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A Biomimetic Route to the Peptide Alkaloid Anachelin

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Procedures and analytical data

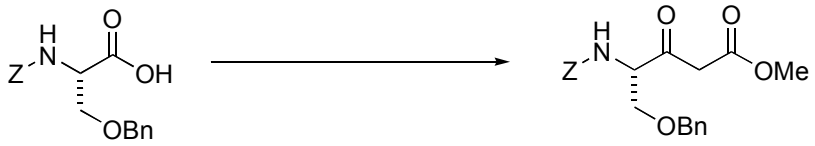
Abbreviations. CDI = Carbonyldiimidazole; DMAP = *N*, *N*-Dimethylaminopyridine; EDC = Ethyl-(*N*, *N*-dimethylaminopropyl)carbodiimide; ether refers to diethylether; HOBt = 1-Hydroxybenzotriazole; NMM = N-Methyl-morpholine; RT = room temperature; TBS = *tert*-Butyl-dimethylsilyl; THQ = 6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-quinolinium; Z = Benzyloxycarbonyl.

General. Unless otherwise stated, chemicals were purchased from Fluka, ABCR or Acros and used without further purification. H-Ser(OBn)-OH was purchased from Senn Chemicals, Switzerland. Commercially available TBSOTf was distilled and stored at 4°C. 2,6-Lutidine was distilled from CaH_2 and stored at 4°C. CDI was recrystallized from THF. Solvents for work-up and chromatography were distilled from technical quality. Solvents used for chemical transformations were either puriss. quality or dried over columns of dry aluminum oxide. Z-Ser(OBn)-OH was prepared according to reference [1]. 2-BnO-salicylic acid was prepared according to reference [2]. Dianisyltelluriumoxide was prepared according to [3]. $MgCl_2$ was stored and weighed in a glove box under inert atmosphere.

Reactions were run under an atmosphere of Ar in dry glassware (at least 24 h in an oven at 140 °C, followed by heating with a heat gun under high vacuum). Analytical thin

layer chromatograpy (TLC) was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) precoated with a fluorescent indicator. The developed plates were examined under UV light and stained with ceric ammonium molybdate (CAM) stain or $KMnO_4$ stain followed by heating. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Fluka. All ^{1}H and ^{13}C NMR spectra were recorded using either Varian Gemini (300 MHz (^{1}H) or 75 MHz (^{13}C)), Varian Mercury (300 MHz (^{1}H) or 75 MHz (^{13}C)), Bruker AMX (500 MHz (^{1}H) or 125 MHz (^{13}C)) or Bruker DMX 500 MHz (^{1}H) or 125 MHz (^{13}C)) FT spectrometers at ambient temperature, chemical shifts δ are given in ppm, coupling constants *J* are in Hz. IR spectra were recorded as $CHCl_3$ solution using a Perkin Elmer RX I FT-IR spectrometer, absorptions are given in cm^{-1}. Optical rotations were measured using a 1 ml cell with a 1 dm path length on a Jasco DID 1000 digital polarimeter, the concentration *c* is given in g/100 ml. Elemental analyses were performed by the Mikroanalyse Labor of the Laboratorium für Organische Chemie der ETH Zürich. All mass spectra were recorded by the Masspectroscopy Service of the Laboratorium für Organische Chemie der ETH Zürich on a Ion spec Ultima 4.7 spectrometer in 2,5-DHB matrix using MALDI, fragment ions are given in *m/z* with relative intensities (%) in parentheses. Nomenclature is according to Autonom 2.0, Beilstein Informationssysteme GmbH.

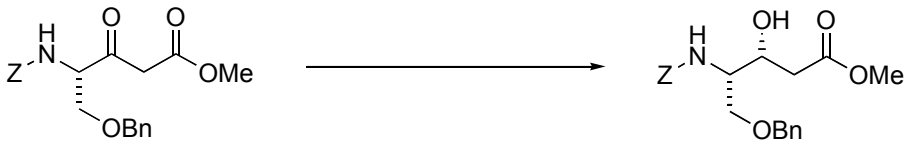
(4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-oxo-pentanoic acid methyl ester



$MgCl_2$ (15.2 g, 0.16 mol) was suspended in THF (300 ml) in a 1 l flask, $KO_2CCH_2CO_2Me$ (31.5 g, 0.202 mol) was added in one portion and the resulting suspension heated to reflux for 5 h. The suspension was then cooled with an ice bath. In the meantime, Z-L-Ser(OBn)-OH (42.5 g, 0.125 mol) was dissolved in THF (300 ml) in a 1 l flask. The solution was cooled in an ice bath, and CDI (22.3 g, 0.1375 mol, 1.1 eq) was added in portions. After 1 minute, gas evolution started and the solution was stirred 1 h at 0 °C and 1 h at RT. This solution containing the activated amino acid was then added dropwise to the K-Mg-enolate suspension via addition funnel at 0 °C. The resulting suspension was warmed up to RT and was stirred for 16 h at RT. The solvent was evaporated, the residue taken up in EtOAc and 1 M HCl solution was added. The mixture was stirred for 10 minutes resulting in a yellowish solution. The layers were separated and the aq. layer extracted 3 x with EtOAc. The combined org. layers were then washed 2 x with 1 N HCl soln, 2 x with satd. $NaHCO_3$ solution and 2 x with brine. The org. layer was dried (Na_2SO_4), filtered and the solvent was evaporated. FC (EtOAc/Hexane 1:4) gave the title compound (34.2 g, 89 mmol,

71 %). Colorless oil. R_f = 0.15 (EtOAc/Hexane 1:2.5). $[\alpha]_D$ = +0.6 (c = 0.75, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 3.68 (s, 2H), 3.70-3.74 (m, 4H), 3.93 (dd, 1 H, J_1 = 9.7, J_2 = 3.7), 4.49 (d, 2 H, J = 4.1), 4.56-4.61 (m, 1H), 5.12 (s, 2H), 5.81 (d, 1H, J = 7.5), 7.24-7.37 (m, 10H). ^{13}C-NMR ($CDCl_3$, 75 MHz) 46.7, 52.7, 60.5, 67.4, 69.4, 73.7, 128.0, 128.3, 128.4, 128.5, 128.77, 128.81, 136.3, 137.3, 156.2, 167.3, 200.4. IR 3019*s*, 2977*m*, 1721*m*. MS 408.1 (65, $[M+Na]^+$), 376.1 (100, $[M+Na-CH_3OH]^+$). HRMS calcd. for $C_{21}H_{23}NO_6Na$ $(M+Na)^+$: 408.1418, found: 408.1422.

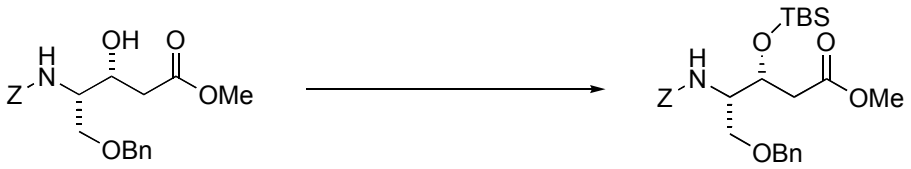
(3*R*, 4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-hydroxy-pentanoic acid methyl ester



