A concise total synthesis of the lichen macrolide (+)-Aspicilin

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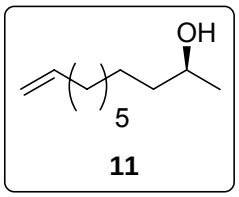
Supplementary material

All the reactions were carried out using anhydrous conditions and in an atmosphere of argon. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Ultrashield (^{1}H 300 MHz and ^{13}C 75 MHz) and Brucker AM 500 (^{1}H 500 MHz and ^{13}C 125 MHz) instruments. Chemical shifts are expressed as parts per million (ppm) down-field from tetramethylsilane or calibrated from $CDCl_3$. Mass spectra were obtained using Varian MAT-44 and Finnigan MAT-TSQ 70 spectrometers with electron impact (70 eV) and chemical ionisation (100 eV, ionisation gas, isobutane). IR spectra were taken with a BIO-RAD FTS 135 spectrometer and Shimadzu FTIR8400s. Microanalyses were performed in Prof. V. Jäger's analytical laboratory (Institut für Organishe Chemie, Universität Stuttgart, Germany) or in Prof. Z. Riedl's laboratory (Hungarian Academy of Science, Hungary). High resolution mass spectra were recorded in Prof. R. Flamant's laboratory (Université de Mons, Belgium).



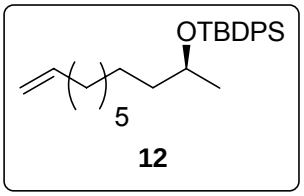
11

(S)-undec-10-en-2-ol : 11

In a 100 ml round bottomed flask equipped with an addition funnel and a condenser, a portion of bromide **10** (3.9 g, 20.4 mmol, 1 equiv) was dissolved in 5 ml of dry THF, the remaining being dissolved in 30 ml of dry THF and placed in the addition funnel. Magnesium (514 mg, 21.4 mmol, 1.05 equiv) and two drops of dibromoethane were added into the flask. The mixture was heated to reflux under vigorous stirring and the solution of bromide **10** was added dropwise. After complete addition, the reflux was maintained for 4 h and the solution was cooled to room temperature.

In a 250 ml round bottomed flask equipped with an addition funnel, (*S*)-propylene oxide (1.16 g, 1.33 ml, 20.4 mmol, 1.0 equiv) and CuCN (90 mg, 1.02 mmol, 0.05 equiv) were dissolved in 50 ml of dry THF. The solution was cooled to –15 °C and the Grignard reagent prepared above was transferred into the addition funnel. This solution was added dropwise and after complete addition, stirring was maintained for 3 hours at -15 °C and 2 additional hours at room temperature. A saturated NH_4Cl solution was added (50 ml) and stirring was continued until a dark blue aqueous layer was obtained. The layers were separated and the aqueous layer was extracted with diethylether (3 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 4/1) to give 2.94 g of a colourless oil (89 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.82 (1H, m), 4.95 (2H, m), 3.79 (1H, sx, *J*=5.4 Hz), 2.07 (2H, m), 1.51-1.23 (12H, m), 1.18 (3H, d, *J*=5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.07, 114.06, 68.15, 39.36, 33.82, 29.63, 29.50, 29.10, 28.94, 25.80, 23.53; I.R. (cm^{-1}) : 3500 (l), 3077, 2927 (f), 2856, 1641, 1465, 1374, 1122 ; MS (CI) *m/z* : 171.0 ($M+H^+$). RN : 213263-50-4



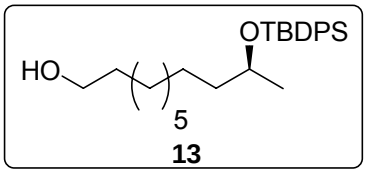
12

(S)-tert-butyldiphenyl(undec-10-en-2-yloxy)silane : 12

In a 250 ml round bottomed flask equipped with an addition funnel, alcohol **11** (2.94 g, 17.2 mmol, 1 equiv), imidazole (2.34 g, 34.5 mmol, 2 equiv) and DMAP (50 mg, cat.) were dissolved in 100 ml of dry DCM. A solution of TBDPSCl (5.19 g, 18.92 mmol, 1.1 equiv) in 100 ml of dry DCM was added *via* the addition funnel and the mixture was stirred for 5 h at room temperature. A saturated $NaHCO_3$ solution (50 ml) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 50 ml). The organic layers

were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 60/1) to give 7.02 g of a colourless oil (99 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61-7.58 (4H, m), 7.28-7.26 (6H, m), 5.69 (1H, m), 4.86 (2H, m), 3.73 (1H, sx, *J*= 5.04 Hz), 1.94 (2H, q, *J*= 6.66 Hz), 1.40-1.10 (15 H, m), 0.97 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.18, 135.88, 134.97, 134.64, 129.40, 129.34, 127.43, 127.36, 114.12, 69.59, 39.43, 33.82, 29.55, 29.40, 29.05, 28.91, 27.05, 25.19, 23.25, 19.27; I.R. (cm^{-1}) : 3070, 2927, 2856, 1461, 1427, 1375, 1110 ; MS (APCI) *m/z* : 409.7 ($M+H^+$); $[\alpha]^D_{20}$: -12.4 (C = 1.2, DCM).

