

Supporting information

Synthesis of Bi- and Tricyclic β -Lactam Libraries in Aqueous Medium

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Experimental

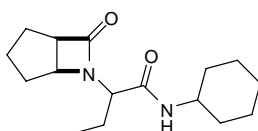
General

¹H NMR and ¹³C NMR spectra were recorded at 400 MHz, in deuteriochloroform at ambient temperature on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to tetramethylsilane (deuteriochloroform) as internal standards. Elemental analyses were performed with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyzer. IR spectra were measured on a Perkin-Elmer model 1000 FT-IR spectrophotometer. Melting points were determined on a Kofler apparatus and are uncorrected. The anisaldehyde was freshly distilled for the reactions.

General Procedure for the Preparation of β -Lactams (2a-q)

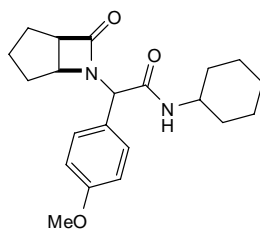
To the β -amino acid (**I-VIII**) (1.1 mmol) dissolved in a few drops of water, the corresponding aldehyde (**A-D**) (1.0 mmol) was added dropwise. Further water was then cautiously added dropwise until the generated Schiff base just dissolved. The reaction mixture was stirred for 1 h at room temperature, followed by addition of the isocyanide (**a, b**) (1.0 mmol). The resulting mixture was stirred for 1 day at room temperature. The precipitate (**2j, 2l** and **2p**) was then filtered off. When the product did not precipitate, evaporation of the aqueous solution *in vacuo* resulted in **2a, 2c-e, 2g-i, 2n** and **2o** in higher than 85% purity. For **2b, 2f, 2k, 2m**, and **2q**, the β -lactams were obtained as solids and were crystallized from EtOH/EtOAc.

N-Cyclohexyl-2-(7-oxo-6-azabicyclo[3.2.0]hept-6-yl) butyramide (**2a**)



This compound was obtained as yellow oil, diastereoisomeric ratio 68:32, (0.19g, 87%). (Found: C, 69.14; H, 9.42; N, 10.05. $C_{16}H_{26}N_2O_2$ requires C, 69.03; H, 9.41; N, 10.06%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3309, 3070, 2932, 2854, 1735, 1649, 1544, 1449, 1327, 1247, 1215, 1193, 1154, 1086 and 1056; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 0.96 (3H, t, J 7.55, CH_2CH_3), 1.08-2.11 (18H, m, $9 \times \text{CH}_2$), 3.45 (1H, q, J 4.03 and 8.06, CH_2CHCO), 3.68-3.77 (1H, m, NHCH), 3.80 (1H, t, J 8.06, CH_2CHN), 4.08 (1H, t, J 4.03, NCHCO) and 6.31 (1H, br s, NH); minor diastereomer: 0.98 (3H, t, J 7.06, CH_2CH_3), 1.08-2.11 (18H, m, $9 \times \text{CH}_2$), 3.54 (1H, t, J 7.76, CH_2CHCO), 3.68-3.77 (2H, m, CH_2CHN and NHCH), 4.05 (1H, t, J 4.03, NCHCO) and 6.83 (1H, br s, NH); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 11.6, 22.6, 23.6, 25.3, 25.7, 26.1, 28.6, 29.1, 33.4, 33.5, 48.9, 54.7, 58.5, 58.9, 169.5 and 170.9; minor diastereomer: 11.5, 22.6, 23.4, 23.6, 25.3, 25.5, 25.6, 26.1, 29.1, 33.4, 48.7, 54.5, 60.3, 62.4, 169.5 and 170.4; m/z (EI) 278 (M^+ , 4), 211 (8), 181 (4), 152 (100), 124 (32), 97 (18), 84 (24), 67 (16), 56 (22), 41 (16).

