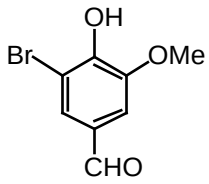
Supporting Information

Studies on the Total Synthesis of RP 66453: Synthesis of fully functionalized 15-membered biaryl containing macrocycle

Sabine Boisnard, Anny-Claude Carbonnelle, Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette cedex, France.

General procedure for the synthesis of 8

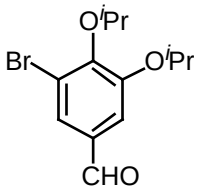


8

To a solution of vanillin (20.0 g, 0.13 mol, 1.0 eq) in acetic acid (50.0 mL), was added Br_2 (6.7 mL, 0.13 mol, 1.0 eq). The mixture was stirred at room temperature for 3h and a precipitate appeared. The reaction mixture was quenched with water and the precipitate was filtered, washed with water then methanol, dried under vacuum to afford **8** (27.0 g, 90%) as a white solid .

8: Rf = 0.27 (1/1, Et_2O/Hep) ; m.p. 127°C ; IR ($CHCl_3$) $\underline{\nu}$ 3688, 3510, 3036, 2942, 2842, 2723, 2414, 2391, 1690, 1598, 1496, 1464, 1423, 1400, 1367, 1282, 1175, 1140, 1046 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.00 (s, 3H), 6.54 (s, 1H), 7,37 (d, *J* = 1.6 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 9.80 (s, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 56.6, 108.0, 108.2, 130.0, 147.6, 148.9, 189.0 ; MS (EI) : *m/z* 231 ; Anal. Calcd for $C_8H_7O_3Br$: C, 41.59; H, 3.05 ; O, 20.77. Found : C, 41.57 ; H, 2.95 ; O, 20.67.

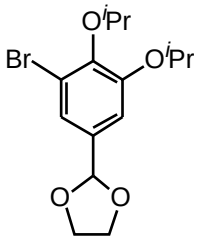
General procedure for the synthesis of 9



9

To a suspension of **8** (27.0 g, 0.11 mol, 1.0 eq) in CH_2Cl_2 (300.0 mL) was added anhydrous $AlCl_3$ (17.1 g, 0.13 mol, 1.1 eq). Pyridine (41.4 mL, 0.50 mol, 4.4 eq) was added slowly over 40 minutes via a dropping funnel. The reaction mixture was stirred for 24h at 40°C, a precipitate appeared. The reaction mixture was quenched with HCl 3N, the precipitate was filtered, dried under vacuum to give the demethylated bromovanillin as a yellow solid (24.8 g, 98%).
To this solide (10.0 g, 46.0 mmol, 1.0 eq) was added DMSO (200.0 mL) and K_2CO_3 (26.0 g, 0.18 mol, 4.0 eq). After being heated at 55°C for 5 days, the mixture was quenched with HCl 3N, extracted with CH_2Cl_2. The combined organic portions were washed with saturated NH_4Cl, a precipitate appeared. After filtration, some starting material was recovered as the filter cake. The filtrate was dried over Na_2SO_4, concentrated, and the resulting crude product was purified by flash chromatography (SiO_2, 15/1 Hep/EtOAc) to afford **9** as an oil (11.5 g, 83%).
9: Rf = 0.75 (1/1, EtOAc/Hep) ; IR ($CHCl_3$) $\underline{\nu}$ 3673, 3536, 3031, 2935, 2831, 2738, 1693, 1585, 1564, 1472, 1425, 1386 cm— ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.1 Hz, 6H), 1.35 (d, *J* = 6.2 Hz, 6H), 4.73 (sept, *J* = 6.1 Hz, 1H), 4.80 (sept, *J* = 6.2 Hz, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 9.81 (s, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.4, 22.3, 71.0, 74.7, 112.5, 127.5, 132.1, 151.9, 162.4, 189.5 ; MS (CI) : *m/z* 301 ; Anal. Calcd for $C_{13}H_{17}O_3Br$: C, 51.84 ; H, 5.69. Found : C, 52.14 ; H, 5.85.

