Supporting Information

Design and Preparation of Potent, Non-Peptidic, Bioavailable Renin Inhibitors

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Numbering of compounds described in the experimental part

(1*R*, 5*S*)-9-Methyl-7-oxo-3,9-diaza-bicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (6)

mp = 54.8 – 55.3 °C. Chiral HPLC: t_R = 8.43 min, er = 99.9 : 0.01. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): 12.1 and 12.0 (s, broad, 1H, OH), 4.23 (m, 2H, ester- CH_2), 4.13 and 3.92 (d and m, J = 12.9 Hz, 1H, H-2, rot.), 3.92 and 3.80 (m and d, J = 12.7 Hz, 1H, H-4, rot.), 3.57 and 3.53 (s, 1H, H-5, rot.), 3.13 and 3.02 (m and d, J = 10.9 Hz, 1H, H-2, rot.), 3.06 and 2.94 (d, and m, J = 12.8 Hz, 1H, H-4, rot.), 2.94 (s, 1H, H-1), 2.63 (m, 1H, H-8), 2.34 (s, 3H, NMe), 2.13 and 2.01 (d and d, J = 19.2 and 18.8 Hz, 1H, H-8, rot.), 1.41 and 1.34 (s, 9H, Boc, rot.), 1.32 (m, 3H, ester- CH_3). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): 171.1 and 170.0 (ester-CO), 155.4 and 155.2 (Boc-CO), 95.1 and 94.7 (C7), 79.7 and 79.4 (Boc-C), 60.4 and 60.2 (ester- CH_2), 53.4 and 53.2 (C5), 52.8 and 52.6 (C1), 50.5 and 49.2 (C2), 48.2 and 46.7 (C4), 41.2 (NMe), 28.3 and 28.2 (Boc- CH_3), 26.7 and 26.4 (C8), 14.3 and 14.2 (ester- CH_3). IR (film): ν 2973, 2930, 2146, 1681, 1635 cm^{-1} . Anal. Calcd for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.59; H, 7.87; N, 8.57.

(1*R*, 5*S*)-9-Methyl-7-trifluoromethanesulfonyloxy-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (7)

R_f = 0.20 (EtOAc/heptane 1:4). $^1\text{H-NMR}$ (CDCl_3): 4.33 (q, J = 7.0 Hz, 1H, H-5), 4.16 (d, J = 12.6 Hz, 1H, H-2), 4.09 (d, J = 12.3 Hz, 1H^R , H-2 ^{R}), 4.00 (d, J = 13.2 Hz, 1H, H-4), 3.83 (s, 1H^R , H-5 ^{R}), 3.77 (s, 1H, H-5), 3.19 (d, J = 12.7 Hz, 1H, H-4), 3.04 (broad, d, $J \approx 9.9$ Hz, 2H, H-1, H-2), 2.75 (dd, J = 18.8, 6.4 Hz, 1H, H-8), 2.436 (s, 3H, NCH₃), 2.24 (d, J = 19.3 Hz, 1H, H-8), 1.40 (broad, s, 9H, Boc), 1.37 (t,

$J = 7.1$ Hz, 3H, H-12). ^{13}C -NMR (CDCl_3): 163.27 (CO), 155.19 (C13), 150.48 (CF_3), 119.30 (C6), 80.21 (OCMe_3), 61.80 (C11), 56.57 (C5), 53.34 (C1), 49.23 (C2), 47.20 (C4), 41.24 (NCH_3), 30.90 (C8), 28.07 ($\text{OC}(\text{CH}_3)_3$), 26.47 (C8), 13.99 (C12). IR (film) $\hat{\nu}$ 2977, 2934, 1694 cm^{-1} . Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_7\text{S}$: C, 44.54; H, 5.50; F, 12.43; N, 6.11; S, 6.99. Fond: C, 45.02; H, 5.42; F, 12.42; N, 6.04; S, 7.07. $[\alpha]_{\text{D}}^{25} = +23.0$ (1.0; MeOH), MS (ESI): m/z $r_t = 0.87$, 561.69 ($\text{M} + 1$) $^+$.

(1R, 5S)-7-{4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl}-9-methyl-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-tert-butyl ester 6-ethyl ester (9)

^1H -NMR (CDCl_3): 7.37 (d, $J = 7.3$ Hz, 1H, H_{arom}), 7.28 (d, $J = 6.5$ Hz, 1H ^{R} , H_{arom}^R), 7.26 (d, $J = 7.8$ Hz, 1H, H_{arom}), 7.07 (d, $J = 7.8$ Hz, 2H, H_{arom}), 6.95 (t, $J = 7.4$ Hz, 1H, H_{arom}), 6.88 (d, $J = 8.2$ Hz, 1H, H_{arom}), 6.83 (d, $J = 8.0$ Hz, 2H, H_{arom}), 4.59 (s, 2H, H-13), 4.24 (d, $J = 13.0$ Hz, 1H, H-2), 4.11 (t, $J = 6.0$ Hz, 2H, H-10), 4.06 – 3.87 (m, 2H and 2H ^{R} , H-15(2x) and H-4 ^{R} (2x)), 3.94 (broad, d, $J \approx 13.6$ Hz, 1H, H-4), 3.83 (s, 3H, OCH_3), 3.77 (s, 1H, H-5), 3.72 (t, $J = 5.9$ Hz, 2H, H-12), 3.19 (d, $J = 13.2$ Hz, 1H, H-4), 3.12 (d, $J = 12.7$ Hz, 1H, H-2), 2.98 (broad, d, 1H, H-1), 2.57 (dd, $J = 19.6, 6.3$ Hz, 1H, H-8), 2.47 (s, 3H ^{R} , NCH_3^R), 2.43 (s, 3H, NCH_3), 2.36 (d, $J = 19.8$ Hz, 1H, H-8), 2.12 (broad, t, $J \approx 6.0$ Hz, 2H and 1H ^{R} , H-11 and H-8 ^{R}), 1.97 (d, $J = 18.8$ Hz, 1H, H-8 ^{R}), 1.42 (broad, s, 9H ^{R} , Boc^R), 1.38 (broad, s, 9H, Boc), 0.94 (t, $J = 6.8$ Hz, 2H, H-16). ^{13}C -NMR (CDCl_3): 167.85 (CO), 158.60, 157.09, 155.35 (3Cq), 148.41 (Cq), 134.07 (Cq), 133.27 (Cq ^{R}), 128.80 (CH_{arom}), 128.59 (CH_{arom}), 128.14 (CH_{arom}), 127.93 ($\text{CH}_{\text{arom}}^R$), 126.80 (Cq), 123.25 (Cq), 120.42 (CH_{arom}), 113.82 (CH_{arom}), 110.23 (CH_{arom}), 79.53 (OCMe_3), 67.75 (C13), 66.99 (C12), 65.02 (C10), 60.37 (C15 ^{R}), 60.06 (C15), 56.03 (C5), 55.80 (C5 ^{R}), 55.32 (OCH_3), 52.93 (C1), 52.73 (C1 ^{R}), 50.91 (C4 ^{R}), 49.37 (C2), 47.29 (C4), 46.37 (C2 ^{R}), 41.47

(NCH₃^R), 41.25 (NCH₃), 30.93 (C8), 29.76 (11), 28.47 (OC(CH₃)₃^R), 28.24 (OC(CH₃)₃), 21.67 (C8^R), 13.73 (C16). IR (film) ν 2930, 1689 cm⁻¹. Anal. Calcd for C₃₃H₄₄N₂O₇: C, 68.25; H, 7.64; N, 4.82. Found: C, 66.35; H, 7.51; N, 4.73. $[\alpha]_D^{25} = +7.0$ (1.00; MeOH). LC-MS: $t_R = 0.92$ min, MS (ESI): m/z 581.51 (M + 1)⁺.

(1R, 5S)-7-{4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (10)

¹H-NMR (CDCl₃): 7.38 (d, J = 7.3 Hz, 1H, H_{arom}), 7.26 (d, J = 7.8 Hz, 1H, H_{arom}), 7.04 (d, J = 6.5 Hz, 2H, H_{arom}), 6.95 (t, J = 7.4 Hz, 1H, H_{arom}), 6.88 (d, J = 8.2 Hz, 1H, H_{arom}), 6.84 (d, J = 7.9 Hz, 2H, H_{arom}), 5.27 (s, 1H, H-5), 5.23 (s, 1H^R, H-5^R), 5.12 (s, 1H^R, H-5^R), 4.58 (s, 2H, H-13),): 4.42 (broad, s, 1H and 1H^R, H-1 and H-1^R), 4.32 (d, J = 13.4 Hz, 1H, H-2), 4.13 – 3.92 (m, 3H and 5H^R, H-4, H-15(2x) and H-4^R, H-10^R(2x) and H-15^R(2x)), 4.10 (t, J = 6.1 Hz, 2H, H-10), 3.83 (s, 3H, OCH₃), 3.71 (t, J = 5.8 Hz, 2H, H-12), 3.14 (d, J = 13.3 Hz, 1H and 1H^R, H-4 and H-4^R), 3.06 (d, J = 11.5 Hz, 1H and 1H^R, H-2 and H-2^R), 2.81 (dd, J = 19.6, 6.1 Hz, 1H, H-8), 2.53 (d, J = 19.8 Hz, 1H, H-8), 2.11 (t, J = 5.9 Hz, 2H, H-11), 1.99 (s, 3H, (CH₃)C-O), 1.95 (s, 3H, (CH₃)C-O), 1.41 (broad, s, 9H^R, Boc^R), 1.38 (broad, s, 9H, Boc), 1.03 (t, J = 6.7 Hz, 2H, H-16). ¹³C-NMR (CDCl₃): 165.80 (CO^R), 165.24 (CO), 165.16 (CO), 158.76, 157.09, 155.24 (3Cq), 151.87 (Cq^R), 151.72 (Cq), 151.11 (Cq), 150.99 (Cq^R), 133.33 (Cq^R), 133.27 (Cq), 128.82 (CH_{arom}), 128.59 (CH_{arom}), 128.23 (CH_{arom}), 128.18 (CH_{arom}), 127.92 (CH_{arom}^R), 126.79 (Cq), 124.05 (Cq), 123.91 (Cq^R), 120.42 (CH_{arom}), 114.00 (CH_{arom}^R), 113.82 (CH_{arom}), 110.23 (CH_{arom}), 106.59 (CCl₃), 106.51 (C^RCl₃), 88.93 (Me₂C^R-O), 88.81 (Cq, Me₂C-O), 80.15

(OCMe₃), 67.75 (C13), 66.98 (C12), 64.97 (C10), 60.24 (C15), 60.18 (C15^R), 55.33 (OCH₃), 49.84 (C5), 48.53 (C2), 48.20 (C5^R), 47.47 (C1), 47.28 (C4), 47.16 (C2^R), 46.06 (C1^R), 37.59, 36.82 (C8 and C8^R), 29.75 (11), 28.43 (OC(CH₃)₃^R), 28.24 (OC(CH₃)₃), 21.67, 21.59 ((CH₃)₂C-O), 13.86 (C16). IR (film) ν 2978, 1695 cm⁻¹. Anal. Calcd for C₃₇H₄₇N₂O₉Cl₃·0.5 H₂O: C, 57.04; H, 6.16; N, 3.59. Found: C, 57.34; H, 6.09; N, 3.68. $[\alpha]_D^{25} = -0.3$ (0.99; MeOH). LC-MS: $t_R = 1.22$ min, MS (ESI): m/z 771.41 (M + 1)⁺.

(1R, 5S)-6-[(2-Chloro-benzyl)-methyl-carbamoyl]-7-[4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-tert-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (12)

¹H-NMR (CDCl₃): 7.39 (d, J = 7.2 Hz, 1H, H_{arom}), 7.32 – 6.99 (m, 7H, H_{arom}), 6.96 (t, J = 7.5 Hz, 1H, H_{arom}), 6.88 (d, J = 8.1 Hz, 1H, H_{arom}), 6.85 – 6.72 (m, 2H, H_{arom}), 4.78 (d, J = 15.9 Hz, 1H, H-15), 4.75 – 4.37 (m, 6H and 5H^R, H-1, H-4, H-5, H-13(2x), H-15 and H-1^R, H-4^R, H-5^R and H-15^R(2x)), 4.10 (broad, d, 2H, H-10), 3.83 (s, 3H, OCH₃), 3.74 (t, J = 5.6 Hz, 2H, H-12), 3.50 – 2.98 (m, 3H and 3H^R, H-2, H-4, H-8 and H-2^R, H-4^R, H-8^R), 2.74, 2.70, 2.54 and 2.43 (NCH₃ and 3x NCH₃^R), 2.37 – 2.21 (m, 1H and 1H^R, H-8 and H-8^R), 2.14 (t, J = 5.9 Hz, 2H, H-11), 1.99 (s, 3H, (CH₃)C-O), 1.94 (s, 3H, (CH₃)C-O), 1.33 (broad, s, 9H^R, Boc^R), 1.29 (broad, s, 9H, Boc). ¹³C-NMR (CDCl₃): 159.13 (CO), 157.09 (Cq), 133.33 (Cq^R), 129.33 (CH_{arom}^R), 128.80 (CH_{arom}), 128.64 (CH_{arom}), 128.39 (CH_{arom}), 128.21 (CH_{arom}), 127.09 (CH_{arom}^R), 126.86 (CH_{arom}), 126.74 (Cq), 120.44 (CH_{arom}), 114.42 (CH_{arom}), 110.23 (CH_{arom}), 106.57 (CCl₃), 88.95 (Cq, Me₂C-O), 80.23 (OCMe₃), 67.78 (C13), 66.92 (C12), 65.02 (C10), 55.33 (OCH₃), 49.83 (C5), 48.26 (C2), 47.69 (C1), 47.19 (C4), 37.59 (C8), 35.50 (NCH₃), 29.73

(C11), 28.42 (OC(CH₃)₃), 21.90, 21.64, 21.58 ((CH₃)₂C-O and (C^RH₃)₂C-O). IR (film) ν 2925, 1697, 1607 cm⁻¹. Anal. Calcd for C₄₃H₅₁N₃O₈Cl₄: C, 58.71; H, 5.84; N, 4.78. Found: C, 58.60; H, 5.83; N, 4.98. $[\alpha]_D^{25} = +47.6$ (1.02; MeOH). LC-MS: $t_R = 1.26$ min, MS (ESI): m/z 880.65 (M + 1)⁺.

(1R, 5S)-6-[(2-Chloro-benzyl)-methyl-carbamoyl]-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (13)

¹H-NMR (CDCl₃): 7.39 (d, J = 7.2 Hz, 1H, H_{arom}), 7.33 – 6.99 (m, 7H, H_{arom}), 6.96 (t, J = 7.4 Hz, 1H, H_{arom}), 6.91 – 6.75 (m, 3H, H_{arom}), 6.63 (d, J = 7.5 Hz, 1H, H^R_{arom}), 6.55 (d, J = 7.3 Hz, 1H, H^R_{arom}), 4.76 (d, J = 15.7 Hz, 1H, H-15), 4.68 – 4.54 (m, 4H and 1H^R, H-1, H-5, H-13(2x) and H-15^R(2x)), 4.43 – 4.26 (m, 2H^R, H-1, H-1^R and H-5^R), 4.42 (d, J = 15.8 Hz, 1H and 1H^R, H-15 and H-15^R), 4.12 (broad, d, 2H, H-10), 3.83 (s, 3H, OCH₃), 3.75 (t, J = 5.6 Hz, 2H, H-12), 3.45, 3.41 (d and d, J = 12.1 Hz, J = 11.8 Hz, 2H, H-2 and H-4), 3.28 – 2.87 (m, 2H and 3H^R, H-2, H-4 and H-2^R, H-4^R and H-8^R), 3.20 (d, J = 15.9 Hz, 1H, H-8), 2.75, 2.71 and 2.59 (3H and 2x3H^R, NCH₃ and 2x NCH₃^R), 2.25 – 2.03 (m, 2H and 1H^R, H-8, NH and H-8^R), 2.10 (t, J = 5.7 Hz, 2H, H-11), 2.00 (s, 3H, (CH₃)C-O), 1.94 (s, 3H, (CH₃)C-O), 1.93 (s, 3H, (CH^R₃)C-O), 1.86 (s, 3H, (CH^R₃)C-O). ¹³C-NMR (CDCl₃): 170.84 (CO), 170.58 (CO^R), 159.12, 159.02, 157.09 (2CO and Cq), 133.83, 137.15, 133.90 (3xCq), , 133.78 (Cq^R), 133.46, 13.40 (2xCq), , 132.72 (Cq^R), 131.64, 131.58 (2xCq), 129.59 (CH_{arom}^R), 129.40 (CH_{arom}), 129.35 (CH_{arom}), 129.24 (CH_{arom}), 128.96 (CH_{arom}), 128.78 (CH_{arom}^R), 128.65 (CH_{arom}), 128.50 (CH_{arom}), 128.36 (CH_{arom}), 128.21 (CH_{arom}), 128.15 (CH_{arom}), 127.41 (CH_{arom}^R), 127.14 (CH_{arom}), 127.05 (CH_{arom}^R), 126.96 (CH_{arom}^R), 126.90 (CH_{arom}), 126.75 (Cq), 126.52 (CH_{arom}^R), 124.48 (CH_{arom}), 120.44 (CH_{arom}), 114.44

(CH_{arom}), 110.26 (CH_{arom}), 106.71 (CCl₃), 88.76 (Cq, Me₂C-O), 88.63 (Cq, Me₂C^R-O), 67.78 (C13), 66.92 (C12), 65.04 (C10), 55.34 (OCH₃), 51.64, 51.48 (C2^R, C4^R), 51.16, 49.79 (C1, C5), 48.78, 47.97 (C2, C4), 47.72, 45.76 (C1^R, C5^R), 35.77 (NC^RH₃), 35.64 (NCH₃), 33.58, 33.23 (C8, C8^R), 29.74 (C11), 21.97, 21.69, 21.59 ((CH₃)₂C-O and (C^RH₃)₂C-O). IR (film) ν 2908, 1698, 1606 cm⁻¹. Anal. Calcd for C₃₈H₄₃N₃O₆Cl₄: C, 58.55; H, 5.56; N, 5.39. Found: C, 58.40; H, 5.51; N, 5.40. $[\alpha]_D^{25} = +18.6$ (1.0; MeOH). LC-MS: t_R = 1.08 min, MS (ESI): m/z 780.11 (M + 1).

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (15)

¹H-NMR (CDCl₃): 7.37 (d, J = 7.4 Hz, 1H, H_{arom}), 7.26 (d, J = 7.4 Hz, 1H, H_{arom}), 7.02 – 6.92 (m, 3H, H_{arom}), 6.90 – 6.81 (m, 3H, H_{arom}), 5.21 (broad, s, 1H^R, H-5^R), 5.16 (s, 1H, H-5), 4.86 (d, J = 13.4 Hz, 1H^R, H-2^R), 4.82 (d, J = 13.9 Hz, 1H^R, H-2^R), 4.76 (d, J = 13.4 Hz, 2H, H-2), 4.58 (s, 2H, H-13), 4.51 (d, J = 7.2 Hz, 1H^R, H-1^R), 4.46 (d, J = 6.5 Hz, 1H, H-1), 4.10 (t, J = 6.3 Hz, 2H, H-10), 4.06 – 3.91 (m, 3H, H-4, H-15(2x)), 3.83 (s, 3H, OCH₃), 3.78 (dd, J = 13.4, 2.2 Hz, 1H^R, H-4^R), 3.71 (t, J = 6.1 Hz, 2H, H-12), 3.49 (dd, J = 13.4, 2.2 Hz, 1H and 1H^R, H-4 and H-4^R), 2.98 – 2.81 (m, 2H and 2H^R, H-2, H-8 and H-2^R, H-8^R), 2.42 (dd, J = 19.4, 2.2 Hz, 1H and 1H^R, H-8 and H-8^R), 2.11 (t, J = 6.2 Hz, 2H, H-11), 2.00, 1.99, 1.96, 1.95 (4 x s, 4 x 3H, 2 x (CH₃)C-O and 2 x (CH^R₃)C-O), 0.98 (t, J = 7.1 Hz, 2H, H-16).

¹³C-NMR (CDCl₃): 170.85 (CO^R), 170.58 (CO), 159.11 (Cq), 159.01 (Cq), 157.07 (Cq), 152.07 (Cq^R), 151.36 Cq), 137.81 (Cq), 137.73 (Cq^R), 137.33 (Cq^R), 137.13 Cq), 133.89 (Cq), 133.76 (Cq), 133.71 (Cq^R), 133.45 (Cq), 133.39 (Cq), 132.74 (Cq^R), 131.72 (Cq^R), 131.64 (Cq), 131.58 (Cq), 129.40 (CH_{arom}), 129.34 (CH_{arom}), 129.27 (Cq), 129.23 (CH_{arom}), 128.94 (CH^R_{arom}), 128.77 (CH_{arom}), 128.65

(CH_{arom}), 128.49 (CH_{arom}), 128.35 (CH^R_{arom}), 128.21 (CH_{arom}), 128.14 (CH_{arom}), 128.10 (CH_{arom}), 127.64 (CH^R_{arom}), 127.40 (CH^R_{arom}), 127.14 (CH_{arom}), 127.04 (CH^R_{arom}), 126.96 (CH_{arom}), 126.90 (CH_{arom}), 126.73 (Cq), 120.43 (CH_{arom}), 114.53 (CH_{arom}), 110.24 (CH_{arom}), 106.71 (CH_{arom}), 88.75 (Cq), 88.62 (Cq), 67.78 (C13), 67.09 (C13^R), 66.92 (12), 66.88 (C12^R), 65.02 (C10), 60.38 (C15), 55.33 (OCH₃), 51.66, 51.61, 51.48 (C4^R), 51.38, 51.17, 49.99 (C5^R), 49.80 (C5), 48.80, 48.00 (C4, C15), 47.58 (C1), 47.23, 47.04 (C2, C2^R), 45.76 (C1^R), 33.57, 33.22 (C8, C8^R), 29.73 (C11), 21.96, 21.91, 21.68, 21.58 (CH₃CO, CH₃CO^R), 13.8 (C16). IR (film) ν 2927, 1706, 1651 cm⁻¹. Anal. Calcd for C₃₄H₄₁N₂O₈Cl₃: C, 57.35; H, 5.80; N, 3.93. Found: C, 57.54; H, 5.87; N, 3.85. $[\alpha]_D^{25} = +55.3$ (1.01; MeOH). LC-MS: t_R = 1.17 min, MS (ESI): m/z 711.41 (M + 1)⁺.

(1R, 5S)-7-{4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-phenyl}-9-methyl-3,9-diazabicyclo-[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (19a)

¹H-NMR (CDCl₃): 7.13 (d, J = 7.4 Hz, 2H, H_{arom}), 7.06 (d, J = 7.0 Hz, 2H, H_{arom}), 4.24 (d, J = 12.9 Hz, 1H, H-2), 4.03 – 3.84 (m, 3H, H-4 and H-14), 3.77 (s, 1H, H-5), 3.70 (s, 1H^R, H-5^R), 3.65 (t, J = 6.0 Hz, 2H, H-12), 3.18 (d, J = 13.2 Hz, 1H, H-4), 3.12 (d, J = 12.7 Hz, 1H, H-2), 2.98 (broad, s, 1H, H-1), 2.68 (t, J = 7.6 Hz, 2H, H-10), 2.59 (dd, J = 19.7, 6.6 Hz, 1H, H-8), 2.47 (s, 3H^R, NCH₃^R), 2.43 (s, 3H, NCH₃), 2.36 (d, J = 19.8 Hz, 1H, H-8), 1.84 (q, 2H, H-11), 1.43 (broad, s, 9H^R, Boc^R), 1.39 (broad, s, 9H, Boc), 0.93 (s, 9H, Si^tBu), 0.86 (t, J = 7.2 Hz, 2H, H-15), 0.12 (s, 6H, Si(CH₃)₂). ¹³C-NMR (CDCl₃): 167.64 (CO), 167.33 (CO^R), 155.29 (CO), 154.81 (CO^R), 148.93 (Cq), 148.35 (Cq^R), 141.58 (Cq), 139.40 (Cq^R), 139.15 (Cq), 127.87 (CH_{arom}), 126.82 (CH_{arom}), 126.59 (CH_{arom}^R), 123.15 (Cq), 79.58 (OCMe₃), 62.31 (C12), 60.07 (C14), 55.92 (C5), 55.62 (C5^R), 52.91 (C1), 52.71 (C1^R), 50.78

(C2^R), 49.24 (C2), 47.16 (C4), 46.22 (C4^R), 41.40 (NCH₃^R), 41.19 (NCH₃), 34.45 (C11), 31.80 (C10), 31.22 (C8^R), 30.93 (C8), 28.46 (OC(CH₃)₃^R), 28.25 (OC(CH₃)₃), 25.95 (SiC(CH₃)₃), 18.33 (SiC(CH₃)₃), 13.52 (C15), -5.28 (Si(CH₃)₂). IR (film) ν 2929, 2857, 1693 cm⁻¹. Anal. Calcd for C₃₁H₅₀N₂O₅Si: C, 66.63; H, 9.02; N, 5.01. Found: C, 66.25; H, 8.92; N, 4.98. $[\alpha]_D^{25} = +1.66(1.28; \text{MeOH})$. LC-MS: $t_R = 0.98$ min, MS (ESI): m/z 559.61 (M + 1)⁺.

(1R, 5S)-7-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxy]-phenyl}-9-methyl-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (19b)

¹H-NMR (CDCl₃): 7.07 (d, J = 8.4 Hz, 2H, H_{arom}), 6.84 (d, J = 8.4 Hz, 2H, H_{arom}), 4.24 (d, J = 12.9 Hz, 1H, H-2), 4.08 – 3.87 (m, 7H, H-4, H-10(2x), H-11(2x) and H-13(2x)), 3.77 (s, 1H, H-5), 3.18 (d, J = 14.5 Hz, 1H, H-4), 3.12 (d, J = 12.0 Hz, 1H, H-2), 2.98 (d, J = 5.8 Hz, 1H, H-1), 2.57 (dd, J = 20.1, 6.5 Hz, 1H, H-8), 2.42 (s, 3H, NCH₃), 2.35 (d, J = 19.7 Hz, 1H, H-8), 1.40 (broad, s, 9H, Boc), 0.93 (s, 12H, Si^tBu and H-14), 0.12 (s, 6H, Si(CH₃)₂). ¹³C-NMR (CDCl₃): 167.89 (CO), 158.49, 155.34 (2Cq), 148.40 (Cq), 134.27 (Cq), 128.15 (CH_{arom}), 123.33 (Cq), 113.84 (CH_{arom}), 79.51 (OCMe₃), 69.36 (C10), 62.01 (C11), 60.06 (C13), 56.02 (C5), 52.93 (C1), 49.42 (C2), 47.32 (C4), 41.29 (NCH₃), 30.90 (C8), 28.48 (OC(CH₃)₃), 25.92 (SiC(CH₃)₃), 18.41 (SiC(CH₃)₃), 13.70 (C14), -5.20 (Si(CH₃)₂). IR (film) ν 2928, 2856, 1683, 1607 cm⁻¹. Anal. Calcd for C₃₀H₄₈N₂O₆Si: C, 64.25; H, 8.63; N, 5.00. Found: C, 64.08; H, 8.44; N, 5.04. $[\alpha]_D^{25} = +4.5 (1.0; \text{MeOH})$. LC-MS: $t_R = 0.98$ min, MS (ESI): m/z 561.69 (M + 1)⁺.

(1R, 5S)-7-{4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tri-carboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (20a)

$^1\text{H-NMR}$ (CDCl_3): 7.13 (d, $J = 7.5$ Hz, 2H, H_{arom}), 7.03 (d, $J = 6$. Hz, 2H, H_{arom}), 5.67 (s, 1H, H-5), 5.24 (s, 1H^{R} , H-5^{R}), 5.14 (s, 1H^{R} , H-5^{R}), 4.41 (broad, s, 1H and 1H^{R} , H-1 and H-1^{R}), 4.32 (d, $J = 13.2$ Hz, 1H, H-2), 4.13 (d, $J = 11.8$ Hz, 1H^{R} , H-4^{R}), 4.09 (d, $J = 11.4$ Hz, 1H, H-4), 4.05 – 3.87 (m, 2H, H-14), 3.65 (t, $J = 6.1$ Hz, 2H, H-12), 3.14 (d, $J = 13.3$ Hz, 1H and 1H^{R} , H-4 and H-4^{R}), 3.07 (d, $J = 13.0$ Hz, 1H, H-2), 2.83 (broad, dd, $J \approx 20.0, 7.0$ Hz, 1H, H-8), 2.68 (t, $J = 7.4$ Hz, 2H, H-10), 2.52 (d, $J = 19.5$ Hz, 1H, H-8), 2.36 (d, $J = 19.8$ Hz, 1H, H-8), 1.99 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.94 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.89 – 1.78 (m, 2H, H-11), 1.43 (broad, s, 9H^{R} , Boc^{R}), 1.39 (broad, s, 9H, Boc), 1.02 - 0.84 (m, 12H, Si^tBu and H-15), 0.86 (t, $J = 7.2$ Hz, 2H, H-15), 0.07 (s, 6H, $\text{Si}(\text{CH}_3)_2$). $^{13}\text{C-NMR}$ (CDCl_3): 165.21, 165.13 (CO and CO^{R}), 155.23, 154.68 (2xCO), 151.90 (Cq^{R}), 151.74 (Cq), 151.49 (Cq^{R}), 151.34 (Cq), 141.75 (Cq), 138.69 (Cq^{R}), 138.61 (Cq), 128.06 (CH_{arom}), 127.89 (CH_{arom}), 126.82 (CH_{arom}), 126.78 (CH_{arom}), 126.54 ($\text{CH}^{\text{R}}_{\text{arom}}$), 124.22 (Cq^{R}), 124.07 (Cq^{R}), 106.58 (CCl_3), 88.94 ($\text{Me}_2\text{C}^{\text{R}}\text{-O}$), 88.81 (Cq, $\text{Me}_2\text{C-O}$), 80.13 (OCMe_3), 77.22 ($\text{OC}^{\text{R}}\text{Me}_3$), 62.34 (C12), 60.21 (C14), 60.15 (C14^{R}), 50.06 (C5^{R}), 49.76 (C5^{R}), 49.42 (C5^{R}), 48.45 (C2), 47.42, 46.01 (C1 and C1^{R}), 47.22, 47.09 (C4 and C4^{R}), 37.58, 36.81 (C8 and C8^{R}), 34.36 (C11), 31.87 (CH_2^{R}), 31.83 (C10), 29.01(CH_2^{R}), 28.43 ($\text{OC}(\text{C}^{\text{R}}\text{H}_3)_3$), 28.25 ($\text{OC}(\text{CH}_3)_3$), 25.95 ($\text{SiC}(\text{CH}_3)_3$), 25.65 ($\text{SiC}(\text{C}^{\text{R}}\text{H}_3)_3$), 24.83 ($\text{SiC}(\text{C}^{\text{R}}\text{H}_3)_3$), 22.68 (CH_2^{R}), 21.71, 21.66, 21.58 ($(\text{CH}_3)_2\text{C-O}$ and $(\text{C}^{\text{R}}\text{H}_3)_2\text{C-O}$), 18.32 ($\text{SiC}(\text{CH}_3)_3$), 14.10 (C15), 13.68, 13.62 (C15^{R}), -3.57 ($\text{Si}(\text{C}^{\text{R}}\text{H}_3)_2$), -5.29 ($\text{Si}(\text{CH}_3)_2$). IR (film) ν 2977, 2932, 1694 cm^{-1} . $[\alpha]_{\text{D}}^{25} = +1.44(1.45; \text{MeOH})$. LC-MS: $t_{\text{R}} = 1.37$ min, MS (ESI): m/z 748.86 ($\text{M} + 1$) $^{+}$.

(1*R*, 5*S*)-7-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (20b)

$^1\text{H-NMR}$ (CDCl_3): 7.04 (broad, d, $J \approx 7.5$ Hz, 2H, H_{arom}), 6.84 (d, $J = 8.1$ Hz, 2H, H_{arom}), 5.26 (broad, s, 1H^{R} , H-5^{R}), 5.23 (broad, s, 1H, H-5), 5.12 (broad, s, 1H^{R} , H-5^{R}), 4.41 (broad, s, 1H and 1H^{R} , H-1 and H-1^{R}), 4.31 (d, $J = 13.5$ Hz, 1H, H-2), 4.15 – 3.89 (m, 7H, H-4, H-10(2x), H-11(2x) and H-13(2x)), 3.22 – 2.93 (m, 2H and 2H^{R} H-2, H-4 and H-2^{R} , H-4^{R}), 2.84 (dd, $J \approx 18.2, 7.6$ Hz, 1H, H-8), 2.78 (dd, $J \approx 18.1, 7.0$ Hz, 1H^{R} , H-8^{R}), 2.53 (broad, d, $J \approx 19.7$ Hz, 1H and 1H^{R} , H-8 and H-8^{R}), 1.99 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.94 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.41 (broad, s, 9H^{R} , Boc^{R}), 1.37 (broad, s, 9H, Boc), 1.02 (t, $J = 6.9$ Hz, 3H, H-14), 0.92 (s, 9H, $\text{Si}^{\text{t}}\text{Bu}$), 0.11 (s, 6H, $\text{Si}(\text{CH}_3)_2$). $^{13}\text{C-NMR}$ (CDCl_3): 165.24, 165.16 (CO and CO^{R}), 158.64, 155.25 (2xCO), 151.87 (Cq^{R}), 151.72 (Cq), 151.08 (Cq^{R}), 150.95 (Cq), 133.51 (Cq^{R}), 133.44 (Cq), 128.23 (CH_{arom}), 128.18 (CH_{arom}), 127.92 ($\text{CH}^{\text{R}}_{\text{arom}}$), 124.09 (Cq), 123.95 (Cq^{R}), 114.03 ($\text{CH}^{\text{R}}_{\text{arom}}$), 113.86 (CH_{arom}), 106.58 (CCl_3), 106.49 ($\text{C}^{\text{R}}\text{Cl}_3$), 88.93 ($\text{Me}_2\text{C}^{\text{R}}\text{-O}$), 88.81 (Cq, $\text{Me}_2\text{C-O}$), 80.14 (OCMe_3), 77.22 ($\text{OC}^{\text{R}}\text{Me}_3$), 69.29 (C10), 61.98 (C11), 60.24 (C13), 60.18 (C13^{R}), 49.83 (C5), 49.53 (C5^{R}), 48.52 (C5^{R}), 48.14 (C2), 48.14 (C2^{R}), 47.45, 46.05 (C1 and C1^{R}), 47.27, 47.15 (C4 and C4^{R}), 37.59, 36.81 (C8 and C8^{R}), 28.42 ($\text{OC}(\text{C}^{\text{R}}\text{H}_3)_3$), 28.23 ($\text{OC}(\text{CH}_3)_3$), 25.91 ($\text{SiC}(\text{CH}_3)_3$), 21.66, 21.58 ($(\text{CH}_3)_2\text{C-O}$), 18.40 ($\text{SiC}(\text{CH}_3)_3$), 13.82 (C14), 13.78 (C14^{R}), -5.21 ($\text{Si}(\text{CH}_3)_2$). IR (film) ν 2929, 2857, 1697, 1604 cm^{-1} . Anal. Calcd for $\text{C}_{34}\text{H}_{51}\text{N}_2\text{O}_8\text{Cl}_3\text{Si}$: C, 54.43; H, 6.85; N, 3.73. Found: C, 54.48; H, 6.77; N, 3.74. $[\alpha]_{\text{D}}^{25} = +1.5$ (1.02; MeOH). LC-MS: $t_{\text{R}} = 1.28$ min, MS (ESI): m/z 751.52 ($\text{M} + 1$) $^{+}$.

(1R, 5S)-7-{4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tri-carboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (21a)

LC-MS: $t_R = 1.23$ min, MS (ESI): m/z 721.41 ($M + 1$)⁺.

(1R, 5S)-7-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tri-carboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (21b)

LC-MS: $t_R = 1.20$ min, MS (ESI): m/z 723.39 ($M + 1$)⁺.

(1R, 5S)-7-{4-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-phenyl}-6-[cyclopropyl-(2,3-dichloro-benzyl)-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (22a)

¹H-NMR (CDCl₃): 7.36 (d, J = 7.6 Hz, 1H, H_{arom}), 7.17 – 6.99 (m, 5H, H_{arom}), 6.96 (d, J = 7.6 Hz, 1H, H_{arom}), 6.85 (d, J = 7.6 Hz, 1H^R, H^R_{arom}), 4.78 (broad, d, J ≈ 15.2 Hz, 2H, H-4, H-14), 4.73 – 4.44 (m, 2H and 4H^R, H-1, H-5, H-1^R, H-5^R, H-14^R(2x)), 4.35 (d, J = 15.4 Hz, 1H, H-14), 4.23 (d, J = 13.0 Hz, 1H, H-2), 4.09 (d, J = 13.0 Hz, 1H^R, H-2^R), 3.70 – 3.57 (m, 2H, H-12), 3.31 – 2.98 (m, 1H and 3H^R, H-8 and H-2^R, H-4^R, H-8^R), 3.16 (broad, d, J ≈ 12.8 Hz, 1H, H-4), 3.04 (d, J = 12.5 Hz, 1H, H-2), 2.77 – 2.58 (m, 2H, H-10), 2.34 (d, J ≈ 18.2 Hz, 1H, H-8), 2.27 (d, J ≈ 18.0 Hz, 1H^R, H-8^R), 2.01 (s, 3H, (CH₃)C-O), 1.97 (s, 3H, (CH₃)C-O), 1.92 – 1.57 (m, 3H and 1H^R, H-11, H-15 and H-15^R), 1.54 (broad, s, 9H^R, Boc^R), 1.48 (broad, s, 9H, Boc), 0.94 (s, 9H, Si^tBu), 0.96 – 0.74 and 0.68 – 0.17 (m, 1H and 1H^R, H-15 and H-15^R), 0.07 (s, 6H, Si(CH₃)₂). ¹³C-NMR (CDCl₃): 172.30 (CO), 155.32 (CO), 150.81 (Cq), 137.73 (Cq^R), 137.61 (Cq), 137.50 (Cq), 137.20 (Cq^R), 132.86 (Cq), 131.25 (Cq^R), 128.91 (CH_{arom}), 128.48 (CH_{arom}), 128.38 (CH_{arom}), 128.15 (CH^R_{arom}), 127.37 (CH^R_{arom}), 127.13 (CH_{arom}), 126.90 (CH_{arom}), 126.67 (CH_{arom}), 126.29 (CH^R_{arom}), 106.64 (CCl₃), 89.14 (Me₂C-O), 88.76 (Cq, Me₂C^R-O), 80.13 (OCMe₃), 77.22 (OC^RMe₃), 62.21 (C12), 62.17 (C12^R), 50.74, 49.36, 47.45, 45.71 (C1, C5 and C1^R, C5^R), 48.98, 48.68, 48.48, 47.81 (C2, C4 and C1⁴, C14^R), 34.48 (C11^R), 34.13 (C11), 33.1, 32.81 (C8 and C8^R), 31.87 (C10^R), 31.73 (C10), 31.08 (C15), 28.47 (OC(CH₃)₃), 25.97 (SiC(CH₃)₃), 22.68 (C^RH₃)₂C-O), 21.68, 21.61 (CH₃)₂C-O), 18.34 (SiC(CH₃)₃), 10.85, 6.84, 6.17 (C16 and C16^R), -5.28 (Si(CH₃)₂). IR (film) ν 2928, 2856, 1698 cm⁻¹. Anal. Calcd for C₄₃H₅₈N₃O₆Cl₅Si: C, 56.24; H, 6.37; N, 4.58. Found: C, 56.79; H, 6.59; N, 4.65. [α]_D²⁵ = +139.9 (0.98; MeOH). LC-MS: t_R = 1.45 min, MS (ESI): m/z 917.87 (M + 1)⁺.

(1*R*, 5*S*)-7-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxy]-phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (22b)

$^1\text{H-NMR}$ (CDCl_3): 7.33 (broad, s, 1H, H_{arom}), 7.17 – 7.02 (m, 3H, H_{arom}), 6.85 – 6.69 (m 3H, H_{arom}), 4.81 – 4.32 (m, 5H and 5H^{R} , H-1, H-4, H-5, H-13(2x), H-1 $^{\text{R}}$, H-4 $^{\text{R}}$, H-5 $^{\text{R}}$, H-13 $^{\text{R}}$ (2x)), 4.23 (d, $J = 13.5$ Hz, 1H, H-2), 4.13 – 3.93 (m, 4H and 1H^{R} , H-10(2x), H-11(2x) and H-2 $^{\text{R}}$), 3.28 – 3.0 (m, 2H and 3H^{R} , H-4, H-8 and H-2 $^{\text{R}}$, H-4 $^{\text{R}}$, H-8 $^{\text{R}}$), 3.04 (broad, d, $J \approx 12.6$ Hz, 1H, H-2), 2.32 (d, $J \approx 18.0$ Hz, 1H, H-8), 2.26 (d, $J \approx 18.1$ Hz, 1H^{R} , H-8 $^{\text{R}}$), 2.17 (broad, d, $J \approx 21.7$ Hz, 1H^{R} , H-8 $^{\text{R}}$), 2.01 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.97 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.82 – 1.59 (m, 1H and 1H^{R} , H-14 and H-14 $^{\text{R}}$), 1.53 (broad, s, 9H^{R} , Boc $^{\text{R}}$), 1.48 (broad, s, 9H, Boc), 0.94 (s, 9H, $\text{Si}^{\text{t}}\text{Bu}$), 0.94 – 0.73 and 0.68 – 0.17 (m, 1H and 1H^{R} , H-15 and H-15 $^{\text{R}}$), 0.13 (s, 6H, $\text{Si}(\text{CH}_3)_2$). $^{13}\text{C-NMR}$ (CDCl_3): 172.88, 172.55 (CO and CO $^{\text{R}}$), 159.11, 159.03 (CO and CO $^{\text{R}}$), 155.34 (CO), 151.62 (Cq), 150.81 (Cq), 137.73 (Cq $^{\text{R}}$), 137.64 (Cq), 137.13 (Cq), 136.96 (Cq $^{\text{R}}$), 132.87 (Cq), 132.36 (Cq $^{\text{R}}$), 131.32 (Cq $^{\text{R}}$), 131.02 (Cq), 128.84 (CH_{arom}), 128.24 ($\text{CH}^{\text{R}}_{\text{arom}}$), 128.10 (CH_{arom}), 128.00 (CH_{arom}), 127.42 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.24 (CH_{arom}), 127.06 (CH_{arom}), 126.79 ($\text{CH}^{\text{R}}_{\text{arom}}$), 125.85 ($\text{CH}^{\text{R}}_{\text{arom}}$), 114.47 ($\text{CH}^{\text{R}}_{\text{arom}}$), 114.37 (CH_{arom}), 106.34 (CCl_3), 89.15 ($\text{Me}_2\text{C-O}$), 88.76 (Cq, $\text{Me}_2\text{C}^{\text{R}}\text{-O}$), 80.10 (OCMe_3), 77.22 ($\text{OC}^{\text{R}}\text{Me}_3$), 69.35 (C10), 61.96 (C11), 51.00, 50.70, 49.50, 49.28 (C1 $^{\text{R}}$ and C5 $^{\text{R}}$), 49.00 (C13 $^{\text{R}}$), 48.67 (C13), 48.51 (C2), 48.28 (C4), 47.75 (C4 $^{\text{R}}$), 47.44, 45.73 (C1 and C5), 33.12, 32.76 (C8 and C8 $^{\text{R}}$), 31.10, 31.04 (C14 and C14 $^{\text{R}}$), 28.48 ($\text{OC}(\text{CH}_3)_3$), 28.34 ($\text{OC}(\text{CH}_3)_3$), 25.93 ($\text{SiC}(\text{CH}_3)_3$), 21.78 ($(\text{CH}_3)_2\text{C-O}$), 21.68, 21.61 ($(\text{CH}_3)_2\text{C-O}$), 18.43 ($\text{SiC}(\text{CH}_3)_3$), 10.53, 10.37, 6.55, 5.89 (C15 and C15 $^{\text{R}}$), -5.18 ($\text{Si}(\text{CH}_3)_2$). IR (film) ν 2928, 2856, 1698, 1608 cm^{-1} . Anal. Calcd for $\text{C}_{42}\text{H}_{56}\text{N}_3\text{O}_7\text{Cl}_5$: C, 54.82; H, 6.13; N, 4.57. Found: C, 55.02; H, 6.09; N, 4.56. $[\alpha]_{\text{D}}^{25} = +126.0$ (1.0; MeOH). LC-MS: $t_{\text{R}} = 1.34$ min, MS (ESI): m/z 920.65 ($\text{M} + 1$) $^{+}$.