2-(4-Methoxyphenyl)-*N*-cyclohexyl-2-(7-oxo-6-azabicyclo[3.2.0]hept-6-yl) acetamide (2b)



This compound was obtained as white crystals, diastereoisomeric ratio 74:26, (0.13g, 44%); mp 208-210 °C; (Found: C, 70.95; H, 7.94; N, 7.76. $C_{21}H_{28}N_2O_3$ requires C, 70.76; H, 7.92; N, 7.86%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2922, 2856, 1726, 1680, 1610, 1514, 1452, 1252, 1182, 1154, 1034 and 750; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 1.01-2.09 (16H, m, $8 \times \text{CH}_2$), 3.35-3.42 (1H, m, CH_2CHCO), 3.70-3.84 (2H, m, CH_2CHN and NHCH), 3.80 (3H, s, OMe), 4.99 (1H, s, NCHCO), 6.56 (1H, br s, NH), 6.88 (2H, d, J 8.56, $\text{C}_6\text{H}_4\text{OMe-}p$) and 7.00 (2H, d, J 8.56, $\text{C}_6\text{H}_4\text{OMe-}p$); minor diastereomer: 1.01-2.09 (16H, m, $8 \times \text{CH}_2$), 3.45-3.51 (1H, m, CH_2CHCO), 3.70-3.84 (2H, m, CH_2CHN and NHCH), 3.80 (3H, s, OMe), 4.96 (1H, s, NCHCO), 6.56 (1H, br s, NH), 6.88 (2H, d, J 8.56, $\text{C}_6\text{H}_4\text{OMe-}p$) and 7.00 (2H, d, J 8.56, $\text{C}_6\text{H}_4\text{OMe-}p$); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 22.6, 23.6, 29.1, 29.3, 33.4, 39.8, 41.9, 52.1, 58.1, 114.8, 128.2, 130.2, 168.0 and 170.4; minor diastereomer: 22.5, 23.6, 29.1, 29.3, 33.3, 39.7, 40.9, 52.2, 58.7, 129.0, 130.92, 168.4 and 170.8; m/z (EI) 356 (M^+ , 1), 337 (5), 316 (2), 309 (3), 279 (1), 256 (4), 231 (33), 230 (100), 219 (3), 202 (4), 167 (5), 163 (7), 162 (45), 149 (15), 135 (16), 134 (18), 121 (8), 84 (7), 83 (10), 71 (9), 57 (16), 28 (6).

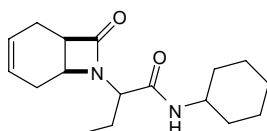
***N*-Cyclohexyl-2-(8-oxo-7-azabicyclo[3.2.0]okt-3-yl) butyramide (2c)**

This compound was obtained as colourless oil, yield 72% (lit.,²⁹ 42%). The spectral data matched those reported previously.^{13a}

***N*-tert-Butyl-2-(8-oxo-7-azabicyclo[4.2.0]oct-3-en-7-yl) butyramide (2d)**

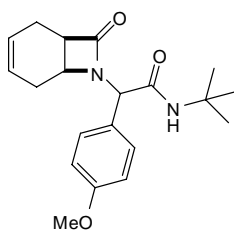
This compound was obtained as colourless oil, yield 74% (lit.,²⁹ 45%). The spectral data and the diastereomeric ratio matched those reported previously.^{13a}