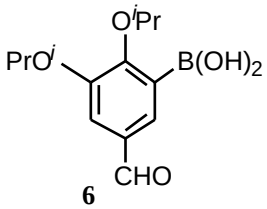
General procedure for the synthesis of 10



10

In a round bottom flask equipped with a Dean-Stark, were placed **9** (8.0 g, 26.50 mmol, 1.0 eq), benzene (120.0 mL), pTSA (46.0 mg, 0.26 mmol, 1%), ethylene glycol (4.4 mL, 79.70 mmol, 3.0 eq). After being refluxed for 5h, the reaction mixture was quenched with saturated $NaHCO_3$, extracted with EtOAc. The organic phase was dried over Na_2SO_4, concentrated, and the resulting oil was purified by flash chromatography (SiO_2, 15/1 Hep/EtOAc) to give **10** as an oil (8.3 g, 91%).
10: Rf = 0.56 (1/1, EtOAc/Hep) ; IR ($CHCl_3$) $\underline{\nu}$ 3673, 3527, 3033, 2934, 2892, 1721, 1599, 1570, 1475, 1374, 1276, 1151, 1103, 1017, 855 cm^{-1} ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (d, *J* = 5.9 Hz, 6H), 1.35 (d, *J* = 6.2 Hz, 6H), 4.00 (m, 2H), 4.09 (m, 2H), 4.57 (m, 2H), 5.68 (s, 1H), 6.95 (d, *J* = 1.7 Hz, 1H), 7.26 (d, *J* = 1.7 Hz, 1H) ; ^{13}C NMR (62,5 MHz, $CDCl_3$) δ 22.0, 22.6, 65.2, 71.3, 75.9, 102.7, 113.0, 123.0, 134.0, 146.4, 151.8 ; MS (CI) : *m/z* 345.

General procedure for the synthesis of 6

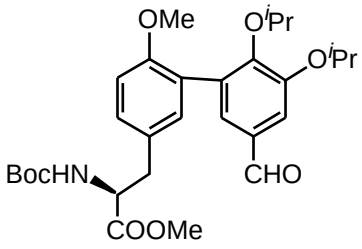


6

Into a two neck round bottom flask under an argon atmosphere at -78°C, were placed **10** (2.0 g, 5.8 mmol, 1.0 eq), anhydrous THF (20.0 mL). BuLi (1.6 M in hexane, 5.5 mL, 8.70 mmol, 1.5 eq) was added dropwise via a syringe. The mixture was stirred at -78°C for 40 minutes, then $B(OMe)_3$ (2.8 mL, 23.20 mmol, 4.0 eq) was added slowly. After being stirred 15 minutes at -78°C, the reaction mixture was brought back to room temperature and stirred for 15h. The mixture was quenched with HCl 3N and stirred for another 2h at room temperature. The reaction mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4, concentrated to give a crude product which was purified by chromatography flash (SiO_2, 4/1 Hep/EtOAc) to afford **6** (1.0 g, 67%) as a white solid.

6: Rf = 0.22 (1/2, EtOAc/Hep) ; m.p. 105°C ; IR ($CHCl_3$) $\underline{\nu}$ 3688, 3497, 3033, 1687, 1595, 1487, 1386, 1262, 1135, 1097 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.2 Hz, 6H), 1.40 (d, *J* = 6.0 Hz, 6H), 4.69 (sept, *J* = 6.0 Hz, 1H), 4.99 (sept, *J* = 6.2 Hz, 1H), 6.36 (s, 2H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.92 (d, *J* = 1.8 Hz, 1H), 9.93 (s, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.0, 22.6, 71.1, 76.4, 114.7, 132.5, 133.1, 150.4, 158.3, 191.8 ; MS (EI) : *m/z* 496 ($2M-2H_2O$) ; Anal. Calcd for $C_{13}H_{19}BO_5$: C, 58.68 ; H, 7.20. Found : C, 58.67 ; H, 7.23.

General procedure for the synthesis of 12



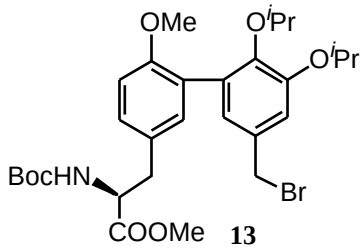
12

Into a round bottom flask were placed **11** (5.3 g, 12.18 mmol, 1.1 eq), $Pd(PPh_3)_4$ (512.0 mg, 0.44 mmol, 4%), DME (50.0 mL), a solution of Na_2CO_3 (2.34 g, 22.14 mmol, 2.0 eq) in H_2O (13.5 mL, 1.8 M). The mixture was stirred for 5 minutes at room temperature. A solution of **6** (2.95 g, 11.10 mmol, 1.0 eq) in DME (30.0 mL) was added via a syringe. After being stirred at 95°C for 16h, the reaction mixture was quenched with saturated NH_4Cl, extracted with EtOAc. The crude product was purified by flash chromatography (SiO_2, 4/1 Hep/EtOAc) to afford aldehyde **12** (5.0 g, 85%) as a visquous solid.

