Ruffling-Induced Chirality: Synthesis, Metalation, and Optical Resolution of Highly Nonplanar, Cyclic, Benzimidazole-Based Ligands

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Supporting Information

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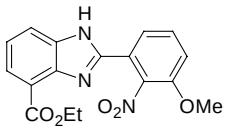
1. Experimental Procedures

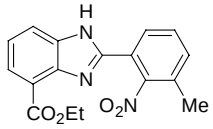
Ethyl 2-(3-Methoxy-2-nitrophenyl)-1*H*-benzimidazole-4-carboxylate (12)



12

To a solution of oxalyl chloride (5.8 mL, 66 mmol) in CH_2Cl_2 (80 mL) were added 3-methoxy-2-nitrobenzoic acid (10.0 g, 50.8 mmol) and a catalytic amount of DMF (1 drop). The reaction mixture was stirred at rt for 8 h to give a clear solution. The volatiles were removed in vacuo to afford a crude acyl chloride as an off-white solid. A solution of the crude acyl chloride in CH_2Cl_2 (70 mL) was added dropwise over 1 h at 0 °C to a solution of diamine **9** (8.86 g, 49.2 mmol) and Et_3N (9.2 mL, 66 mmol) in CH_2Cl_2 (600 mL). After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h, and at rt for 1 h. The volatiles were removed in vacuo to give an off-white solid, which was refluxed in glacial AcOH (100 mL) in the presence of AcONa (4.0 g, 50 mmol) for 15 h. The reaction mixture was cooled to rt and evaporated in vacuo. The resulting brown oil was partitioned between CH_2Cl_2 and water. After neutralization with solid K_2CO_3, the phases were separated and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and evaporated in vacuo to give an off-white solid. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) furnished the title compound **12** (15.4 g, 92% over two steps from diamine **9**) as a pale yellow solid: R_f = 0.70 (CH_2Cl_2/EtOAc, 4/1); mp 158.0-159.0 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 3.82 (s, 3H), 4.34 (q, J = 7.0 Hz, 2H), 7.03 (dd, J = 8.0, 1.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.50 (dd, J = 8.0, 1.0 Hz, 1H), 7.82 (dd, J = 8.0, 1.0 Hz, 1H), 7.88 (dd, J = 8.0, 1.0 Hz, 1H), and 10.6 (br s, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.76, 57.15, 61.85, 114.6, 114.7, 121.6, 122.8, 123.5, 125.9, 126.3, 131.7, 135.0, 140.4, 144.7, 147.3, 151.7, and 166.5; IR ($CHCl_3$) ν_{max} 1720, 1694, 1540, 1477, 1373, and 1276 cm^{-1}; MS (ESI) *m/z* (rel intensity) 364 (100%, MNa^+), 342 (25), 328 (30), 314 (30), and 296 (25); HRMS calcd for $C_{17}H_{15}N_3NaO_5$ (MNa^+) 364.0909, found 364.0915; Anal. Calcd for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 60.05; H, 4.45; N, 12.33.

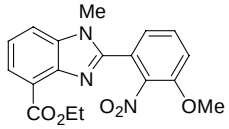
Ethyl 2-(3-Methyl-2-nitrophenyl)-1*H*-benzimidazole-4-carboxylate (13)



13

To a solution of oxalyl chloride (6.5 mL, 74 mmol) in CH_2Cl_2 (80 mL) were added 3-methyl-2-nitrobenzoic acid (10.3 g, 57.0 mmol) and a catalytic amount of DMF (1 drop). The reaction mixture was stirred at rt for 3 h to give a clear solution. The volatiles were removed in vacuo to afford a crude acyl chloride as a yellow solid. A solution of the crude acyl chloride in CH_2Cl_2 (70 mL) was added dropwise over 1 h at 0 °C to a solution of diamine **9** (9.95 g, 55.7 mmol) and Et_3N (10.1 mL, 72.4 mmol) in CH_2Cl_2 (600 mL). After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h and at rt for an additional 1 h. The volatiles were removed in vacuo to give a brown oil, which was refluxed in glacial AcOH (150 mL) in the presence of AcONa (4.7 g, 57 mmol) for 15 h. The reaction mixture was cooled to rt and evaporated in vacuo. The resulting brown oil was partitioned between CH_2Cl_2 and water. After neutralization with solid K_2CO_3, the phases were separated and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and evaporated in vacuo to give an off-white solid. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **13** (16.3g, 91% over two steps from diamine **9**) as a pale yellow solid: R_f = 0.35 (petroleum ether/EtOAc, 2/1); mp 133.5-134.5 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 4.33 (q, J = 7.0 Hz, 2H), 7.20 (t, J = 8.0 Hz, 1H), 7.29 (~d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.73 (~d, J = 7.5 Hz, 1H), 7.82 (dd, J = 7.5, 1.0 Hz, 1H), 7.88 (dd, J = 8.0, 1.0 Hz, 1H), and 10.5 (br s, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.77, 17.70, 61.80, 114.6, 122.7, 122.8, 125.8, 126.1, 128.4, 130.8, 131.1, 133.5, 135.0, 144.6, 147.9, 150.3, and 166.6; IR ($CHCl_3$) ν_{max} 1721, 1693, 1536, 1372, and 1283 cm^{-1}; MS (ESI) *m/z* (rel intensity) 348 (100%, MNa^+), 326 (50), 312 (60), 298 (70), and 280 (70); HRMS calcd for $C_{17}H_{15}N_3NaO_4$ (MNa^+) 348.0960, found 348.0956; Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.94; H, 4.63; N, 12.95.

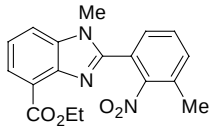
Ethyl 2-(3-Methoxy-2-nitrophenyl)-1-methyl-1*H*-benzimidazole-4-carboxylate (15)



15

To a solution of benzimidazole **12** (7.80 g, 22.9 mmol) in THF (100 mL) was slowly added NaH (60% w/w dispersion in mineral oil, 1.00 g, 25 mmol) in small portions at 0 °C. After 30 min, the reaction mixture was warmed up to rt, and stirred for an additional 40 min. The resulting brown solution was re-cooled to 0 °C, and quenched with MeI (3.6 mL, 57 mmol). After 13 h at rt, the volatiles were removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The phases were separated and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and evaporated in vacuo to give a yellow solid. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **15** (7.39 g, 91%) as a white solid: R_f = 0.40 (EtOAc); mp 163.5-165.0 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (t, J = 7.0 Hz, 3H), 3.62 (s, 3H), 3.82 (s, 3H), 4.33 (q, J = 7.0 Hz, 2H), 7.04 (dd, J = 7.5, 1.0 Hz, 1H), 7.09 (dd, J = 8.5, 1.0 Hz, 1H), 7.23 (dt, J = 7.5, 7.5 Hz, 1H), 7.39-7.45 (m, 2H), and 7.83 (dd, J = 8.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.75, 31.78, 57.21, 61.43, 114.5, 115.1, 122.8, 123.0, 123.1, 125.3, 125.8, 131.8, 137.4, 141.9, 142.1, 149.9, 152.1, and 166.6; IR ($CHCl_3$) ν_{max} 1706, 1613, 1581, 1541, 1466, 1367, and 1283 cm^{-1}; MS (ESI) *m/z* (rel intensity) 378 (50%, MNa^+), 356 (100), 342 (45), and 328 (80); HRMS calcd for $C_{18}H_{18}N_3O_5$ (MH^+) 356.1246, found 356.1229; Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 61.07; H, 4.76; N, 11.77.

Ethyl 1-Methyl-2-(3-methyl-2-nitrophenyl)-1*H*-benzimidazole-4-carboxylate (16)

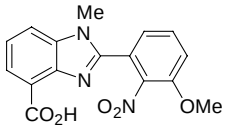


16

To a solution of benzimidazole **13** (8.15 g, 25.1 mmol) in THF (100 mL) was added NaH (60% w/w dispersion in mineral oil, 1.1 g, 28 mmol) at 0 °C. After 30 min, the reaction mixture was warmed up to rt, and stirred for an additional 40 min. The resulting brown solution was re-cooled to 0 ºC, and quenched with MeI (3.9 mL, 63 mmol). After 12 h at rt, the volatiles were

removed in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The phases were separated and the extraction was completed with additional portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and evaporated in vacuo to give a yellow solid. Purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/EtOAc, 1/1) gave the title compound **16** (7.30 g, 86%) as a white solid: R_f = 0.60 (EtOAc); mp 155.5-156.5 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0 Hz, 3H), 2.32 (s, 3H), 3.60 (s, 3H), 4.32 (q, J = 7.0 Hz, 2H), 7.20 (dt, J = 4.0, 4.0 Hz, 1H), 7.27-7.43 (m, 4H), and 7.82 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.76, 18.65, 31.68, 61.36, 114.5, 122.7, 122.9, 124.6, 125.7, 129.7, 130.8, 132.1, 133.9, 137.3, 142.1, 150.8, 151.6, and 166.5; IR ($CHCl_3$) ν_{max} 1715, 1609, 1536, 1462, 1421, 1363, and 1294 cm^{-1}; MS (ESI) *m/z* (rel intensity) 362 (40%, MNa^+), 340 (100), 326 (30), and 312 (90); HRMS calcd for $C_{18}H_{18}N_3O_4$ (MH^+) 340.1297, found 340.1315; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.71; H, 5.06; N, 12.43.

2-(3-Methoxy-2-nitrophenyl)-1-methyl-1*H*-benzimidazole-4-carboxylic acid (18)

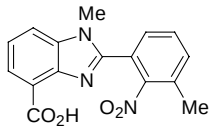


18

To a methanolic solution of NaOH (5%, 30 mL) was added ester **15** (2.72 g, 7.7 mmol) and the mixture was refluxed for 30 min (TLC). The reaction mixture was cooled to rt, diluted with water (150 mL), and neutralized at 0 °C with concd HCl. The precipitate formed was isolated by filtration, washed with a copious amount of water, and dried in vacuo to give the title compound **18** (2.43 g, 97%) as a white solid. This product was used in the next step without further purification. For analytical purposes, a small amount of the product was re-crystallized from MeOH: mp 240.5-242.0 °C (MeOH); ^{1}H NMR (250 MHz, d_6-DMSO) δ 3.72 (s, 3H), 3.87 (s, 3H), 7.35 (t, J = 8.0 Hz, 1H), 7.36 (dd, J = 7.5, 1.0 Hz, 1H), 7.49 (dd, J = 8.5, 1.0 Hz, 1H), 7.67 (dd, J = 8.5, 7.5 Hz, 1H), 7.74 (dd, J = 7.5, 1.0 Hz, 1H), and 7.85 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_6-DMSO) δ 32.38, 57.94, 116.8, 117.0, 121.4, 123.3, 123.9, 124.0, 125.7, 133.2, 137.2, 141.2, 141.6, 149.7, 151.9, and 167.0; IR ($CHCl_3$) ν_{max} 1739, 1612, 1540, 1465, 1426, 1391, and 1282 cm^{-1}; MS (ESI) *m/z* (rel intensity) 350 (100%, MNa^+), 328 (90), and

310 (60); HRMS calcd for $C_{16}H_{14}N_3O_5$ (MH^+) 328.0933, found 328.0934; Anal. Calcd for $C_{16}H_{13}N_3O_5$: C, 58.72; H, 4.00; N, 12.84. Found: C, 58.96; H, 4.06; N, 12.97.

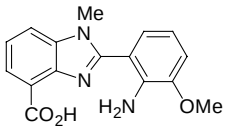
1-Methyl-2-(3-methyl-2-nitrophenyl)-1*H*-benzimidazole-4-carboxylic acid (19)



19

To a methanolic solution of NaOH (5%, 35 mL) was added ester **16** (3.01 g, 8.9 mmol) and the mixture was refluxed for 50 min (TLC). The reaction mixture was cooled to rt, diluted with water (150 mL), and neutralized at 0 °C with concd HCl. The precipitate formed was filtered, washed with a copious amount of water, and dried in vacuo to give the title compound **19** (2.71 g, 98%) as a white solid that could be used in the subsequent step without further purification. For analytical purposes, a small amount of the product was re-crystallized from MeOH: mp 257.0-258.0 °C (MeOH); ^{1}H NMR (250 MHz, d_6-DMSO) δ 2.30 (s, 3H), 3.71 (s, 3H), 7.35 (t, J = 8.0 Hz, 1H), 7.58-7.69 (m, 3H), 7.74 (dd, J = 7.5, 1.0 Hz, 1H), and 7.85 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_6-DMSO) δ 18.28, 32.27, 116.7, 121.4, 123.6, 123.8, 125.7, 130.2, 132.1 (2 × C), 134.9, 137.1, 141.6, 150.5, 151.2, and 167.0; IR ($CHCl_3$) ν_{max} 1740, 1610, 1537, 1428, and 1391 cm^{-1}; MS (ESI) *m/z* (rel intensity) 334 (100%, MNa^+), 326 (60), 312 (100), and 294 (85); HRMS calcd for $C_{16}H_{14}N_3O_4$ (MH^+) 312.0984, found 312.0968; Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.92; H, 4.28; N, 13.53.

2-(2-Amino-3-methoxyphenyl)-1-methyl-1*H*-benzimidazole-4-carboxylic acid (21)

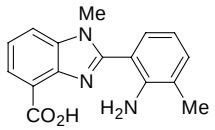


21

A suspension of benzimidazole **18** (2.20 g, 6.7 mmol) in MeOH (80 mL) was hydrogenated at normal pressure in the presence of Pd/C (10% w/w, 350 mg) for 7 h (TLC). The resulting mixture was diluted with 5% HCl (50 mL), and passed through a thin pad of Celite®. The filtrate was concentrated in vacuo, diluted with water to a volume of 20 mL, and neutralized with 2 M NaOH. The mixture was extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$), and evaporated in vacuo to give the title compound **21** (2.00 g, 98%) as a yellow solid.