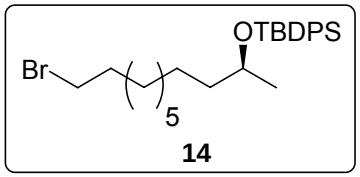


13

(S)-10-(tert-butyldiphenylsilyloxy)undecan-1-ol : 13

In a 250 ml round bottomed flask equipped with an addition funnel and a condenser, olefin **12** (7.0 g, 17.1 mmol, 1 equiv) was dissolved in 100 ml of dry THF. A 1 M solution of 9-BBN-H in THF (18.81 ml, 18.81 mmol, 1.1 equiv) was added *via* the addition funnel and the solution was refluxed for 4 hours. Then, the reaction was cooled to room temperature and an aqueous solution of NaOH (2 M, 15 ml) followed by an aqueous solution of H_2O_2 (30 %, 15 ml) were added. Stirring was continued at room temperature for 12 hours. Diethylether (50 ml) was added, the layers were separated and the aqueous layer was extracted with diethylether (3 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 4/1) to give 6.56 g of a colourless oil (90 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75-7.60 (4H, m), 7.45-7.30 (6H, m), 3.81 (1H, sx, *J*= 5.7 Hz), 3.63 (2H, t, *J*= 6.9 Hz), 1.6-1.1 (19H, m), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.87, 134.96, 134.64, 129.38, 129.32, 127.40, 127.34, 69.59, 63.09, 39.41, 32.79, 29.58, 29.50, 29.49, 29.38, 27.02, 25.71, 25.18, 23.21, 19.25; I.R. (cm^{-1}) : 2927, 2854, 2358, 2337, 1463, 1427, 1375, 1352, 1134, 1110, 1033 ; MS (APCI) *m/z* : 427.2 ($M+H^+$); $[\alpha]^D_{20}$: -11.5 (C = 0.53, DCM).



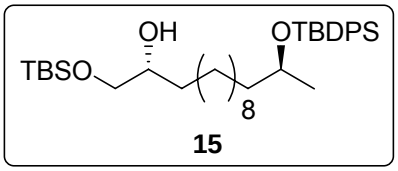
14

(S)-(11-bromoundecan-2-yloxy)(tert-butyl)diphenylsilane : 14

In a 250 ml round bottomed flask equipped with an addition funnel, alcohol **13** (4.88 g, 11.4 mmol, 1 equiv) and CBr_4 (4.16 g, 12.5 mmol, 1.1 equiv) were dissolved in 50 ml of dry DCM. A solution of triphenylphosphine (3.19 g, 13.1 mmol, 1.15 equiv) in dry DCM

was placed in the addition funnel and added dropwise. After complete addition, the reaction was stirred 24 h at room temperature and 175 ml of petroleum ether were added. A white precipitate was formed and filtered over celite. The solvent was then removed under reduced pressure. 50 ml of petroleum ether were added and the white precipitate formed was filtered again. The process was repeated until a clear oil was obtained. After concentration, this crude material was purified by silica gel column chromatography (PE/Et_2O 50/1) to give 5.13 g of a colourless oil (92 %)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73-7.70 (4H, m), 7.44-7.36 (6H, m), 3.86 (1H, m), 3.42 (1H, t, *J*= 6.6 Hz), 1.85 (1H, qu, *J*= 6.6 Hz), 1.50-1.02 (26H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.86, 134.94, 134.62, 129.37, 129.32, 127.40, 127.33, 69.56, 39.39, 34.03, 32.80, 29.52, 29.40, 29.31, 28.70, 28.14, 27.01, 25.15, 23.12, 19.24; I.R. (cm^{-1}) : 2960, 2927, 2854, 1461, 1427, 1375, 1107, 1064 ; MS (APCI) *m/z* : 490.1 ($M+H^+$); $[\alpha]^D_{20}$: -12.0 (C = 0.57, DCM); Anal. for $C_{27}H_{41}BrOSi$: Calculated C, 66.24 %; H, 8.44 %; Br, 16.12 %. Found C, 66.29 %; H, 8.44 %; Br, 16.18 %.



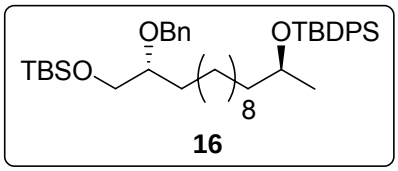
15

(6R,17S)-2,2,3,3,17,20,20-heptamethyl-19,19-diphenyl-4,18-dioxa-3,19-disilahenicosan-6-ol : 15 (85 % purity)**.**

In a 250 ml round bottomed flask equipped with an addition funnel and a condenser, a portion of bromide **14** (18.46 g, 37.7 mmol, 1 equiv) was dissolved in 10 ml of dry THF, the remaining being dissolved in 150 ml of dry THF and placed in the addition funnel. Magnesium (1.37 g, 56.5 mmol, 1.5 equiv) and two drops of dibromoethane were added into the flask. The mixture was heated to reflux under vigorous stirring and the solution of bromide **10** was added dropwise. After complete addition, the reflux was maintained for 4 h and the solution was cooled to room temperature.

In a 250 ml round bottomed flask equipped with an addition funnel, epoxyde **9** (7.81 g, 41.4 mmol, 1.1 equiv) and $CuBr.Me_2S$ (387 mg, 1.88 mmol, 0.05 equiv) were dissolved in 150 ml of dry THF. The solution was cooled to –25 °C and the Grignard reagent prepared above was transferred into the addition funnel. This solution was added dropwise and after complete addition, stirring was maintained for 5 hours at -25 °C and 2 additional hours at room temperature. A saturated NH_4Cl solution was added (400 ml) and stirring was continued until a dark blue aqueous layer was obtained. The layers were separated and the aqueous layer was extracted with diethylether (3 x 150 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/Et_2O 20/1) to give 19.87 g of a colourless oil (88 %, 85 % purity).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70-7.67 (4H, m), 7.39-7.36 (6H, m), 3.87-3.35 (4H, m), 1.49-1.11 (23H, m), 1.06 (9H, s), 0.91 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.84, 134.94, 134.60, 129.35, 129.29, 127.38, 127.31, 71.80, 69.56, 67.26, 39.41, 32.77, 29.71-29.54, 27.00, 25.85, 25.57, 25.18, 23.19, 19.22, 18.25, -5.35; I.R. (cm^{-1}) : 3467, 2927, 2854, 1471, 1461, 1427, 1388, 1253, 1105; MS (APCI) *m/z* : 599.08 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{36}H_{62}O_3NaSi_2$, Calculated 621.4135 Found 621.4116.