12: Rf = 0.36 (1/2, EtOAc/Hep) ; $[\alpha]_D$ +31.6 (*c* 1.8, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3684, 3439, 3032, 2981, 1742, 1708, 1692, 1575, 1461, 1385, 1281, 1165, 928 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ

0.99 (m, 12H), 1.41 (s, 9H), 3.00 (dd, *J* = 6.2, 13.8 Hz, 1H), 3.10 (dd, *J* = 5.7, 13.8 Hz, 1H), 3.72 (s, 3H), 3.77 (s, 3H), 4.21 (sept, *J* = 6.0 Hz, 1H), 4.56 (m, 1H), 4.70 (sept, *J* = 6.0 Hz, 1H), 5.01 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 7.04 (brs, 1H), 7.08 (brs, 1H), 7.11 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 9.88 (s, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.9, 22.4, 28.3, 37.3, 52.2, 54.6, 55.7, 70.7, 79.8, 110.8, 111.1, 111.7, 126.9-134.3, 140.2, 155.1, 155.9, 172.4, 191.4 ; MS (EI) : *m/z* 456 (M-tBu).

General procedure for the synthesis of 13



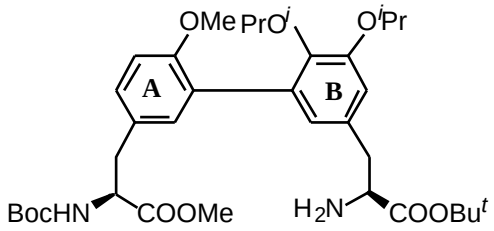
13

To a solution of **12** (3.4 g, 6.40 mmol, 1.0 eq) in anhydrous THF (300.0 mL) at -78°C, under an argon atmosphere, was slowly added $NaBH_4$ (3.9 g, 10.24 mmol, 1.6 eq). After being stirred 1h at -78°C, the mixture was slowly brought back to room temperature. The reaction was monitored by TLC until disappearance of the starting material and immediately quenched with saturated NH_4Cl, extracted with EtOAc. The combined organic portions were dried over Na_2SO_4, concentrated. The crude product was purified by flash chromatography (SiO_2, 3/1 Hep/EtOAc) to give the alcohol (2.7 g, 80%).

To a solution of the alcohol (2.6 g, 4.90 mmol, 1.0 eq) in CH_2Cl_2 (100.0 mL) at 0°C, were added NEt_3 (1.0 mL, 7.35 mmol, 1.5 eq) and MsCl (498 µL, 6.37 mmol, 1.3 eq). The mixture was stirred 2h at room temperature. LiBr (4.2 g, 49.00 mmol, 10.0 eq) in acetone (100.0 mL) was added and the mixture stirred at room temperature for 16h. The solvants were removed, the crude product was dissolved in Et_2O, extracted with Et_2O. The organic phase was dried over Na_2SO_4, concentrated. A flash chromatography (SiO_2, 7/2 Hep/EtOAc) delivered the pure compound **13** (2.0 g, 69%) as a yellow oil.

13: Rf = 0.49 (1/2, EtOAc/Hep) ; $[\alpha]_D$ +23.7 (*c* 0.7, $CHCl_3$) ; IR ($CHCl_3$) ν̲ 3440, 3026, 2400, 1742, 1709, 1601, 1580, 1503, 1462, 1438, 1255, 1165, 1029 cm^{-1} ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.1 Hz, 6H), 1.30 (d, *J* = 6.2 Hz, 6H), 1.41 (s, 9H), 3.00 (dd, *J* = 6.5, 13.8 Hz, 1H), 3.08 (dd, *J* = 5.4, 13.8 Hz, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 3.99 (m, 1H), 4.47-4.65 (m, 4H), 4.98 (d, *J* = 8.1 Hz, 1H), 6.85 (brs, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.92 (brs, 1H), 7.02 (brs, 1H), 7.04 (brd, *J* = 8.1 Hz, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.2, 22.5, 28.4, 36.9, 46.8, 52.3, 55.0, 55.9, 70.8, 75.8, 111.2, 114.1, 114.6, 123.6, 127.3-133.0, 151.7, 158.6, 172.5 ; MS (EI) : *m/z* 594.