Acid **21** could be used in the subsequent step without further purification. For analytical purposes, a small amount of the product was re-crystallized from MeOH: mp 230.5-231.5 °C (MeOH); ^{1}H NMR (250 MHz, d_6-DMSO) δ 3.69 (s, 3H), 3.73 (s, 3H), 5.43 (br s, 2H), 6.59 (t, J = 8.0 Hz, 1H), 6.88 (~d, J = 8.0 Hz, 1H), 6.91 (dd, J = 8.0, 1.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.72 (dd, J = 7.5, 1.0 Hz, 1H), and 7.75 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_6-DMSO) δ 32.77, 56.58, 112.2, 112.6, 116.2, 116.3, 120.3, 122.9, 123.1, 125.1, 137.3, 138.7, 141.9, 147.8, 154.4, and 167.3; IR (KBr) ν_{max} 1731, 1611, 1489, 1450, 1432, 1262, and 1231 cm^{-1}; MS (ESI) *m/z* (rel intensity) 320 (20%, MNa$^+$), 312 (80), and 298 (100); HRMS calcd for $C_{16}H_{16}N_3O_3$ (MH$^+$) 298.1113, found 298.1111; Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.58; H, 5.11; N, 14.04.

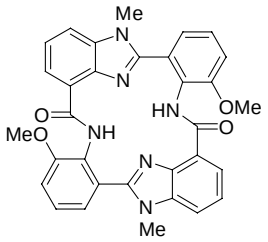
2-(2-Amino-3-methylphenyl)-1-methyl-1*H*-benzimidazole-4-carboxylic acid (22)



22

A suspension of benzimidazole **19** (2.40 g, 7.7 mmol) in MeOH (100 mL) was hydrogenated at normal pressure in the presence of Pd/C (10% w/w, 350 mg) for 5 h (TLC). The resulting mixture was diluted with 5% HCl (50 mL), and passed through a thin pad of Celite®. The filtrate was concentrated in vacuo, diluted with water to a volume of 20 mL, and neutralized with 2 M NaOH. The mixture was extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$), and evaporated in vacuo to give the title compound **22** (2.14 g, 99%) as a yellow solid. Acid **22** could be used in the subsequent step without further purification. For analytical purposes, a small amount of the product was re-crystallized from MeOH: mp 254.0-256.0 °C (MeOH); ^{1}H NMR (250 MHz, d_6-DMSO) δ 2.06 (s, 3H), 3.68 (s, 3H), 5.51 (br s, 2H), 6.54 (t, J = 7.5 Hz, 1H), 7.04 (dd, J = 7.5, 0.5 Hz, 1H), 7.13 (dd, J = 7.5, 1.0 Hz, 1H), 7.30 (dd, J = 7.5, 1.0 Hz, 1H), 7.72 (dd, J = 7.5, 1.0 Hz, 1H), and 7.78 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_6-DMSO) δ 18.80, 32.76, 112.1, 116.3 (2 × C), 120.3, 122.9, 123.7, 125.0, 129.3, 132.9, 137.3, 141.9, 146.8, 154.9, and 167.4; IR (KBr) ν_{max} 1728, 1612, 1479, 1447, 1432, 1381, and 1262 cm^{-1}; MS (ESI) *m/z* (rel intensity) 304 (10%, MNa$^+$), 296 (90), and 282 (100); HRMS calcd for $C_{16}H_{16}N_3O_2$ (MH$^+$) 282.1242, found 282.1223; Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 67.85; H, 5.41; N, 14.88.

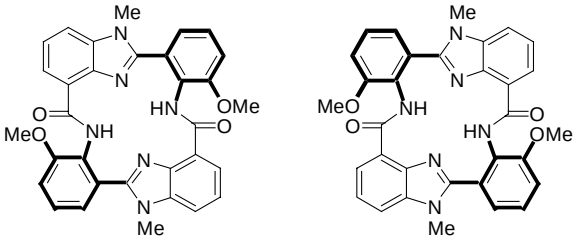
Cyclic diamide (23)



23

To a suspension of amino acid **21** (1.49 g, 5.0 mmol) in CH_2Cl_2 (250 mL) was added NMM (1.2 mL, 11 mmol), followed by BOP (2.43 g, 5.5 mmol). The reaction mixture was stirred at rt for 7 days, and washed with satd $NaHCO_3$. The organic layer was dried ($MgSO_4$), and evaporated in vacuo to give a pale yellow solid. Purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 30/1) furnished the title compound **23** (1.09 g, 78%) as a white powder: R_f = 0.45 (CH_2Cl_2/methanol, 10/1); mp > 260 °C (EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.92 (s, 3H), 7.10 (dd, J = 8.0, 1.0 Hz, 1H), 7.18 (dd, J = 8.5, 1.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.51 (dd, J = 9.0, 1.0 Hz, 1H), 8.16 (dd, J = 7.5, 1.0 Hz, 1H), and 12.2 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 31.11, 55.29, 112.5, 112.9, 120.5, 121.6, 121.7, 123.4, 125.2, 125.6, 126.1, 135.1, 139.3, 150.5, 155.6, and 162.0; IR (KBr) ν_{max} 1674, 1660, 1521, 1483, 1456, 1381, and 1287 cm^{-1}; MS (ESI) *m/z* (rel intensity) 559 (100%, MH$^+$); HRMS calcd for $C_{32}H_{27}N_6O_4$ (MH$^+$) 559.2094, found 559.2089. The cyclic amide **23** was optically resolved by analytical CSP HPLC (Figure S2).

Optical resolution of cyclic amide (23)

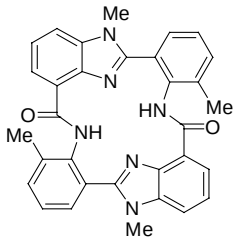


(±)-23

The enantiomers of cyclic amide **23** were separated using analytical CSP HPLC (Chiralpak AD column, 4.6 mm × 25 cm; 2-propanol/hexanes/diethylamine, 20/80/0.5; 1 ml min^{-1}, 40 °C). UV detection was performed at 254 nm. Injections of ~70 μg of the racemate in 20

μL of CH_2Cl_2 were made every 25 min. The fast-eluting enantiomer was collected between 17.0 and 20.5 min, and the slow-eluting enantiomer was collected between 22.8 and 27.5 min. The collected products were enantiomerically enriched (ee = 84.0% and 74.3%, respectively) by CSP HPLC. Only the fast-eluting enantiomer was used in subsequent racemization studies.

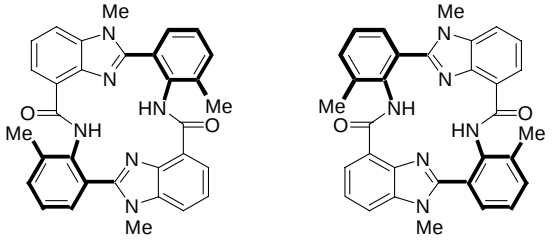
Cyclic diamide (24)



24

To a suspension of amino acid **22** (1.41 g, 5.0 mmol) in CH_2Cl_2 (250 mL) was added NMM (1.2 mL, 11 mmol), followed by BOP (2.43 g, 5.5 mmol). The reaction mixture was stirred at rt for 7 days, and washed with satd $NaHCO_3$. The organic layer was dried ($MgSO_4$), and evaporated in vacuo to give a pale yellow solid. The crude product was suspended in EtOAc (15 mL), and stirred at rt for 20 min. The suspension was filtered, and the collected solid was washed with cold EtOAc (50 mL). After drying in vacuo, the title compound **24** (1.13 g, 86%) was obtained as a white powder: R_f = 0.50 (EtOAc); mp > 260 °C (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.90 (s, 3H), 7.36-7.45 (m, 3H), 7.54 (t, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.0, 1.0 Hz, 1H), 8.17 (dd, J = 7.5, 1.0 Hz, 1H), and 12.4 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.35, 33.00, 114.6, 123.3, 123.5, 125.3, 126.1, 127.1, 128.6, 134.1, 136.9, 137.1, 139.7, 141.3, 153.1, and 164.0; IR (KBr) ν_{max} 1739, 1669, 1607, 1526, 1474, 1447, 1379, 1297, and 1253 cm^{-1}; MS (ESI) *m/z* (rel intensity) 549 (8%, MNa^+) and 527 (100%, MH^+); HRMS calcd for $C_{32}H_{27}N_6O_2$ (MH^+) 527.2195, found 527.2166. The cyclic amide **24** was optically resolved by analytical CSP HPLC (Figure S3).

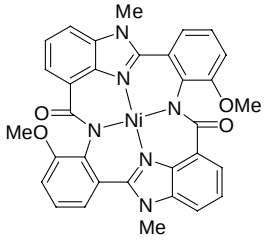
Optical resolution of cyclic amide (24)



(±)-24

The enantiomers of cyclic amide **24** were separated using analytical CSP HPLC (Chiralpak AD column, 4.6 mm × 25 cm; 2-propanol/hexanes/diethylamine, 20/80/0.5; 1 ml min^{-1}, 40 °ºC). UV detection was performed at 254 nm. Injections of ~60 μg of the racemate in 20 μL of CH_2Cl_2 were made every 15 min. The fast-eluting enantiomer was collected between 8.5 and 10.0 min, and the slow-eluting enantiomer was collected between 12.2 and 15.0 min. The collected products were enantiomerically pure (ee > 99.9% for each enantiomer) by CSP HPLC, and were used in the subsequent racemization studies.

Ni(II) complex (26)

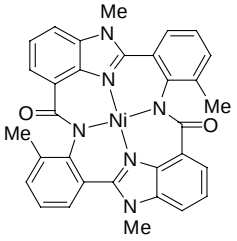


26

To a suspension of cyclic amide **23** (100 mg, 0.18 mmol) in MeOH (10 mL) was added $Ni(OAc)_2 \cdot 4H_2O$ (46.9 mg, 0.19 mmol), and the mixture was refluxed for 5 h (TLC) to give an orange suspension. After cooling to rt, the suspension was filtered, and the collected solid washed with cold MeOH (5 mL), and dried to give the title compound **26** (101 mg, 92%) as a deep-orange solid: R_f = 0.50 (MeOH); mp > 260 °C (MeOH); ^{1}H NMR (250 MHz, d_4-MeOH + $CDCl_3$) δ 3.72 (s, 3H), 4.14 (s, 3H), 7.05 (dd, J = 8.0, 1.5 Hz, 1H), 7.20 (dd, J = 8.0, 1.5 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.0, 1.0 Hz, 1H) and 7.99 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, d_4-MeOH + $CDCl_3$) δ 35.25, 58.05, 115.7, 116.4, 121.5, 124.3, 126.0, 126.7 (2 × C), 126.9, 137.7, 139.1, 139.2, 152.5, 157.6, and 168.3; IR (KBr) ν_{max} 1582, 1599, 1482, 1452, 1434, 1317, 1283, and 1264 cm^{-1}; MS (ESI) *m/z* (rel intensity) 615

(100%, MH^+) and 559 (85); HRMS calcd for $C_{32}H_{24}N_6NaNiO_4$ (MNa^+) 637.1110, found 637.1107; Anal. Calcd for $C_{32}H_{24}N_6NiO_4$: C, 62.47; H, 3.93; N, 13.66. Found: C, 62.69; H, 4.00; N, 13.58. Crystals suitable for X-ray analysis were grown by slow evaporation of a CH_2Cl_2/MeOH solution. For crystallographic data, see Supporting Information, Section 3.3. The Ni(II) complex **26** was optically resolved by analytical CSP HPLC (Figure S4).

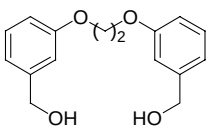
Ni(II) complex (27)



27

To a suspension of cyclic amide **24** (100 mg, 0.19 mmol) in MeOH (10 mL) was added $Ni(OAc)_2{\cdot}4H_2O$ (49.7 mg, 0.20 mmol), and the mixture was refluxed for 3 h (TLC) to give an orange suspension. After cooling to rt, the suspension was filtered, and the collected solid washed with cold MeOH (5mL), and dried to give the title compound **27** (91 mg, 82%) as an orange solid: R_f = 0.65 (MeOH); mp > 260 °C (MeOH); ^{1}H NMR (250 MHz, d_4-MeOH + $CDCl_3$) δ 2.03 (s, 3H), 4.16 (s, 3H), 7.25 (t, J = 7.5 Hz, 1H), 7.38 (~d, J = 7.5 Hz, 1H), 7.44-7.50 (m, 2H), 7.64 (~d, J = 8.0 Hz, 1H), and 7.99 (dd, J = 7.5, 0.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, d_4-MeOH + $CDCl_3$) δ 20.77, 34.75, 115.4, 123.1, 125.5, 125.6, 126.2, 126.5, 127.1, 135.4, 137.2, 138.7, 139.2, 147.7, 152.7, and 167.2; IR (KBr) ν_{max} 1597, 1570, 1497, 1441, 1394, 1325, and 1291 cm^{-1}; MS (ESI) *m/z* (rel intensity) 583 (100%, MH^+) and 527 (60); HRMS calcd for $C_{32}H_{25}N_6NiO_2$ (MH^+) 583.1392, found 583.1395; Anal. Calcd for $C_{32}H_{25}N_6NiO_{2.5}$ ($M{\cdot}0.5H_2O$): C, 64.89; H, 4.25; N, 14.19. Found: C, 64.60; H, 4.50; N, 13.99. The Ni(II) complex **27** was optically resolved by analytical CSP HPLC (Figure S5).

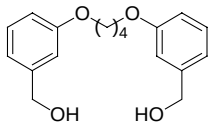
1,2-Bis(3-hydroxymethylphenoxy)ethane (32)



32

Following the general procedure described for the preparation of diol **34** (see main text), phenol **31** (10.2 g, 82.0 mmol) was reacted with 1,2-dibromoethane (7.74 g, 41.0 mmol) in the presence of 10 M NaOH (8.2 mL, 82 mmol) in EtOH (40 mL) for 42 h to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/Me_2CO, 5/1) and crystallization from CH_2Cl_2, the title compound **32** (3.30 g, 29%) as a white solid: R_f = 0.40 (CH_2Cl_2/EtOAc, 1/1); mp 127.5-128.0 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, d_6-Me_2CO) δ 4.19 (t, J = 6.0 Hz, 0.6H), 4.37 (s, 2H), 4.63 (d, J = 6.0 Hz, 2H), 6.87 (dd, J = 8.0, 2.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.03 (s, 1H), and 7.26 (t, J = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_4-MeOH) δ 64.09, 66.88, 113.1, 113.6, 119.5, 129.5, 143.5, and 159.4; IR (KBr) ν_{max} 1596, 1492, 1446, 1323, and 1253 cm^{-1}; MS (ESI) *m/z* (rel intensity) 297 (100%, MNa^+); HRMS calcd for $C_{16}H_{18}NaO_4$ (MNa^+) 297.1103, found 297.1092; Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.80; H, 6.59.