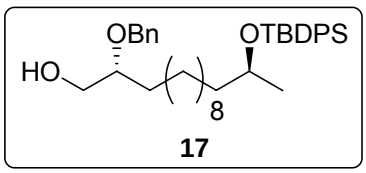


16

(5S,16R)-16-(benzyloxy)-2,2,5,19,19,20,20-heptamethyl-3,3-diphenyl-4,18-dioxa-3,19-disilahenicosane : 16

In a 250 ml round bottomed flask equipped with an addition funnel, compound **15** (5.47 g, 9.13 mmol, 1 equiv) was dissolved in dry DCM (5 ml). At room temperature, a solution of benzyl-2,2,2,-trichloroacetimidate (3.45 g, 13.6 mmol, 1.5 equiv) in hexane (50 ml) was added *via* the addition funnel followed by triflic acid (136 mg, 81 µl, 0.91 mmol, 0.1 equiv). The reaction was stirred for 48 h at room temperature. At this stage, the white precipitate formed was filtered and rinsed with hexane (100 ml). The solution was then treated with a saturated $NaHCO_3$ solution (10 ml). The layers were separated and the aqueous layer was extracted with hexane (3 x 25 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/Et_2O 60/1) to give 5.55 g of a colourless oil (89 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62-7.60 (4H, m); 7.34-7.23 (11H, m), 4.63 (1H, d, *J*= 11.7 Hz), 4.51 (1H, d, *J*= 11.7 Hz), 3.75 (1H, sx, *J*= 5.7 Hz), 3.63 (1H, dd, *J*= 5.7, 10.5 Hz), 3.52 (1H, qu, *J*= 5.7 Hz), 3.38 (1H, qu, *J*= 5.7 Hz), 1.45-1.03 (23H, m), 0.98 (9H, s), 0.83 (9H, s), 0.00 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.10, 135.86, 135.61, 134.77, 129.62, 128.46, 128.22, 127.76, 127.68, 127.63, 127.39, 79.66, 72.08, 71.47, 64.20, 38.76, 30.69, 29.56-29.38, 27.01, 26.82, 26.52, 25.67, 25.55, 25.36, 18.98, 18.10, -2.96; I.R. (cm^{-1}) : 2955, 2931, 2857, 1769, 1463, 1428, 1389, 1110 ; MS (APCI) *m/z* : 689.9 ($M+H^+$).



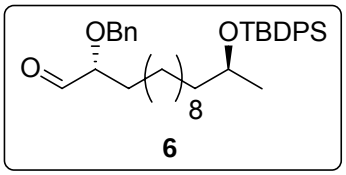
17

(2R,13S)-2-(benzyloxy)-13-(tert-butyldiphenylsilyloxy)tetradecan-1-ol : 17

In a 250 ml round bottomed flask equipped with an addition funnel, compound **16** (5.55 g, 8.05 mmol, 1 equiv) was dissolved in dry THF (100 ml). At room temperature, a 1 M solution of TBAF in THF (8.05 ml, 8.05 mmol, 1.0 equiv) was added over 2 hours *via* the addition funnel. The reaction was stirred 2 additional hours and quenched with a saturated $NaHCO_3$ solution (50 ml). The layers were separated and the aqueous layer was extracted

with diethylether (2 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/Et_2O 20/1) to give 4.58 g of a colourless oil (99 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (4H, m), 7.43-7.34 (11H, m), 4.65 (1H, d, *J*= 11.4 Hz), 4.56 (1H, d, *J*= 11.4 Hz), 3.85 (1H, sx, *J*= 5.7 Hz), 3.72 (1H, d, *J*= 7.8 Hz), 3.57 (1H, d, *J*= 6.6 Hz), 3.54 (1H, m), 2.03 (1H, bs), 1.65-1.23 (23H, m), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.35, 135.75, 134.83, 134.50, 129.49, 128.36, 127.68, 127.25, 79.78, 71.46, 69.57, 64.25, 39.46, 30.82, 29.85, 29.65, 29.60, 28.35, 27.07, 26.48, 25.43, 25.32, 25.26, 23.29, 19.31; I.R. (cm^{-1}) : 3426, 2929, 2854, 1957, 1889, 1820, 1471, 1427, 1110, 1028 ; MS (APCI) *m/z* : 575.0 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{37}H_{54}O_3NaSi$, Calculated 597.3740 Found 597.3763 ; HPLC : AD-H, Hex/*i*-PrOH 99.5/0.5, 1 ml/min, 17.44 min 98.0 %, 21.48 min 2.0 %.

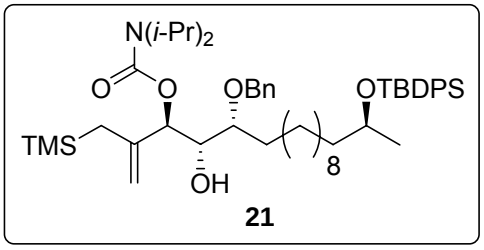


6

(2R,13S)-2-(benzyloxy)-13-(tert-butyldiphenylsilyloxy)tetradecanal : 6

In a 250 ml round bottomed flask, alcohol **17** (6.1 g, 10.6 mmol, 1 equiv) was dissolved in 75 ml of dry DCM. Dess-Martin's reagent (6.74 g, 15.9 mmol, 1.5 equiv) was added by portions and the suspension was stirred 1 hour at room temperature. An aqueous solution of NaOH (1 M, 20 ml) was added and the solution was stirred vigorously for 15 minutes. The layers were separated and the aqueous layer was extracted with DCM (3 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 10/1) to give 5.39 g of a colourless oil (89 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.66 (1H, d, *J*= 1.8 Hz), 7.70 (4H, m), 7.42-7.33 (11H, m), 4.69 (1H, d, *J*= 11.7 Hz), 4.54 (1H, d, *J*= 11.7 Hz), 3.84 (1H, sx, *J*= 6.6 hz), 3.77 (1H, td, *J*= 1.8, 6.6 Hz), 1.68 (2H, q, *J*= 6.6 Hz), 1.50-1.21 (21H, m), 1.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.02, 140.18, 135.86, 134.95, 134.62, 129.74, 129.37, 129.31, 128.55, 128.38, 127.65, 127.39, 77.00, 69.59, 65.37, 39.41, 33.89, 29.57-29.04, 27.01, 25.18, 24.66, 23.20, 19.24; ; I.R. (cm^{-1}) : 2927, 2855, 1708, 1589, 1461, 1427, 1110 ; ; MS (APCI) *m/z* : 465 ($M+H^+$-OBn) ; Anal. for $C_{37}H_{52}O_3Si$: Calculated C, 77.57 %; H, 9.15 %; Found C, 77.52 %; H, 9.28 %; HPLC : AD-H, Hex/*i*-PrOH 99.8/0.2, 1 ml/min, 6.01 min 97.7%, 7.38 min 2.3 %.