General procedure for the synthesis of 4

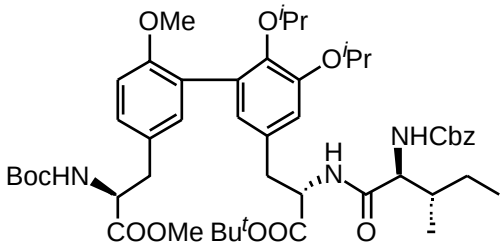


4

Into a round bottom flask were placed $CsOH.H_2O$ (1.18 g, 7.00 mmol, 10.0 eq),N-(diphenylmethylene)glycine *tert*-butyl ester (414.0 mg, 1.40 mmol, 2.0 eq), *N*-methyl anthracene-*O* -allyl cinchonidinium bromide (36.7 mg, 0.07 mmol, 10%), anhydrous CH_2Cl_2 (1.0 mL) at -50°C. To the mixture was added a solution of **13** (417.0 mg, 0.70 mmol, 1.0 eq) in CH_2Cl_2 (1.0 mL). After being stirred at -50°C for 20h, the reaction mixture was extracted with CH_2Cl_2. The combined organic portions were dried over Na_2SO_4, concentrated to give the crude imine which was hydrolysed as follows ; to a solution of the imine in THF (3.0 mL) were added citric acid (3.0 mL) and a little spoon of silica gel. The mixture was stirred for 2h, then quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, concentrated. Purification by flash chromatography (SiO_2, 7/2 Hep/EtOAc) afforded the amine **4** (294.0 mg, 65%) as a white visquous solid.

4: Rf = 0.51 (EtOAc) ; $[\alpha]_D$ +11.2 (*c* 1.1, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3440, 2980, 1713, 1578, 1503, 1462, 1369, 1211, 1156, 1025, 909 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.1 Hz, 6H), 1.37 (s, 18H), 2.75 (dd, *J* = 7.8, 13.5 Hz, 1H), 2.94 (dd, *J* = 5.6, 13.5 Hz, 1H), 2.90-3.06 (m, 2H), 3.57 (dd, *J* = 5.9, 7.4, 1H), 3.66 (s, 3H), 3.69 (s, 3H), 3.90 (m, 1H), 4.45-4.57 (m, 2H), 4.94 (d, *J* = 8.2 Hz, 1H), 6.66 (brs, 1H), 6.69 (brs, 1H), 6.81 (d, *J* = 8.9 Hz, 1H), 6.98 (s, 1H), 6.99 (d, *J* = 8.9 Hz, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 20.2, 20.8, 28.0, 28.4, 37.3, 41.3, 52.2, 54.7, 55.8, 56.3, 70.6, 75.6, 79.9, 81.1, 111.1, 115.7, 124.3, 127.2-133.7, 151.2, 156.1, 172.5, 174.4 ; MS (EI) : *m/z* 645.

General procedure for the synthesis of 16



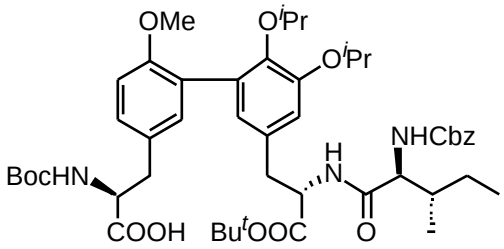
16

To a solution of amine **4** (300.0 mg, 0.46 mmol, 1.0 eq) in CH_2Cl_2 (14.0 mL) were added (2S, 3S) N-Cbz isoleucine (148.1 mg, 0.56 mmol, 1.4 eq), HOBt (88.0 mg, 0.65 mmol, 1.4 eq) and EDC (124.0 mg, 0.65 mmol, 1.4 eq). After being stirred for 15h under an argon atmosphere at room

temperature, the reaction mixture was quenched with saturated NH_4Cl, extracted with EtOAc. The organic phase was dried over Na_2SO_4, concentrated. The crude product was purified by flash chromatography (SiO_2, 5/1 Hep/EtOAc) to give **16** (373.0 mg, 90%).

16: Rf = 0.27 (1/2, EtOAc/Hep) ; m.p. 58-60°C ; $[\alpha]_D$ +24.3 (*c* 0.2, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3752, 3569, 2400, 1718, 1676, 1578, 1502, 1437, 1281, 1156, 930 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81-0.86 (m, 12H), 1.14-1.38 (m, 26H), 1.80 (m, 1H), 2.88-2.98 (m, 4H), 3.62 (s, 3H), 3.64 (s, 3H), 3.88 (m, 1H), 3.95-4.00 (m, 1H), 4.43-4.50 (m, 2H), 4.63 (q, *J* = 6.8 Hz, 1H), 4.90 (m, 1H), 5.00 (s, 2H), 5.35 (d, *J* = 8.9 Hz, 1H), 6.24 (d, *J* = 7.0 Hz, 1H), 6.54 (brs, 1H), 6.63 (brs, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.92 (brs, 1H), 6.96 (brd, *J* = 8.3 Hz, 1H), 7.19-7.25 (m, 5H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 11.7, 14.2, 22.4-22.9, 25.0, 28.1, 28.6, 37.5, 37.9, 38.3, 52.4, 53.8, 54.9, 56.0, 67.2, 70.8, 75.7, 80.1, 82.5, 111.3, 115.6, 124.5-136.6, 145.5, 151.5, 155.5, 156.2, 156.4, 170.7-172.7 ; MS (ES) : *m/z* 892 $[M+H]^+$; Anal. Calcd for $C_{49}H_{69}N_3O_{12}$: C, 65.97 ; H, 7.80 ; N, 4.71. Found : C, 65.75 ; H, 7.59 ; N, 4.52.