(1R, 5S)-3-Acetyl-6-[cyclopropyl-(2,3-dichloro-benzyl)-carbamoyl]-7-[4-(3-hydroxy-propyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid trichloromethyl ester (23a)

$^1\text{H-NMR}$ (CDCl_3): 7.36 (t, $J = 6.6$ Hz, 1H, H_{arom}), 7.18 – 7.00 (m, 4H, H_{arom}), 6.77 (d, $J = 7.7$ Hz, 1H, H_{arom}), 6.72 (d, $J = 7.7$ Hz, 1H, H_{arom}), 4.74 (s, 1H and 1H^{R} , H-5 and H-5 $^{\text{R}}$), 4.72 (broad, d, $J \approx 14.9$ Hz, 1H, H-2), 4.68 (broad, d, $J \approx 16.3$ Hz, 1H, H-14), 4.65 – 4.00 (m, 1H and 2H^{R} , H-1, H-1 $^{\text{R}}$ and H-14 $^{\text{R}}$), 4.48 (broad, d, $J = 12.8$ Hz, 1H, H-4), 4.41 (d, $J = 15.9$ Hz, 1H^{R} , H-14 $^{\text{R}}$), 4.38 (d, $J = 15.7$ Hz, 1H, H-14), 3.73 – 3.61 (m, 2H, H-12), 3.46 (d, $J = 14.7$ Hz, 1H, H-4), 3.22 (dd, $J = 18.3, 7.5$ Hz, 1H, H-8), 3.13 (d, $J = 18.1, 7.4$ Hz, 1H, H-8 $^{\text{R}}$), 2.88 (broad, d, $J = 12.8$ Hz, 1H, H-2), 2.70 (q, $J = 7.4$ Hz, 2H, H-10), 2.38 – 2.21 (m, 1H and 1H^{R} , H-8 and H-8 $^{\text{R}}$), 2.29 (s, 3H, CH_3CO), 2.27 (s, 3H^{R} , $\text{CH}_3^{\text{R}}\text{CO}$), 2.03 (s, 3H, $(\text{CH}_3)\text{C-O}$), 2.01 (s, 3H, $(\text{CH}_3)\text{C-O}$), 1.98 (s, 3H^{R} , $(\text{CH}_3^{\text{R}})\text{C-O}$), 1.93 – 1.60 (m, 3H and 1H^{R} , H-11, H-15 and H-15 $^{\text{R}}$), 0.95 – 0.77, 0.73 – 0.51, 0.45 – 0.31 and 0.29 – 0.19 (m, 4H and 4H^{R} , H-16 and H-16 $^{\text{R}}$). $^{13}\text{C-NMR}$ (CDCl_3): 173.07, 172.87, 171.24, 171.21 (CO and CO^{R}), 151.59 (Cq), 150.61 (Cq $^{\text{R}}$), 142.59 (Cq), 142.44 (Cq $^{\text{R}}$), 138.49 (Cq), 138.22 (Cq $^{\text{R}}$), 137.14 (Cq), 137.07 (Cq $^{\text{R}}$), 133.06 (Cq), 133.00 (Cq $^{\text{R}}$), 131.30 (Cq $^{\text{R}}$), 131.00 (Cq), 129.04 (CH_{arom}), 129.02 (CH_{arom}), 128.79 (CH_{arom}), 128.70 (CH_{arom}), 128.60 ($\text{CH}_{\text{arom}}^{\text{R}}$), 128.53 ($\text{CH}_{\text{arom}}^{\text{R}}$), 127.42 ($\text{CH}_{\text{arom}}^{\text{R}}$), 127.26 (CH_{arom}), 127.15 (CH_{arom}), 127.07 (CH_{arom}), 126.73 ($\text{CH}_{\text{arom}}^{\text{R}}$), 126.56 (CH_{arom}), 126.47 (CH_{arom}), 126.36 (CH_{arom}), 126.18 ($\text{CH}_{\text{arom}}^{\text{R}}$), 125.42 (Cq), 106.65 (CCl_3), 106.53 ($\text{C}^{\text{R}}\text{Cl}_3$), 89.32 ($\text{Me}_2\text{C-O}$), 88.95 (Cq, $\text{Me}_2\text{C}^{\text{R}}\text{-O}$), 62.02 (C12), 51.00, 49.54 (C5 and C5 $^{\text{R}}$), 50.52 (C4), 49.97 (C4 $^{\text{R}}$), 49.33, 49.02 (C14 and C14 $^{\text{R}}$), 47.55, 45.82 (C1 and C1 $^{\text{R}}$), 46.92, 46.77 (C2 and C2 $^{\text{R}}$), 34.23 (C11 $^{\text{R}}$), 33.97 (C11), 33.17, 32.83 (C8 and C8 $^{\text{R}}$), 31.73 (C10), 31.21, 31.12 (C15 and C15 $^{\text{R}}$), 21.77, 21.69, 21.61, 21.32 and 21.29 (CH_3CO , $\text{CH}_3^{\text{R}}\text{CO}$, $(\text{CH}_3)_2\text{C-O}$, $(\text{CH}_3^{\text{R}})_2\text{C-O}$), 10.72, 10.54, 6.58, 6.00 (C16 and C16 $^{\text{R}}$). IR (film) ν 2925, 2159, 2025, 1703, 1620 cm^{-1} .

Anal. Calcd for C₃₄H₃₈N₃O₅Cl₅: C, 54.75; H, 5.13; N, 5.63. Found: C, 54.52; H, 5.15; N, 5.34. $[\alpha]_D^{25} = +177.0$ (1.02; MeOH). LC-MS: $t_R = 1.15$ min, MS (ESI): m/z 746.43 (M + 1)⁺.

(1*R*, 5*S*)-3-Acetyl-6-[cyclopropyl-(2,3-dichloro-benzyl)-carbamoyl]-7-[4-(2-hydroxy-ethoxy)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (23b)

¹H-NMR (CDCl₃): 7.36 (t, J = 6.7 Hz, 1H, H_{arom}), 7.18 – 7.02 (m, 3H, H_{arom}), 6.83 (d, J = 8.4 Hz, 1H, H_{arom}), 6.77 (d, J = 8.4 Hz, 1H, H_{arom}), 6.69 (t, J = 9.7 Hz, 1H, H_{arom}), 4.74 (s, 1H and 1H^R, H-5 and H-5^R), 4.72 (broad, d, J ≈ 14.4 Hz, 1H, H-2), 4.62 (broad, d, J ≈ 16.0 Hz, 1H and 2H^R, H-13 and H-13^R and H-1^R), 4.58 – 4.47 (m, 1H and 2H^R, H-1, H-1^R and H-4^R), 4.46 (broad, d, J = 10.4 Hz, 1H and 1H^R, H-4 and H-13^R), 4.40 (d, J = 12.4 Hz, 1H^R, H-13^R), 4.36 (d, J = 16.2 Hz, 1H, H-13), 4.11 – 4.02 (m, 2H, H-10(2x)), 4.01 – 3.92 (m, 2H, H-11(2x)), 3.48 (d, J = 14.1 Hz, 1H^R, H-4^R), 3.44 (d, J = 14.0 Hz, 1H, H-4), 3.20 (dd, J = 18.1, 7.4 Hz, 1H, H-8), 3.10 (d, J = 17.9, 7.4 Hz, 1H^R, H-8^R), 2.88 (broad, d, J ≈ 11.1 Hz, 1H, H-2), 2.38 – 2.20 (m, 1H and 1H^R, H-8 and H-8^R), 2.29 (s, 3H, CH₃CO), 2.27 (s, 3H^R, CH₃^RCO), 2.03 (s, 3H, (CH₃)C-O), 2.01 (s, 3H, (CH₃)C-O), 1.99 (s, 3H^R, (CH₃^R)C-O), 1.97 (s, 3H, (CH₃^R)C-O), 1.82 – 1.66 (m, 1H and 1H^R, H-14 and H-14^R), 0.92 – 0.77, 0.72 – 0.50, 0.47 – 0.30 and 0.29 – 0.19 (m, 4H and 4H^R, H-15 and H-15^R). ¹³C-NMR (CDCl₃): 173.24, 173.03, 171.23, 171.20 (CO and CO^R), 158.91, 158.80 (CO and CO^R), 151.57 (Cq), 150.61 (Cq), 138.04 (Cq), 137.75 (Cq^R), 137.22 (Cq^R), 137.16 (Cq), 133.08 (Cq), 133.02 (Cq^R), 132.40 (Cq^R), 132.32 (Cq), 131.30 (Cq^R), 130.88 (Cq), 129.00 (CH_{arom}), 128.03 (CH^R_{arom}), 127.87 (CH_{arom}), 127.76 (CH_{arom}), 127.44 (CH^R_{arom}), 127.31 (CH_{arom}), 127.14 (CH_{arom}), 126.72 (CH_{arom}), 126.46 (Cq), 125.99 (CH_{arom}), 125.08 (Cq), 114.74 (CH^R_{arom}), 114.66 (CH_{arom}), 106.65 (CCl₃), 106.52 (C^RCl₃), 89.32 (Me₂C-O), 88.95 (Cq, Me₂C^R-O),

69.25 (C10), 61.30 (C11), 50.97, 49.51 (C5 and C5^R), 50.50 (C4), 49.93 (C4^R), 49.45, 49.13 (C13 and C13^R), 47.53, 45.82 (C1 and C1^R), 46.92, 46.76 (C2 and C2^R), 33.15, 32.81 (C8 and C8^R), 31.31, 31.22 (C14 and C14^R), 21.78, 21.69, 21.61, 21.32 and 21.29 ($\underline{\text{C}}\text{H}_3\text{CO}$, $\underline{\text{C}}^{\text{R}}\text{H}_3\text{CO}$, $(\underline{\text{C}}\text{H}_3)_2\text{C-O}$, $(\underline{\text{C}}^{\text{R}}\text{H}_3)_2\text{C-O}$), 10.54, 10.35, 6.37, 5.79 (C15 and C15^R). IR (film) ν 2925, 1703, 1607 cm^{-1} . Anal. Calcd for $\text{C}_{33}\text{H}_{36}\text{N}_3\text{O}_6\text{Cl}_5$: C, 52.99; H, 4.85; N, 5.62. Found: C, 54.21; H, 5.30; N, 5.25. $[\alpha]_{\text{D}}^{25} = +117.3$ (1.0; MeOH). LC-MS: $t_{\text{R}} = 1.12$ min, MS (ESI): m/z 748.36 ($\text{M} + 1$)⁺.

Experimental part of precursors

2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethoxy]-thiazole

NaH (50% in oil, 18.3 g, 383 mmol) was suspended in pentane, and the suspension was filtered. This operation was repeated twice. The pure NaH was suspended in THF (210 mL), and a sol. of 2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (McDougal, P. G.; Rico, J. G.; Oh, Young I.; Condon, B. D. A convenient procedure for the monosilylation of symmetric 1,n-diols. *J. Org. Chem.* 1986, 51, 3388-90, 53.9 g, 306 mmol) in THF (150 mL) was added dropwise. The mixture was stirred for 2 h at rt, and 2-bromothiazole (41.8 g, 255 mmol) was added dropwise. The mixture was heated to reflux overnight, and was allowed to cool to rt. Aq. sat. NH_4Cl was added carefully, and the mixture was extracted with TBME (3x). The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (Et_2O /heptane 1:19) yielded the title compound (21.3 g, 32%). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) 7.04 (d, $J = 4.1$ Hz, 1H), 6.57 (d, $J = 3.5$ Hz, 1H), 4.42 (t, $J = 5.0$ Hz, 2H), 3.90 (t, $J = 5.0$ Hz, 2H), 0.83 (s, 9H), 0.01 (s, 6H).

2-(Thiazol-2-yloxy)-ethanol

p-Toluene sulfonic acid (11.2 g, 58.0 mmol) was added to a sol. of 2-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethoxy]-thiazole (15.0 g, 58.0 mmol) in MeOH (400 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C. Aq. sat. NaHCO₃ was added until a pH of 6 or 7 was reached. EtOAc was added, the phases were separated, and the org. layer was extracted back with EtOAc. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:1) yielded the title compound (5.43 g, 65%). ¹H-NMR (CDCl₃, 300 MHz) 7.04 (d, *J* = 4.1 Hz, 1H), 6.66 (d, *J* = 4.1 Hz, 1H), 4.48 (t, *J* = 4.4 Hz, 2H), 3.92 (m, 2H).

2-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-thiazole.

A mixture of 2-(thiazol-2-yloxy)-ethanol (6.39 g, 44.0 mmol), 2,6-dichloro-*p*-cresol (15.6 g, 88 mmol), 1,1'-(azodicarbonyl)dipiperidine (22.2 g, 88.0 mmol) and PBu₃ (85%, 38.3 mL, 132 mmol) in toluene (325 mL) was heated to reflux for 30 min. The mixture was allowed to cool to rt, and was filtered. The precipitate was washed with little EtOAc, and the solvents were removed under reduced pressure. The residue was diluted with EtOAc, and the mixture was washed with aq. 2M NaOH (4x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:19 → 1:9 → 1:4) yielded the title compound (9.24 g, 69%). ¹H-NMR (CDCl₃, 300 MHz) 7.08 (m, 3H), 6.68 (d, *J* = 3.5 Hz, 1H), 4.77 (t *J* = 5.2 Hz, 2H), 4.37 (t, *J* = 5.2 Hz, 2H), 2.26 (s, 3H).

2-Chloro-3-methyl-pyridine-4-carbaldehyde

To the sol. of 2-chloro-3,*N*-dimethyl-*N*-phenyl-isonicotinamide (Epszajn, J.; Bieniek, A.; Plotka, M. W.; Suwald, K. Application of organolithium and related reagents in synthesis. Part 7. Synthesis and metalation of 4-methoxypicolin- and 2-methoxyisonicotinanilides. A useful method for preparation of 2,3,4-trisubstituted pyridines. *Tetrahedron*, **1989**, 45, 7469-76, 7.0 g, 26.8 mmol) in CH₂Cl₂ (160 mL) was added at -78 °C diisobutylaluminium hydride (1M in CH₂Cl₂, 41.0 mL, 41.0 mmol) during 30 min. The reaction mixture was stirred at this temperature for 1.5h. Sat. aq. Rochelle's salt (60 mL) was added and the mixture was allowed to warm up to rt and extracted with CH₂Cl₂ (2x 50 mL). The org. layer was concentrated and the crude aldehyde (6.23 g) was used in the next step without purification.

(2-Chloro-3-methyl-pyridin-4-ylmethyl)-cyclopropyl-amine

A sol. of crude 2-chloro-3-methyl-pyridine-4-carbaldehyde (6.23 g) and cyclopropylamine (5.6 mL, 80.1 mmol) in MeOH (90 mL) was stirred overnight at rt. NaBH₄ (1.97 g, 52.0 mmol) was added at 0 °C, and the mixture was allowed to warm up to rt. After 2 h, aq. 1M NaOH (35 mL) was added at 0 °C, and the mixture was extracted with EtOAc (2 x 100 mL). The org. layer was concentrated and the residue was purified by FC (heptane/EtOAc = 75/25 → 65/35) to provide the title compound (2.1 g, 40% over 2 steps). ¹H-NMR (CDCl₃): 8.19 (d, J = 4.9 Hz, 1H, H_{arom}), 7.23 (d, J = 4.9 Hz, 1H, H_{arom}), 3.88 (s, 2H, N-CH₂), 2.40 (s, 3H, CH₃), 2.23 – 2.16 (m, 1H, cyclopropyl), 0.52 – 0.37 (m, 4H, cyclopropyl). ¹³C-NMR (CDCl₃): 152.18 (Cq), 150.53 (Cq), 146.57 (CH_{arom}), 130.53 (Cq), 122.23

(CH_{arom}), 50.89 (NCH₂), 30.42 (CH-cyclopropyl), 15.11 (CH₃), 6.59 (CH₂-cyclopropyl). MS (ESI): m/z mass peak not visible.

Cyclopropyl-(2-methoxy-3-methyl-pyridin-4-ylmethyl)-amine

A sol. of (2-chloro-3-methyl-pyridin-4-ylmethyl)-cyclopropyl-amine (2.57 g, 13.1 mmol) and NaOMe (3.5 g, 65.3 mmol) in dioxane (60 mL) was stirred over 48 h at 115 °C. After filtration was the residue was purified by FC (CH₂Cl₂/MeOH = 97/3) to provide the title compound (1.74 g, 69%). ¹H-NMR (CDCl₃): 7.97 (d, J = 5.2 Hz, 1H, H_{arom}), 6.85 (d, J = 5.2 Hz, 1H, H_{arom}), 3.96 (s, 2H, OCH₃), 3.82 (s, 2H, N-CH₂), 2.19 (s, 3H, CH₃), 2.22 – 2.12 (m, 1H, cyclopropyl), 0.51 – 0.35 (m, 4H, cyclopropyl). ¹³C-NMR (CDCl₃): 152.51 (Cq), 148.77 (Cq), 143.37 (CH_{arom}), 118.49 (Cq), 116.89 (CH_{arom}), 53.47 (OCH₃), 50.17 (NCH₂), 30.28 (CH-cyclopropyl), 10.79 (CH₃), 6.54 (CH₂-cyclopropyl). Anal. Calcd. for C₁₁H₁₆N₂O: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.48; H, 8.43; N, 14.52. MS (ESI): m/z 193.55 (M + 1)⁺.

1-(4-Bromophenoxy)-2-(2,6-dichloro-4-methylphenoxy)ethane

To a sol. of 4-bromophenol (40 g, 231 mmol) in EtOH (140 mL) was added NaOH (10.2 g, 254 mmol). The resulting mixture was stirred at 70 °C for 30 min until the whole amount of NaOH had dissolved. A sol. of 2-bromoethanol (17.3 mL, 231 mmol) in EtOH (40 mL) was added dropwise at 70 °C. The sol. rapidly turned milky. The mixture was heated to reflux overnight. The solvents were removed under reduced pressure, and the residue was dissolved in EtOAc. The mixture was washed with water and brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:5 → 1:4 → 1:3 → 1:2 → EtOAc) yielded 2-(4-bromophenoxy)ethanol (39.2 g, 78%) as a pale brown oil that crystallized when placed at –18 °C. R_f = 0.3 in (EtOAc/heptane 1:1).

To a sol. of 2-(4-bromophenoxy)ethanol (39.2 g, 181 mmol) in dry toluene (500 mL) was added imidazole (61.5 g, 903 mmol), PPh₃ (90 g, 343 mmol), and iodine (87.1 g, 343 mmol). This mixture was stirred at 60 °C for 2 h. The mixture was filtered over celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:5 → 1:4 → 1:3 → 1:2 → 1:1) yielded 1-bromo-4-(2-iodoethoxy)benzene (39.9 g, 67%).

In a 500-mL 3-necked flask equipped with a mechanical stirrer and a reflux condenser were mixed 1-bromo-4-(2-iodoethoxy)benzene (39.9 g, 122 mmol) and 2,6-dichloro-*p*-cresol (21.6 g, 122 mmol) in dry acetone (1200 mL). To this mixture was added K₂CO₃ (16.86 g, 122 mmol), and the resulting suspension was heated to reflux for 20 h. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc and this org. phase was washed with water (2x), and with brine (1x). The org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by a short FC (EtOAc/heptane 1:9) yielded the title compound (44.4 g, 96%). ¹H-NMR (CDCl₃) 7.40 (d, *J* = 8.7 Hz, 2H), 7.13 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.37 (s, 2H), 4.34 (s, 2H), 2.31 (s, 3H).

Experimental part of final compounds

(1*R*, 5*S*)-3-[2-(4-Chloro-phenyl)-acetyl]-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-methyl-amide (14a). Using (4-chloro-phenyl)-acetyl chloride, the title compound (210 mg, 72%) was obtained.

$^1\text{H-NMR}$ (CD_3OD): 7.48 – 7.02 (m, 10H, H_{arom}), 6.99 – 6.77 (m, 4H, H_{arom}), 6.75 (d, $J = 7.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.68 (d, $J = 8.6$ Hz, 1H, H_{arom}), 6.57 (d, $J = 7.4$ Hz, 1H, H_{arom}), 4.85 – 4.78 (a signal below solvent peak, 1H and 1H^{R} , H-15 and H-15 $^{\text{R}}$), 4.67 – 4.51 (m, 3H and 1H^{R} , H-4, H-13(2x) and H-4 $^{\text{R}}$), 4.45 (broad, d, $J \approx 12.4$ Hz, 1H^{R} , H-2 $^{\text{R}}$), 4.39 (d, $J = 15.7$ Hz, 1H, H-15), 4.33 (broad, d, 1H^{R} , $J \approx 13.2$ Hz, H-2 $^{\text{R}}$), 4.21 (d, $J = 15.8$ Hz, 1H, H-16), 4.18 – 4.05 (m, 2H and 1H^{R} , H-10 and H-16 $^{\text{R}}$), 3.97 (d, $J = 15.6$ Hz, 1H, H-16), 3.98 – 3.88 (m, 1H and 2H^{R} , H-16 and H-15 $^{\text{R}}$, H-16 $^{\text{R}}$), 3.82 (s, 3H^{R} , OCH_3^{R}), 3.81 (s, 3H, OCH_3), 3.75 (t, $J = 6.1$ Hz, 2H, H-12), 3.63 (s, 1H, H-5), 3.60 – 3.52 (m, 2H^{R} , H-5 $^{\text{R}}$, H-16 $^{\text{R}}$), 3.49 – 3.38 (m, 2H and 2H^{R} , H-1, H-2, H-1 $^{\text{R}}$, H-2 $^{\text{R}}$), 3.33 (a signal below solvent peak, 1H, H-1 $^{\text{R}}$), 3.10 – 2.93 (m, 2H and 2H^{R} , H-4, H-8, H-4 $^{\text{R}}$, H-8 $^{\text{R}}$), 2.81 (s, 3H, NCH_3), 2.69 (s, 3H^{R} , NCH_3^{R}), 2.64 (s, 3H^{R} , NCH_3^{R}), 2.54 (s, 3H^{R} , NCH_3^{R}), 2.26 (s, 3H^{R} , NCH_3^{R}), 2.22 – 2.02 (m, 3H and 1H^{R} , H-8, H-11 and H-8 $^{\text{R}}$). $^{13}\text{C-NMR}$ (CD_3OD): 172.65 (CO^{R}), 171.98 (CO), 171.89 (CO^{R}), 171.74 (CO), 171.46 (CO^{R}), 159.34 (Cq^{R}), 159.19 (Cq^{R}), 159.08 (Cq), 157.37 (Cq), 138.33 (Cq^{R}), 138.15 (Cq), 137.27 (Cq^{R}), 134.23 (Cq), 134.01 (Cq^{R}), 133.86 (Cq^{R}), 133.43 (Cq), 133.32 (Cq), 133.14 (Cq^{R}), 133.00 (Cq), 132.87 (Cq^{R}), 132.34 (Cq), 132.15 (Cq), 131.51 (Cq^{R}), 130.61 (CH_{arom}), 130.55 (CH_{arom}), 130.28 (CH_{arom}), 130.14 ($\text{CH}^{\text{R}}_{\text{arom}}$), 130.01 ($\text{CH}^{\text{R}}_{\text{arom}}$), 129.79 ($\text{CH}^{\text{R}}_{\text{arom}}$), 129.38 ($\text{CH}^{\text{R}}_{\text{arom}}$), 129.19 (CH_{arom}), 129.12 (CH_{arom}),

129.01 (CH_{arom}), 128.86 (CH_{arom}), 128.77 (CH_{arom}), 128.66 (CH_{arom}), 128.49 (CH_{arom}), 128.41 (CH_{arom}), 128.35 (CH^R_{arom}), 128.28 (Cq), 128.25 (CH_{arom}), 128.18 (Cq), 128.16 (CH_{arom}), 127.91 (CH_{arom}), 127.74 (CH_{arom}), 127.38 (Cq^R), 127.02 (Cq^R), 126.78 (CH_{arom}), 126.29 (Cq), 120.01 (CH_{arom}), 114.31 (CH_{arom}), 114.10 (CH^R_{arom}), 110.12 (CH_{arom}), 67.48 (C13), 66.51 (C12), 64.62 (C10), 54.50 (OCH₃), 51.48 (C15^R), 50.01 (C5^R), 49.90 (C2^R), 49.63 (C2), 49.41 (C5), 48.05 (C4), 47.91 (C4^R), 47.05 (C15), 46.60 (C1), 46.18 (C1^R), 38.99 (C16^R), 38.68 (C16), 35.62, 35.20, 31.56 (NCH₃, NCH₃^R), 33.39, 32.62 (C8, C8^R, C16), 29.34 (C11). IR (film) ν 2922, 2856, 1605 cm⁻¹. Anal. Calcd for C₄₁H₄₃N₃O₅Cl₂·0.5H₂O: C, 66.75; H, 5.96; N, 5.69. Found: C, 66.46; H, 6.08; N, 5.40. $[\alpha]_D^{25} = +76.5$ (1.0; MeOH). LC-MS: t_R = 1.01 min, MS (ESI): *m/z* 728.15 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-7-{4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl}-3-phenylmethanesulfonyl-3,9 -diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-methyl-amide (14b). From phenylmethanesulfonyl chloride, the title compound (180 mg, 62%) was obtained.

¹H-NMR (CDCl₃): 7.49 – 7.24 (m, 9H, H_{arom}), 7.22 (d, J = 7.8 Hz, 2H, H_{arom}), 7.15 – 7.05 (m, 2H, H_{arom}), 6.96 (t, J = 7.4 Hz, 1H, H_{arom}), 6.88 (d, J = 8.3 Hz, 1H, H_{arom}), 6.78 (d, J = 7.9 Hz, 1H, H_{arom}), 4.67 (broad, d, J = 15.5 Hz, 1H and 1H^R, H-15 and H-15^R), 4.61 (s, 2H, H-13), 4.58 – 4.47 (m, 2H^R, H-15^R and CH^R), 4.46 (d, J = 15.6 Hz, 1H, H-15), 4.26 (s, 2H, H-16), 4.20 (s, 2H^R, H-16^R), 4.15 – 4.02 (m, 2H and 3H^R, H-10 and OCH₃), 3.83 (s, 3H, OCH₃), 3.79 – 3.68 (m, 3H, H-4, H-12), 3.65 (d, J = 13.2 Hz, 1H^R, H-4^R), 3.58 (broad, d, J ≈ 7.7 Hz, 1H^R, H-2^R), 3.52 – 3.38 (m, 3H, H-1, H-2, H-5), 3.60 – 3.52 (m, 2H^R, H-5^R, H-16^R), 3.49 – 3.38 (m, 2H and 2H^R, H-1, H-2, H-1^R, H-2^R), 3.32 (broad, s, 1H^R, CH^R), 3.31 (d, J = 11.0 Hz, 1H, H-4), 3.09 – 2.99 (m, 2H^R, H-2^R, H-4^R), 2.87 (d, J = 11.3 Hz, 1H, H-2), 2.79

(s, 3H^R, NCH^R₃), 2.64 (dd, J = 18.7, 7.6 Hz, 1H, H-8), 2.62 (s, 3H^R, NCH^R₃), 2.55 (s, 3H, NCH₃), 2.45 (dd, J = 18.8, 7.2 Hz, 1H, H-8), 2.13 (t, J = 6.0 Hz, 2H, H-11). ¹³C-NMR (CDCl₃): 171.41 (CO), 159.02 (Cq), 157.09 (Cq), 137.50 (Cq), 133.89 (Cq), 133.53 (Cq), 132.27 (Cq), 131.89 (Cq), 130.84 (CH_{arom}), 130.72 (CH_{arom}), 129.70 (CH^R_{arom}), 129.38 (CH_{arom}), 129.15 (CH_{arom}), 128.97 (CH_{arom}), 128.92 (CH_{arom}), 128.82 (CH_{arom}), 128.67 (CH_{arom}), 128.65 (CH_{arom}), 128.41 (Cq), 128.31 (CH_{arom}), 128.19 (CH_{arom}), 127.69 (CH^R_{arom}), 127.13 (CH^R_{arom}), 126.89 (CH^R_{arom}), 126.76 (CH_{arom}), 126.38 (CH^R_{arom}), 120.44 (CH_{arom}), 114.55 (CH^R_{arom}), 114.40 (CH_{arom}), 110.26 (CH_{arom}), 67.79 (C13), 66.95 (C12), 65.02 (C10), 58.17 (C16^R), 5.90 (C16), 55.34 (OCH₃), 52.55, 52.08 (C2^R, C4^R), 52.44 (C4), 50.31 (OCH₃^R), 48.21 (C2), 47.78 (C15), 46.69 (C1, C5), 36.52, 35.62 (NCH₃, NCH₃^R), 32.90 (C8), 29.75 (C11). IR (film) ν 2922, 2854, 1603 cm⁻¹. Anal. Calcd for C₄₀H₄₄N₃O₆Cl·0.5H₂O: C, 64.98; H, 6.09; N, 5.68. Found: C, 64.87; H, 6.24; N, 5.42. $[\alpha]_D^{25} = +34.1$ (1.0; MeOH). LC-MS: t_R = 1.01 min, MS (ESI): m/z 730.28 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-7-{4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl}-3-(2-thiophen-2-yl-acetyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-methyl-amide (14c). From thiophen-2-yl-acetyl chloride, the title compound (130 mg, 46%) was obtained.

¹H-NMR (CD₃OD): 7.41 – 7.01 (m, 8H, H_{arom}), 6.99 – 6.70 (m, 7H, H_{arom}), 6.53 (d, J = 7.5 Hz, 1H^R, H^R_{arom}), 4.80 (broad, d, J ≈ 16.2 Hz, 1H and 1H^R, H-15 and H-15^R), 4.67 – 4.47 (m, 3H and 2H^R, H-4, H-13(2x) and H-2^R, H-4^R), 4.50 (d, 1H, J = 16.4 Hz, H-16), 4.39 (d, 1H, J = 11.7 Hz, H-2), 4.36 (d, J = 14.9 Hz, 1H, H-15), 4.29 (d, J = 13.2 Hz, 1H^R, H-16^R), 4.26 (d, J = 13.2 Hz, 1H^R, H-16^R), 4.17 (d, J = 16.2 Hz, H-16), 4.10 (broad, t, J = 6.1 Hz, 2H and 1H^R, H-10 and H-16^R), 4.00 (s, 3H^R, OCH^R₃), 3.91

(d, $J = 15.8$ Hz, $1H^R$, H-15^R), 3.80 (s, 3H, OCH₃), 3.75 (broad, s, 2H and $1H^R$, H-12 and H-16^R), 3.65 (s, 1H, H-5), 3.63 – 3.44 (m, 1H and $4H^R$, H-2 and H-1^R, H-2^R, H-5^R, H-16^R), 3.41 (d, $J = 5.8$ Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.19 – 2.92 (m, 2H and $2H^R$, H-4, H-8, H-4^R, H-16^R), 2.78 (s, 3H, NCH₃), 2.69 (s, $3H^R$, NCH₃^R), 2.55 (s, $3H^R$, NCH₃^R), 2.33 (s, $3H^R$, NCH₃^R), 2.42 (dd, $J = 18.6, 6.8$ Hz, $1H^R$, H-8^R), 2.28 (d, $J = 18.8$ Hz, $1H^R$, H-8^R), 2.09 (broad, s, 2H, H-11). ¹³C-NMR (CD₃OD): 172.55 (CO^R), 171.88 (CO^R), 171.63 (CO), 171.32 (CO), 171.24 (CO^R), 170.87 (CO), 159.32 (Cq^R), 159.24 (Cq^R), 159.08 (Cq), 157.36 (Cq), 138.50 (Cq^R), 138.27 (Cq), 137.50 (Cq^R), 136.69 (Cq), 136.65 (Cq^R), 133.86 (Cq^R), 133.42 (Cq), 133.37 (Cq^R), 133.14 (Cq^R), 132.99 (Cq), 132.86 (Cq), 132.32 (Cq), 132.17 (Cq^R), 131.64 (Cq^R), 130.09 (Cq^R), 129.36 (CH^R_{arom}), 129.16 (CH^R_{arom}), 129.08 (CH_{arom}), 129.04 (CH_{arom}), 128.84 (CH^R_{arom}), 128.77 (CH_{arom}), 128.72 (CH^R_{arom}), 128.68 (CH_{arom}), 128.62 (CH_{arom}), 128.49 (CH_{arom}), 128.43 (CH_{arom}), 128.38 (CH_{arom}), 128.10 (Cq), 127.95 (CH_{arom}), 127.77 (CH_{arom}), 127.24 (CH^R_{arom}), 127.00 (CH^R_{arom}), 126.77 (CH_{arom}), 126.40 (CH^R_{arom}), 126.35 (CH_{arom}), 126.32 (CH_{arom}), 126.21 (CH_{arom}), 126.16 (CH^R_{arom}), 124.94 (CH^R_{arom}), 124.38 (CH_{arom}), 120.00 (CH_{arom}), 114.30 (CH_{arom}), 114.02 (CH^R_{arom}), 67.48 (C13), 66.52 (C12), 66.47 (C12^R), 64.59 (C10), 54.47 (OCH₃), 51.47 (C15^R), 50.09 (C2^R), 50.02 (C5), 49.80 (C2), 49.39 (C5^R), 48.13 (C4), 47.47 (C4^R), 49.98 (C15), 46.64 (C1), 46.25 (C1^R), 43.14 (C16^R), 35.82, 35.17, 31.50 (NCH₃, NCH₃^R), 34.28, 33.84, 33.41, 32.59 (C8, C8^R, C16, C16^R), 29.35 (C11). IR (film) ν 2922, 2855, 1605 cm⁻¹. Anal. Calcd for C₃₉H₄₂N₃O₅ClS·0.5H₂O: C, 66.04; H, 6.06; N, 5.92. Found: C, 66.66; H, 6.53; N, 5.37. $[\alpha]_D^{25} = +5.3$ (1.0; MeOH). LC-MS: $t_R = 0.98$ min, MS (ESI): m/z 700.27 (M + 1)⁺; purity at 230 nm: 97.2%; at 254 nm: 99.0%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-methyl-amide (14d). From acetyl chloride, the title compound (242 mg, 97%) was obtained.

$^1\text{H-NMR}$ (CDCl_3): 7.39 (d, $J = 7.3$ Hz, 1H, H_{arom}), 7.34 (d, $J = 7.7$ Hz, 1H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 7.31 – 7.07 (m, 3H, H_{arom}), 7.02 (t, $J = 7.4$ Hz, 1H, H_{arom}), 6.96 (t, $J = 7.3$ Hz, 1H, H_{arom}), 6.91 – 6.76 (m, 3H, H_{arom}), 6.52 (d, $J = 7.4$ Hz, 1H, H_{arom}), 4.71 (d, $J = 16.3$ Hz, 1H, H-15), 4.70 (d, $J \approx 10.0$ Hz, 1H, H-4), 4.66 (d, $J = 16.8$ Hz, 1H^{R} , H-15 $^{\text{R}}$), 4.64 – 4.54 (m, 2H and 1H $^{\text{R}}$, H-13 and H-4 $^{\text{R}}$), 4.44 (d, $J = 15.8$ Hz, 1H, H-15), 4.38 (d, $J = 12.9$ Hz, 1H, H-2), 4.34 (d, $J = 13.3$ Hz, 1H, H-2), 4.17 – 4.05 (m, 2H and 3H $^{\text{R}}$, H-10 and OCH_3^{R}), 3.83 (s, 3H, OCH_3), 3.74 (t, $J = 5.8$ Hz, 2H, H-12), 3.66 (d, $J = 16.3$ Hz, 1H^{R} , H-15 $^{\text{R}}$), 3.61 (s, 1H, H-5), 3.52 (d, $J = 13.2$ Hz, 1H, H-2), 3.46 (d, $J = 13.0$ Hz, 1H^{R} , H-2 $^{\text{R}}$), 3.44 (s, 1H^{R} , H-1 $^{\text{R}}$), 3.34 (broad, s, 1H and 1H^{R} , H-1 and H-5 $^{\text{R}}$), 3.02 – 2.85 (m, 2H and 2H $^{\text{R}}$, H-4, H-8, and H-4 $^{\text{R}}$, H-8 $^{\text{R}}$), 2.80 (s, 3H, NCH_3), 2.69 (s, 3H $^{\text{R}}$, NCH_3^{R}), 2.41 (s, 3H $^{\text{R}}$, NCH_3^{R}), 2.35 (s, 3H $^{\text{R}}$, NCH_3^{R}), 2.32 (s, 3H, CH_3CO), 2.29 (s, 3H $^{\text{R}}$, $\text{CH}_3\text{CO}^{\text{R}}$), 2.21 (d, $J = 14.5$ Hz, 1H, H-8), 2.14 (broad, t, $J \approx 6.0$ Hz, 2H and 1H^{R} , H-11 and H-8 $^{\text{R}}$). $^{13}\text{C-NMR}$ (CDCl_3): 172.56 (CO), 171.53 (CO), 171.36 (CO $^{\text{R}}$), 171.06 (CO), 170.94 (CO), 159.05 (Cq), 158.89 (Cq), 157.10 (Cq), 137.74 (Cq), 137.52 (Cq), 135.44 (Cq $^{\text{R}}$), 134.74 (Cq), 133.82 (Cq $^{\text{R}}$), 133.68 (Cq), 133.35 (Cq), 132.91 (Cq), 132.29 (Cq), 132.22 (Cq), 129.77 (CH_{arom}), 129.39 (CH_{arom}), 129.06 (CH_{arom}), 128.88 ($\text{CH}_{\text{arom}}^{\text{R}}$), 128.84 (CH_{arom}), 128.65 (CH_{arom}), 128.55 ($\text{CH}_{\text{arom}}^{\text{R}}$), 128.46 (CH_{arom}), 128.41 (CH_{arom}), 128.01 (CH_{arom}), 127.86 (CH_{arom}), 127.16 ($\text{CH}_{\text{arom}}^{\text{R}}$), 126.91 (CH_{arom}), 126.74 (Cq), 120.44 (CH_{arom}), 114.63 (CH_{arom}), 114.56 ($\text{CH}_{\text{arom}}^{\text{R}}$), 110.26 (CH_{arom}), 67.78 (C13), 66.94 (C12), 66.90 (C12 $^{\text{R}}$), 65.03 (C10), 65.00 (C10 $^{\text{R}}$), 55.35 (OCH_3), 51.68 (C15 $^{\text{R}}$), 50.64 (C5 $^{\text{R}}$), 50.59 (C2), 50.34 (C5), 49.96 (OCH_3^{R}), 48.08 (C4), 47.88 (C4 $^{\text{R}}$), 47.07 (C15), 47.00 (C1), 46.88 (C1 $^{\text{R}}$), 35.90, 33.27 (NCH_3^{R}), 35.77 (NCH_3), 33.75, 33.04 (C8 and C8 $^{\text{R}}$), 29.73 (C11), 21.55, 21.27 ($\text{CH}_3\text{CO}^{\text{R}}$), 21.20 (CH_3CO). IR (film) ν 2922, 2855, 1604 cm^{-1} . Anal. Calcd for $\text{C}_{35}\text{H}_{40}\text{N}_3\text{O}_5\text{Cl} \cdot 0.5\text{H}_2\text{O}$: C, 67.03; H, 6.54; Cl, 6.54.

N, 6.70. Found: C, 67.21; H, 6.69; N, 6.42. $[\alpha]_D^{25} = +130.7$ (1.0; MeOH). LC-MS: $t_R = 0.92$ min, MS (ESI): m/z 618.10 ($M + 1$)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-7-{4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl}-3-methyl-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-methyl-amide (14e)

To a sol. of compound **13** (0.4 g, 0.51 mmol) in 1,2-dichloroethane (10 mL) was added 37% aq. formaldehyde (0.14 mL) followed by NaBH(OAc)₃ (0.17 g) in one portion. The reaction mixture was stirred at rt overnight. The mixture was quenched with aq. 1M NaOH, and diluted with CH₂Cl₂. The org. layer was washed with water, dried over MgSO₄, filtered, and the solvents were concentrated under reduced pressure. Purification by FC (1 – 5% MeOH in CH₂Cl₂) yielded 0.27 g of a white foam. A suspension of this foam, and Zn-powder (4 mmol) in THF (10 mL) were stirred in the presence AcOH (0.25 mL) at rt for 3 h. The mixture was filtered through celite, and the solvents were evaporated. The residue was dissolved in CH₂Cl₂ (10 mL), and aq. 0.1M EDTA (5 mL) was added. The mixture was stirred at rt for 6 h. The organic layer was concentrated under reduced pressure, and the residue was purified by FC (1 – 5% MeOH in CH₂Cl₂) to provide the title compound (97 mg, 41%). ¹H-NMR (CD₃OD): 7.38 – 7.18 (m, 4H, H_{arom}), 7.17 – 7.00 (m, 3H, H_{arom}), 6.98 – 6.78 (m, 4H, H_{arom}), 6.58 (d, J = 7.0 Hz, 1H^R, H^R_{arom}), 6.55 (d, J = 8.0 Hz, 1H, H_{arom}), 6.39 (d, J = 8.0 Hz, 1H^R, H^R_{arom}), 5.26, 5.22 (2 x broad, s, 2H^R), 4.77 (d, J = 15.5 Hz, 1H, H-15), 4.72 (d, J ≈ 16.5 Hz, 1H^R, H-15^R), 4.58 (s, 2H, H-13), 4.46 (broad, s, 1H^R), 4.37 (d, J = 15.1 Hz, 1H, H-15), 4.33 (d, J = 15.6 Hz, 1H, H-15^R), 4.26 (d, J = 14.2 Hz, 1H^R), 4.15 – 3.90 (m, 7H^R, CH₂^R(3x), CH^R), 4.11 (t, J = 5.7 Hz, H-10), 3.85 (s, 3H^R, OCH^R₃), 3.81 (s, 3H, OCH₃), 3.74 (t, J = 5.4 Hz, 2H, H-12), 3.50 – 3.38 (m, 1H and 1H^R, H-5 and H-5^R), 3.27 (d, J =

11.1 Hz, 1H^R), 3.17 (d, $J \approx 9.0$ Hz, 1H^R), 3.08 (d, $J = 13.5$ Hz, 1H^R), 2.94 (d, $J = 11.2$ Hz, 1H, H-4), 2.87 (d, $J = 11.5$ Hz, 1H, H-2), 2.82 – 2.62 (m, 5H and 6H^R, H-1, H-8, NCH₃ and NCH₃^R(2x)), 2.60 – 2.49 (m, 2H^R, H-8^R and 1H^R), 2.46 (d, $J = 11.5$ Hz, 1H, H-4), 2.37 (d, $J = 10.6$ Hz, 1H, H-2), 2.34 – 2.20 (m, 4H and 3H^R, H-8, NCH₃ and NCH₃^R), 2.18 – 2.03 (m, 2H and 1H^R, H-11 and H-8^R), 1.98 (s, 3H^R, NCH₃^R), 1.93 (s, 3H, NCH₃). ¹³C-NMR (CD₃OD): 172.77 (CO), 159.29 (Cq^R), 159.11 (Cq), 157.34 (Cq), 155.44 (Cq^R), 137.82 (Cq^R), 137.70 (Cq), 137.66 (Cq^R), 134.20 (Cq), 133.50 (Cq^R), 133.37 (Cq), 133.03 (Cq^R), 132.48 (Cq), 132.36 (Cq^R), 131.98 (Cq^R), 131.33 (Cq), 131.01 (Cq^R), 129.10 (CH_{arom}), 129.02 (CH_{arom}), 128.79 (CH_{arom}^R), 128.74 (CH_{arom}^R), 128.59 (CH_{arom}^R), 128.51 (CH_{arom}), 128.41 (CH_{arom}), 128.34 (CH_{arom}), 128.30 (CH_{arom}^R), 128.15 (CH_{arom}^R), 127.99 (CH_{arom}), 127.71 (CH_{arom}), 126.72 (CH_{arom}^R), 126.60 (CH_{arom}), 126.34 (CH_{arom}), 119.99 (CH_{arom}), 114.18 (CH_{arom}), 114.09 (CH_{arom}^R), 110.07 (CH_{arom}), 69.40 (CH₂^R), 67.45 (C13), 66.56 (C12), 66.52 (C12^R), 64.58 (C10), 64.52 (C10^R), 61.94 (CH₂^R), 60.83, 60.74 (C2, C4), 60.01 (CH₂^R), 55.92, 55.85 (C8, C8^R), 54.46 (OCH₃), 51.46 (C15^R), 50.83, 50.70 (OCH₃^R), 50.04, 49.69 (CH₂^R), 47.28 (C15), 47.19 (C5), 46.98 (C5^R), 46.25 (CH^R), 45.18, 44.74, 44.51, 34.76, 32.20 (NCH₃, NCH₃^R), 35.18 (C1), 33.70 (C8), 33.33 (CH₂^R), 29.38 (C11), 27.39, 37.34, 25.00, 20.71, 20.61 (NCH₃, NCH₃^R). IR (film) ν 2925, 2790, 1604 cm⁻¹. Anal. Calcd for C₃₄H₄₀N₃O₄Cl·0.5H₂O: C, 68.16; H, 6.84; N, 7.00. Found: C, 68.05; H, 6.95; N, 6.34. $[\alpha]_D^{25} = +3.0$ (1.0; MeOH), LC-MS: $t_R = 0.92$ min, MS (ESI): m/z 590.18 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-7-{4-[3-(2-Methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-methyl-amide (14f).