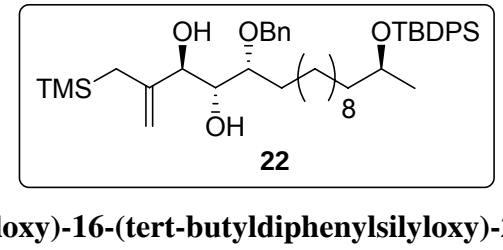


21

(3R,4S,5R,16S)-5-(benzyloxy)-16-(tert-butyldiphenylsilyloxy)-4-hydroxy-2-((trimethylsilyl)methyl)heptadec-1-en-3-yl diisopropylcarbamate : 21

In a 1 L round bottom flask equipped with a refrigerated addition funnel, allylstannane **1** (8.04 g, 14.34 mmol, 1.05 equ.) was dissolved in DCM (500 ml). At -78 °C, tin tetrachloride (3.72 g, 1.67 ml, 14.34 mmol, 1.05 équ.) was added and the mixture was stirred for one hour. A solution of aldehyde **6** (7.82 g, 13.66 mmol, 1 equ) in DCM (75 ml) was cooled to -78 °C and added quickly *via* the addition funnel. The solution was stirred 30 minutes at -78 °C and a saturated $NaHCO_3$ solution (150 ml) was added. The solution was diluted with DCM (150 ml) and the layers were separated. The aqueous layer was extracted with DCM (2 x 150 ml) and the organic layers were combined, dried over $MgSO_4$, filtrated and evaporated under reduced pressure. The resulting crude oil was purified by silica gel column chromatography (PE/EA 25/1) to give 7.95 g of alcohol **21** as a colourless syrup (69 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67 (4H, m), 7.43-7.26 (11H, m), 5.22 (1H, d, *J*= 7.5 Hz), 5.05 (1H, s), 4.89 (1H, s), 4.57 (1H, d, *J*= 12.1 Hz), 4.53 (1H, d, *J*= 12.1 Hz), 3.90 (2H, bs), 3.81 (1H, sx, *J*= 6.6 Hz), 3.62 (1H, bt, *J*= 7.5 Hz), 3.50 (1H, td, *J*= 1.8, 6.6 Hz), 2.38 (1H, bd, *J*= 7.5 Hz), 1.59 (2H, s), 1.69-1.11 (35H, m), 1.05 (9H,s), 0.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.71, 144.32, 138.21, 135.75, 134.84, 134.51, 129.27, 129.22, 128.22, 128.03, 127.55, 127.31, 127.23, 112.11, 77.62, 77.32, 72.61, 72.36, 69.57, 45.88, 39.47, 31.18, 29.77, 29.67, 29.63(b), 27.87, 27.07, 26.87, 25.70, 25.26, 23.27, 22.36, 21.49-20.90, 19.31, -0.95; I.R. (cm^{-1}) : 3553, 2961, 2925, 2856, 1958, 1890, 1817, 1742, 1701, 1428, 1376, 1110, 1048 ; MS (APCI) *m/z* : 845.1 ($M+H^+$) ; AE for $C_{51}H_{81}NO_5Si_2$: Calculated C, 72.55 %; H, 9.67 %; N, 1.66 %. Found C, 72.75 %; H, 9.57 %; N, 1.74 % ; $[\alpha]^D_{20}$ **:** -3.2 (C = 0.9, DCM) ; HPLC : AD-H, Hex/*i*-PrOH 99.55/0.45, 1 ml/min, 8.83 min 1.0%, 10.31 min 99.0 %.



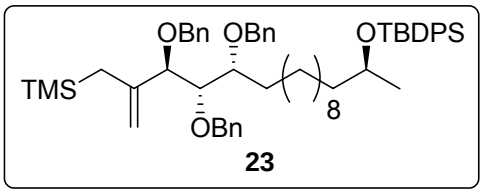
22

(3R,4R,5R,16S)-5-(benzyloxy)-16-(tert-butyldiphenylsilyloxy)-2-((trimethylsilyl)methyl)heptadec-1-ene-3,4-diol : 22

In a 500 ml round bottomed flask, allylsilane **21** (5.0 g, 5.92 mmol, 1.0 equiv) was dissolved in dry THF (150 ml). A 1 M solution of $LiAlH_4$ in THF (29.6 ml, 29.6 mmol, 5 equiv) was added and the reaction was heated to reflux for 3 hours. The solution was cooled to 0 °C, diluted with diethylether (150 ml) and a saturated NH_4Cl solution (100 ml) was added dropwise. The layers were separated and the aqueous layer was extracted with diethylether

(2 x 150 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 2/1) to give 4.20 g of a colourless oil (99 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71-7.67 (4H, m), 7.44-7.30 (11H, m), 4.99 (1H, s), 4.81 (1H, s), 4.65 (1H, d, *J*= 11.01 Hz), 4.45 (1H, d, *J*= 11.01 Hz), 4.13 (1H, bt, *J*= 5.73 Hz), 3.86 (1H, sx, *J*= 5.88 Hz), 3.69 (2H, m), 3.07 (1H, bd, *J*= 6.57 Hz), 2.53 (1H, bd, *J*= 7.95 Hz), 1.75-1.11 (22H, m), 1.06 (3H, d, *J*= 5.88 Hz), 1.05 (9H, s), 0.05 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.90, 137.80, 135.84, 134.95, 134.63, 129.35, 129.29, 128.51, 128.04, 127.95, 127.37, 127.31, 108.83, 78.90, 77.39, 71.78, 70.95, 68.58, 39.41, 29.94, 29.75-29.54, 27.00, 25.60, 25.18, 13.18, 22.88, 19.23, -1.30; I.R. (cm^{-1}) : 3463 (b), 2925, 2854, 1461, 1427, 1110, 1066; MS (APCI) *m/z* : 717.3 ($M+H^+$); $[\alpha]^D_{20}$ **:** -2.4 (C = 0.8, DCM); HRMS (ES+, $M+Na^+$) for $C_{44}H_{68}O_4NaSi_2$, Calculated 739.4553 Found 739.4549.