General procedure for the synthesis of 17

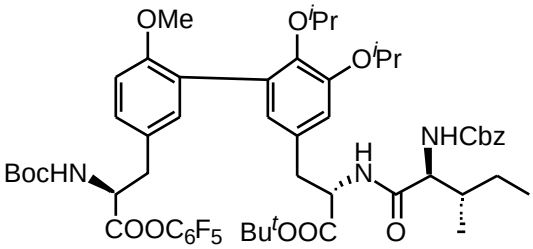


17

To a solution of ester **16** (415.2 mg, 0.47 mmol, 1.0 eq) in THF / H_2O (30.0 mL/30.0 mL) was added $LiOH.H_2O$ (39.1 mg, 0.93 mmol, 2.5 eq). After being stirred 5h at room temperature, the reaction mixture was quenched with saturated NH_4Cl, extracted with EtOAc. The organic phase was dried over Na_2SO_4, concentrated to afford **17** (400.0 mg) as a white cristalline solid with a quasi quantitatif yield.

17: Rf = 0.54 (EtOAc) ; m.p. 67°C ; $[\alpha]_D$ +20.3 (*c* 0.3, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3687, 3429, 3017, 2932, 1708, 1602, 1505, 1464, 1369, 1225, 1212, 1156 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 0.79-0.92 (m, 12H), 1.38 (s, 18H), 1.22-1.42 (m, 8H), 1.79 (m, 1H), 2.88-3.09 (m, 4H), 3.70 (s, 3H), 3.94 (sept, *J* = 5.5 Hz, 1H), 4.50-4.57 (m, 1H), 4.53 (sept, *J* = 5.9 Hz, 1H), 4.92-5.14 (m, 4H), 6.59 (s, 1H), 6.66 (s, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.94 (brs, 1H), 7.10 (brd, *J* = 8.5 Hz, 1H), 7.30 (brs, 5H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 11.4, 15.5, 22.5, 22.6, 24.9, 28.2, 28.6, 30.6, 36.5, 38.3, 55.9, 59.9, 67.3, 70.7, 75.7, 80.1, 82.6, 111.1, 115.6, 123.7-136.5, 151.3, 155.6, 156.1, 156.7, 170.9, 171.8, 176.6 ; MS (ES): *m/z* 878 $[M+H]^+$, 900 $[M+Na]^+$; Anal. Calcd for $C_{48}H_{67}N_3O_{12}$: C, 65.66 ; H, 7.69 ; N, 4.79. Found : C, 65.06 ; H, 7.66 ; N, 4.26.

General procedure for the synthesis of 18

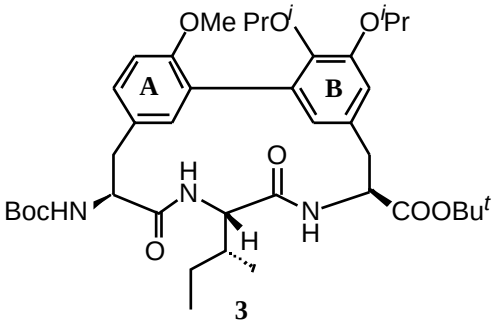


18

Into a round bottom flask were placed **17** (409.0 mg, 0.47 mmol, 1.0 eq), pentafluorophenol (103.0 mg, 0.56 mmol, 1.2 eq), EDC (135.0 mg, 0.70 mmol, 1.5 eq), at 0°C. The mixture was brought back slowly to room temperature and stirred for 4h. The solvant was removed under vacuum. The crude product was dissolved in EtOAc, quenched with saturated NH_4Cl, extracted with EtOAc. The organic phase was dried over Na_2SO_4, concentrated to afford after flash chromatography (SiO_2, 4/1 Hep/EtOAc) **18** (394.0 mg, 81%).