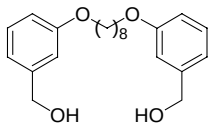
1,4-Bis(3-hydroxymethylphenoxy)butane (33)



33

Following the general procedure described for the preparation of diol **34** (see main text), phenol **31** (15.5 g, 125 mmol) was reacted with 1,4-dibromobutane (13.5 g, 62.5 mmol) in the presence of 10 M NaOH (12.5 mL, 125 mmol) in EtOH (200 mL) for 20 h to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/EtOAc, 7/1), the title compound **33** (11.9 g, 63%) as a white solid: R_f = 0.70 (EtOAc); mp 103.0-104.0 °C (Me_2CO/petroleum ether); ^{1}H NMR (250 MHz, d_4-MeOH) δ 1.83 (m, 2H), 3.92 (t, J = 6.0 Hz, 2H), 4.44 (s, 2H), 6.68 (dd, J = 8.0, 2.0 Hz, 1H), 6.76-6.81 (m, 2H), and 7.10 (dt, J = 8.0, 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_4-MeOH) δ 26.19, 64.14, 67.63, 113.0, 113.4, 119.1, 129.4, 143.3, and 159.7; IR ($CHCl_3$) ν_{max} 1601, 1585, 1488, 1447, and 1262 cm^{-1}; MS (ESI) *m/z* (rel intensity) 325 (100%, MNa^+) and 285 (15); HRMS calcd for $C_{18}H_{22}NaO_4$ (MNa^+) 325.1416, found 325.1399; Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.45; H, 7.53.

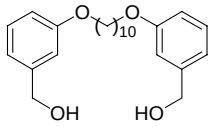
1,8-Bis(3-hydroxymethylphenoxy)octane (35)



35

Following the general procedure described for the preparation of diol **34** (see main text), phenol **31** (9.1 g, 74 mmol) was reacted with 1,8-dibromooctane (10.0 g, 36.8 mmol) in the presence of 10 M NaOH (7.4 mL, 74 mmol) in EtOH (150 mL) for 18 h to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/EtOAc, 7/1) the title compound **35** (8.55 g, 65%) as a white solid: R_f = 0.70 (EtOAc/CH_2Cl_2, 1/1); mp 94.5-96.0 °C (Me_2CO/petroleum ether); ^{1}H NMR (250 MHz, d_4-MeOH) δ 1.31-1.40 (m, 4H), 1.63 (dt, J = 6.5, 6.0 Hz, 2H), 3.84 (t, J = 6.0 Hz, 2H), 4.44 (s, 2H), 6.67 (~d, J = 8.0 Hz, 1H), 6.75-6.78 (m, 2H), and 7.09 (dt, J = 7.5, 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_4-MeOH) δ 26.13, 29.42, 29.45, 64.16, 67.92, 113.0, 113.4, 119.0, 129.4, 143.3, and 159.9; IR ($CHCl_3$) ν_{max} 2937, 2859, 1601, 1585, 1488, 1448, and 1264 cm^{-1}; MS (ESI) *m/z* (rel intensity) 381 (100%, MNa^+), 341 (20), and 323 (15); HRMS calcd for $C_{22}H_{30}NaO_4$ (MNa^+) 381.2042, found 381.2015; Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.49; H, 8.69.

1,10-Bis(3-hydroxymethylphenoxy)decane (36)

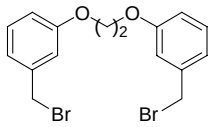


36

Following the general procedure described for the preparation of diol **34** (see main text), phenol **31** (14.3 g, 115 mmol) was reacted with 1,10-dibromodecane (17.3 g, 57.5 mmol) in the presence of 10 M NaOH (11.5 mL, 115 mmol) in EtOH (150 mL) for 18 h to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/EtOAc, 7/1), the title compound **36** (15.6 g, 70%) as a white solid: R_f = 0.75 (EtOAc/CH_2Cl_2, 1/1); mp 98.5-100.0 °C (Me_2CO/petroleum ether); ^{1}H NMR (250 MHz, d_4-MeOH) δ 1.17-1.37 (m, 6H), 1.64 (dt, J = 6.5, 6.5 Hz, 2H), 3.84 (t, J = 6.5 Hz, 2H), 4.44 (s, 2H), 6.67 (dd, J = 8.0, 2.5 Hz, 1H), 6.76 (dd, J = 7.5, 2.5 Hz, 1H), 6.78 (s, 1H), and 7.09 (dd, J = 8.0, 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, d_4-MeOH) δ 26.16, 29.42, 29.46, 29.62, 64.15, 67.93, 113.0, 113.4, 119.0, 129.3, 143.3, and 159.7;

IR ($CHCl_3$) ν_{max} 2932, 2857, 1601, 1585, 1488, 1448, and 1264 cm^{-1}; MS (ESI) *m/z* (rel intensity) 409 (100%, MNa^+) and 369 (10); HRMS calcd for $C_{24}H_{34}NaO_4$ (MNa^+) 409.2355, found 409.2346; Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.41; H, 9.08.

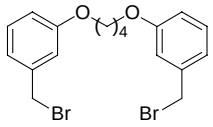
1,2-Bis(3-bromomethylphenoxy)ethane (37)



37

Following the general procedure described for the preparation of dibromide **39** (see main text), diol **32** (7.72 g, 28.1 mmol) was reacted with PBr_3 (3.5 mL, 37 mmol) in CH_2Cl_2 (150 mL) for 17 h to give, after purification by flash chromatography (CH_2Cl_2/petroleum ether, 1/1), the title compound **37** (8.03 g, 71%) as a white solid: R_f = 0.70 (petroleum ether/CH_2Cl_2, 1/1); mp 156.0-156.5 °C (CH_2Cl_2/petroleum ether); ^1H NMR (250 MHz, d_6-Me_2CO) δ 4.42 (s, 2H), 4.64 (s, 2H), 6.97 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 7.08 (dd, J = 7.5, 1.0 Hz, 1H), 7.13 (t, J = 2.5 Hz, 1H), and 7.32 (t, J = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, d_6-DMSO) δ 34.68, 66.68, 114.8, 115.7, 122.1, 130.2, 139.9, and 158.7; IR (KBr) ν_{max} 1595, 1489, 1446, 1263, 1210, and 1174 cm^{-1}; MS (ESI) *m/z* (rel intensity) 425 [50%, MNa^+ ($^{81}Br/^{81}Br$)], 423 [100%, MNa^+ ($^{79}Br/^{81}Br$)], and 421 [50%, MNa^+ ($^{79}Br/^{79}Br$)]; HRMS calcd for $C_{16}H_{16}(^{79}Br)(^{81}Br)NaO_2$ (MNa^+) 422.9395, found 422.9372; Anal. Calcd for $C_{16}H_{16}Br_2O_2$: C, 48.03; H, 4.03; Br, 39.94. Found: C, 48.20; H, 3.97; Br, 39.74.

1,4-Bis(3-bromomethylphenoxy)butane (38)

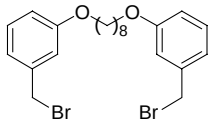


38

Following the general procedure described for the preparation of dibromide **39** (see main text), diol **33** (4.44 g, 14.7 mmol) was reacted with PBr_3 (1.8 mL, 19 mmol) in CH_2Cl_2 (100 mL) for 14 h to give, after purification by flash chromatography (CH_2Cl_2/petroleum ether, 1/1), the title compound **38** (4.72 g, 75%) as a white solid: R_f = 0.80 (EtOAc/petroleum ether, 1/1); mp 119.5-120.0 °C (EtOAc/petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 2.03-2.08 (m, 2H),

4.09-4.15 (m, 2H), 4.53 (s, 2H), 6.90 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 7.00 (dd, J = 2.5, 1.0 Hz, 1H), 7.03 (ddd, J = 9.0, 1.0, 1.0 Hz, 1H), and 7.31 (dd, J = 9.0, 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$) δ 26.40, 33.95, 67.90, 115.1, 115.5, 121.7, 130.2, 139.6, and 159.6; IR ($CHCl_3$) ν_{max} 1600, 1585, 1489, 1446, and 1264 cm^{-1}; MS (ESI) *m/z* (rel intensity) 453 [50%, MNa^+ ($^{81}Br/^{81}Br$)], 451 [100%, MNa^+ ($^{79}Br/^{81}Br$)], and 449 [50%, MNa^+ ($^{79}Br/^{79}Br$)]; HRMS calcd for $C_{18}H_{20}(^{79}Br)_2NaO_2$ (MNa^+) 448.9728, found 448.9695; Anal. Calcd for $C_{18}H_{20}Br_2O_2$: C, 50.49; H, 4.71; Br, 37.32. Found: C, 50.63; H, 4.77; Br, 37.09.

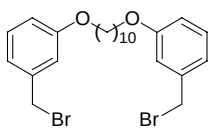
1,8-Bis(3-bromomethylphenoxy)octane (40)



40

Following the general procedure described for the preparation of dibromide **39** (see main text), diol **35** (7.16 g, 20.0 mmol) was reacted with PBr_3 (2.5 mL, 26 mmol) in CH_2Cl_2 (150 mL) for 21 h to give, after purification by flash chromatography (CH_2Cl_2/petroleum ether, 1/1), the title compound **40** (7.17 g, 74%) as a white solid: R_f = 0.85 (CH_2Cl_2/petroleum ether, 1/1); mp 86.0-87.0 °C (EtOAc/petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 1.32-1.43 (m, 4H), 1.67 (dt, J = 6.5, 6.5 Hz, 2H), 3.85 (t, J = 6.5 Hz, 2H), 4.35 (s, 2H), 6.72 (ddd, J = 7.5, 2.5, 1.0 Hz, 1H), 6.80-6.88 (m, 2H), and 7.13 (dd, J = 8.0, 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$) δ 26.41, 29.65, 29.71, 33.99, 68.40, 115.1, 115.5, 121.5, 130.2, 139.5, and 159.8; IR ($CHCl_3$) ν_{max} 2938, 2859, 1600, 1585, 1489, 1446, and 1266 cm^{-1}; MS (ESI) *m/z* (rel intensity) 509 [50%, MNa^+ ($^{81}Br/^{81}Br$)], 507 [100%, MNa^+ ($^{79}Br/^{81}Br$)], and 505 [50%, MNa^+ ($^{79}Br/^{79}Br$)]; HRMS calcd for $C_{22}H_{28}(^{79}Br)_2NaO_2$ (MNa^+) 505.0354, found 505.0324; Anal. Calcd for $C_{22}H_{28}Br_2O_2$: C, 54.56; H, 5.83; Br, 33.00. Found: C, 54.80; H, 5.82; Br, 32.76.

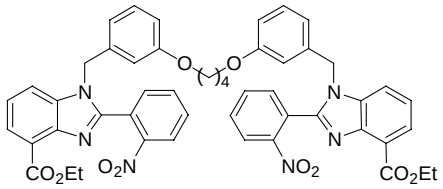
1,10-Bis(3-bromomethylphenoxy)decane (41)



41

Following the general procedure described for the preparation of dibromide **39** (see main text), diol **36** (7.45 g, 19.3 mmol) was reacted with PBr_3 (2.4 mL, 25 mmol) in CH_2Cl_2 (150 mL) for 18 h to give, after purification by flash chromatography (CH_2Cl_2/petroleum ether, 1/1), the title compound **41** (7.85 g, 79%) as a white solid: R_f = 0.85 (CH_2Cl_2/petroleum ether, 1/1); mp 88.5-90.0 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25-1.43 (m, 6H), 1.68 (dt, J = 6.5, 6.5 Hz, 2H), 3.85 (t, J = 6.5 Hz, 2H), 4.35 (s, 2H), 6.72 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 6.80-6.88 (m, 2H), and 7.13 (dd, J = 8.0, 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 26.46, 29.67, 29.79, 29.90, 34.00, 68.45, 115.1, 115.5, 121.5, 130.2, 139.5, and 159.8; IR ($CHCl_3$) ν_{max} 2932, 2857, 1600, 1585, 1489, 1446, and 1266 cm^{-1}; MS (ESI) *m/z* (rel intensity) 537 [50%, MNa^+ (^{81}Br/^{81}Br)], 535 [100%, MNa^+ (^{79}Br/^{81}Br)], and 533 [50%, MNa^+ (^{79}Br/^{79}Br)]; HRMS calcd for $C_{24}H_{32}(^{79}Br)_2NaO_2$ (MNa^+) 533.0667, found 533.0705; Anal. Calcd for $C_{24}H_{32}Br_2O_2$: C, 56.27; H, 6.30; Br, 31.19. Found: C, 56.48; H, 6.31; Br, 30.99.

1,4-Bis{3-[4-ethoxycarbonyl-2-(2-nitrophenyl)-benzimidazol-1-ylmethyl]phenoxy}butane (42)

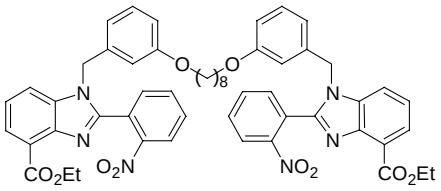


42

Following the general procedure described for the preparation of benzimidazole **43** (see main text), a solution of benzimidazole **11** (10.2 g, 32.7 mmol) in THF (180 mL) was reacted with NaH (60% w/w dispersion in mineral oil, 1.44 g, 36 mmol) at 0 °C for 30 min, and alkylated with dibromide **38** (7.00 g, 16.4 mmol) for 20 h at rt. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **42** (13.7 g, 94%) as a pale yellow solid: R_f = 0.30 (EtOAc); mp 173.5-175.0 °C (EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.44 (t, J = 7.0 Hz, 3H), 1.86 (s, 2H), 3.90 (s, 2H), 4.45 (q, J = 7.0 Hz, 2H), 5.27 (s, 2H), 6.59 (s, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.81 (dd, J = 8.0, 2.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.60-7.63 (m, 1H), 7.73-7.78 (m, 2H), 7.97 (dd, J = 7.5, 0.5 Hz, 1H), and 8.22-8.26 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ 14.99, 26.56, 49.19, 61.59, 68.27, 113.6, 114.7, 115.9, 119.6, 123.1, 123.2, 125.7, 125.9, 126.5, 130.7, 132.1, 133.5, 134.3, 137.1, 137.7, 142.9, 149.6, 152.2, 160.3, and 166.4; IR ($CHCl_3$) ν_{max} 1716, 1604,

1534, 1451, 1428, 1346, and 1282 cm^{-1}; MS (ESI) *m/z* (rel intensity) 911 (5%, MNa^+) and 889 (100); HRMS calcd for $C_{50}H_{45}N_6O_{10}$ (MH^+) 889.3197, found 889.3209; Anal. Calcd for $C_{50}H_{44}N_6O_{10}$: C, 67.56; H, 4.99; N, 9.45. Found: C, 67.46; H, 5.06; N, 9.34.