***N*-Cyclohexyl-2-(8-oxo-7-azabicyclo[4.2.0]oct-3-en-7-yl) butyramide (2e)**



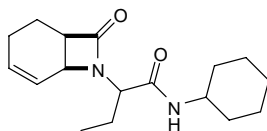
This compound was obtained as colourless oil, diastereoisomeric ratio 66:34, (0.15g, 70%); (Found: C, 70.42; H, 9.04; N, 9.62. C₁₇H₂₆N₂O₂ requires C, 70.31; H, 9.02; N, 9.65%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3324, 3040, 2965, 1732, 1655, 1454, 1392, 1362, 1226, 1163, 1086, 956, 816; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 0.97 (3H, t, *J* 7.55, CH₂CH₃), 1.06-2.20 (14H, m, 7 × CH₂), 2.40-2.56 (2H, dt, *J* 5.04 and 17.12, CH₂CH₃), 3.35-3.41 (1H, m, CH₂CHCO), 3.64-3.77 (1H, m, NHCH), 3.85 (1H, 2 × d, *J* 6.04 and 9.06, CH₂CHN), 4.05 (1H, t, *J* 4.03, NCHCO), 5.62-5.74 (1H, m, CHCH), 5.80-5.91 (1H, m, CHCH) and 6.45 (1H, br s, NH); minor diastereomer: 0.99 (3H, t, *J* 7.55, CH₂CH₃), 1.06-2.20 (14H, m, 7 × CH₂), 2.40-2.56 (2H, dt, *J* 5.04 and 17.12, CH₂CH₃), 3.30-3.40 (1H, m, CH₂CHCO), 3.51 (1H, t, *J* 7.55, NHCH), 3.64-3.77 (1H, m, CH₂CHN), 3.99 (1H, t, *J* 4.03, NCHCO), 5.62-5.74 (1H, m, CHCH), 5.80-5.91 (1H, m, CHCH) and 6.73 (1H, br s, NH); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 11.8, 21.7, 22.4, 25.3, 25.7, 25.8, 33.4, 47.0, 51.3, 58.9, 62.2, 125.2, 127.1, 169.7 and 171.1; minor diastereomer: 11.8, 21.7, 21.9, 25.7, 25.8, 26.1, 30.3, 48.8, 49.0, 53.5, 62.2, 125.3, 127.1, 169.7 and 171.2; *m/z* (EI) 290 (M⁺, 8), 211 (8), 191 (2), 169 (8), 164 (100), 136 (18), 86 (4), 58 (4), 43 (1).

2-(4-Methoxyphenyl)-*N*-tert-butyl-2-(8-oxo-7-azabicyclo[4.2.0]oct-3-en-7-yl) acetamide (2f)



This compound was obtained as white crystals, diastereoisomeric ratio 63:36, (0.14g, 50%); mp 204-207 °C; (Found: C, 70.24; H, 7.68; N, 8.15. $C_{20}H_{26}N_2O_3$ requires C, 70.15; H, 7.65; N, 8.18%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2923, 2852, 2364, 1732, 1606, 1514, 1374, 1260, 1170, 1122, 1074, 846; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 1.36 (9H, s, *t*Bu), 1.95-2.17 (2H, m, CH_2CHCO), 2.29-2.50 (2H, m, CH_2CHN), 3.30 (1H, t, J 6.04, CH_2CHCO), 3.71-3.76 (1H, m, CH_2CHN), 3.81 (3H, s, OMe), 5.06 (1H, s, NCHCO), 5.58-5.73 (1H, m, CHCH), 5.85-5.99 (1H, m, CHCH), 6.42 (1H, br s, NH), 6.88 (2H, d, J 8.56, $\text{C}_6\text{H}_4\text{OMe-}p$) and 7.25 (2H, d, J 8.06, $\text{C}_6\text{H}_4\text{OMe-}p$); minor diastereomer: 1.36 (9H, s, *t*Bu), 1.95-2.17 (2H, m, CH_2CHCO), 2.29-2.40 (1H, m, CH_2CHN), 2.46-2.56 (1H, m, CH_2CHN), 3.38 (1H, t, J 5.54, CH_2CHCO), 3.71-3.76 (1H, m, CH_2CHN), 3.81 (3H, s, Me), 4.91 (1H, s, NCHCO), 5.37-5.47 (1H, m, CHCH), 5.75-5.85 (1H, m, CHCH), 6.75 (2H, d, J 9.06, $\text{C}_6\text{H}_4\text{OMe-}p$) and 7.00 (2H, d, J 9.06, $\text{C}_6\text{H}_4\text{OMe-}p$); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 21.9, 25.0, 28.5, 29.2, 33.3, 37.1, 46.1, 50.1, 51.2, 52.4, 56.1, 114.5, 120.2, 127.2, 128.2, 129.3, 130.0, 160.0 and 169.8; minor diastereomer: δ 21.9, 24.9, 28.5, 29.3, 33.2, 37.0, 46.1, 50.5, 51.1, 52.4, 57.0, 114.4, 120.1, 127.2, 128.3, 129.2, 160.0 and 169.9; m/z (EI) 342 (M^+ , 1), 322 (1), 280 (2), 279 (9), 265 (2), 168 (2), 167 (21), 150 (11), 149 (100), 111 (14), 97 (21), 83 (24), 71 (35), 57 (51), 41 (32), 28 (35).