(4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-oxo-pentanoic acid methyl ester (1.70 g, 4.41 mmol) was dissolved in MeOH (40 ml) / Et_2O (5 ml) and cooled to -60 °C ($CHCl_3$/dry ice bath). $NaBH_4$ (183.5 mg, 4.85 mmol) was added in one portion, stirring was continued for 6 h, and the reaction mixture was poured into a stirring solution of 10 % citric acid/EtOAc (100 ml, 1:1 v/v). After 20 min., the layers were separated and the aq. layer was 2 x extracted with EtOAc. The comb. organic layers were washed 2 x with brine, dried ($MgSO_4$), filtered and the solvent evaporated. FC (EtOAc/Hexane 1:1)

gave the title compound (1.538 g, 3.97 mmol, 90 %) as a mixture of 2 diastereoisomers (dr = 2.4 : 1 according to ^{1}H-NMR analysis of the crude reaction mixture). Recrystallization from EtOAc/Hexane (1:2.5) gave the diastereomerically pure title compound (821 mg, 2.12 mmol, 48 %). Colorless crystalline solid. Mp = 80-82 °C. R_f = 0.41 (EtOAc/Hexane 1:1). $[\alpha]_D$ = +0.03 (c = 0.56, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 2.51-2.67 (m, 2H), 3.39 (d, 1H, *J* = 5.9), 3.59-3.62 (m, 1 H), 3.69 (s, 3H), 3.82-3.84 (m, 2H), 4.11-4.17 (m, 1H), 4.51 (s, 2H), 5.10 (s, 2H, *J* = 7.5), 5.39 (d, 1H, *J* = 8.1), 7.26-7.35 (m, 10H). ^{13}C-NMR ($CDCl_3$, 75 MHz) 38.5, 51.9, 54.0, 67.0, 68.9, 69.0, 73.5, 127.6, 127.8, 128.0, 128.1, 128.39, 128.44, 136.1, 137.4, 156.1, 172.7. IR 3437*w*, 3020*s*, 1720*s,* 1508*m*. MS 410.2 (100, $[M+Na]^+$), 344.2 (89, $[M+Na-CH_3OH]^+$). HRMS calcd. for $C_{21}H_{23}NO_6Na$ $(M+Na)^+$: 410.1574, found: 410.1570. Anal. calcd. for $C_{21}H_{25}NO_6$ (387.43): C 65.10, H 6.50, N 3.62; found: C 64.94, H 6.34, N 3.63.

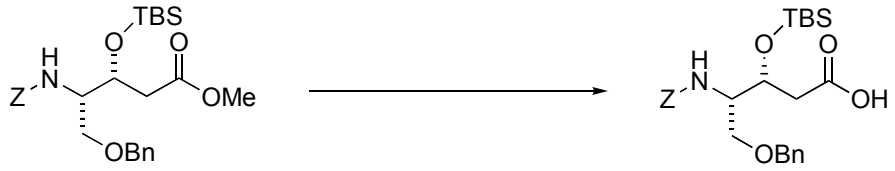
(3*R*, 4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-(*tert*-butyl-dimethyl-silanoxy)-pentanoic acid methyl ester



(3*R*, 4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-hydroxy-pentanoic acid methyl ester (1.0455 g, 2.698 mmol) was

dissolved in CH_2Cl_2 and the solution was cooled to – 20 °C. 2,6-Lutidine (0.63 ml, 5.396 mmol) was added dropwise, followed by the dropwise addition of TBSOTf (0.93 ml, 4.05 mmol). The reaction was allowed to stir at –20 °C for 30 min. and 15 min. at RT, after which the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed 3 x using 10 % citric acid solution, 1 x with H_2O, dried ($MgSO_4$) and the solvent evaporated. FC (EtOAc/Hexane 1:6) followed by FC (EtOAc/Hexane 1:7) gave the title compound (1.057 g, 2.109 mmol, 78 %). Colorless oil. R_f = 0.16 (EtOAc/Hexane 1:7). $[\alpha]_D$ = +0.15 (c = 1.14, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 2.48 (dd, 1H, J_1 = 15.9, J_2 = 6.2), 2.64 (dd, 1H, J_1 = 15.9, J_2 = 5.9), 3.50 (dd, 1H, J_1 = 9.4, J_2 = 4.4), 3.61 (s, 3H), 3.70 (dd, 1H, J_1 = 9.4, J_2 = 3.7), 3.84-3.88 (m, 1H), 4.33-4.36 (m, 1H), 4.44 (d, 1H, J = 11.8), 4.51 (d, 1H, J = 11.8), 5.05-5.19 (m, 3H), 7.28-7.36 (m, 10 H). ^{13}C-NMR ($CDCl_3$, 75 MHz) –4.9, -4.6, 18.0, 25.8, 40.1, 51.6, 55.4, 66.8, 68.3, 69.0, 73.1, 127.6 (2 C), 128.0 (2 C), 128.3, 128.4, 136.4, 137.7, 155.9, 171.8. IR 3028*w*, 1728*s,* 1508*m*. MS 524.2 (100, $[M+Na]^+$), 458.3 (11), 394.2 (17). HRMS calcd. for $C_{27}H_{39}NO_6SiNa$ $(M+Na)^+$: 524.2439, found: 524.2434.

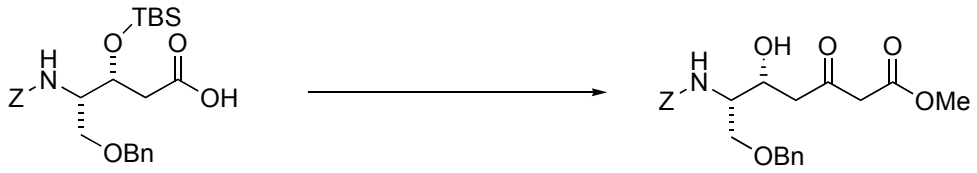
(3*R*, 4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-(*tert*-butyl-dimethyl-silanoxy)-pentanoic acid



(3*R*, 4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-(*tert*-butyl-dimethyl-silanoxy)-pentanoic acid methyl ester (7.8 g, 15.5 mmol) was dissolved in THF (150 ml) / MeOH (75 ml) and cooled with an ice-bath. A solution of 1 N NaOH (75 ml) was added dropwise over 15 minutes and the reaction was allowed to stir at 0 °C for 1h and at RT for 3h. The reaction mixture was then acidified to pH = 7 with 10 % citric acid solution and the organic solvent removed. The pH of the aqueous layer was adjusted to pH = 1-2 with 1 N HCl solution and followed by extraction of the aqueous layer 3 x with EtOAc. The comb. organic layers were washed with 2 x NaCl soln, dried ($MgSO_4$), filtered and the solvent evaporated. FC (EtOAc/Hexane 1:1) and subsequent drying under high vacuum (3 x 10^{-2} mbar at 65 °C) gave the title compound (4.05 g, 8.3 mmol, 54 %). Colorless oil. R_f = 0.45 (EtOAc/Hexane 1:1). $[\alpha]_D$ = +0.24 (c = 0.67, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.10 (s, 6H), 0.91 (s, 9H), 2.57 (dd, 1H, J_1 = 15.9, J_2 = 6.2), 2.72 (dd, 1H, J_1 = 15.9, J_2 = 4.7), 3.56 (dd, 1H, J_1 = 9.7, J_2 = 4.4), 3.65-3.76 (m, 1H), 3.95-4.00 (m, 1H), 4.38-4.39 (m, 1H), 4.49 (d, 1H, J = 11.8), 4.56 (d, 1H, J = 11.8), 5.15-5.2 (m, 2H), 5.28 (d, 1H, J = 9.0), 7.29-7.39 (m, 10 H). ^{13}C-NMR ($CDCl_3$, 75 MHz) –4.8, -4.4, 18.1, 25.9, 40.1, 55.2, 67.0, 68.2, 69.0, 73.2, 127.7, 128.0, 128.3 (2

C), 128.4 (2 C), 136.3, 137.6, 156.2, 176.7. IR 3021*w*, 1720*s*, 1510*m*. MS 510.2 (100, $[M+Na]^+$), 444.3 (25). HRMS calcd. for $C_{26}H_{37}NO_6SiNa$ $(M+Na)^+$: 510.2282, found: 510.2278.