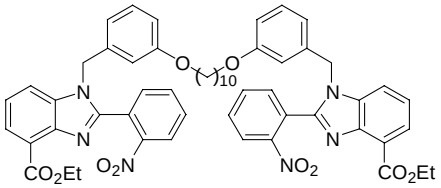
1,8-Bis{3-[4-ethoxycarbonyl-2-(2-nitrophenyl)-benzimidazol-1-ylmethyl]phenoxy}octane (44)



44

Following the general procedure described for the preparation of benzimidazole **43** (see main text), a solution of benzimidazole **11** (4.98 g, 16.0 mmol) in THF (80 mL) was reacted with NaH (60% w/w dispersion in mineral oil, 704 mg, 17.6 mmol) at 0 °C for 30 min, and alkylated with dibromide **40** (3.87 g, 8.00 mmol) for 14 h at rt. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **44** (6.93 g, 92%) as a pale yellow solid: R_f = 0.40 (EtOAc); mp 82.0-84.0 °C (CH_2Cl_2/petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 1.21-1.33 (m, 4H), 1.29 (t, J = 7.0 Hz, 3H), 1.54-1.60 (m, 2H), 3.69 (t, J = 6.5 Hz, 2H), 4.34 (q, J = 7.0 Hz, 2H), 5.07 (s, 2H), 6.40-6.46 (m, 2H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.30 (dd, J = 8.0, 1.0 Hz, 1H), 7.43-7.58 (m, 3H), 7.83 (dd, J = 7.5, 1.0 Hz, 1H), and 8.03-8.11 (m, 1H); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$) δ 14.81, 26.32, 29.51, 29.64, 48.87, 61.34, 68.35, 113.2, 114.4, 115.4, 119.0, 122.7, 122.9, 125.2, 125.6, 126.4, 130.4, 131.6, 133.5, 133.7, 136.6, 137.2, 142.7, 149.3, 151.9, 160.0, and 166.2; IR ($CHCl_3$) ν_{max} 1716, 1603, 1534, 1453, 1429, 1396, 1346, and 1282 cm^{-1}; MS (ESI) *m/z* (rel intensity) 945 (100%, MH^+); HRMS calcd for $C_{54}H_{53}N_6O_{10}$ (MH^+) 945.3825, found 945.3846; Anal. Calcd for $C_{54}H_{52}N_6O_{10}$: C, 68.63; H, 5.55; N, 8.89. Found: C, 68.38; H, 5.50; N, 8.89.

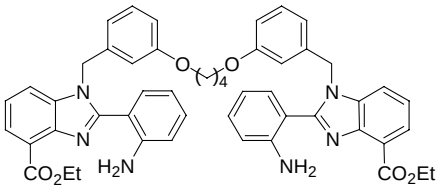
1,10-Bis{3-[4-ethoxycarbonyl-2-(2-nitrophenyl)-benzimidazol-1-ylmethyl]phenoxy}decane (45)



45

Following the general procedure described for the preparation of benzimidazole **43** (see main text), a solution of benzimidazole **11** (2.96 g, 9.53 mmol) in THF (70 mL) was reacted with NaH (60% w/w dispersion in mineral oil, 420 mg, 10.5 mmol) at 0 °C for 30 min, and alkylated with dibromide **41** (2.44 g, 4.77 mmol) for 20 h at rt. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **45** (4.32 g, 93%) as a pale yellow solid: R_f = 0.40 (EtOAc); mp 101.0-103.0 °C (EtOAc/petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17-1.39 (m, 6H), 1.30 (t, J = 7.0 Hz, 3H), 1.52-1.62 (m, 2H), 3.69 (t, J = 6.5 Hz, 2H), 4.34 (q, J = 7.0 Hz, 2H), 5.07 (s, 2H), 6.40-6.45 (m, 2H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 7.02 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.30 (dd, J = 8.0, 1.0 Hz, 1H), 7.41-7.58 (m, 3H), 7.84 (~dd, J = 7.5, 1.0 Hz, 1H), and 8.04-8.11 (m, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.81, 26.38, 29.54, 29.74, 29.85, 48.87, 61.33, 68.40, 113.2, 114.4, 115.4, 118.9, 122.7, 122.9, 125.2, 125.6, 126.4, 130.4, 131.6, 133.5, 133.7, 136.6, 137.2, 142.7, 149.3, 151.9, 160.0, and 166.2; IR ($CHCl_3$) ν_{max} 1716, 1604, 1534, 1453, 1429, 1346, and 1282 cm^{-1}; MS (ESI) *m/z* (rel intensity) 973 (100%, MH^+); HRMS calcd for $C_{56}H_{57}N_6O_{10}$ (MH^+) 973.4136, found 973.4114; Anal. Calcd for $C_{56}H_{56}N_6O_{10}$: C, 69.12; H, 5.80; N, 8.64. Found: C, 69.02; H, 5.79; N, 8.63.

1,4-Bis{3-[2-(2-aminophenyl)-4-ethoxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}butane (46)

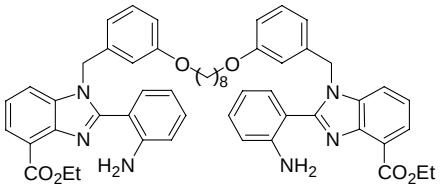


46

Following the general procedure described for the preparation of benzimidazole **47** (see main text), nitroarene **42** (2.20 g, 2.47 mmol) was reacted with $SnCl_2$ (4.70 g, 24.7 mmol) in

boiling EtOH (70 mL) for 45 min to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc), the title compound **46** (1.95 g, 95%) as a yellow foam: R_f = 0.65 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 1.72 (s, 2H), 3.76 (s, 2H), 4.37 (q, J = 7.0 Hz, 2H), 5.28 (s, 4H), 6.47-6.70 (m, 5H), 7.00-7.14 (m, 4H), 7.23 (dd, J = 8.0, 1.0 Hz, 1H), and 7.84 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.91, 26.25, 49.15, 61.29, 67.81, 112.6, 112.8, 114.2, 115.3, 117.3, 117.4, 118.6, 121.6, 122.5, 125.7, 129.8, 130.6, 131.5, 137.0, 138.2, 142.2, 148.5, 154.8, 160.0, and 166.8; IR ($CHCl_3$) ν_{max} 1708, 1617, 1586, 1488, 1447, 1428, 1384, 1290, and 1251 cm^{-1}; MS (ESI) *m/z* (rel intensity) 851 (20%, MNa^+) and 829 (100); HRMS calcd for $C_{50}H_{49}N_6O_6$ (MH^+) 829.3713, found 829.3708.

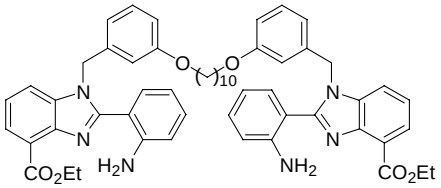
1,8-Bis{3-[2-(2-aminophenyl)-4-ethoxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}octane (48)



48

Following the general procedure described for the preparation of benzimidazole **47** (see main text), nitroarene **44** (1.71 g, 1.81 mmol) was reacted with $SnCl_2$ (3.43 g, 18.1 mmol) in boiling EtOH (60 mL) for 45 min to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc), the title compound **48** (1.54 g, 96%) as a yellow foam: R_f = 0.75 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.10-1.22 (m, 4H), 1.32 (t, J = 7.0 Hz, 3H), 1.52-1.59 (m, 2H), 3.69 (t, J = 6.0 Hz, 2H), 4.36 (q, J = 7.0 Hz, 2H), 5.24 (s, 2H), 5.50 (br s, 2H), 6.44-6.68 (m, 5H), 6.98-7.14 (m, 4H), 7.20 (d, J = 7.5 Hz, 1H), and 7.84 (d, J = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.93, 26.34, 29.55, 29.66, 49.13, 61.27, 68.33, 112.6, 112.7, 114.2, 115.3, 117.3, 118.4, 121.5, 122.5, 125.7, 129.8, 130.6, 131.0, 131.5, 137.0, 138.2, 142.2, 148.6, 154.9, 160.2, and 166.8; IR ($CHCl_3$) ν_{max} 1707, 1617, 1602, 1488, 1449, 1428, 1290, 1265, and 1251 cm^{-1}; MS (ESI) *m/z* (rel intensity) 885 (100%, MH^+); HRMS calcd for $C_{54}H_{57}N_6O_6$ (MH^+) 885.4339, found 885.4334.

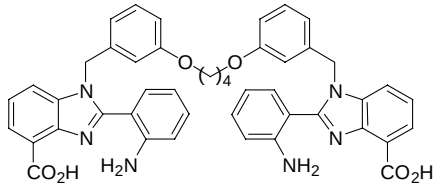
1,10-Bis{3-[2-(2-aminophenyl)-4-ethoxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}decane (49)



49

Following the general procedure described for the preparation of benzimidazole **47** (see main text), nitroarene **45** (4.32 g, 4.44 mmol) was reacted with $SnCl_2$ (8.42 g, 44.4 mmol) in boiling EtOH (70 mL) for 45 min to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc), the title compound **49** (3.76 g, 93%) as a yellow foam: R_f = 0.80 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29-1.52 (m, 6H), 1.50 (t, J = 7.0 Hz, 3H), 1.74 (dt, J = 6.5, 6.5 Hz, 2H), 3.87 (t, J = 6.5 Hz, 2H), 4.52 (q, J = 7.0 Hz, 2H), 5.45 (s, 2H), 5.56 (br s, 2H), 6.63-6.72 (m, 3H), 6.83-6.87 (m, 2H), 7.18-7.30 (m, 4H), 7.39 (dd, J = 8.0, 1.0 Hz, 1H), and 8.00 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.90, 26.39, 29.58, 29.75, 29.85, 49.22, 61.27, 68.41, 112.5, 112.8, 114.2, 115.2, 117.3, 117.4, 118.4, 121.6, 122.5, 125.7, 129.9, 130.6, 131.5, 137.0, 138.1, 142.2, 148.5, 154.8, 160.2, and 166.8; IR ($CHCl_3$) ν_{max} 1707, 1617, 1602, 1488, 1449, 1428, 1290, 1265, and 1251 cm^{-1}; MS (ESI) *m/z* (rel intensity) 913 (100%, MH^+); HRMS calcd for $C_{56}H_{61}N_6O_6$ (MH^+) 913.4652, found 913.4649.

1,4-Bis{3-[2-(2-aminophenyl)-4-hydroxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}butane (50)

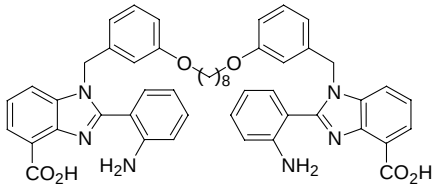


50

Following the general procedure described for the preparation of amino acid **51** (see main text), ester **46** (1.95 g, 2.35 mmol) was reacted with 1 M LiOH (14 mL, 14 mmol) in THF (60 mL) for 20 h to give, after neutralization with 1M HCl, the title compound **50** (1.66 g, 92%) as a yellow powder, which was used in the next step without any further purification. Amino acid **50**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.74 (s, 2H), 3.87 (s, 2H), 5.49 (s, 2H), 5.89 (br s, 2H), 6.54-

6.67 (m, 3H), 6.77 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), and 7.84 (d, J = 7.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, d_6-DMSO) δ 25.60, 48.11, 67.35, 112.0, 113.1, 114.0, 116.0, 116.3 (2 × C?), 118.9, 120.3, 122.7, 124.7, 130.2, 130.5, 131.6, 136.0, 138.3, 141.8, 148.3, 154.1, 159.1, and 166.8; IR (KBr) ν_{max} 1730, 1609, 1487, 1434, 1386, and 1258 cm^{-1}; MS (ESI) *m/z* (rel intensity) 795 (20%, MNa^+) and 773 (100); HRMS calcd for $C_{46}H_{40}N_6NaO_6$ (MNa^+) 795.2907, found 795.2894.

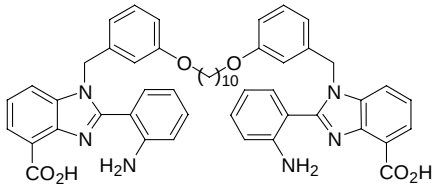
1,8-Bis{3-[2-(2-aminophenyl)-4-hydroxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}octane (52)



52

Following the general procedure described for the preparation of amino acid **51** (see main text), ester **48** (1.54 g, 1.74 mmol) was reacted with 1 M LiOH (11 mL, 11 mmol) in THF (45 mL) for 15 h to give, after neutralization with 1M HCl, the title compound **52** (1.35 g, 94%) as a yellow powder. The crude product could be used in the subsequent step without further purification. Amino acid **52**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.15-1.36 (m, 4H), 1.52-1.66 (m, 2H), 3.81 (t, J = 6.5 Hz, 2H), 5.50 (s, 2H), 6.05 (br s, 2H), 6.57-6.63 (m, 2H), 6.65 (t, J = 7.5 Hz, 1H), 6.76 (dd, J = 7.5, 2.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.24 (dt, J = 8.5, 1.0 Hz, 1H), 7.29 (dd, J = 7.5, 1.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), and 7.86 (d, J = 7.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, d_6-DMSO) δ 25.75, 28.87, 29.03, 48.18, 67.66, 111.8, 113.0, 114.1, 116.0, 116.3, 116.4, 118.8, 120.2, 122.8, 124.8, 130.2, 130.6, 131.7, 135.9, 138.2, 141.4, 148.3, 154.0, 159.2, and 166.7; IR (KBr) ν_{max} 1741, 1610, 1488, 1433, 1388, and 1260 cm^{-1}; MS (ESI) *m/z* (rel intensity) 851 (100%, MNa^+) and 829 (100); HRMS calcd for $C_{50}H_{48}N_6NaO_6$ (MNa^+) 851.3533, found 851.3529.