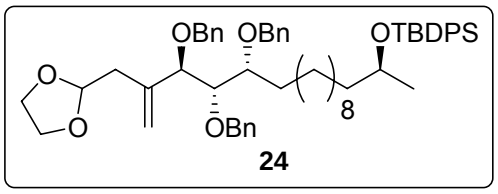


23

tert-butyldiphenyl((2S,13R,14S,15R)-13,14,15-tris(benzyloxy)-16-((trimethylsilyl)methyl)heptadec-16-en-2-yloxy)silane : 23

In a 250 ml round bottomed flask, allylsilane **22** (1 g, 1.39 mmol, 1.0 equiv) was dissolved in dry THF (25 ml). Benzylbromide (12.5 ml) was added followed by TBAI (50 mg, cat.). The reaction was cooled to 0 °C and NaH (60 % in mineral oil, 111 mg, 2.78 mmol, 2.0 equiv) was added by portions. The suspension was stirred 12 h at 0 °C, diluted with diethylether (50 ml) and a saturated NH_4Cl solution (50 ml) was added dropwise. The layers were separated and the aqueous layer was extracted with diethylether (2 x 150 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 30/1) to give 985 mg of a colourless oil (79 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (4H, m), 7.41-7.25 (21H, m), 5.11 (1H, s); 4.99 (1H, s); 4.58 (1H, d, *J*= 11Hz), 4.53-4.45 (4H, m), 3.90 (2H, m), 3.80 (1H, sx, *J*= 6.0 Hz), 3.61 (1H, td, *J*= 3.5, 6.5 Hz), 3.56 (1H, dd, *J*= 3.5, 7.5 Hz), 1.48 (2H, s), 1.58-1.10 (23H, m), 1.02 (9H, s), 0.05 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 141.89, 139.21, 138.58, 138.50, 135.84, 134.90, 134.72, 129.48, 128.25, 128.11, 128.08, 127.95, 127.65, 127.44, 127.30, 127.20, 127.14, 112.16, 80.56, 80.01, 77.62, 74.16, 72.82, 70.25, 69.54, 36.71, 31.15, 29.81, 29.62(b), 29.54, 27.01, 25.21, 24.12, 23.21, 19.24, -1.02; I.R. (cm^{-1}) : 2932, 2850, 1485, 1454, 1419, 1356, 1142, 1110, 1089; MS (ESI) *m/z* : 897.9 (M^+); HRMS (ES+, $M+Na^+$) for $C_{58}H_{80}O_4NaSi_2$, Calculated 919.5493 Found 919.5491.

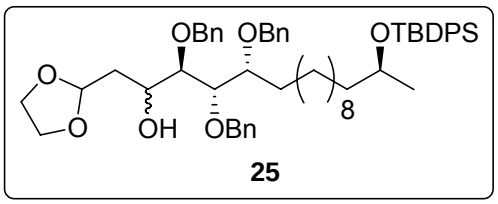


24

((2S,13R,14S,15R)-16-((1,3-dioxolan-2-yl)methyl)-13,14,15-tris(benzyloxy)heptadec-16-en-2-yloxy)(tert-butyl)diphenylsilane : 24

In a 250 ml round bottomed flask, 2-methoxy-1,3-dioxolane (0.637 ml, 695 mg, 6.68 mmol, 5 equiv) and a 1 M solution of $ZnCl_2.Et_2O$ in diethylether (13.3 ml, 13.3 mmol, 10 equiv) were mixed. The solution was stirred for 15 minutes, then, a solution of allylsilane **23** (1.2 g, 1.33 mmol, 1 equiv) in 15 ml of DCM was added at once. The reaction was heated to reflux for 72 hours. After cooling to 0 °C, a saturated $NaHCO_3$ solution (25 ml) was added. The layers were separated and the aqueous layer was extracted with DCM (2 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 10/1) to give 795 mg of **24** (69 %) and 396 mg of starting material **23**.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (4H, m), 7.41-7.25 (21H, m), 5.36 (1H, s), 5.33 (1H, s), 5.06 (1H, t, *J*= 5.0 Hz), 4.65 (1H, d, *J*= 11.0 Hz), 4.53-4.45 (4H, m), 4.12 (2H, m), 3.94 (2H, m), 3.80 (3H, m), 3.65 (1H, td, *J*= 3.5, 6.5 Hz), 3.51 (1h, dd, *J*= 3.5, 7.5 Hz), 2.59 (1H, dd, *J*= 5.5, 15.0 Hz), 2.49 (1H, dd, *J*= 4.0, 15.0 Hz), 1.58-1.10 (23H, m), 1.02 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 142.29, 139.15, 138.61, 138.51, 135.84, 134.95, 134.61, 129.36, 129.30, 128.18, 128.10, 127.84, 127.68, 127.39, 127.32, 127.23, 117.16, 103.76, 81.98, 81.80, 79.24, 74.16, 72.66, 70.01, 69.59, 64.75, 64.63, 39.43, 36.89, 31.15, 29.82, 29.63(b), 29.58, 27.02, 25.92, 25.21, 23.21, 19.24; I.R. (cm^{-1}) : 2927, 2854, 1496, 1454, 1427, 1390, 1377, 1361, 1130, 1110, 1091 ; MS (ESI) *m/z* : 897.7 (M+) ; HRMS (ES+, M+Na^+) for $C_{58}H_{76}O_6NaSi$, Calculated 919.5309 Found 919.5309.