(5*R*, 6*S*)-7-Benzyloxy-6-benzyloxycarbonylamino-5-hydroxy-3-oxo-heptanoic acid methyl ester

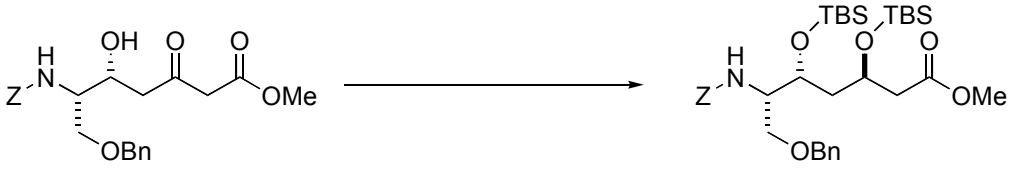


$MgCl_2$ (1.27 g, 13.3 mmol) was dissolved in THF (60 ml), $KO_2CCCH_2CO_2Me$ (2.85 g, 18.26 mmol) was added and the resulting suspension stirred at reflux for 5h. In the meantime in another flask, (3*R*, 4*S*)-5-Benzyloxy-4-benzyloxycarbonylamino-3-(*tert*-butyl-dimethyl-silanoxy)-pentanoic acid (4.05 g, 8.30 mmol) was dissolved in THF (60 ml), cooled to 0 °C, CDI (1.48 g, 9.13 mmol) added and the resulting solution was stirred for 1 h at 0 °C. The suspension containing the Mg-K-enolate was cooled to RT and added dropwise via addition funnel to the cooled solution of the activated amino acid. The reaction mixture was allowed to warm to RT and stirred for 16 h. The solvent was evaporated and the residue was taken up in 100 ml 10 % citric acid solution/100 ml EtOAc and stirred for 20 minutes after which the suspension turned clear. The layers were separated and the aqueous layer was extracted 3 x with EtOAc. The combined organic layers were washed 3 x with satd. $NaHCO_3$ solution, 3 x with 10 % citric acid solution

and 3 x with brine. The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. FC (EtOAc/Hexane 1:5, R_f = 0.21) gave 3.38 g (6.21 mmol, 75 %) of (5*R*, 6*S*)-7-Benzyloxy-6-benzyloxycarbonylamino-5-(*tert*-butyl-dimethyl-silanoxy)-3-oxo-heptanoic acid methyl ester. (5*R*,6*S*)-7-Benzyloxy-6-benzyloxycarbonylamino-5-(*tert*-butyl-dimethyl-sila-noxy)-3-oxo-heptanoic acid methyl ester (2.72 g, 5.0 mmol) was dissolved in THF (50 ml) and the solution was cooled with an ice bath. TBAF (12.5 ml, 1 M in THF) was added dropwise via syringe and the resulting solution was stirred at 0 °C for 1h and at RT for 2.5 h. The reaction was quenched with saturated $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted 4 x with EtOAc, the organic layers were combined and washed 3 x with brine. After drying with $MgSO_4$, the solvent was evaporated. FC (EtOAc/Hexane 1:1) gave the title compound (1.28 g, 3.0 mmol, 60 %). Colorless needles. Mp = 81-83 °C. R_f = 0.26 (EtOAc/Hexane 1:1). $[\alpha]_D$ = +0.25 (c = 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 2.78 (d, 2H, *J* = 5.6), 3.40-3.44 (m, 3H), 3.56-3.59 (m, 1H), 3.70 (m, 3H), 3.71-3.81 (m, 2H), 4.15-4.19 (m, 1H), 4.50 (s, 2H), 5.01 (s, 2H), 5.45 (d, 1H, *J* = 8.4), 7.25-7.35 (m, 10 H). ^{13}C-NMR ($CDCl_3$, 75 MHz) 46.6, 49.6, 52.4, 54.1, 67.0, 68.2, 68.8, 73.4, 127.6, 127.8, 128.0, 128.1, 128.4, 128.5, 136.2, 137.5, 156.2, 167.2, 202.9. IR 3435*w*, 3022*m*, 1716*s* (shoulder 1737*m*), 1508*m*. MS 452.2 (100, $[M+Na]^+$), 420.1 (54), 368.2 (63). HRMS calcd.

for $C_{23}H_{27}NO_7Na$ $(M+Na)^+$: 452.1680, found: 452.1688. Anal. calcd. for $C_{23}H_{27}NO_7$ (429.47): C 64.32, H 6.34, N 3.26; found: C 64.48, H 6.19, N 3.21.

(3*R*, 5*R*, 6*S*)-7-Benzyloxy-6-benzyloxycarbonylamino-3,5-bis-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid methyl ester

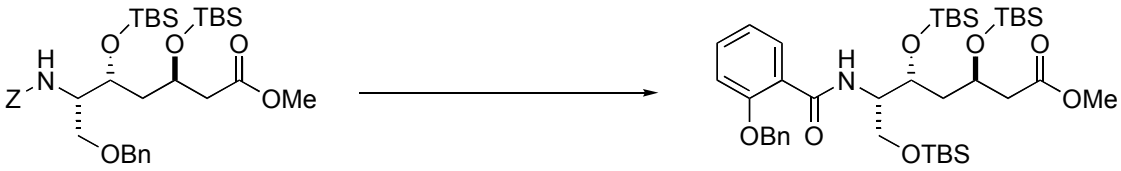


(5*R*, 6*S*)-7-Benzyloxy-6-benzyloxycarbonylamino-5-hydroxy-3-oxo-heptanoic acid methyl ester (144.6 mg, 0.336 mmol) was dissolved in CH_3CN (1.5ml) and cooled to –40 °C. $Me_4NBH(OAc)_3$ (612 mg, 2.3 mmol) was dissolved in CH_3CN/AcOH 1:1 (1.5 ml) and stirred at RT for 30 minutes. This solution was then added dropwise to the –40 °C solution of the substrate. The reaction mixture was stirred for 64 h at –37 °C (bath temp) and was then allowed to warm up to 0 °C. Saturated Na-K-tartrate solution (5 ml) was added, the suspension was stirred for 4h at 0°C. The layers were separated and the aqueous layer was 3 x extracted with EtOAc. The combined organic layers were washed 3 x with brine, dried ($MgSO_4$), filtered and the solvent evaporated. ^{1}H-NMR analysis of the crude reaction product revealed dr > 96:4. This intermediate was used without further purification.

The resulting dihydroxyester was dissolved in CH_2Cl_2 (0.6 ml) and cooled to –20 °C. 2,6-Lutidine (156 µl, 1.34 mmol) was

added dropwise followed by the dropwise addition of TBSOTf (232 μl, 1.0 mmol). The reaction was stirred at –20 °C for 1.5 h and was then diluted with CH_2Cl_2 (5 ml). The organic layer was washed with 3 x 10 % citric acid solution and 2 x with H_2O. The solution was dried ($MgSO_4$), filtered and the solvent was evaporated. FC (EtOAc/Hexane 1:1) gave the title compound (166.8 mg, 0.252 mmol, 75 %). Colorless oil. R_f = 0.72 (EtOAc/Hexane 1:1). $[\alpha]_D$ = +0.5 (c = 0.83, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.04-0.10 (m, 12H), 0.86 (s, 9H), 0.87 (s, 9H), 1.62-1.71 (m, 1H), 1.80-1.88 (m, 1H), 2.46-2.58 (m, 2H), 3.55-3.60 (m, 2H), 3.65 (s, 3H), 3.84-3.89 (m, 1H), 4.01-4.03 (m, 1H), 4.21-4.26 (m, 1H), 4.50 (s, 2H), 5.07-5.16 (m, 3H), 7.29-7.36 (m, 10H). ^{13}C-NMR ($CDCl_3$, 75 MHz). –4.44, -4.40, -4.09, -4.04, 18.0, 18.1, 25.8, 25.9, 26.0, 42.4, 43.0, 51.5, 54.8, 66.6, 67.3, 68.1, 69.8, 73.1, 127.6 (2 C), 128.0, 128.3 (2 C), 128.4, 136.5, 137.9, 156.0, 171.3. IR 2955*w*, 1722*s*, 1508*m*. MS 682.4 (100, $[M+Na]^+$). HRMS calcd. for $C_{35}H_{57}NO_7Si_2Na$ $(M+Na)^+$: 682.3566, found: 682.3561.

