, 29.12, 29.05, 29.01, 28.8 (12 t, C-7 to C-14, C-20 to C-29), 27.4 (d, C-15, C-30), 26.8, 25.2, 24.6 (3 t, C-7 to C-14, C-20 to C-29), 22.5 (q, C-16, C-17, C-31, C-32) ppm.

HRMS (ESI-TOF): calculated for $C_{32}H_{63}NNaO_5$ $[M+Na]^+$ 564.4598 found 564.4606.

$[\alpha]_D^{25}$: -70.7° (*c* = 0.04; MeOH)

(*R*)-2-Hydroxy-*N*-((2*S*,3*S*,6*R*,*E*)-1,3,6-trihydroxyoctadec-4-en-2-yl)octadecanamide (30)



According to **GP11b,** reaction of amide **29** (7.2 mg, 8.71 µmol) yielded **30** as a colorless solid (0.4 mg, 8% yield).

^{1}H NMR (600 MHz, DMSO) δ 7.11 (d, *J* = 8.9 Hz, 1H, N-H), 5.60 (d, *J* = 5.1 Hz, 1H, O-H), 5.53 (dd, *J* = 15.6, 5.5 Hz, 1H, 5-H), 5.47 (dd, *J* = 15.6, 5.8 Hz, 1H, 4-H), 5.13 (d, *J* = 4.7 Hz, 1H, O-H), 4.72 (t, *J* = 5.5 Hz, 1H, O-H), 4.55 (d, *J* = 4.8 Hz, 1H, O-H), 4.30 – 4.26 (m, 1H, 20-H), 3.85 – 3.80 (m, 2H, 3-H, 6-H), 3.66 (dt, *J* = 10.6, 7.2 Hz, 1H, 2-H), 3.42 (ddd, *J* = 9.9, 7.9, 6.1 Hz, 1H, 1-H) , 1.61 – 1.54 (m, 2H, 7-H to 17-H, 21-H to 35-H), 1.49 – 1.41 (m, 4H, 7-H to 17-H, 21-H to 35-H), 1.36 – 1.17 (m, 46H, 7-H to 17-H, 21-H to 35-H), 0.97 – 0.82 (m, 6H, 18-H, 36-H) ppm.

^{13}C NMR (151 MHz, DMSO) δ 175.0 (s, C-19), 134.4 (d, C-5), 129.6 (d, C-4), 70.3 (d, C-3, C-6), 67.4 (d, C-20), 54.4 59.8 (t, C-1) , (d, C-2), 28.7 (t, C-7 to C-17, C-21 to C-35), 13.4 (q, C-18, C-36) ppm. Data extracted from HSQC/HMBC.

HRMS (ESI-TOF): calculated for $C_{36}H_{71}NNaO_5$ $[M+Na]^+$ 620.5224 found 620.5225.

IR (ATR) ν_{max}: 3296 (broad), 2917, 2848, 1599, 1531, 1404, 1319, 1086 cm^{-1}.$[\alpha]_D^{25}$: -52.7° (*c* = 0.04; MeOH)

5. References

[1] H. Takikawa, D. Nozawa, A. Kayo, S.-e. Muto and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2467.
[2] J. Klimentová, P. Kosák, K. Vávrová, T. Holas and A. Hrabálek, *Bioorg. Med. Chem.*, 2006, **14**, 7681.
[3] H. Takikawa, D. Nozawa, A. Kayo, S.-e. Muto and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2467.
[4] P. van de Weghe, S. Bourg and J. Eustache, *Tetrahedron*, 2003, **59**, 7365.
[5] K. Mori and Y. Masuda, *Tetrahedron Lett.*, 2003, **44**, 9197.
[6] J. R. Gage and D. A. Evans, *Org. Synth.*, 1990, **68**, 77.
[7] J. Eustache and A. Grob, *Tetrahedron*, 1994, **50**, 6271.
[8] P. Garner and J. M. Park, *Org. Synth.*, 1992, **70**, 18.
[9] P. Garner and J. M. Park, *Org. Synth.*, 1992, **70**, 18.