Supporting Information

Title: A New Versatile Synthesis of Macrotricyclic Tetraazacycloalkane-Based Ligands from Bis-aminal Derivatives

Author(s): Stéphanie Develay, Raphaël Tripier, Françoise Chuburu, Michel Le Baccon, Henri Handel*

Ref. No.: O03188
Experimental data:

NMR $^{13}$C Italic values: broad signals.

**Compound 3a** was obtained as a white powder in 97 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta$ = 46.8, 50.1, 50.4, 51.0, 51.2, 54.2, 60.8, 62.1, 63.0, 74.4, 84.5, 131.2, 135.1, 138.4. FAB-MS: $m/z$ 651.42, [M + H]$^+$. Calc. for C$_{27}$H$_{44}$N$_8$Br$_2$: C, 51.54; H, 6.80; N, 17.17 %. Found: C, 51.38; H, 6.69; N, 16.99 %.

**Compound 6a** was obtained as a white powder in 100 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta$ = 46.6, 50.5, 50.9, 51.2, 54.2, 60.1, 64.6, 65.6, 65.7, 74.52, 86.5, 131.6, 143.2, 152.0. FAB-MS: $m/z$ 652.31, [M + H]$^+$. Calc. for C$_{27}$H$_{43}$N$_9$Br$_2$, H$_2$O: C, 48.29; H, 6.75; N, 18.77 %. Found: C, 49.36; H, 6.49; N, 18.78 %.

**Compound 3b** was obtained as a white powder in 75 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): mixture of the meso and racemic isomers. FAB-MS: $m/z$ 913.15, [M + H]$^+$. Calc. for C$_{36}$H$_{52}$N$_8$Br$_4$, 3H$_2$O: C, 44.55; H, 6.02; N, 11.55 %. Found: C, 44.35; H, 6.32; N, 11.78 %.

**Compound 3c** was obtained as a white powder in 80% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 2.58 (t, 16H), 2.63 (t, 16H), 3.66 (s, 8H), 7.12-7.68 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 45.0, 51.5, 56.2, 126.8, 129.6, 136.8. FAB-MS (MeOH): $m/z$ 549.44, [M + H]$^+$. Calc. for C$_{32}$H$_{52}$N$_8$: C, 70.03; H, 9.55; N, 20.42 %. Found: C, 70.12; H, 9.86; N, 20.74 %.
Compound 4b was obtained as a white powder in 100 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta =$ 45.5, 49.0, 57.6, 63.1, 63.9, 80.7, 130.8, 134.2, 138.1, 138.9. FAB-MS: $m/z$ 913.14, [M + H]$^+$. Calc. for C$_{36}$H$_{52}$N$_8$Br$_4$, 5H$_2$O: C, 42.96; H, 6.32; N, 11.31 %. Found: C, 42.96; H, 6.29; N, 11.28 %.

Compound 4c was obtained as a white powder in 98.2 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta =$ 2.60 (t, 16H), 2.65 (t, 16H), 3.62 (s, 8H), 7.18-7.62 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta =$ 45.2, 51.3, 59.7, 127.7, 128.4, 129.9, 138.6. FAB-MS (MeOH): $m/z$ 549.44, [M + H]$^+$. Calc. for C$_{32}$H$_{52}$N$_8$: C, 70.03; H, 9.55; N, 20.42 %. Found: C, 69.90; H, 9.38; N, 20.21 %.

Compound 5b was obtained as a white powder in 90.8 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): mixture of the meso and racemic isomers. FAB-MS: $m/z$ 913.16, [M + H]$^+$. Calc. for C$_{36}$H$_{52}$N$_8$Br$_4$, 4H$_2$O: C, 43.74; H, 6.12; N, 11.34 %. Found: C, 43.72; H, 6.22; N, 11.31 %.

Compound 5c was obtained as a white powder in 100 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta =$ 2.67 (m, 32H), 3.36 (s, 8H), 7.22-7.34 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta =$ 45.2, 51.3, 61.3, 121.1, 136.6, 158.4. FAB-MS (MeOH): $m/z$ 551.32, [M + H]$^+$. Calc. for C$_{30}$H$_{50}$N$_{10}$: C, 65.42; H, 9.15; N, 25.43 %. Found: C, 65.35; H, 9.22; N, 25.44 %.

Compound 6b was obtained as a white powder in 100 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta =$ 45.6, 49.4, 58.7, 63.7, 65.4, 81.3, 131.9, 143.5, 151.6. FAB-MS: $m/z$ 914.28, [M + H]$^+$. Calc. for C$_{34}$H$_{50}$N$_{10}$Br$_4$, H$_2$O: C, 43.61; H, 5.60; N, 14.96 %. Found: C, 43.62; H, 5.55; N, 15.01 %.

Compound 6c was obtained as a white powder in 98.4 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta =$ 2.57 (m, 32H), 3.71 (s, 8H), 7.15-7.60 (m, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta =$ 45.4, 51.6, 61.3, 121.1, 136.6, 158.4. FAB-MS (MeOH): $m/z$ 551.32, [M + H]$^+$. Calc. for C$_{30}$H$_{50}$N$_{10}$: C, 65.42; H, 9.15; N, 25.43 %. Found: C, 65.35; H, 9.22; N, 25.44 %.