(3*R*, 5*R*, 6*S*)-6-(2-Benzyloxy-benzoylamino)-3,5,7-tris-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid methyl ester



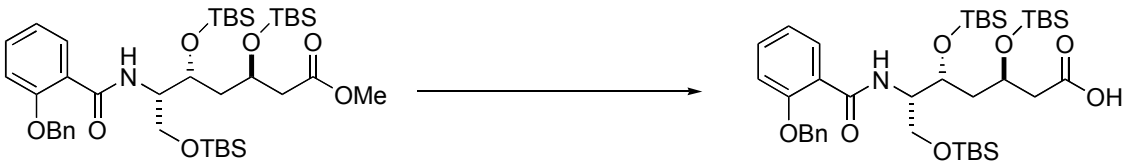
(3*R*, 5*R*, 6*S*)-7-Benzyloxy-6-benzyloxycarbonylamino-3,5-bis-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid methyl ester (169.8 mg, 0.257 mmol) was dissolved in CH_3OH (2 ml), the flask was flushed 3 x with Ar, and 2 small spatula of Pd/C (10%) were added. The flask was flushed 3 x with H_2, and the black suspension was vigorously stirred for 4h at RT. The suspension was filtered over Celite, and the solvent evaporated. ^{1}H-NMR analysis showed complete deprotection. This intermediate was used without further purification.

The intermediate amino ester was suspended in $CHCl_3$, hydroxybenzotriazole (47.2 mg, 0.308 mmol), 2-BnO-salicylic acid (70.4 mg, 0.309 mmol), *N*-methylmorpholine (84.7 µl, 0.771 mmol) and EDC (59.1 mg, 0.308 mmol) were added. The resulting solution was stirred for 3 d at RT and was then diluted with $CHCl_3$. The organic layer was washed 3 x with 10 % citric acid solution, 3 x with saturated $NaHCO_3$ solution and 1 x with H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. This intermediate was used without further purification.

The hydroxy amino ester was dissolved in DMF (0.5 ml) and the solution was cooled with an ice-bath. TBSCl (42.6 mg, 0.282 mmol), Imidazole (21.0 mg, 0.308 mmol) and DMAP (3.0 mg, 0.025 mmol) were added, the reaction mixture was allowed to warm up to RT and stirred for 16 h. After this time, additional TBSCl (20 mg) and imidazole (10 mg) were added and stirred for another 24 h at RT. DMF was then removed

under high vacuum. FC (EtOAc/Hexane 1:7) gave the title compound (137.0 mg, 0.180 mmol, 70 %). Colorless oil. R_f = 0.3 (EtOAc/Hexane 1:7). $[\alpha]_D$ = +0.16 (c = 2.49, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) -0.02 (s, 3H), 0.03 (s, 3H), 0.038 (s, 3H), 0.043 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.80 (s, 9H), 0.85 (s, 9H), 0.86 (s, 9H), 1.48-1.56 (m, 1H), 1.68-1.74 (m, 1H), 2.39 (dd, 1H, J_1 = 14.6, J_2 = 7.8), 2.62 (dd, J_1 = 14.3, J_2 = 4.4, 1H), 3.58 (s, 3H), 3.59-3.64 (m, 1H), 3.76 (dd, J_1 = 10.6, J_2 = 6.2, 1H), 4.06-4.12 (m, 1H), 4.18-4.25 (m, 2H), 5.23 (s, 2H), 6.97 (d, J = 8.4, 1H), 7.07 (t, J = 6.5, 1H), 7.34-7.45 (m, 6H), 8.05 (d, J = 7.47, 1H), 8.23 (d, J = 8.0, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) -5.2, -5.1, -4.5, -4.3, -4.2, -3.9, 18.0, 18.3, 25.8, 25.9, 26.0, 41.5, 43.2, 51.3, 55.7, 61.1, 67.4, 69.0, 71.0, 112.7, 121.3, 121.8, 127.3, 128.4, 128.7, 132.3, 132.4, 135.7, 156.5, 164.9, 171.5. IR 2955*m*, 1734*m*, 1648*m*. MS 782.4 (59, $[M+Na]^+$), 760.5 (13, $[M+H]^+$), 628.4 (100, $[M-Boc+Na]^+$). HRMS calcd. for $C_{40}H_{69}NO_7Si_3Na$ $(M+Na)^+$: 782.4274, found: 782.4282.

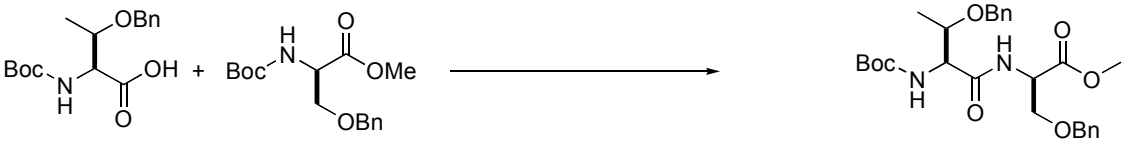
(3*R*, 5*R*, 6*S*)-6-(2-Benzyloxy-benzoylamino)-3,5,7-tris-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid



(3*R*, 5*R*, 6*S*)-6-(2-Benzyloxy-benzoylamino)-3,5,7-tris-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid methyl ester (28.7

mg, 37.7 μmol) was dissolved in MeOH (377 μl) and 1 M NaOH soln. (41.5 μl) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1h then at RT for 2 h. Additional MeOH (500 μl) and 1 M NaOH soln. (100 μl) were added and the reaction mixture was stirred over night. Additional MeOH (500 μl), THF (500 μl) and 1 M NaOH soln. (100 μl) were added and the reaction mixture stirred for 3 h. The solvent was removed under reduced pressure, and the aqueous layer acidified to pH = 2. The aqueous layer was three times extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Drying under HV gave the title compound (27.9 mg, 37.3 μ□□l, quant.), which was used without further purification.

(2*R*)-3-benzyloxy-2-((2*S*)-3-benzyloxy-2-*tert*-butoxycarbonylamino-butyrylamino)-propionic acid methyl ester

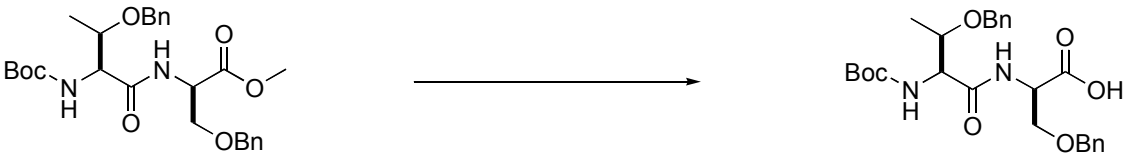


To a solution of Boc-L-Ser(OBn)-OMe (0.480mg, 1.55mmol) dissolved in dry CH_2Cl_2 (4 ml) at 0 °C was added TFA (4 ml). The reaction mixture was stirred for 30 min at 0 °C and then at RT for 2 hours. The solvent was removed under reduced

pressure and the residue three times taken up in chloroform and evaporated.

