Synthesis of Chiral Macrocycles by Cyclodimerization of Diamines with Stepwise Nucleophilic Aromatic Substitution of 1,5-Difluoro-2,4-dinitrobenzene

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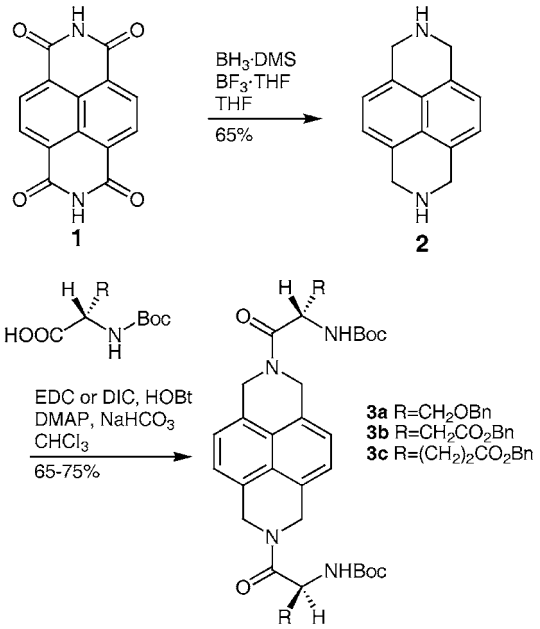
Abstract: Chiral cyclophanes were synthesized by cyclodimerization of 2,7-diaza-1,2,3,6,7,8-hexahydropyrene N-acylated with L-amino acids through stepwise nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene.

Key words: macrocycles, chiral, nucleophilic aromatic substitution, cyclophanes, diazapyrene

The study of supramolecular properties of macrocyclic molecules has been particularly successful over the years in providing detailed insight into the mechanisms of molecular recognition. This is largely due to that macrocycles are inherently more or less fairly rigid and preorganized and can, if properly designed, despite their relatively small size, present organized grooves or cavities for the binding of other small(er) molecules. Within this context, cyclophanes[1–8] appear attractive as their aromatic nature allow for interactions with guest molecules e.g. via π-π, hydrophobic, π-hydrogen bonding, and cation-π forces. Although nature's receptors are chiral and have often been mimicked for molecular recognition studies, relatively few chiral macrocycles have been reported as model systems for biomimetic molecular recognitions.[2,9–18] Small macrocycles are typically more flexible than protein binding sites unless the building blocks used for the macrocycle assembly are designed to confer conformational rigidity. The conformational flexibility of a macrocycle intended to mimic protein binding sites has to be lowered in order not to loose entropy upon ligand binding, yet high enough to adjust to the ligand structure, i.e. allow for induced fit. One way of modulating the flexibility of macrocycles is to vary the number and the structure of small rings (aromatic or aliphatic) in the macrocycle. Herein, we disclose a macrocyclization reaction sequence, which results in the introduction of two dinitroaniline rings into chiral cyclophanes. The reaction sequence involves cyclodimerizations of L-amino acid-functionalized 2,7-diaza-1,2,3,6,7,8-hexahydropyrenes through stepwise nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene.

The synthesis of 2,7-diaza-1,2,3,6,7,8-hexahydropyrene **2** from 1,4,5,8-naphthalenetetracarboxylic diimide[19] (**1**) has recently been reported (Scheme 1).[20] Upon following the reported synthesis, we found that the time-consuming Soxhlet extraction for purification of crude **2** could be replaced by a considerably faster flash chromatography. The diamine **2** has a limited stability and is not suited for long-term storage. Consequently, the subsequent acylation of diamine with Boc-protected amino acids produce better yields of **3** with a freshly prepared **2**.