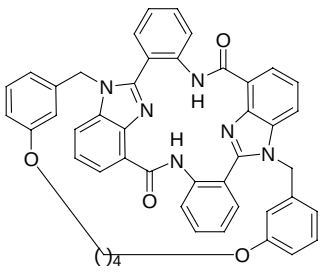
1,10-Bis{3-[2-(2-aminophenyl)-4-hydroxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}decane (53)



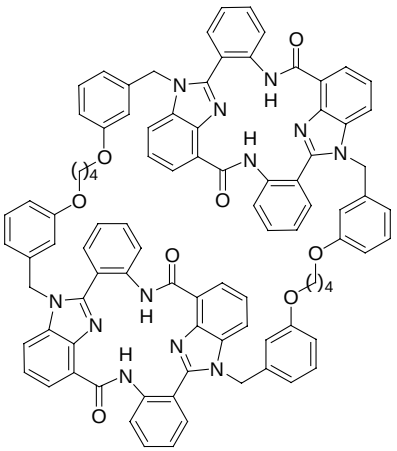
53

Following the general procedure described for the preparation of amino acid **51** (see main text), ester **49** (3.76 g, 4.12 mmol) was reacted with 1 M LiOH (25 mL, 25 mmol) in THF (100 mL) for 16 h to give, after neutralization with 1M HCl, the title compound **53** (3.30 g, 94%) as a yellow powder. The crude product could be used in the subsequent step without further purification. Amino acid **53**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.15-1.39 (m, 6H), 1.54-1.63 (m, 2H), 3.82 (t, J = 6.5 Hz, 2H), 5.49 (s, 2H), 5.92 (br s, 2H), 6.56-6.61 (m, 2H), 6.64 (dt, J = 7.5, 0.5 Hz, 1H), 6.77 (dd, J = 7.5, 2.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.24 (dt, J = 7.0, 1.5 Hz, 1H), 7.27 (dd, J = 7.5, 1.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.77 (dd, J = 8.0, 0.5 Hz, 1H), and 7.84 (dd, J = 7.0, 0.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO) δ 25.77, 28.87, 29.06, 29.24, 48.12, 67.66, 111.9, 113.0, 114.1, 116.0, 116.3 (2 × C), 118.8, 120.6, 122.7, 124.7, 130.2, 130.5, 131.6, 136.0, 138.2, 141.6, 148.3, 154.0, 159.2, and 166.7; IR (KBr) ν_{max} 1741, 1610, 1488, 1433, 1387, and 1260 cm^{-1}; MS (ESI) *m/z* (rel intensity) 857 (100%, MH$^+$); HRMS calcd for $C_{52}H_{52}N_6NaO_6$ (MNa$^+$) 879.3846, found 879.3843.

Monomer (54) and Dimer (58)



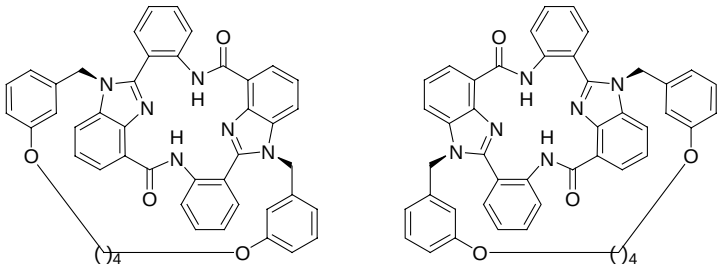
54



58

Following the general procedure described for the preparation of monomer **55** and dimer **59** (see main text), amino acid **50** (3.12 g, 4.19 mmol), BOP (4.10 g, 9.21 mmol), and NMM (2.5 mL, 23 mmol) in CH_2Cl_2 (1000 mL) were reacted for 8 days at rt. Standard workup, followed by purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 20/1), gave the title compound **54** (470 mg, 15%) and **58** (320 mg, 10%) as white powders. Monomer **54**: R_f = 0.65 (CH_2Cl_2/EtOAc, 5/1); mp > 260 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04-0.09 (m, 1H), 0.23-0.31 (m, 1H), 2.91-3.04 (m, 2H), 5.22 (s, 1H), 5.38 and 5.77 (ABq, J = 16.0 Hz, 2H), 6.58 (dd, J = 8.0, 2.0 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.23-7.29 (m, 2H), 7.39 (ddd, J = 8.0, 8.0, 0.5 Hz, 1H), 7.56 (dd, J = 7.5, 1.5 Hz, 1H), 7.62 (ddd, J = 8.5, 8.5, 1.5 Hz, 1H), 8.13-8.17 (m, 2H), and 12.1 (s, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 24.07, 49.30, 66.45, 109.9, 116.1, 117.6, 118.8, 122.4, 123.4, 123.5, 125.4, 125.7, 128.5, 130.2, 130.6, 131.5, 135.5, 137.0, 137.7, 140.9, 154.0, 158.4, and 163.9; IR (KBr) ν_{max} 1678, 1606, 1533, 1520, 1475, 1382, 1302, and 1243 cm^{-1}; MS (ESI) *m/z* (rel intensity) 759 (65%, MNa^+) and 737 (100); HRMS calcd for $C_{46}H_{36}N_6NaO_4$ (MNa^+) 759.2696, found 759.2677; Anal. Calcd for $C_{46}H_{36}N_6O_4$: C, 74.98; H, 4.92; N, 11.41. Found: C, 75.05; H, 4.93; N, 11.41. Monomer **54** was optically resolved by analytical CSP HPLC (Figure S6). Dimer **58**: R_f = 0.65 (CH_2Cl_2/EtOAc, 2/1); mp > 260 °C (EtOAc); IR (KBr) ν_{max} 1676, 1605, 1528, 1534, 1516, 1382, 1302, and 1247 cm^{-1}; MS (ESI) *m/z* (rel intensity) 1495 (20%, MNa^+) and 1474 (100); HRMS calcd for $C_{92}H_{73}N_{12}O_8$ (MH^+) 1473.5674, found 1473.5668; Anal. Calcd for $C_{92}H_{76}N_{12}O_{10}$ ($M{\cdot}2H_2O$): C, 73.19; H, 5.07; N, 11.13. Found: C, 73.47; H, 5.07; N, 10.85.

Optical resolution of the strapped cyclic amide (54)

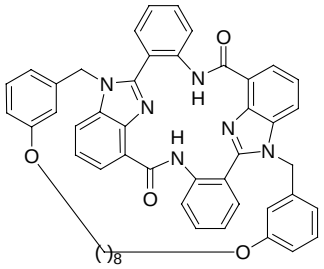


(±)-54

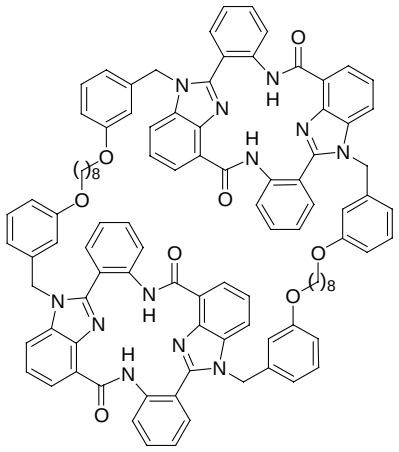
The enantiomers of the strapped cyclic amide **54** were separated using semi-preparative CSP HPLC (Chiralcel OD column, 1.0 cm × 25 cm; 2-propanol/hexanes, 40/60; 4 ml min^{-1}, 40 °C). UV detection was performed at 254 nm. Injections of ~0.16 mg of the racemate in 30 μL of

CH_2Cl_2 were made every 23 min. The fast-eluting enantiomer was collected between 13.6 and 17.4 min, and the slow-eluting enantiomer was collected between 18.9 and 26.0 min. The collected products were enantiomerically pure (ee > 99.9% and 99.4%, respectively) by analytical CSP HPLC, and were used in the subsequent racemization studies (see Table 2, main text).

Monomer (56) and Dimer (60)



56

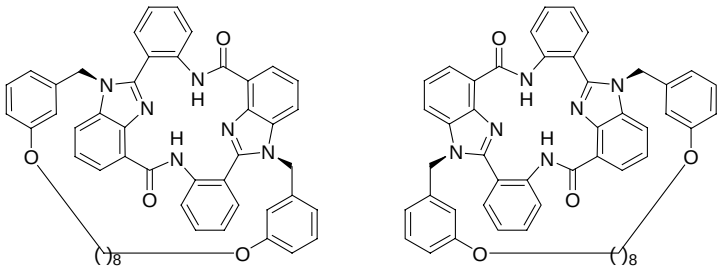


60

Following the general procedure described for the preparation of monomer **55** and dimer **59** (see main text), amino acid **52** (4.15 g, 5.00 mmol), BOP (4.86 g, 11.0 mmol), and NMM (2.4 mL, 22 mmol) in CH_2Cl_2 (1000 mL) were reacted for 7 days at rt. Standard workup, followed by purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 20/1), gave the title compound **56** (673 mg, 17%) and **60** (515 mg, 13%) as white powders. Monomer **56**: R_f = 0.70 (CH_2Cl_2/EtOAc, 5/1); mp > 260 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-1.01 (m, 2H), 1.30-1.69 (m, 2H), 3.51-3.58 (m, 1H), 3.69-3.74 (m, 1H), 5.27 and 5.78 (ABq, J = 15.5 Hz, 2H), 6.17 (s, 1H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.37 (dt, J = 7.5, 1.0 Hz, 1H), 7.46 (dd, J = 8.0, 1.0 Hz, 1H), 7.55 (dd, J = 8.0, 1.5 Hz, 1H), 7.60 (dt, J = 8.5, 1.5 Hz, 1H), 8.18 (dd, J = 7.5, 1.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), and 12.1 (s, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 25.67, 28.73, 28.78, 49.70, 67.46, 113.0, 115.7, 115.8, 119.9, 122.3, 123.1, 123.6, 125.3 (2 × C?) 128.0, 130.2, 130.6, 131.3, 135.5, 136.5, 137.9, 141.0, 152.6, 159.8, and 163.9; IR (KBr) ν_{max} 1667, 1607, 1583, 1531, 1477, 1426, 1383, 1301, and 1245 cm^{-1}; MS (ESI) *m/z* (rel intensity) 793 (100%, MH^+); HRMS calcd for $C_{50}H_{44}N_6NaO_4$ (MNa^+) 815.3322, found 815.3323; Anal. Calcd for $C_{50}H_{48}N_6O_6$ (M·2H_2O): C,

72.45; H, 5.84; N, 10.14. Found: C, 72.54; H, 5.59; N, 9.81. Monomer **56** was optically resolved by analytical CSP HPLC (Figure S8). Dimer **60**: R_f = 0.60 (CH_2Cl_2/EtOAc, 5/1); mp > 260 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.30 (m, 4H), 1.50-1.62 (m, 2H), 3.64-3.71 (m, 2H), 5.28 and 5.34 (ABq, J = 16.5 Hz, 2H), 6.34 and 6.37 (2 × s, 1H), 6.59-6.60 (m, 1H), 6.69 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.37 (dt, J = 7.5, 1.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.08-7.29 (m, 5H), 7.42-7.47 (m, 1H), 8.00-8.10 (m, 2H), and 12.0 (2 × s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 24.38, 27.57, 27.67, 27.70, 47.35, 66.35, 110.5 (2 × C), 112.7, 113.5, 116.7, 116.8, 120.5 (2 × C), 121.6, 121.7, 123.3, 123.4, 126.4, 128.1, 128.6, 128.7, 129.4, 134.1, 135.6, 135.7, 138.9, 150.7, 150.8, 158.3 (2 × C), and 162.3; IR (KBr) ν_{max} 1672, 1608, 1583, 1533, 1478, 1427, 1385, 1303, and 1246 cm^{-1}; MS (ESI) *m/z* (rel intensity) 1586 (100%, MH^+); HRMS calcd for $C_{100}H_{88}N_{12}NaO_8$ (MNa^+) 1607.6746, found 1607.6760; Anal. Calcd for $C_{100}H_{90}N_{12}O_9$ ($M{\cdot}H_2O$): C, 74.89; H, 5.66; N, 10.48. Found: C, 74.93; H, 5.74; N, 10.29.

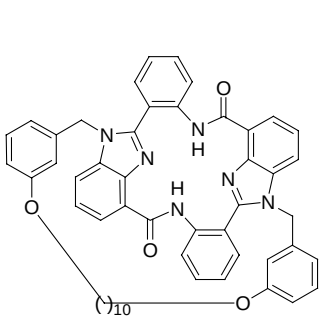
Optical resolution of the strapped cyclic amide (56)



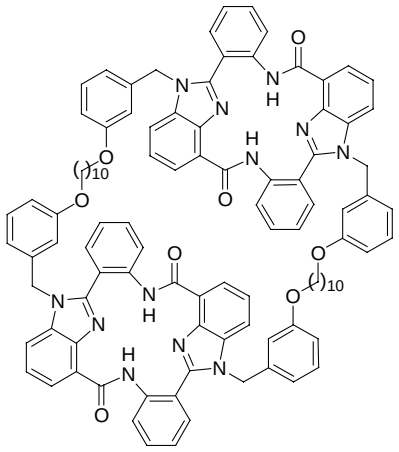
(±)-56

The enantiomers of the strapped cyclic amide **56** were separated using semi-preparative CSP HPLC (Chiralcel OD column, 1.0 cm × 25 cm; 2-propanol/hexanes, 50/50; 4 ml min^{-1}, 40 °C). UV detection was performed at 254 nm. Injections of ~1.3 mg of the racemate in 50 μL of CH_2Cl_2 were made every 22 min. The fast-eluting enantiomer was collected between 8.1 and 11.7 min, and the slow-eluting enantiomer was collected between 14.4 and 21.0 min. The collected products were enantiomerically pure (ee > 99.9% and 99.7%, respectively) by analytical CSP HPLC, and were used in the subsequent racemization studies (see Table 2).