18: Rf = 0.42 (1/2, EtOAc/Hep) ; m.p. 59°C ; $[\alpha]_D$ +2.5 (*c* 0.4, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3667, 3431, 2934, 2567, 1790, 1715, 1676, 1520, 1462, 1369, 1153, 1108, 997 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81-0.90 (m, 12H), 1.33-1.40 (m, 8H), 1.34 (s, 9H), 1.40 (s, 9H), 1.83 (m, 1H), 2.90-3.27 (m, 4H), 3.70 (s, 3H), 3.90-4.07 (m, 1H), 4.12 (dd, *J* = 7.0, 14.5 Hz, 1H), 4.52-4.61 (m, 2H), 4.72 (m, 1H), 4.81 (d, *J* = 6.0 Hz, 1H), 5.05 (brs, 2H), 5.39 (d, *J* = 6.8 Hz, 1H), 6.39 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 6.71 (s, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 7.11 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.32 (m, 5H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 11.4, 14.1, 22.1-22.3, 24.7, 28.0, 28.2, 36.7, 37.6, 37.9, 53.6, 54.7, 55.7, 59.6, 67.0, 70.5, 75.5, 82.3, 82.9, 111.3, 115.3, 124.1-136.1, 145.0, 151.2, 154.8-156.2, 168.0, 168.4 ; MS (ES) : *m/z* 1044 $[M+H]^+$, 1066 $[M+Na]^+$, 1082 $[M+K]^+$; Anal. Calcd for $C_{54}H_{66}F_5N_3O_{12}$: C, 62.12 ; H, 6.37 ; N, 4.02. Found : C, 61.91 ; H, 6.46 ; N, 3.87.

General procedure for the synthesis of 3



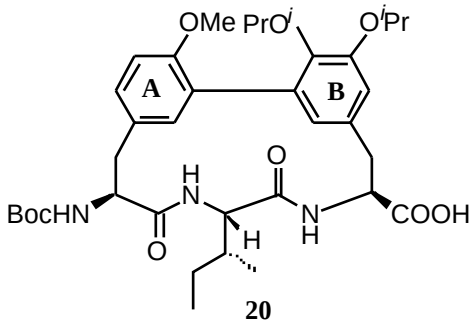
3

In a two neck round bottom flask equipped with a condenser and a dropping funnel, were placed tBuOH (300.0 mL), Pd/C (1.04 g), diisopropylethylamine (197 µL, 1.13 mmol, 3.0 eq) under an argon atmosphere at 85°C. A solution of tBuOH (53.0 mL), cyclohexene (28 mL) and **18** (394.0 mg, 0.38 mmol, 1.0 eq) was added slowly via the dropping funnel over 2h. The reaction mixture was

stirred 15h at 85°C, filtered on celite, the filter cake was washed with EtOAc, the filtrate was concentrated to give a crude product which was purified by flash chromatography (SiO_2, 4/1 Hep/EtOAc) to give the cyclic compound **3** (238.0 mg, 87%).

3: Rf = 0.35 (1/2, EtOAc/Hep) ; m.p. 112°C ; $[\alpha]_D$ -4.8 (*c* 0.9, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3431, 2980, 2877, 1706, 1666, 1518, 1370, 1289, 1156, 1015, 997 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.0 Hz, 3H), 0.84-0.89 (m, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.27-1.40 (m, 2H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.54 (s, 18H), 1.70-1.83 (m, 1H), 2.64 (brd, *J* = 12.9 Hz, 1H), 2.98 (dd, *J* = 7.8, 15.7 Hz, 1H), 3.35 (brd, *J* = 12.9 Hz, 1H), 3.47 (dd, *J* = 5.1, 15.7 Hz, 1H), 3.75 (s, 3H), 3.99-4.07 (m, 1H), 4.03 (sept, *J* = 6.0 Hz, 1H), 4.31 (m, 1H), 4.50 (m, 1H), 4.79 (dd, *J* = 5.1, 7.9 Hz, 1H), 5.14 (d, *J* = 9.7 Hz, 1H), 6.04 (d, *J* = 5.4 Hz, 1H), 6.31 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.77 (brd, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 7.12 (dd, *J* = 2.3, 8.3 Hz, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 11.2, 15.5, 22.3, 22.8, 24.9, 28.2, 35.4, 37.4, 38.8, 52.4, 55.9, 57.1, 58.1, 70.8, 75.6, 80.2, 82.7, 110.9, 115.1, 123.6, 130.1, 132.4, 128.3-129.5, 131.2-134.5, 150.9, 155.0, 155.9, 170.4, 170.8, 172.0 ; MS (ES) : *m/z* 726 $[M+H]^+$, 748 $[M+Na]^+$, 764 $[M+K]^+$.

General procedure for the synthesis of 20



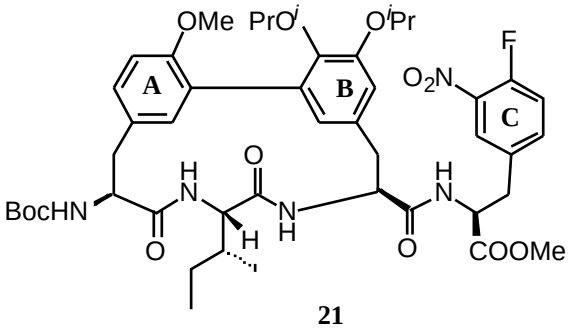
20

3 (120.0 mg, 0.16 mmol, 1.0 eq) was dissolved in TFA (3.0 mL) at room temperature and stirred for 5h. The TFA was removed under vacuum, to give a crude product which was immediately converted into the *N*-Boc compound by treatment with di-tert butyldicarbonate according to classical method to give **20** with a quantitative yield.