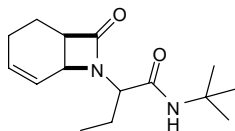
***N*-Cyclohexyl-2-(8-oxo-7-azabicyclo[4.2.0]oct-4-en-7-yl) butyramide (2g)**



This compound was obtained as yellow oil, diastereoisomeric ratio 68:32, (0.19g, 86%); (Found: C, 70.41; H, 9.04; N, 9.62. $C_{17}H_{26}N_2O_2$ requires C, 70.31; H, 9.02; N, 9.65%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3310, 2931, 2936, 2856, 2364, 1731, 1654, 1540, 1452, 1354, 1226; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 0.93 (3H, t, J 7.55, CH_2CH_3), 1.23-2.20 (16H, m, $8 \times \text{CH}_2$), 3.42-3.50 (1H, m, NHCH), 3.62-3.78 (1H, m, CH_2CHCO), 3.85 (1H, 2 \times d, J 6.04 and 9.06, CH_2CHN), 4.07 (1H, t, J 5.04, NHCHCO), 5.90-5.98 (1H, m, CHCH), 6.15-6.22 (1H, m, CHCH) and 6.37 (1H, br s, NH); minor diastereomer: 0.97 (3H, t, J 7.55, CH_2CH_3), 1.23-2.20 (16H, m, $8 \times \text{CH}_2$), 3.42-3.50 (1H, m, NHCH), 3.62-3.78 (2H, m, CH_2CHCO and CH_2CHN), 4.11 (1H, t, J 4.53, NHCHCO), 5.98-6.04 (1H, m, CHCH), 6.12-6.16 (1H, m, CHCH) and 6.37 (1H, br s, NH); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 11.7, 22.2, 22.7, 23.2, 25.3, 26.1, 33.4, 33.5, 125.7, 136.2; minor diastereomer: 11.5, 22.2, 22.7, 23.2, 25.3, 26.1, 33.4, 33.5, 48.6, 50.1, 61.0, 125.9 and 135.8; m/z (EI) 291

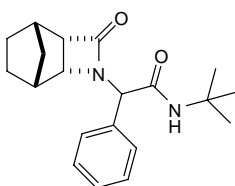
(M⁺+H, 1), 276 (1), 248 (1), 211 (4), 177 (30), 176 (55), 148 (18), 110 (100), 83 (16), 57 (10), 41 (7), 29 (2).

***N*-tert-Butyl-2-(8-oxo-7-azabicyclo[4.2.0]oct-4-en-7-yl) butyramide (2h)**



This compound was obtained as pale-yellow oil, diastereoisomeric ratio 67:33, (0.19g, 91%); (Found: C, 68.22; H, 9.16; N, 10.62. C₁₅H₂₄N₂O₂ requires C, 68.15; H, 9.15; N, 10.60%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3324, 3036, 2967, 2936, 2874, 2364, 1732, 1684, 1559, 1455, 1226; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 0.94 (3H, t, *J* 7.55, CH₂CH₃), 1.21-1.39 (9H, s, *t*Bu), 1.48-2.25 (6H, m, 3 × CH₂), 3.40-3.50 (1H, m, CH₂CHCO), 3.83 (1H, 2 × d, *J* 5.97 and 9.02, CH₂CHN), 4.07 (1H, t, *J* 4.86, NHCHCO), 5.91-5.98 (1H, m, CHCH), 6.11-6.21 (1H, m, CHCH) and 6.33 (1H, br s, NH); minor diastereomer: 0.96 (3H, t, *J* 7.55, CH₂CH₃), 1.21-1.39 (9H, m, *t*Bu), 1.48-2.25 (6H, m, 3 × CH₂), 3.40-3.50 (1H, m, CH₂CHCO), 3.71 (1H, 2 × d, *J* 6.78 and 8.35, CH₂CHN), 4.13 (1H, t, *J* 4.81, NHCHCO), 6.00-6.06 (1H, m, CHCH), 6.11-6.21 (1H, m, CHCH) and 6.29 (1H, br s, NH); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 11.1, 22.4, 23.0, 26.8, 27.7, 30.9, 44.6, 46.2, 47.9, 57.8, 122.1, 124.9 and 134.5; minor diastereomer: 11.3, 22.3, 23.5, 26.9, 27.9, 30.9, 43.9, 46.0, 47.5, 57.7, 122.1, 124.9, 134.5; *m/z* (EI) 264 (M⁺, 1), 236 (28), 164 (100), 136 (18), 129 (4), 84 (5), 80 (8), 58 (26).