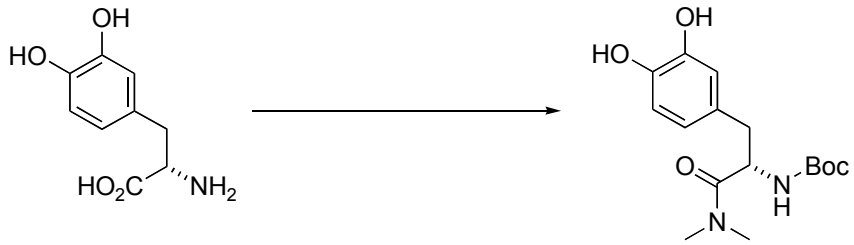
To a solution of 3-benzyloxy-2-*tert*-butoxycarbonylamino-butyric acid in dry CH_2Cl_2 was added EDC.HCl (671 mg, 3.5 mmol), HOBt (473 mg, 3.5 mmol) and NMM (411mg, 3.5mmol). Then the above amino acid was added and the reaction mixture was stirred overnight at RT. The solution was washed with 3 x $NaHCO_3$ solution, 3 x 1 M HCl solution, H_2O and NaCl soln. before being dried over Na_2SO_4, filtered and evaporated under reduced pressure. FC (Hexane/EtOAc 7:3) gave the title compound (663mg, 1.32 mmol, 85.5%). White solid. M_p = 57-59 °C. R_f = 0.26 (Hexane/AcOEt 7:3). $[\alpha]_D$ = +10.54 (c = 0.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300Mhz) 1.13 (d, 3H, *J* = 6.53), 1.41 (s, 9H), 3.58-3.61 (m, 1H), 3.62 (s, 3H), 3.81 (dd, 1H, J_1 = 3.43, J_2 = 9.65), 4.15 (m, 1H), 4.32-4.44 (m, 3H), 4.53 (s, 2H), 4.72-4.77 (m, 1H), 5.60 (br. d, 1H, *J* = 7.16), 7.16-7.30 (m, 10H), 7.42 (br. d, 1H, *J* = 8.1). ^{13}C-NMR ($CDCl_3$, 75MHz) 14.3, 15.9, 21.0, 28.3, 52.4, 52.7, 57.7, 60.2, 69.4, 71.5, 73.0, 74.6, 79.8, 127.36, 127.48, 127.54, 127.60, 127.9, 128.1, 128.2, 137.3, 137.9, 155.6, 169.6, 170.1. IR, 3024*m*, 1748*s*, 1712*s*, 1675*s*. MS 523.2 (20, $[M+Na]^+$), 423.2 (34, $[M-Boc+Na]^+$), 401.2 (100, $[M-Boc+H]^+$). HRMS calcd. for $C_{27}H_{36}N_2O_7Na$ $(M+H)^+$:523.2415 found: 523.2420.

(2R)-3-benzyloxy-2-((2S)-3-benzyloxy-2-*tert*-butoxycarbonylamino-butyrylamino)-propionic acid



To a solution of Boc-L-Thr(OBn)-D-Ser(OBn)-OMe (50 mg, 0.1 mmol) in THF (0.5 mL) / H_2O (0.5 mL) at 0 °C was added LiOH monohydrate (8.2 mg, 0.19 mmol) and the reaction mixture was stirred at 0 °C for 1.5 hours. Then the reaction mixture was diluted with H_2O and the two phases separated. The aqueous layer was extracted 2 x with EtOAc, acidified with HCl (1N), extracted 3 x with AcOEt. The combined organic layers were washed 3 x with H_2O, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. FC (EtOAc/Hexane 8:2) gave the title compound (35mg, 0.07 mmol, 70%). Colorless oil. R_f = 0.19 (EtOAc/Hexane 8:2). $[\alpha]_D$ = +4.97 (c = 1.15, $CHCl_3$). ^{1}H-NMR (MeOH, 300Hz) 1.18 (d, 3H, *J* = 6.2), 1.43 (s, 9H), 3.67 (dd, 1H, J_1 = 3.4, J_2 = 9.6), 3.87 (dd, J_1 = 4.04, J_2 = 9.3, 1H), 4.02-4.05 (m, 1H), 4.23 (d, *J* = 2.8, 1H), 4.40-4.55 (m, 4H), 4.64 (t, *J* = 3.73, 2H), 7.20-7.31 (m, 10H), 7.4, br. d, 1H, *J* = 7.8). ^{13}C-NMR (MeOH, 75MHz) 16.6, 28.5, 53.8, 59.6, 70.3, 72.1, 73.9, 75.8, 80.7, 128.20, 128.29, 128.53, 128.85, 128.93, 138.6, 139.0, 157.4, 172.1, 172.4. IR 3420*w*, 3000*m*, 1713*s*, 1671*s*. MS 509.2 (43, $[M+Na]^+$), 409.2 (44, $[M-Boc+Na]^+$), 387.2 (100, $[M-Boc+H]^+$). HRMS calcd. for $C_{26}H_{34}N_2O_7Na$ $(M+H)^+$:509.2258 found: 509.2252.

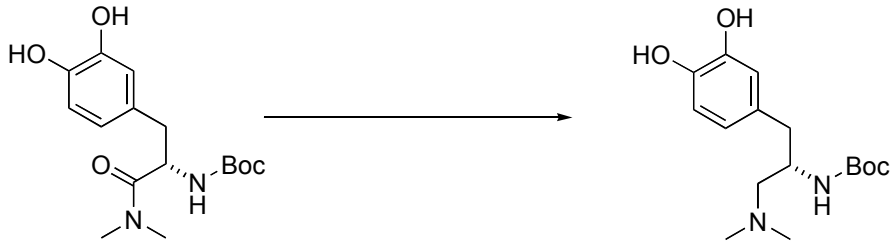
(*S*)-[2-(3,4-Dihydroxy-phenyl)-1-dimethylcarbamoyl-ethyl]-carbamic acid *tert*-butyl ester



L-DOPA (5 g, 25.4 mmol) was dissolved in dioxane (40 ml), 1 M NaOH solution (28 ml) and H_2O (25 ml). Boc_2O (6.1 g, 1.1 eq.) dissolved in dioxane (10 ml) was added to the above orange solution and stirred at room temperature. The pH was controlled after 30 minutes, 1 h, 2 h and 10 h, and, if necessary, adjusted to 9-10 by adding 1 M NaOH solution. After 16 h, the resulting brown solution was concentrated under reduced pressure and acidified to pH = 2 with 1 N HCl solution. The resulting brown suspension was four times extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting brown slurry was dissolved in THF (50 ml) and cooled to –40 °C. N-Methylmorpholine (2.91 ml) and *i*BuOCOCl (3.44 ml, 26.5 mmol, 1.1 eq.) were added and the resulting suspension stirred at –35 °C for 0.5 h. A solution of $HNMe_2$ in THF (2 M, 38.1 ml, 3 eq.) was added and the reaction mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed under reduced pressure and the residue dissolved in EtOAc. The organic phase was washed three times with 10 % citric acid, three times with saturated $NaHCO_3$ solution and three times with saturated NaCl solution. The organic layer was dried ($MgSO_4$)

and the solvent removed under reduced pressure. Recrystallisation from EtOAc gave the title compound (5.03 g, 15.5 mmol, 61 %). Colorless crystalline solid. Mp = 156-157 °C. R_f = 0.5 (EtOAc). $[\alpha]_D$ = +56.8 (*c* = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.40 (s, 9H), 2.62 (s, 3H), 2.74-2.81 (m, 2H), 2.85 (s, 3H), 4.77 (q, *J* = 6.2, 1H), 5.55 (d, *J* = 8.7, 1H), 6.56 (dd, J_1 = 1.9, J_2 = 8.1, 1H), 6.74 (d, *J* = 1.9, 1H), 6.77 (d, *J* = 8.1, 1 H), 7.02 (br. s, 1H), 7.95 (br. s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) 28.4, 36.0, 37.2, 39.4, 51.7, 80.2, 115.2, 116.1, 121.1, 127.8, 143.5, 144.0, 155.3, 172.3. IR 3431*w*, 3278*w*, 3022*m*, 1703*s*, 1637*s*, 1497*s*, 1369*s*. MS 347.2 (79, $[M+Na]^+$), 225.1 (100, $[M-Boc]^+$). HRMS calcd. for $C_{16}H_{24}N_2O_5Na$ $(M+Na)^+$: 347.1577, found: 347.1578. Anal. calcd. for $C_{16}H_{24}N_2O_5$ (387.43): C 59.24, H 7.46, N 8.64; found: C 59.29, H 7.51, N 8.53.

(*S*)-[1-(3,4-Dihydroxy-benzyl)-2-dimethylamino-ethyl]-carbamic acid *tert*-butyl ester



Boc-L-DOPA-dimethylamide (1.2785 g, 3.94 mmol) was suspended in CH_2Cl_2 (4 ml) and cooled under Ar to 0 °C. Trifluoroacetic acid (4 ml) was added dropwise and the resulting solution was stirred for 1 h at 0 °C and for 1 h at room temperature.