A suspension of compound **13** (ca. 0.4 mmol), and Zn-powder (4 mmol) in THF (10 mL) was stirred in the presence AcOH (0.25 mL) at rt for 3 h. The mixture was filtered through celite, and the solvents were evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ (10 mL), and aq. 0.1M EDTA (5 mL) was added. The mixture was stirred at rt for 6 h. The org. layer was concentrated under reduced pressure, and the residue was purified by FC (1 – 5% MeOH in CH₂Cl₂) to provide the title compound (160 mg, 54%). ¹H-NMR (CDCl₃): 7.39 (d, J = 7.3 Hz, 1H, H_{arom}), 7.34 (d, J = 7.7 Hz, 1H^R, H^R_{arom}), 7.31 – 7.07 (m, 3H, H_{arom}), 7.02 (t, J = 7.4 Hz, 1H, H_{arom}), 6.96 (t, J = 7.3 Hz, 1H, H_{arom}), 6.91 – 6.76 (m, 3H, H_{arom}), 6.52 (d, J = 7.4 Hz, 1H, H_{arom}), 4.71 (d, J = 16.3 Hz, 1H, H-15), 4.70 (d, J ≈ 10.0 Hz, 1H, H-4), 4.66 (d, J = 16.8 Hz, 1H^R, H-15^R), 4.64 – 4.54 (m, 2H and 1HR, H-13 and H-4^R), 4.44 (d, J = 15.8 Hz, 1H, H-15), 4.38 (d, J = 12.9 Hz, 1H, H-2), 4.34 (d, J = 13.3 Hz, 1H, H-2), 4.17 – 4.05 (m, 2H and 3H^R, H-10 and OCH₃^R), 3.83 (s, 3H, OCH₃), 3.74 (t, J = 5.8 Hz, 2H, H-12), 3.66 (d, J = 16.3 Hz, 1H^R, H-15^R), 3.61 (s, 1H, H-5), 3.52 (d, J = 13.2 Hz, 1H, H-2), 3.46 (d, J = 13.0 Hz, 1H^R, H-2^R), 3.44 (s, 1H^R, H-1^R), 3.34 (broad, s, 1H and 1H^R, H-1 and H-5^R), 3.02 – 2.85 (m, 2H and 2H^R, H-4, H-8, and H-4^R, H-8^R), 2.80 (s, 3H, NCH₃), 2.69 (s, 3H^R, NCH₃^R), 2.41 (s, 3H^R, NCH₃^R), 2.35 (s, 3H^R, NCH₃^R), 2.32 (s, 3H, CH₃CO), 2.29 (s, 3H^R, CH₃CO^R), 2.21 (d, J = 14.5 Hz, 1H, H-8), 2.14 (broad, t, J ≈ 6.0 Hz, 2H and 1H^R, H-11 and H-8^R). ¹³C-NMR (CDCl₃): 172.56 (CO), 171.53 (CO), 171.36 (CO^R), 171.06 (CO), 170.94 (CO), 159.05 (Cq), 158.89 (Cq), 157.10 (Cq), 137.74 (Cq), 137.52 (Cq), 135.44 (Cq^R), 134.74 (Cq), 133.82 (Cq^R), 133.68 (Cq), 133.35 (Cq), 132.91 (Cq), 132.29 (Cq), 132.22 (Cq), 129.77 (CH_{arom}), 129.39 (CH_{arom}), 129.06 (CH_{arom}), 128.88 (CH^R_{arom}), 128.84 (CH_{arom}), 128.65 (CH_{arom}), 128.55 (CH^R_{arom}), 128.46 (CH_{arom}), 128.41 (CH_{arom}), 128.01 (CH_{arom}), 127.86 (CH_{arom}), 127.16 (CH^R_{arom}), 126.91 (CH_{arom}), 126.74 (Cq), 120.44 (CH_{arom}), 114.63 (CH_{arom}), 114.56 (CH^R_{arom}), 110.26 (CH_{arom}), 67.78 (C13), 66.94 (C12), 66.90 (C12^R), 65.03 (C10), 65.00 (C10^R), 55.35 (OCH₃), 51.68 (C15^R), 50.64 (C5^R), 50.59 (C2), 50.34 (C5), 49.96 (OCH₃^R), 48.08 (C4), 47.88 (C4^R), 47.07 (C15), 47.00 (C1), 46.88 (C1^R), 35.90, 33.27 (NCH₃^R), 35.77 (NCH₃), 33.75, 33.04 (C8 and C8^R), 29.73 (C11), 21.55, 21.27 (CH₃CO^R), 21.20 (CH₃CO). IR (film) ν 2922, 2855, 1604 cm⁻¹. Anal. Calcd for C₃₅H₄₀N₃O₅Cl·0.5H₂O:

C, 67.03; H, 6.54; N, 6.70. Found: C, 67.21; H, 6.69; N, 6.42. $[\alpha]_D^{25} = +130.7$ (1.0; MeOH). LC-MS: $t_R = 0.84$ min, MS (ESI): m/z 618.10 ($M + 1$)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid benzylamide (17a). From benzylamine (799 mg, 7.45 mmol). The title product was obtained (390 mg, 30%).

¹H-NMR (CD₃OD): 7.34 (d, $J = 7.4$ Hz, 1H, H_{arom}), 7.27 (t, $J = 8.4$ Hz, 1H, H_{arom}), 7.17 – 7.07 (m, 5H, H_{arom}), 6.95 (d, $J = 8.2$ Hz, 1H, H_{arom}), 6.92 (d, $J = 7.5$ Hz, 1H, H_{arom}), 6.91 – 6.74 (m, 4H, H_{arom}), 4.67 (d, $J = 13.9$ Hz, H-4), 4.64 (d, $J = 13.8$ Hz, 1H^R, H-4^R), 4.58 (s, 2H, H-13), 4.35 (d, $J = 14.8$ Hz, 1H, H-15), 4.31 (d, $J = 15.0$ Hz, 1H^R, H-15^R), 4.23 (d, $J = 13.8$ Hz, 1H, H-2), 4.17 (d, $J = 14.0$ Hz, 1H, H-2^R), 4.12 – 4.04 (m, 2H^R, H-5^R, H-15^R), 4.08 (t, $J = 6.3$ Hz, 2H, H-10), 4.04 (d, $J = 14.8$ Hz, 1H, H-15), 4.06 (broad s, 1H, H-5), 3.81 (s, 3H, OCH₃), 3.79 (a signal below OCH₃-signal, 1H, H-1), 3.73 (t, $J = 6.3$ Hz, 2H, H-12), 3.64 (d, $J \approx 13.7$ Hz, 1H and 1H^R, H-2 and H-2^R), 3.22 – 3.06 (m, 2H and 1H^R, H-4, H-8 and H-4^R), 2.91 (dd, $J = 19.5, 6.7$ Hz, 1H^R, H-8^R), 2.56 (d, $J = 19.1$ Hz, 1H^R, H-8^R), 2.32 (d, $J = 19.0$ Hz, 1H, H-8), 2.22 (s, 3H^R, CH₃CO^R), 2.21 (s, 3H, CH₃CO), 2.03 – 1.93 (m, 2H, H-11). ¹³C-NMR (CD₃OD): 172.82 (CO), 171.87 (CO^R), 169.39 (CO), 159.09 (Cq), 157.37 (Cq), 140.63 (Cq), 138.67 (Cq), 137.58 (Cq), 131.76 (Cq), 128.77 (CH_{arom}), 128.61 (CH_{arom}), 128.24 (CH_{arom}), 127.96 (CH_{arom}), 127.93 (Cq), 127.32 (CH_{arom}), 127.06 (CH_{arom}), 126.74 (CH^R_{arom}), 126.65 (Cq^R), 126.31 (Cq), 119.98 (CH_{arom}), 114.28 (CH^R_{arom}), 110.10 (CH_{arom}), 67.45 (C13), 66.54 (C12), 64.56 (C10), 54.47 (OCH₃), 49.31 (C5), 49.05 (C2), 46.97 (C4), 46.44 (C4^R), 43.90 (C15), 42.74 (C15^R), 33.97, 33.55 (C8 and C8^R), 29.35 (C11), 19.94 (CH₃CO), 19.83 (CH₃CO^R). IR (film) ν 2922, 2857, 1621 cm⁻¹. Anal. Calcd for

C₃₄H₃₉N₃O₅·2.0H₂O: C, 67.42; H, 7.10; N, 6.93. Found: C, 67.64; H, 7.14; N, 6.46. [α]_D²⁵ = +127.4 (1.0; MeOH). LC-MS: t_R = 0.87 min, MS (ESI): *m/z* 570.23 (M + 1); purity at 230 nm: 98.2%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid 2-chloro-benzylamide (17b). From 2-chlorobenzylamine (1.05 g, 7.5 mmol). The title product was obtained (410 mg, 30%).

¹H-NMR (CD₃OD): 7.35 (d, *J* = 7.4 Hz, 1H, H_{arom}), 7.30 – 7.19 (m, 2H, H_{arom}), 7.16 – 7.02 (m, 4H, H_{arom}), 6.95 (d, *J* = 8.6 Hz, 1H, H_{arom}), 6.90 (d, *J* = 7.5 Hz, 1H, H_{arom}), 6.80 – 6.72 (m, 4H, H_{arom}), 4.62 (d, *J* = 13.7 Hz, H-4), 4.58 (d, *J* = 13.7 Hz, 1H^R, H-4^R), 4.58 (s, 2H, H-13), 4.44 (d, *J* = 15.2 Hz, 1H, H-15), 4.41 (d, *J* = 15.3 Hz, 1H^R, H-15^R), 4.22 (d, *J* = 15.9 Hz, 1H, H-15), 4.19 (d, *J* ≈ 14.0 Hz, 1H, H-2), 4.18 (d, *J* = 15.5 Hz, 1H^R, H-15^R), 4.10 – 4.02 (m, 2H^R, H-2^R, H-5^R), 4.06 (t, *J* = 6.1 Hz, 2H, H-10), 3.98 (broad, s, 1H, H-5), 3.80 (s, 3H, OCH₃), 3.79 (a signal below OCH₃-signal, 1H, H-1), 3.73 (t, *J* = 6.1 Hz, 2H, H-12), 3.64 (d, *J* ≈ 13.7 Hz, 1H and 1H^R, H-2 and H-2^R), 3.58 – 3.49 (m, 1H^R, H-1^R), 3.10 – 2.94 (m, 2H and 1H^R, H-4, H-8 and H-4^R), 2.79 (dd, *J* = 19.0, 7.0 Hz, 1H^R, H-8^R), 2.54 (d, *J* = 19.3 Hz, 1H^R, H-8^R), 2.26 (d, *J* = 19.0 Hz, 1H, H-8), 2.23 (s, 3H^R, CH₃CO^R), 2.16 (s, 3H, CH₃CO), 2.12 – 2.04 (m, 2H, H-11). ¹³C-NMR (CD₃OD): 171.77 (CO), 171.58 (CO^R), 169.32 (CO^R), 169.21 (CO), 159.14 (Cq), 157.33 (Cq), 141.18 (Cq), 138.95 (Cq), 134.78 (Cq), 132.93 (Cq), 132.81 (Cq^R), 131.62 (Cq), 131.35 (Cq^R), 130.15 (Cq^R), 129.30 (CH_{arom}), 129.00 (CH^R_{arom}), 128.91 (CH_{arom}), 128.84 (CH^R_{arom}), 128.75 (CH_{arom}), 128.61 (CH_{arom}), 128.46 (CH_{arom}), 128.31 (CH^R_{arom}), 128.19 (CH_{arom}), 127.88 (CH_{arom}), 126.58 (CH_{arom}), 126.51 (CH_{arom}), 126.33 (CH^R_{arom}), 119.98 (CH_{arom}), 114.33 (CH_{arom}), 114.26

(CH^R_{arom}), 110.07 (CH_{arom}), 67.45 (C13), 66.53 (C12), 64.52 (C10), 54.46 (OCH₃), 51.70 (C2^R), 49.32 (C5), 49.22 (C2), 49.06 (C5^R), 46.57 (C4), 46.52 (C1^R), 43.81 (C4^R), 40.46 (C15^R), 40.42 (C15), 34.19, 33.49 (C8 and C8^R), 29.35 (C11), 19.94 (CH₃CO), 19.86 (CH₃CO^R). IR (film) ν 2921, 2855, 1627 cm⁻¹. Anal. Calcd for C₃₄H₃₈N₃O₅Cl: C, 67.60; H, 6.34; N, 6.96. Found: C, 64.40; H, 6.56; N, 6.13. $[\alpha]_D^{25} = +139.9$ (1.0; MeOH). LC-MS: $t_R = 0.89$ min, MS (ESI): m/z 604.22 (M + 1)⁺; purity at 230 nm: 98%; at 254 nm: 97.9%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid benzyl-methyl-amide (17c). From *N*-methylbenzylamine (903 mg, 7.5 mmol). The title product was obtained (242 mg, 18%).

¹H-NMR (CD₃OD): 7.34 (d, J = 7.3 Hz, 1H, H_{arom}), 7.30 – 7.08 (m, 6H, H_{arom}), 7.05 (d, J = 6.9 Hz, 1H^R, H^R_{arom}), 6.99 – 6.84 (m, 5H, H_{arom}), 6.81 (d, J = 8.6 Hz, 1H, H_{arom}), 6.75 (d, J = 8.5 Hz, 1H^R, H^R_{arom}), 4.77 (d, J = 14.7 Hz, 1H, H-15), 4.61 (d, J ≈ 14.6 Hz, H-4), 4.59 (s, 2H, H-13), 4.57 (d, J ≈ 16.1 Hz, 1H^R, H-15^R), 4.56 (d, J ≈ 12.9 Hz, 1H^R, H-4^R), 4.32 (d, J = 13.5 Hz, 1H, H-2), 4.128 (d, J = 13.0 Hz, 1H, H-2^R), 4.16 – 3.97 (m, 1H and 1H^R, H-15 and H-15^R), 4.09 (t, J = 6.9 Hz, 2H, H-10), 3.81 (s, 3H, OCH₃), 3.73 (t, J = 6.1 Hz, 2H, H-12), 3.60 (s, 1H, H-5), 3.54 (d, J ≈ 15.4 Hz, 1H and 1H^R, H-2 and H-2^R), 3.50 (s, 1H^R, H-5^R), 3.40 (broad, d, 1H, J = 6.9 Hz, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.04 (dd, J = 18.1, 7.0 Hz, 1H, H-8), 2.99 (broad, d, J ≈ 14.8 Hz, 1H, H-4), 2.96 (broad, d, J ≈ 12.7 Hz, 1H^R, H-4^R), 2.70 (s, 3H, NCH₃), 2.67 (s, 3H^R, NCH₃^R), 2.32 (s, 3H, CH₃CO), 2.20 – 2.03 (m, 3H and 1H^R, H-8, H-11 and H-8^R). ¹³C-NMR (CD₃OD): 172.01 (CO^R), 171.96 (CO), 171.45 (CO), 171.28 (CO^R), 159.16 (Cq), 157.35 (Cq), 137.76 (Cq), 137.46 (Cq^R), 137.30 (Cq^R), 136.77 (Cq), 136.10

(Cq), 135.89 (Cq^R), 132.28 (Cq), 131.74 (Cq^R), 128.74 (Cq), 128.60 (CH_{arom}), 128.31 (CH_{arom}), 128.11 (CH_{arom}), 127.94 (CH_{arom}^R), 127.74 (CH_{arom}^R), 127.69 (CH_{arom}), 127.67 (CH_{arom}), 127.13 (CH_{arom}), 126.98 (CH_{arom}), 126.94 (CH_{arom}), 126.34 (Cq), 119.99 (CH_{arom}), 114.20 (CH_{arom}), 114.16 (CH_{arom}^R), 110.09 (CH_{arom}), 67.46 (C13), 66.56 (C12), 64.54 (C10), 54.47 (OCH₃), 53.89 (C15^R), 51.71 (C5^R), 50.07 (C2^R), 49.93 (C2), 49.66 (C5), 49.33 (C15), 47.48 (C4^R), 47.20 (C4), 46.55 (C1), 46.45 (C1^R), 34.55 (NCH₃), 33.24, 32.81 (C8 and C8^R), 31.46 (NCH₃^R), 29.37 (C11), 20.05 (CH₃CO), 19.97 (CH₃CO^R). IR (film) ν 2921, 2855, 1603 cm⁻¹. Anal. Calcd for C₃₅H₄₁N₃O₅·0.5H₂O: C, 70.92; H, 7.09; N, 7.09. Found: C, 71.01; H, 7.22; N, 6.86. $[\alpha]_D^{25} = +48.6$ (1.0; MeOH). LC-MS: t_R = 0.89 min, MS (ESI): *m/z* 584.31 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid methyl-phenethyl-amide (17d) From *N*-methylphenethylamine (1.01 g, 7.5 mmol). The title product was obtained (380 mg, 28%).

¹H-NMR (CD₃OD): 7.35 – 7.05 (m, 9H, H_{arom}), 6.97 – 6.83 (m, 4H, H_{arom}), 4.59 (d, J = 11.5 Hz, 1H, H-4), 4.58 – 4.46 (m, 2H and 3H^R, H-13 and H-4^R, H-13^R), 4.15 (broad, d, J = 14.0 Hz, H-2), 4.12 – 4.03 (m, 2H and 1H^R, H-10 and H-2^R), 3.80 (s, 3H^R, OCH₃^R), 3.78 (s, 3H, OCH₃), 3.73 – 3.63 (m, 2H and 2H^R, H-12 and H-12^R), 3.67 – 3.57 (m, 1H^R, H-15^R), 3.55 – 3.44 (m, 2H, H-2 and H-15), 3.43 – 3.25 (m, 3H and 3H^R, H-1, H-5, H-15 and H2^R, H-5^R, H-15^R), 3.15 – 3.0 (m, 1H and 1H^R, H-8 and H-8^R), 2.97 (broad, d, 1H, J = 13.4 Hz, H-4), 2.92 – 2.82 (m, 2H^R, H-4^R, H-15^R), 2.75 (s, 3H, NCH₃), 2.73 – 2.64 (m, 1H and 1H^R, H-16 and H-16^R), 2.69 (s, 3H^R, NCH₃^R), 2.63 – 2.50 (m, 1H, H-16), 2.47 – 2.39 (m, 1H^R, H-16^R), 2.34 (s, 3H^R, CH₃CO^R), 2.29 (s, 3H, CH₃CO), 2.26 (s, 3H^R, CH₃CO^R), 2.22 (s, 3H^R, CH₃CO^R), 2.19 (s, 3H^R, CH₃CO^R), 2.14 (d, J = 18.4 Hz, 1H, H-8), 2.09 – 1.97 (m, 2H and 1H^R, H-11

and H-8^R). ¹³C-NMR (CD₃OD): 171.98 (CO), 171.86 (CO^R), 171.71 (CO^R), 171.12 (CO), 159.32 (Cq^R), 159.07 (Cq), 157.34 (Cq), 138.89 (Cq), 138.84 (Cq), 138.72 (Cq^R), 137.32 (Cq), 136.77 (Cq^R), 132.31 (Cq), 132.25 (Cq), 131.87 (Cq^R), 130.36 (Cq), 128.74 (CH_{arom}), 128.70 (CH_{arom}), 128.59 (CH_{arom}), 128.54 (CH^R_{arom}), 128.48 (CH_{arom}), 128.43 (CH_{arom}), 128.34 (CH_{arom}), 128.13 (CH^R_{arom}), 128.08 (CH_{arom}), 127.93 (CH^R_{arom}), 127.72 (CH_{arom}), 127.53 (CH^R_{arom}), 127.48 (CH_{arom}), 126.38 (CH_{arom}), 126.32 (Cq), 126.30 (Cq), 125.98 (CH_{arom}), 119.97 (CH_{arom}), 114.18 (CH_{arom}), 114.11 (CH_{arom}), 110.07 (CH_{arom}), 67.42 (C13), 66.47 (C12), 64.59 (C10), 54.45 (OCH₃), 51.78, 51.67 (C15^R), 49.84, 49.78 (C2, C2^R), 49.61 (C5), 49.45 (C5^R), 49.13 (CH₃CO^R), 48.19 (C15), 47.41, 47.20 (C4, C4^R), 46.52 (C1), 46.46 (C1^R), 35.50 (CH₃CO^R), 35.40 (NCH₃), 33.27, 32.93, 32.73, 32.57 (C8, C16 and C8^R, C16^R), 30.94 (NCH₃^R), 29.31, 29.27 (C11, C11^R), 20.01, 19.87 (CH₃CO, CH₃CO^R). IR (film) ν 2922, 2855, 1602 cm⁻¹. Anal. Calcd for C₃₆H₄₃N₃O₅·1.0H₂O: C, 70.22; H, 7.31; N, 6.82. Found: C, 70.69; H, 7.35; N, 6.46. [α]_D²⁵ = +143.6 (1.0; MeOH). LC-MS: t_R = 0.90 min, MS (ESI): *m/z* 598.29 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 97.8%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid methyl-(3-phenyl-propyl)-amide (17e) From methyl-(3-phenyl-propyl)-amine (1.05 g, 7.01 mmol). The title product was obtained (650 mg, 46%).

¹H-NMR (CD₃OD): 7.34 – 7.03 (m, 9H, H_{arom}), 6.95 – 6.87 (m, 2H, H_{arom}), 6.86 – 6.77 (m, 2H, H_{arom}), 4.57 (d, J = 13.5 Hz, 1H, H-4), 4.56 – 4.49 (m, 2H and 3H^R, H-13 and H-4^R, H-13^R), 4.28 – 4.18 (m, 1H and 1H^R, H-2 and H-2^R), 4.05 – 3.80 (m, 4H and 4H^R, H-10, H-15 and H-10^R, H-15^R), 3.78 (s, 3H,

OCH₃), 3.68 – 3.55 (m, 2H and 3H^R, H-12 and H-4^R, H-12^R), 3.54 – 3.43 (m, 2H and 1H^R, H-2, H-5 and H-2^R), 3.41 – 3.33 (m, 1H and 1H^R, H-1 and H-5^R), 3.30 – 2.94 (m, 1H^R, H-1^R), 3.02 (dd, J = 18.5, 7.2 Hz, 1H, H-8), 2.98 – 2.82 (m, 2H and 3H^R, H-4, H-8 and H-4^R(2x), H-8^R), 2.72 (s, 3H, NCH₃), 2.48 – 2.28 (m, 2H and 2H^R, H-17 and H-17^R), 2.36 (s, 3H^R, CH₃CO^R), 2.30 (s, 3H, CH₃CO), 2.27 (s, 3H^R, CH₃CO^R), 2.23 (s, 3H^R, CH₃CO^R), 2.18 (s, 3H^R, CH₃CO^R), 2.09 (d, J = 18.4 Hz, 1H, H-8), 2.05 – 1.89 (m, 2H and 3H^R, H-11 and H-8^R, H-11^R), 1.67 – 1.44 (m, 2H, H-16), 1.33 – 1.21 (m, 2H^R, H-16^R). ¹³C-NMR (CD₃OD): 171.91 (CO), 171.85 (CO^R), 171.48 (CO^R), 171.22 (CO), 159.03 (Cq^R), 158.97 (Cq), 157.29 (Cq), 141.62 (Cq), 141.57 (Cq^R), 141.54 (Cq), 141.44 (Cq^R), 137.38 (Cq), 136.95 (Cq^R), 136.66 (Cq), 135.95 (Cq^R), 132.65 (Cq), 132.37 (Cq), 132.20 (Cq), 131.96 (Cq^R), 130.71 (Cq^R), 128.67 (CH^R_{arom}), 128.65 (CH_{arom}), 128.62 (CH^R_{arom}), 128.57 (CH_{arom}), 128.35 (CH^R_{arom}), 128.24 (CH_{arom}), 128.18 (CH_{arom}), 128.03 (CH_{arom}), 127.99 (CH^R_{arom}), 127.92 (CH_{arom}), 127.73 (CH_{arom}), 127.67 (CH^R_{arom}), 127.53 (CH_{arom}), 125.72 (CH_{arom}), 125.52 (CH_{arom}), 120.01 (CH_{arom}), 114.21 (CH_{arom}), 114.16 (CH_{arom}), 110.08 (CH_{arom}), 67.40 (C13), 66.58 (C12), 66.53 (C12^R), 64.58 (C10), 64.53 (C15), 54.50 (OCH₃), 50.03 (C2), 49.80 (C5^R), 49.60 (C5), 49.51 (C2^R), 47.52 (C4), 46.53 (C1), 46.43 (C1^R), 46.31 (C4^R), 35.14 (NCH₃), 33.10, 32.75, 32.69, 32.63, 32.57, 32.30 (C8, C17 and C8^R, C17^R), 30.84 (NCH₃^R), 29.40, 29.34, 29.31 (C11, C11^R), 20.23, 20.09, 20.01, 19.84 (CH₃CO, CH₃CO^R). IR (film) ν 2925, 1603 cm⁻¹. Anal. Calcd for C₃₇H₄₅N₃O₅·1.0H₂O: C, 70.46; H, 7.53; N, 6.66. Found: C, 69.34; H, 7.44; N, 6.36. [α]_D²⁵ = +120.3 (1.0; MeOH). LC-MS: t_R = 0.91 min, MS (ESI): m/z 612.34 (M + 1)⁺; purity at 230 nm: 99.1%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-cyclopropyl-amide (17f). From *N*-(2-chlorobenzyl)-*N*-cyclopropylamine (prepared by reductive amination from 2-chlorobenzaldehyde and cyclopropylamine, 1.35 g, 7.5 mmol). The title product was obtained (234 mg, 16%).

$^1\text{H-NMR}$ (CD_3OD): 7.34 (d, $J = 7.3$ Hz, 1H, H_{arom}), 7.27 (t, $J = 8.2$ Hz, 1H, H_{arom}), 7.19 – 7.09 (m, 3H, H_{arom}), 7.05 (t, $J = 7.3$ Hz, 1H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 6.99 – 6.87 (m, 3H, H_{arom}), 6.80 (d, $J = 8.7$ Hz, 1H, H_{arom}), 6.66 (d, $J = 7.6$ Hz, 1H, H_{arom}), 4.86 (a signal below solvent peak, m, 1H^{R} , H-15 $^{\text{R}}$), 4.81 (d, $J = 16.0$ Hz, 1H, H-15), 4.61 (d, $J \approx 15.0$ Hz, H-4), 4.59 (s, 2H, H-13), 4.57 (d, $J \approx 12.9$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 4.41 (d, $J = 13.5$ Hz, 1H^{R} , H-2 $^{\text{R}}$), 4.34 (d, $J = 13.0$ Hz, 1H, H-2), 4.27 (d, $J = 15.8$ Hz, 1H, H-15), 4.18 – 4.10 (m, 2H^{R} , H-10 $^{\text{R}}$), 4.09 (t, $J = 6.2$ Hz, 2H, H-10), 3.82 (s, 3H^{R} , OCH_3^{R}), 3.81 (s, 3H, OCH_3), 3.77 – 3.67 (m, 3H and 4H^{R} , H-5, H-12 and H-5 $^{\text{R}}$, H-12 $^{\text{R}}$ and H-15 $^{\text{R}}$), 3.60 (d, $J \approx 12.9$ Hz, 1H, H-2), 3.57 (d, $J \approx 12.0$ Hz, 1H^{R} , H-2 $^{\text{R}}$), 3.46 (broad, d, 1H, $J = 7.1$ Hz, H-1), 3.33 (a signal below solvent peak, 1H, H-1 $^{\text{R}}$), 3.14 (dd, $J = 18.3, 7.2$ Hz, 1H, H-8), 3.10 (dd, $J \approx 19.0, 7.1$ Hz, 1H^{R} , H-8 $^{\text{R}}$), 3.02 (broad, d, $J \approx 12.1$ Hz, 1H, H-4), 2.95 (broad, d, $J \approx 13.6$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 2.31 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.29 (s, 3H, CH_3CO), 2.28 – 2.18 (m, 1H^{R} , H-16 $^{\text{R}}$), 2.18 – 1.98 (m, 4H and 1H^{R} , H-8, H-11, H-16 and H-8 $^{\text{R}}$), 0.97 - 0.83 (m, 1H, H-17), 0.80-0.64 (m, 1H and 1H^{R} , H-17 and H-17 $^{\text{R}}$), 0.60 - 0.37 (m, 2H and 2H^{R} , H-17(2x) and 1H-17^{R} (2x)), 0.07 - -0.03 (m, 1H^{R} , H-17 $^{\text{R}}$). $^{13}\text{C-NMR}$ (CD_3OD): 173.74 (CO^{R}), 173.69 (CO), 171.95 (CO), 171.84 (CO^{R}), 159.42 (Cq^{R}), 159.06 (Cq), 157.35 (Cq), 139.75 (Cq^{R}), 137.44 (Cq), 134.51 (Cq^{R}), 134.41 (Cq), 132.87 (Cq^{R}), 132.70 (Cq), 132.67 (Cq), 131.99 (Cq^{R}), 129.62 (Cq^{R}), 129.42 (CH_{arom}), 129.02 (CH_{arom}), 128.76 (CH_{arom}), 128.72 (Cq^{R}), 128.61 ($\text{CH}_{\text{arom}}^{\text{R}}$), 128.51 (CH_{arom}), 128.17 (CH_{arom}), 127.81 (CH_{arom}), 127.57 ($\text{CH}_{\text{arom}}^{\text{R}}$), 126.96 ($\text{CH}_{\text{arom}}^{\text{R}}$), 126.51 (CH_{arom}), 126.35 (Cq), 120.00 (CH_{arom}), 114.30 (CH_{arom}), 114.20 ($\text{CH}_{\text{arom}}^{\text{R}}$), 110.10 (CH_{arom}), 67.46 (C13), 66.53 (C12), 66.47 (C12 $^{\text{R}}$), 64.73 (C10 $^{\text{R}}$), 64.60 (C10), 54.43 (OCH_3), 50.57 (C15 $^{\text{R}}$), 50.05 (C5), 49.86 (C2), 49.77 (C5 $^{\text{R}}$), 48.12 (C4 $^{\text{R}}$), 47.91 (C4), 46.69 (C1), 46.50 (C15), 46.43 (C1 $^{\text{R}}$), 33.31, 33.20 (C8 and C8 $^{\text{R}}$), 30.63 (C16), 29.36 (C11), 29.28 (C11 $^{\text{R}}$),

27.92 (C16^R), 20.03 (CH₃CO), 19.98 (CH₃CO^R), 9.47, 5.50 (2 x C17), 7.62, 5.84 (2 x C17^R). IR (film) ν 2922, 2856, 1605 cm⁻¹. Anal. Calcd for C₃₇H₄₂N₃O₅Cl·H₂O C, 67.11; H, 6.70; N, 6.35. Found: C, 66.26; H, 6.60; N, 5.96. $[\alpha]_D^{25} = +113.3$ (1.0; MeOH). LC-MS: $t_R = 0.94$ min, MS (ESI): m/z 644.22 (M + 1)⁺; purity at 230 nm: 95.5%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (3-chloro-benzyl)-cyclopropyl-amide (17g). From *N*-(3-chlorobenzyl)-*N*-cyclopropylamine (prepared by reductive amination from 3-chlorobenzaldehyde and cyclopropylamine, 1.35 g, 7.5 mmol). The title product was obtained (416 mg, 28%).

¹H-NMR (CD₃OD): 7.34 (d, $J = 7.3$ Hz, 1H, H_{arom}), 7.27 (broad, d, $J \approx 7.5$ Hz, 1H, H_{arom}), 7.21 – 7.09 (m, 3H, H_{arom}), 7.05 (broad, d, $J \approx 8.6$ Hz, 1H, H_{arom}), 6.99 – 6.84 (m, 5H, H_{arom}), 6.68 (d, $J = 8.6$ Hz, 1H, H_{arom}), 4.93 (d, $J = 14.6$ Hz, 1H, H-15), 4.65 – 4.51 (m, H-4, 3H and 2H^R, H-13(2x) and H-4^R, H-15^R), 4.36 (d, $J = 13.0$ Hz, 1H, H-2), 4.33 (d, $J = 11.1$ Hz, 1H, H-2^R), 4.16 – 4.07 (m, 2H^R, H-10^R), 4.03 (t, $J = 6.0$ Hz, 2H, H-10), 3.91 (d, $J = 14.6$ Hz, 1H, H-15), 3.82 (broad, s, 3H and 1H^R, OCH₃ and H-15^R), 3.72 (t, $J = 6.1$ Hz, 2H, H-12), 3.61 – 3.52 (m, 2H and 1H^R, H-2, H-5 and H-2^R), 3.47 (s, 1H^R, H-5^R), 3.47 (broad, d, 1H, $J = 6.8$ Hz, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.10 (broad, dd, $J \approx 18.2, 7.1$ Hz, 1H and 1H^R, H-8 and H-8^R), 3.04 (broad, d, $J \approx 13.3$ Hz, 1H, H-4), 2.94 (broad, d, $J \approx 13.2$ Hz, 1H^R, H-4^R), 2.32 (s, 3H^R, CH₃CO^R), 2.30 (s, 3H, CH₃CO), 2.13 – 1.97 (m, 3H and 1H^R, H-8, H-11 and H-8^R), 1.82 – 1.74 (m, 1H, H-16), 0.95 - 0.83 (m, 1H, H-17), 0.77-0.64 (m, 1H and 1H^R, H-17 and H-17^R), 0.60 - 0.45 (m, 2H and 2H^R, H-17(2x) and 1H-17^R(2x)), 0.17 - 0.07 (m, 1H^R, H-17^R).

¹³C-NMR (CD₃OD): 173.76 (CO), 171.91 (CO), 159.29 (Cq^R), 158.89 (Cq), 157.33 (Cq), 139.85 (Cq^R),

139.06 (Cq), 138.88(Cq^R), 137.18 (Cq), 134.18 (Cq^R), 133.73 (Cq), 132.60 (Cq), 132.05 (Cq^R), 129.86 (CH_{arom}), 129.51 (CH_{arom}), 128.74 (CH_{arom}), 128.71 (Cq), 128.60 (CH_{arom}), 128.53 (CH_{arom}), 128.25 (CH_{arom}), 128.14 (Cq^R), 127.73 (CH_{arom}), 127.41 (CH_{arom}), 127.16 (CH^R_{arom}), 127.05 (CH_{arom}), 126.81 (CH^R_{arom}), 126.58 (CH_{arom}), 126.35 (Cq), 125.46 (CH^R_{arom}), 119.99 (CH_{arom}), 114.17 (CH^R_{arom}), 114.07 (CH_{arom}), 110.09 (CH_{arom}), 67.44 (C13), 66.60 (C12), 66.51 (C12^R), 64.66 (C10^R), 64.49 (C10), 54.47 (OCH₃), 52.15 (C15^R), 50.32 (C5), 50.16 (C2), 50.08 (C2^R), 49.99 (C5^R), 48.12 (C4^R), 47.91 (C4), 47.46 (C15), 46.70 (C1), 46.42 (C1^R), 33.25 (C8), 29.76 (C16), 29.38 (C11), 29.30 (C11^R), 27.88 (C16^R), 20.04 (CH₃CO), 20.00 (CH₃CO^R), 10.19, 5.64 (2 x C17), 7.46, 5.96 (2 x C17^R). IR (film) ν 2920, 2855, 1605 cm⁻¹. Anal. Calcd for C₃₇H₄₂N₃O₅Cl·0.5H₂O: C, 68.03; H, 6.58; N, 6.43. Found: C, 68.04; H, 6.76; N, 6.17. $[\alpha]_D^{25} = +117.8$ (1.0; MeOH). LC-MS: $t_R = 0.93$ min, MS (ESI): m/z 644.28 (M + 1); purity at 230 nm: 97.2%; at 254 nm: 97.2%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (4-chloro-benzyl)-cyclopropyl-amide (17h). From *N*-(4-chlorobenzyl)-*N*-cyclopropylamine (prepared by reductive amination from 4-chlorobenzaldehyde and cyclopropylamine, 1.35 g, 7.5 mmol). The title product was obtained (270 mg, 18%).

¹H-NMR (CD₃OD): 7.34 (d, J = 7.4 Hz, 1H, H_{arom}), 7.30 (d, J = 8.5 Hz, 1H, H_{arom}), 7.26 (d, J = 7.7 Hz, 1H, H_{arom}), 7.19 (d, J = 8.3 Hz, 2H, H_{arom}), 7.14 (d, J = 8.5 Hz, 1H^R, H^R_{arom}), 7.04 (d, J = 8.6 Hz, 2H, H_{arom}), 6.95 (d, J = 8.3 Hz, 2H, H_{arom}), 6.91 (t, J = 7.1 Hz, 2H, H_{arom}), 6.68 (d, J = 8.6 Hz, 1H, H_{arom}), 4.94 (d, J = 14.6 Hz, 1H, H-15), 4.64 – 4.52 (m, 3H and 2H^R, H-4, H-13(2x) and H-4^R, H-15^R), 4.36 (broad, d, J ≈ 13.5 Hz, 1H and 1H^R, H-2 and H-2^R), 4.13 (t, J = 6.2 Hz, 2H^R, H-10^R), 4.05 (t, J = 6.2 Hz,

2H, H-10), 3.88 (d, $J = 14.6$ Hz, 1H, H-15), 3.82 (broad, s, 3H and $1H^R$, OCH₃ and H-15^R), 3.78 – 3.69 (m, 2H, H-12), 3.62 – 3.52 (m, 2H and $1H^R$, H-2, H-5 and H-2^R), 3.47 (s, $1H^R$, H-5^R), 3.41 (broad, d, 1H, $J = 6.7$ Hz, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.09 (broad, dd, $J \approx 18.2, 7.1$ Hz, 1H and $1H^R$, H-8 and H-8^R), 3.00 (broad, d, $J \approx 13.2$ Hz, 1H, H-4), 2.95 (broad, d, $J \approx 14.0$ Hz, $1H^R$, H-4^R), 2.32 (s, $3H^R$, CH₃CO^R), 2.30 (s, 3H, CH₃CO), 2.16 – 1.99 (m, 3H and $1H^R$, H-8, H-11 and H-8^R), 1.83 – 1.74 (m, 1H, H-16), 0.97 – 0.83 (m, 1H, H-17), 0.79–0.65 (m, 1H and $1H^R$, H-17 and H-17^R), 0.62 – 0.44 (m, 2H and $2H^R$, H-17(2x) and $1H-17^R(2x)$), 0.14 – 0.04 (m, $1H^R$, H-17^R). ¹³C-NMR (CD₃OD): 173.61 (CO), 171.91 (CO), 159.28 (Cq^R), 158.89 (Cq), 157.33 (Cq), 138.82 (Cq^R), 137.66 (Cq^R), 137.12 (Cq), 136.28 (Cq^R), 135.52 (Cq), 132.93 (Cq^R), 132.78 (Cq^R), 132.72 (Cq), 132.57 (Cq), 132.12 (Cq^R), 130.04 (CH^R_{arom}), 129.85 (CH_{arom}), 129.68 (CH^R_{arom}), 128.70 (Cq), 128.58 (CH_{arom}), 128.56 (CH_{arom}), 128.38 (CH_{arom}), 128.17 (CH^R_{arom}), 128.04 (CH_{arom}), 127.85 (CH^R_{arom}), 127.73 (CH_{arom}), 127.53 (CH_{arom}), 126.37 (Cq), 119.97 (CH_{arom}), 114.15 (CH_{arom}), 110.07 (CH_{arom}), 67.44 (C13), 66.64 (C12), 66.50 (C12^R), 64.71 (C10^R), 64.60 (C10), 54.47 (OCH₃), 52.70 (C15^R), 52.03 (C5), 50.25 (C2), 50.10 (C2^R), 49.93 (C5^R), (C4^R), 47.91 (C4), 47.70 (C4^R), 47.41 (C15), 46.69 (C1), 46.41 (C1^R), 33.29 (C8), 33.19 (C8^R), 29.68 (C16), 29.42 (C11), 29.29 (C11^R), 27.80 (C16^R), 20.06 (CH₃CO), 20.00 (CH₃CO^R), 10.19, 5.56 (2 x C17), 7.57, 5.86 (2 x C17^R). IR (film) ν 2922, 2856, 1605 cm⁻¹. Anal. Calcd for C₃₇H₄₂N₃O₅Cl·0.5H₂O: C, 68.03; H, 6.58; N, 6.43. Found: C, 68.53; H, 6.96; N, 6.04. $[\alpha]_D^{25} = +114.3$ (1.0; MeOH). LC-MS: $t_R = 0.92$ min, MS (ESI): m/z 644.29 (M + 1)⁺; purity at 230 nm: 98.9%; at 254 nm: 99.5%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide (17i) From cyclopropyl-(2,3-dimethyl-benzyl)-amine (prepared by reductive amination from 2,3-dimethylbenzaldehyde and cyclopropylamine, 1.31 g, 7.46 mmol). The title product was obtained (270 mg, 17%).

$^1\text{H-NMR}$ (CD_3OD): 7.34 (d, $J = 7.5$ Hz, 1H, H_{arom}), 7.27 (t, $J = 7.9$ Hz, 1H, H_{arom}), 7.16 (d, $J = 8.6$ Hz, 1H, H_{arom}), 7.11 (d, $J = 8.6$ Hz, 1H, H_{arom}), 7.00 – 6.87 (m, 4H, H_{arom}), 6.83 (t, $J = 7.6$ Hz, 1H, H_{arom}), 6.79 (d, $J = 7.3$ Hz, 1H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 6.74 (d, $J = 8.6$ Hz, 1H, H_{arom}), 6.51 (t, $J = 7.6$ Hz, 1H, H_{arom}), 4.74 (d, $J = 15.3$ Hz, 1H, H-15), 4.66 – 4.49 (m, 3H and 2H^{R} , H-4, H-13(2x) and H-4^{R} , H-15^{R}), 4.36 (broad, d, $J \approx 13.5$ Hz, 1H and 1H^{R} , H-2 and H-2^{R}), 4.17 (d, $J = 15.4$ Hz, 1H, H-15), 4.11 – 4.10 (m, 2H^{R} , H-10 $^{\text{R}}$), 4.06 (t, $J = 6.2$ Hz, 2H, H-10), 3.82 (s, 3H^{R} , OCH_3^{R}), 3.81 (broad, s, 3H, OCH_3), 3.73 (t, $J = 6.1$ Hz, 2H, H-12), 3.70 (d, $J = 12.6$ Hz, 1H^{R} , H-15^{R}), 3.65 (s, 1H, H-5), 3.59 (d, $J = 13.3$ Hz, 1H, H-2), 3.52 (d, $J = 12.9$ Hz, 1H^{R} , H-2^{R}), 3.43 (broad, d, 1H, $J = 6.2$ Hz, H-1), 3.33 (a signal below solvent peak, 1H^{R} , H-1^{R}), 3.13 (dd, $J = 17.9, 7.0$ Hz, 1H, H-8), 3.09 (dd, $J \approx 19.0, 6.5$ Hz, 1H^{R} , H-8^{R}), 3.05 (broad, d, $J \approx 10.0$ Hz, 1H, H-4), 2.91 (broad, d, $J \approx 13.5$ Hz, 1H^{R} , H-4^{R}), 2.29 (s, 3H, CH_3CO), 2.30 (a signal below solvent peak, 1H^{R} , H16^{R}), 2.24 (s, 3H, CH_3Ar), 2.18 – 2.03 (m, 5H and 1H^{R} , H-8, H-11, CH_3Ar and H-8^{R}), 2.12 – 1.93 (m, 1H, H-16), 0.97 - 0.83 (m, 1H, H-17), 0.80-0.64 (m, 1H and 1H^{R} , H-17 and H-17^{R}), 0.60 - 0.38 (m, 2H and 2H^{R} , H-17(2x) and $1\text{H-17}^{\text{R}}(2\text{x})$), 0.09 - -0.02 (m, 1H^{R} , H-17^{R}). $^{13}\text{C-NMR}$ (CD_3OD): 173.52 (CO), 171.94 (CO), 171.83 (CO^{R}), 159.37 (Cq^{R}), 158.94 (Cq), 157.34 (Cq), 138.97 (Cq^{R}), 137.14 (Cq), 136.87 (Cq^{R}), 136.34 (Cq), 135.39 (Cq^{R}), 134.52 (Cq), 133.81 (Cq), 132.72 (Cq), 132.13 (Cq^{R}), 128.71 (CH_{arom}), 128.63 (Cq), 128.59 (CH_{arom}), 128.29 (Cq), 128.05 ($\text{CH}_{\text{arom}}^{\text{R}}$), 127.75 (CH_{arom}), 127.66 (CH_{arom}), 126.36 ($\text{CH}_{\text{arom}}^{\text{R}}$), 125.41 (CH_{arom}), 125.26 (CH_{arom}), 125.01 (CH_{arom}), 124.82 (Cq), 120.00 (CH_{arom}), 114.18 (CH_{arom}), 110.10 (CH_{arom}), 67.45 (C13), 66.58 (C12), 66.48 (C12^{R}), 64.74 (C10^{R}), 64.56 (C10), 54.49 (OCH_3), 51.22 (C15^{R}), 50.27 (C5), 50.03 (C2), 49.89 (C5^{R}), 47.34 (C4), 47.20 (C15), 46.72 (C1), 46.38 (C1^{R}), 33.30, 33.09 (C8 and C8^{R}), 30.53 (C16), 29.39 (C11), 29.28

(C11^R), 28.58 (C16^R), 20.03 (CH₃CO), 19.98 (CH₃CO^R), 19.29, 19.12 (2 x ArCH₃), 9.64, 5.61 (2 x C17), 7.58, 5.85 (2 x C17^R). IR (film) ν 2920, 2856, 1605 cm⁻¹. $[\alpha]_D^{25} = +111.2$ (1.0; MeOH). LC-MS: $t_R = 0.95$ min, MS (ESI): m/z 638.36 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (17j). From *N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)-amine (prepared by reductive amination from 2,3-dichlorobenzaldehyde and cyclopropylamine, 1.61 g, 7.5 mmol). The title product was obtained (420 mg, 26%).