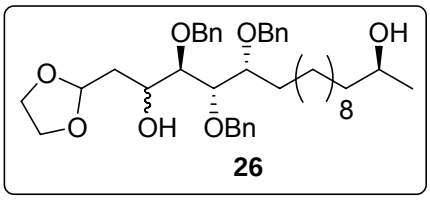
25

(3R,4S,5R,16S)-3,4,5-tris(benzyloxy)-16-(tert-butyldiphenylsilyloxy)-1-(1,3-dioxolan-2-yl)heptadecan-2-ol : 25

In a 50 ml round bottomed flask equipped for ozonolysis, compound **24** (1.83 g, 2.03 mmol, 1 equiv) was dissolved in 10 ml of dry DCM and 10 ml of MeOH. The solution was cooled to –78 °C and an ozone stream was applied for 25 minutes. The flask was then purged with argon and $NaBH_4$ (387 mg, 10.1 mmol, 5 equiv) was added by portions. The solution was allowed to reach 0 °C and was stirred for 2 h. A saturated NH_4Cl solution was added (15 ml). The layers were separated and the aqueous layer was extracted with DCM (3 x 15 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced

pressure. The crude material was purified by silica gel column chromatography (PE/EA 2/1) to give 1.61 g of 2 isomers (88 %)

Major isomer : ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72-7.68 (4H, m), 7.41-7.25 (21H, m), 5.01 (1H, dd, *J*= 3.93, 5.76 Hz), 4.84 (1H, d, *J*= 11.16 Hz), 4.74 (1H, d, *J*= 11.16 Hz), 4.64 (3H, m), 4.55 (1H, d, *J*= 11.49 Hz), 4.21 (1H, bdd, *J*= 2.61, 8.82 Hz), 3.99-3.64 (7H, m), 3.59 (1H, dd, *J*= 1.32, 5.28), 3.48 (1H, bs), 2.14 (1H, ddd, *J*= 3.93, 8.82, 13.92), 1.82 (1H, ddd, *J*= 3.99, 5.76, 13.92), 1.61-1.17 (23H, m), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.76, 138.21, 138.02, 135.85, 134.95, 134.63, 129.36, 129.30, 128.32, 128.26, 128.08, 127.98, 127.81, 127.71, 127.39, 127.32, 102.87, 81.22, 79.58, 79.11, 74.96, 73.13, 71.99, 69.59, 67.85, 64.77, 64.65, 39.43, 38.24, 30.59, 29.76, 29.63(b), 29.59(b), 27.01, 25.51, 25.21, 23.20, 19.24;
Minor isomer : ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72-7.68 (4H, m), 7.41-7.25 (21H, m), 5.07 (1H, dd, *J*= 3.99, 5.1 Hz), 4.77 (1H, d, *J*= 11.16 Hz), 4.73 (1H, d, *J*= 11.16 Hz), 4.64-4.57 (4H, m), 4.28 (1H, bdd, *J*= 1.8, 9.78 Hz), 3.99-3.64 (7H, m), 3.48 (1H, dd, *J*= 2.49, 5.28 Hz), 3.48 (1H, bs), 2.14 (1H, ddd, *J*= 1.8, 3.99, 14.43 Hz), 1.82 (1H, ddd, *J*= 5.1, 9.78, 14.43 Hz), 1.61-1.17 (23H, m), 1.07 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.84, 138.57, 138.49, 135.85, 134.95, 134.63, 129.36, 129.30, 128.22, 128.26, 128.08, 127.92, 127.71, 127.65, 127.46, 127.32, 103.71, 82.32, 81.61, 79.73, 74.21, 73.20, 72.77, 69.59, 68.65, 64.89, 64.60, 41.31, 36.42, 31.37, 29.76, 29.63(b), 29.59(b), 27.01, 25.74, 25.21, 22.59, 19.41;
Mix: I.R. (cm^{-1}) : 3425 (b), 2927, 2854, 1458, 1424, 1390, 1342, 1112, 1033; MS (APCI) *m/z* : 901.9 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{57}H_{76}O_7NaSi$, Calculated 923.5258 Found 923.5216.



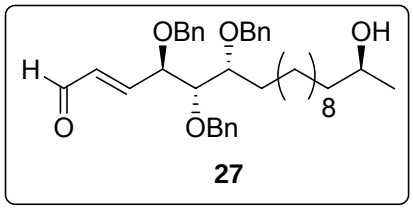
26

(3R,4S,5R,16S)-3,4,5-tris(benzyloxy)-1-(1,3-dioxolan-2-yl)heptadecane-2,16-diol : 26

In a 250 ml round bottomed flask, acetal **25** (1.61 g, 1.79 mmol, 1.0 equiv) was dissolved in 50 of dry THF. A 1 M solution of TBAF in THF (4.48 ml, 4.48 mmol, 2.5 equiv) was added and the reaction was heated to reflux for 5 hours. The solution was then cooled to room temperature and a saturated $NaHCO_3$ solution (25 ml) was added followed by diethylether (50 ml). The layers were separated and the aqueous layer was extracted with diethylether (3 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 1/2) to give 1.17 g of 2 isomers (99 %)

Major isomer : ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35-7.24 (15H, m), 4.98 (1H, dd, *J*= 3.7, 5.5 Hz), 4.80 (1H, d, 11.0 Hz), 4.70 (1H, d, *J*= 11.0 Hz), 4.61-4.55 (3H, m), 4.51 (1H, d, 11.5 Hz), 4.18 (1H, m), 3.96-3.75 (6H, m), 3.65 (1H, q, *J*= 6.0 Hz), 3.56 (1H, dd, *J*= 1.5, 5.5 Hz), 3.46 (1H, d, *J*= 4.5 Hz), 2.40 (1H, bs), 2.10 (1h, ddd, *J*= 3.7, 9.0, 13.5 Hz), 1.79 (1H, ddd, *J*= 4.0, 5.5, 13.5 Hz), 1.59-1.23 (20H, m), 1.17 (3H, d, *J*= 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)