Scheme 1

Initially, acylation of **2** was found to be difficult due to poor solubility of **2** in solvents normally used in peptide couplings (i.e. CH_2Cl_2, DMF and THF). The diamine **2** dissolves well in a mixture of CH_2Cl_2 and MeOH, but this solvent mixture did however produce large amounts of amino acid methyl esters upon attempted acylation of **2** with amino acids. A reliable procedure for acylating the diamine **2** was finally found by using regular coupling agents, such as EDC or DIC, in chloroform. The bis-acylated compounds **3a**–**c** were obtained in good yields and were also found to be stable upon long-term storage. Deprotection of **3a**–**c** to diamines **4a**–**c** proceeded smoothly with HCl or TFA (Scheme 2). The hydrochloride salts corresponding to **4a**–**c** showed poor solubility, which limited their use as nucleophiles in subsequent

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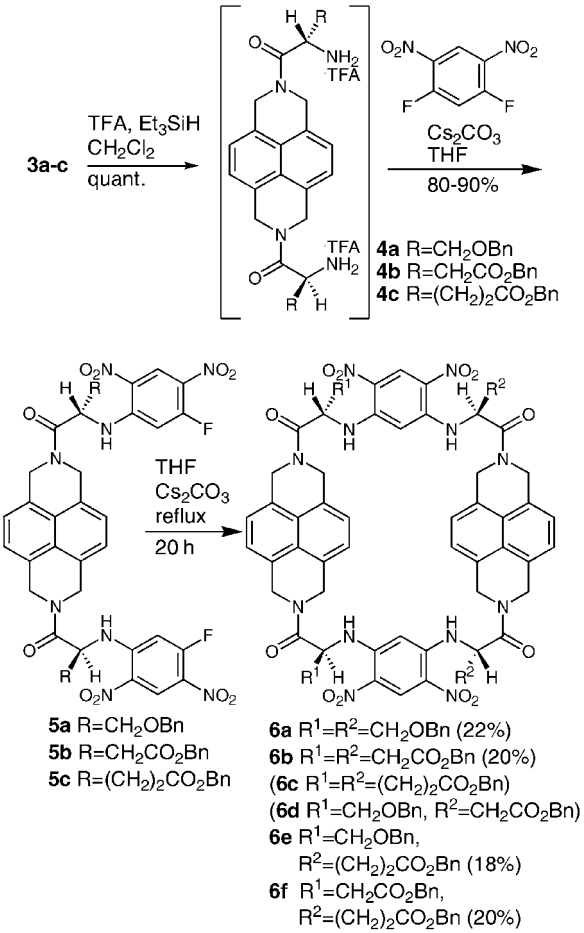
reactions. Treatment of the crude *bis*-ammonium TFA salts **4a**–**c** with 1,5-difluoro-2,4-dinitrobenzene in the presence of cesium carbonate in THF afforded **5a**–**c** doubly equipped with monofluorobenzene moieties ready for cyclodimerization in a second nucleophilic aromatic substitution with **4a**–**c**. Substitution of the second fluoride required harsher conditions. Refluxing equimolar amounts of **4** and **5** and 6 equivalents of cesium carbonate in THF for 20 hours furnished the target macrocycles **6a**–**f** in relatively good yields of 15–25% after purification with flash chromatography followed by precipitation. Attempts to increase the cyclodimerization yields and to shorten reactions times by adding copper iodide to the reaction mixtures failed.[21] The purities of **6a**–**f** were analyzed with RP-HPLC and macrocycles **6a**,**b**,**e**,**f** yielded chromatograms with one peak corresponding to a purity of >95%. Macrocycles **6c**,**d** were of lower purity and gave unfortunately less satisfactory chromatograms, though the identity of **6c**–**d** were confirmed with FAB-HRMS. FAB-HRMS and ^{13}C-NMR analysis of the macrocycles **6a**–**f** confirmed their structures, whereas ^{1}H NMR analyses of **6a**–**f** proved difficult due to poor resolution presumably caused by slow conformational exchange. High-temperature NMR experiments in deuterated DMSO were unsuccessful as the macrocycles **6a**–**f** decomposed spontaneously at elevated temperatures.