¹H-NMR (CD₃OD): 7.44 (d, J = 7.37 Hz, 1H^R, H^R_{arom}), 7.37 – 7.23 (m, 3H, H_{arom}), 7.21 (t, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.13 (d, J = 8.6 Hz, 2H, H_{arom}), 7.01 (t, J = 7.9 Hz, 1H, H_{arom}), 6.98 – 6.87 (m, 2H, H_{arom}), 6.80 (d, J = 8.6 Hz, 1H, H_{arom}), 6.55 (d, J = 7.6 Hz, 1H, H_{arom}), 4.86 (a signal below solvent peak, m, 1H and 1H^R, H-15 and H-15^R), 4.64 – 4.51 (m, 3H and 1H^R, H-4, H-13(2x) and H-4^R), 4.40 (d, J = 13.4 Hz, 1H^R, H-2^R), 4.31 (d, J = 13.0 Hz, 1H, H-2), 4.25 (d, J = 15.9 Hz, 1H, H-15), 4.17 – 4.10 (m, 2H^R, H-10^R), 4.09 (t, J = 6.2 Hz, 2H, H-10), 3.82 (s, 3H^R, OCH^R₃), 3.81 (broad, s, 3H and 1H^R, OCH₃ and H-15^R), 3.77 – 3.69 (m, 2H and 3H^R, H-12 and H-5^R, H-12^R), 3.66 (s, 3H, H-5), 3.58 (broad, d, J ≈ 13.4 Hz, 1H and 1H^R, H-2 and H-2^R), 3.43 (broad, d, 1H, J = 6.8 Hz, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.12 (dd, J = 18.4, 7.2 Hz, 1H, H-8), 3.07 (dd, J ≈ 15.5, 7.1 Hz, 1H^R, H-8^R), 3.01 (broad, d, J ≈ 10.8 Hz, 1H, H-4), 2.94 (broad, d, J ≈ 13.0 Hz, 1H^R, H-4^R), 2.35 (s, 3H^R, CH₃CO^R), 2.31 (s, 3H, CH₃CO), 2.30 – 2.20 (m, 1H^R, H-16^R), 2.17 – 1.98 (m, 4H and 1H^R, H-8, H-11, H-16 and H-8^R), 0.97 - 0.84 (m, 1H, H-17), 0.79-0.66 (m, 1H and 1H^R, H-17 and H-17^R), 0.58 - 0.37 (m, 2H and 2H^R, H-17(2x) and 1H-17^R(2x)), 0.08 - -0.03 (m, 1H^R, H-17^R). ¹³C-NMR (CD₃OD): 173.81 (CO),

171.92 (CO), 171.83 (CO^R), 159.39 (Cq^R), 159.05 (Cq), 157.32 (Cq), 139.83 (Cq^R), 137.54 (Cq^R), 137.11 (Cq^R), 137.02 (Cq), 130.92 (Cq^R), 132.80 (Cq), 132.51 (Cq), 132.06 (Cq^R), 130.75 (Cq^R), 131.68 (Cq), 129.23 (CH^R_{arom}), 128.85 (CH_{arom}), 128.81 (CH_{arom}), 128.71 (Cq), 128.60 (CH_{arom}), 127.85 (CH_{arom}), 127.80 (CH_{arom}), 127.57 (CH^R_{arom}), 127.52 (CH^R_{arom}), 127.20 (CH_{arom}), 127.06 (CH_{arom}), 126.33 (Cq), 119.99 (CH_{arom}), 114.23 (CH_{arom}), 110.08 (CH_{arom}), 67.44 (C13), 66.52 (C12), 66.46 (C12^R), 64.70 (C10^R), 64.56 (C10), 54.43 (OCH₃), 51.04 (C15^R), 50.23 (C2^R), 50.07 (C5), 49.97 (C2), 49.79 (C5^R), 47.41, 47.20 (C4, C15), 46.68 (C1), 46.41 (C1^R), 33.43, 33.31 (C8 and C8^R), 30.70 (C16), 29.34 (C11), 29.27 (C11^R), 27.81 (C16^R), 20.04 (CH₃CO), 19.99 (CH₃CO^R), 9.59, 5.52 (2 x C17), 7.49, 5.89 (2 x C17^R). IR (film) ν 2921, 1605 cm⁻¹. Anal. Calcd for C₃₇H₄₁N₃O₅Cl₂·1.0H₂O: C, 63.79; H, 6.17; N, 6.03. Found: C, 63.75; H, 6.12; N, 5.86. $[\alpha]_D^{25} = +43.9$ (1.0; MeOH). LC-MS: $t_R = 0.96$ min, MS (ESI): m/z 678.23 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)-amide (17k) From cyclopropyl-(3-methoxy-2-methyl-benzyl)-amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde (Comins, D. L.; Brown, J. D. Ortho substitution of m-anisaldehyde via α -amino alkoxide directed lithiation. *J. Org. Chem.* 1989, 54, 3730-2, 1.43 g, 7.45 mmol). The title product was obtained (560 mg, 37%).

¹H-NMR (CD₃OD): 7.34 (d, J = 7.4 Hz, 1H, H_{arom}), 7.27 (t, J = 8.3 Hz, 1H, H_{arom}), 7.15 (d, J = 8.7 Hz, 1H, H_{arom}), 7.11 (d, J = 8.6 Hz, 2H, H_{arom}), 6.99 – 6.87 (m, 3H, H_{arom}), 6.85 (t, J = 8.3 Hz, 1H^R, H^R_{arom}), 6.74 (d, J = 8.4 Hz, 1H, H_{arom}), 6.71 (d, J = 6.5 Hz, 1H^R, H^R_{arom}), 6.56 (d, J = 7.7 Hz, 1H^R, H^R_{arom}), 6.28

(d, $J = 7.7$ Hz, 1H, H_{arom}), 4.74 (d, $J = 15.3$ Hz, 1H, H-15), 4.63 – 4.48 (m, 3H and $2H^R$, H-4, H-13(2x) and $H-4^R$, $H-15^R$), 4.35 (broad, d, $J \approx 12.8$ Hz, 1H and $1H^R$, H-2 and $H-2^R$), 4.18 – 4.09 (m, $2H^R$, $H-10^R$), 4.13 (d, $J = 15.2$ Hz, 1H, H-15), 4.08 (t, $J = 6.2$ Hz, 2H, H-10), 3.82 (s, $3H^R$, OCH_3^R), 3.81 (broad, s, 3H, OCH_3), 3.76 (s, 3H, CH_3OAr), 3.74 (t, $J = 6.5$ Hz, 2H, H-12), 3.69 (d, $J \approx 16.0$ Hz, $1H^R$, $H-15^R$), 3.60 (s, 1H, H-5), 3.55 (d, $J \approx 16.0$ Hz, 1H, H-2), 3.52 (d, $J \approx 12.9$ Hz, $1H^R$, $H-2^R$), 3.41 (broad, d, 1H, $J = 7.0$ Hz, H-1), 3.33 (a signal below solvent peak, $2H^R$, $H-1^R$, $H-5^R$), 3.12 (dd, $J = 18.2, 7.2$ Hz, 1H, H-8), 3.07 (dd, $J \approx 19.0, 7.7$ Hz, $1H^R$, $H-8^R$), 3.00 (broad, d, $J \approx 10.0$ Hz, 1H, H-4), 2.90 (broad, d, $J \approx 11.0$ Hz, $1H^R$, $H-4^R$), 2.40 – 2.30 (m, $1H^R$, $H-16^R$), 2.29 (s, $3H^R$, CH_3CO^R), 2.28 (s, 3H, CH_3CO), 2.15 – 2.00 (m, 6H and $1H^R$, H-8, H-11, CH_3Ar and $H-8^R$), 1.97 – 1.89 (m, 1H, H-16), 0.96 - 0.82 (m, 1H, H-17), 0.80-0.63 (m, 1H and $1H^R$, H-17 and $H-17^R$), 0.59 - 0.37 (m, 2H and $2H^R$, H-17(2x) and $H-17^R(2x)$), 0.10 - -0.03 (m, $1H^R$, $H-17^R$). ^{13}C -NMR (CD_3OD): 174.00 (CO^R), 173.64 (CO), 171.92 (CO), 171.82 (CO^R), 159.35 (Cq^R), 158.92 (Cq), 157.75 (Cq^R), 157.55 (Cq), 157.33 (Cq), 138.89 (Cq^R), 137.12 (Cq), 136.83 (Cq^R), 135.89 (Cq), 132.79 (Cq), 132.17 (Cq^R), 128.86 (Cq), 128.69 (CH_{arom}), 128.58 (CH_{arom}), 128.31 (Cq), 127.75 (CH_{arom}), 127.62 (CH_{arom}), 126.39 (Cq), 126.36 (Cq^R), 126.18 (CH_{arom}), 125.61 (CH_{arom}), 123.93 (Cq), 123.72 (Cq^R), 120.00 (CH_{arom}), 119.91 (CH_{arom}), 119.30 (CH_{arom}), 114.18 (CH_{arom}), 110.09 (CH_{arom}), 109.02 (CH_{arom}^R), 108.65 (CH_{arom}), 67.46 (C13), 66.59 (C12), 66.48 ($C12^R$), 64.73 ($C10^R$), 64.53 (C10), 54.73 (OCH_3^R), 54.65 (OCH_3), 54.48 (OCH_3), 50.83 ($C15^R$), 50.36 (C5), 50.16 (C2), 50.10 ($C2^R$), 49.94 ($C5^R$), 47.49, 47.41 (C4, $C4^R$), 46.73 (C1), 46.69 (C15), 46.39 ($C1^R$), 33.35, 33.13 (C8 and $C8^R$), 30.44 (C16), 29.41 (C11), 29.29 ($C11^R$), 28.63 ($C16^R$), 20.04 (CH_3CO), 19.98 (CH_3CO^R), 10.01, 9.69 ($ArCH_3$ and $ArCH_3^R$), 9.69, 5.59 (2 x C17), 7.56, 5.81 (2 x $C17^R$). IR (film) ν 2921, 1604 cm^{-1} . Anal. Calcd for $C_{39}H_{47}N_3O_6 \cdot 1.0 H_2O$: C, 69.72; H, 7.29; N, 6.25. Found: C, 69.83; H, 7.13; N, 6.10. $[\alpha]_D^{25} = +49.1$ (1.0; MeOH). LC-MS: $t_R = 0.94$ min, MS (ESI): m/z 654.35 ($M + 1$) $^+$; purity at 230 nm: 99.9%; at 254 nm: 99.7%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-methoxy-benzyloxy)-propoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2-methoxy-3-methyl-pyridin-4-ylmethyl)-amide (17l) From

(CH_{arom}), 114.20 (CH_{arom}), 110.04 (CH_{arom}), 67.45 (C13), 66.56 (C12), 66.50 (C12^R), 64.73 (C10^R), 64.561 (C10), 54.46 (OCH₃), 52.83 (OCH₃), 52.79 (OCH₃^R), 50.14 (C5), 49.99 (C2), 49.80 (C5^R), 49.47 (C2^R), 47.64 (C4), 46.68 (C1), 46.34 (C1^R), 45.96 (C15), 33.40, 33.24 (C8 and C8^R), 30.64 (C16), 29.40 (C11), 29.29 (C11^R), 28.17 (C16^R), 20.05 (CH₃CO), 20.01 (CH₃CO^R), 9.78, 9.54 (ArCH₃ and ArCH₃^R), 9.67, 5.45 (2 x C17), 7.31, 5.77 (2 x C17^R). IR (film) ν 2923, 2854, 1604 cm⁻¹. Anal. Calcd for C₃₈H₄₆N₄O₆·1.0 H₂O: C, 67.84; H, 7.13; N, 8.33. Found: C, 67.63; H, 7.41; N, 7.67. $[\alpha]_D^{25} = +41.4$ (1.0; MeOH). LC-MS: t_R = 0.90 min, MS (ESI): *m/z* 655.38 (M + 1)⁺; purity at 230 nm: 98.2%; at 254 nm: 96.4%.

[3-(4-Bromo-phenyl)-propoxy]-*tert*-butyl-dimethyl-silane (18a)

A sol. of 3-(4-bromo-phenyl)-propan-1-ol (195 g, 908 mmol), TBDMS-Cl (171 g, 1130 mmol) and imidazole (93.1 g, 1360 mmol) in THF (3600 mL) was stirred at rt for 3 h. After evaporation of ca. 2000 mL of solvents under reduced pressure, sat. aq. NH₄Cl (1000 mL) was added, and the mixture was extracted with EtOAc (2 x 500 mL). The combined org. layers were concentrated under reduced pressure, and the residue was purified by FC (heptane/EtOAc = 98/2) to provide the title compound (284 g, 95%). ¹H-NMR (CDCl₃): 7.41 (d, J = 8.3 Hz, 2H, H_{arom}), 7.08 (d, J = 8.3 Hz, 2H, H_{arom}), 3.63 (t, J = 6.2 Hz, 2H, H-1), 2.66 (t, J = 7.9 Hz, 2H, H-3), 1.86 – 1.78 (m, 2H, H-2), 0.93 (s, 9H, OTBDMS), 0.07 (s, 6H, OTBDMS). ¹³C-NMR (CDCl₃): 141.22 (Cq), 131.31 (CH_{arom}), 130.25 (CH_{arom}), 119.38 (Cq), 62.05 (C1), 34.24 (C2), 31.51 (C3), 25.94 (SiC(CH₃)₃), 18.31 (SiC(CH₃)₃), -5.30 (Si(CH₃)₂). LC-MS: t_R = 1.23 min, MS(ESI): *m/z* mass peak not visible.

(1*R*, 5*S*)-3-Acetyl-7-[4-(3-phenoxy-propyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24a).

Using phenol (252 mg, 2.68 mmol), the title product was obtained (223 mg, 28%). $^1\text{H-NMR}$ (CD_3OD): 7.45 (d, $J = 8.1$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.38 (d, $J = 7.9$ Hz, 1H , H_{arom}), 7.31 - 7.18 (m, 3H , H_{arom}), 7.16 - 7.02 (m, 4H , H_{arom}), 6.98 - 6.86 (m, 3H , H_{arom}), 6.76 (d, $J = 7.7$ Hz, 1H , H_{arom}), 4.92 - 4.77 (a signal below solvent peak, m, 1H and 1H^{R} , H-14 and H-14^{R}), 4.58 (d, $J = 12.3$ Hz, 1H , H-4), 4.54 (d, $J \approx 12.1$ Hz, 1H^{R} , H-4^{R}), 4.40 (d, $J = 12.8$ Hz, 1H^{R} , H-2^{R}), 4.33 (d, $J = 12.9$ Hz, 1H , H-2), 4.25 (d, $J = 15.7$ Hz, 1H , H-14), 4.02 - 3.86 (m, 2H and 2H^{R} , H-12 and H-12^{R}), 3.73 (d, $J = 16.0$ Hz, 1H^{R} , H-14^{R}), 3.63 (s, 1H , H-5), 3.58 (broad, d, $J = 11.2$ Hz, 1H and 2H^{R} , H-2 and H-2^{R} , H-5^{R}), 3.41 (d, $J = 5.7$ Hz, 1H , H-1), 3.33 (a signal below solvent peak, 1H , H-1^{R}), 3.13 (dd, $J = 18.3, 6.6$ Hz, 1H , H-8), 2.99 (broad, d, $J = 12.9$ Hz, 1H , H-4), 2.93 (broad, d, $J = 13.3$ Hz, 1H^{R} , H-4^{R}), 2.85 (t, $J = 7.1$ Hz, 2H^{R} , $\text{H-10}^{\text{R}}(2\text{x})$), 2.81 (t, $J = 7.8$ Hz, 2H , $\text{H-10}(2\text{x})$), 2.32 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.28 (s, 3H , CH_3CO), 2.19 - 1.89 (m, 4H , and 3H^{R} , H-8 , $\text{H-11}(2\text{x})$, H-15 and H-8^{R} , $\text{H-11}^{\text{R}}(2\text{x})$), 1.30 (broad, s, 1H , NH), 0.98 - 0.83 (m, 1H , H-16), 0.78-0.63 (m, 1H and 1H^{R} , H-16 and H-16^{R}), 0.57 - 0.41 (m, 2H and 1H^{R} , $\text{H-16}(2\text{x})$ and 1H-16^{R}), 0.40 - 0.28 (m, 1H^{R} , H-16^{R}), -0.07 - -0.18 (m, 1H^{R} , H-16^{R}). $^{13}\text{C-NMR}$ (CD_3OD): 173.76 (CO^{R}), 173.72 (CO), 171.93 (CO), 171.85 (CO^{R}), 159.07 (Cq), 142.25 (Cq^{R}), 141.73 (Cq), 140.30 (Cq^{R}), 138.23 (Cq), 137.82 (Cq), 137.59 (Cq^{R}), 137.08 (Cq), 137.02 (Cq^{R}), 132.98 (Cq^{R}), 132.54 (Cq), 130.90 (Cq), 129.35 (CH_{arom}), 129.06 (CH_{arom}), 128.93 (CH_{arom}), 128.51 (Cq^{R}), 128.41 (CH^{R}), 127.81 (Cq^{R}), 127.72 (CH^{R}), 127.53 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.05 (Cq), 126.65 ($\text{CH}^{\text{R}}_{\text{arom}}$), 126.58 (CH_{arom}), 120.30 (Cq), 120.26 (CH_{arom}), 114.20 (CH_{arom}), 114.16 (CH_{arom}), 66.37 (CH_2 , C12), 66.25 (CH_2^{R} , C12^{R}), 51.20 (CH_2 , C14^{R}), 50.28 (C2^{R}), 50.21 (C5), 50.14 (C2), 49.73 (C5^{R}), 47.62 (C4 and C4^{R}), 47.53 (C14), 46.67 (C1), 46.37 (C1^{R}), 33.45 (C8^{R}), 33.39 (C8), 31.41 (C10), 31.34 (C10^{R}), 30.74 (CH , C15), 30.48 (CH_2 , C11), 27.68 (CH ,

C15^R), 20.03 (CH₃CO), 20.01 (CH₃CO^R), 9.87, 5.72 (2x CH₂, 2 x C16), 7.70 (CH₂^R, C16^R). IR (film) ν 2920, 2018, 1619 cm⁻¹. Anal. Calcd for C₃₆H₃₇N₃O₄Cl₄·0.5 H₂O: C, 66.98; H, 6.05; N, 7.17. Found: C, 66.82; H, 5.93; N, 6.67. $[\alpha]_D^{25} = +159.0$ (1.06; MeOH). LC-MS: $t_R = 0.94$ min, MS (ESI): m/z 618.13 (M + 1)⁺; purity at 230 nm: 93.3%; at 254 nm: 92.5%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-chloro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24b)

Using 2-chlorophenol (344 mg, 2.68 mmol), the title product was obtained (250 mg, 29%). ¹H-NMR (CD₃OD): 7.45 (d, J = 8.1 Hz, 1H^R, H^R_{arom}), 7.42 - 7.33 (m, 2H, H_{arom}), 7.28 - 7.17 (m, 2H, H_{arom}), 7.17 - 7.00 (m, 4H, H_{arom}), 6.97 (d, J = 7.8 Hz, H_{arom}), 6.91 (t, J = 7.5 Hz, 1H, H_{arom}), 6.76 (d, J = 7.7 Hz, H_{arom}), 4.95 - 4.75 (a signal below solvent peak, m, 1H and 1H^R, H-14 and H-14^R), 4.57 (d, J = 12.8 Hz, 1H, H-4), 4.54 (d, J ≈ 12.1 Hz, 1H^R, H-4^R), 4.40 (d, J = 13.3 Hz, 1H^R, H-2^R), 4.33 (d, J = 12.9 Hz, 1H, H-2), 4.23 (d, J = 15.7 Hz, 1H, H-14), 4.10 - 3.90 (m, 2H and 2H^R, H-12 and H-12^R), 3.73 (d, J = 16.0 Hz, 1H^R, H-14^R), 3.62 (s, 1H, H-5), 3.57 (broad, d, J = 11.8 Hz, 1H and 2H^R, H-2 and H-2^R, H-5^R), 3.40 (d, J = 5.9 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.12 (dd, J = 18.4, 7.0 Hz, 1H, H-8), 2.99 (broad, d, J = 12.9 Hz, 1H, H-4), 2.98 - 2.88 (m, 2H and 3H^R, H-10(2x), , H-10^R(2x), H-4^R), 2.31 (s, 3H^R, CH₃CO^R), 2.27 (s, 3H, CH₃CO), 2.22 - 1.88 (m, 4H and 3H^R, H-8, H-11(2x), H-15 and H-8^R, H-11^R(2x)), 1.30 (broad, s, 1H, NH), 0.98 - 0.82 (m, 1H, H-16), 0.78 - 0.63 (m, 1H and 1H^R, H-16 and H-16^R), 0.57 - 0.40 (m, 2H and 1H^R, H-16(2x) and 1H-16^R), 0.40 - 0.26 (m, 1H^R, H-16^R), -0.07 - -0.18 (m, 1H^R, H-16^R). ¹³C-NMR (CD₃OD): 173.76 (CO^R), 173.69 (CO), 171.93 (CO), 171.85 (CO^R),

154.46 (Cq), 142.07 (Cq^R), 141.56 (Cq), 140.27 (Cq^R), 138.25 (Cq), 137.81 (Cq), 137.61 (Cq^R), 137.24 (Cq^R), 137.06 (Cq), 137.03 (Cq^R), 132.98 (Cq^R), 132.55 (Cq), 130.93 (Cq), 130.87 (Cq^R), 129.79 (CH_{arom}), 129.36 (Cq), 129.31 (CH_{arom}), 128.93 (CH_{arom}), 128.52 (Cq^R), 128.43 (CH), 127.75 (CH_{arom}), 127.64 (CH_{arom}), 127.52 (CH^R_{arom}), 127.03 (CH_{arom}), 126.66 (CH^R_{arom}), 126.59 (CH_{arom}), 122.53 (Cq^R), 122.48 (Cq), 121.09 (CH^R_{arom}), 121.03 (CH_{arom}), 113.46 (CH^R_{arom}), 113.33 (CH_{arom}), 67.41 (CH₂, C12), 67.26 (CH₂^R, C12^R), 51.18 (CH₂, C14^R), 50.27 (C2^R), 50.21 (C5), 50.13 (C2), 49.72 (C5^R), 47.62 (C4 and C4^R), 47.51 (C14), 46.67 (C1), 46.37 (C1^R), 33.45 (C8^R), 33.40 (C8), 31.23 (C10), 31.14 (C10^R), 30.71 (CH, C15), 30.51 (CH₂, C11^R), 30.28 (CH, C11), 27.69 (CH₂, C15^R), 20.03 (CH₃CO), 20.00 (CH₃CO^R), 9.92, 5.76 (2x CH₂, 2 x C16), 7.69 (CH₂^R, C16^R). IR (film) ν 2922, 2018, 1619 cm⁻¹. Anal. Calcd for C₃₆H₃₇N₃O₄Cl₄·1.0 H₂O: C, 62.64; H, 5.66; N, 6.26. Found: C, 62.77; H, 5.77; N, 6.16. $[\alpha]_D^{25}$ = +150.8 (1.02; MeOH). LC-MS: t_R = 0.97 min, MS (ESI): m/z 654.10 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(3-chloro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24c)

Using 3-chlorophenol (344 mg, 2.68 mmol), the title product was obtained (306 mg, 36%). ¹H-NMR (CD₃OD): 7.47 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.42 (d, J = 8.0 Hz, 1H, H_{arom}), 7.30 - 7.19 (m, 2H, H_{arom}), 7.18 - 7.05 (m, 4H, H_{arom}), 7.00 - 6.80 (m, 4H, H_{arom}), 4.94 - 4.79 (a signal below solvent peak, m, 1H and 1H^R, H-14 and H-14^R), 4.63 (d, J = 13.2 Hz, 1H, H-4), 4.60 (d, J ≈ 11.2 Hz, 1H^R, H-4^R), 4.47 (d, J = 12.9 Hz, 1H^R, H-2^R), 4.41 (d, J = 13.1 Hz, 1H, H-2), 4.2 (d, J = 15.7 Hz, 1H, H-14), 4.25 - 3.88 (m, 2H and 2H^R, H-12 and H-12^R), 3.82 (s, 1H, H-5), 3.76 (s, 1H^R, H-5^R), 3.71 (d, J = 15.8 Hz, 1H^R, H-14^R),

3.64 (broad, d, $J = 13.2$ Hz, 1H and 1H^R, H-2 and H-2^R), 3.54 (broad, d, $J = 6.5$ Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.21 (dd, $J = 18.6, 7.2$ Hz, 1H, H-8), 3.06 (broad, d, $J \approx 15.7$ Hz, 1H, H-4), 2.87 (t, $J = 7.2$ Hz, 2H^R, H-10^R(2x)), 2.82 (t, $J = 7.4$ Hz, 2H, H-10(2x)), 2.33 (s, 3H^R, CH₃CO^R), 2.29 (s, 3H, CH₃CO), 2.22 - 1.98 (m, 3H and 4H^R, H-8, H-11(2x), and H-8^R, H-15^R, H-11^R(2x)), 1.98 - 1.90 (m, 1H, H-15), 1.30 (broad, s, 1H, NH), 0.98 - 0.83 (m, 1H, H-16), 0.78 - 0.66 (m, 1H and 1H^R, H-16 and H-16^R), 0.58 - 0.42 (m, 2H and 1H^R, H-16(2x) and 1H-16^R), 0.39 - 0.28 (m, 1H^R, H-16^R), -0.07 - -0.17 (m, 1H^R, H-16^R). ¹³C-NMR (CD₃OD): 173.75 (CO^R), 173.70 (CO), 171.93 (CO), 171.85 (CO^R), 159.96 (Cq), 142.06 (Cq^R), 141.55 (Cq), 140.29 (Cq^R), 138.28 (Cq), 137.80 (Cq), 137.64 (Cq^R), 137.08 (Cq), 137.01 (Cq^R), 134.49 (Cq), 132.99 (Cq^R), 132.54 (Cq), 130.93 (Cq), 130.14 (CH_{arom}), 129.36 (Cq), 129.32 (CH_{arom}), 128.92 (CH_{arom}), 128.52 (Cq^R), 128.39 (CH), 127.76 (CH_{arom}), 127.68 (CH_{arom}), 127.53 (CH^R_{arom}), 127.03 (CH_{arom}), 126.67 (CH^R_{arom}), 126.60 (CH_{arom}), 120.34 (CH^R_{arom}), 120.30 (CH_{arom}), 114.43 (CH_{arom}), 114.41 (CH^R_{arom}), 112.89 (CH^R_{arom}), 112.79 (CH_{arom}), 66.82 (CH₂, C12), 66.66 (CH₂^R, C12^R), 51.20 (CH₂, C14^R), 50.27 (C2^R), 50.21 (C5), 50.13 (C2), 49.71 (C5^R), 47.89 (C4 and C4^R), 47.51 (C14), 46.66 (C1), 46.36 (C1^R), 33.46 (C8^R), 33.38 (C8), 31.31 (C10), 31.22 (C10^R), 30.75 (CH, C15), 30.52 (CH₂, C11^R), 30.27 (CH, C11), 27.68 (CH₂, C15^R), 20.02 (CH₃CO), 20.00 (CH₃CO^R), 9.91, 5.74 (2x CH₂, 2 x C16), 7.71 (CH₂^R, C16^R). IR (film) ν 2924, 2024, 1618 cm⁻¹. Anal. Calcd for C₃₆H₃₇N₃O₄Cl₄·1.0 H₂O: C, 62.64; H, 5.66; N, 6.26. Found: C, 63.01; H, 5.62; N, 6.13. $[\alpha]_D^{25} = +154.9$ (1.00; MeOH). LC-MS: $t_R = 0.96$ min, MS (ESI): m/z 654.14 (M + 1)⁺; purity at 230 nm: 98.7%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(4-chloro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24d)

Using 4-chlorophenol (344 mg, 2.68 mmol), the title product was obtained (311 mg, 36%). $^1\text{H-NMR}$ (CD_3OD): 7.46 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.39 (d, $J = 7.9$ Hz, 1H , H_{arom}), 7.30 (broad, d, $J = 7.5$ Hz, 2H , H_{arom}), 7.17 - 7.02 (m, 4H , H_{arom}), 6.96 (d, $J = 7.7$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.94 – 6.84 (m, 3H , H_{arom}), 6.77 (d, $J = 7.6$ Hz, 1H , H_{arom}), 4.93 - 4.78 (a signal below solvent peak, m, 1H and 1H^{R} , H-14 and H-14^{R}), 4.58 (d, $J = 12.7$ Hz, 1H , H-4), 4.54 (d, $J \approx 12.1$ Hz, 1H^{R} , H-4^{R}), 4.40 (d, $J = 12.4$ Hz, 1H^{R} , H-2^{R}), 4.33 (d, $J = 13.0$ Hz, 1H , H-2), 4.25 (d, $J = 15.7$ Hz, 1H , H-14), 4.02 - 3.86 (m, 2H and 2H^{R} , H-12 and H-12^{R}), 3.73 (d, $J = 16.0$ Hz, 1H^{R} , H-14^{R}), 3.63 (s, 1H , H-5), 3.58 (broad, d, $J = 11.1$ Hz, 1H and 2H^{R} , H-2 and H-2^{R} , H-5^{R}), 3.40 (broad, d, $J = 5.3$ Hz, 1H , H-1), 3.33 (a signal below solvent peak, 1H , H-1^{R}), 3.12 (dd, $J = 18.3, 6.7$ Hz, 1H , H-8), 2.99 (broad, d, $J \approx 12.8$ Hz, 1H , H-4), 2.93 (d, $J = 13.2$ Hz, 1H^{R} , H-4^{R}), 2.89 – 2.74 (m, 2H and 2H^{R} , $\text{H-10}(2\text{x})$ and $\text{H-10}^{\text{R}}(2\text{x})$), 2.32 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.28 (s, 3H , CH_3CO), 2.20 - 1.89 (m, 4H and 4H^{R} , H-8 , $\text{H-11}(2\text{x})$, H-15 and H-8^{R} , $\text{H-11}^{\text{R}}(2\text{x})$, H-15^{R}), 1.30 (broad, s, 1H , NH), 0.98 - 0.82 (m, 1H , H-16), 0.78 - 0.63 (m, 1H and 1H^{R} , H-16 and H-16^{R}), 0.58 - 0.41 (m, 2H and 1H^{R} , $\text{H-16}(2\text{x})$ and 1H-16^{R}), 0.40 - 0.28 (m, 1H^{R} , H-16^{R}), -0.07 - -0.17 (m, 1H^{R} , H-16^{R}). $^{13}\text{C-NMR}$ (CD_3OD): 173.74 (CO^{R}), 173.69 (CO), 171.92 (CO), 171.85 (CO^{R}), 157.82 (Cq), 142.13 (Cq^{R}), 141.61 (Cq), 140.27 (Cq^{R}), 138.25 (Cq), 137.80 (Cq), 137.62 (Cq^{R}), 137.25 (Cq^{R}), 137.08 (Cq), 137.02 (Cq^{R}), 133.00 (Cq^{R}), 132.54 (Cq), 130.92 (Cq), 130.87 (Cq^{R}), 129.35 (CH_{arom}), 128.92 (CH_{arom}), 128.50 (Cq^{R}), 128.39 (CH_{arom}), 127.75 (CH_{arom}), 127.66 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.53 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.03 (CH_{arom}), 126.67 ($\text{CH}^{\text{R}}_{\text{arom}}$), 126.60 (CH_{arom}), 125.09 (Cq), 125.05 (Cq^{R}), 115.66 ($\text{CH}^{\text{R}}_{\text{arom}}$), 115.61 (CH_{arom}), 66.87 (CH_2 , C12), 66.75 (CH_2^{R} , C12^{R}), 51.19 (CH_2 , C14^{R}), 50.27 (C2^{R}), 50.20 (C5), 50.12 (C2), 49.72 (C5^{R}), 47.55 (C4 and C4^{R}), 47.51 (C14), 46.66 (C1), 46.37 (C1^{R}), 33.45 (C8^{R}), 33.39 (C8), 31.36 (C10), 31.28

(C10^R), 30.75 (CH, C15), 30.63 (CH, C11^R), 30.36 (CH, C11), 27.68 (CH₂, C15^R), 20.04 (CH₃CO), 20.01 (CH₃CO^R), 9.89, 5.74 (2x CH₂, 2 x C16), 7.70 (CH₂^R, C16^R). IR (film) ν 2921, 2017, 1618 cm⁻¹. Anal. Calcd for C₃₆H₃₇N₃O₄Cl₄·0.5 H₂O: C, 63.50; H, 5.59; N, 6.34. Found: C, 63.49; H, 5.62; N, 6.32. $[\alpha]_D^{25} = +142.4$ (0.99; MeOH). LC-MS: $t_R = 0.99$ min, MS (ESI): m/z 654.18 (M + 1)⁺; purity at 230 nm: 98.5%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-methoxy-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24e)

Using 2-methoxyphenol (333 mg, 2.68 mmol), the title product was obtained (233 mg, 28%). ¹H-NMR (CD₃OD): 7.45 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.39 (d, J = 7.9 Hz, 1H, H_{arom}), 7.25 (d, J = 8.0 Hz, 1H, H_{arom}), 7.20 (d, J = 8.1 Hz, 1H^R, H^R_{arom}), 7.16 - 7.02 (m, 4H, H_{arom}), 7.01 - 6.83 (m, 4H, H_{arom}), 6.74 (d, J = 7.7 Hz, H_{arom}), 4.95 - 4.75 (a signal below solvent peak, m, 1H and 1H^R, H-14 and H-14^R), 4.57 (d, J = 12.7 Hz, 1H, H-4), 4.54 (d, J ≈ 12.3 Hz, 1H^R, H-4^R), 4.40 (d, J = 13.0 Hz, 1H^R, H-2^R), 4.33 (d, J = 12.9 Hz, 1H, H-2), 4.24 (d, J = 15.7 Hz, 1H, H-14), 4.05 - 3.90 (m, 2H and 2H^R, H-12 and H-12^R), 3.86 (s, 3H, OCH₃), 3.72 (d, J = 15.9 Hz, 1H^R, H-14^R), 3.63 (s, 1H, H-5), 3.57 (broad, d, J = 11.0 Hz, 1H and 2H^R, H-2 and H-2^R, H-5^R), 3.40 (d, J = 5.6 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.12 (dd, J = 18.4, 6.9 Hz, 1H, H-8), 2.99 (broad, d, J = 12.7 Hz, 1H, H-4), 2.90 - 2.76 (m, 2H and 3H^R, H-10(2x), H-10^R(2x), H-4^R), 2.31 (s, 3H^R, CH₃CO^R), 2.28 (s, 3H, CH₃CO), 2.22 - 1.90 (m, 4H and 3H^R, H-8, H-11(2x), H-15 and H-8^R, H-11^R(2x)), 1.30 (broad, s, 1H, NH), 0.97 - 0.85 (m, 1H, H-16), 0.76 - 0.65 (m, 1H and 1H^R, H-16 and H-16^R), 0.57 - 0.41 (m, 2H and 1H^R, H-16(2x) and 1H-

16^R), 0.39 - 0.24 (m, 1H^R, H-16^R), -0.07 - -0.18 (m, 1H^R, H-16^R). ¹³C-NMR (CD₃OD): 173.76 (CO^R), 173.71 (CO), 171.93 (CO), 171.85 (CO^R), 149.73 (Cq), 148.56 (Cq), 142.33 (Cq^R), 141.80 (Cq), 140.32 (Cq^R), 138.20 (Cq), 137.83 (Cq), 137.55 (Cq^R), 137.06 (Cq), 137.02 (Cq^R), 132.97 (Cq^R), 132.53 (Cq), 130.87 (Cq), 129.34 (CH_{arom}), 128.93 (CH_{arom}), 128.42 (Cq), 127.71 (CH^R_{arom}), 127.67 (CH_{arom}), 127.54 (CH^R_{arom}), 127.07 (CH_{arom}), 126.62 (CH^R_{arom}), 126.56 (CH_{arom}), 121.14 (Cq^R), 121.07 (Cq), 120.81 (CH_{arom}), 113.87 (CH^R_{arom}), 113.74 (CH_{arom}), 112.25 (CH_{arom}), 67.82 (CH₂, C12), 67.74 (CH₂^R, C12^R), 55.18 (OCH₃), 51.19 (CH₂, C14^R), 50.28 (C2^R), 50.20 (C5), 50.12 (C2), 49.73 (C5^R), 47.49 (C14), 46.67 (C1), 46.37 (C1^R), 33.40 (C8), 31.36 (C10), 31.31 (C10^R), 30.79 (C11^R), 30.71 (CH, C15), 30.50 (CH₂, C11), 27.68 (CH₂, C15^R), 20.03 (CH₃CO), 20.00 (CH₃CO^R), 9.85, 5.71 (2x CH₂, 2 x C16), 7.69, 5.75 (2xCH₂^R, 2xC16^R). IR (film) ν 2921, 2018, 1619 cm⁻¹. Anal. Calcd for C₃₆H₃₉N₃O₄Cl₂·0.5 H₂O: C, 65.75; H, 6.08; N, 6.84. Found: C, 65.72; H, 6.07; N, 6.38. $[\alpha]_D^{25} = +160.2$ (1.03; MeOH). LC-MS: t_R = 0.92 min, MS (ESI): m/z 648.15 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]-non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24f)

Using 2-bromo-5-fluorophenol (512 mg, 2.68 mmol), the title product was obtained (304 mg, 33%). ¹H-NMR (DMSO-d₆): 7.61 (t, J = 7.5 Hz, 1H, H_{arom}), 7.53 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.46 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.26 (t, J = 7.5 Hz, 1H^R, H^R_{arom}), 7.21 (d, J = 7.5 Hz, 1H^R, H^R_{arom}), 7.15 – 6.94 (m, 6H, H_{arom}), 6.77 (t, J = 8.3 Hz, H_{arom}), 6.62 (d, J = 7.2 Hz, H_{arom}), 4.70 (broad, d, J ≈ 15.9 Hz, 1H and 1H^R, H-14 and H-14^R), 4.40 (d, J = 12.6 Hz, 1H, H-4), 4.36 (d, J ≈ 12.4 Hz, 1H^R, H-4^R), 4.14 (d, J = 16.1 Hz,

1H, H-14), 4.10 – 3.98 (m, 3H and 2H^R, H-2 and H-12 and H-12^R), 3.70 (d, J = 16.3 Hz, 1H^R, H-14^R), 3.51 (s, 1H, H-5), 3.41 (broad, d, J = 12.6 Hz, 1H, H-2), 3.27 (d, J = 5.3 Hz, 1H, H-1), 2.99 (dd, J = 18.0, 6.7 Hz, 1H, H-8), 2.85 – 2.71 (m, 3H and 2H^R, H-10(2x), H-10^R(2x), H-4), 2.14 (s, 3H^R, CH₃CO^R), 2.10 (s, 3H, CH₃CO), 2.09 - 1.97 (m, 2H and 2H^R, H-11(2x) and H-11^R(2x)), 1.85 (broad, d, J ≈ 17.5 Hz, H and 1H^R, H-8, H-15, H-15^R), 0.90 - 0.77 (m, 1H, H-16), 0.75 - 0.63 (m, 1H, H-16), 0.62 - 0.54 (m, 1H^R, H-16^R), 0.51 - 0.35 (m, 2H, H-16(2x)), 0.33 - 0.22 (m, 1H^R, H-16^R), -0.13 - -0.22 (m, 1H^R, H-16^R). ¹³C-NMR (DMSO-d₆): 173.79 (CO), 173.22 (CO^R), 169.74 (CO), 163.98 (Cq), 161.56 (Cq), 156.34 (d, J = 7Hz, Cq), 141.31 (Cq^R), 141.04 (Cq), 139.11 (Cq^R), 137.97 (Cq), 136.50 (Cq), 133.99 (CH_{arom}), 133.89 (CH_{arom}), 130.97 (Cq), 130.61 (Cq^R), 130.41 (Cq), 129.68 (CH^R_{arom}), 128.33 (CH_{arom}), 128.76 (CH_{arom}), 128.64 (CH^R_{arom}), 128.08 (CH_{arom}), 127.91 (CH_{arom}), 127.03 (CH_{arom}), 108.86 (d, J = 23 Hz, CH_{arom}), 106.3 (d, J = 23Hz, Cq), 102.48(d, J = 27 Hz, CH_{arom}), 68.61 (CH₂, C12), 68.37 (CH₂^R, C12^R), 50.72 (C5^R), 50.56 (C2), 50.43 (C5), 50.09 (C2^R), 48.04 (C4), 47.74 (C14), 46.69 (C1), 46.51 (C1^R), 33.79 (C8), 31.41 (C10), 30.98 (C15), 30.49 (C11^R), 30.28 (CH, C11), 28.11 (CH₂, C15^R), 21.50 (CH₃CO), 10.54, 6.50 (2x CH₂, 2 x C16), 8.33 (CH₂^R, 2xC16^R).). IR (film) ν 2922, 2019, 1619 cm⁻¹. Anal. Calcd for C₃₅H₃₅N₃O₃BrCl₂·0.5 H₂O: C, 58.02; H, 4.97; N, 5.80. Found: C, 57.76; H, 5.06; N, 5.55. [α]_D²⁵ = +138.4 (1.02; MeOH), MS (ESI): m/z 716.12 (M + 1)⁺. LC-MS: t_R = 1.00 min, MS (ESI): m/z 716.12 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2,6-dichloro-4-methyl-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24g)