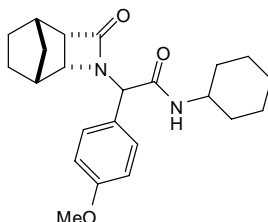
***diendo*-*N*-tert-Butyl-2-(4-oxo-3-azatricyclo[4.2.1.0^{2,5}]non-3-yl)-2-phenyl-acetamide (2j)**



This compound was precipitated and obtained as white solid product, diastereoisomeric ratio 100:0, (0.13g, 45%); mp 117-120 °C; (Found: C, 74.11; H, 7.48; N, 8.62. C₂₀H₂₄N₂O₂ requires C, 74.04; H, 7.46; N, 8.64%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3332, 3078, 2966, 2870, 1740, 1681, 1553, 1452, 1321; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 1.34 (9H, s, *t*Bu), 1.51-1.66 (m, 6H, 2 × CH₂ and 2 × CH), 2.35-2.47 (2H, m, CHCH₂CH), 3.34 (1H, t, *J* 5.65, CHCHCO), 3.87 (1H, t, *J* 4.97, CHCHN), 5.22 (1H, s, NCHCO), 6.68 (1H, bs, NH) and 7.28-7.43 (5H, m, *Ph*); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 24.5, 26.6, 29.1, 36.9, 39.4, 43.2, 59.1, 60.9, 61.9, 129.0, 129.2, 129.3, 129.5, 136.3, 167.9 and 171.7; *m/z* (EI) 327 (M+H⁺, 1), 228 (12), 227 (96), 212 (36),

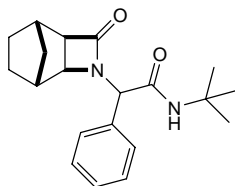
198 (6), 173 (8), 159 (24), 158 (8), 132 (22), 123 (10), 106 (34), 105 (100), 91 (20), 77 (259, 57 (18).

diendo-2-(4-Methoxyphenyl)-N-cyclohexyl-2-(4-oxo-3-azatricyclo[4.2.0.1^{2,5}]non-3-yl)acetamide (2k)



This compound was obtained as white crystals, diastereoisomeric ratio 100:0, (0.14g, 51%), mp 251-254 °C, (Found: C, 72.31; H, 7.95; N, 7.30. C₂₃H₃₀N₂O₃ requires C, 72.22; H, 7.91; N, 7.32%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3276, 2940, 2870, 2364, 1740, 1640, 1554, 1448, 1352, 1252; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 1.07-1.75 (14H, m, 7 × CH₂), 1.78-1.97 (2H, m, 2 × CH), 2.34-2.42 (2H, m, CHCH₂CH), 3.31 (1H, t, *J* 5.04, CHCHCO), 3.68-3.87 (5H, m, OMe, CHCHN and NHCH), 5.15 (1H, s, NCHCO), 6.62 (1H, d, *J* 7.55, NH), 6.87 (2H, d, *J* 8.56, C₆H₄OMe-*p*), 7.32 (2H, d, *J* 9.06, C₆H₄OMe-*p*); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 25.1, 25.3, 26.2, 26.8, 33.4, 36.9, 39.3, 43.1, 49.1, 55.9, 59.0, 60.9, 61.8, 114.8, 128.0, 130.6, 160.3, 168.3 and 171.7; *m/z* (EI) 382 (M⁺, 1), 258 (4), 257 (36), 256 (100), 226 (3), 188 (2), 163 (4), 162 (30), 135 (10), 121 (11), 93 (4), 67 (3).