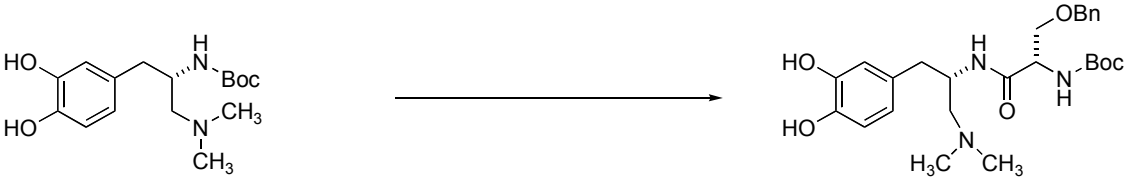
The solvent was removed under reduced pressure, and the residue was twice dissolved in toluene and the solvent removed under reduced pressure. The residue was dried under high vacuum and used without further purification.

The residue was dissolved in THF (8 ml), cooled under Ar to 0 °C and BH3 * THF complex (1 M in THF, 20 ml) was added dropwise (gas evolution). The solution was stirred at 0 °C for 2 h, warmed to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C, 6 N HCl (3 ml) was added dropwise (gas evolution), and stirred at 0 °C for 3 h. The solvent was removed under reduced pressure. The resulting diamine hydrochloride was used without further purification.

The oily residue was dissolved in dioxane (4 ml), H_2O (1 ml) and the pH was adjusted to ~9-10 by the addition of 1 N NaOH solution. Boc_2O (860 mg, 3.94 mmol) was dissolved in dioxane (1 ml) and added to the reaction mixture. Gas evolution started and the pH was controlled and adjusted to ~9-10 by the addition of 1 N NaOH solution every 30 min for 4 h. The reaction mixture was then stirred overnight at room temperature. The solvent was removed under reduced pressure, the residue partitioned between EtOAc and satd. $NaHCO_3$ solution. The layers were separated and the aqueous layer was three times extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. FC (10 g SiO_2, CH_2Cl_2/MeOH

7:1 -> 1:1) gave the title compound (194.8 mg, 0.63 mmol, 16 %). Colorless oil. R_f = 0.05 (CH_2Cl_2/MeOH 7:1). $[\alpha]_D$ = -4.2 (*c* = 1, MeOH). ^{1}H-NMR (CD_3OD, 300 MHz) 1.37, 1.40 (s, 9 H, Boc-rotamers), 2.20 (s, 6 H), 2.25 (dd, J_1 = 12.4, J_2 = 5.0, 1 H), 2.39 (dd, J_1 = 12.4, J_2 = 8.7, 1H), 2.46 (br. m, 2H), 3.80 (br. m, 1H), 6.48-6.56 (m, 2 H), 6.63-6.65 (m, 1H). ^{13}C-NMR (CD_3OD, 75 MHz) 28.0, 28.5 (Boc-rotamers), 40.2, 45.4, 51.0, 63.3, 79.5, 115.7, 117.1, 121.3, 130.7, 144.4, 145.7, 157.4. IR 3432*w*, 3019*m*, 1766*w*, 1700*s*, 1492*s*, 1368*s*. MS 643.4 (72, $[2M+Na]^+$), 333.2 (40, $[M+Na]^+$), 311.2 (100, $[M+H]^+$),. HRMS calcd. for $C_{16}H_{27}N_2O_4$ $(M+H)^+$: 311.1965, found: 311.1967.

(*S*,*S*)-{2-Benzyloxy-1-[1-(3,4-dihydroxy-benzyl)-2-dimethylamino-ethylcarbamoy]-ethyl}-carbamic acid *tert*-butyl ester



The Boc-diamine (108 mg, 0.348 mmol) was dissolved in CH_2Cl_2 (1 ml), and cooled to 0 °C under Ar. Trifluoroacetic acid (1 ml) was added dropwise and the resulting solution was stirred for 1 h at 0 °C and for 1 h at room temperature. The solvent was removed under reduced pressure, and the residue was twice dissolved in toluene and the solvent removed under reduced pressure. The residue was dried under high vacuum and used without further purification.

Boc-L-Ser(OBn)-OH (102.9 mg, 0.348 mmol) was dissolved in THF (1 ml) under Ar and cooled to –20 °C (bath temp.). To this solution, Et_3N (48.5 μl, 0.348 mmol) and iBuOCOCl (45.3 μl, 0.348 mmol) were added dropwise and a precipitate began to form after 5 min. The reaction mixture was stirred for 15 min at –20 °C. In the meantime, the diamine trifluoroacetate prepared above was dissolved in THF (1ml) and Et_3N (0.97 μl, 0.696 mmol) was added. This solution of the free base was slowly added to the above mixture of the mixed anhydride at –20 °C. The reaction mixture was allowed to warm to 10 °C in three hours. The solvent was evaporated under reduced pressure, and the residue taken up in EtOAc. The organic layer was twice washed with 10 % citric acid solution, twice with brine, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. FC (CH_2Cl_2/MeOH 10:1) gave the title compound (98.0 mg, 0.20 mmol, 58 %). Colorless oil. R_f = 0.12 (CH_2Cl_2/MeOH 10:1). $[\alpha]_D$ = -12.3 (*c* = 1, MeOH). ^{1}H-NMR (CD_3OD, 300 MHz) 1.45 (s, 9H), 2.63-2.76 (m, 2H), 2.82 (br. s, 6H), 3.14-3.25 (m, 2H), 3.57 (d, *J* = 5.6, 2 H), 4.15 (t, *J* = 5.3, 1 H), 4.36-4.40 (m, 1H), 4.47 (s, 2H), 6.53 (dd, J_1 = 8.1, J_2 = 2.0, 1H), 6.66 (d. *J* = 2.0, 1H), 6.70 (d, *J* = 8.1, 1H), 7.24-7.35 (m, 5H). ^{13}C-NMR (CD_3OD, 75 MHz) 27.5, 37.6, 43.2, 55.6, 60.6, 69.4, 73.1, 80.3, 115.4, 116.3, 120.6, 127.7, 127.9, 128.3, 137.9, 144.3, 145.3, 157.3, 172.4. IR (thin film) 3313s, 2947*m*, 1674*s*, 1529*m*. MS 488.3 (100, $[M+H]^+$), 432.2 (31, $[M-t\text{Bu}+H]^+$),

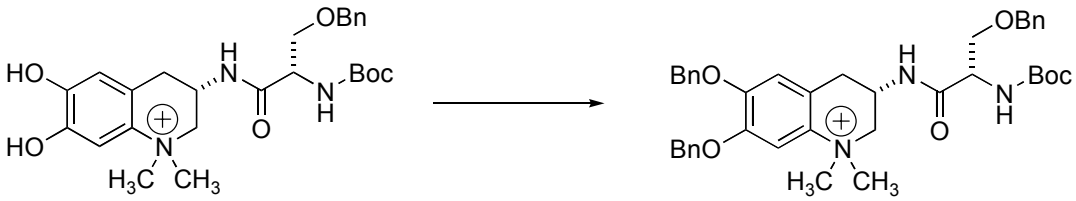
388.2 (17, $[M\text{-}Boc]^+$). HRMS calcd. for $C_{26}H_{38}N_3O_6$ $(M+H)^+$: 488.2755, found: 488.2750.