Using 2,6-dichloro-*p*-cresol (475 mg, 2.68 mmol), the title product was obtained (330 mg, 36%). ¹H-NMR (CD₃OD): 7.46 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.40 (d, J = 7.8 Hz, H_{arom}), 7.30 - 7.12 (m, 5H, H_{arom}), 7.08 (t, J = 7.9 Hz, 1H, H_{arom}), 6.99 (d, J = 7.8 Hz, H_{arom}), 6.79 (d, J = 7.6 Hz, 1H, H_{arom}), 4.93 - 4.83 (a signal below solvent peak, m, 1H^R, H-14^R), 4.80 (d, J = 15.7 Hz, 1H, CH₂N), 4.58 (d, J = 12.7 Hz, 1H, H-4), 4.54 (d, J ≈ 12.1 Hz, 1H^R, H-4^R), 4.41 (d, J = 13.6 Hz, 1H^R, H-2^R), 4.34 (d, J = 12.9 Hz, 1H, H-2), 4.27 (d, J = 15.7 Hz, 1H, H-14), 4.08 - 3.91 (m, 2H and 2H^R, H-12 and H-12^R), 3.74 (d, J = 16.0 Hz, 1H^R, H-14^R), 3.63 (s, 1H, H-5), 3.58 (broad, d, J = 12.1 Hz, 1H and 2H^R, H-2 and H-2^R, H-5^R), 3.41 (d, J = 5.6 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.14 (dd, J = 18.4, 7.0 Hz, 1H, H-8), 3.00 (broad, d, J = 11.6 Hz, 1H, H-4), 2.97 - 2.80 (m, 2H and 3H^R, H-10(2x), H-10^R(2x), H-4^R), 2.32 (s, 3H^R, CH₃CO^R), 2.28 (s, 6H, CH₃CO and CH₃Ar), 2.23 - 1.91 (m, 4H and 3H^R, H-8, H-11(2x), H-15 and H-8^R, H-11^R(2x)), 0.99 - 0.84 (m, 1H, H-16), 0.77 - 0.64 (m, 1H and 1H^R, H-16 and H-16^R), 0.58 - 0.41 (m, 2H and 1H^R, H-16(2x) and 1H-16^R), 0.39 - 0.27 (m, 1H^R, H-16^R), -0.06 - -0.17 (m, 1H^R, H-16^R). ¹³C-NMR (CD₃OD): 173.77 (CO), 171.93 (CO), 171.85 (CO^R), 149.07 (Cq), 142.35 (Cq^R), 141.82 (Cq), 140.31 (Cq^R), 138.24 (Cq), 137.84 (Cq), 137.58 (Cq^R), 137.11 (Cq), 137.08 (Cq^R), 135.73 (Cq), 133.00 (Cq^R), 132.53 (Cq), 130.89 (Cq), 129.31 (CH_{arom}), 129.17 (CH_{arom}), 128.89 (CH_{arom}), 128.50 (Cq), 128.36 (CH), 127.70 (CH_{arom}), 127.65 (CH^R_{arom}), 127.52 (CH^R_{arom}), 127.03 (CH_{arom}), 126.64 (CH^R_{arom}), 126.55 (CH_{arom}), 72.53 (CH₂, C12), 51.19 (CH₂, C14^R), 50.29 (C2^R), 50.24 (C5), 50.16 (C2), 49.74 (C5^R), 47.71 (C4 and C4^R), 47.52 (C14), 46.68 (C1), 46.38 (C1^R), 33.45 (C8^R), 33.36 (C8), 31.61 (C10^R), 31.44 (C10), 31.30 (CH, C11), 30.81 (CH₂, C15), 27.69 (CH₂, C15^R), 20.03 (CH₃CO), 19.07 (CH₃Ar), 9.95, 5.74 (2x CH₂, 2 x C16), 7.69 (CH₂^R, C16^R). IR (film) ν 2923, 2019, 1618 cm⁻¹. Anal. Calcd for C₃₆H₃₇N₃O₃Cl₄·1.0 H₂O: C, 60.10; H, 5.42; N, 5.84. Found: C, 60.43; H, 5.33; N, 5.68. [α]_D²⁵ = +132.9 (1.01; MeOH). LC-MS: t_R = 1.00 min, MS (ESI): m/z 702.08 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2,6-dichloro-4-fluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24h)

Using 2,6-dichloro-4-fluorophenol (485 mg, 2.68 mmol), the title product was obtained (355 mg, 39%). $^1\text{H-NMR}$ (CD_3OD): 7.47 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.41 (d, $J = 7.9$ Hz, H_{arom}), 7.32 - 7.21 (m, 3H, H_{arom}), 7.19 - 7.05 (m, 3H, H_{arom}), 6.99 (d, $J = 7.7$ Hz, H_{arom}), 6.81 (d, $J = 7.7$ Hz, 1H, H_{arom}), 4.93 - 4.83 (a signal below solvent peak, m, 1H^{R} , H-14^{R}), 4.81 (d, $J = 15.8$ Hz, 1H, CH_2N), 4.58 (d, $J = 12.7$ Hz, 1H, H-4), 4.55 (d, $J \approx 12.3$ Hz, 1H^{R} , H-4^{R}), 4.41 (d, $J = 13.1$ Hz, 1H^{R} , H-2^{R}), 4.35 (d, $J = 12.7$ Hz, 1H, H-2), 4.27 (d, $J = 15.7$ Hz, 1H, H-14), 4.10 - 3.93 (m, 2H and 2H^{R} , H-12 and H-12^{R}), 3.75 (d, $J = 16.0$ Hz, 1H^{R} , H-14^{R}), 3.63 (s, 1H, H-5), 3.58 (broad, d, $J = 12.1$ Hz, 1H and 2H^{R} , H-2 and H-2^{R} , H-5^{R}), 3.41 (d, $J = 6.2$ Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^{R}), 3.15 (dd, $J = 18.3, 7.0$ Hz, 1H, H-8), 3.00 (broad, d, $J = 12.6$ Hz, 1H, H-4), 2.97 - 2.81 (m, 2H and 3H^{R} , $\text{H-10}(2\text{x})$, $\text{H-10}^{\text{R}}(2\text{x})$, H-4^{R}), 2.32 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.28 (s, 3H, CH_3CO), 2.23 - 1.91 (m, 4H and 3H^{R} , H-8 , $\text{H-11}(2\text{x})$, H-15 and H-8^{R} , $\text{H-11}^{\text{R}}(2\text{x})$), 0.99 - 0.85 (m, 1H, H-16), 0.80 - 0.66 (m, 1H and 1H^{R} , H-16 and H-16^{R}), 0.58 - 0.42 (m, 2H and 1H^{R} , $\text{H-16}(2\text{x})$ and 1H-16^{R}), 0.39 - 0.28 (m, 1H^{R} , H-16^{R}), -0.07 - -0.17 (m, 1H^{R} , H-16^{R}). $^{13}\text{C-NMR}$ (CD_3OD): 173.74 (CO), 171.92 (CO), 171.85 (CO^{R}), 158.98 (Cq), 156.53 (Cq), 148.48 (Cq^{R}), 148.88 (Cq), 142.25 (Cq^{R}), 141.71 (Cq), 140.28 (Cq^{R}), 138.27 (Cq), 137.82 (Cq), 137.62 (Cq^{R}), 137.11 (Cq), 137.08 (Cq^{R}), 133.00 (Cq^{R}), 132.54 (Cq), 130.93 (Cq), 130.86 (Cq^{R}), (CH_{arom}), 129.73 (Cq), 129.61 (Cq), 129.33 (CH_{arom}), 128.89 (CH_{arom}), 128.51 (Cq^{R}), 128.34 (CH), 127.80 (CH_{arom}), 127.61 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.53 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.03 (CH_{arom}), 126.66 ($\text{CH}^{\text{R}}_{\text{arom}}$), 126.56 (CH_{arom}), 116.15 (CH_{arom}), 115.89 (CH_{arom}), 72.80 (CH_2 , C12), 51.18 (CH_2 , C14^{R}), 50.23 (C5), 50.16 (C2), 49.72 (C5^{R}), 47.68 (C4 and C4^{R}), 47.52 (C14), 46.67 (C1), 46.37 (C1^{R}), 33.45 (C8^{R}), 33.36 (C8), 31.58 (C10^{R}), 31.39 (C10), 31.26 (CH, C11), 30.81 (CH_2 , C15), 27.68 (CH_2 , C15^{R}), 20.03 (CH_3CO), 9.99, 5.75 (2x

CH₂, 2 x C16), 7.68, 5.70 (2xCH₂^R, 2xC16^R). IR (film) ν 2920, 2022, 1620 cm⁻¹. [α]_D²⁵ = +132.9 (0.98; MeOH). LC-MS: t_R = 0.97 min, MS (ESI): *m/z* 708.04 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24i)

Using 2,3,6-trifluorophenol (397 mg, 2.68 mmol), the title product was obtained (125 mg, 14%). ¹H-NMR (CD₃OD): 7.47 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.41 (d, J = 8.1 Hz, H_{arom}), 7.25 (broad, d, J = 7.5 Hz, H_{arom}), 7.19 - 7.05 (m, 4H, H_{arom}), 7.04 – 6.94 (m, 2H, H_{arom}), 6.79 (d, J = 7.6 Hz, H_{arom}), 4.93 - 4.77 (a signal below solvent peak, m, 1H and 1H^R, CH₂N and H-14^R), 4.58 (d, J = 12.6 Hz, 1H, H-4), 4.55 (d, J ≈ 11.9 Hz, 1H^R, H-4^R), 4.41 (d, J = 12.7 Hz, 1H^R, H-2^R), 4.34 (d, J = 12.9 Hz, 1H, H-2), 4.27 (d, J = 15.7 Hz, 1H, H-14), 4.23 – 4.10 (m, 2H and 2H^R, H-12 and H-12^R), 3.74 (d, J = 16.0 Hz, 1H^R, H-14^R), 3.64 (s, 1H, H-5), 3.58 (broad, d, J = 12.7 Hz, 1H and 2H^R, H-2 and H-2^R, H-5^R), 3.42 (d, J = 5.9 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.15 (dd, J = 18.3, 7.0 Hz, 1H, H-8), 3.00 (broad, d, J = 12.9 Hz, 1H, H-4), 2.94 – 2.73 (m, 2H and 3H^R, H-10(2x), H-10^R(2x), H-4^R), 2.32 (s, 3H^R, CH₃CO^R), 2.28 (s, 3H, CH₃CO), 2.23 - 1.91 (m, 4H and 3H^R, H-8, H-11(2x), H-15 and H-8^R, H-11^R(2x)), 1.00 - 0.83 (m, 1H, H-16), 0.78 - 0.65 (m, 1H and 1H^R, H-16 and H-16^R), 0.58 - 0.40 (m, 2H and 1H^R, H-16(2x) and 1H-16^R), 0.39 - 0.28 (m, 1H^R, H-16^R), -0.07 - -0.18 (m, 1H^R, H-16^R). ¹³C-NMR (CD₃OD): 173.71 (CO), 171.95 (CO), 171.87 (CO^R), 153.27 (Cq^R), 150.85 (Cq^R), 141.99 (Cq^R), 141.49 (Cq), 141.03 (Cq^R), 140.30 (Cq^R), 138.39 (Cq^R), 138.29 (Cq), 137.82 (Cq), 137.82 (Cq), 137.66 (Cq^R),

137.09 (Cq), 137.03 (Cq^R), 133.00 (Cq^R), 132.54 (Cq), 130.92 (Cq), 130.87 (Cq^R), (CH_{arom}), 129.31 (Cq), 128.89 (CH_{arom}), 128.48 (Cq^R), 128.37 (CH), 127.81 (CH^R_{arom}), 127.75 Cq), 127.65 (CH^R_{arom}), 127.53 (CH^R_{arom}), 129.69 (CH_{arom}), 126.65 (Cq), 126.56 (CH_{arom}), 110.50 (dd, J = 22, 8.0 Hz, CH_{arom}), 109.84 (dd, J = 19.1, 9.0 Hz, CH_{arom}), 73.70 (CH₂, C12), 73.54 (CH₂, C12^R), 51.18 (CH₂, C14^R), 50.26 (C2^R), 50.21 (C5), 50.12 (C2), 49.71 (C5^R), 47.61 (C4 and C4^R), 47.49 (C14), 46.67 (C1), 46.37 (C1^R), 33.81 (C8^R), 33.44 (C8), 32.08 (C10^R), 31.43 (C11^R), 31.20 (C10), 31.05 (CH, C11), 30.98 (CH₂, C15), 27.62 (CH₂, C15^R), 20.01 (CH₃CO), 9.90, 5.70 (2x CH₂, 2 x C16), 7.63, 5.63 (2xCH₂^R, 2xC16^R). IR (film) ν 2922, 2019, 1618 cm⁻¹. Anal. Calcd for C₃₅H₃₄N₃O₃ClF₃·0.5 H₂O: C, 61.68; H, 5.13; N, 6.16. Found: C, 61.96; H, 5.37; N, 6.16. $[\alpha]_D^{25} = +141.5$ (1.00; MeOH). LC-MS: t_R = 0.97 min, MS (ESI): m/z 671.29 (M + 1)⁺; purity at 230 nm: 87.2%; at 254 nm: 87.2%.

(1R, 5S)-3-Acetyl-7-{4-[3-(3-chloro-2,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo-[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24j)

Using 3-chloro-2,6-difluorophenol (441 mg, 2.68 mmol), the title product was obtained (329 mg, 37%). ¹H-NMR (CD₃OD): 7.48 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.42 (d, J = 8.0 Hz, H_{arom}), 7.27 (t, J = 7.7 Hz, H_{arom}), 7.24 – 9.97 (m, 6H, H_{arom}), 6.84 (d, J = 7.6 Hz, H_{arom}), 4.93 - 4.80 (a signal below solvent peak, m, 1H and 1H^R, CH₂N and H-14^R), 4.63 (d, J = 13.2 Hz, 1H, H-4), 4.60 (d, J ≈ 11.0 Hz, 1H^R, H-4^R), 4.47 (d, J = 13.4 Hz, 1H^R, H-2^R), 4.41 (d, J = 13.2 Hz, 1H, H-2), 4.27 (d, J = 15.6 Hz, 1H, H-14), 4.23 – 4.08 (m, 2H and 2H^R, H-12 and H-12^R), 3.81 (s, 1H, H-5), 3.75 (s, 1H, H-5^R), 3.71 (d, J = 15.9 Hz, 1H^R, H-14^R), 3.64 (broad, d, J = 13.3 Hz, 1H and 2H^R, H-2 and H-2^R, H-5^R), 3.53 (d, J = 7.2 Hz,

1H, H-1), 3.47 (d, J = 7.1 Hz, 1H, H-1^R), 3.21 (dd, J = 18.8, 7.6 Hz, 1H, H-8), 3.14 (dd, J = 19.0, 7.7 Hz, 1H, H-8^R), 3.05 (broad, d, J = 13.9 Hz, 1H, H-4), 3.01 (broad, d, J ≈ 15.8 Hz, 1H, H-4), 2.90 (t, J = 7.2 Hz, H-10^R(2x)), 2.84 (t, J = 6.1 Hz, H-10(2x)), 2.34 (s, 3H^R, CH₃CO^R), 2.29 (s, 3H, CH₃CO), 2.22 - 1.91 (m, 4H and 3H^R, H-8, H-11(2x), H-15 and H-8^R, H-11^R(2x)), 0.97 - 0.86 (m, 1H, H-16), 0.88 - 0.67 (m, 1H and 1H^R, H-16 and H-16^R), 0.59 - 0.40 (m, 2H and 2H^R, H-16(2x) and 1H-16^R(2x)), 0.38 - 0.28 (m, 1H^R, H-16^R). ¹³C-NMR (CD₃OD): 173.76 (CO), 173.73 (CO^R), 171.95 (CO), 171.87 (CO^R), 154.85 (d, J = 243 Hz, Cq), 152.13 (d, J = 243 Hz, Cq), 141.98 (Cq^R), 141.47 (Cq), 140.31 (Cq^R), 138.30 (Cq), 137.82 (Cq), 136.67 (Cq^R), 137.08 (Cq), 137.02 (t, J = 6.0 Hz, Cq^R), 136.65 (t, J = 15.0 Hz, Cq^R), 133.00 (Cq^R), 132.54 (Cq), 130.93 (Cq), 130.88 (Cq^R), 129.34 (CH_{arom}), 128.90 (CH_{arom}), 128.52 (Cq^R), 128.36 (CH_{arom}), 127.76 (CH_{arom}), 127.66 (CH^R_{arom}), 127.53 (CH^R_{arom}), 127.01 (CH_{arom}), 126.68 (CH_{arom}), 126.60 (CH_{arom}), 123.45 (CH^R_{arom}), 123.39 (CH_{arom}), 123.36 (CH^R_{arom}), 123.31 (CH_{arom}), 116.88 (d, J = 21. Hz, CH^R_{arom}), 112.09 (dd, J = 20.1, 3.0 Hz), 73.76 (CH₂, C12), 73.60 (CH₂, C12^R), 51.18 (CH₂, C14^R), 50.28 (C2^R), 50.21 (C5), 50.14 (C2), 49.71 (C5^R), 47.61 (C4 and C4^R), 47.51 (C14), 46.66 (C1), 46.36 (C1^R), 33.44 (C8^R), 33.36 (C8), 31.42 (C10^R), 31.19 (C10), 31.06 (C11), 30.98 (C11^R), 30.78 (CH₂, C15), 27.63 (CH₂, C15^R), 20.02 (CH₃CO), 9.94, 5.73 (2x CH₂, 2 x C16), 7.66, 5.65 (2xCH₂^R, 2xC16^R). IR (film) ν 2925, 2016, 1619 cm⁻¹. Anal. Calcd for C₃₅H₃₄N₃O₃Cl₃F₂·0.5 H₂O: C, 60.22; H, 5.01; N, 6.02. Found: C, 60.60; H, 5.05; N, 6.04. [α]_D²⁵ = +149.9 (1.00; MeOH). LC-MS: t_R = 0.99 min, MS (ESI): m/z 690.19 (M + 1)⁺; purity at 230 nm: 96.9%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (24k)

Using 2-chloro-3,6-difluorophenol (441 mg, 2.68 mmol), the title product was obtained (285 mg, 32%). $^1\text{H-NMR}$ (CD_3OD): 7.47 (d, $J = 7.9$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.40 (d, $J = 8.0$ Hz, 1H , H_{arom}), 7.25 (broad, t, $J \approx 8.0$ Hz, 1H , H_{arom}), 7.21 - 7.04 (m, 5H , H_{arom}), 6.79 (d, $J = 7.6$ Hz, 1H , H_{arom}), 4.92 - 4.77 (a signal below solvent peak, m, 1H and 1H^{R} , H-14 and H-14^{R}), 4.58 (d, $J = 12.6$ Hz, 1H , H-4), 4.55 (d, $J \approx 12.0$ Hz, 1H^{R} , H-4^{R}), 4.40 (d, $J = 13.0$ Hz, 1H^{R} , H-2^{R}), 4.34 (d, $J = 12.9$ Hz, 1H , H-2), 4.2 (d, $J = 15.7$ Hz, 1H , H-14), 4.22 - 4.07 (m, 2H and 2H^{R} , H-12 and H-12^{R}), 3.74 (d, $J = 16.1$ Hz, 1H^{R} , H-14^{R}), 3.64 (s, 1H , H-5), 3.58 (broad, d, $J \approx 11.3$ Hz, 1H and 2H^{R} , H-2 and H-2^{R} , H-5^{R}), 3.41 (d, $J = 5.8$ Hz, 1H , H-1), 3.33 (a signal below solvent peak, 1H , H-1^{R}), 3.14 (dd, $J = 18.4, 7.0$ Hz, 1H , H-8), 3.00 (broad, d, $J = 12.7$ Hz, 1H , H-4), 2.96 - 2.80 (m, 2H and 2H^{R} , H-10(2x) and $\text{H-10}^{\text{R(2x)}}$), 2.32 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.28 (s, 3H , CH_3CO), 2.22 - 1.90 (m, 4H , and 3H^{R} , H-8 , H-11(2x) , H-15 and H-8^{R} , $\text{H-11}^{\text{R(2x)}}$), 0.98 - 0.83 (m, 1H , H-16), 0.78-0.64 (m, 1H and 1H^{R} , H-16 and H-16^{R}), 0.58 - 0.40 (m, 2H and 1H^{R} , H-16(2x) and 1H-16^{R}), 0.40 - 0.28 (m, 1H^{R} , H-16^{R}), -0.07 - -0.20 (m, 1H^{R} , H-16^{R}). $^{13}\text{C-NMR}$ (CD_3OD): 173.77 (CO), 173.73 (CO^{R}), 171.94 (CO), 171.86 (CO^{R}), 155.23 (d, $J = 244$ Hz, Cq), 152.35 (d, $J = 244$ Hz, Cq), 144.45 (d, $J = 17$ Hz, Cq), 142.06 (Cq^{R}), 141.56 (Cq), 140.29 (Cq^{R}), 138.30 (Cq), 137.81 (Cq), 136.66 (Cq^{R}), 137.10 (Cq), 137.05 (Cq^{R}), 133.00 (Cq^{R}), 132.54 (Cq), 130.92 (Cq), 130.88 (Cq^{R}), 129.35 (CH_{arom}), 129.32 ($\text{CH}^{\text{R}}_{\text{arom}}$), 128.89 (Cq), 128.53 (Cq^{R}), 128.36 (CH_{arom}), 127.75 (CH_{arom}), 127.64 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.52 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.02 (CH_{arom}), 126.68 (CH_{arom}), 126.60 (CH_{arom}), 115.81 (d, $J = 15$ Hz, $\text{CH}^{\text{R}}_{\text{arom}}$), 114.73 (dd, $J = 22, 9.0$ Hz), 110.15 (dd, $J = 23, 8.0$ Hz), 73.48 (CH_2 , C12), 73.34 (CH_2 , C12^{R}), 51.18 (CH_2 , C14^{R}), 50.28 (C2^{R}), 50.22 (C5), 50.15 (C2), 49.72 (C5^{R}), 47.61 (C4 and C4^{R}),

47.52 (C14), 46.67 (C1), 46.37 (C1^R), 33.45 (C8^R), 33.37 (C8), 31.52 (C10^R), 31.31 (C10), 31.24 (C11), 31.17 (C11^R), 30.80 (CH₂, C15), 27.64 (CH₂, C15^R), 20.02 (CH₃CO), 19.72 (CH₃CO^R), 9.92, 5.72 (2x CH₂, 2 x C16), 7.65, 5.66 (2xCH₂^R, 2xC16^R). IR (film) ν 2925, 2018, 1618 cm⁻¹. Anal. Calcd for C₃₅H₃₄N₃O₃Cl₃F₂·0.5 H₂O: C, 60.22; H, 5.01; N, 6.02. Found: C, 59.98; H, 5.09; N, 5.85. $[\alpha]_D^{25} = +141.3$ (1.06; MeOH). LC-MS: $t_R = 0.98$ min, MS (ESI): m/z 690.19 (M + 1)⁺; purity at 230 nm: 97.8%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-[4-(2-phenoxy-ethoxy)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclo-propyl-(2,3-dichloro-benzyl)-amide (25a)

Using phenol (419 mg, 4.46 mmol), the title product was obtained (160 mg, 11%). ¹H-NMR (CD₃OD): 7.46 (d, J = 8.0 Hz, 1H^R, H^R_{arom}), 7.35 (d, J = 7.9 Hz, 1H, H_{arom}), 7.26 - 7.19 (m, 2H, H_{arom}), 7.19 - 7.02 (m, 3H, H_{arom}), 7.09 (d, J = 7.9 Hz, 1H, H_{arom}), 6.98 (d, J = 7.8 Hz, 1H^R, H^R_{arom}), 6.94 (d, J = 8.5 Hz, 1H, H_{arom}), 6.86 (d, J = 8.6 Hz, 2H, H_{arom}), 6.57 (d, J = 7.7 Hz, 1H, H_{arom}), 4.97 - 4.70 (a signal below solvent peak, m, 1H and 1H^R, NCH₂ and NCH₂^R), 4.59 (d, J = 13.3 Hz, 1H, H-4), 4.55 (d, J ≈ 16.5 Hz, 1H^R, H-4^R), 4.46 - 4.28 (m, 4H and 1H^R, H-10(2x), H-11(2x) and H-2^R), 4.31 (d, J ≈ 12.4 Hz, 1H, H-2), 4.27 (d, J = 15.9 Hz, 1H, CH₂-N), 3.77 (d, J = 16.1 Hz, 1H^R, CH₂^R-N), 3.65 (s, 1H, H-5), 3.58 (broad, d, J = 13.0 Hz, 1H and 1H^R, H-2 and H-2^R), 3.42 (d, J = 6.4 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.12 (dd, J = 18.4, 7.2 Hz, 1H, H-8), 3.01 (broad, d, J = 13.0 Hz, 1H, H-4), 2.94 (broad, d, J = 13.1 Hz, 1H^R, H-4^R), 2.38 - 2.18 (m, 1H^R, H-14^R), 2.31 (s, 3H^R, CH₃CO^R), 2.29 (s, 3H, CH₃CO), 2.18 - 1.95 (m, 1H, H-14), 2.12 (d, J = 18.2 Hz, 1H, H-8), 1.00 - 0.82 (m, 1H, H-15), 0.80 - 0.66 (m, 1H and 1H^R, H-15 and H-15^R), 0.60 - 0.35 (m, 2H and 2H^R, H-15(2x) and 1H-15^R(2x)), 0.10 -

0.00 (m, 1H^R, H-15^R). ¹³C-NMR (CD₃OD): 173.91 (CO), 171.95 (CO), 158.73 (Cq), 148.88 (Cq), 139.66 (Cq^R), 137.50 (Cq), 137.10 (Cq), 136.03 (Cq), 133.16 (Cq), 132.50 (Cq), 130.60 (Cq), 129.27 (CH^R_{arom}), 129.21 (CH_{arom}), 129.08 (Cq), 128.78 (CH_{arom}), 128.48 (Cq), 127.87 (CH_{arom}), 127.80 (CH^R_{arom}), 127.21 (CH_{arom}), 127.08 (CH_{arom}), 114.42 (2xCH_{arom}), 114.33 (CH^R_{arom}), 71.66, 67.06 (2xCH₂, C10, C11),), 71.74, 67.19 (2x CH₂^R, C10^R, C11^R), 51.08 (CH₂, C13^R), 50.31 (C2^R), 50.09 (C5), 50.05 (C2), 49.84 (C5^R), 47.40 (C4 and C4^R), 47.018 (C13), 46.97 (C1), 46.67 (C1^R), 33.40 (C8), 30.75 (C14), 20.02 (CH₃CO), 9.50, 5.44 (2 x C15), 7.44, 5.98 (2 x C15^R). IR (film) ν 2921, 2856, 1607 cm⁻¹. Anal. Calcd for C₃₄H₃₅N₃O₄Cl₂·1.0 H₂O: C, 63.95; H, 5.84; N, 6.58. Found: C, 62.58; H, 5.55; N, 6.24. $[\alpha]_D^{25} = +178.9$ (0.33; MeOH). LC-MS: $t_R = 0.94$ min, MS (ESI): m/z 620.11 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[2-(2-chloro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25b)

Using 2-chlorophenol (573 mg, 4.46 mmol), the title product was obtained (214 mg, 14%). ¹H-NMR (CD₃OD): 7.43 (d, J = 7.4 Hz, 1H^R, H^R_{arom}), 7.38 (d, J = 7.8 Hz, 1H, H_{arom}), 7.30 - 7.25 ("t", 2H, H_{arom}), 7.22 (d, J = 7.8 Hz, 1H^R, H^R_{arom}), 7.20 - 7.10 (m, 3H, H_{arom}), 7.06 - 6.86 (m, 4H, H_{arom}), 6.43 (d, J = 7.6 Hz, 1H, H_{arom}), 4.97 - 4.70 (a signal below solvent peak, m, 1H and 1H^R, NCH₂ and NCH₂^R), 4.59 (d, J = 13.2 Hz, 1H, H-4), 4.54 (d, J ≈ 16.0 Hz, 1H^R, H-4^R), 4.48 - 4.33 (m, 4H and 1H^R, H-10(2x), H-11(2x) and H-2^R), 4.29 (d, J = 13.1 Hz, 1H, H-2), 4.22 (d, J = 16.3 Hz, 1H, CH₂-N), 3.84 (d, J = 16.1 Hz, 1H^R,

CH₂^R-N), 3.65 (s, 1H, H-5), 3.58 (broad, d, J = 13.5 Hz, 1H and 1H^R, H-2 and H-2^R), 3.41 (d, J = 6.6 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.10 (dd, J = 18.3, 7.2 Hz, 1H, H-8), 3.05 (broad, d, J = 12.9 Hz, 1H, H-4), 2.94 (broad, d, J = 13.0 Hz, 1H^R, H-4^R), 2.39 – 2.20 (m, 1H^R, H-14^R), 2.37 (s, 3H^R, CH₃CO^R), 2.30 (s, 3H, CH₃CO), 2.19 - 1.98 (m, 1H, H-14), 2.10 (d, J = 18.5 Hz, 1H, H-8), 1.00 - 0.84 (m, 1H, H-15), 0.79-0.66 (m, 1H and 1H^R, H-15 and H-15^R), 0.59 - 0.38 (m, 2H and 2H^R, H-15(2x) and 1H-15^R(2x)), 0.11 - 0.01 (m, 1H^R, H-15^R). ¹³C-NMR (CD₃OD): 173.94 (CO^R), 173.80 (CO), 171.93 (CO), 171.83 (CO^R), 159.10 (Cq^R), 158.73 (Cq), 154.38 (Cq), 139.66 (Cq^R), 137.43 (Cq), 137.10 (Cq^R), 136.99 (Cq), 133.27 (Cq), 132.51(Cq^R), 132.47 (Cq), 130.73 (Cq^R), 130.58 (Cq), 129.92 (CH_{arom}), 129.27 (Cq), 129.20 (CH^R_{arom}), 128.77 (CH_{arom}), 128.06 (CH^R_{arom}), 127.97 (CH_{arom}), 127.85 (CH^R_{arom}), 127.72 (CH_{arom}), 127.56 (CH^R_{arom}), 127.52 (CH^R_{arom}), 127.13 (CH_{arom}), 127.01 (CH_{arom}), 122.78 (Cq^R), 122.63 (Cq), 121.61 (CH^R_{arom}), 121.55 (CH_{arom}), 114.51 (2xCH_{arom}), 114.37 (CH^R_{arom}), 114.33 (CH^R_{arom}), 114.06 (CH^R_{arom}), 113.84 (CH_{arom}), 67.81, 66.52 (2xCH₂, C10, C11), , 66.72, 66.36 (2x CH₂^R, C10^R, C11^R), 51.02 (CH₂, C13^R), 50.26 (C2^R), 50.04 (C5), 49.96 (C2), 49.82 (C5^R), 47.48 (C4 and C4^R), 47.03 (C13), 46.67 (C1), 46.41 (C1^R), 33.50 (C8), 33.32 (C8^R), 30.67 (C14), 27.82 (C14^R), 20.06 (CH₃CO), 20.00 (CH₃CO^R), 9.49, 5.45 (2 x C15), 7.43, 5.97 (2 x C15^R). IR (film) ν 1922, 1620 cm⁻¹. Calcd for C₃₄H₃₄N₃O₄Cl₃·0.5 H₂O: C, 61.50; H, 5.27; N, 6.32. Found C, 61.33; H, 5.38; N, 6.15. [α]_D²⁵ = +28.0 (1.0; MeOH). LC-MS: t_R = 0.96 min, no mass peak; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[2-(3-chloro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25c)

Using 3-chlorophenol (573 mg, 4.46 mmol), the title product was obtained (315 mg, 22%). $^1\text{H-NMR}$ (CD_3OD): 7.44 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 7.32 (d, $J = 7.5$ Hz, 1H , H_{arom}), 7.27 (d, $J = 8.2$ Hz, 1H , H_{arom}), 7.22 (t, 1H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 7.16 (d, $J = 8.5$ Hz, 2H , H_{arom}), 7.08 – 6.91 (m, 4H , H_{arom}), 6.88 (d, $J = 8.5$ Hz, 2H , H_{arom}), 6.51 (d, $J = 7.7$ Hz, 1H , H_{arom}), 4.94 - 4.77 (a signal below solvent peak, m, 1H and 1H^{R} , NCH_2 and NCH_2^{R}), 4.59 (d, $J = 13.3$ Hz, 1H , H-4), 4.55 (d, $J \approx 15.9$ Hz, 1H^{R} , H-4^{R}), 4.44 - 4.27 (m, 5H and 1H^{R} , $\text{H-10}(2\text{x})$, $\text{H-11}(2\text{x})$, H-2 and H-2^{R}), 4.25 (d, $J = 16.2$ Hz, 1H , H-2), 3.82 (d, $J = 16.0$ Hz, 1H^{R} , $\text{CH}_2^{\text{R}}\text{-N}$), 3.65 (s, 1H , H-5), 3.58 (broad, d, $J = 13.5$ Hz, 1H and 1H^{R} , H-2 and H-2^{R}), 3.41 (d, $J = 6.2$ Hz, 1H , H-1), 3.33 (a signal below solvent peak, 1H , H-1^{R}), 3.11 (dd, $J = 18.6, 7.1$ Hz, 1H , H-8), 3.01 (broad, d, $J = 12.7$ Hz, 1H , H-4), 2.94 (broad, d, $J = 13.1$ Hz, 1H^{R} , H-4^{R}), 2.37 – 2.20 (m, 1H^{R} , H-14^{R}), 2.31 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.29 (s, 3H , CH_3CO), 2.19 - 1.98 (m, 1H , H-14), 2.10 (d, $J = 18.4$ Hz, 1H , H-8), 1.03 - 0.83 (m, 1H , H-15), 0.81-0.66 (m, 1H and 1H^{R} , H-15 and H-15^{R}), 0.61 - 0.38 (m, 2H and 2H^{R} , $\text{H-15}(2\text{x})$ and $1\text{H-15}^{\text{R}}(2\text{x})$), 0.09 - 0.00 (m, 1H^{R} , H-15^{R}). $^{13}\text{C-NMR}$ (CD_3OD): 173.92 (CO^{R}), 173.80 (CO), 171.92 (CO), 171.83 (CO^{R}), 159.70 (Cq), 158.98 (Cq^{R}), 158.64 (Cq), 139.66 (Cq^{R}), 139.69 (Cq^{R}), 137.40 (Cq), 137.11 (Cq^{R}), 137.06 (Cq), 134.58 (Cq), 133.29 (Cq), 132.94 (Cq^{R}), 132.52 (Cq), 130.77 (Cq^{R}), 130.66 (Cq), 130.25 (CH_{arom}), 129.24 (CH_{arom}), 128.77 (CH_{arom}), 128.08 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.97 (CH_{arom}), 127.89 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.57 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.51 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.11 (CH_{arom}), 127.07 (CH_{arom}), 120.74 (CH_{arom}), 114.74 (CH_{arom}), 114.38 (CH_{arom}), 112.98 ($\text{CH}^{\text{R}}_{\text{arom}}$), 112.95 (CH_{arom}), 66.81, 66.41 (2x CH , C10 , C11), , 66.76, 66.54 (2xCH^{R} , C10^{R} or C11^{R}), 51.05 (C13^{R}), 50.27 (C2^{R}), 50.07 (C5), 49.98 (C2), 49.81 (C5^{R}), 47.84 (C4 and C4^{R}), 47.41 (C13), 46.67 (C1), 46.41 (C1^{R}), 33.47 (C8), 33.34 (C8^{R}), 30.73 (C14), 27.83 (C14^{R}), 20.05 (CH_3CO), 20.00 ($\text{CH}_3\text{CO}^{\text{R}}$), 9.52, 5.50 ($2 \times \text{C15}$), 7.51,

5.91 (2 x C15^R). IR (film) ν 2922, 1618 cm⁻¹. Anal. Calcd for C₃₄H₃₄N₃O₄Cl₃·0.5 H₂O: C, 61.50; H, 5.27; N, 6.32. Found: C, 61.90; H, 5.39; N, 6.18. $[\alpha]_D^{25} = +107.5$ (1.0; MeOH). LC-MS: t_R = 0.97 min, MS (ESI): no mass peak; purity at 230 nm: 97.2%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[2-(4-chloro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25d)

Using 4-chlorophenol (573 mg, 4.46 mmol), the title product was obtained (250 mg, 17%). ¹H-NMR (CD₃OD): 7.45 (d, J = 7.8 Hz, 1H^R, H^R_{arom}), 7.34 - 7.25 (m, 3H, H_{arom}), 7.22 (t, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.15 (d, J = 8.5 Hz, 2H, H_{arom}), 7.07 - 6.92 (m, 3H, H_{arom}), 6.88 (d, J = 8.6 Hz, 2H, H_{arom}), 6.51 (d, J = 7.7 Hz, H, H_{arom}), 4.91 - 4.78 (a signal below solvent peak, m, 1H and 1H^R, NCH₂ and NCH₂^R), 4.59 (d, J = 13.3 Hz, 1H, H-4), 4.55 (d, J = 15.6 Hz, 1H^R, H-4^R), 4.42 - 4.25 (m, 5H and 1H^R, H-10(2x), H-11(2x), H-2 and H-2^R), 4.25 (d, J = 16.3 Hz, 1H, CH₂-N), 3.82 (d, J = 16.1 Hz, 1H^R, CH₂^R-N), 3.65 (s, 1H, H-5), 3.58 (broad, d, J = 13.1 Hz, 1H and 1H^R, H-2 and H-2^R), 3.42 (d, J = 6.6 Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1^R), 3.10 (dd, J = 18.6, 7.2 Hz, 1H, H-8), 3.01 (broad, d, J = 13.1 Hz, 1H, H-4), 2.94 (broad, d, J = 15.0 Hz, 1H^R, H-4^R), 2.37 - 2.20 (m, 1H^R, H-14^R), 2.31 (s, 3H^R, CH₃CO^R), 2.29 (s, 3H, CH₃CO), 2.19 - 1.98 (m, 1H, H-14), 2.10 (d, J = 18.4 Hz, 1H, H-8), 1.01 - 0.85 (m, 1H, H-15), 0.80 - 0.66 (m, 1H and 1H^R, H-15 and H-15^R), 0.59 - 0.37 (m, 2H and 2H^R, H-15(2x) and H-15^R(2x)), 0.10 - 0.00 (m, 1H^R, H-15^R). ¹³C-NMR (CD₃OD): 173.9 (CO^R), 173.80 (CO), 171.95 (CO), 171.86 (CO^R), 159.00 (Cq^R), 158.65 (Cq), 157.56 (Cq), 139.66 (Cq^R), 137.44 (Cq), 137.09 (Cq^R), 137.04 (Cq), 133.23 (Cq), 132.52 (Cq), 130.67 (Cq), 129.27 (CH^R_{arom}), 129.16 (Cq), 129.05 (CH_{arom}),

128.79 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.98 (CH_{arom}), 127.89 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.54 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.12 (CH_{arom}), 127.09 (CH_{arom}), 125.52 (Cq), 115.87 (CH_{arom}), 115.84 (CH_{arom}), 114.38 (CH_{arom}), 66.82, 66.5 (2x CH , C10, C11),), 66.59 (C^{R} , C10 $^{\text{R}}$ or C11 $^{\text{R}}$), 51.06 (C13 $^{\text{R}}$), 50.26 (C2 $^{\text{R}}$), 50.04 (C5), 49.97 (C2), 49.80 (C5 $^{\text{R}}$), 47.44 (C4 and C4 $^{\text{R}}$), 47.01 (C13), 46.65 (C1), 46.39 (C1 $^{\text{R}}$), 33.47 (C8), 33.34 (C8 $^{\text{R}}$), 30.74 (C14), 27.85 (C14 $^{\text{R}}$), 20.08 (CH_3CO), 20.03 ($\text{CH}_3\text{CO}^{\text{R}}$), 9.56, 5.52 (2 x C15), 7.55, 5.93 (2 x C15 $^{\text{R}}$). IR (film) ν 2922, 1619 cm^{-1} . Anal. Calcd for $\text{C}_{34}\text{H}_{34}\text{N}_3\text{O}_4\text{Cl}_3 \cdot 0.5 \text{H}_2\text{O}$: C, 61.50; H, 5.27; N, 6.32. Found: C, 62.13; H, 5.46; N, 6.12. $[\alpha]_{\text{D}}^{25} = +130.4$ (1.0; MeOH). LC-MS: $t_{\text{R}} = 0.96$ min, MS (ESI): m/z 656.05 ($\text{M} + 1$) $^{+}$; purity at 230 nm: 97.7%; at 254 nm: 96.5%.

(1R, 5S)-3-Acetyl-7-{4-[2-(2-methoxy-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25e)

Using 2-methoxyphenol (554 mg, 4.46 mmol), the title product was obtained (375 mg, 26%). ^1H -NMR (CD_3OD): 7.44 (d, $J = 7.9$ Hz, 1H $^{\text{R}}$, H $^{\text{R}}_{\text{arom}}$), 7.31 (d, $J = 7.8$ Hz, 1H, H $_{\text{arom}}$), 7.21 (t, 1H, H $^{\text{R}}_{\text{arom}}$), 7.19 - 7.11 (m, 2H, H $_{\text{arom}}$), 7.09 - 6.83 (m, 7H, H $_{\text{arom}}$), 6.44 (d, $J = 7.7$ Hz, 1H, H $_{\text{arom}}$), 4.93 - 4.77 (a signal below solvent peak, m, 1H and 1H $^{\text{R}}$, NCH $_2$ and NCH $_2^{\text{R}}$), 4.59 (d, $J = 13.2$ Hz, 1H, H-4), 4.55 (d, $J \approx 17.0$ Hz, 1H $^{\text{R}}$, H-4 $^{\text{R}}$), 4.42 - 4.30 (m, 4H and 1H $^{\text{R}}$, H-10(2x), H-11(2x) and H-2 $^{\text{R}}$), 4.29 (d, $J = 13.1$ Hz, 1H, H-2), 4.22 (d, $J = 16.1$ Hz, 1H, CH $_2$ -N), 3.84 (s, 3H, OCH $_3$), 3.83 (s, 3H, OCH $_3^{\text{R}}$ + signal below OCH $_3$, 1H $^{\text{R}}$, CH $_2^{\text{R}}$ -N), 3.64 (s, 1H, H-5), 3.58 (broad, d, $J = 14.3$ Hz, 1H and 1H $^{\text{R}}$, H-2 and H-2 $^{\text{R}}$), 3.41 (d, $J = 6.6$ Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1 $^{\text{R}}$), 3.10 (dd, $J = 18.2, 7.2$ Hz, 1H, H-8), 3.00 (broad, d, $J = 13.0$ Hz, 1H, H-4), 2.94 (broad, d, $J = 13.4$ Hz, 1H $^{\text{R}}$, H-4 $^{\text{R}}$), 2.37 - 2.20

(m, 1H^R, H-14^R), 2.31 (s, 3H^R, CH₃CO^R), 2.29 (s, 3H, CH₃CO), 2.19 - 1.98 (m, 1H, H-14), 2.10 (d, J = 18.4 Hz, 1H, H-8), 1.00 - 0.85 (m, 1H, H-15), 0.79-0.67 (m, 1H and 1H^R, H-15 and H-15^R), 0.60 - 0.37 (m, 2H and 2H^R, H-15(2x) and 1H-15^R(2x)), 0.11 - 0.01 (m, 1H^R, H-15^R). ¹³C-NMR (CD₃OD): 173.96 (CO^R), 173.81 (CO), 171.92 (CO), 171.82 (CO^R), 159.10 (Cq^R), 158.77 (Cq), 149.96 (Cq^R), 149.88 (Cq), 148.32 (Cq), 148.28 (Cq^R), 139.968 (Cq^R), 137.43 (Cq), 137.10 (Cq^R), 136.98 (Cq), 133.20 (Cq), 132.89 (Cq^R), 132.45 (CH_{arom}), 130.71 (Cq^R), 130.52 (CH^R_{arom}), 129.29 (CH_{arom}), 129.24 (CH^R_{arom}), 128.86 (CH_{arom}), 128.04 (CH^R_{arom}), 127.97 (CH_{arom}), 127.84 (CH^R_{arom}), 127.56 (CH^R_{arom}), 127.24 (CH_{arom}), 126.98 (CH_{arom}), 121.77 (CH^R_{arom}), 121.65 (CH_{arom}), 120.83 (CH_{arom}), 114.67 (CH^R_{arom}), 114.46 (CH_{arom}), 114.41 (CH^R_{arom}), 114.34 (CH_{arom}), 112.46 (CH^R_{arom}), 112.39 (CH_{arom}), 67.84, 66.77 (2xCH₂, C10, C11), , 67.91, 66.68 (2x CH₂^R, C10^R, C11^R), 55.19 (OCH₃^R), 55.14 (OCH₃), 51.02 (CH₂, C13^R), 50.28 (C2^R), 50.03 (C5), 49.96 (C2), 49.83 (C5^R), 47.49 (C4 and C4^R), 47.04 (C13), 46.67 (C1), 46.41 (C1^R), 33.51 (C8), 33.33 (C8^R), 30.67 (C14), 27.84 (C14^R), 20.07 (CH₃CO), 20.00 (CH₃CO^R), 9.47, 5.46 (2 x C15), 7.45, 5.96 (2 x C15^R). IR (film) ν 2920, 1619 cm⁻¹. Anal. Calcd for C₃₅H₃₇N₃O₅Cl₂·0.5 H₂O: C, 63.73; H, 5.76; N, 6.36. Found: C, 64.02; H, 5.78; N, 6.08. $[\alpha]_D^{25} = +77.4$ (1.0; MeOH). LC-MS: t_R = 0.93 min, MS (ESI): *m/z* 650.17 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[2-(2-bromo-5-fluoro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]-non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25f)

Using 2-bromo-5-fluorophenol (852 mg, 4.46 mmol), the title product was obtained (390 mg, 25%).