20: mixture of two atropisomers Rf = 0.61 (10/1, EtOAc/MeOH) ; m.p. 169°C ; $[\alpha]_D$ -40.2 (*c* 0.9, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3426, 3023, 2977, 2400, 1706, 1603, 1579, 1436, 1369, 1226, 1208, 1164, 1017, 931 cm^{-1} ; ^1H NMR (300 MHz, MeOD) δ 0.64 (d, *J* = 6.1 Hz, 3H), 0.73 (d, *J* = 6.1 Hz, 3H), 0.87-1.11 (m, 6H), 1.27-1.38 (m, 8H), 1.49 (s, 9H), 1.70-1.80 (m, 1H), 2.60 (dd, *J* = 2.0, 12.8 Hz, 1H), 2.85 (m, 1H), 2.99-3.16 (m, 1H), 3.45 (m, 1H), 3.71, 3.74 (s, 3H), 3.99 (sept, *J* = 6.1 Hz, 1H), 4.04-4.10 (m, 1H), 4.42-4.71 (m, 2H), 4.63 (sept, *J* = 6.6 Hz, 1H), 6.31 (s, 1H), 6.69 (s, 1H), 6.77 (s, 0.5H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.82 (s, 0.5H), 6.88 (d, *J* = 8.7 Hz, 0.5H), 6.89 (d, *J* = 8.7 Hz, 0.5H), 7.03 (dd, *J* = 2.0, 8.7 Hz, 0.5H), 7.15 (dd, *J* = 2.0, 8.7 Hz, 0.5H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 11.5, 11.7, 15.9, 16.3, 22.9-23.0, 26.0, 29.0, 36.1, 37.9, 38.1, 39.6, 56.4, 59.0, 59.4, 71.7, 76.5, 81.0, 112.2, 112.5, 116.5, 124.0-124.8, 130.6-130.8, 131.0,

132.7-135.9, 151.7, 152.0, 157.5, 157.6, 172.3, 173.1, 173.9 ; MS (ES) : *m/z* 670 $[M+H]^+$, 692 $[M+Na]^+$, 708 $[M+K]^+$.

General procedure for the synthesis of 21

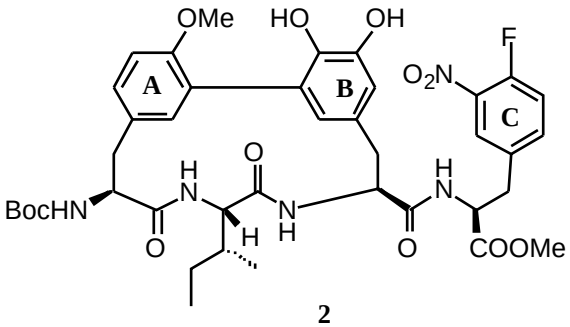


21

20 (111.0 mg, 0.16 mmol, 1.0 eq), L-Methyl-4-fluoro-3-nitro-phenylalanate (100.0 mg, 0.41 mmol, 2.5 eq), HOBt (32.0 mg, 0.23 mmol, 1.4 eq), EDC (45.0 mg, 0.23 mmol, 1.4 eq) were dissolved in CH_2Cl_2 (10.0 mL). After being stirred for 15h at room temperature, the mixture was quenched with NH_4Cl, extracted with EtOAc. The combined organic phase were dried over Na_2SO_4, concentrated. The crude product was purified by flash chromatography (SiO_2, 1/1 CH_2Cl_2/EtOAc) to afford compound **21** (136.0 mg, 92%).