Scheme 2

Monte-Carlo conformational searches[22] of **6a** (side-chains protected as methyl ethers in order to simplify calculations) gave the one dominating group of closely related conformers (150–200 similar conformers within 5 kcal/mol) with cleft-like collapsed structures in which the two naphthalene units were face-to-face stacked (Figure 1). The two dinitroaniline units were oriented perpendicular to the naphthalene units in opposite directions. The main group conformers differed by small changes in the angle between the naphthalene and dinitroaniline units and the conformations of the flexible amino acid side chain, which suggests that the macrocycles indeed are conformationally well-defined. A few minor conformers with either a naphthalene sandwiched between the dinitroanilines or a dinitroaniline sandwiched between two naphthalenes were found, however, with higher energies than the main group conformers.

Figure 1 Stereo representation of the global energy minimum conformation of an analog of **6a** with side-chains protected as methyl ethers in order to simplify calculations

In summary, we have developed a short synthesis of cyclophanes via step-wise nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene with diamines obtained by acylation of 2,7-diaza-1,2,3,6,7,8-hexahydropyrene with amino acids. The method is versatile as variation of the diamine component opens up for the construction of a range of related 1,5-difluoro-2,4-dinitrobenzene derived cyclophanes as receptors with potential of mimicking biomolecule recognition.

2,7-Diaza-1,2,3,6,7,8-hexahydropyrene (2):
1,4,5,8-Naphthalenetetracarboxylic diimide (**1**, 3.00 g, 11.3 mmol) was suspended in dry THF (75 mL, dried over MS 4Å) in an oven-dried and nitrogen-flushed 250 mL three-necked flask. To this mixture BF_3·THF (5.0 mL, 45 mmol) was added, followed by BH_3·DMS in THF (70 mL, 2 M). The reaction was refluxed for 64 h, cooled to 0 °C and slowly quenched with MeOH (15 mL) while immersed in an ice-bath. (CAUTION: Excessive foaming may occur at this moment). Then, 6 M HCl (25 mL) was added and the reaction was refluxed for another 3 h. After cooling to ambient temperature, the reaction was adjusted to pH 13 with 50% NaOH. The organic solvents were evaporated and the remaining aqueous suspension was filtered. Filtered solids were dried in vacuo and further purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH–Et_3N 20:0:1 → 20:1:1 → 20:2:1 gradient) yielding 1.55 g (65%) of **2** as a pale solid. TLC (EtOAc–MeOH–Et_3N 16:4:1): R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (s, 4 H), 4.20 (s, 8 H).

Typical Acylation of 2: [*S,S*]-*N,N′*-*Bis*-[3-benzyloxy-2-(*N*-*t*-butoxycarbonylamino)-propionyl]-2,7-diaza-1,2,3,6,7,8-hexahydropyrene (3a):
Compound **2** (0.60 g, 2.9 mmol) was suspended and sonicated for 5 min at ambient temperature in $CHCl_3$ (150 mL, purified on basic Al_2O_3). To the suspension was added BOC-Ser(OBn)-OH (2.53 g, 8.6 mmol), EDC (2.19 g, 11.4 mmol), HOBt (0.88 g, 5.7 mmol), DMAP (1.44 g, 11.4 mmol) and $NaHCO_3$ (0.96 g, 11.4 mmol) and the resulting mixture was stirred for 18 h. The reaction was washed with 5% HCl (2 × 200 mL), sat. $NaHCO_3$ (3 × 200 mL), and sat. NaCl (3 × 200 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated into a pale solid (2.50 g), which was purified by flash chromatography (SiO_2, heptane–EtOAc 1:1) to give **3a** (1.57 g, 72%). A sample of analytical purity was prepared by precipitation from MeOH–H_2O (9:1). TLC (heptane–EtOAc 1:1): R_f = 0.25. $[\alpha]_D^{23}$ –3.9 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.00 (m, 14 H), 5.50 (d, 2 H, *J* = 8 Hz), 5.17–4.92 (m, 10 H), 4.37 (s, 4 H), 3.67–3.52 (m, 4 H), 1.41 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 155.3, 137.7, 130.5, 130.2, 128.4, 127.7, 127.6, 122.7, 122.5, 122.1, 121.8, 80.0, 77.4, 73.3, 71.2, 50.5, 48.9, 45.4, 28.5. FAB-HRMS: *m/z* calcd for $C_{44}H_{53}N_4O_8$ $[M + H]^+$: 765.3864. Found: 765.3859.