¹H-NMR (CDCl₃): 7.51 (dd, J = 8.5, 6.3 Hz, 1H, H_{arom}), 7.39 (d, J = 7.9 Hz, 1H^R, H^R_{arom}), 7.31 (d, J =

8.1 Hz, 1H, H_{arom}), 7.20 - 7.08 (m, 2H and 1H^R, 2xH_{arom} and 1H^R_{arom}), 6.97 (t, J = 7.8 Hz, 1H, H_{arom}), 6.92 (t, J = 6.5 Hz, 1H, H_{arom}), 6.85 (d, J = 8.5 Hz, 1H, H_{arom}), 6.77 (dd, J = 10.3, 2.2 Hz, 1H, H_{arom}), 6.64 (td, J = 8.3, 2.4 Hz, 1H, H_{arom}), 6.41 (d, J = 7.7 Hz, 1H, H_{arom}), 4.73 (d, J = 16.0 Hz, 1H, NCH₂), 4.68 (d, J = 13.0 Hz, 1H, H-4), 4.70 - 4.54 (m, 2H^R, CH₂N^R and H-4^R), 4.48 - 4.34 (m, 4H and 1H^R, H-10(2x), H-11(2x) and H-2^R), 4.33 (d, J = 12.2 Hz, 1H, H-2), 4.28 (d, J = 16.0 Hz, 1H, CH₂-N), 3.77 (d, J = 17.0, 1H^R, CH₂N^R), 3.55 (s, 1H, H-5), 3.54 (d, J = 10.0 Hz, 1H, H-2), 3.45 (broad, d, J = 6.8 Hz, 1H and 1H^R, H-1 and H-2^R), 3.31 (d, J = 6.6 Hz, 1H^R, H-1^R), 3.13 (s, 1H^R, H-5^R), 3.02 - 2.80 (m, 2H and 2H^R, H-4, H-8 and H-4^R and H-8^R), 2.66 - 2.50 (m, 1H^R, H-14^R), 2.28 (s, 3H, CH₃CO), 2.23 (d, J = 18.4 Hz, 1H, H-8), 2.20 - 1.90 (m, 1H and 1H^R, H-14 and H-8^R), 0.92 - 0.78 (m, 1H, H-15), 0.69-0.43 (m, 3H and 2H^R, H-15(3x) and H-15^R(2x)), 0.21 - 0.10 (m, 1H^R, H-15^R). ¹³C-NMR (CDCl₃): 173.88 (CO), 170.89 (CO), 163.88 (Cq), 161.42 (Cq), 158.6 (Cq^R), 158.30 (Cq), 156.1 (d, j = 10.1 Hz, Cq), 138.18 (Cq), 137.04 (Cq), 136.97 (Cq), 133.77 (CH_{arom}), 133.67 (CH_{arom}), 133.50 (Cq^R), 133.47 (Cq), 132.98 (Cq), 132.76 (Cq^R), 131.11 (Cq), 130.70 (Cq^R), 130.01 (Cq^R), 129.44 (CH^R_{arom}), 128.99 (CH_{arom}), 128.13 (2xCH_{arom}), 127.52 (CH^R_{arom}), 127.07 (CH_{arom}), 126.62 (CH_{arom}), 126.26 (CH^R_{arom}), 114.92 (2xCH^R_{arom}), 114.79 (CH^R_{arom}), 109.2 (d, J = 22.1 Hz, CH^R_{arom}), 109.1 (d, J = 23.2 Hz, CH_{arom}), 106.70 (d, J = 3.0 Hz, Cq), 102.2 (d, J = 26.2 Hz, CH^R_{arom}), 102.1 (d, J = 27.2 Hz, CH_{arom}), 68.17, 66.54 (2xCH₂^R, C10^R, C11^R), 68.13, 66.36 (2x CH₂, C10, C11), 51.07 (CH₂, C13^R), 50.87 (C5), 50.52 (C2), 50.45 (C5^R), 47.90 (C4 and C13), 47.79 (C4^R), 47.07 (C1), 46.77 (C1^R), 33.77 (C8), 33.25 (C8^R), 30.81 (C14), 29.39 (C14^R), 21.31 (CH₃CO^R), 21.28 (CH₃CO^R), 10.57, 6.23 (2 x C15), 8.06, 6.76 (2 x C15^R). IR (film) ν 2924, 1615 cm⁻¹. Anal. Calcd for C₃₄H₃₃N₃O₄BrCl₂F·0.5 H₂O: C, 56.21; H, 4.68; N, 5.78. Found: C, 56.57; H, 4.60; N, 5.67. $[\alpha]_D^{25}$ = +105.9 (1.0; MeOH). LC-MS: t_R = 0.97 min, MS (ESI): m/z 717.86 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo-[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25g)

Using 2,6-dichloro-*p*-cresol (790 mg, 4.46 mmol), the title product was obtained (240 mg, 16%). ^1H -NMR (CD_3OD): 7.45 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.35 (d, $J = 7.8$ Hz, 1H, H_{arom}), 7.24 (d, $J = 7.9$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.21 (s, 2H, H_{arom}), 7.16 (d, $J = 8.5$ Hz, 2H, H_{arom}), 7.13 (broad, d, $J \approx 5.2$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.09 (t, $J = 7.9$ Hz, 1H, H_{arom}), 6.98 (d, $J = 7.8$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.94 (d, $J = 8.5$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.85 (d, $J = 8.5$ Hz, 2H, H_{arom}), 6.57 (d, $J = 7.7$ Hz, 1H, H_{arom}), 4.95 - 4.71 (a signal below solvent peak, m, 1H and 1H^{R} , NCH_2 and NCH_2^{R}), 4.59 (d, $J = 13.3$ Hz, 1H, H-4), 4.54 (d, $J = 16.6$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 4.48 - 4.30 (m, 5H and 1H^{R} , H-10(2x), H-11(2x), H-2 and H-2 $^{\text{R}}$), 4.27 (d, $J = 15.9$ Hz, 1H, $\text{CH}_2\text{-N}$), 3.78 (d, $J = 16.1$ Hz, 1H^{R} , $\text{CH}_2^{\text{R}}\text{-N}$), 3.65 (s, 1H, H-5), 3.58 (broad, d, $J = 13.2$ Hz, 1H and 1H^{R} , H-2 and H-2 $^{\text{R}}$), 3.42 (d, $J = 6.4$ Hz, 1H, H-1), 3.33 (a signal below solvent peak, 1H, H-1 $^{\text{R}}$), 3.12 (dd, $J = 18.4, 7.1$ Hz, 1H, H-8), 3.00 (broad, d, $J = 12.9$ Hz, 1H, H-4), 2.94 (broad, d, $J = 13.2$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 2.37 - 2.19 (m, 1H^{R} , H-14 $^{\text{R}}$), 2.31 (s, 3H, ArCH_3), 2.28 (s, 3H, CH_3CO), 2.18 - 1.95 (m, 1H, H-14), 2.11 (d, $J = 18.3$ Hz, 1H, H-8), 1.02 - 0.83 (m, 1H, H-15), 0.80 - 0.66 (m, 1H and 1H^{R} , H-15 and H-15 $^{\text{R}}$), 0.59 - 0.45 (m, 2H and 2H^{R} , H-15(2x) and H-15 $^{\text{R}}$ (2x)), 0.43 - 0.34 (m, 1H^{R} , H-15 $^{\text{R}}$). ^{13}C -NMR (CD_3OD): 173.94 (CO^{R}), 173.90 (CO), 171.9 (CO), 171.84 (CO^{R}), 159.06 (Cq^{R}), 158.72 (Cq), 148.87 (Cq), 139.89 (Cq^{R}), 137.49 (Cq), 137.30 (Cq^{R}), 137.10 (Cq), 136.03 (Cq), 135.97 (Cq^{R}), 133.16 (Cq), 132.94 (Cq^{R}), 132.50 (Cq), 132.36 (Cq^{R}), 130.82 (Cq^{R}), 130.60 (Cq), 129.28 ($\text{CH}^{\text{R}}_{\text{arom}}$), 129.21 (CH_{arom}), 129.19 (Cq), 129.08 (Cq), 128.78 (CH_{arom}), 128.74 (Cq), 127.87 (CH_{arom}), 127.80 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.67 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.53 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.21 (CH_{arom}), 127.08 (CH_{arom}), 114.42 (CH_{arom}), 114.33 ($\text{CH}^{\text{R}}_{\text{arom}}$), 71.74, 67.19 (2xCH_2^{R} , C10^{R} , C11^{R}), 71.66, 67.106 (2xCH_2 , C10, C11), 51.08 (CH_2 , C13^{R}), 50.30 (C2^{R}), 50.09 (C5), 50.02 (C2), 49.84 (C5^{R}), 47.90 (C4 and C4^{R}), 47.47 (C13), 46.67 (C1), 46.41

(C1^R), 33.40 (C8), 33.31 (C8^R), 30.75 (C14), 27.78 (C14^R), 20.04 (CH₃CO), 19.98 (CH₃CO^R), 19.08 (CH₃Ph), 9.51, 5.4 (2 x C15), 7.58, 5.85 (2 x C15^R). IR (film) ν 2924, 1615 cm⁻¹. Anal. Calcd for C₃₅H₃₅N₃O₄Cl₄·0.5 H₂O: C, 59.00; H, 5.05; N, 5.89. Found: C, 59.25; H, 5.06; N, 5.68. $[\alpha]_D^{25} = +123.9$ (1.0; MeOH). LC-MS: $t_R = 1.01$ min, MS (ESI): m/z no mass peak; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[2-(2,6-dichloro-4-fluorophenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo-[3.3.1]non-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25h)

Using 2,6-dichloro-4-fluorophenol (807 mg, 4.46 mmol), the title product was obtained (230 mg, 15%). ¹H-NMR (CD₃OD): 7.44 (d, J = 8.7 Hz, 1H^R, H^R_{arom}), 7.38 (d, J = 7.8 Hz, 1H^R, H^R_{arom}), 7.35 - 7.25 (m, 2H, H_{arom}), 7.16 (d, J = 8.5 Hz, 2H, H_{arom}), 7.11 (t, J = 8.0 Hz, 1H^R, H^R_{arom}), 7.04 (7, J = 8.0 Hz, 1H, H_{arom}), 7.03 - 6.92 (m, 2H, H_{arom}), 6.89 (d, J = 8.6 Hz, 1H, H_{arom}), 6.85 (d, J = 8.7 Hz, 1H^R, H^R_{arom}), 6.63 (d, J = 7.7 Hz, 1H^R, H^R_{arom}), 6.53 (d, J = 7.7 Hz, 1H, H_{arom}), 4.99 - 4.70 (a signal below solvent peak, m, 1H and 1H^R, NCH₂ and NCH₂^R), 4.63 (d, J = 13.4 Hz, 1H, H-4), 4.58 (d, J = 14.7 Hz, 1H^R, H-4^R), 4.48 - 4.28 (m, 5H and 1H^R, H-10(2x), H-11(2x), H-2 and H-2^R), 4.25 (d, J = 15.8 Hz, 1H, CH₂-N), 3.82 (d, J = 18.9 Hz, 1H^R, CH₂^R-N), 3.79 (s, 1H, H-5), 3.70 (s, 1H^R, H-5^R), 3.63 (broad, d, J = 11.7 Hz, 1H and 1H^R, H-2 and H-2^R), 3.51 (d, J = 6.2 Hz, 1H, H-1), 3.44 (d, J = 6.0 Hz, 1H^R, H-1^R), 3.16 (dd, J = 18.5, 6.9 Hz, 1H, H-8), 3.05 (broad, d, J = 12.0 Hz, 1H, H-4), 3.00 (broad, d, J = 13.7 Hz, 1H^R, H-4^R), 2.32 (s, 3H^R, CH₃CO^R), 2.30 (s, 3H, CH₃CO), 2.30 - 2.00 (m, 1H and 1H^R, H-14 and H-14^R), 2.16 (d, J = 18.6 Hz, 1H, H-8), 1.13 - 0.84 (m, 1H, H-15), 0.80-0.66 (m, 1H and 1H^R, H-15 and H-15^R), 0.60 - 0.47 (m, 2H and 1H^R, H-15(2x) and H-15^R), 0.48 - 0.37 (m, 1H^R, H-15^R), 0.12 - 0.01 (m, 1H^R, H-15^R).

^{13}C -NMR (CD_3OD): 173.95 (CO^{R}), 173.90 (CO), 171.93 (CO), 171.83 (CO^{R}), 159.13 (Cq^{R}), 158.98 (Cq^{R}), 158.64 (Cq), 156.67 (Cq^{R}), 148.32 (Cq^{R}), 148.28 (Cq^{R}), 139.82 (Cq^{R}), 137.44 (Cq), 137.13 (Cq), 136.99 (Cq), 133.24 (Cq), 132.96 (Cq^{R}), 132.51 (Cq), 132.46 (Cq^{R}), 130.81 (Cq^{R}), 130.64 (Cq), 129.74 (Cq), 129.62 (Cq), 129.27 ($\text{CH}^{\text{R}}_{\text{arom}}$), 129.16 (Cq), 128.78 (CH_{arom}), 128.03 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.89 (CH_{arom}), 127.83 (Cq), 127.61 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.53 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.18 (CH_{arom}), 127.15 (CH_{arom}), 116.20 (CH_{arom}), 116.17 ($\text{CH}^{\text{R}}_{\text{arom}}$), 115.94 (CH_{arom}), 114.37 (CH_{arom}), 114.28 ($\text{CH}^{\text{R}}_{\text{arom}}$), 71.92, 67.05 ($2\times\text{CH}_2$, C10 , C11), 72.00, 67.17 ($2\times\text{CH}_2^{\text{R}}$, C10^{R} , C11^{R}), 51.07 (CH_2 , C13^{R}), 50.32 (C2^{R}), 50.13 (C5), 50.05 (C2), 49.85 (C5^{R}), 47.51 (C4 and C4^{R}), 47.38 (C13), 46.68 (C1), 46.41 (C1^{R}), 33.41 (C8), 33.34 (C8^{R}), 30.76 (C14), 27.81 (C14^{R}), 20.04 (CH_3CO), 19.99 ($\text{CH}_3\text{CO}^{\text{R}}$), 9.53, 5.47 ($2\times\text{C15}$), 7.58, 5.84 ($2\times\text{C15}^{\text{R}}$). IR (film) ν 2922, 1603 cm^{-1} . Anal. Calcd for $\text{C}_{34}\text{H}_{32}\text{N}_3\text{O}_4\text{Cl}_4\text{F}\cdot 0.5\text{H}_2\text{O}$: C, 57.00; H, 4.61; N, 5.86. Found: C, 57.09; H, 4.74; N, 5.65. $[\alpha]_{\text{D}}^{25} = +125.9$ (1.0; MeOH). LC-MS: $t_{\text{R}} = 0.99$ min, MS (ESI): m/z 708.01 ($\text{M} + 1$) $^{+}$; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-3-Acetyl-7-{4-[2-(2,3,6-trifluoro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25i)

Using 2,3,6-trifluorophenol (660 mg, 4.46 mmol), the title product was obtained (581 mg, 39%). ^1H -NMR (CD_3OD): 7.46 (d, $J = 7.8$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.38 (d, $J = 7.9$ Hz, 1H , H_{arom}), 7.23 ($J = 7.8$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.20 - 7.12 (m, 2H , H_{arom}), 7.08 (t, $J = 7.9$ Hz, 1H , H_{arom}), 7.05 - 6.93 (m, 2H , 2H_{arom}), 6.96 (d, $J = 7.8$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.91 (d, $J = 8.6$ Hz, 1H , H_{arom}), 6.81 (d, $J = 8.6$ Hz, 1H , H_{arom}), 6.60 (d, $J = 7.7$ Hz, 1H , H_{arom}), 4.93 - 4.77 (a signal below solvent peak, m, 1H and 1H^{R} , NCH_2 and NCH_2^{R}),

4.65 (d, $J = 13.5$ Hz, 1H, H-4), 4.62–4.52 (m, 2H and $1H^R$, H-11(2x), H-4^R), 4.48 (d, $J = 13.2$ Hz, $1H^R$, H-2^R), 4.43 - 4.21 (m, 3H and $1H^R$, H-10(2x), H-2 and H-2^R), 4.28 (d, $J = 16.4$ Hz, 1H, CH₂-N), 3.93 (s, 1H, H-5), 3.86 (s, $1H^R$, H-5^R), 3.76 (d, $J = 16.1$ Hz, $1H^R$, CH₂^R-N), 3.71 (broad, d, $J = 13.0$ Hz, 1H and $1H^R$, H-2 and H-2^R), 3.62 (d, $J = 6.1$ Hz, 1H, H-1), 3.55 (d, $J = 6.8$ Hz, $1H^R$, H-1^R), 3.24 (dd, $J = 18.4, 7.1$ Hz, 1H, H-8), 3.12 (broad, d, $J = 13.4$ Hz, 1H, H-4), 3.07 (broad, d, $J = 13.0$ Hz, $1H^R$, H-4^R), 2.33 (s, $3H^R$, CH₃CO^R), 2.30 (s, 3H, CH₃CO), 2.27 – 2.16 (m, $1H^R$, H-14^R), 2.11 (d, $J = 18.5$ Hz, 1H, H-8), 2.14 – 2.06 (m, 1H, H-14), 1.01 - 0.84 (m, 1H, H-15), 0.80-0.68 (m, 1H and $1H^R$, H-15 and H-15^R), 0.60 - 0.35 (m, 2H and $2H^R$, H-15(2x) and H-15^R(2x)), 0.09 - 0.02 (m, $1H^R$, H-15^R). ¹³C-NMR (CD₃OD): δ : 172.96 (CO^R), 172.83 (CO), 172.02 (CO), 171.93 (CO^R), 159.11 (Cq), 158.78 (Cq), 151.95 (d, $J = 242$ Hz, Cq), 147.74 (dd, $J = 242, 10$ Hz, Cq), 144.58 (dd, $J = 247, 9$ Hz, Cq), 140.22 (Cq), 137.80 (Cq), 136.98 (Cq), 136.74 (Cq), 132.93 (Cq^R), 132.61 (Cq), 132.54 (Cq), 131.91 (Cq^R), 130.90 (Cq^R), 130.68 (Cq), 129.34 (Cq), 128.84 (CH_{arom}), 128.15 (CH^R_{arom}), 127.94 (CH_{arom}), 127.88 (CH_{arom}), 127.54 (CH^R_{arom}), 127.21 (CH_{arom}), 127.15 (CH_{arom}), 126.98 (Cq), 125.92 (Cq^R), 114.41 (2xCH_{arom}), 114.35 (CH^R_{arom}), 110.45 (ddd, $J = 22.0, 8.0, 4.0$ Hz, CH_{arom}), 110.05 (dd, $J = 20.0, 9.0$ Hz, CH_{arom}), 72.83 (CH₂, C11), 67.45 (CH₂^R, C10^R), 67.28 (CH₂, C10), 51.12 (CH₂, C13^R), 49.63 (C5), 49.51 (C2^R), 49.39 (C5^R), 49.21 (C2), 47.32 (C13), 46.67 (C1), 46.40 (C4), 32.99 (C8), 30.77 (C14), 27.59 (C14^R), 19.95 (CH₃CO), 19.92 (CH₃CO^R), 9.51, 5.52 (2 x C15), 7.50, 5.82 (2 x C15^R). IR (film) ν 2924, 1607 cm⁻¹. Anal. Calcd for C₃₄H₃₂N₃O₄Cl₂F₃·0.5 H₂O: C, 59.74; H, 4.83; N, 6.14. Found: C, 58.46; H, 4.80; N, 5.90. $[\alpha]_D^{25} = +88.9$ (1.0; MeOH). LC-MS: $t_R = 0.95$ min, MS (ESI): m/z 675.92 (M + 1)⁺; purity at 230 nm: 96.1%; at 254 nm: 97.6%.

(*IR*, **5*S***)-3-Acetyl-7-{4-[2-(3-chloro-2,6-difluoro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (**25j**)

Using 3-chloro-2,6-difluorophenol (734 mg, 4.46 mmol), the title product was obtained (346 mg, 23%). $^1\text{H-NMR}$ (CD_3OD): 7.46 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.37 (d, $J = 7.7$ Hz, 1H , H_{arom}), 7.27 - 7.10 (m, 3H , H_{arom}), 7.10 - 7.00 (m, 2H , H_{arom}), 6.97 (, $J = 7.6$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.88 (d, $J = 8.6$ Hz, 1H , H_{arom}), 6.80 (d, $J = 8.6$ Hz, 1H , H_{arom}), 6.54 (d, $J = 7.6$ Hz, 1H , H_{arom}), 4.92 - 4.77 (a signal below solvent peak, m, 1H and 1H^{R} , NCH_2 and NCH_2^{R}), 4.59 (d, $J = 13.4$ Hz, 1H , H-4), 4.59 - 4.48 (m, 2H and 1H^{R} , H-11(2x), H-4 $^{\text{R}}$), 4.40 (d, $J = 13.6$ Hz, 1H^{R} , H-2 $^{\text{R}}$), 4.37 - 4.25 (m, 3H , H-10(2x), H-2), 4.26 (d, $J = 16.0$ Hz, 1H , $\text{CH}_2\text{-N}$), 3.80 (d, $J = 18.9$ Hz, 1H^{R} , $\text{CH}_2^{\text{R}}\text{-N}$), 3.65 (s, 1H , H-5), 3.58 (broad, d, $J = 13.5$ Hz, 1H and 1H^{R} , H-2 and H-2 $^{\text{R}}$), 3.42 (d, $J = 6.6$ Hz, 1H , H-1), 3.11 (dd, $J = 18.2, 7.1$ Hz, 1H , H-8), 3.00 (broad, d, $J = 13.0$ Hz, 1H , H-4), 2.94 (broad, d, $J = 12.9$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 2.33 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.31 (s, 3H , CH_3CO), 2.35 - 2.20 (m, 1H^{R} , H-14 $^{\text{R}}$), 2.19 - 1.97 (m, 1H , H-14), 2.11 (d, $J = 18.2$ Hz, 1H , H-8), 1.01 - 0.83 (m, 1H , H-15), 0.80-0.66 (m, 1H and 1H^{R} , H-15 and H-15 $^{\text{R}}$), 0.59 - 0.37 (m, 2H and 2H^{R} , H-15(2x) and H-15 $^{\text{R}}$ (2x)), 0.10 - 0.01 (m, 1H^{R} , H-15 $^{\text{R}}$). $^{13}\text{C-NMR}$ (CD_3OD):): 173.92 (CO^{R}), 173.85 (CO), 171.95 (CO), 171.85 (CO^{R}), 158.85 (Cq), 158.53 (Cq), 154.67 (dd, $J = 251, 4.4$ Hz, Cq), 152.08 (dd, $J = 249, 6.0$ Hz, Cq), 139.80 (Cq), 137.43 (Cq), 137.10 (t, $J = 19.1$ Hz, Cq), 137.07 (Cq), 136.74 (t, $J = 14.1$ Hz, Cq), 133.32 (Cq), 132.95 (Cq^{R}), 132.56 (Cq^{R}), 132.51 (Cq), 130.81 (Cq^{R}), 130.63 (Cq), 129.27 ($\text{CH}^{\text{R}}_{\text{arom}}$), 129.16 (Cq), 128.78 (CH_{arom}), 128.13 ($\text{CH}^{\text{R}}_{\text{arom}}$), 128.05 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.93 (CH_{arom}), 127.85 (Cq), 127.64 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.52 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.13 (CH_{arom}), 127.10 (CH_{arom}), 123.62 (d, $J = 8.0$ Hz, $\text{CH}^{\text{R}}_{\text{arom}}$), 123.54 (d, $J = 9.0$ Hz, CH_{arom}), 116.85 (dd, $J = 16.1, 4.0$ Hz, Cq), 114.36 ($2\text{xCH}_{\text{arom}}$), 114.26 ($\text{CH}^{\text{R}}_{\text{arom}}$), 112.05 (dd, $J = 21.1, 4.0$ Hz, CH_{arom}), 72.88 (CH_2 , C11), 67.48

(CH₂^R, C10^R), 67.31 (CH₂, C10), 51.10 (CH₂, C13^R), 50.29 (C2^R), 50.09 (C5), 50.01 (C2), 49.82 (C5^R), 47.49 (C4 and C4^R), 47.28 (C13), 46.67 (C1), 46.41 (C1^R), 33.44 (C8), 33.34 (C8^R), 30.74 (C14), 27.79 (C14^R), 20.05 (CH₃CO), 20.00 (CH₃CO^R), 9.51, 5.49 (2 x C15), 7.56, 5.86 (2 x C15^R). IR (film) ν 2922, 2028, 1619 cm⁻¹. Anal. Calcd for C₃₄H₃₂N₃O₄Cl₃F₂·0.5 H₂O: C, 58.34; H, 4.71; N, 6.00. Found: C, 58.02; H, 4.60; N, 5.85. $[\alpha]_D^{25} = +168.2$ (1.0; MeOH). LC-MS: $t_R = 0.97$ min, MS (ESI): m/z 692.04 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[2-(2-chloro-3,6-difluoro-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25k)

Using 2-chloro-3,6-difluorophenol (734 mg, 4.46 mmol), the title product was obtained (470 mg, 31%). ¹H-NMR (CD₃OD): 7.46 (d, J = 8.0 Hz, 1H^R, H^R_{arom}), 7.37 (d, J = 7.9 Hz, 1H, H_{arom}), 7.27 - 7.11 (m, 3H, H_{arom}), 7.11 - 7.00 (m, 2H, H_{arom}), 6.98 (, J = 7.8 Hz, 1H^R, H^R_{arom}), 6.89 (d, J = 8.7 Hz, 1H, H_{arom}), 6.81 (d, J = 8.7 Hz, 1H, H_{arom}), 6.58 (d, J = 7.7 Hz, 1H, H_{arom}), 4.92 - 4.81 (a signal below solvent peak, m, 1H^R, NCH₂^R), 4.82 (d, J = 16.2 Hz, 1H, NCH₂), 4.59 (d, J = 13.3 Hz, 1H, H-4), 4.59 - 4.49 (m, 2H and 1H^R, H-11(2x), H-4^R), 4.40 (d, J = 13.3 Hz, 1H^R, H-2^R), 4.38 - 4.20 (m, 3H, H-10(2x), H-2), 4.28 (d, J = 15.9 Hz, 1H, CH₂-N), 3.77 (d, J = 16.0 Hz, 1H^R, CH₂^R-N), 3.65 (s, 1H, H-5), 3.58 (broad, d, J = 12.9 Hz, 1H and 1H^R, H-2 and H-2^R), 3.41 (d, J = 6.7 Hz, 1H, H-1), 3.12 (dd, J = 18.3, 7.2 Hz, 1H, H-8), 3.00 (broad, d, J = 13.1 Hz, 1H, H-4), 2.94 (broad, d, J = 13.4 Hz, 1H^R, H-4^R), 2.31 (s, 3H^R, CH₃CO^R), 2.28 (s, 3H, CH₃CO), 2.33 - 2.19 (m, 1H^R, H-14^R), 2.18 - 1.97 (m, 1H, H-14), 2.11 (d, J = 18.4 Hz, 1H, H-8), 1.00 - 0.86 (m, 1H, H-15), 0.80-0.66 (m, 1H and 1H^R, H-15 and H-15^R), 0.58

- 0.36 (m, 2H and 2H^R, H-15(2x) and H-15^R(2x)), 0.08 - 0.03 (m, 1H^R, H-15^R). ¹³C-NMR (CD₃OD):): 173.91 (CO^R), 173.88 (CO), 171.95 (CO), 171.85 (CO^R), 158.89 (Cq), 158.58 (Cq), 154.96 (dd, J = 243, 4.4 Hz, Cq), 152.32 (dd, J = 242, 6.0 Hz, Cq), 144.45 (d, J = 15.0 Hz, Cq), 139.85 (Cq), 137.44 (Cq), 137.12 (Cq), 133.27 (Cq), 132.96 (Cq^R), 132.51 (Cq), 130.83 (Cq^R), 130.64 (Cq), 129.28 (CH^R_{arom}), 129.11 (Cq), 128.77 (CH_{arom}), 128.00 (CH^R_{arom}), 127.90 (CH_{arom}), 127.84 (CH_{arom}), 127.66 (CH_{arom}), 127.52 (CH^R_{arom}), 127.15 (CH_{arom}), 127.11 (CH_{arom}), 114.69 (dd, J = 22.0, 10.0 Hz, Cq), 114.35 (2xCH_{arom}), 114.24 (CH^R_{arom}), 110.41 (dd, J = 24.0, 9.0 Hz, CH_{arom}), 72.63 (CH₂, C11), 67.36 (CH₂^R, C10^R), 67.24 (CH₂, C10), 51.09 (CH₂, C13^R), 50.30 (C2^R), 50.11 (C5), 50.03 (C2), 49.83 (C5^R), 47.49 (C4 and C4^R), 47.20 (C13), 46.67 (C1), 46.41 (C1^R), 33.41 (C8), 33.33 (C8^R), 30.76 (C14), 27.77 (C14^R), 20.04 (CH₃CO), 19.99 (CH₃CO^R), 9.51, 5.46 (2 x C15), 7.57, 5.83 (2 x C15^R). IR (film) ν 2920, 2027, 1607 cm⁻¹. Anal. Calcd for C₃₄H₃₂N₃O₄Cl₃F₂·0.5 H₂O: C, 58.34; H, 4.71; N, 6.00. Found: C, 57.63; H, 4.56; N, 5.78. [α]_D²⁵ = +170.3 (1.0; MeOH). LC-MS: t_R = 0.97 min, MS (ESI): m/z no mass peak; purity at 230 nm: 100%; at 254 nm: 100%.

(1R, 5S)-3-Acetyl-7-{4-[2-(2,6-dichloro-3,4-dimethyl-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide (25I)

Using 2,6-dichloro-3,4-dimethylphenol (Bergquist, K.-E.; Nilsson, A.; Ronlan, A. Electrophilic chlorination of 4-methylphenols with molecular chlorine. Synthesis of dimethoxy aromatics by methanolysis of 4-chloro-4-methylcyclohexa-2,5-dienones. *Acta Chem. Scand., Series B: Org. Chem. and Biochem.*, **1982**, B36, 675-83, 500 mg, 4.46 mmol), the title product was obtained (318 mg, 20%).

$^1\text{H-NMR}$ (CD_3OD): 7.46 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.39 (d, $J = 8.0$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 7.3 (dd, $J = 8.0$, 1.1 Hz, 1H , H_{arom}), 7.23 (t, $J = 7.9$ Hz, 1H , H_{arom}), 7.21 - 7.12 (m, 2H , H_{arom}), 7.09 (t, $J = 7.9$ Hz, 1H , H_{arom}), 6.98 (broad, d, $J = 8.9$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 6.95 (d, $J = 8.7$ Hz, 1H , H_{arom}), 6.89 - 6.81 (m, 2H , H_{arom}), 6.57 (d, $J = 7.7$ Hz, 1H , H_{arom}), 6.53 (d, $J = 7.9$ Hz, 1H^{R} , $\text{H}^{\text{R}}_{\text{arom}}$), 4.91 - 4.77 (a signal below solvent peak, m, 1H and 1H^{R} , NCH_2 and NCH_2^{R}), 4.59 (d, $J = 13.3$ Hz, 1H , H-4), 4.55 (d, $J \approx 16.2$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 4.45 - 4.20 (m, H and 1H^{R} , H-10(2x), H-11(2x), H-2 and H-2 $^{\text{R}}$), 4.27 (d, $J = 16.2$ Hz, 1H , $\text{CH}_2\text{-N}$), 3.78 (d, $J = 16.0$ Hz, 1H^{R} , $\text{CH}_2^{\text{R}}\text{-N}$), 3.64 (s, 1H , H-5), 3.58 (broad, d, $J = 13.0$ Hz, 1H and 1H^{R} , H-2 and H-2 $^{\text{R}}$), 3.42 (d, $J = 6.5$ Hz, 1H , H-1), 3.33 (a signal below solvent peak, 1H , H-1 $^{\text{R}}$), 3.13 (dd, $J = 18.3$, 7.1 Hz, 1H , H-8), 3.01 (broad, d, $J = 13.0$ Hz, 1H , H-4), 2.94 (broad, d, $J = 13.0$ Hz, 1H^{R} , H-4 $^{\text{R}}$), 2.32 (s, 3H , CH_3CO), 2.31 (s, 3H^{R} , $\text{CH}_3\text{CO}^{\text{R}}$), 2.33, 2.29 (2xs, 3H (2x), CH_3Ar (2x)), 2.30 - 2.19 (m, 1H^{R} , H-14 $^{\text{R}}$), 2.1 - 1.98 (m, 1H , H-14), 2.12 (d, $J = 18.3$ Hz, 1H , H-8), 1.02 - 0.83 (m, 1H , H-15), 0.80-0.66 (m, 1H and 1H^{R} , H-15 and H-15 $^{\text{R}}$), 0.59 - 0.43 (m, 2H and 1H^{R} , H-15(2x) and H-15 $^{\text{R}}$), 0.42 - 0.35 (m, 1H^{R} , H-15 $^{\text{R}}$), 0.11 - 0.01 (m, 1H^{R} , H-15 $^{\text{R}}$). $^{13}\text{C-NMR}$ (CD_3OD): 173.89 (CO^{R}), 173.84 (CO), 171.95 (CO), 171.85 (CO^{R}), 159.09 (Cq^{R}), 158.73 (Cq), 149.00 (Cq), 139.91 (Cq^{R}), 137.51 (Cq), 137.39 (Cq^{R}), 137.08 (Cq), 133.04 (Cq), 134.84 (Cq), 134.65 (Cq), 134.61 (Cq^{R}), 133.43 (Cq^{R}), 133.11 (Cq), 132.94 (Cq^{R}), 132.49 (Cq), 132.32 (Cq^{R}), 130.82 (Cq^{R}), 130.61 (Cq), 129.28 (Cq), 129.19 (Cq^{R}), 128.96 (Cq), 128.84 (CH_{arom}), 128.81 (CH_{arom}), 128.09 ($\text{CH}^{\text{R}}_{\text{arom}}$), 128.01 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.87 (CH_{arom}), 127.81 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.69 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.55 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.23 (CH_{arom}), 127.18 ($\text{CH}^{\text{R}}_{\text{arom}}$), 127.12 (CH_{arom}), 125.06 (Cq), 114.546 (CH_{arom}), 114.38 (CH_{arom}), 71.52, 68.12 (2x CH_2^{R} , C10^{R} , C11^{R}), 71.40, 67.07 (2x CH_2 , C10, C11), 51.09 (CH_2 , C13^{R}), 50.27 (C2^{R}), 50.09 (C5), 49.99 (C2), 49.8 (C5^{R}), 47.43 (C4 and C4 $^{\text{R}}$), 47.38 (C13), 46.67 (C1), 46.41 (C1 $^{\text{R}}$), 33.39 (C8), 33.30 (C8^{R}), 30.76 (C14), 27.81 (C14 $^{\text{R}}$), 20.07 (CH_3CO), 20.01 ($\text{CH}_3\text{CO}^{\text{R}}$), 18.99, 15.39 (CH_3Ar (2x)), 9.56, 5.50 (2 x C15), 7.61, 5.89 (2 x C15 $^{\text{R}}$). IR (film) ν 2921, 2018, 1620 cm^{-1} . Anal. Calcd for $\text{C}_{36}\text{H}_{37}\text{N}_3\text{O}_4\text{Cl}_4 \cdot 0.5 \text{H}_2\text{O}$: C, 59.52; H, 5.23; N, 5.78. Found: C, 59.82; H, 5.22; N, 5.76. $[\alpha]_{\text{D}}^{25} = +82.0$ (1.0; MeOH). LC-MS: $t_{\text{R}} = 1.02$ min, MS (ESI): m/z 718.13 ($\text{M} + 1$) $^{+}$; purity at 230 nm: 94.0%; at 254 nm: 93.3%.

(rac.)-(1*RS*, 5*SR*)-7-[4-[3-(2-Bromo-5-fluoro-phenoxy)-propyl]-phenyl]-3-(4-carbamoyl-butyryl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-cyclopropyl-amide ((rac.)-26a)

A mixture of (rac.)-(1*RS*, 5*SR*)-7-[4-(3-hydroxy-propyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (see preparation of compound (rac.)-26b, 27.6 g, 43.6 mmol), 2-bromo-5-fluorophenol (9.70 mL, 87.2 mmol), 1,1'-(azodicarbonyl)dipiperidine (22.0 g, 87.2 mmol) and PBu₃ (85%, 32.2 mL, 131 mmol) in toluene (550 mL) was heated to reflux for 2. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:19 → 1:9 → 1:4) yielded (rac.)-(1*RS*, 5*SR*)-7-[4-[3-(2-bromo-5-fluoro-phenoxy)-propyl]-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (31.7 g, 90%). ¹H-NMR (CDCl₃, 300 MHz) 7.47 (dd, J₁ = 9.4 Hz, J₂ = 6.5 Hz, 1H), 7.23 (m, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.60 – 6.50 (m, 2H), 5.28 – 5.10 (m, 1H), 4.44 – 4.24 (m, 2H), 4.414 - 3.86 (m, 5H), 3.20 – 3.08 (m, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.84 – 2.72 (m, 1H), 2.51 (d, J = 19.3 Hz, 1H), 2.15 (quint., J = 6.9 Hz, 2H), 1.98 (s, 3H), 1.94 (s, 3H), 1.38 (s, 9H), 1.02 – 0.88 (m, 3H).

A mixture of this compound (29.7 g, 36.8 mmol) in aq. 1M NaOH (700 mL) and EtOH (700 mL) was stirred at 80 °C for 7 h. The mixture was allowed to cool to rt, and was diluted with EtOAc. The mixture was acidified with aq. 1M HCl (1 L). The two-phasic mixture was shaken, and the phases were separated. The aq. phase was extracted with EtOAc (2x). The combined org. layers were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield a crude mixture of (rac.)-(1*RS*, 5*SR*)-7-[4-[3-(2-bromo-5-fluoro-phenoxy)-propyl]-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester and (rac.)-(1*RS*, 5*SR*)-7-[4-[3-(2-bromo-5-fluoro-phenoxy)-propyl]-phenyl]-3,9-diaza-bicyclo[3.3.1]non-7-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (26.7 g) that was used further without purification.

A mixture of this crude compound mixture (2.70 g), *N*-(2-chlorobenzyl)-*N*-cyclopropylamine (1.90 g, 10.4 mmol), DIPEA (2.39 mL, 13.9 mmol), DMAP (106 mg, 0.87 mmol), HOBt (520 mg, 3.83 mmol) and EDC·HCl (1.01 g, 5.22 mmol) in CH₂Cl₂ (120 mL) was stirred at rt overnight. The mixture was washed with aq. 1M HCl (3x) and aq. sat. NaHCO₃ (1x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:5 → 1:3 → 1:2) yielded (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-bromo-5-fluoro-phenoxy)-propyl]-phenyl}-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-tert-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (1.86 g, 54% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.14 (dd, J₁ = 9.4 Hz, J₂ = 6.4 Hz, 1H), 7.00 – 6.52 (m, 8H), 6.24 (m, 2H), 4.55 – 3.6 (m, 6H), 3.64 – 3.45 (m, 2H), 2.90 – 2.65 (m, 3H), 2.48 (m, 2H), 2.05 – 1.70 (m, 4H), 1.67, 1.66 (s, 3H, rot.), 1.63 (s, 3H), 1.14, 0.95 (s, 9H, rot.), 0.50 - -0.15 (m, 4H).

HCl (4M in dioxane, 20 mL) was added to a sol. of the former product (1.86 g, 1.98 mmol) in CH₂Cl₂ (20 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, and the solvents were removed under reduced pressure. The residue was thoroughly dried under high vacuum to yield the crude hydrochloride salt of (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-bromo-5-fluoro-phenoxy)-propyl]-phenyl}-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester that was used further without purification.

A mixture of this product (4.67 g, 5.31 mmol), 5-amino-5-oxopentanoic acid (2.08 g, 15.9 mmol), DIPEA (3.63 mL, 21.4 mmol), DMAP (163 mg, 1.33 mmol), HOBt (790 mg, 5.84 mmol) and EDC·HCl (1.53 g, 7.97 mmol) in CH₂Cl₂ (80 mL) was stirred at rt overnight. The mixture was washed with aq. 1M HCl (3x) and with aq. sat. NaHCO₃ (1x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 1:19) yielded (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-bromo-5-fluoro-phenoxy)-propyl]-phenyl}-3-(4-carbamoyl-butyl)-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (2.83 g, 56% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.12 (dd, J₁ = 8.8 Hz, J₂ = 5.8 Hz, 1H), 7.07 – 6.60 (m, 8H), 6.40 – 6.30 (m, 2H), 5.82 (s, broad, 1H),

5.23 (s, broad, 1H), 4.55 – 4.05 (m, 6H), 3.73 (m, 2H), 3.20 (m, 1H), 3.07 (m, 1H), 2.72 – 2.48 (m, 4H), 2.35 (m, 1H), 2.20 – 1.80 (m, 4H), 1.80, 1.79, 1.77 (s, 6H, rot.), 1.44 – 1.30 (m, 1H), 0.72 - -0.04 (m, 3H).

A mixture of the former product (2.83 g, 2.97 mmol) and Zn (powder, 2.80 g) in THF (48 mL) and AcOH (16 mL) was stirred efficiently at rt for 1 h. The mixture was filtered, and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc, and the resulting mixture was washed with aq. 1M NaOH (5x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 1:5) yielded the title compound (1.28 g, 58%). ¹H-NMR (CDCl₃): 7.50 (dd, J₁ = 8.8 Hz, J₂ = 2.8 Hz, 1H, C_{arom}), 7.40 – 7.00 (m, 8H, C_{arom}), 6.81 (dd, J₁ = 7.6 Hz, J₂ = 0.8 Hz, 0.5H, C_{arom}), 6.66 – 6.57 (m, 1.5H, C_{arom}), 6.25 (s, broad, 1H, NH), 5.38 (s, broad, 1H, NH), 4.78 (d, J = 15.6 Hz, 1H, H-14), 4.65 (d, J = 13.2 Hz, 1H, H-4), 4.59 (d, J = 16.8 Hz, 1H^R, H-14^R), 4.55 (d, J = 13.6 Hz, 1H^R, H-4^R), 4.39 (d, J = 12.8 Hz, 1H, H-2), 4.33 (d, J = 12.8 Hz, 1H^R, H-2^R), 4.27 (d, J = 15.6 Hz, 1H, H-14), 3.98 (m, 2H, H-12 (2x)), 3.64 (d, J = 16.8 Hz, 1H^R, H-14^R), 3.54 (m, 1H, H-2), 3.48 (m, 1H, H-1), 3.39 (dd, J₁ = 12.8 Hz, J₂ = 2.8 Hz, 1H^R, H-2^R), 3.31 (d, J = 6.8 Hz, 1H^R, H-1^R), 3.15 (s, 1H^R, H-5^R), 3.05 – 2.94 (m, 2H, H-8 and H-4), 2.93 – 2.81 (m, 2H and 2H^R, H-4^R, H-8^R, H-10 (2x)), 2.79 – 2.69 (m, 1H, H-18), 2.61 – 2.48 (m, 1H, H-18), 2.33 – 2.28 (m, 2H, 2-20 (2x)), 2.26 (d, J = 15.2 Hz, 1H, H-8), 2.20 – 2.11 (m, 2H and 1H^R, H-8^R and H-11 (2x)), 1.99 (quint., J = 7.2 Hz, 2H, H-19 (2x)), 1.84 (m, 1H, H-15), 0.90 – 0.76 and 0.63 – 0.44 (m, 4H, H-16 (4x)). ¹³C-NMR (CDCl₃): 175.48 (C21), 174.43 (C21^R), 173.68 (C13), 172.85 (C17), 172.82

(C17^R), 16162.72 (d, J = 245 Hz, Cq), 156.17 (d, J = 10 Hz, Cq), 141.64 (Cq), 141.16 (Cq^R), 138.38 (Cq), 137.97 (Cq^R), 137.40 (Cq^R), 137.19 (Cq), 135.86 (Cq^R), 134.57 (Cq), 133.52 (CH_{arom}), 133.43 (CH^R_{arom}), 133.26 (Cq), 132.60 (Cq^R), 129.99 (Cq^R), 129.76 (Cq), 129.52 (CH^R_{arom}), 129.38 (CH_{arom}), 128.92, 128.78, 128.71, 128.65, 128.60, 128.37 (CH_{arom} and CH^R_{arom}), 127.26 (CH^R_{arom}), 126.94 (CH_{arom}), 126.67 (CH_{arom}), 126.65 (CH^R_{arom}), 108.39 (d, J = 22 Hz, CH_{arom}), 106.38 (d, J = 4 Hz, Cq), 101.39 (d, J = 30 Hz, CH_{arom}), 67.91 (C12), 67.79 (C12^R), 50.86 (C5), 50.64 (C14^R), 50.27 (C5^R), 49.79 (C2), 49.52 (C2^R), 48.00 (C4), 47.85 (C4^R), 47.35 (C14), 46.99 (C1), 46.66 (C1^R), 35.63 (C20), 33.56 (C8), 33.16 (C8^R), 31.84 (C18), 31.58 (C10), 30.73 (C15), 30.41 (C11^R), 30.23 (C11), 29.68 (C15^R), 21.23 (C19), 10.94, 8.31, 6.57, 6.52 (C16). IR (film) ν 3318, 2924, 2163, 1979, 1681, 1604 cm⁻¹. Anal. Calcd for C₃₈H₄₁N₄O₄ClFBr·0.18H₂O: C, 60.42; H, 5.52; N, 7.42. Found: C, 60.20; H, 5.62; N, 7.28, H₂O, 0.46. LC-MS: t_R = 0.93 min, MS (ESI): *m/z* 752.86 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(*rac.*)-(IRS, 5SR)-3-(3-Carbamoyl-propionyl)-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-cyclopropyl-amide ((*rac.*)-26b**)**

To a sol. of compound (*rac.*)-**20b** (prepared as **20b**, but from (*rac.*)-**6**, 45.6 g, 60.9 mmol) in THF (900 mL) at 0 °C was added TBAF (28.8 g, 91.4 mmol). The mixture was stirred for 20 min at 0 °C, and for 5 h at rt. EtOAc was added, and the mixture was washed with water (2x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded (*rac.*)-(IRS, 5SR)-7-[4-(3-hydroxy-propyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (27.6 g, 72%). ¹H-NMR (CDCl₃, 300 MHz) 7.12 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 7.6 Hz, 2H), 5.26 – 5.09 (m, 1H), 4.44 – 4.25 (m, 2H), 4.15 – 3.85 (m, 3H), 3.67 (t, J = 6.4 Hz, 2H), 3.19 – 2.98 (m, 2H), 2.86 (dd, J₁ = 18.7 Hz, J₂ = 6.4 Hz, 1H), 2.70 (t, J = 7.60 Hz, 2H), 2.50 (d, J = 19.3 Hz, 1H), 1.98 (s, 3H), 1.93 (s, 3H), 1.88 (m, 2H), 1.38 and 1.27 (s, 9H, rot.), 1.00 – 0.85 (m, 3H).