Compound 7b was obtained as a white powder in 72 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta =$ 21.1, 49.1, 49.7, 54.0, 63.9, 64.3, 80.1, 129.4, 133.8, 139.2, 140.7. FAB-MS: $m/z$ 973.18, [M + H]$^+$. Calc. for C$_{40}$H$_{60}$N$_8$Br$_4$, 2H$_2$O: C, 47.63; H, 6.40; N, 11.11 %. Found: C, 47.65; H, 6.48; N, 11.28 %.
**Compound 7c** was obtained as a white powder in 94 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.66$ (m, 8H), 1.95-3.91 (m, 32H), 7.01-7.41 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 25.0$, 47.1, 48.6, 50.3, 53.1, 57.6, 127.7, 130.2, 137.4, 137.7. FAB-MS (MeOH): $m/z$ 605.89, [M + H]$^+$. Calc. for C$_{36}$H$_{60}$N$_8$: C, 71.48; H, 10.00; N, 18.52 %. Found: C, 71.40; H, 10.09; N, 18.68 %.

**Compound 8b** was obtained as a white powder in 67.5 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta = 19.8$, 46.4, 49.1, 56.2, 64.4, 66.2, 79.8, 131.0, 137.4. FAB-MS: $m/z$ 973.17, [M + H]$^+$. Calc. for C$_{40}$H$_{60}$N$_8$Br$_4$: C, 49.40; H, 6.22; N, 11.52 %. Found: C, 49.31; H, 6.28; N, 11.62 %.

**Compound 8c** was obtained as a white powder in 91 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.81$ (m, 8H), 2.22-3.91 (m, 32H), 7.11-7.33 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 24.9$, 46.8, 47.0, 52.6, 52.9, 56.9, 128.4, 136.1. FAB-MS (MeOH): $m/z$ 605.80, [M + H]$^+$. Calc. for C$_{36}$H$_{60}$N$_8$: C, 71.48; H, 10.00; N,18.52 %. Found: C, 71.55; H, 10.22; N, 18.65 %.

**Compound 9b** was obtained as a white powder with 80 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta = 45.0$, 48.5, 57.0, 62.4, 63.4, 80.5, 130.3, 130.6, 131.7, 133.0, 135.1, 136.2. FAB-MS: $m/z$ 913.12, [M + H]$^+$. Calc. for C$_{35}$H$_{51}$N$_9$Br$_4$: C, 45.39; H, 5.93; N, 11.79 %. Found: C, 45.42; H, 5.93 ; N, 11.85%.

**Compound 9c** was obtained as a white powder with 94 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 2.6-2.8$ (m, 32H), 3.6 (brs, 8H), 7.15-7.50 (m, 8H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 45.4$, 51.1, 59.7, 127.9, 128.1, 128.9, 137.5, 138.7, 141.0. FAB-MS (MeOH): $m/z$ 549.41, [M + H]$^+$. Calc. for C$_{32}$H$_{52}$N$_8$: C, 70.03; H, 9.55; N, 20.42 %. Found: C, 70.21; H, 9.69; N, 20.66 %.

**Compound 10b** was obtained as a white powder in 89 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): mixture of the meso and racemic isomers. FAB-MS: $m/z$ 914.12, [M + H]$^+$. Calc. for C$_{35}$H$_{51}$N$_9$Br$_4$: C, 45.82; H, 5.60; N, 13.74 %. Found: C, 46.00; H, 5.78 ; N, 13.61 %.

**Compound 10c** was obtained as a white powder in 90 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 2.34$ (s, 4H), 2.40-2.90 (m, 34H), 3.55 (s, 2H), 3.75 (s, 2H), 3.76 (s, 2H), 3.98 (s, 2H), 7.00-7.80 (m, 7H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 44.3$ (2C), 46.3 (2C), 50.9, 51.2, 52.1, 52.8, 59.0, 59.1, 60.6, 61.3, 119.8, 120.7, 125.7, 127.5, 127.9, 129.8, 136.4, 138.3, 139.6, 158.1, 159.2. FAB-MS (MeOH): $m/z$ 549.51, [M + H]$^+$. Calc. for C$_{31}$H$_{51}$N$_9$: C, 67.72; H, 9.35; N, 22.93 %. Found: C, 67.82; H, 9.44; N, 23.00 %.
**Compound 11b** was obtained as a white powder in 70 % yield. $^{13}$C NMR (D$_2$O, 400 MHz): $\delta = 21.0$, 48.5-49.5 (m), 53.0-55.0 (m), 63.5, 64.5, 80.1, 129.2, 130.9, 133.7, 137.3, 137.4, 139.1, 142.3. FAB-MS: $m/z$ 973.17, [M + H]$^+$. Calc. for C$_{40}$H$_{60}$N$_8$Br$_4$, H$_2$O: C, 48.50; H, 6.31; N, 11.31 %. Found: C, 48.56; H, 6.44 ; N, 11.44 %.

**Compound 11c** was obtained as a white powder in 90 % yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.97$ (m, 8H), 2.20-7.01 (m, 32H), 7.10-7.43 (m, 8H) $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 25.1$, 47.0, 49.0, 50.7, 52.8, 57.3, 126.0, 127.7, 135.5, 136.6, 136.9, 137.6. FAB-MS (MeOH): $m/z$ 605.91, [M + H]$^+$. Calc. for C$_{36}$H$_{60}$N$_8$: C, 71.48; H, 10.00; N, 18.52 %. Found: C, 71.55; H, 10.12; N, 18.71 %.