In a similar manner were prepared:

[*S,S*]-*N,N′*-*Bis*-[3-(benzyloxycarbonyl)-2-(*N*-*t*-butoxycarbonylamino)-propionyl]-2,7-diaza-1,2,3,6,7,8-hexahydropyrene (3b):
TLC (heptane–EtOAc 1:1): R_f = 0.17. $[\alpha]_D^{21}$ –4.6 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 14 H), 5.42 (d, 2 H, *J* = 7 Hz), 5.23–4.60 (m, 14 H), 2.95–2.75 (m, 2 H), 2.67–2.59 (br, 2 H), 1.42 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 169.4, 155.0, 135.8, 130.7, 130.2, 129.9, 128.7, 128.4, 128.3, 127.7, 127.4, 122.5, 122.0, 80.4, 77.4, 66.8, 47.9, 45.5, 38.0, 28.5. FAB-HRMS: *m/z* calcd for $C_{46}H_{53}N_4O_{10}$ $[M + H]^+$: 821.3762. Found: 821.3759.

[*S,S*]-*N,N′*-*Bis*-[4-(benzyloxycarbonyl)-2-(*N*-*t*-butoxycarbonylamino)-butanoyl]-2,7-diaza-1,2,3,6,7,8-hexahydropyrene (3c):
TLC (heptane–EtOAc 1:1): R_f = 0.20. $[\alpha]_D^{21}$ +41 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 14 H), 5.50 (d, 2 H, *J* = 7 Hz), 5.35–5.15 (m, 8 H), 5.05–4.80 (m, 6 H), 2.65–2.50 (br, 2 H), 2.45–2.30 (br, 2 H), 2.10–1.90 (br, 2 H), 1.65–1.50 (br, 2 H), 1.45 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 170.7, 156.0, 136.2, 130.8, 130.4, 130.2, 129.8, 128.8, 128.4, 127.9, 122.7, 122.7, 122.5, 79.9, 66.6, 49.8, 48.3, 45.4, 29.5, 29.0, 28.5. FAB-HRMS: *m/z* calcd for $C_{48}H_{56}N_4O_{10}Na$ $[M + Na]^+$: 871.3894. Found: 871.3907.

Typical Synthesis of *Bis*-fluorophenyls 5a-c: [*S,S*]-*N,N′*-*Bis*-[3-benzyloxy-2-(*N*-5-fluoro-2,4-dinitrophenylamino)-propionyl]-2,7-diaza-1,2,3,6,7,8-hexahydropyrene (5a):
Compound **3a** (100 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (5 mL) and triethylsilane (85 μL, 0.50 mmol) was added, followed by TFA (290 μL, 3.9 mmol). After 16 h, the solution was concentrated, the residue dissolved in THF (5 mL, dried over MS), and Cs_2CO_3 (256 mg, 0.80 mmol) and 1,5-difluoro-2,4-dinitrobenzene (214 mg, 0.50 mmol) were added. The resulting suspension was stirred for 2 h and then concentrated. Flash chromatography (SiO_2, heptane–EtOAc 1:1) yielded product **5a** as a yellow solid (102 mg, 84%). TLC (heptane–EtOAc 1:1): R_f = 0.23. $[\alpha]_D^{24}$ +24 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62–9.55 (br, 2 H), 8.90 (d, 2 H, *J* = 13 Hz), 7.29–7.10 (m, 14 H), 6.72 (d, 2 H, *J* = 13 Hz), 5.15–4.87 (m, 10 H), 4.43 (s, 4 H), 3.82–3.66 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 161.0, 158.4, 148.0, 147.9, 136.7, 130.6, 129.2, 128.7, 128.4, 127.9, 127.8, 127.6, 126.0, 125.9, 122.8, 122.4, 102.7, 102.4, 73.9, 70.9, 55.2, 48.9, 46.1. FAB-HRMS: *m/z* calcd for $C_{46}H_{39}F_2N_8O_{12}$ $[M + H]^+$: 933.2656. Found: 933.2657.