Monomer (57) and Dimer (61)



57

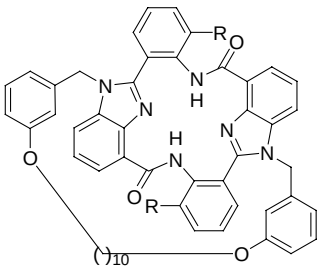


61

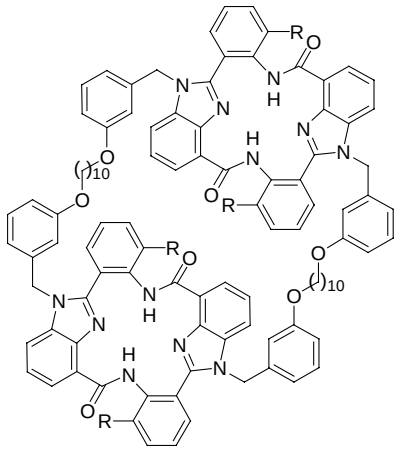
Following the general procedure described for the preparation of monomer **55** and dimer **59** (see main text), amino acid **53** (2.57 g, 3.00 mmol), BOP (2.92 g, 6.6 mmol), and NMM (1.45 mL, 13.2 mmol) in CH_2Cl_2 (320 mL) were reacted for 7 days at rt. Standard workup, followed by purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 20/1), gave the title compound **57** (547 mg, 22%) and **61** (329 mg, 13%) as white powders. Monomer **57**: R_f = 0.75 (CH_2Cl_2/EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.27 (m, 6H), 1.58-1.72 (m, 2H), 3.63-3.69 (m, 1H), 3.79-3.84 (m, 1H), 5.18 and 5.72 (ABq, J = 15.0 Hz, 2H), 6.43 (s, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.63 (dd, J = 8.0, 2.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.39 (dt, J = 7.5, 1.0 Hz, 1H), 7.52-7.57 (m, 2H), 7.63 (dt, J = 8.5, 1.5 Hz, 1H), 8.14 (dd, J = 7.5, 1.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), and 12.0 (s, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 26.02, 29.21, 29.33, 29.45, 49.57, 67.77, 114.1, 115.2, 115.4, 120.4, 122.7, 123.2, 123.7, 125.0, 125.4, 128.2, 130.5 (2 × C), 131.3, 135.5, 136.5, 138.0, 141.0, 152.1, 159.6, and 163.9; IR (KBr) ν_{max} 1671, 1607, 1534, 1478, 1426, 1382, 1303, and 1244 cm^{-1}; MS (ESI) *m/z* (rel intensity) 821 (100%, MH^+); HRMS calcd for $C_{52}H_{48}N_6NaO_4$ (MNa^+) 843.3635, found 843.3622; Anal. Calcd for $C_{52}H_{49}N_6O_{4.5}$ (M·0.5H_2O): C, 75.25; H, 5.95; N, 10.13. Found: C, 75.10; H, 6.03; N, 9.97. Dimer **61**: R_f = 0.65 (CH_2Cl_2/EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.48 (m, 6H), 1.63-1.70 (m, 2H), 3.80 (~t, J = 6.0 Hz, 1H), 5.41 (~s, 2H), 6.50 (s, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.79 (dd, J = 8.0, 2.0 Hz, 1H), 7.19-7.40 (m, 5H), 7.55 (m, 1H), 8.13 (dd, J = 8.0, 4.0 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), and 12.1 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 26.35, 29.51, 29.70, 29.77, 49.26, 68.34, 112.5, 114.5, 115.4, 118.6, 122.5, 123.5, 123.7, 125.2, 125.4,

128.3, 130.0, 130.6, 131.3, 136.1, 137.5 (2 × C) 137.6, 140.8, 152.7, 160.2, and 164.3; IR (KBr) ν_{max} 1673, 1607, 1583, 1533, 1478, 1426, 1384, 1302, and 1247 cm^{-1}; MS (ESI) *m/z* (rel intensity) 1642 (100%, MH^+); HRMS calcd for $C_{104}H_{96}N_{12}NaO_8$ (MNa^+) 1663.7372, found 1663.7404; Anal. Calcd for $C_{104}H_{96}N_{12}O_8$: C, 76.07; H, 5.89; N, 10.24. Found: C, 75.63; H, 5.97; N, 10.08.

Monomer (66) and Dimer (69)



66: R = Me

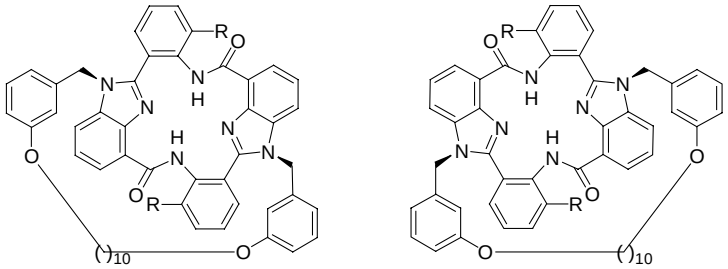


69: R = Me

Following the general procedure described for the preparation of monomer **55** and dimer **59** (see main text), amino acid **63** (442 mg, 0.5 mmol), BOP (486 mg, 1.1 mmol), and NMM (296 μL, 2.7 mmol) in CH_2Cl_2 (100 mL) were reacted for 7 days at rt. Standard workup, followed by purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 20/1), gave the title compound **66** (96 mg, 23%) and **69** (41 mg, 10%) as white powders. Monomer **66**: R_f = 0.85 (CH_2Cl_2/EtOAc, 5/1); mp > 260 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05-1.30 (m, 6H), 1.60-1.75 (m, 2H), 2.53 (s, 3H), 3.66-3.72 (m, 1H), 3.86-3.92 (m, 1H), 5.14 and 5.80 (ABq, J = 15.0 Hz, 2H), 6.48 (s, 1H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.40-7.57 (m, 4H), 8.13 (d, J = 7.5 Hz, 1H), and 12.4 (s, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 19.93, 26.06, 29.29, 29.46, 29.59, 49.83, 67.73, 114.1, 115.5, 115.6, 120.7, 122.8, 122.9, 124.8, 126.1, 126.9, 128.1, 130.5, 133.7, 135.4, 136.5, 136.9, 139.5, 141.2, 152.4, 159.5, and 163.0; IR (KBr) ν_{max} 1670, 1607, 1527, 1469, 1384, 1294, and 1253 cm^{-1}; MS (ESI) *m/z* (rel intensity) 849 (100%, MH^+); HRMS calcd for $C_{54}H_{52}N_6NaO_4$ (MNa^+) 871.3948, found 871.3931. Monomer **66** was optically resolved by analytical CSP HPLC (Figure S10). Dimer **69**: R_f = 0.65 (CH_2Cl_2/EtOAc, 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ

1.25-1.43 (m, 6H), 1.66-1.73 (m, 2H), 2.50 (s, 3H), 3.82-3.90 (m, 2H), 5.40-5.45 (m, 2H), 6.59 (s, 1H), 6.68 (d, J = 6.5 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.22-7.30 (m, 4H), 7.35 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 6.5 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), and 12.4 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 19.82, 26.33, 29.50, 29.67, 29.73, 49.24, 68.32, 112.7 (2 × C), 114.2, 114.3, 115.3, 118.6, 122.9, 123.1, 124.9, 125.6, 126.7, 127.6, 130.6, 133.7, 135.9, 136.4, 137.6, 139.2, 141.0, 160.1, and 163.2; IR (KBr) ν_{max} 1672, 1605, 1527, 1470, 1451, 1382, 1342, 1294, and 1255 cm^{-1}; MS (ESI) *m/z* (rel intensity) 1698 (100%, MH^+); HRMS calcd for $C_{108}H_{105}N_{12}O_8$ (MH^+) 1697.8178, found 1697.8154; Anal. Calcd for $C_{108}H_{104}N_{12}O_8$: C, 76.39; H, 6.17; N, 9.90. Found: C, 75.98; H, 6.18; N, 9.84. Dimer **69** was optically resolved by analytical CSP HPLC (Figure S11).

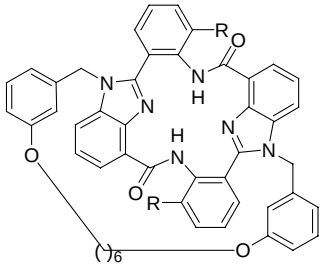
Optical resolution of the strapped cyclic amide (66)



(±)-66: R = Me

The enantiomers of the strapped cyclic amide **66** were separated using semi-preparative CSP HPLC (Chiralcel OD column, 1.0 cm × 25 cm; 2-propanol/hexanes, 30/70; 4 ml min^{-1}, 40 °C). UV detection was performed at 254 nm. Injections of ~1.0 mg of the racemate in 100 μL of CH_2Cl_2 were made every 32 min. The fast-eluting enantiomer was collected between 3.4 and 10.0 min, and the slow-eluting enantiomer was collected between 15.9 and 25.0 min. The collected products were enantiomerically pure (ee > 99.9% and 99.7%, respectively) by analytical CSP HPLC, and were used in the subsequent racemization studies (see Table 2).

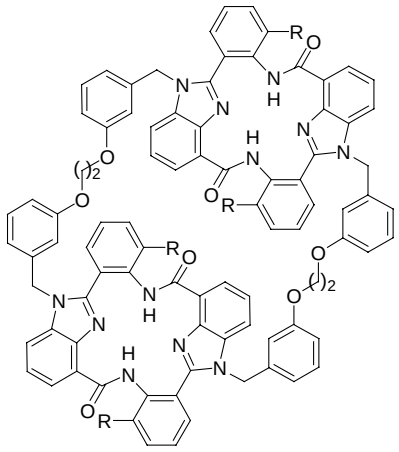
Monomer (67)



67: R = Me

Following the general procedure described for the preparation of monomer **55** and dimer **59** (see main text), amino acid **64** (3.00 g, 3.62 mmol), BOP (3.52 g, 7.96 mmol), and NMM (1.75 mL, 15.9 mmol) in CH_2Cl_2 (400 mL) were reacted for 9 days at rt. Standard workup, followed by purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 20/1), gave the title compound **67** (45 mg, 1.6%) as a white powder: R_f = 0.4 (CH_2Cl_2/EtOAc, 10/1); mp > 260 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18-0.44 (m, 4H), 2.46 (s, 3H), 3.43-3.59 (m, 2H), 5.26 and 5.92 (ABq, J = 15.5 Hz, 2H), 5.76 (s, 1H), 6.65 (dd, J = 8.0, 2.0 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 7.15-7.21 (m, 3H), 7.43 (t, J = 7.5 Hz, 1H), 7.47 (dd, J = 7.5, 1.5 Hz, 1H), 7.52 (~d, J = 7.5 Hz, 1H), 8.08 (dd, J = 6.5, 2.0 Hz, 1H), and 12.6 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 19.82, 24.98, 27.62, 49.84, 66.96, 110.8, 115.9, 117.5, 119.2, 122.7, 122.9, 124.9, 125.6, 126.8, 128.1, 130.0, 133.8, 135.2, 136.6, 136.8, 139.4, 141.0, 153.0, 159.4, and 162.9; IR (KBr) ν_{max} 1668, 1605, 1529, 1470, 1382, 1296, and 1254 cm^{-1}; MS (ESI) *m/z* (rel intensity) 793 (100%, MH^+); HRMS calcd for $C_{50}H_{44}N_6NaO_4$ (MNa^+) 815.3322, found 815.3317; Anal. Calcd for $C_{50}H_{44}N_6O_4$: C, 75.74; H, 5.59; N, 10.60. Found: C, 75.48; H, 5.60; N, 10.48.

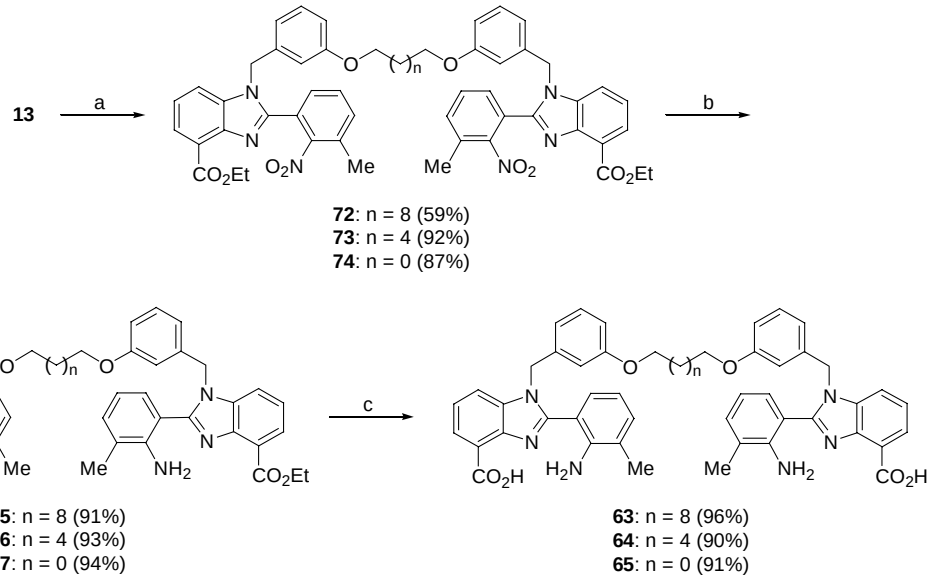
Dimer (71)



71: R = Me

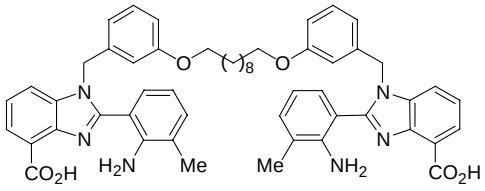
Following the general procedure described for the preparation of monomer **55** and dimer **59** (see main text), amino acid **65** (2.24 g, 2.90 mmol), BOP (2.82 g, 6.38 mmol), and NMM (1.4 mL, 12.8 mmol) in CH_2Cl_2 (200 mL) were reacted for 8 days at rt. Standard workup, followed by purification by flash chromatography (silica gel, CH_2Cl_2 → CH_2Cl_2/MeOH, 20/1), gave the title compound **71** (232 mg, 11%) as a white powder: R_f = 0.25 (CH_2Cl_2/EtOAc, 5/1); mp > 260 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.91 and 4.22 (ABq, J = 8.0 Hz, 2H), 5.39 and 5.55 (ABq, J = 16.0 Hz, 2H), 6.43 (s, 1H), 6.76 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.87 (dd, J = 8.0, 2.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 6.5 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), and 12.5 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 19.83, 49.57, 67.08, 113.1, 114.4, 115.3, 119.4, 122.8, 122.9, 124.9, 125.6, 126.9, 127.7, 130.5, 133.8, 135.5, 136.6, 137.2, 139.4, 141.1, 152.7, 159.9, and 163.2; IR (KBr) ν_{max} 1731, 1672, 1606, 1529, 1470, 1383, 1294, and 1255 cm^{-1}; MS (ESI) *m/z* (rel intensity) 1496 (100%, MNa^+); HRMS calcd for $C_{92}H_{72}N_{12}NaO_8$ (MNa^+) 1495.5495, found 1495.5521.