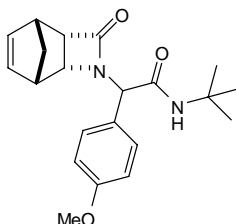
diexo-N-tert-Butyl-2-(4-oxo-3-azatricyclo[4.2.1.0^{2,5}]non-3-yl)-2-phenyl-acetamide (2l)



This compound was precipitated as white solid product, diastereoisomeric ratio 92:8, (0.13g, 35%); mp 140-146 °C; (Found: C, 73.66; H, 8.05; N, 8.56. C₂₀H₂₆N₂O₂ requires C, 73.59; H, 8.03; N, 8.58%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3303, 3074, 2964, 2874, 1728, 1681, 1548, 1451, 1364; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: major diastereomer: 0.86-1.21 (4H, m, 2 × CH₂), 1.35 (9H, s, *t*Bu), 1.42-1.66 (2H, m, CHCH₂CH), 2.41-2.46 (1H, m, CHCHCO), 2.49-2.54 (1H, m, CHCHN), 2.86 (1H, d, *J* 3.79, CHCHCO), 3.32 (1H, d, *J* 3.71, CHCHN), 5.01 (1H, s, NCHCO) and 6.40 (1H, br s, NH); minor diastereomer: 0.86-1.21 (4H, m, 2 × CH₂), 1.35 (9H, s, *t*Bu), 1.42-1.66 (2H, m, CHCH₂CH), 1.71-1.76 (1H, m, CHCHCO), 2.37-2.41 (1H, m, CHCHN), 2.95-2.99 (1H, m, CHCHCO), 3.70-3.73 (1H, m, CHCHN), 5.08 (1H, s, NCHCO)

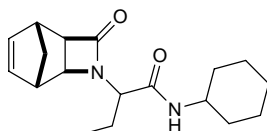
and 6.15 (1H, br s, NH); δ_C (100MHz, CDCl₃, Me₄Si): major diastereomer: 28.2, 30.7, 36.9, 39.3, 40.1, 53.4, 55.8, 57.5, 127.2, 128.3, 137.1, 166.7 and 171.7; minor diastereomer: 24.0, 26.9, 37.1, 39.5, 49.9, 53.4, 58.0, 127.5, 128.3, 167.4 and 171.7; m/z (EI) 326 (M⁺, 1), 311 (1), 228 (4), 227 (26), 226 (25), 212 (34), 194 (4), 159 (10), 106 (14), 105 (100), 77 (16), 57 (11), 41 (4)..

diendo-2-(4-Methoxyphenyl)-N-tert-butyl-2-(4-oxo-3-azatricyclo[4.2.0.1^{2,5}]non-7-en-3-yl) acetamide (2m)



This compound was obtained as yellowish crystals, diastereoisomeric ratio 100:0, (0.12g, 48%), mp 193-196 °C; (Found: C, 71.25; H, 7.41; N, 7.93. C₂₁H₂₆N₂O₃ requires C, 71.16; H, 7.39; N, 7.90%); ν_{\max} (film)/cm⁻¹ 3329, 3074, 2965, 2870, 1740, 1673, 1551, 1451, 1303; δ_H (400MHz, CDCl₃, Me₄Si): 1.36 (9H, s, *t*Bu), 1.46 (1H, d, *J* 9.24, CHCHCO), 1.87 (1H, d, *J* 9.17, CHCHN), 2.92 (2H, bd, CHCH₂CH), 3.44 (1H, t, *J* 4.91, CHCHCO), 3.81 (3H, s, OMe), 3.90 (1H, t, *J* 4.54, CHCHN), 4.96 (1H, s, NCHCO), 5.94-6.00 (1H, 2 × d, *J* 3.02 and 5.01, CHCH), 6.18-6.23 (1H, 2 × d, *J* 3.02 and 5.01, CHCH), 6.33 (1H, bs, NH), 6.88 (2H, d, *J* 8.68, C₆H₄OMe-*p*) and 7.28 (2H, d, *J* 8.69, C₆H₄OMe-*p*); δ_C (100MHz, CDCl₃, Me₄Si): 29.2, 42.6, 45.3, 52.8, 53.9, 55.6, 56.2, 57.3, 60.2, 115.5, 130.0, 130.5, 132.5, 134.7, 135.7, 169.7 and 172.9; m/z (EI) 355 (M+H⁺, 1), 255 (52), 254 (100), 228 (1), 227 (4), 189 (20), 188 (24), 170 (2), 136 (2), 121 (4), 120 (2), 88 (3), 66 (2), 57 (1).