21: mixture of two atropisomers Rf = 0.47 (1/1, EtOAc/CH_2Cl_2) ; m.p. 163-164°C ; $[\alpha]_D$ -7 (*c* 0.4, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3420, 3007, 2978 2360, 1701, 1663, 1541, 1541, 1368, 1290, 1255, 1163, 1017, 908 cm^{-1} ; ^1H NMR (300 MHz, MeOD) δ 0.56 (dd, *J* = 5.6, 6.6 Hz, 3H), 0.67 (dd, *J* = 6.1, 5.6 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H), 1.03 (dd, *J* = 6.1, 6.6 Hz, 3H), 1.27-1.36 (m, 8H), 1.46 (s, 9H), 1.53-1.60 (m, 1H), 2.61 (dd, *J* = 3.6, 15.4 Hz, 1H), 2.86-3.07 (m, 2H), 3.16-3.31 (m, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 4.02 (sept, *J* = 6.15 Hz, 1H), 4.61 (sept, *J* = 5.9 Hz, 1H), 4.30-4.80 (m, 4H), 6.27 (brs, 1H), 6.68 (brs, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.85 (brd, *J* = 8.2 Hz, 1H), 7.27 (dd, *J* = 2.6, 8.2 Hz, 1H), 7.56 (m, 1H), 7.96 (dd, *J* = 2.0, 7.7 Hz, 1H) ; ^1H NMR (400 MHz, DMSO-d_6, 333K) δ 0.61 (d, *J* = 5.9 Hz, 6H), 0.66-0.79 (m, 6H), 1.03 (d, *J* = 5.9 Hz, 6H), 1.28-1.34 (m, 2H), 1.41, 1.45 (s, 9H), 2.79 (brd, *J* = 13.8 Hz, 2H), 2.94-3.28 (m, 5H), 3.67 (s, 6H), 3.98-4.07 (m, 2H), 4.39 (m, 1H), 4.56-4.66 (m, 2H), 4.72 (m, 1H), 6.22 (s, 1H), 6.64 (s, 1H), 6.75 (s, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 7.9, 11.3 Hz, 1H), 7.69 (m, 1H), 8.02 (m, 2H), 8.15 (d, *J* = 7.9 Hz, NH), 8.25 (d, *J* = 7.9 Hz, NH), 8.39 (d, *J* = 9.4 Hz, NH), 8.44 (d, *J* = 8.4 Hz, NH); MS (ES) : *m/z* 894 $[M+H]^+$, 916 $[M+Na]^+$.

General procedure for the synthesis of 2



2

To a solution of **21** (100.0 mg, 0.11 mmol, 1.0 eq) in CH_2Cl_2 (1.0 mL), at -78°C, was added BCl_3 (448 µL, 0.45 mmol, 4.0 eq). The mixture was slowly brought back to room temperature. After being stirred for 4h, the reaction was quenched with MeOH. The solvants were removed to afford a crude product which was immediately converted into the *N*-Boc compound by treatment with di-tert butyldicarbonate according to classical method. The resulting crude product was purified by flash chromatography (SiO_2, CH_2Cl_2, then 10/1 CH_2Cl_2/MeOH) to afford **2** (74.0 mg, 82%).

2: Rf = 0.40 (10/0.5, CH_2Cl_2 /MeOH) ; $[\alpha]_D$ +18.5 (*c* 0.3, $CHCl_3$) ; IR ($CHCl_3$) $\underline{\nu}$ 3631, 3400, 3007, 2944, 2936, 1733, 1651, 1463, 1333, 1235, 1074 cm^{-1} ; ^1H NMR (250 MHz, MeOD) δ 0.58 (d, *J* = 6.1 Hz, 3H), 0.78 (t, *J* = 7.3 Hz, 3H), 1.24 (m, 2H), 1.46 (s, 9H), 1.52-1.64 (m, 1H), 2.63-3.09 (m, 6H), 3.73 (s, 3H), 3.76 (s, 3H), 4.28-4.32 (m, 1H), 4.54-4.69 (m, 3H), 6.43 (brs, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.26 (dd, *J* = 2.5 Hz, 1H), 7.54 (m, 1H), 7.92 (dd, *J* = 1.9, 7.3 Hz, 1H) ; ^1H NMR (400 MHz, DMSO-d_6, 333K) δ 0.68 (d, *J* = 6.9 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H), 1.25-1.30 (m, 2H), 1.41 (s, 9H), 1.43-1.56 (m, 1H), 2.61 (brd, *J* = 15.8 Hz, 1H), 2.74-2.80 (m, 2H), 2.99-3.25 (m, 3H), 3.67 (s, 3H), 3.71 (s, 3H), 4.23 (m, 1H), 4.34 (m, 1H), 4.49 (m, 1H), 4.63 (m, 1H), 6.29 (s, 1H), 6.56 (s, 1H), 6.66 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.9, 11.3 Hz, 1H), 7.69 (m, 1H), 7.75 (m, NH), 8.01 (brd, *J* = 6.4 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, NH), 8.38 (d, *J* = 9.3 Hz, NH) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 10.8, 15.5, 25.7, 28.4, 36.6, 37.5, 38.9, 52.4, 52.7, 54.2, 54.7, 55.7, 56.0, 58.3, 80.3, 111.9, 116.1, 119.0 (d, *J* = 20.6 Hz), 124.0-134.0, 127.3, 135.62, 137.6 (d, *J* = 7.5 Hz), 138.0 (d, *J* = 8.0 Hz), 146.2, 154.9 (d, *J* = 223.0 Hz), 155.9, 172.4, 172.8, 173.3 ; MS (ES) : *m/z* 810 $[M+H]^+$, 832 $[M+Na]^+$, 848 $[M+K]^+$.