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Efficient synthesis of *N,N′*-methylenebisglycolurils

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Experimental

†[1]H and [13]C NMR spectra were recorded using Bruker AM-250 ([1]H, 250.13 MHz) and Bruker AM-300 spectrometers ([1]H, 300.13 MHz; [13]C, 75.5 MHz) in DMSO-d_6 and $CDCl_3$. Chemical shifts are reported in the δ scale relative to Me_4Si internal standard. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II instrument using the electrospray ionization method (ESI). Melting points were determined in a GALLENKAMP instrument (Sanyo). Elementary analyses were carried out using Perkin Elmer 2400 CHN Analyzer and EuroVector Euro EA Elemental Analyzer.

(1R,1'R*,5S*,5'S*)-2,2'-Methylenebis(6,8-dimethyl-3,7-dioxo-2,4,6,8-tetraaza-bicyclo[3.3.0]octane-4-butanoic acid* **1d**′ (racemate): yield 79%, mp 209–211 °C (decomp.). [1]H NMR (DMSO-d_6) δ: 1.69-1.82 (m, 4H, $2CH_2$); 2.26 (t, ^3J = 6.7 Hz, 6H, $2CH_2$); 2.84 (s, 12H, $4CH_3$); 3.18-3.43 (m, 4H, $2CH_2$); 4.82 (s, 2H, NCH_2); 5.10 (d, ^3J = 7.9 Hz, 2H, 2CH,); 5.19 (d, ^3J = 8.5 Hz, 2H, 2CH) 12.10 (br. s, 2H, COOH). HRMS, m/z: 525.2410 $[M + H]^+$ ($C_{21}H_{32}N_8O_8$), Δ = 1.1 ppm). Found (%):C, 48.18; H, 6.19; N, 21.28. Calc. for $C_{21}H_{32}N_8O_8$ (%): C, 48.09; H, 6.15; N, 21.36.

(1R,1'R*,5S*,5'S*)-2,2'-Methylenebis(4,6,8-trimethyl-2,4,6,8-tetraaza-bicyclo[3.3.0]octane-3,7-dione)* **1e**′ (racemate): yield 70%, mp 320 °C , [1]H NMR ($CDCl_3$) δ: 2.80 (s, 12H, $4CH_3$), 2.83 (s, 6H, $2CH_3$), 4.75 (br. s, 2H, CH_2), 5.04 (d, ^3J = 8.5 Hz, 2H, 2CH), 5.10 (d, ^3J = 8.5 Hz , 2H, 2CH). [13]C NMR ($CDCl_3$) δ: 29.9 (CH_3), 30.2 (CH_3), 51.2 (CH_2), 69.2, 71.9 (both CH), 158.7 (2 CO). Found (%): C, 47.41; H, 6.38; N, 29.42. Calc. for $C_{15}H_{24}N_8O_4$ (%): C 47.36; H, 6.36; N, 29.46.

(1R,1'R*,5S*,5'S*)-2,2'-Methylenebis(6,8-diethyl-4-methyl-2,4,6,8-tetraaza-bicyclo[3.3.0]octane-3,7-dione)* **1f**′ (racemate): yield 60%, mp 225−227 °C , [1]H NMR ($CDCl_3$) δ: 1.25 (t, ^3J = 7.0 Hz, 6H, 2C-CH_3), 1.29 (t, ^3J = 7.0 Hz, 6H, 2C-CH_3), 2.95 (s, 6H, 2N-CH_3), 3.19 (m, 2H, N-CH_2), 3.35 (m, 2H, N-CH_2), 3.49 (m, 2H, N-CH_2), 3.63 (m, 2H, N-CH_2), 4.81 (s, 2H, NCH_2N), 5.04 (d, ^3J = 8.5 Hz , 2H, 2CH), 5.53 (d, ^3J = 8.5 Hz, 2H, 2CH). **[13]C** NMR

(DMSO-d_6) δ: 13.19, 13.26 (both C-CH_3), 29.75 (NCH_3), 37.14, 37.36 (both NCH_2), 50.30 (NCH_2N), 66.83, 69.82 (both CH), 157.92, 158.70 (both C=O). HRMS, m/z: 459.2437 [M + Na]$^+$ ($C_{19}H_{32}N_8O_4$), Δ = 0.4 ppm). Found (%):C, 52.25; H, 7.37; N, 25.68. Calc. for $C_{19}H_{32}N_8O_4$ (%): C, 52.28; H, 7.39; N, 25.67.