Scheme S1. Synthesis of Amino Acids **63-65**.[a]



[a] Reagents and conditions: (a) NaH, THF, 0 °C → rt (for **72**) and 50 °C (for **73** and **74**), 16-24 h; (b) $SnCl_2$, EtOH, reflux, 45-60 min; (c) LiOH, THF, H_2O, rt, 16-20 h.

1,10-Bis{3-[2-(2-amino-3-methylphenyl)-4-hydroxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}decane (63)

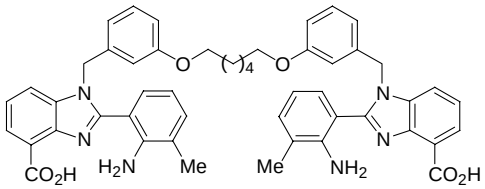


63

Following the general procedure described for the preparation of amino acid **51** (see main text), ester **75** (1.55 g, 1.65 mmol) was reacted with 1 M LiOH (10 mL, 10 mmol) in THF (40 mL) for 17 h to give, after neutralization with 1M HCl, the title compound **63** (1.40 g, 96%) as a yellow powder, which was used in the next step without any further purification: Amino acid **63**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.13-1.38 (m, 6H), 1.55-1.67 (m, 2H), 2.19 (s, 3H), 3.81 (t, J = 6.5 Hz, 2H), 5.47 (s, 2H), 5.65 (br s, 2H), 6.53-6.64 (m, 3H), 6.77 (dd, J = 8.0, 2.0 Hz, 1H), 7.12-7.18 (m, 3H), 7.36 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), and 7.84 (d, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO) δ 18.30, 25.78, 28.88, 29.06, 29.23, 48.16, 67.64, 111.7, 112.9, 114.1, 115.9, 116.3, 118.9, 120.3, 122.7, 123.4, 124.7, 128.3, 130.2, 132.5, 136.0, 138.2, 141.6, 146.2, 154.3, 159.2, and 166.8; IR (KBr) ν_{max} 1741, 1609, 1473, 1435, 1386, and

1262 cm^{-1}; MS (ESI) *m/z* (rel intensity) 885 (100%, MH^+); HRMS calcd for $C_{54}H_{57}N_6O_6$ (MH^+) 907.4159, found 907.4176.

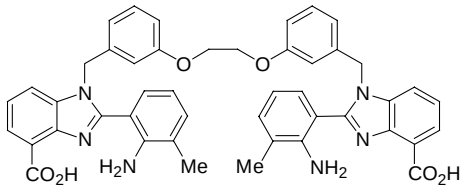
1,6-Bis{3-[2-(2-amino-3-methylphenyl)-4-hydroxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}hexane (64)



64

Following the general procedure described for the preparation of amino acid **51** (see main text), ester **76** (4.36 g, 4.93 mmol) was reacted with 1 M LiOH (30 mL, 30 mmol) in THF (120 mL) for 20 h to give, after neutralization with 1M HCl, the title compound **64** (3.69 g, 90%) as a pale yellow solid, which was used in the next step without any further purification. Amino acid **64**: ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.36 (br s, 2H), 1.62 (br s, 2H), 2.19 (s, 3H), 3.82 (t, J = 6.0 Hz, 2H), 5.47 (s, 2H), 5.65 (br s, 2H), 6.52-6.66 (m, 3H), 6.77 (d, J = 8.0 Hz, 1H), 7.09-7.20 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), and 7.84 (d, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO) δ 18.30, 25.58, 28.85, 48.16, 67.58, 111.7, 112.9, 114.1, 115.9, 116.3, 118.9, 120.3, 122.7, 123.4, 124.7, 128.3, 130.2, 132.5, 136.0, 138.2, 141.6, 146.2, 154.3, 159.2, and 166.8; IR (KBr) ν_{max} 1741, 1609, 1473, 1435, 1386, and 1261 cm^{-1}; MS (ESI) *m/z* (rel intensity) 829 (100%, MH^+); HRMS calcd for $C_{50}H_{48}N_6NaO_6$ (MNa^+) 851.3533, found 851.3536.

1,2-Bis{3-[2-(2-amino-3-methylphenyl)-4-hydroxycarbonyl-benzimidazol-1-ylmethyl]phenoxy}ethane (65)

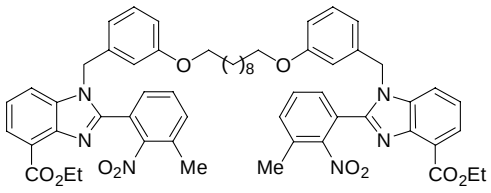


65

Following the general procedure described for the preparation of amino acid **51** (see main text), ester **77** (2.63 g, 3.17 mmol) was reacted with 1 M LiOH (19 mL, 19 mmol) in THF (80

mL) for 16 h to give, after neutralization with 1M HCl, the title compound **65** (2.24 g, 91%) as a pale yellow solid, which was used in the next step without any further purification. For analytical purposes, a small amount of the product was recrystallized from CH_2Cl_2/petroleum ether. Acid **65**: mp 140.0-142.0 °C (CH_2Cl_2/petroleum ether); ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.18 (s, 3H), 4.13 (s, 2H), 5.47 (s, 2H), 5.67 (br s, 2H), 6.58-6.63 (m, 3H), 6.80 (dd, J = 7.5, 1.5 Hz, 1H), 7.14-7.19 (m, 3H), 7.35 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), and 7.84 (d, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO) δ 18.30, 48.13, 66.42, 111.7, 113.0, 114.0, 115.9, 116.3, 119.2, 120.3, 122.7, 123.4, 124.7, 128.3, 130.3, 132.5, 135.9, 138.3, 141.7, 146.2, 154.3, 158.8, and 166.8; IR (KBr) ν_{max} 1732, 1608, 1452, 1434, 1391, and 1253 cm^{-1}; MS (ESI) *m/z* (rel intensity) 795 (40%, MNa^+) and 773 (100); HRMS calcd for $C_{46}H_{41}N_6O_6$ (MH^+) 773.3087, found 773.3048.

1,10-Bis{3-[4-ethoxycarbonyl-2-(3-methyl-2-nitrophenyl)-benzimidazol-1-ylmethyl]phenoxy}decane (72)

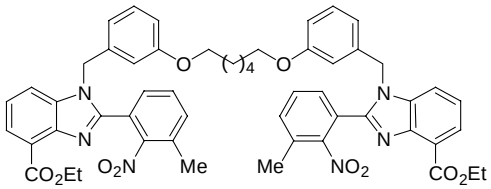


72

Following the general procedure described for the preparation of benzimidazole **43** (see main text), a solution of benzimidazole **13** (2.00 g, 6.15 mmol) in THF (30 mL) was reacted with NaH (60% w/w dispersion in mineral oil, 271 mg, 6.8 mmol) at 0 °C for 30 min, and alkylated with dibromide **41** (1.58 g, 3.08 mmol) for 24 h at rt. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **72** (1.87 g, 59%) as a white foam: R_f = 0.55 (CH_2Cl_2/EtOAc, 1/1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16-1.32 (m, 6H), 1.33 (t, J = 7.0 Hz, 3H), 1.51-1.59 (m, 2H), 2.33 (s, 3H), 3.70 (t, J = 6.5 Hz, 2H), 4.35 (q, J = 7.0 Hz, 2H), 5.23 (s, 2H), 6.46-6.51 (m, 2H), 6.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.20-7.34 (m, 4H), and 7.82 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.77, 18.62, 26.38, 29.55, 29.74, 29.85, 48.95, 61.49, 68.41, 112.9, 114.4, 115.6, 118.7, 122.9, 123.2, 124.2, 126.0, 129.3, 130.5, 130.6, 132.1, 133.9, 136.7, 137.4, 142.3, 150.8, 151.8, 160.2, and 166.5; IR ($CHCl_3$) ν_{max} 2933, 1708, 1604, 1537, 1452, 1429, 1292, and 1255 cm^{-1}; MS (ESI)

m/z (rel intensity) 1023 (20%, MNa^+) and 1001 (100); HRMS calcd for $C_{58}H_{61}N_6O_{10}$ (MH^+) 1001.4449, found 1001.4459.

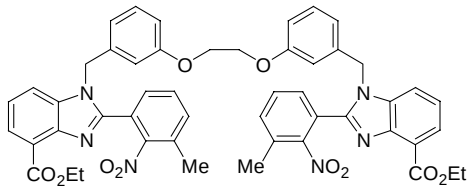
1,6-Bis{3-[4-ethoxycarbonyl-2-(3-methyl-2-nitrophenyl)-benzimidazol-1-ylmethyl]phenoxy}hexane (73)



73

Following the general procedure described for the preparation of benzimidazole **43** (see main text), a solution of benzimidazole **13** (5.70 g, 17.5 mmol) in THF (60 mL) was reacted with NaH (60% w/w dispersion in mineral oil, 772 mg, 19 mmol) at 0 °C for 30 min, and alkylated with dibromide **39** (4.00 g, 8.77 mmol) for 16 h at 50 °C. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **73** (7.60 g, 92%) as a pale yellow solid: R_f = 0.60 (EtOAc); mp 202.0-203.5 °C (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25-1.38 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H), 1.50-1.68 (m, 2H), 2.34 (s, 3H), 3.71 (t, J = 6.5 Hz, 2H), 4.36 (q, J = 7.0 Hz, 2H), 5.24 (s, 2H), 6.45 (s, 1H), 6.51 (d, J = 7.5 Hz, 1H), 6.67 (dd, J = 8.5, 2.0 Hz, 1H), 7.04-7.34 (m, 6H), and 7.82 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.76, 18.59, 26.18, 29.45, 48.92, 61.48, 68.23, 112.8, 114.4, 115.6, 118.7, 123.0, 123.1, 124.3, 125.9, 129.2, 130.5, 130.6, 132.1, 133.8, 136.7, 137.4, 142.4, 150.8, 151.8, 160.1, and 166.6; IR ($CHCl_3$) ν_{max} 1706, 1604, 1537, 1455, 1429, 1292, and 1255 cm^{-1}; MS (ESI) *m/z* (rel intensity) 967 (5%, MNa^+) and 945 (100); HRMS calcd for $C_{54}H_{53}N_6O_{10}$ (MH^+) 945.3823, found 945.3834.

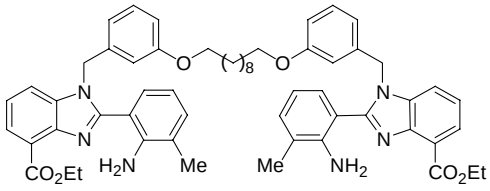
1,2-Bis{3-[4-ethoxycarbonyl-2-(3-methyl-2-nitrophenyl)-benzimidazol-1-ylmethyl]phenoxy}ethane (74)



74

Following the general procedure described for the preparation of benzimidazole **43** (see main text), a solution of benzimidazole **13** (2.52 g, 7.75 mmol) in THF (30 mL) was reacted with NaH (60% w/w dispersion in mineral oil, 341 mg, 8.5 mmol) at 0 °C for 30 min, and alkylated with dibromide **37** (1.55 g, 3.88 mmol) for 22 h at 50 °C. Purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc) gave the title compound **74** (3.00 g, 87%) as a white foam: R_f = 0.40 (CH_2Cl_2/EtOAc, 1/1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 3.98 (s, 2H), 4.31 (q, J = 7.0 Hz, 2H), 5.22 (s, 2H), 6.46 (~s, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 8.0, 2.0 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 7.19-7.30 (m, 4H), and 7.79 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.76, 18.57, 48.87, 61.45, 66.84, 113.0, 114.6, 115.6, 119.4, 122.9, 123.2, 124.2, 125.9, 129.2, 130.5, 130.7, 132.1, 133.9, 136.6, 137.5, 142.4, 150.8, 151.8, 159.6, and 166.5; IR ($CHCl_3$) ν_{max} 1706, 1605, 1537, 1448, 1429, 1294, and 1255 cm^{-1}; MS (ESI) *m/z* (rel intensity) 911 (20%, MNa^+) and 889 (100); HRMS calcd for $C_{50}H_{45}N_6O_{10}$ (MH^+) 889.3197, found 889.3205.