δ: 138.73, 138.18, 137.98, 128.29, 128.24, 128.19, 128.05, 127.96, 127.78, 127.69, 127.62, 127.43, 102.74, 81.16, 79.56, 79.06, 74.92, 73.12, 71.94, 68.07, 67.82, 64.75, 64.63, 39.31, 38.21, 30.53, 29.68, 29.60, 29.57, 29.52(b), 29.47, 25.72, 25.45, 23.44;
Minor isomer : ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35-7.24 (15H, m), 5.04 (1H, t, *J*= 4.5 Hz), 4.75 (1H, d, *J*= 11.0 Hz), 4..67 (1H, d, *J*= 11.0 Hz), 4.66-4.51 (4H, m), 4.24 (1H, m), 3.96-3.75 (6h, m), 3.73 (1H, q, *J*= 6.0 Hz), 3.56 (1H, dd, *J*= 1.5, 5.5 Hz), 2.20 (1H, ddd, *J*= 1.5, 4.5, 14.5 Hz), 1.79 (1H, ddd, *J*= 4.5, 9.5, 14.5 Hz), 1.59-1.23 (20H, m), 1.17 (3H, d, *J*= 6.0 Hz);); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.32, 138.18, 137.98, 128.29, 128.24, 128.19, 128.05, 127.96, 127.89, 127.69, 127.62, 127.62, 127.36, 103.66, 82.29, 81.57, 79.69, 74.19, 73.16, 72.73, 68.61, 67.62, 64.86, 64.57, 39.31, 36.40, 31.32, 29.68, 29.60(b), 29.57, 29.52, 29.47, 25.72, 25.45, 23.44;
Mix: I.R. (cm^{-1}): 3433, 2921, 2856, 1461, 1379, 1338, 1109, 1026; MS (APCI) *m/z* : 663.4 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{41}H_{58}O_7Na$, Calculated 685.4080 Found 685.4072.

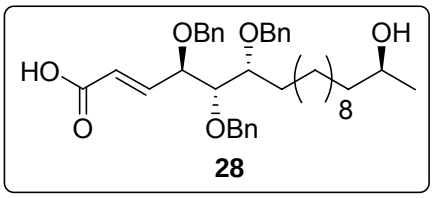


27

(4R,5S,6R,17S,E)-4,5,6-tris(benzyloxy)-17-hydroxyoctadec-2-enal : 27

In a 100 ml round bottomed flask, acetal **26** (1.0 g, 1.50 mmol, 1 equiv) was dissolved in 50 ml of dry acetone. PTSA (29 mg, 0.15 mmol, 0.1 equiv), dried by azeotropic distillation with benzene, was added and the solution was stirred for 2 hours at room temperature and 2 hours at 40 °C. The solution was cooled to room temperature and a saturated Na_2CO_3 solution (20 ml) was added. The solution was diluted with diethylether (50 ml) and stirred vigorously. The layers were separated and the aqueous layer was extracted with diethylether (3 x 50 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 4/1) to give 585 mg of a colourless oil (65 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.56 (1H, d, *J*= 8.0 Hz), 7.33-7.28 (15H, m), 6.98 (1H, dd, *J*= 5.5, 16.0 Hz), 6.40 (1H, dd, *J*= 8.0, 16.0 Hz), 4.71 (1H, d, *J*= 11.5 Hz), 4.66 (1H, d, *J*= 11.5 Hz), 4.62 (1H, d, *J*= 11.5 Hz), 4.55 (1H, d, *J*= 11.5 Hz), 4.50 (1H, d, *J*= 11.5 Hz), 4.35 (1H, dd, *J*= 4.5, 5.5 Hz), 4.31 (1H, d, *J*= 11.5 Hz), 3.82 (1H, sx, *J*= 6.0 Hz), 3.74 (1H, t, *J*= 4.5 Hz), 3.56 (1H, td, *J*= 4.5, 6.5 Hz), 1.62-1.19 (20H, m), 1.20 (3H, d, *J*= 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 193.43, 155.04, 138.38, 137.87, 137.51, 133.23, 128.39, 128.30(b), 127.97, 127.81, 127.61, 82.10, 79.14, 79.02, 74.28, 72.36, 71.55, 68.09, 39.31, 30.35, 29.64, 29.59, 29.55-29.50, 25.71, 23.45; : I.R. (cm^{-1}) : 3379, 1691, 1496, 1454, 1365, 1307, 1209, 1095, 1068; MS (APCI) *m/z* : 601.5 ($M+H^+$) ;

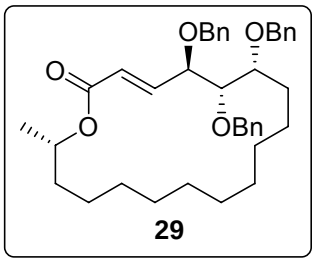


28

(4R,5S,6R,17S,E)-4,5,6-tris(benzyloxy)-17-hydroxyoctadec-2-enoic acid : 28

In a 100 ml round bottomed flask, aldehyde **27** (233 mg, 0.387 mmol, 1 equiv) was dissolved in 10 ml of a 5/1 *t*-BuOH/H_2O solution and 2 ml of 2-methyl-but-2-ene were added. An aqueous solution (2 ml) of $NaClO_2$ (105 mg, 1.16 mmol, 3 equiv) and NaH_2PO_4 (135 mg, 1.16 mmol, 3 equiv) was prepared and added dropwise. The reaction was stirred 30 min and a saturated NaCl solution (25 ml) followed by ethylacetate (25 ml) were added. The layers were separated and the aqueous layer was extracted with diethylether (3 x 25 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (pur EA) to give 228 mg of a colourless oil (96 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.21 (15H, m), 7.13 (1H, dd, *J*= 6.18, 15.9 Hz), 6.08 (1H, d, *J*= 15.9 Hz), 6.0-5.0 (1H, bs), 4.65 (1H, d, *J*= 11.43 Hz), 4.50 (1H, d, *J*= 11.43 Hz), 4.50-4.40 (4H, m), 4.22-4.18 (2H, m), 3.75 (1H, sx, *J*= 5.7 Hz), 3.59 (1H, t, *J*= 4.5 Hz), 3.46 (1H, m), 1.49-1.11 (23 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.45, 148.46, 138.60, 138.05, 137.75, 128.38-128.26, 128.26, 127.99, 127.64, 127.52, 122.64, 82.39, 78.93, 78.61, 74.39, 72.49, 71.33, 68.30, 39.20, 30.51, 30.29, 29.68, 29.59, 29.50, 29.43, 29.40, 25.66, 23.40; I.R. (cm^{-1}) : 3419, 2925, 2854, 1701, 1454, 1365, 1095, 1068, 1027 ; MS (APCI) *m/z* : 617.9 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{39}H_{52}O_6Na$, Calculated 639.3662 Found 639.3674.