(1R,1'S*,5S*,5'R*)-2,2'-Methylenebis(4-methyl-6,8-diethyl-2,4,6,8-tetraaza-bicyclo[3.3.0]octane-3,7-dione)* **1f**'' (*meso*-form): yield 6%, mp 171-173 °C ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, ^3J = 7.1 Hz, 6H, 2C-CH_3), 1.29 (t, ^3J = 7.0 Hz , 6H, 2C-CH_3), 2.93 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 3.25 (m, 2H, N-CH_2), 3.41 (m, 2H, N-CH_2), 3.56 (m, 2H, N-CH_2), 3.69 (m, 2H, N-CH_2), 4.94 (dd, 1H, J = 14.5 Hz, NCH_2N), 5.03 (dd, 1H, J = 14.5 Hz NCH_2N), 5.10 (d, ^3J = 8.5, 2H, 2CH), 5.15 (d, ^3J = 8.5, 2H, 2CH). Found (%):C, 52.31; H, 7.42; N, 25.65. Calc. for $C_{19}H_{32}N_8O_4$ (%): C, 52.28; H, 7.39; N, 25.67.

2,2'-Methylenebis(4,6,8-triethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) **1g:** yield 62%, mp 171-173 °C, ^{1}H NMR ($CDCl_3$), δ: 1.13-1.41 (m, 18H, 6C-CH_3), 3.19-3.87 (m, 12H, 6CH_2), 4.92-5.86 (m, 6H, 2CH-CH + CH_2). Found (%): C, 54.34; H, 7.84; N, 24.07. Calc. for $C_{21}H_{36}N_8O_4$ (%): C, 54.29; H, 7.81; N, 24.12.

4-Ethyl-6,8-dimethyl-2-{(4,6,8-trimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octan-2-yl)methyl}-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **1h** (racemate): yield 20%, mp 291–293 °C (decomp.). ^{1}H NMR (DMSO-d_6), δ: 1.08 (t, 3H, J = 7.0 Hz, C-CH_3), 2.81 (s, 12H, 4N-CH_3), 2.84 (s, 3H, N-CH_3), 3.12-3.42 (m, 2H, CH_2), 4.76 (dd, 2H, J = 2.5 Hz, CH_2), 5.03-5.14 (m, 4H, 4CH). ^{13}C NMR (DMSO-d_6), δ: 13.61 (C-CH_3); 27.53 (2N-CH_3), 29.32 (2N-CH_3); 29.80 (N-CH_3); 38.23 (C-CH_2), 64.99 (CH_2); 71.32 (CH); 73.07 (CH), 74.14 (2CH); 158.67, 158.86 (2CO), 167.73 (2CO). Found (%): C, 48.78; H, 6.69; N, 28.37. Calc. for $C_{16}H_{26}N_8O_4$ (%): C, 48.72; H, 6.64; N, 28.41.

6,8-Diethyl-4-methyl-2-{(4-ethyl-6,8-dimethyl-3,7-dioxo-2,4,6,8-tetraaza-bicyclo[3.3.0]octan-2-yl)methyl}-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione **1i** (racemate): yield 17%, mp 279–280 °C (decomp.).^{1}H NMR (DMSO-d_6) δ: 0.98-1.12 (m, 9H, 3C-CH_3), 2.72 (s, 3H, N-CH_3), 2.81 (s, 3H, N-CH_3), 2.85 (s, 3H, N-CH_3), 3.05-3.45 (m, 6H, 3N-CH_2), 4.80 (dd, 2H, J = 2.5 Hz, CH_2), 5.05-5.51 (m, 4H, 4CH). ^{13}C NMR (DMSO-d_6), δ: 13.21 (C-CH_3), 13.27 (C-CH_3), 13.33 (C-CH_3), 30.23 (2N-CH_3), 30.66 (N-CH_3), 37.24 (N-CH_2), 37.40 (2N-CH_2), 66.97 (CH_2), 68.91 (CH), 69.14 (CH), 69.94 (CH), 70.08 (CH), 158.06 (CO), 158.24 (CO), 158.80 (CO), 158.88 (CO). Found (%): C, 51.11; H, 7.13; N, 26.58. Calc. for $C_{18}H_{30}N_8O_4$ (%): C, 51.17; H, 7.16; N, 26.52.