In a similar manner were prepared:

[*S,S*]-*N,N′*-Bis-[3-(benzyloxycarbonyl)-2-(*N*-5-fluoro-2,4-dinitrophenylamino)-propionyl]-2,7-diaza-1,2,3,6,7,8-hexahydropyrene (5b):
TLC (heptane–EtOAc 1:1): R_f = 0.21. $[\alpha]_D^{25}$ +35 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.34–9.20 (br, 2 H), 8.94–8.86 (br, 2 H), 7.32–7.07 (m, 10 H), 6.64 (m, 2 H), 5.25–4.93 (m, 14 H), 3.00–2.87 (m, 2 H), 2.85–2.74 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 167.9, 147.8, 147.7, 135.2, 135.19, 131.10, 130.0, 129.12, 129.06, 128.9, 128.3, 128.1, 127.9, 126.5, 123.7, 123.2, 122.5, 121.9, 102.3, 102.0, 68.0, 51.2, 51.1, 49.3, 46.6, 38.5. FAB-HRMS: *m/z* calcd for $C_{48}H_{39}F_2N_8O_{14}$ $[M + H]^+$: 989.2555. Found: 989.2556.

[*S,S*]-*N,N′*-*Bis*-[4-(benzyloxycarbonyl)-2-(*N*-5-fluoro-2,4-dinitrophenylamino)-butanoyl]-2,7-diaza-1,2,3,6,7,8-hexahydropyrene (5c):
TLC (heptane–EtOAc 1:1): R_f = 0.16. $[\alpha]_D^{21}$ +58 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.10 (dd, 2 H, *J* = 7, 23 Hz), 8.98 (d, 2 H, *J* = 8 Hz), 7.34–7.20 (m, 14 H), 6.43 (t, 2 H, *J* = 14 Hz), 5.19–4.91 (m, 14 H), 2.49–2.39 (br, 4 H), 2.25–2.10 (br, 2 H), 1.98–1.85 (br, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 173.4, 168.6, 168.5, 161.4, 158.7, 148.5, 148.4, 135.4, 131.0, 130.3, 130.1, 129.3, 128.9, 128.63, 128.56, 128.2, 127.9, 126.3, 126.2, 123.5, 123.0, 122.5, 122.0, 101.6, 101.4, 67.3, 52.7, 48.8, 46.2, 29.0, 28.0. FAB-HRMS: *m/z* calcd for $C_{50}H_{42}F_2N_8O_{14}Na$ $[M + Na]^+$: 1039.2687. Found: 1039.2675.

Typical Synthesis of Macrocycles 6a–f: Macrocycle 6a:
Compound **3a** (84 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (5 mL). Triethylsilane (75 μL, 0.40 mmol) was added, followed by TFA (270 μL, 3.3 mmol). The solution was stirred at ambient temperature for 16 h and then evaporated into a syrup. This syrup was dissolved in THF (130 mL, dried over MS) to which was added Cs_2CO_3 (215 mg, 0.70 mmol) and compound **5a** (102 mg, 0.11 mmol). The resulting suspension was refluxed for 20 h and then evaporated. Flash chromatography (SiO_2, heptane–EtOAc 1:4) followed by precipitation from $CHCl_3$–MeOH (1:2) yielded **6a** as a yellow solid (36 mg, 22%). TLC (heptane–EtOAc 1:4): R_f = 0.10. HPLC (Column: Supelcosil 250 mm × 10 mm, 5 μm. Eluent: H_2O–MeCN 1:0 over 5 min, 1:0 → 0:1 over 1 h, 0:1 over 5 min. Flow: 5 mL/min) t_R = 47 min. $[\alpha]_D^{21}$ –38 (*c* 0.5, $CHCl_3$). The ^{1}H NMR spectrum showed poorly resolved broad peaks. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 147.4, 137.2, 130.6, 129.4, 128.7, 128.6, 128.3, 128.1, 127.7, 124.8, 123.5, 121.2, 93.0, 73.8, 67.7, 54.1, 48.7, 46.0. FAB-HRMS: *m/z* calcd for $C_{80}H_{73}N_{12}O_{16}$ $[M + H]^+$: 1457.5268. Found: 1457.5251.