(2*S*, 3*S*)-3-(3-Benzyloxy-2-*tert*-butoxycarbonylamino-propionylamino)-6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-quinolinium

(*S*,*S*)-{2-Benzyloxy-1-[1-(3,4-dihydroxy-benzyl)-2-dimethylamino-ethylcarba-moyl]-ethyl}-carbamic acid *tert*-butyl ester (61.3 mg, 0.125 mmol) was dissolved in CH_2Cl_2 (1.25 ml) under Ar. Dianisyltellurium oxide (49.2 mg, 0.1375 mmol) was added in one portion, and the resulting solution was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (1 ml). The organic layer was three times extracted with H_2O and the aqueous layers combined. Lyophilization gave the title compound (48 mg, 0.1 mmol, 80 %). Colorless fluffy powder. ^{1}H-NMR (CD_3OD, 300 MHz) 1.44 (s, 9H), 2.88 (dd, J_1 = 16.2, J_2 = 10.6, 1H), 3.03 (dd, J_1 = 16.2, J_2 = 5.6, 1H), 3.54 (s, 6H), 3.57-3.81 (m, 2 H), 4.28 (t, J = 5.3, 1 H), 4.53 (s, 2 H), 4.53-4.60 (m, 1H), 6.64 (s, 1 H), 7.16 (s, 1H), 7.26-7.36 (m, 5H). ^{13}C-NMR (CD_3OD, 75 MHz) 28.4, 32.0, 41.3, 55.8, 58.4, 58.9, 66.1, 70.7, 73.9, 80.6, 107.8, 116.3, 119.8, 128.4, 128.5, 129.0, 133.7, 138.8, 146.8,

148.2, 172.8. MS 486.2 (100, M^+), 430.2 (74, $[M-t\text{Bu}+H]^+$), 386.2 (16, $[M-\text{Boc}]^+$). HRMS calcd. for $C_{26}H_{36}N_3O_6$ (M^+): 486.2599, found: 486.2595.

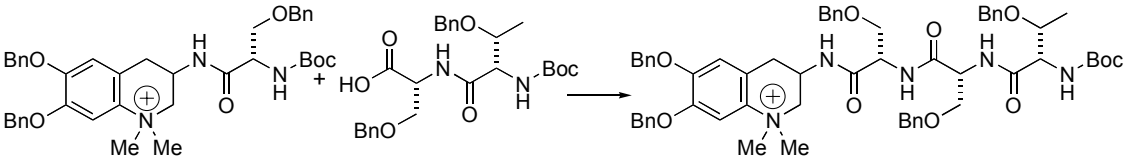
(2*S*, 3*S*)-6,7-Bis-benzyloxy-3-(3-Benzyloxy-2-*tert*-butoxycarbonylamino-propionylamino)-6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-quinolinium



(2*S*, 3*S*)-3-(3-Benzyloxy-2-*tert*-butoxycarbonylamino-propionylamino)-6,7-dihydroxy-1,1-dimethyl-1,2,3,4-tetrahydro-quinolinium (149.2 mg, 0.3 mmol) was dissolved under Ar in dry acetone (3 ml). To this solution, Cs_2CO_3 (300 mg, 0.92 mmol) and BnBr (110 µl, 0.93 mmol) were added, and the resulting reddish solution was heated to reflux for 4 h. The color changed to white, and the solvent was removed under reduced pressure. The residue was taken up in EtOAc, and the organic layer was washed three times with 1 N HCl solution, and twice with brine. The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. FC (5 g SiO_2, CH_2Cl_2/MeOH 10:1) gave the title compound (169.0 mg, 0.253 mmol, 85 %). Colorless oil. R_f = 0.11 (CH_2Cl_2/MeOH 10:1). ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.41 (s, 9H),

2.94 (dd, J_1 = 16.5, J_2 = 5.3, 1H), 3.24 (br. dd, J_1 = 16.5, J_2 = 10.6, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 3.69-3.83 (m, 2H), 3.96-4.01 (m, 1H), 4.40-4.53 (m, 1H), 4.53 (d, *J* = 3.7, 2H), 5.11 (s, 2H), 5.37 (d, *J* = 3.4, 2H), 5.58 (d, *J* = 7.5, 1H), 6.58 (s, 1H), 7.22-7.35 (m, 16H), 7.37 (d, *J* = 4, 1H), 7.39 (br. s, 1H), 8.30 (br. s, 1H). MS 666.3 (43, M^+), 610.3 (100, [M-*t*Bu+H]$^+$), 566.3 (28, [M-Boc]$^+$). HRMS calcd. for $C_{40}H_{48}N_3O_6$ (M^+): 666.3538, found: 666.3531.

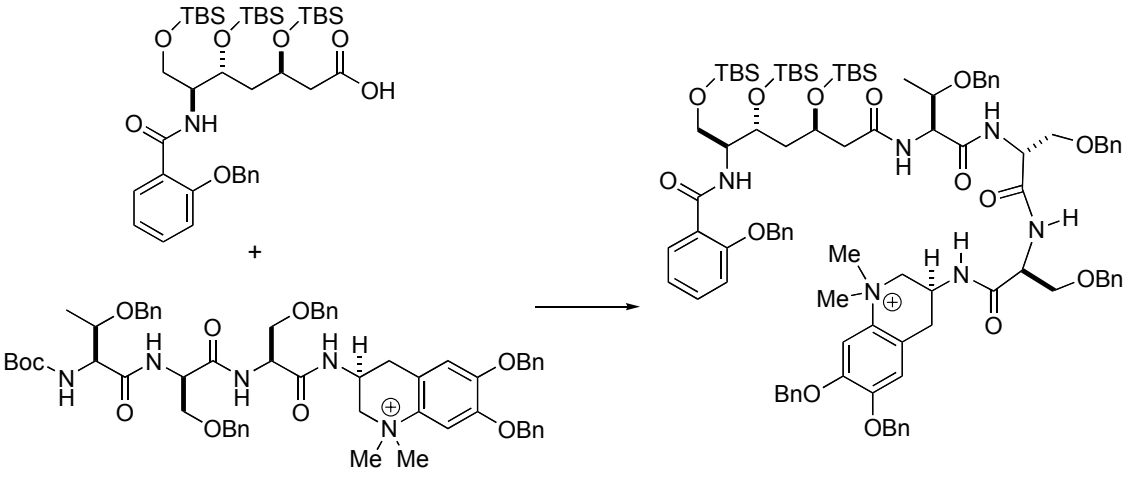
Boc-L-Thr(OBn)-L-Ser(OBn)-L-Ser(OBn)-(3*S*)-THQ(OBn)



The Boc-Ser(OBn)-THQ(OBn) (4.6 mg, 0.007 mmol) was dissolved in CH_2Cl_2 (0.1 ml), and cooled to 0 °C under Ar. Trifluoroacetic acid (0.1 ml) was added dropwise and the resulting solution was stirred for 1 h at 0 °C and for 1 h at room temperature. The solvent was removed under reduced pressure, and the residue was twice dissolved in toluene and the solvent removed under reduced pressure. The residue was dried under high vacuum and used without further purification. The residue was dissolved in $CHCl_3$ (0.25 ml), NMM (2.3 ml, 0.021 mmol), HOBt (1.2 mg, 0.008 mmol), Boc-L-Thr(OBn)-D-Ser(OBn)-OH (3.8 mg, 0.008 mmol and EDC (1.5 mg, 0.008 mmol) were added to the solution. The reaction was stirred overnight under Ar. The reaction mixture was then

diluted with $CHCl_3$ (2 ml) and three times washed with 1 N HCl solution, three times with 1 N NaOH solution, and three times with H_2O. The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. FC (CH_2Cl_2/MeOH 10:1) gave the title compound (5.3 mg, 5.1 mmol, 73 %). R_f = 0.23 (CH_2Cl_2/MeOH 10:1). ^{1}H-NMR (CD_3OD, 300 MHz, Rotamers of Boc-Thr) 1.15-1.18 (br. 3H), 1.42/1.43 (s, 9H), 3.00 (d, J = 8.1, 2H), 3.52-3.60 (m, 7H), 3.68-3.73 (m, 3H), 3.86-3.90 (m, 2H), 4.24 (br. s, 1H), 4.40-4.56 (m, 14H), 5.17 (s, 2H), 5.20 (s, 2H), 6.89 (s, 1H), 7.22-7.47 (m, 26 H).