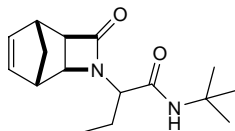
diexo-N-Cyclohexyl-2-(4-oxo-3-azatricyclo[4.2.1.0^{2,5}]non-7-en-3-yl) butyramide (2n)



This compound was obtained as colourless oil, diastereoisomeric ratio 62:38, (0.19g, 90%); (Found: C, 71.54; H, 8.69; N, 9.23. C₁₈H₂₆N₂O₂ requires C, 71.49; H, 8.67; N, 9.26%) ν_{\max} (film)/cm⁻¹ 3304, 3063, 2989, 2853, 1740, 1677, 1540, 1451, 1321; δ_H (400MHz, CDCl₃): major diastereomer: 0.94 (3H, t, *J* 7.64, CH₂CH₃), 1.07-2.05 (16H, m, 8 × CH₂), 2.90-3.01 (2H, m, CHCHCO and NHCH), 3.52-3.59 (1H, m, CHCHN), 3.67-3.79 (1H, m, NCHCO), 6.06-6.12 (1H, m, CHCH), 6.15-6.26 (1H, m, CHCH) and 6.63 (1H, d, *J* 7.22, NH); minor

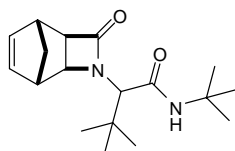
diastereomer: 0.96 (3H, t, J 7.79, CH_2CH_3), 1.07-2.05 (16H, m, $8 \times \text{CH}_2$), 3.02-3.07 (2H, m, CHCHCO and NHCH), 3.91 (2H, t, J 7.54, CHCHN) and 6.15-6.26 (2H, m, CHCH and CHCH); δ_{C} (100MHz, CDCl_3 , Me_4Si): major diastereomer: 11.3, 26.1, 33.5, 39.6, 41.6, 43.3, 56.7, 57.2, 58.2, 136.1, 139.1, 169.0 and 170.6; minor diastereomer: 11.6, 22.8, 25.4, 39.9, 41.8, 43.7, 56.4, 58.6, 61.3, 136.2, 139.1, 169.0 and 170.6; m/z (EI) 302 (M^+ , 16), 274 (8), 372 (6), 211 (4), 177 (36), 176 (62), 148 (44), 110 (16), 84 (100), 57 (2).

diexo-N-tert-Butyl-2-(4-oxo-3-azatricyclo[4.2.0.1^{2,5}]non-7-en-3-yl)-acetamide (2o)



This compound was obtained as yellow oil, diastereoisomeric ratio 60:40 (0.19g, 95%); (Found: C, 69.62; H, 8.79; N, 10.12. $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$ requires C, 69.53; H, 8.75; N, 10.14%); ν_{max} (film)/ cm^{-1} 3358, 3062, 2967, 1736, 1674, 1546, 1455, 1225; δ_{H} (400MHz, CDCl_3 , Me_4Si): major diastereomer: δ 0.93 (3H, t, J 7.55, CH_2CH_3), 1.34 (9H, s, *t*Bu), 1.59-1.69 (2H, m, CH_2CH_3), 1.69-1.85 (1H, m, CHCHCO), 1.87-2.04 (1H, m, CHCHN), 2.89-2.99 (2H, m, CHCH_2CH), 3.05-3.10 (1H, m, CHCHCO), 3.55 (1H, d, J 3.78, CHCHN), 3.88 (1H, t, J 7.54, NCHCO), 6.05-6.12 (1H, m, CHCH), 6.16 (1H, *br s*, NH) and 6.20-6.27 (1H, m, CHCH); minor diastereomer: 0.96 (3H, t, J 7.55, CH_2CH_3), 1.34 (9H, s, *t*Bu) 1.59-1.69 (2H, m, CH_2CH_3), 1.69-1.85 (1H, m, CHCHCO), 1.87-2.04 (1H, m, CHCHN), 2.89-2.99 (2H, m, CHCH_2CH), 2.97-3.02 (1H, m, CHCHCO), 3.60 (1H, d, J 3.84, CHCHN), 3.74 (1H, t, J 7.54, NCHCO), 6.05-6.12 (1H, m, CHCH), 6.20-6.27 (1H, m, CHCH) and 6.47 (1H, *br s*, NH); δ_{C} (100MHz, CDCl_3 , Me_4Si): major diastereomer: 11.0, 22.8, 29.1, 39.7, 41.7, 43.3, 51.9, 56.3, 56.5, 58.2, 136.2, 138.9, 169.7 and 170.1 ; minor diastereomer: 11.4, 24.9, 29.2, 39.4, 41.5, 43.7, 56.3, 56.9, 58.3, 60.9, 136.0, 169.7 and 170.1; m/z (EI) 277 ($\text{M}+\text{H}^+$, 1), 276 (M^+ , 1), 248 (2), 211 (4), 177 (30), 176 (55), 148 (20), 110 (100), 83 (16), 57 (11), 41 (7).