In a similar manner were prepared:

Macrocycle 6b:
Compound **4b** and **5b** gave **6b** in 20% yield. TLC (heptane–EtOAc 1:4): R_f = 0.50. HPLC: t_R = 46 min. $[\alpha]_D^{21}$ +18 (*c* 0.5, $CHCl_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 168.8, 146.5, 135.5, 135.2, 131.4, 129.8, 128.82, 128.77, 128.71, 128.65, 128.61, 128.4, 128.3, 128.0, 127.9, 127.6, 127.4, 124.5, 122.7, 92.7, 67.1, 49.0, 46.5, 37.5. FAB-HRMS: *m/z* calcd for $C_{84}H_{72}N_{12}O_{20}Na$ $[M + Na]^+$: 1591.4884. Found: 1591.4904.

Macrocycle 6c:
Compound **4c** and **5c** gave impure **6c**. FAB-HRMS: *m/z* calcd for $C_{88}H_{81}N_{12}O_{20}$ $[M + H]^+$: 1625.5691. Found: 1625.5717.

Macrocycle 6d:
Compound **4a** and **5b** (or **4b** and **5a**) gave impure **6d**. FAB-HRMS: *m/z* calcd for $C_{82}H_{72}N_{12}O_{18}Na$ $[M + Na]^+$: 1535.4986. Found: 1535.4996.

Macrocycle 6e:
Compound **4a** and **5c** (or **4c** and **5a**) gave **6e** in 18% yield. TLC (heptane–EtOAc 1:4): R_f = 0.10. HPLC: t_R = 49 min. $[\alpha]_D^{21}$ +13 (*c* 0.5, $CHCl_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 168.5, 166.9, 147.4, 147.3, 136.9, 135.2, 130.6, 130.4, 129.6, 128.9, 128.7, 128.5, 128.2, 128.0, 127.9, 127.8, 124.8, 124.7, 123.8, 123.6, 122.1, 121.l, 92.8, 73.6, 68.4, 66.7, 54.1, 51.4, 48.9, 48.2, 45.7, 29.9, 28.7, 27.1. FAB-HRMS: *m/z* calcd for $C_{84}H_{77}N_{12}O_{18}$ $[M + H]^+$: 1541.5480. Found: 1541.5490.

Macrocycle 6f:
Compound **4b** and **5c** (or **4c** and **5b**) gave **6b** in 20% yield. TLC (heptane–EtOAc 1:4): R_f = 0.20. HPLC: t_R = 45 min. $[\alpha]_D^{21}$ +80 (*c* 0.5, $CHCl_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 172.2, 168.7, 167.8, 147.3, 146.4, 135.1, 134.6, 130.7, 130.4, 130.2, 129.8, 128.88, 128.83, 128.76, 128.73, 128.59, 128.49, 127.8, 127.6, 126.5, 124.64, 124.58, 123.8, 123.7, 122.1, 122.0, 95.6, 92.6, 68.2, 67.2, 67.0, 66.8, 66.3, 51.0, 50.0, 48.5, 45.8, 28.5, 27.3, 25.8. FAB-HRMS: *m/z* calcd for $C_{86}H_{76}N_{12}O_{20}Na$ $[M + Na]^+$: 1619.5197. Found: 1619.5199.

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