(3*R*, 5*R*, 6*S*)-6-(2-Benzyloxy-benzoylamino)-3,5,7-tris-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid-L-Thr(OBn)-D-Ser(OBn)-L-Ser(OBn)-(3*S*)-THQ(OBn)



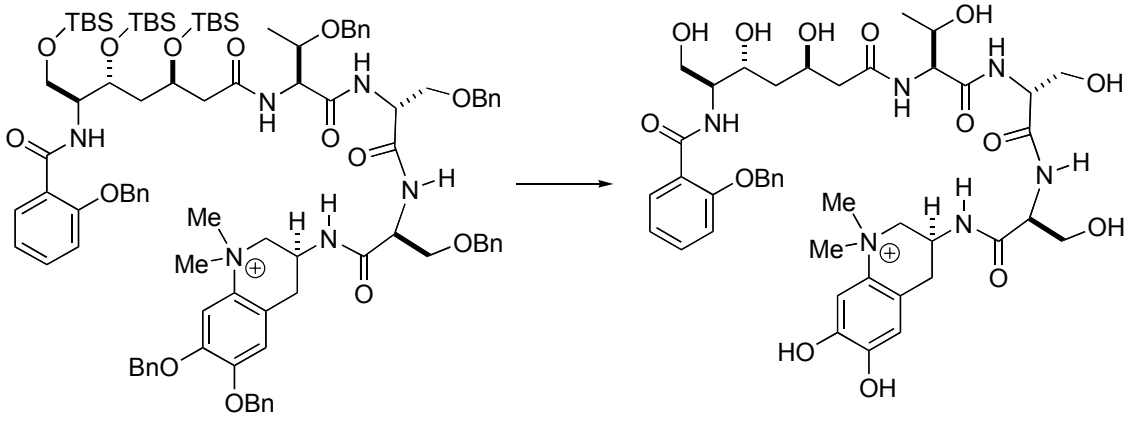
Boc-L-Thr(OBn)-L-Ser(OBn)-L-Ser(OBn)-(3*S*)-THQ(OBn) (10.0 mg, 9.66 μmol) were dissolved in CH_2Cl_2 (0.25 ml) under Ar and cooled to 0 °C. Trifluoroacetic acid (0.25 ml) was added dropwise and the resulting solution was stirred for 1 h at 0 °C and 1 h at room temperature. The solvent was removed under reduced pressure and the residual acid was twice azeotropically removed using toluene. The oil was dried under high vacuum for 3 hours and used without further purification.

This compound was then dissolved under Ar in $CHCl_3$ (0.25 ml), (3*R*, 5*R*, 6*S*)-6-(2-Benzyloxy-benzoylamino)-3,5,7-tris-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid (7.9 mg, 10.6 μmol), NMM (10.4 μml, 96 μmol), HOBt (1.6 mg, 10.6 μmol) and EDC (2.0 mg, 10.6 μmol) were added. The reaction mixture was stirred for 16 h under Ar at room temperature and then diluted with $CHCl_3$ (3 ml). The organic layer was washed three times each with 1 N HCl solution, 1 N NaOH solution and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure.

FC (2 g SiO_2, CH_2Cl_2/MeOH 10:1) gave the title compound (10.2 mg, 6.13 μmol, 63 %). Colorless oil. R_f = 0.1 (CH_2Cl_2/MeOH 10:1). ^{1}H-NMR ($CDCl_3$, 300 MHz, rotamers) –0.18-0.09 (m, 18 H), 0.71-0.88 (m, 27 H), 1.25-1.29 (m, 3 H), 1.50-1.90 (m, 2 H), 2.22-2.45 (m, 2 H), 2.84-2.91 (m, 1 H), 3.17-3.80 (m, 16 H), 3.85-4.13 (m, 6 H), 4.41-4.78 (m, 12 H), 5.02-5.4 (m, 6 H), 6.58 (s, 1 H), 6.91-7.04 (m, 3 H), 7.17-7.40 (m, 30 H),

8.08 (d, *J* = 6.5, 1 H), 8.18 (t, *J* = 8.1, 1H). MS 1663. (43, M^+), 1555 (100, $[M-t\text{Bu}+H]^+$).

(3*R*, 5*R*, 6*S*)-6-(2-Hydroxy-benzoylamino)-3,5,7-trihydroxy-heptanoic acid-L-Thr-D-Ser-L-Ser-(3*S*)-THQ



(3*R*, 5*R*, 6*S*)-6-(2-Benzyloxy-benzoylamino)-3,5,7-tris-(*tert*-butyl-dimethyl-silanoxy)-heptanoic acid-L-Thr(OBn)-D-Ser(OBn)-L-Ser(OBn)-(3*S*)-THQ(OBn) (3.3 mg, 2 μmol) was dissolved in CH_3OH (0.5 ml) and glacial acetic acid (15 drops) was added. The reaction vessel was flushed three times with Ar, and then Pd/C (10 %, 2.5 mg) was added. The reaction vessel was three times flushed with H_2, and the reaction mixture was stirred 16 h under H_2 (balloon pressure). The reaction mixture was then filtered over Celite and the solvent removed under reduced pressure. The residue was then dissolved in MeOH containing 1 % conc. HCl solution under Ar at 0 °C and stirred for 1 h at 0 °C and for 2.5 h at room temperature. The solvent was removed under reduced pressure, the residue triturated three times with

ether, dried, H_2O added and the supernatant was lyophilized to give the title compound (0.7 mg, 0.89 μmol, 45 %). Light-violet fluffy powder. ^{1}H-NMR: see table 1. HRMS calcd. for $C_{35}H_{51}N_6O_{14}^+$: 779.3463, found: 779.3466.

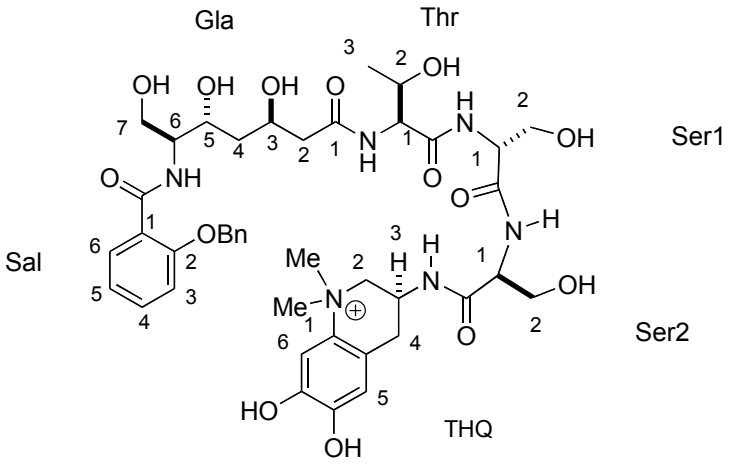


Table 1. ^{1}H-NMR data of natural anachelin (**1**) and synthetic anachelin (**22**) (300 MHz, D_2O, 298 K). An asterisk (*) denotes a tentative assignment.

Position	Natural	Synthetic	Position	Natural	Synthetic
Sal-H3	6.99	6.99	Thr-H3	1.19	1.18
Sal-H4	7.47	7.49	Ser1-H1	4.41	4.42*
Sal-H5	7.04	7.05	Ser1-H2	3.86	3.86*
Sal-H6	7.79	7.78	Ser2-H1	4.38	4.40*
Gla-H2	2.32/2.03	2.45*/2.56*	Ser2-H2	3.94	3.94*
Gla-H3	4.11	4.19*	THQ-Me1	3.53	3.55/3.58
Gla-H4	1.58/1.67	1.64/1.74	THQ-H2	3.40/3.80	3.32/3.81
Gla-H5	4.06	4.00	THQ-H3	4.60	4.64
Gla-H6	4.21	4.23*	THQ-H4	2.95/3.08	2.93/3.09

Gla-H7	3.72/3.74	3.75/3.80*	THQ-H5	6.75	6.78
Thr-H1	4.39	4.40*	THQ-H6	7.08	7.21
Thr-H2	4.21	4.20*			

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