To a mixture of this compound (23.8 g, 37.6 mmol), 2,3,6-trifluorophenol (11.1 g, 75.2 mmol) and 1,1'-(azodicarbonyl)dipiperidine (19.0 g, 75.2 mmol) in toluene (550 mL) was added PBu₃ (85%, 27.8 mL, 113 mmol). The mixture was heated to reflux for 30 min, and was allowed to cool to rt. The mixture was filtered, and the precipitate was washed with EtOAc. The filtrate was evaporated under reduced pressure and was diluted with EtOAc. This mixture was washed with aq. 1M NaOH (2x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (21.5 g, 75%). ¹H-NMR (CDCl₃, 300 MHz) 7.12 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 6.82 – 6.78 (m, 2H), 5.26 – 5.09 (m, 1H), 4.44 – 4.34 (m, 2H), 4.17 (t, J = 6.2 Hz, 2H), 4.15 – 3.80 (m, 4H), 3.20 – 2.98 (m, 2H), 2.82 (t, J = 7.6 Hz, 2H), 2.51 (d, J = 19.9 Hz, 1H), 2.13 (m, 2H), 1.98 (s, 3H), 1.93 (s, 3H), 1.38 (s, 9H), 1.00 – 0.86 (m, 3H).

A mixture of this product (21.5 g, 28.3 mmol) in EtOH (560 mL) and aq. 1M NaOH (240 mL) was stirred at 80 °C for 7 h. The mixture was allowed to cool to rt, and was acidified to pH 6 with aq. 1M HCl. The resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:4 → 1:2 → 1:1) yielded a 1:1 crude mixture of (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester and (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-7-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (11.7 g).

This crude mixture (14.7 g) was dissolved in CH₂Cl₂ (250 mL). *N*-(2-chlorobenzyl)-*N*-cyclopropylamine (11.9 g, 60.0 mmol), DIPEA (13.7 mL, 80.0 mmol), DMAP (610 mg, 5.00 mmol), HOBt (2.98 g, 22.0 mmol) and EDC·HCl (5.75 g, 30.0 mmol) were added. The mixture was stirred at rt for 2 days. More CH₂Cl₂ was added, and the mixture was washed with aq. 1M HCl and aq. sat. NaHCO₃. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced

pressure. Purification of the crude by FC yielded (*rac.*)-(1*RS*, 5*SR*)-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (11.2 g, 33% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.54 – 6.64 (m, 10H), 5.00 – 4.00 (m, 8H), 3.36 – 2.96 (m, 3H), 2.80 (m, 2H), 2.30 (d, J = 18.2 Hz, 1H), 2.20 (m, 2H), 2.00 (s, 3H), 1.96 (s, 3H), 1.43 and 1.24 (s, 9H, rot.).

A sol. of this product (4.61 g, 5.14 mmol) in CH₂Cl₂ (40 mL) was cooled to 0 °C. HCl (4M in dioxane, 40 mL) was added, and the mixture was stirred for 2 h at 0 °C. The solvents were removed under reduced pressure and the resulting oil was dried under high vacuum to yield the crude hydrochlorid salt of (*rac.*)-(1*RS*, 5*SR*)-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (4.66 g) that was used without further purification.

A mixture of this crude material (2.00 g, 2.39 mmol), succinamic acid (840 mg, 7.17 mmol), DIPEA (1.64 mL, 9.56 mmol), DMAP (74 mg, 0.60 mmol), HOBt (355 mg, 2.63 mmol) and EDC·HCl (710 mg, 3.70 mmol) in CH₂Cl₂ (50 mL) was stirred at rt overnight. The mixture was washed with aq. 1M HCl (3x) and with aq. sat. NaHCO₃ (1x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 1:19) yielded (*rac.*)-(1*RS*, 5*SR*)-3-(3-carbamoyl-propionyl)-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (1.36 g, 64% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.10 – 6.55 (m, 10H), 5.91 (s, broad, 1H), 5.02 (s, broad, 1H), 4.56 – 4.24 (m, 5H), 4.15 (dd, J₁ = 15.2 Hz, J₂ = 5.8 Hz, 1H), 3.95 (m, 2H), 3.22 (ddd, J₁ = J₂ = 12.3 Hz, J₃ = 3.3 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.72 – 2.52 (m, 4H), 2.38 – 1.98 (m, 2H), 1.85 (m, 2H), 1.80, 1.79, and 1.75 (s, 6H, rot.), 1.50 – 1.33 (m, 1H), 0.70 – -0.02 (m, 3H).

A mixture of the last product (1.36 g, 1.52 mmol) and Zn (powder, 1.38 g) in THF (24 mL) and AcOH (8 mL) was stirred efficiently at rt for 1 h. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was diluted with EtOAc and washed with aq. 1M NaOH (5x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:4) yielded the title compound (603 mg, 75%). ¹H-NMR (CDCl₃) 7.38 – 7.04 (m, 7H, H_{arom}), 6.85 (m, 2H, H_{arom}), 6.77 (dd, J₁ = 7.6 Hz, J₂ = 1.2 Hz, 1H, H_{arom}), 6.36 (s, broad, 1H, NHH), 5.27 (s, broad, 1H, NHH), 4.75 (d, J = 15.6 Hz, 1H, H-14), 4.65 (d, J = 13.1 Hz, 1H, H-4), 4.58 (d, J = 16.6 Hz, 1H^R, H-14^R), 4.55 (d, J = 11.6 Hz, 1H^R, H-4^R), 4.41 (d, J = 12.7 Hz, 1 H, H-2), 4.36 (d, J = 12.9 Hz, 1H^R, H-2^R), 4.31 (d, J = 15.6 Hz, 1H, H-14), 4.19 (m, 2H, H-12), 3.65 (d, J = 16.7 Hz, 1H^R, H-14^R), 3.57 (s, 1H, H-5), 3.53 (dd, J₁ = 12.8 Hz, J₂ = 2.4 Hz, 1H, H-2), 3.47 (d, J = 6.7 Hz, 1H, H-1), 3.40 (dd, J₁ = 12.9 Hz, J₂ = 2.5 Hz, 1H^R, H-2^R), 3.30 (d, J = 7.0 Hz, 1H^R, H-1^R), 3.24 – 3.10 (m, 2H and 1H^R, H-5^R, H-4, H-17), 3.05 – 2.93 (m, 1H and 1H^R, H-4^R, H-8), 2.93 – 2.73 (m, 3H, H-17 and H-10 (2x)), 2.61 – 2.43 (m, 2H, H-18 (2x)), 2.21 (d, J = 18.4 Hz, 1H, H-8), 2.16 – 2.02 (m, 2H and 1H^R, H-8^R and H₂-11), 1.87 (m, 1H, H-15), 0.90 – 0.72, 0.65 – 0.43, 0.08 – -0.02 (m, 4H, H-16 (4x)). ¹³C-NMR (CDCl₃) 175.26 (C17 or C20), 175.22 (C17^R or C20^R), 173.67 (C13), 172.26 (C17 or C20), 172.23 (C17^R or C20^R), 151.99 (d, J = 243 Hz, Cq), 147.79 (dd, J₁ = 244 Hz, J₂ = 10 Hz, Cq), 144.83 (dd, J₁ = 249 Hz, J₂ = 19 Hz, Cq), 141.76 (Cq^R), 141.28 (Cq), 138.30 (Cq^R), 137.97 (Cq), 137.40 (Cq^R), 137.08 (Cq), 136.98 (broad, Cq), 135.91 (Cq^R), 134.60 (Cq), 133.17 (Cq), 132.58 (Cq^R), 130.20 (CH^R_{arom}), 129.74 (CH_{arom}), 129.39 (CH^R_{arom}), 129.32 (CH_{arom}), 128.89 (CH^R_{arom}), 128.73

(CH_{arom}), 128.64 (CH^R_{arom}), 128.52 (CH^R_{arom}), 128.28 (CH_{arom}), 127.26 (CH^R_{arom}), 126.94 (CH_{arom}), 126.70 (CH^R_{arom}), 126.67 (CH_{arom}), 110.41 (ddd, J1 = 22 Hz, J2 = 8 Hz, J3 = 4 Hz, CH_{arom}), 109.82 (ddd, J1 = 20 Hz, J2 = 8 Hz, J3 = 3 Hz, CH_{arom}), 73.78 (dd, J1 = 6 Hz, J2 = 3 Hz, C12), 50.90 (C5), 50.57 (C14^R), 50.29 (C5^R), 49.69 (C2), 49.41 (C2^R), 48.27 (C4), 48.10 (C4^R), 47.28 (C14), 40.04 (C1), 46.70 (C1^R), 33.65 (C8), 33.22 (C8^R), 31.54, 31.45, 31.35 (C10 and C11), 31.05 (C18), 30.68 (C15), 28.71 (C17), 10.67, 8.26, 6.47, 6.42 (C16). IR (film) ν 3419, 3214, 2919, 1695, 1656, 1599 cm⁻¹. Anal. Calcd for C₃₇H₃₈N₃O₄ClF₃·0.35H₂O: C, 63.35; H, 5.56; N, 7.99. Found: C, 63.25; H, 5.47; N, 8.08, H₂O, 0.91. LC-MS: t_R = 0.91 min, MS (ESI): *m/z* 694.98 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(*rac.*)-(IRS, 5SR)-3-(2-Hydroxy-acetyl)-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid (2-chloro-benzyl)-cyclopropyl-amide ((*rac.*)-26c)

The crude hydrochlorid salt of (*rac.*)-(IRS, 5SR)-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (see preparation of compound (*rac.*)-26b, 2.00 g, 2.39 mmol) was dissolved in CH₂Cl₂ (50 mL). Glycolic acid (545 mg, 7.17 mmol), DIPEA (1.64 mL, 9.56 mmol), DMAP (74 mg, 0.60 mmol), HOBt (355 mg, 2.63 mmol) and EDC·HCl (550 mg, 2.87 mmol) were added, and the mixture was stirred at rt overnight. The mixture was washed with aq. 1M HCl (3x) and with aq. sat. NaHCO₃ (1x). The org. Layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 1:19) yielded (*rac.*)-(IRS, 5SR)-6-[(2-chloro-benzyl)-cyclopropyl-carbamoyl]-3-(2-hydroxy-acetyl)-7-{4-[3-(2,3,6-trifluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester (1.05 g, 51%). ¹H-NMR (CDCl₃, 300 MHz) 7.10 – 6.55 (m, 10H), 4.64 – 3.86 (m, 10H), 3.26 – 2.70 (m, 6H), 2.57 (m, 2H), 2.05 (m, 1H), 1.80, 1.79, 1.76 (s, 6H, rot.), 1.40 – 1.28, 0.74 – 0.06 (m, 4H).

A mixture of the last product (1.05 g, 1.23 mmol) and Zn (powder, 1.38 g) in THF (24 mL) and AcOH (8 mL) was stirred efficiently at rt for 1 h. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was diluted with EtOAc and washed with aq. 1M NaOH (5x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:4) yielded the title compound (397 mg, 49%). ¹H-NMR (CDCl₃) 7.39 – 7.05 (m, 6H, H_{arom}), 7.04 (s, 2H, H_{arom}), 6.90 – 6.79 (m, 2H, H_{arom}), 4.81 (dd, J₁ = 15.7 Hz, J₂ = 3.4 Hz, 1H, H-18), 4.78 (d, J = 15.4 Hz, 1H, H-14), 4.63 (d, J = 4.2 Hz, 1H, H-2), 4.59 (s, 1H^R, H-2^R), 4.52 (d, J = 13.0 Hz, 1H^R, H-14^R), 4.27 (d, J = 15.4 Hz, 1H, H-14), 4.21 (m, 2H, H-12 (2x)), 4.15 (dd, J₁ = 15.8 Hz, J₂ = 4.1 Hz, 1H, H-18), 4.11 – 4.00 (m, 1 H, H-4), 3.58 (s, 1H, H-5), 3.52 (d, J = 2.0 Hz, 1H, H-1), 3.54 – 3.46 (m, 1H, H-4), 3.38 – 3.33 (m, 1H^R, H-1^R), 3.20 (s, 1H^R, H-5^R), 3.18 – 2.93 (m, 2H and 1H^R, H-2, H-8, H-14^R), 2.87 (t, J = 7.4 Hz, H-10), 2.80 (t, J = 7.7 Hz, 1H, H-10), 2.48 (m, 1H^R, H-15^R), 2.24 (d, J = 18.9 Hz, 1H, H-8), 2.16 (d, J = 18.6 Hz, 1H^R, H-8^R), 2.12 – 2.02 (m, 2H, H-11 (2x)), 1.81 (m, 1H, H-15), 0.94 – 0.77, 0.63 – 0.41, -0.03 – -0.10 (m, 4 H, H-16 (4x)). ¹³C-NMR (CDCl₃) 173.36 (C13), 173.20 (C13^R), 172.33 (C17), 172.29 (C17^R), 151.99 (d, J = 242 Hz, Cq), 147.78 (d, J = 234 Hz, Cq), 144.79 (d, J = 249 Hz, Cq), 141.90 (Cq^R), 141.40 (Cq), 138.89 (Cq^R), 137.75 (Cq), 137.50 (Cq), 137.22 (Cq^R), 130.80 (broad, Cq), 135.81 (Cq^R), 134.52 (Cq), 133.27 (Cq), 132.71 (Cq^R), 129.75 (CH^R_{arom}), 129.73 (CH_{arom}), 129.22 (CH_{arom}), 128.94 (CH^R_{arom}), 128.81 (CH_{arom}), 128.61 (CH_{arom}), 128.32 (CH^R_{arom}), 127.24 (CH^R_{arom}), 126.87 (CH_{arom}), 126.71 (CH^R_{arom}), 126.60 (CH_{arom}), 110.41 (ddd, J₁ = 21 Hz, J₂ = 8 Hz, J₃ = 4Hz, CH_{arom}), 109.82 (ddd, J₁ = 21 Hz, J₂ = 9 Hz, J₃ = 5 Hz,

H_{arom}), 73.79 (C12), 73.71 (C12^R), 59.87 (C18), 59.82 (C18^R), 50.72 (C2^R), 50.62 (C5), 49.97 (C5^R), 48.70 (C2), 48.56 (C14^R), 48.07 (C4), 47.81 (C4^R), 47.32 (C14), 46.87 (C1), 46.56 (C1^R), 33.54 (C8), 33.23 (C8^R), 31.56, 31.47, 31.33 (C10, C11), 30.65 (C15), 29.45 (C15^R), 11.13, 8.49, 6.53 (C16). IR (film) ν 3270, 3107, 2923, 2850, 2158, 1016, 1632, 1610 cm⁻¹. Anal. Calcd for C₃₅H₃₅N₃O₄ClF₃·0.29H₂O: C, 63.76; H, 5.44; N, 6.37. Found: C, 62.03; H, 5.78; N, 6.26, H₂O, 0.80. LC-MS: t_R = 0.93 min, MS (ESI): *m/z* 654.00 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 97.0%.

(1*R*, 5*S*)-7-{2-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-thiazol-5-yl}-3,9-diaza-bicyclo[3.3.1]-non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide ((+)-26d)

Compound (*rac.*)-**6** (25.6 g, 78.4 mmol) was dissolved in aq. 6M HCl (125 mL). The resulting orange sol. was heated to 105 °C for 3 days to give a black reaction mixture. This mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dried under high vacuum at 50 °C. This black residue was dissolved in water (100 mL), and the resulting sol. was cooled to 0 °C. NaOH (6.00 g, 153 mmol) was added carefully until a pH of ca. 8 was reached. Dioxane (30 mL), DIPEA (40 mL; 230 mmol) and Boc₂O (25.0 g, 115 mmol) were added. The resulting black mixture was further stirred at 0 °C for 20 min, and at rt for 3 days. The crude reaction mixture was concentrated under reduced pressure, and the black residue was further dried under high vacuum overnight. EtOH (300 mL) was added, and the mixture was stirred at rt for 2.5 h. Filtration and concentration under reduced pressure led to a black, oily residue which was purified by FC (MeOH/CH₂Cl₂ 1:9) to yield 9-methyl-7-oxo-3,9-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester (3.89 g, 15%). ¹H-NMR (CDCl₃, 300 MHz) 3.88 (s, broad, 2H), 3.24 – 2.96 (m, broad, 4H), 2.65 (dd, J1 = 15.8 Hz, J2 = 4.7 Hz, 2H), 2.59 (s, 3H), 2.18 (d, J = 15.2 Hz, 2H), 1.42 (s, 9H).

To a sol. of this product (7.30 g, 28.7 mmol) in 1,2-dichloroethane (300 mL) were added successively at rt NaHCO₃ (24.1 g, 287 mmol) and 1-chloroethyl chloroformate (31.3 mL, 287 mmol). The resulting suspension was heated to reflux for 6 h. The mixture was allowed to cool to rt, and was filtered. The precipitate was washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure to yield a yellow oil that was dissolved in anhydrous MeOH (300 mL). The yellow sol. was stirred at 40 °C under

nitrogen for 1 h. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure to lead to a beige foam which was further dried under high vacuum (25 min). The remaining material was dissolved in CH₂Cl₂ (300 mL), and the resulting yellow sol. was cooled to 0 °C. DIPEA (29.4 mL, 172 mmol) was added, followed by Boc₂O (18.8 g, 86.1 mmol). The resulting sol. was further stirred at 0 °C for 30 min and then at rt overnight. The reaction mixture was cooled to 0 °C, and aq. 1M HCl (172 mL) was added dropwise. The phases were shaken and separated. The org. layer was washed with an aq. sat. NaHCO₃, dried over MgSO₄, filtered, and concentrated under reduced pressure to give an orange oil. Purification of the crude by FC (EtOAc/heptane 3:7) yielded 7-oxo-3,9-diaza-bicyclo[3.3.1]nonane-3,9-dicarboxylic acid di-*tert*-butyl ester (3.97 g, 41%). R_f = 0.25 (EtOAc/heptane 3:7). ¹H-NMR (CDCl₃, 300 MHz) 4.68 – 4.45 (m, broad, 2H), 4.03 (s, broad, 2H), 2.98 (s, broad, 2H), 2.62 – 2.41 (m, 2H), 2.33 (d, J = 15.8 Hz, 2H), 1.49 (s, 9H), 1.44 (s, 9H).

To a sol. of this compound (6.02 g, 17.7 mmol) in anhydrous THF at rt was added portionwise NaH (55% in oil, 1.62 g, 37.1 mmol). MeOCOOME (3.35 mL, 39.8 mmol) was added dropwise, and the resulting mixture was heated to reflux for 1 h. The reaction mixture was allowed to cool to 0 °C, and water (25 mL) was added dropwise. EtOAc (100 mL) was added followed by aq. 1M HCl (54 mL) to pH 3. The phases were shaken, separated, and the org. layer was further washed with brine (40 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure to give an orange oil. Purification by FC (EtOAc/heptane 3:7) yielded (*rac.*)-(1*RS*, 5*SR*)-7-oxo-3,9-diaza-bicyclo[3.3.1]nonane-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-methyl ester 6.38g (91%). ¹H-NMR (CDCl₃, 300 MHz) 12.08 and 11.97 (s, broad, 1H, rot.), 5.00 (s, broad, 1H), 4.87 (m, 1H), 4.45 – 4.15 (m, 2H), 4.05 – 3.65 (m, 3H), 3.55 (s, 3H), 3.10 – 2.85 (m, 1H), 2.35 – 2.15 (m, 1H), 1.44 ad 1.34 (s, 9H, rot.).

To a sol. of the former product (6.71 g, 16.8 mmol) in dry THF (113 mL) at 0 °C was added portionwise NaH (55% in oil, 918 mg, 21.1 mmol). This mixture was stirred at 0 °C for 75 min, and Tf₂NPh (7.1 g, 19.9 mmol) was added. The mixture was stirred at rt for 3 days. The mixture was poured into a mix of ice and water (100mL), and was partially concentrated under reduced pressure. The residue was extracted with EtOAc (3x). The combined org. extracts were washed with water (1x) and with brine

(1x). The org. layer was dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 6:1 $\rightarrow$ 5:1 $\rightarrow$ 4:1 $\rightarrow$ 3:1) yielded (*rac.*)-(1*RS*, 5*SR*)-7-trifluoromethanesulfonyloxy-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-methyl ester (7.86 g, 88%). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) 5.25 – 4.95 (m, 1H), 4.50 – 3.95 (m 3H), 3.82 (s, 3H), 3.20 – 2.80 (m, 3H), 2.36 (d, $J = 18.8$ Hz, 1H), 1.42 (s, 9H), 1.38 (s, 9H).

2-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-thiazole (3.58 g, 11.8 mmol) was dissolved in dry THF (94 mL). The sol. was cooled to -78°C . $n\text{-BuLi}$ (1.6 M in hexane, 8.10 mL, 13.0 mmol) was added dropwise. The reaction was stirred at -78°C . After 30min the reaction mixture was heterogeneous. It was left an additional 30 min at -78°C . ZnCl_2 (1M in THF, 14.2 mL, 14.2 mmol) was added dropwise at -78°C . The mixture was allowed to warm up to rt, whereas the solid finally dissolved after 2 min to form a clear-yellow sol. The sol. was stirred for 90 min at rt. The vinylic triflate from the former step (5.00 g, 9.43 mmol), and then $\text{Pd(PPh}_3)_4$ (327 mg, 0.283 mmol), were added. The mixture was heated to 50°C and stirred at this temperature for 1 h. The mixture was allowed to cool to rt and was diluted with EtOAc. The resulting mixture was washed with aq. sat. NH_4Cl , brine, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 4:6) yielded (*rac.*)-(1*RS*, 5*SR*)-7-{2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-thiazol-5-yl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-methyl ester (5.11 g, 79%). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) 7.09 (s, 2H), 7.02 (m, broad, 1H), 5.11 and 4.94 (s, broad, 1H, rot.), 4.76 (m, 2H), 4.35 (t, $J = 4.4$ Hz, 2H), 4.30 – 4.15 (m, 2H), 3.71 (s, 3H), 3.18 – 2.68 (m, 3H), 2.55 – 2.25 (m, 1H), 2.23 (s, 3H), 2.43 (s, 9H), 2.38 (s, 9H).

This product (10.1 g, 14.7 mmol) was dissolved in MeOH (200 mL). Aq. 1M NaOH (100 mL) was added dropwise at 0°C . The mixture became immediately turbid and a fine powder precipitated. The suspension was heated to reflux while turning into a yellow-brown sol. with an oil residue at the bottom. MeOH (100 mL) was added, and the oil dissolved. After 45min at reflux, the mixture was allowed to cool to rt. The solvents were partially removed under reduced pressure. Water (100 mL) was added, and

the resulting mixture was cooled to 0 °C. Aq. 1M HCl (100 mL) was slowly added in order to reach pH ca. 2-3. The mixture was extracted with EtOAc (3x). The combined org. layers were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The crude mixture of (*rac.*)-(1*RS*, 5*SR*)-7-{2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-thiazol-5-yl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*rac.*)-(1*RS*, 5*SR*)-7-{2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-thiazol-5-yl}-3,9-diaza-bicyclo[3.3.1]non-7-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (10.2 g) was used further without purification.

This crude product mixture (3.40 g) was dissolved in CH₂Cl₂ (51 mL). DMAP (155 mg, 1.27 mmol), HOBt (822 mg, 6.08 mmol), EDC·HCl (2.43 g, 12.7 mmol) and DIPEA (3.47 mL, 20.3 mmol) were added at rt, and the mixture was stirred for 30min at rt. 2,3-Dimethylbenzyl-*N*-cyclopropylamine (2.67 g, 15.2 mmol) was added at rt, and the reaction was stirred for 5 days. The mixture was diluted with CH₂Cl₂ (100 mL), washed with aq. 1M HCl (2x), and brine (1x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 4:6) yielded (*rac.*)-(1*RS*, 5*SR*)-6-[cyclopropyl-(2,3-dimethyl-benzyl)-carbamoyl]-7-{2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-thiazol-5-yl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (3.15 g, 75% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.12 – 6.78 (m, 6H), 5.04 – 4.68 (m, 3H), 4.60 – 4.18 (m, 5H), 3.16 – 2.78 (m, 3H), 2.40 (d, J = 17.6 Hz, 1H), 2.30 – 2.20 (m, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H), 2.46 (s, 9H), 2.44 (s, 9H), 1.40 – 1.26 (m, 1H), 0.82 – 0.40 (m, 3H).

This product (2.7 g, 3.26 mmol) was dissolved in CH₂Cl₂ (16.5 mL). The sol. was cooled to 0 °C. HCl (4M in dioxane, 16.5 mL) was added dropwise. The mixture was stirred for 1 h at rt and was quenched with aq. 10% Na₂CO₃ (100 mL). The aq. layer was extracted with EtOAc (3x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 3:7) yielded the racemic title product (1.85 g, 90%). Separation of the enantiomer on a Regis Whelk 01 column (50x250 mm and a flow of 100 mL/min, under isocratic conditions, 70% hexane and 30% MeOH with 0.5% NH₃) yielded the title compound (560 mg, 35%). $\alpha_D = 48.4$. ¹H-NMR (CDCl₃) 7.17 (s, 1H, H-11), 7.12 (s, 2H, H_{arom}), 7.09 – 7.00 (m, 2H, H_{arom}), 6.89 (d, J = 6.8 Hz, 1H, H_{arom}), 5.04 (d, J = 15.2 Hz, 1H, H-16), 4.84 – 4.78 (m, 2H, H-13 (2x)), 4.58 (d, J = 16.8 Hz, 1H^R, H-16^R), 4.42 – 4.37 (m, 2H, H-14 (2x)), 4.26 (d, J = 15.2 Hz, 1H, H-16), 4.11 (d, J = 16.8 Hz, 1H^R, H-16^R), 3.50 (s, 1H, H-5), 3.26 – 2.80 (m, 6H, H-1, H-2 (2x), H-2 (2x), H-8), 2.64 (dd, J₁ = 17.6 Hz, J₂ = 7.2 Hz, 1H^R, H-8^R), 2.40 – 2.25 (2H, H-8, H-17), 2.29 (s, 6H, 2xMe), 2.22 (s, 3H, Me), 0.70 – 0.63 (m, 4H, H-18 (4x)). ¹³C-NMR (CDCl₃) 174.00 (C12), 173.93 (C12^R), 172.85 (C15^R), 172.12 (C15), 148.70 (Cq), 137.05 (Cq^R), 136.99 (Cq), 136.74 (Cq^R), 136.75 (Cq), 135.02 (Cq^R), 134.57 (Cq^R), 134.42 (Cq), 134.36 (Cq), 134.32 (Cq), 133.93 (Cq^R), 133.25 (Cq^R), 129.4 (CH_{arom}), 129.13 (Cq^R), 129.09 (Cq), 128.91 (CH^R_{arom}), 128.63 (CH_{arom}), 126.21 (CH^R_{arom}), 125.96 (CH_{arom}), 125.79 (CH_{arom}), 125.38 (CH^R_{arom}), 70.97 (C13), 70.12 (C12^R), 69.92 (C12), 52.38 (C4), 50.95 (C5), 50.89 (C16^R), 48.64 (C2^R), 48.30 (C16 and C2), 46.54 (C1), 46.14 (C1^R), 33.25 (C8), 30.44 (C17), 29.69 (C17^R), 20.55 (CH₃), 20.51 (CH₃), 15.03 (CH₃), 14.78 (CH₃^R), 8.44, 7.37, 7.15, 6.76 (C18). IR (film) ν 1610 cm⁻¹. Anal. Calcd for C₃₂H₃₆N₄O₃Cl₂S·0.24H₂O: C, 60.82; H, 5.82; N, 8.90. Found: C, 59.91; H, 5.69; N, 8.54, H₂O, 0.90. $[\alpha]_D^{25} = +48.4$ (1.0; MeOH). t_R (Regis Whelk) = 17.5 min. LC-MS: t_R = 0.91 min, MS (ESI): m/z 627.31 (M + 1)⁺; purity at 230 nm: 97.1%; at 254 nm: 98.0%.

(rac.)-(IRS, 5SR)-7-(4-[(2-Chloro-3,6-difluoro-benzyl)-methyl-amino]-methyl)-phenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)-amide ((rac.)-26e)

BuLi (1.60 M in hexane, 34.00 mL, 53.87 mmol) was added dropwise to a cooled (-78 °C) sol. of (4-bromobenzyloxy)-*tert*-butyldimethylsilane (Nassal, M. 4-(1-Azi-2,2,2-trifluoroethyl)benzoic acid, a highly photolabile carbene generating label readily fixable to biochemical agents. *Liebigs Ann. Chem.* **1983**, 1510-23, 15.30 g, 51.05 mmol) in THF (0.47 L). The reaction mixture was stirred at -78 °C for 1 h, and ZnCl₂ (1M in THF, 68.0 mL, 68.0 mmol) was added dropwise at -78 °C. The cooling bath was removed, and the reaction stirred for 1 h at rt. A sol. of (*rac.*)-**7** (13.0 g, 28.4 mmol) in THF (50 mL) was added dropwise, followed by Pd(PPh₃)₄ (0.95 g, 0.82 mmol). The reaction mixture was stirred at rt for 1 h, partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc) yielded (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)phenyl]-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (17.85 g, >99%) as an orange oil. ¹H-NMR (CDCl₃, 300 MHz) 7.14 (d, J = 7.6 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 4.63 (s, 2H), 4.25 – 4.10 (m, 2H), 3.95 – 3.75 (m, 2H), 3.55 (s, 3H), 3.55 – 3.30 (m, 4H), 2.55 – 2.25 (m, 3H), 1.14 (s, 9H), 0.86 (s, 9H), 0.80 (m, 3H), 0.00 (s, 6H).

1-Chloroethyl chloroformate (37.00 mL, 0.33 mol) was added dropwise to a suspension of (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (17.9 g, 33.6 mmol) and NaHCO₃ (28.0 g, 0.33 mol) in 1,2-dichloroethane (0.23 L). The mixture was heated to reflux for 3 h, then allowed to cool to rt, filtered, and the solvents were thoroughly removed under reduced pressure. MeOH (0.23 L) was added and the mixture was stirred at 50 °C for 60 min. The sol. was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (0.23 L), DIPEA (29.0 mL, 0.17 mol) was added, followed by Boc₂O (22.0 g, 0.100 mol). The mixture was stirred at rt for 45 min. The mixture was washed with aq. 1M HCl, and aq. sat. NaHCO₃. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (50% EtOAc in heptane) yielded (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-

ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (11.62 g, 69%). ¹H-NMR (CDCl₃, 300 MHz) 7.30 (d, J = 7.2 Hz, 2H), 7.10 (s, broad, 2H), 5.28 – 5.08 (m, 1H), 4.69 (s, 2H), 4.50 – 4.20 (m, 2H), 4.10 – 3.90 (m, 3H), 3.20 – 2.95 (m, 3H), 2.90 – 2.60 (m, 1H), 2.48 (d, J = 19.3 Hz, 1H), 1.51 (s, 9H), 1.38 (s, 9H), 1.05 – 0.85 (m, 3H).

Aq. 1M NaOH (162 mL) was added to a sol. of the former product (8.20 g, 16.3 mmol) in EtOH (320 mL). The resulting mixture was stirred at 70 °C for 3 h, cooled to rt, and the solvents were removed under reduced pressure. The crude mixture was partitioned between TBME and aq. sat. 1M HCl. The aq. layer was extracted twice more with TBME, the combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield a crude mixture of (*rac.*)-(1*RS*, 5*SR*)-7-(4-hydroxymethylphenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*rac.*)-(1*RS*, 5*SR*)-8-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-7-(4-hydroxymethyl-phenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (5.80 g), which was not further purified. LC-MS: t_R = 0.88 min, MS (ESI): *m/z* 475.05 (M + 1)⁺.

TBDMS-Cl (4.51 g, 29.92 mmol) and imidazole (3.26 g, 47.87 mmol) were added to a stirred sol. of the former crude mixture of products (5.68 g, 12.0 mmol) in DMF (50 mL). The reaction mixture was stirred at rt over 15 h. The solvents were removed under reduced pressure, the crude mixture partitioned between Et₂O and water. The aq. phase was extracted again with Et₂O. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in THF (100 mL), MeOH (21 mL), and water (21 mL), and K₂CO₃ (0.83 g, 6.00 mmol) was added. The mixture was stirred at rt for 1 h. The mixture was partitioned between Et₂O and aq. sat. NH₄Cl, the phases were separated, and the aq. layer was extracted once more with Et₂O. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield a crude mixture of (*rac.*)-(1*RS*, 5*R**)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*rac.*)-(1*RS*, 5*SR*)-7-[4-(*tert*-butyl-dimethyl-silanyloxymethyl)-phenyl]-8-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-

dicarboxylic acid di-*tert*-butyl ester (7.53 g) as a yellow foam that was used further without purification.

LC-MS: t_R = 1.14 min, MS (ESI): m/z 589.53 ($M + 1$)⁺.

To a stirred sol. of the former crude mixture of products (7.53 g, 12.0 mmol) in CH₂Cl₂ (100 mL) were added EDC·HCl (5.73 g, 29.9 mmol), HOBt (2.19 g, 14.4 mmol), DMAP (0.36 g, 3.0 mmol), cyclopropyl-(3-methoxy-2-methylbenzyl)amine (3.43 g, 17.9 mmol) and DIPEA (9.37 mL, 53.8 mmol). The mixture was stirred at rt for 5 days. The reaction mixture was partitioned between aq. sat. NaHCO₃ and EtOAc, the phases were separated, and the aq. layer was extracted once more with EtOAc. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (10-30% EtOAc in heptane) yielded (*rac.*)-(1*RS*, 5*SR*)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (7.74 g, 63% over 3 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.12 – 6.92 (m, 4H), 6.88 – 6.76 (m, 1H), 6.68 – 6.52 (m, 1H), 6.36 – 6.16 (m, 1H), 4.70 – 3.90 (m, H), 3.70 (m, 5H), 3.16 – 2.80 (m, 3H), 2.20 – 1.84 (m, 5H), 1.40 (s, 9H), 1.37 (s, 9H), 0.80 – 0.10 (m, 4H).

TBAF (6.42 g, 20.3 mmol) was added to a sol. of the former product (7.74 g, 10.2 mmol) in THF (70 mL), and the mixture was stirred at rt for 2 h. The mixture was partitioned between water and EtOAc, and the aq. layer was extracted again with EtOAc. The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (0-100% EtOAc in heptane followed by 10% MeOH in CH₂Cl₂) yielded (*rac.*)-(1*RS*, 5*SR*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (6.53 g, 99 %). ¹H-NMR (CDCl₃, 300 MHz) 7.20 – 6.85 (m, 5H), 6.80 – 6.60 (m, 2H), 5.50 – 4.30 (m, 5H), 4.22 – 3.95 (m, 2H), 3.83 (m, 5H), 3.2 – 2.93 (m, 3H), 2.28 – 2.00 (m, 5H), 1.52 (s, 9H), 1.49 (s, 9H), 0.95 – 0.38 (m, 4H).

Anhydrous DMSO (0.44 mL, 6.17 mmol) in CH₂Cl₂ (4.00 mL) was added dropwise over 10 min to a cooled (-63 °C) sol. of oxalyl chloride (0.392 mL, 3 mmol) in CH₂Cl₂ (8.00 mL). After additional 30 min at -63 °C, the reaction mixture was treated dropwise over 20 min with the product from the last step

(1.00 g, 1.54 mmol) in CH₂Cl₂ (8.00 mL), and the mixture was stirred for 30 min at –63 °C, followed by warming to –30 °C for 1 h, and finally cooled back to –63 °C. Et₃N (1.29 mL, 9.26 mmol, 6.00 eq.) was added dropwise over 20 min, and the mixture was stirred for additional 30 min at –63 °C. The reaction mixture was allowed to warm up to rt, and poured onto aq. 10% citric acid (10 mL). The org. layer was separated, and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined org. extracts were washed with aq. sat. NaHCO₃ (10 mL), brine (10 mL), dried over MgSO₄, and filtered. The solvents were removed under reduced pressure to yield (*rac.*)-(1*RS*, 5*SR*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-formylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (0.99 g, 99%), which was not further purified. ¹H-NMR (CDCl₃, 300 MHz) 9.80 (s, 1H), 7.44 (d, J = 7.6 Hz, 2H), 7.21 (m, 2H), 6.85 (m, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.46 (m, 1H), 4.90 – 4.30 (m, 5H), 4.20 – 3.90 (m, 3H), 3.80 (s, 3H), 3.20 – 2.90 (m, 3H), 2.30 – 2.00 (m, 5H), 1.47 (s, 9H), 1.45 (s, 9H), 0.90 – 0.35 (m, 4H).

The former product (5.00 g, 7.74 mmol) and *N*-methyl-amine (41% in H₂O, 20 mL) were mixed in MeOH (20 mL), and the mixture was heated to reflux under N₂ for 4 h. The mixture was cooled to rt, and carefully treated with solid NaBH₄ (1.10 g, 28.40 mmol). The reaction was stirred for 30 min and partitioned between EtOAc and H₂O. The phases were separated, and the aq. phase was extracted with EtOAc. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield the crude (*rac.*)-(1*RS*, 5*SR*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-methylaminomethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (4.33 g). No further purification was necessary. LC-MS: t_R = 0.91 min, MS (ESI): *m/z* 661.66 (M + 1)⁺. ¹H-NMR (CDCl₃, 300 MHz) 7.20 – 6.90 (m, 5H), 6.75 – 6.50 (m, 2H), 4.90 – 4.35 (m, 3H), 4.20 – 3.95 (m, 3H), 3.83, 3.78 (s, 3H, rot.), 3.75 (m, 2H), 3.25 – 2.95 (m, 3H), 2.47, 2.45 (s, 3H, rot.), 2.30 – 2.00 (m, 5H), 1.51, 1.50, 1.49 (s, 18H, rot.), 0.90 – 0.30 (m, 4H).

To a sol. of the former product (520 mg, 0.787 mmol) in CH₃CN (15 mL) were added the 2-chloro-3,6-difluorobenzaldehyde (208 mg, 1.18 mmol) and NaHB(OAc)₃ (424 mg, 2.00 mmol). The mixture

was stirred at rt overnight. 2-Chloro-3,6-difluorobenzaldehyde (30 mg, 0.17 mmol) and NaHB(OAc)₃ (100 mg, 0.47 mmol) were added again, and the mixture was stirred for 7 h. The mixture was partitioned between EtOAc (50 mL) and aq. sat. NaHCO₃ (30 mL). The aq. layer was extracted with EtOAc (2x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 3:7) (*rac.*)-(1*RS*, 5*SR*)-7-(4-{[(2-chloro-3,6-difluoro-benzyl)-methyl-amino]-methyl}-phenyl)-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (498 mg, 65% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 6.83 – 6.56 (m, 7H), 6.40 – 6.28 (m, 2H), 4.45 – 3.95 (m, 3H), 3.88 – 3.60 (m, 2H), 3.46, 3.42 (s, 3H, rot.), 3.32 – 3.04 (m, 4H), 2.92 – 2.60 (m, 3H), 1.96 – 1.60 (m, 3H), 1.77 (s, 6H), 1.16, 1.14, 1.12 (s, 18H, rot.).

To a sol. of this product (498 mg, 0.607 mmol) in CH₂Cl₂ (5 mL) was added HCl (4M in dioxane, 5 mL). The mixture was stirred at 0 °C for 2.5 h and at rt for 3 h. The mixture was basified to pH 14 with aq. 1M NaOH. The aq. phase was extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by over HPLC (2% CH₃CN and 98% H₂O/0.05% TFA → 100% CH₃CN), followed by basification of the aq. layer to pH = 12 by the addition of aq. 3M NaOH, and extraction of the aq. layer with CH₂Cl₂ (4x) yielded the title compound (281 mg, 75%). ¹H-NMR (CDCl₃) 7.43 – 6.43 (m, 9H, H^{arom}), 4.61 (d, J = 15.4 Hz, 1H, H-14), 4.14 (d, J = 15.4 Hz, 1H, H-14), 3.99 – 2.79 (m, 13H, OMe, H-11 (2x), H-10 (2x), H-5, H-1, H-2 (2x), H-4 (2x)), 2.32 – 2.05 (m, 3H, H-8 (2x), H-15), 2.26 and 2.18 (s, 3H, H-12 (3x), rot.), 2.09 (s, 3H, Me), 1.85 8m, 1H, H-15), 0.92 – 0.80 (m, 1H, H-16), 0.63 – 0.24 (m, 3H, H-16 (3x)).

^{13}C -NMR (CDCl_3) 157.45 (Cq), 138.84 (Cq), 136.34 (Cq), 129.21 (CH^{arom}), 129.01 (CH^{arom}), 126.88, 126.73, 126.40, 120.30, 15.79, 124.53 (Cq and CH^{arom}), 120.65 (CH^{arom}), 114.25 (m, CH^{arom}), 109.00, 108.73 (CH^{arom}), 62.09, 62.00 (C10), 55.55, 55.47 (OMe), 51.96 (C11), 50.87 (C5), 48.31 (C2), 47.29 (C14), 46.39 (C1), 41.72, 41.49 (C12), 33.75 (C8), 30.52, 29.69 (C15), 11.21, 10.97, 10.65 (Me), 8.25, 6.69, 6.27 (C16). IR (film) ν 2920, 2847, 2793, 2195, 1976, 1614 cm^{-1} . Anal. Calcd for $\text{C}_{35}\text{H}_{39}\text{N}_4\text{O}_2\text{ClF}_2 \cdot 0.45\text{H}_2\text{O}$: C, 66.80; H, 6.39; N, 8.90. Found: C, 66.10; H, 6.34; N, 8.71, H_2O , 1.28. LC-MS: t_R = 0.68 min, ES (ESI): m/z 621.43 ($\text{M} + 1$) $^+$; purity at 230 nm: 96.1%; at 254 nm: 96.3%.

(*rac.*)-(IRS, 5SR)-7-(4-{2-[Methyl-(2,3,6-trichloro-benzyl)-amino]-ethyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)-amide ((*rac.*)-26f)

BuLi (1.60 M in hexane, 34.0 mL, 53.87 mmol) was added dropwise to a cooled ($-78\text{ }^\circ\text{C}$) sol. of (4-bromobenzyloxy)-*tert*-butyldimethylsilane (15.30 g, 51.05 mmol) in THF (0.47 L). The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h, and ZnCl_2 (1M in THF, 68.0 mL, 68.0 mmol) was added dropwise at $-78\text{ }^\circ\text{C}$. The cooling bath was removed, and the reaction stirred for 1 h at rt. A sol. of compound (*rac.*)-7 (13.00 g, 28.36 mmol) in THF (50.0 mL) was added dropwise, followed by $\text{Pd}(\text{PPh}_3)_4$ (0.95 g, 0.82 mmol). The reaction mixture was stirred at rt for 1 h, partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc) yielded (*rac.*)-(IR*, 5S*)-7-[4-(*tert*-butyldimethylsilyloxymethyl)phenyl]-9-methyl-3,9-diazabicyclo[3.3.1]-non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (17.9 g, >99%) as an orange oil that was launched directly in the next step.