29

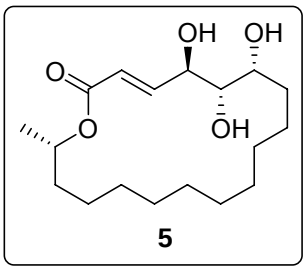
(5S,6R,7S,18R,E)-5,6,7-tris(benzyloxy)-18-methyloxacyclooctadec-3-en-2-one : 29

Yamaguchi's macrocyclisation: In a 25 ml round bottomed flask, acid **28** (228 mg, 0.369 mmol, 1 equiv) was dissolved in 6 ml of dry THF and TEA (195 mg, 268 µl, 1.84 mmol, 5 equiv) was added. The solution was stirred for 15 min and 2,4,6-trichlorobenzoylchloride (141 mg, 90 µl, 0.553 mmol, 1.5 equiv) was added. Stirring was maintained for 2 hours and 50 ml of toluene were added. A white precipitate was formed and filtrated under argon. The resulting clear liquid was injected very slowly in a refluxing solution of DMAP (235 mg, 1.92 mmol, 5 equiv) in 50 ml of toluene. After complete addition, reflux was kept for 15 min. 2/3 of the solvent were evaporated under reduced pressure and diethylether (25 ml) and water (25 ml) were added. The layers were separated and the aqueous layer was extracted with diethylether (3 x 25 ml). The organic layers were

combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 10/1) to give 203 mg of macrocycle (92 %).

MnO_2 mediated tandem oxidation/macrocyclisation: In a 25 ml round bottomed flask, aldehyde **27** (50 mg, 0.0832 mmol, 1 equiv) was dissolved in 3 ml of dry THF. MnO_2 (147 mg, 2.08 mmol, 25 equiv) and KCN (27 mg, 0.416 mmol, 5 equiv) were added and the reaction was stirred for 48 h at room temperature. The suspension was filtered through a celite/silica pad and the solvent was removed under reduced pressure. The residue was dissolved in 20 ml of toluene and injected very slowly in a refluxing solution of DMAP (5 equiv.) in 20 ml of toluene. After complete addition, reflux was kept for 15 min. 2/3 of the solvent were evaporated under reduced pressure and diethylether (15 ml) and water (15 ml) were added. The layers were separated and the aqueous layer was extracted with diethylether (3 x 15 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (PE/EA 10/1) to give 8.8 mg of macrocycle (18 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32-7.21 (15H, m), 7.11 (1H, dd, *J*= 8.67, 15.96 Hz), 5.96 (1H, d, *J*= 15.96 Hz), 5.02 (1H, sx, *J*= 5.13 Hz), 4.93 (1H, d, *J*= 14.49 Hz), 4.66 (1H, d, *J*= 14.49 Hz), 4.64 (1H, d, *J*= 11.25 Hz), 4.57 (1H, d, *J*= 11.91 Hz), 4.39 (1H, d, *J*= 11.25 Hz), 4.32 (1H, d, 11.91 Hz), 4.12 (1H, d, *J*= 8.61 Hz), 3.84 (1H, dd, *J*= 1.05, 8.61 Hz), 3.31 (1H, m), 1.62-0.99 (23H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.43, 144.05, 138.93, 138.68, 138.18, 128.35, 128.27, 128.20, 128.13, 128.00, 127.99, 127.85, 127.53, 127.39, 125.34, 84.23, 79.55, 78.66, 74.62, 74.18, 71.00, 70.57, 35.20, 31.24, 29.35, 28.18, 28.06, 27.41, 26.82, 26.52, 25.98, 23.22, 20.42; I.R. (cm^{-1}) : 2925, 2854, 1718, 1454, 1361, 1242, 1176, 1089, 1066 ; MS (APCI) *m/z* : 599.1 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{39}H_{50}O_5Na$, Calculated 621.3556 Found 621.3563 ; $[\alpha]^D_{20}$ **:** -9.1 (C = 0.59, DCM);



5

(+)-aspicilin: 5

In a 50 ml round bottomed flask, macrocycle **29** (26 mg, 0.0434 mmol, 1 équ.) was dissolved in 2 ml of dry DCM. At –78 °C, a 1 M solution of BCl_3 in heptane (521 µl, 0.521 mmol, 12 equiv) was added dropwise and the reaction was stirred 11 h at this temperature. Methanol (0.5 ml) was added slowly and stirring was maintained 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in methanol (5 ml). The solvent was evaporated and this process was repeated 3 times. The crude material was

purified by silica gel column chromatography (Et_2O then Et_2O/MeOH 100/5) and recrystallised from Et_2O to give 9.8 mg of (+)-aspiciline (68 %)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.92 (1H, dd, *J*= 5.0, 15.8 Hz), 6.14 (1H, dd, *J*= 1.8, 15.8 Hz), 5.08 (1H, sx, *J*= 6.2 Hz), 4.60 (1H, bs), 3.81 (1H, m), 3.60 (1H, m), 3.14 (1H, bs), 2.97 (1H, bs), 2.37 (1H, sl), 1.61-1.27 (23H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.50, 144.61, 123.19, 74.92, 73.30, 71.20, 70.00, 35.81, 32.19, 28.11, 27.86, 27.67, 27.34, 27.20, 26.49, 24.37, 23.71, 20.58; I.R. (cm^{-1}) : 3286 (b), 2923, 2852, 1714, 1460, 1363, 1242, 1180, 1076; MS (APCI) *m/z* : 328.9 ($M+H^+$) ; HRMS (ES+, $M+Na^+$) for $C_{18}H_{32}O_5Na$, Calculated 351.2147 Found 351.2158 ; $[\alpha]^D_{20}$ **:** +36.2 (C= 0.9, DCM) ; m.p. : 153-154 °C;