1,10-Bis{3-[4-ethoxycarbonyl-2-(3-methyl-2-aminophenyl)-benzimidazol-1-ylmethyl]phenoxy}decane (75)

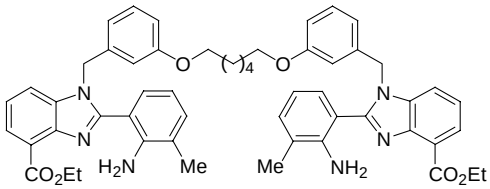


75

Following the general procedure described for the preparation of benzimidazole **47** (see main text), nitroarene **63** (1.81 g, 1.81 mmol) was reacted with $SnCl_2$ (3.43 g, 18.1 mmol) in boiling EtOH (60 mL) for 1 h to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc), the title compound **75** (1.55 g, 91%) as a pale yellow foam: R_f = 0.80 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.18-1.32 (m, 6H), 1.35 (t, J = 7.0 Hz, 3H), 1.53-1.61 (m, 2H), 2.10 (s, 3H), 3.72 (t, J = 6.5 Hz, 2H), 4.38 (q, J = 7.0 Hz, 2H), 5.35 (s, 2H), 5.41 (br s, 2H), 6.44-6.57 (m, 3H), 6.69 (dd, J = 8.0, 2.0 Hz, 1H), 6.98-7.14 (m, 4H), 7.24 (dd, J = 8.0, 1.0 Hz, 1H), and 7.84 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.95, 18.35, 26.41, 29.60, 29.77, 29.86, 49.26, 61.26, 68.38, 112.2, 112.6, 114.2, 115.3, 116.9, 118.5, 121.5, 122.5, 123.8, 125.7, 127.9, 130.5, 132.6, 136.9, 138.1, 142.1, 146.7, 155.3, 160.2, and 166.8; IR

($CHCl_3$) ν_{max} 2933, 1706, 1611, 1474, 1448, 1429, 1290, and 1261 cm^{-1}; MS (ESI) *m/z* (rel intensity) 941 (100%, MH^+); HRMS calcd for $C_{58}H_{65}N_6O_6$ (MH^+) 941.4965, found 941.4968.

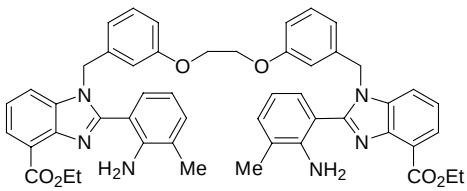
1,6-Bis{3-[4-ethoxycarbonyl-2-(3-methyl-2-aminophenyl)-benzimidazol-1-ylmethyl]phenoxy}hexane (76)



76

Following the general procedure described for the preparation of benzimidazole **47** (see main text), nitroarene **73** (5.02 g, 5.31 mmol) was reacted with $SnCl_2$ (10.0 g, 53.1 mmol) in boiling EtOH (100 mL) for 50 min to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc), the title compound **76** (4.36 g, 93%) as a yellow foam: R_f = 0.80 (EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (br s, 2H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.60 (t, *J* = 6.5 Hz, 2H), 2.10 (s, 3H), 3.72 (t, *J* = 6.5 Hz, 2H), 4.38 (q, *J* = 7.0 Hz, 2H), 5.24 (br s, 2H), 5.31 (s, 2H), 6.47 (t, *J* = 7.5 Hz, 1H), 6.50 (s, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 6.68 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.99 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.07-7.16 (m, 3H), 7.25 (dd, *J* = 8.0, 1.0 Hz, 1H), and 7.84 (dd, *J* = 7.5, 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$) δ 14.91, 18.32, 26.22, 29.50, 49.33, 61.32, 68.21, 112.1, 112.6, 114.2, 115.4, 116.9, 118.5, 121.5, 122.6, 123.9, 125.8, 127.9, 130.6, 132.7, 136.8, 138.0, and 141.7; IR ($CHCl_3$) ν_{max} 1701, 1610, 1521, 1508, 1474, 1428, and 1289 cm^{-1}; MS (ESI) *m/z* (rel intensity) 885 (90%, MH^+) and 849 (100); HRMS calcd for $C_{54}H_{57}N_6O_6$ (MH^+) 885.4339, found 885.4346.

1,2-Bis{3-[4-ethoxycarbonyl-2-(3-methyl-2-aminophenyl)-benzimidazol-1-ylmethyl]phenoxy}ethane (77)



77

Following the general procedure described for the preparation of benzimidazole **47** (see main text), nitroarene **74** (3.00 g, 3.37 mmol) was reacted with $SnCl_2$ (6.40 g, 33.7 mmol) in boiling EtOH (60 mL) for 45 min to give, after purification by flash chromatography (silica gel, CH_2Cl_2 → EtOAc), the title compound **77** (2.63 g, 94%) as a pale yellow foam: R_f = 0.65 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H), 2.06 (s, 3H), 3.98 (s, 2H), 4.36 (q, J = 7.0 Hz, 2H), 5.25 (s, 2H), 5.43 (br s, 2H), 6.44 (t, J = 7.5 Hz, 1H), 6.50 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.66 (dd, J = 8.0, 2.0 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.19 (dd, J = 8.0, 1.0 Hz, 1H), and 7.82 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (63 MHz, $CDCl_3$) δ 14.96, 18.32, 49.12, 61.25, 66.80, 112.3, 112.8, 114.3, 115.3, 116.9, 119.1, 121.6, 122.5, 123.8, 125.7, 127.8, 130.6, 132.6, 136.9, 138.3, 142.2, 146.7, 155.3, 159.6, and 166.7; IR ($CHCl_3$) ν_{max} 3019, 1706, 1611, 1474, 1428, and 1289 cm^{-1}; MS (ESI) *m/z* (rel intensity) 829 (100%, MH^+); HRMS calcd for $C_{50}H_{49}N_6O_6$ (MH^+) 829.3713, found 829.3729.

2. Selected CSP HPLC Traces

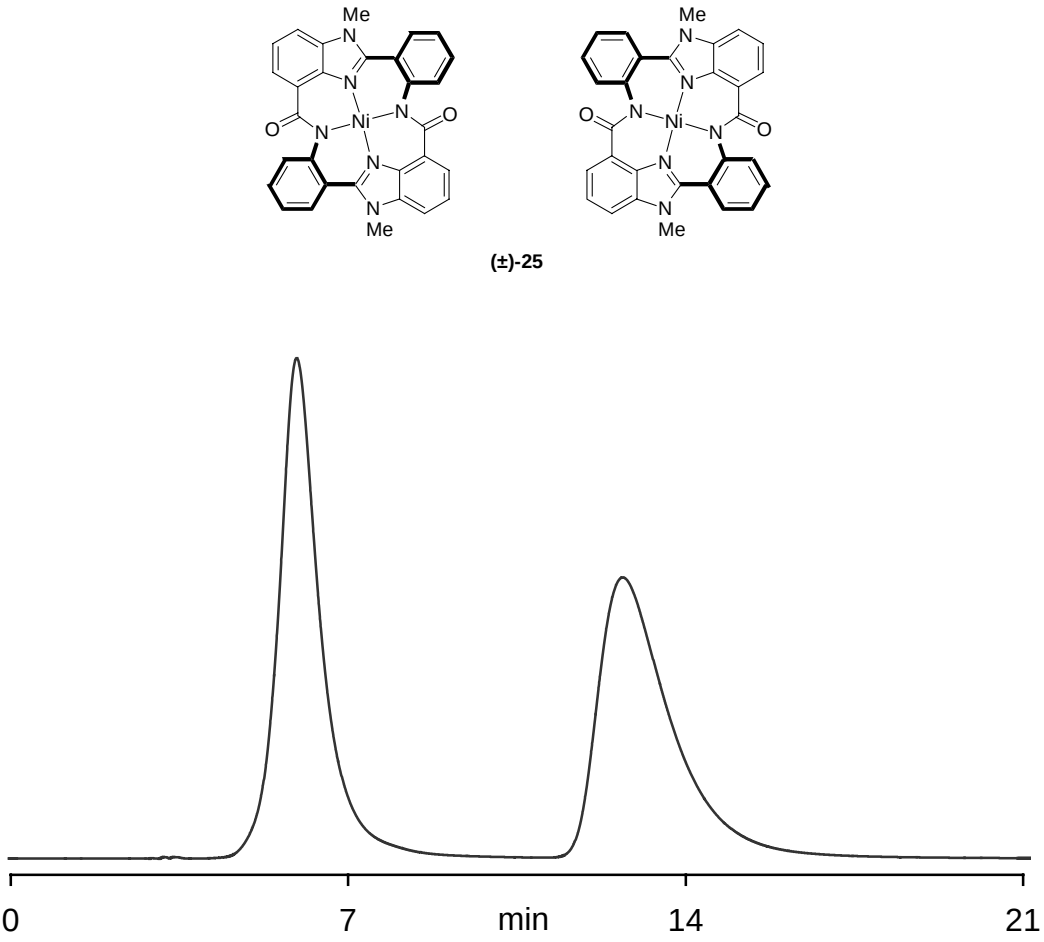
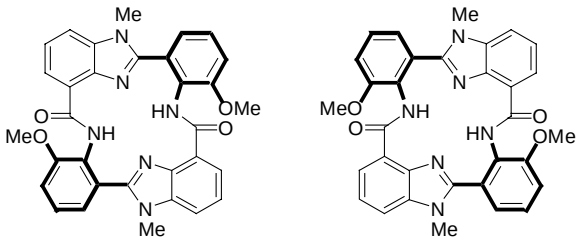


Figure S1. Optical resolution of the Ni(II) complex **25** (3.0 μg) by CSP HPLC (Chiralpak AD column, 4.6 mm × 25 cm; 2-propanol/hexanes, 80/20; 1 mL min^{-1}; 30 °C).



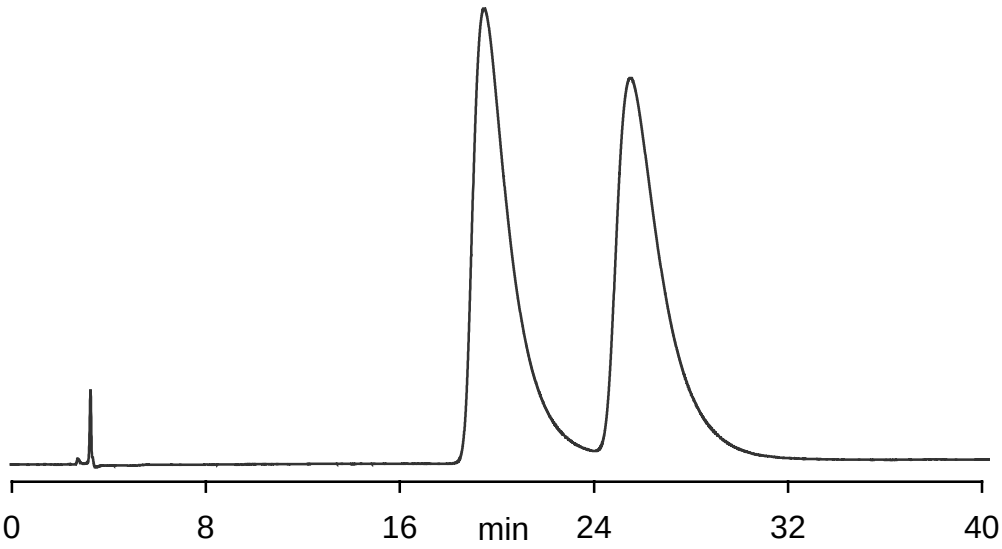


Figure S2. Optical resolution of the cyclic amide **23** (5.2 μg) by CSP HPLC (Chiralpak AD column, 4.6 mm × 25 cm; 2-propanol/hexanes/diethylamine, 80/20/0.5; 1 mL min^{-1}; 40 °C).

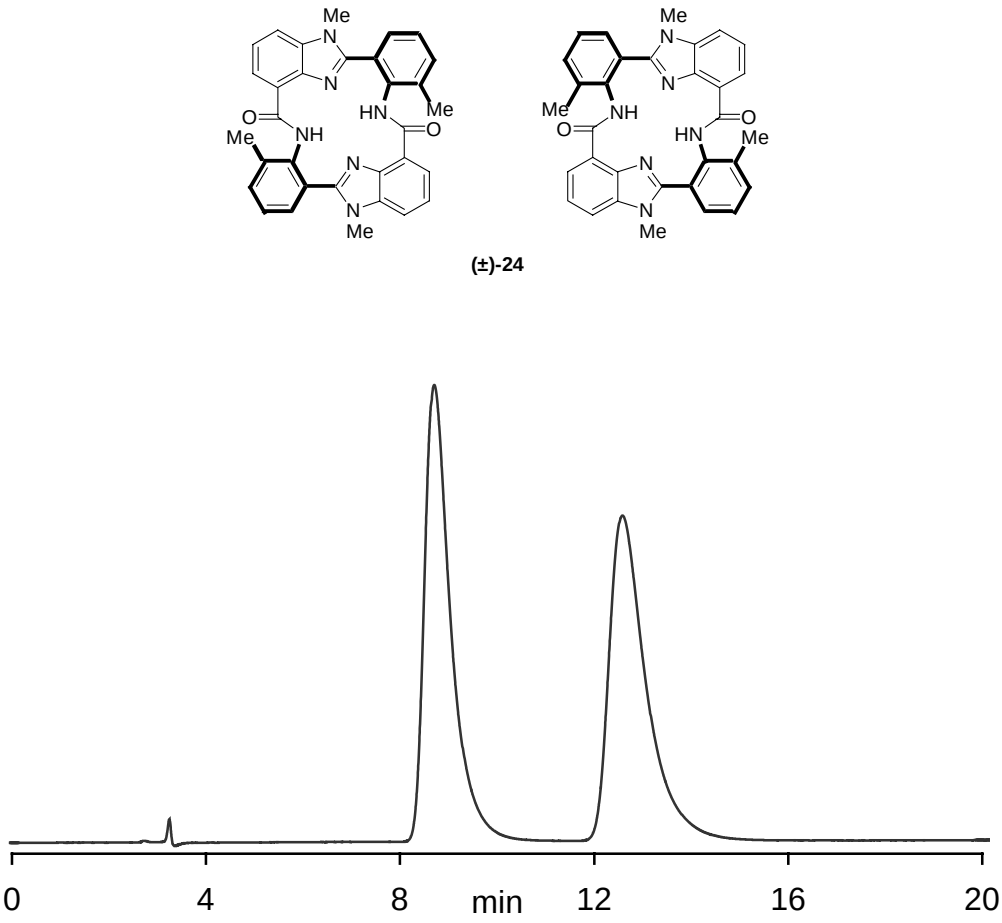


Figure S3. Optical resolution of the cyclic amide **24** (2.9 μg) by CSP HPLC (Chiralcel OD column, 4.6 mm × 25 cm; 2-propanol/hexanes/diethylamine, 79/20/1; 1 mL min^{-1}; 40 °C).