1-Chloroethyl chloroformate (37.00 mL, 0.33 mol) was added dropwise to a suspension of the former product (17.9 g, 33.6 mmol) and NaHCO_3 (28.0 g, 0.33 mol) in 1,2-dichloroethane (0.23 L). The mixture was heated to reflux for 3 h, then allowed to cool to rt, filtered, and the solvents were thoroughly removed under reduced pressure. MeOH (0.23 L) was added and the mixture was stirred at

50 °C for 60 min. The sol. was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (0.23 L), DIPEA (29.0 mL, 0.17 mol) was added, followed by Boc₂O (22.0 g, 0.10 mol), and the mixture was stirred at rt for 45 min. The mixture was washed with aq. 1M HCl, and aq. sat. NaHCO₃. The organic phase was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (50% EtOAc in heptane) yielded (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (11.6 g, 69%). ¹H-NMR (CDCl₃, 300 MHz) 7.13 (d, J = 6.2 Hz, 2H), 7.08 (d, J = 7.2 Hz, 2H), 5.25 – 5.05 (m, 1H), 4.45 – 4.20 (m, 2H), 4.10 – 3.90 (m, 3H), 3.84 (t, J = 6.4 Hz, 2H), 3.15 – 2.95 (m, 3H), 2.85 (t, J = 6.3 Hz, 2H), 2.45 (d, J = 19.3 Hz, 1H), 1.49 (s, 9H), 1.37 (s, 9H), 1.28 (m, 3H).

Aq. 1M NaOH (162 mL) was added to a sol. of the former product (8.20 g, 16.3 mmol) in EtOH (320 mL). The resulting mixture was stirred at 70 °C for 3 h, cooled to rt, and the solvents were removed under reduced pressure. The crude mixture was partitioned between TBME and aq. sat. 1M HCl. The aq. layer was extracted twice more with TBME, the combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield a crude mixture of (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,8,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (5.80 g), which was not further purified.

TBDMS-Cl (4.51 g, 29.9 mmol) and imidazole (3.26 g, 47.9 mmol) were added to a stirred sol. of the former crude product mixture (5.68 g) in DMF (50 mL). The reaction mixture was stirred at rt over 15 h. The solvents were removed under reduced pressure, the crude mixture partitioned between Et₂O and water. The aq. phase was extracted again with Et₂O. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in THF (100 mL), MeOH (21 mL), and water (21 mL), and K₂CO₃ (0.83 g, 6.00 mmol) was added. The mixture was stirred at rt for 1 h. The mixture was partitioned between Et₂O and aq. sat. NH₄Cl, the phases were separated, and the aq. layer was extracted once more with

Et₂O. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield a crude product mixture of (*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,8,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (7.53 g) that was used further without purification.

To a stirred sol. of the former crude product mixture (7.53 g) in CH₂Cl₂ (100 mL) were added EDC·HCl (5.73 g, 29.9 mmol), HOBt (2.19 g, 14.4 mmol), DMAP (0.36 g, 3.0 mmol), cyclopropyl-(3-methoxy-2-methylbenzyl)amine (3.43 g, 17.94 mmol) and DIPEA (9.37 mL, 53.8 mmol). The mixture was stirred at rt for 5 days. The reaction mixture was partitioned between aq. sat. NaHCO₃ and EtOAc, the phases were separated, and the aq. layer was extracted once more with EtOAc. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (10-30% EtOAc in heptane) yielded (*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)-phenyl]-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (7.74 g, 64% over 3 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.10 – 6.92 (m, 2H), 6.88 – 6.70 (m, 2H), 6.70 – 6.60 (m, 2H), 6.50 – 6.45 (m, 1H), 4.80 – 4.40 (m, 4H), 4.10 – 3.90 (m, 2H), 3.80 – 3.60 (m, 7H), 3.10 – 2.60 (m, 3H), 2.14 (s, 3H), 2.10 – 1.90 (m, 2H), 1.42, 1.40, 1.37 (s, 18H, rot.), 0.90 (s, 9H), 0.80 – 0.20 (m, 4H), 0.00 (s, 6H).

A mixture of the former product (8.67 g, 11 mmol) and TBAF (7.05 g, 22 mmol) in THF (80 mL) was stirred at rt overnight. The mixture was diluted with EtOAc, and washed with aq. sat. NH₄Cl (2x). The org. layer was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 1:49) yielded crude (*rac.*)-(*1R*S, *5SR*)-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-7-[4-(2-hydroxy-ethyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (8.14 g). ¹H-NMR (CDCl₃, 300 MHz) 7.10 – 6.92 (m, 2H), 6.88 – 6.70 (m, 2H), 6.70 – 6.60 (m, 2H), 6.50 – 6.45 (m, 1H), 4.80 – 4.40 (m, 4H), 4.10 – 3.90 (m, 2H),

3.80 – 3.60 (m, 7H), 3.10 – 2.60 (m, 3H), 2.14 (s, 3H), 2.10 – 1.90 (m, 2H), 1.42, 1.40, 1.37 (s, 18H, rot.), 0.80 – 0.20 (m, 4H).

To a cooled (ice bath, 0 °C) sol. of the former crude product (3.31 g, 5.00 mmol) were added Et₃N (1.05 mL, 7.5 mmol) and slowly methanesulfonylchloride (0.58 mL, 7.5 mmol). The mixture was stirred overnight, while warming up to rt. The mixture was poured onto ice water, and was extracted with CH₂Cl₂ (3x). The combined org. extracts were washed with aq. 1M HCl, aq. sat. NaHCO₃, and brine. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield crude (*rac.*)-(IRS, 5SR)-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-7-[4-(2-methanesulfonyl-oxy-ethyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (3.76 g) that was not further purified.

The former crude product (3.70 g, 5.00 mmol) and *N*-benzylmethylamine (2.57 mL, 20.0 mmol) were dissolved in EtOH (30 mL), and the mixture was heated to reflux for 5 h. The solvents were removed under reduced pressure, and the mixture was partitioned between CH₂Cl₂ and brine. The aq. layer was extracted with CH₂Cl₂ (3x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (1-20% MeOH in CH₂Cl₂) yielded (*rac.*)-(IRS, 5SR)-7-{4-[2-(benzyl-methyl-amino)-ethyl]-phenyl}-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (1.69 g, 44% over 3 steps). ¹H-NMR (CDCl₃, 300 MHz) 6.96 (s, 5H), 6.80 – 6.00 (m, 7H), 4.44 – 4.00 (m, 4H), 3.8 – 3.72 (m, 2H), 3.44 (s, 3H), 3.20 (s, 2H), 2.84 – 2.56 (m, 3H), 2.45 – 2.20 (m, 4H), 1.92 (s, 3H), 1.92 – 1.72 (m, 5H), 1.12, 1.13, 1.15 (s, 18H, rot.), 0.60 - -0.10 (m, 4H).

To a sol. of the former product (1.69 g, 2.21 mmol) in EtOAc (20 mL), were added glacial AcOH (0.50 mL) and Pd (10% on charcoal, 170 mg). The mixture was submitted to a H₂ atmosphere for 2 days. Pd (10% on charcoal, 50 mg) was added again, and the mixture stirred again under H₂ overnight. The mixture was filtered through celite, washed with EtOAc, and the solvents were removed under reduced pressure to yield crude (*rac.*)-(IRS, 5SR)-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-

carbamoyl]-7-[4-(2-methylamino-ethyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (1.35 g) that was used further without purification.

To a sol. of the former crude product (675 mg, 1.00 mmol) in CH₃CN (15 mL) were added the 2,3,6-trichlorobenzaldehyde (209 mg, 1.00 mmol) and NaBH(OAc)₃ (424 mg, 2.00 mmol). The mixture was stirred at rt overnight. 2,3,6-Trichlorobenzaldehyde (50 mg, 0.23 mmol) and NaBH(OAc)₃ (100 mg, 0.23 mmol) were added again, and the mixture was stirred again overnight. The mixture was partitioned between EtOAc and aq. sat. NaHCO₃. The aq. layer was extracted with EtOAc (2x). The combined org. layers were washed with brine, dried over MgSO₄, filtered, and solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 3:7) yielded (*rac.*)-(1*RS*, 5*SR*)-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)-carbamoyl]-7-(4-{2-[methyl-(2,3,6-trichloro-benzyl)-amino]-ethyl}-phenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (683 mg, 72% over 2 steps). ¹H-NMR (CDCl₃, 300 MHz) 7.00 – 6.00 (m, 9H), 4.50 – 4.00 (m, 4H), 3.84 – 3.60 (m, 2H), 3.50 – 3.40 (m, 5H), 2.72 – 2.60 (m, 3H), 2.40 (s, broad, 2H), 1.96 (s, broad, 3H), 1.92 – 1.60 (m, 2H), 1.76 (s, 3H), 1.16 (s, 18H), 0.60 - -0.10 (m, 4H).

To a cooled (0°C, ice bath) solution of the former product (683 mg, 0.787 mmol) in CH₂Cl₂ (7 mL) was added HCl (4M dioxane, 7 mL). The reaction mixture was stirred at 0 °C for 3 h and was basified to pH = 14 with aq. 1M NaOH. The aq. phase was extracted with CH₂Cl₂ (3x). The combined org. layers were dried over MgSO₄, filtered, and solvents were removed under reduced pressure. Purification of the crude by HPLC (2%CH₃CN and H₂O with 0.05% TFA to 100% CH₃CN gradient over 5 min), followed

by basification of the aq. layer to pH = 12 with aq. 3M NaOH and extraction with CH₂Cl₂ (4x) yielded the title compound (232 mg, 44%). ¹H-NMR (CDCl₃) 7.35 (d, J = 9.5 Hz, 2H, H^{arom}), 7.27 (m, 2H, H^{arom}), 7.12 (t, J = 7.9 Hz, 1H^R, H^{arom}), 7.02 (d, J = 8.1 Hz, 1H, H^{arom}), 6.78 – 6.56 (m, 1H and 1H^R, H^{arom}), 6.40 (d, J = 7.6 Hz, 1H^R, H^{arom}), 4.70 (d, J = 15.2 Hz, 1H, H-15), 4.43 (d, J = 16.4 Hz, 1H^R, H-15^R), 4.17 (d, J = 15.2 Hz, 1H, H-15), 3.89 (s, 2H, H-12 (2x)), 3.88 (s, 2H^R, H-12^R (2x)), 3.82 (s, 3H, OMe), 3.80 (s, 3H^R, OMe), 3.64 (m, 1H^R, H-15^R), 3.48 – 3.36 (m, 2H and 1H^R, H-5, H-4, H-4^R), 3.29 – 3.23 (m, 3H, H-2, H-4, H-1), 3.17 – 3.08 (m, 1H and 5HR, H-1^R, H-2^R, H-4^R, H-5^R, H-8, H-8^R), 2.89 – 2.78 (m, 5H and 5H^R, H-2, H-2^R, H-11 (2x), H-11^R (2x), H₂-10, H-10^R (2x)), 2.53 (m, 1H^R, H-16^R), 2.38 (s, 3H^R, H-13^R (3x)), 2.37 (s, 3H, H-13 (3x)), 2.20 – 2.02 (m, 1H and 1H^R, H-8 and H-8^R), 2.10 (s, 3H, Me) 2.09 (s, 3H^R, Me), 1.87 (m, 1H, H-16), 0.94 – 0.76, 0.63 – 0.60, 0.52 – 0.43, -0.02 - -0.05 (m, 4H and 4H^R, H-17 (4x) and H-17^R (4x)). ¹³C-NMR (CDCl₃) 173.16 (C14), 157.54 (Cq), 157.49 (Cq^R), 140.77, 140.11, 138.11, 137.84, 137.76, 136.90, 136.51, 136.43, 135.38, 134.87, 132.19 (Cq and Cq^R), 129.57, 128.76, 128.63, 128.53, 127.57, 126.93, 126.60, 126.48, 125.76, 124.62, 123.51, 120.72, 119.02 (CH^{arom} and CH^{Rarom}), 59.44 (C11^R), 59.32 (C11), 56.80 (C12), 56.75 (C12^R), 55.54 (OMe), 52.47 (C2), 51.21 (C5), 50.93 (C15^R), 50.67 (C5^R), 49.08 (C4), 47.26 (C15), 46.82 (C4), 46.42 (C4^R), 41.69 (C13), 34.24 (C8), 33.85 (C8^R), 33.06 (C10^R), 33.01 (C10), 30.48 (C16), 29.69 (C16^R), 11.27 and 10.96 (Me), 10.53, 8.26, 6.60, 6.41 (C17 and C17^R). IR (film) ν 2919, 2849, 2175, 2020, 1611 cm⁻¹. Anal. Calcd for C₃₆H₄₁N₄O₂Cl₃·0.34H₂O: C, 64.13; H, 6.23; N, 8.31. Found: C, 64.28; H, 6.27; N, 8.29, H₂O, 0.91. LC-MS: t_R = 0.71 min, MS (ESI): *m/z* 667.36 (M + 1)⁺; purity at 230 nm: 95.3%; at 254 nm: 95.4%.

(1*R*, 5*S*)-7-{4-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide ((+)-26g)

A sol. of 1-(4-bromophenoxy)-2-(2,6-dichloro-4-methylphenoxy)ethane (49.8 g, 132 mmol) in THF (1.10 L) under nitrogen was cooled to -78 °C. BuLi (1.6M in hexane, 88.0 mL, 143 mmol) was added. After 1 h, ZnCl₂ (1M in THF, 198 mL, 198 mmol) was added. The mixture was allowed to warm up to rt. Compound **7** (55.0 g, 112 mmol) in THF (100 mL) and then Pd(PPh₃)₄ (3.47 g, 3.00 mmol) were added. The mixture was heated to reflux for 1 h, and allowed to cool to rt. The mixture was diluted with

EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:49 → 1:24 → 3:47 → 4:45) yielded (*IR*, *5S*)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (47.3 g, 79%). ¹H-NMR (300 MHz, CDCl₃) 7.10 (s, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 4.34 (s, 4H), 4.20 (m, 1H), 3.96 – 3.84 (m, 3H), 3.75 and 3.65 (s, 1H, rot.), 3.20 – 2.90 (m, 3H), 2.55 (dd, *J*₁ = 19.3 Hz, *J*₂ = 6.4 Hz, 1H), 2.40 (s, 3H), 2.39 (m, 1H), 2.28 (s, 3H), 1.35 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H). LC-MS: *t*_R = 0.95 min, MS (ESI): *m/z* 605.34 (*M* + 1)⁺.

The former compound (57.3 g, 94.6 mmol) was dissolved in dry 1,2-dichloroethane (1.00 L). NaHCO₃ (80.4 g, 946 mmol) and 1-chloroethyl chloroformate (103 mL, 946 mmol) were added, and the suspension was heated to 80 °C for 3 h. The reaction mixture was allowed to cool to rt. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dried for 15 min under high vacuum. The product was then diluted in MeOH (900 mL), and the mixture was heated to 60 °C for 30 min. The reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dried under high vacuum for 1 h. The residue was dissolved in CH₂Cl₂ (1.00 L), and the sol. was cooled to 0 °C. DIPEA (97.2 mL, 567 mmol), and Boc₂O (62.0 g, 283 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min, then at rt for 30 min. The reaction mixture was diluted with CH₂Cl₂ (110 mL). The org. layer was washed with aq. 1M HCl (2 x 300mL), and aq. sat. NaHCO₃ (300mL). The org. layer was dried over MgSO₄, filtered, and the solvents were evaporated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:5 → 1:38 → 1:1 → EtOAc) yielded (*IR*, *5S*)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (47.9 g, 73%). ¹H-NMR (300 MHz, CDCl₃) 7.10 (s, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.25 – 4.90 (m, 1H), 4.44 – 4.20 (m, 2H), 4.34 (s, 4H), 4.10 – 3.85 (m, 3H), 3.15 – 2.60 (m, 3H), 2.47 (d, *J* = 19.0 Hz, 1H), 2.27 (s, 3H), 1.49 (s, 9H), 1.36 (s, 9H), 1.04 – 0.85 (m, 3H). LC-MS: *t*_R = 1.22 min, MS (ESI): *m/z* 691.37 (*M* + 1)⁺.

A mixture of the former compound (47.8 g, 69.1 mmol) in aq. 1M NaOH (350 mL) and EtOH (700 mL) was stirred at 80 °C overnight. The mixture was partially evaporated under reduced pressure, and EtOAc (500 mL) was added. The aq. phase was acidified with aq. 3M HCl, and the mixture was extracted. The org. layer was separated, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum, giving a 1:1 crude mixture of (*1R*, *5S*)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*1R*, *5S*)-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-7-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester, which was used further without purification (50.2 g). LC-MS: *t*_R = 1.12 min, MS (ESI): *m/z* 663.33 (*M* + 1)⁺.

A mixture of the former crude compounds (14.6 g, 22.0 mmol), cyclopropyl-(2,3-dimethyl-benzyl)-amine (9.64 g, 55 mmol), EDC·HCl (12.7 g, 66.0 mmol), HOBT (3.72 g, 27.5 mmol), DMAP (672 mg, 5.50 mmol) and DIPEA (15.1 mL, 88 mmol) in CH₂Cl₂ (300 mL) was stirred at rt for 4 days. Twice were added EDC·HCl (2.10 g, 10.6 mmol) and cyclopropyl-(2,3-dimethyl-benzyl)-amine (3.85 g, 22.0 mmol). The mixture was diluted with more CH₂Cl₂, and was washed with aq. 1M HCl (3x), and aq. sat. NaHCO₃ (2x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded (*1R*, *5S*)-6-[cyclopropyl-(2,3-dimethylbenzyl)carbamoyl]-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (13.8 g, 76% over 2 steps). ¹H-NMR (300 MHz, CDCl₃) 6.95 - 6.30 (m, 8H), 4.45 - 4.15 (m, 3H), 4.10 - 3.65 (m, 6H), 2.90 - 2.60 (m, 3H), 2.00 - 1.70 (m, 11H), 1.16, 1.11, 0.92 (s, 18H, rot.), 0.60 - -0.10 (m, 4H). LC-MS: *t*_R = 1.20 min, MS (ESI): *m/z* 820.53 (*M* + 1)⁺.

A sol. of the former compound (13.8 g, 16.9 mmol) in CH_2Cl_2 (120 mL) was cooled to 0 °C. HCl (4M in dioxane, 120 mL) was added. The mixture was stirred for 1 h at 0 °C, then 2 h at rt. The solvents were removed under reduced pressure, and the residue was dried under high vacuum. The residue was diluted with CH_2Cl_2 , and washed with aq. 1M NaOH until the aq. layer remained basic. The org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($\text{MeOH}/\text{CH}_2\text{Cl}_2$ 5:95 $\rightarrow$ 10:90 $\rightarrow$ 20:80 with 1% Et_3N all the time) yielded the title compound (9.45 g, 90%). The bis-mesylate salt of this compound was prepared in CH_3CN by adding 2 eq. of $\text{CH}_3\text{SO}_3\text{H}$, stirring the resulting mixture at 80 °C overnight, and cooling down to rt. mp = 186 °C (dec.). ^1H -NMR (CD_3OD) 7.40 (d, J = 8.7 Hz, 2H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 7.31 (d, J = 8.7 Hz, 2H, H_{arom}), 7.23 (s, 2H and 2H^{R} , H_{arom}), 7.10 – 6.99 (m, 1H and 3H^{R} , H_{arom}), 6.96 (t, J = 7.6 Hz, 1H, H_{arom}), 6.79 (d, J = 7.8 Hz, 1H, H_{arom}), 6.71 (d, J = 8.7 Hz, 2H, H_{arom}), 6.62 (d, J = 7.3 Hz, 1H^{R} , $\text{H}_{\text{arom}}^{\text{R}}$), 4.79 (d, J = 15.2 Hz, 1H, H-13), 4.72 (s, 1H, H-5), 4.65 (d, J = 15.8 Hz, 1H^{R} , H-13 $^{\text{R}}$), 4.51 (s, 1H^{R} , H-5 $^{\text{R}}$), 4.43 – 4.33 (m, 5H, H-10 (2x), H-11 (2x), H-1), 4.23 (d, J = 15.0 Hz, 1H, H-13), 4.16 (d, J = 13.7 Hz, 1H, H-4), 3.81 – 3.61 (m, 4H, H-8, H-4, H-2 (2x)), 3.53 (d, J = 15.8 Hz, 1H^{R} , H-13 $^{\text{R}}$), 2.72 (d, J = 19.4 Hz, 1H, H-8), 2.71 (s, 6H, $\text{CH}_3\text{SO}_3\text{H}$ (2x)), 2.32 (s, 3H, Me), 2.29 and 2.27 (s, 3H, Me, rot.), 2.19 and 2.09 (s, 3H, Me, rot.), 1.82 (m, 1H, H-14), 0.91 – 0.84, 0.79 – 0.72, 0.69 – 0.62, 0.58 – 0.50, 0.39 – 0.32, 0.15 – 0.08 (m, 4H, H-15 (4x)). ^{13}C -NMR (CD_3OD) 170.28 (C12), 170.01 (C12 $^{\text{R}}$), 159.97 (Cq $^{\text{R}}$), 159.48 (Cq), 148.84 (Cq), 140.85 (Cq $^{\text{R}}$), 138.43 (Cq), 136.83 (Cq $^{\text{R}}$), 136.64 (Cq), 136.07 (Cq), 136.03 (Cq $^{\text{R}}$), 134.21 (Cq), 134.13 (Cq), 133.90 (Cq $^{\text{R}}$), 133.85 (Cq $^{\text{R}}$), 129.92 (Cq), 129.55 (Cq $^{\text{R}}$), 129.21 (CH_{arom}), 128.74 ($\text{CH}_{\text{arom}}^{\text{R}}$), 128.67

(CH_{arom}), 128.55 (CH^R_{arom}), 128.45 (CH_{arom}), 128.22 (CH_{arom}), 126.23 (CH_{arom}), 125.38 (CH^R_{arom}), 124.83 (CH_{arom}), 124.83 (CH^R_{arom}), 122.01 (Cq), 121.34 (Cq^R), 114.32 (CH_{arom}), 71.77 (C10^R), 71.57 (C10), 67.29 (C11^R), 67.07 (C11), 47.5 (under solvent peak, C13), 46.42 (C5), 46.27 (C5^R), 45.55 (C2), 44.27 (C4), 44.10 (C1), 43.82 (C1^R), 31.31 (C8^R), 31.15 (C8), 30.49 (C14), 19.38 (Me), 19.10 (Me^R), 19.05 (Me), 13.96 (Me), 13.53 (Me^R), 9.56 (C15), 7.17 (C15^R), 5.69 (C15), 5.60 (C15^R). IR (film) ν 2967, 2812, 2160, 2035, 1606. Anal. Calcd for C₃₇H₄₇N₃O₉Cl₂S₂·H₂O: C, 53.49; H, 5.94; N, 5.06. Found: C, 52.95; H, 5.91; N, 4.95. $[\alpha]_D^{25} = +50.6$ (1.0; MeOH). LC-MS: $t_R = 0.92$ min, MS (ESI): m/z 620.40 (M + 1)⁺; purity at 230 nm: 100%; at 254 nm: 100%.

(1*R*, 5*S*)-7-{4-[3-(2-Chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)-amide ((+)-26h)

Compound (*rac.*)-**19** (prepared as compound **19**, but from (*rac.*)-**6**, 32.0 g, 57.3 mmol) was dissolved in dry 1,2-dichloroethane (590 mL). NaHCO₃ (48.2 g, 573 mmol) and 1-chloroethyl chloroformate (62.5 mL, 573 mmol) were added. The suspension was heated to 80 °C. After 3 h the reaction mixture was allowed to cool to rt. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dried 15 min under high vacuum. The product was then diluted in MeOH (400 mL), and the mixture was heated to 50 °C for 20 min. The reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The yellow solid was dried under high vacuum for 1 h. The solid was dissolved in CH₂Cl₂ (190 mL), and the solution was cooled to 0 °C. DIPEA (49.1 mL, 287 mmol), and Boc₂O (37.5 g, 172 mmol) were added. The reaction mixture was stirred overnight while warming up to rt. The reaction mixture was diluted with CH₂Cl₂ (110 mL). The organic layer was washed with aq. 1M HCl (2 x 300mL), and aq. sat. NaHCO₃ (300mL). The org. layer was dried over MgSO₄, filtered, and the solvents were evaporated under reduced pressure. Purification of the residue by FC (CH₂Cl₂/MeOH 100:0 → 2:98 → 5:95) yielded (*rac.*)-(1*RS*, 5*SR*)-7-[4-(3-hydroxypropyl)-phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (26.2 g, 86%). ¹H-NMR (300 MHz, CDCl₃) 7.14 (d, J = 7.6 Hz, 2H), 7.00 (d, J = 7.6 Hz, 2H), 5.23 – 4.97 (m, 1H), 4.44 – 4.20 (m, 2H), 4.10 – 3.88 (m, 3H), 3.67 (m, 2H), 3.15 – 2.95 (m, 2H), 2.85 –

2.75 (m, 1H), 2.68 (t, $J = 7.2$ Hz, 2H), 2.45, 2.20 (d, $J = 19.3$ Hz, 1H), 1.88 (quint., $J = 7.1$ Hz, 2H), 1.48 (s, 9H), 1.37 (s, 9H), 1.00 – 0.80 (m, 3H). LC-MS: $t_R = 1.05$ min, MS (ESI): m/z 531.33 ($M + 1$)⁺.

A mixture of the former compound (56.0 g, 106 mmol), 2-chloro-3,6-difluorophenol (34.8 g, 211 mmol), 1,1'-(azodicarbonyl)dipiperidine (53.4 g, 211 mmol) and PBu_3 (85%, 83 mL, 317 mmol) in toluene (1.20 L) was heated to reflux under nitrogen for 1 h. The mixture was allowed to cool to rt. The mixture was diluted with EtOAc (2.00 L), and the mixture was washed with aq. 1M NaOH (2 x 900 mL). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:19 → 1:1) yielded (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (67.5 g, 94%). ¹H-NMR (300 MHz, $CDCl_3$) 7.15 (d, $J = 7.6$ Hz, 2H), 7.05 – 6.92 (m, 3H), 6.88 – 6.78 (m, 1H), 5.25 – 4.96 (m, 1H), 4.45 – 4.20 (m, 2H), 4.16 (t, $J = 5.9$ Hz, 2H), 4.10 – 3.90 (m, 3H), 3.16 – 2.96 (m, 2H), 2.85 (t, $J = 7.1$ Hz, 2H), 2.85 – 2.70 (m, 1H), 2.47, 2.26 (d and d, $J = 19.3$ Hz, 1H, rot.), 2.10 (m, 2H), 1.50 (s, 9H), 1.38 (s, 9H), 1.00 – 0.03 (m, 3H). LC-MS: $t_R = 1.24$ min, MS (ESI): m/z 617.25 ($M + 1$)⁺.

A mixture of the former compound (67.5 g, 99.6 mmol) in aq. 1M NaOH (700 mL) and EtOH (1.40 L) was stirred at 80 °C overnight. The mixture was partially evaporated under reduced pressure, and EtOAc (500 mL) was added. The aq. phase was acidified with aq. 3M HCl, and the mixture was extracted. The org. layer was separated, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum, giving a 1:1 crude mixture of (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-7-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester, which was used further without purification (61.8 g). LC-MS: $t_R = 1.12$ min, MS (ESI): m/z 649.37 ($M + 1$)⁺.

A mixture of the former crude compound mixture (20.7 g), *N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)amine (17.3 g, 80 mmol), EDC·HCl (18.4 g, 96 mmol), HOBt (5.40 g, 40.0 mmol),

DMAP (0.98 g, 8.00 mmol) and DIPEA (22.0 mL, 128 mmol) in CH₂Cl₂ (540 mL) was stirred at rt. The reaction was checked each day by LC-MS, and EDC·HCl (6.13 g, 32 mmol) and DIPEA (5.5 mL, 32 mmol) were added if the reaction was not complete. When the reaction was complete, the mixture was diluted with more CH₂Cl₂, and was washed with aq. 1M HCl (3x), and aq. sat. NaHCO₃ (2x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded (*rac.*)-(1*RS*, 5*SR*)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-6-[cyclopropyl-(2,3-dichloro-benzyl)-carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (16.5 g, 57% over 2 steps). ¹H-NMR (300 MHz, CDCl₃) 7.00 – 6.40 (m, 9H), 4.60 – 3.83 (m, 4H), 3.82 – 3.60 (m, 3H), 2.88 – 2.55 (m, 2H), 2.55 – 2.38 (m, 3H), 1.90 – 1.60 (m, 4H), 1.20 – 1.00 (m, 18H), 0.60 - -0.10 (m, 4H). LC-MS: t_R = 1.29 min, MS (ESI): *m/z* 848.35 (M + 1)⁺.

A sol. of the former compound (16.5 g, 19.4 mmol) in CH₂Cl₂ (100 mL) was cooled to 0 °C. HCl (4M in dioxane, 100 mL) was added. The mixture was stirred for 1 h at 0 °C, then 1 h at rt. The solvents were removed under reduced pressure, and the residue was dried under high vacuum. The residue was diluted with CH₂Cl₂, and washed with aq. 1M NaOH until the aq. layer staid basic. The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 5:95 → 10:90 → 20:80) yielded the title racemic compound (12.0 g, 95%). LC-MS: t_R = 0.91 min; ES⁺: 648.16 (M + 1)⁺.

The racemic title compound (1.00 g, 1.55 mmol) was purified on a Regis Whelk 01 column, 50x250 mm using isocratic conditions (25% EtOH, 0.1% diethylamine, 75% hexane) and a flow of 100 mL/min. The desired compound came as first enantiomer (t_R = 20.0 min). After evaporating the solvents under reduced pressure, the residue was dried under high vacuum. The residue was dissolved in CH_2Cl_2 , and washed with aq. 10% K_2CO_3 . The org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the title compound (350 mg). ^1H -NMR (CDCl_3) 7.37 – 7.33 (m, 1H, H_{arom}), 7.30 – 7.26 (m, 1H, H_{arom}), 7.24 – 7.19 (m, 2H, H_{arom}), 7.11 – 6.94 (m, 4H, H_{arom}), 6.89 – 6.81 (m, 1H, H_{arom}), 4.81 (d, J = 15.4 Hz, 1H, H-14), 4.69 (d, J = 16.8 Hz, 1H^R, H-14^R), 4.32 (d, J = 16.3 Hz, 1H, H-14), 4.18 (m, 2H, H-12 (2x)), 3.73 (d, J = 16.8 Hz, 1H^R, H-14^R), 3.46 – 3.38 (m, 2H, H-5, H-4), 3.31 – 3.21 (m, 2H, H-4, H-1), 3.16 – 3.01 (m, 2H and 2H^R, H-2, H-8, H1^R, H5^R), 2.85 (m, 3H, H-10 (2x), H-2), 2.3 (m, 3H, H-11 (2x), H-8), 1.95 (m, 1H, H-15), 0.89 – 0.74, 0.60, 0.58 – 0.23, -0.02 - -0.09, -0.20 - -0.24 (m, 4H, H-16 (4x)). ^{13}C -NMR (CDCl_3) 173.67 (C13), 173.52 (C13q), 155.03 (dd, J_1 = 244 Hz, J_2 = 3 Hz, Cq), 152.24 (dd, J_1 = 244 Hz, J_2 = 3 Hz, Cq), 144.57 (dd, J_1 = 12 Hz, J_2 = 3 Hz, Cq), 141.77 (CqR), 141.36 (Cq), 138.38 (Cq^R), 138.19 (Cq), 138.01 (Cq^R), 137.73 (Cq^R), 137.24 (Cq), 137.08 (Cq), 133.43 (Cq^R), 132.88 (Cq), 131.90 (Cq), 131.57 (Cq), 129.63 (Cq^R), 129.40 (Cq), 129.02 (CH_{arom}), 128.78 ($\text{CH}_{\text{arom}}^{\text{R}}$), 128.58 (CH_{arom}), 138.50 (CH_{arom}), 128.39 ($\text{CH}_{\text{arom}}^{\text{R}}$), 127.72 (Cq^R), 127.57 (Cq^R), 127.46 (Cq), 127.17 (CH_{arom}), 126.94 (CH_{arom}), 126.49 ($\text{CH}_{\text{arom}}^{\text{R}}$), 116.45 (dd, J_1 = 22 Hz, J_2 = 9 Hz, $\text{CH}_{\text{arom}}^{\text{R}}$), 114.55 (dd, J_1 = 22 Hz, J_2 = 9 Hz, CH_{arom}), 110.17 (dd, J_1 = 24 Hz, J_2 = 8 Hz, CH_{arom}), 73.65 (d, J = 5 Hz, C12), 73.51 (d, J = 5 Hz, C12^R), 52.58 (C2), 51.23 (C5), 51.18 (C14^R), 50.65 (C5), 49.19 (C4), 48.15 (C14), 46.80 (C1), 46.46 (C1^R), 34.30 (C8), 34.14 (C8^R), 31.73, 31.66, 31.51 (C11, C11^R, C10, C10^R), 31.03 (C15), 10.86 (C16), 8.30 (C16^R), 6.66 (C16), 6.44 (C16^R). IR (film) ν 3283, 2916, 2159, 2035, 1609 cm^{-1} . Anal. Calcd for $\text{C}_{33}\text{H}_{32}\text{N}_3\text{O}_2\text{Cl}_3\text{F}_2 \cdot 0.29\text{H}_2\text{O}$: C, 60.77; H, 5.03; N, 6.44. Found: C, 60.54; H, 4.90; N, 6.56. $[\alpha]_{\text{D}}^{25}$ = +51.1 (1.0; MeOH). LC-MS: t_R = 0.92 min, MS (ESI): m/z 646.64 ($\text{M} + 1$)⁺; purity at 230 nm: 97.1%; at 254 nm: 94.7%.

(1*S*, 5*R*)-7-{4-[3-(2-Chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide ((-)-26h)

From compound (**rac.**)-**26h**, the chiral separation used to prepare compound (+)-**26h** yielded compound (-)-**26h** as well (t_R = 35.2 min, 320 mg). Anal. Calcd for $C_{33}H_{32}N_3O_2Cl_3F_2 \cdot 0.09H_2O$: C, 61.11; H, 5.00; N, 6.48. Found: C, 60.76; H, 5.29; N, 6.37. $[\alpha]_D^{25} = -50.7$ (1.0; MeOH). LC-MS: t_R = 0.92 min, MS (ESI): m/z 646.78 ($M + 1$)⁺; purity at 230 nm: 97.6%; at 254 nm: 94.7%.

Purity of final compounds by LC-MS: Summary

In grey: compounds with a combustion analysis out of range

Numbers in *italic*: less than 95% by LC-MS. RT = retention time.

CmpsNr	RT	LC-MS purity (%)	
		230 nM	254 nM
14a	1.01	100	100
14b	1.01	100	100
14c	0.98	97.2	99
14d	0.92	100	100
14e	0.92	100	100
14f	0.84	100	100
17a	0.87	98.2	100
17b	0.89	98	97.9
17c	0.89	100	100
17d	0.90	100	97.8
17e	0.91	99.1	100
17f	0.94	95.5	100
17g	0.93	97.2	97.2
17h	0.92	98.9	99.5
17i	0.95	100	100
17j	0.96	100	100
17k	0.94	99.9	99.7
17l	0.90	98.2	96.4
24a	0.94	93.3	92.5
24b	0.97	100	100
24c	0.96	98.7	100
24d	0.99	98.5	100
24e	0.92	100	100
24f	1.00	100	100
24g	1.00	100	100

24h	0.97	100	100
24i	0.97	87.2	87.2
24j	0.99	96.9	100
24k	0.98	97.8	100
25a	0.94	100	100
25b	0.96	100	100
25c	0.97	97.2	100
25d	0.96	97.7	96.5
25e	0.93	100	100
25f	0.97	100	100
25g	1.01	100	100
25h	0.99	100	100
25i	0.95	96.1	97.6
25j	0.97	100	100
25k	0.97	100	100
25l	1.02	94	93.3
(rac)-26a	0.93	100	100
(rac)-26b	0.91	100	100
(rac)-26c	0.93	100	97
(+)-26d	0.91	97.1	98
(rac)-26e	0.68	96.1	96.3
(rac)-26f	0.71	95.3	95.4
(+)-26g	0.92	100	100
(+)-26h	0.92	97.1	94.7
(-)-26h	0.92	97.6	94.7

X-ray structures analysis

Table of Data-processing and Refinement

	Complex with 77815	Complex with 77816
Spacegroup	P21212	P212121
Cell constant (Å)	65.7 89.5 118.4	64.8 87.5 117.0
Resolution range	70 – 2.0	70 - 1.9
No of observed reflections	103242	184536
Unique Observations	40473	51537
Multiplicity	2.6	3.6

Completeness	85%	97.2%
R _{merge}	7.5%	9.4%
Number of atoms	5706	5885
Used reflections	38393 (2042 R _{free} set)	48830 (2628 R _{free} set)
Deviation bond length	0.013	0.015
Deviation Bond angles	1.488	1.677
R _{fac}	0,196	0,183
Free R _{fac}	0,263	0,235

Material and Methods: For crystallization the hanging drop method were used with ratios of 2:1 and 3:1. Crystals were obtained at 25-30% PEG4000, 0.6M NaCl at pH 4.0 to 5.0 after two to four weeks. Data were collected at the PX beamline at the Swiss Light Source, Paul Scherrer Institute, Villigen, Switzerland. Data processing, structure solution and refinement were done with programs from the ccp4-program package (CCP4). For manual rebuilding of the structure the program Moloc were used (www.moloc.ch). Summary of the dataprocessing and refinement is given in the table here above.

Inhibition assay in buffer or plasma using 384-well MTP. The renin assay was adapted from an assay described before (*Fischli W, Clozel JP, El Amrani K, Wostl W, Neidhart W, Stadler H, Branca Q. Ro 42-5892 is a potent orally active renin inhibitor in primates. Hypertension 1991; 18:22-31*) and consists of two steps: in the first step, renin inhibitors were incubated with recombinant human renin and its substrate (commercial human tetradecapeptide renin substrate) in buffer or with citrate plasma containing endogenous renin and angiotensinogen substrate to create angiotensinI (AngI). In the second step, the accumulated AngI is measured by an immunoassay assay.

For estimation of inhibitory potency of compounds in plasma (rather than in buffer) the trapping assay methodology of Poulson and Joergensen was used (*J Clin Endocrinol Metab* 1974; 39:816-825). The method was adapted and described in detail by Nussberger et al. (*J Cardiovasc Pharmacol* 1987; 9:39-44). In this assay, degradation of the produced AngI is prevented by addition of an excess of anti-AngI antibodies prior to incubation of the plasma/inhibitor mix. Thus, the inhibition assay is measured under conditions as close to physiologic as possible, without the addition of angiotensinase inhibitors like the widely used 8-hydroxyquinoline sulfate or phenylmethyl sulfonyl fluoride.

A - Methodology in buffer Recombinant human renin [3pg/ μ l] in assay buffer (PBS1X, 1mM EDTA, 0.1% BSA, pH7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 μ M in 10mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30mM in H₂O] and assay buffer were premixed at 4°C at a ratio of 100:30:10:145. 47.5 μ l per well of this premix was transferred into polypropylene plates (MTP384, Nunc). Test compounds were dissolved and diluted in 100% DMSO and 2.5 μ l added to the premix, then incubated at 37°C for 3 hours.

At the end of the incubation period, 5 μ l of the renin reaction (or standards in assay buffer) were measured for AngI accumulation. The percentage of renin inhibition (AngI decrease) was calculated for each concentration of compound by a custom-tailored software, which allows direct visualization of the raw data and interactive curve fitting.

B – Methodology in human plasma Citrate-plasma from human volunteers was pooled, aliquoted and stored frozen at -20°C. Renin activity in pooled plasma was supplemented with recombinant human renin (150pg/ml final concentration), in order to increase the readout (production of AngI) of the assay. 5 μ l of renin inhibitors, at various concentrations, in DMSO was added to 80 μ l of a mixture (70:10) of human plasma and a fast trapping primary AngI antibody (anti-AngI : AS1, bleed 6, pre-diluted 1:10 in horse serum) diluted initially 1:26.5 in assay buffer (PBS1X, 1mM EDTA, 0.1% BSA, pH7.4) and then diluted 1:3.3 in 3M Tris, 200mM EDTA, pH7.2, (final antiserum dilution 1:50'000) and was incubated at 37°C for 2 hours.

Similar as in the buffer assay, 12µl of the renin reaction (or standards in assay buffer) were measured for AngI accumulation by immunoassay.

Pharmacokientic experiments in the rat

Pharmacokinetic experiments were performed in male Wistar rats weighing 250-300 g ($n = 3$). Two days prior to the experiments, animals used for oral administration had a catheter implanted into the left carotid artery under anesthesia with Brietal^{TM} (70 mg/kg). For intravenous dosing, an additional catheter was implanted into the jugular vein for drug administration. During the recovery period, animals were housed in individual cages with free access to food and water. Access to water was maintained during the experiment, but food was deprived the night before the experiment and until 4 h after drug administration. Rats received oral doses of the renin inhibitors formulated as microsuspensions in 7.5% modified gelatin at a dose of 10 mg/kg by gavage. For intravenous application at a dose of 1.0 mg/kg, the compounds were dissolved in 30% kleptose. Blood samples of about 300 µL volume were drawn at pre-defined timepoints over a period of 48 h and fortified with EDTA as anticoagulant. Plasma was generated by centrifugation at 4000 rpm for 10 min at 4 °C. Samples were stored at -20 °C pending analysis. All experiments with rats and mice were performed in accordance with the NIH guidelines and approved by the Cantonal Veterinary Office (permit no. 169, Kantonales Veterinäramt Liestal, Switzerland). The analysis of rat plasma samples and samples from in vitro experiments was done with LC-MS/MS using a modified method published earlier (Lausecker, B.; Hess, B.; Fischer, G.; Mueller, M.; Hopfgartner, G. Simultaneous determination of bosentan and its three major metabolites in various biological matrices and species using narrow bore liquid chromatography with ion spray tandem mass spectrometric detection. *J. Chromatography B* **2000**, 749, 67-83).

For analytical purposes, plasma proteins were precipitated with acetonitrile followed by centrifugation at 4000 rpm for 10 min at 4 °C. Plasma concentrations were then quantified using a Sciex API 3000 mass spectrometer (PE Applied Biosystems, Foster City, CA, USA) operated in positive ion mode. In most experiments, the limit of quantification was 1.0 ng/mL.

Pharmacokinetic parameters were estimated using the WinNonLin software package (Professional version 3.1, Pharsight Corporation, Mountain View, CA, USA). Total plasma clearance (CL) was calculated as $D/AUC_{0-inf.}$, with D equals dose and $AUC_{0-inf.}$ equals the area under the plasma concentration-time curve calculated by the linear/logarithmic trapezoidal rule and extrapolated to infinity using the apparent terminal rate constant λ_z . The apparent terminal half-life ($T_{1/2}$) was estimated from the terminal rate constant λ_z with $T_{1/2} = \ln 2 / \lambda_z$ (λ_z was determined from the linear terminal portion of the log plasma concentration-time curve). The volume of distribution at steady state (V_{ss}) was calculated as $V_{ss} = MRT \times CL$ with the mean residence time (MRT) being defined as the area under the first moment curve $AUMC_{0-inf.}$ divided by $AUC_{0-inf.}$. Peak plasma concentrations (C_{max}) and the time to reach peak plasma concentrations (T_{max}) were directly taken from the respective plasma concentration-time curves. Oral bioavailabilities (F) were calculated by the ratios of dose-normalized $AUC_{0-inf.}$ after oral and intravenous dosing.

Double transgenic rats: methodology

The anaesthesia of the dTGRs was induced and maintained by inhalation of 2.5% isoflurane (70% O₂ + 30% N₂O). A pressure transmitter was implanted into the peritoneal cavity under aseptic conditions [1-3]. The sensing catheter of the pressure transmitter was placed in the descending aorta below the renal arteries, pointing upstream. The transmitter was sutured to the abdominal musculature, and the skin was closed (ref. 16a; ref. 16c; Hess P.; Rey M.; Wanner D.; Steiner B.; Clozel M. Measurements of blood pressure and electrocardiogram in conscious freely moving guinea pigs: a model for screening QT interval prolongation effects. *Lab Anim.* **2007**, 41, 470-80).