diexo-2-tert-butyl-N-tert-Butyl-2-(4-oxo-3-azatricyclo[4.2.0.1^{2,5}]non-7-ene-3-yl)-acetamide (2p)



This compound was obtained as precipitated white solid product, diastereoisomeric ratio 100:0, (0.11g, 51%), mp 200-202 °C; (Found: C, 71.25; H, 9.41; N, 9.01. $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$

requires C, 71.02; H, 9.27; N, 9.20%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3340, 3066, 2966, 1736, 1672, 1548, 1452, 1370, 1226; $\delta_{\text{H}}(400\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 1.06 (9H, s, *t*Bu), 1.34 (9H, s, *t*Bu), 1.58 (2H, 2 × d, *J* 9.60 and 20.10 CHCH₂CH), 2.91 (1H, s, CHCHCO), 3.03 (1H, d, *J* 4.03, CHCHCO), 3.25 (1H, s, CHCHN), 3.75 (1H, s, NCHCO), 3.83 (1H, d, *J* 4.03, CHCHN), 5.73 (1H, br s, NH), 6.07 (1H, 2 × d, *J* 3.02 and 5.04, CHCH), 6.22 (1H, 2 × d, *J* 3.02 and 5.04, CHCH); $\delta_{\text{C}}(100\text{MHz}, \text{CDCl}_3, \text{Me}_4\text{Si})$: 27.8, 29.1, 36.9, 39.7, 41.7, 43.6, 52.0, 57.3, 61.1, 64.0, 81.3, 136.4, 139.1, 168.2 and 171.2; *m/z* (EI) 304 (M⁺, 16), 231 (8), 204 (100), 176 (24), 138 (64), 119 (14), 83 (10), 69 (26), 57 (6), 41 (1).

X-ray Crystallographic Study: Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer using graphite-monochromatized Mo-K_α radiation ($\lambda = 0.71073 \text{ \AA}$). The data were collected by φ and ω rotation scans and processed with the DENZO-SMN v0.93.0 software package.³²

Crystal data for 2q C₂₁H₂₆N₂O₃, *M_r* = 354.44, triclinic, space group *P*-1 (no. 2), *a* = 9.4031(5), *b* = 9.3855(5), *c* = 11.0060(6) Å, $\alpha = 78.010(3)$, $\beta = 84.307(3)$, $\gamma = 82.744(3)^\circ$, *V* = 939.84(9) Å³, *T* = 173 K, *Z* = 2, $\mu(\text{Mo-K}\alpha) = 0.084 \text{ mm}^{-1}$, 3897 unique reflections (*R_{int}* = 0.0348) which were used in calculations. The final $wR(F^2)$ was 0.1110 (all data).

The structure was solved by direct methods by use of the SIR97 program³³ and full-matrix, least-squares refinements on *F*² were performed by use of the SHELXL-97 program.³⁴ The CH hydrogen atoms were included at the fixed distances with the fixed displacement parameters from their host atoms. The NH hydrogen atom was refined isotropically. The figure was drawn with ORTEP-3 for Windows.³⁵ The deposition number CCDC 625418 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].