Azabicycloalkenes as synthetic intermediates – Synthesis of azabicyclo[X.3.0]alkane scaffolds

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General Remarks: Melting points were determined in open capillaries in a Dr. Lindström instrument and are uncorrected. – ¹H-NMR and ¹³C-NMR spectra were recorded with a Bruker-Karlsruhe AMX 400 spectrometer (400 MHz / 100.6 MHz) or on a Bruker-Karlsruhe DRX 5001 spectrometer (500 MHz / 125.8 MHz). Chemical shifts, δ , are presented in part per million (ppm) and coupling constants, J , in Hertz (Hz) from tetramethylsilane (TMS, 0 ppm) as the internal standard for CDCl₃ and residual solvent peaks for other deuterated solvents. – Mass spectra were obtained with a Varian MS MAT 311A in EI mode or a VG/70-250 F (VG Analytical) instrument in FAB mode in a *p*-nitrobenzylalcohol matrix. – Elemental analyses were performed with a C, H, N-Analyser EA 1108 from Carlo Erba. – The following educts were synthesized according to literature procedures: azabicycloalkenes **11** and **13**,¹ azabicycloalkene **21**.²

¹ A. H. G. P. Prenzel, N. Deppermann, W. Maison, *Org. Lett.* **2006**, 8, 1681–1684.

² Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, 4, 3465–3468.

Azabicycloalkene **9**

The title compound was prepared according to a slightly modified known protocol for the synthesis of its methyl and ethyl ester analogs.³ A solution of 2.5 g *tert*-butyl glyoxylate (19 mmol) in 3.01 g saturated aqueous NH_4Cl (~19 mmol NH_4Cl) was treated with 3.2 g (4.0 ml) cyclopentadiene and stirred for 17 h at rt. The reaction mixture was diluted with 5 ml water and washed two times with each 10 ml diethylether. The aqueous phase was adjusted to pH~10 with saturated aqueous K_2CO_3 solution and extracted three times with each 20 ml ethyl acetate. The combined organic phases were dried over Na_2SO_4 , filtered and the solvent was removed *in vacuo* to give 2.99 g of the title compound as a yellow oil. This crude product contained impurities but was used in the next steps without further purification. R_f = 0.51 (CH_2Cl_2 / MeOH 9:1; ninhydrine); $^1\text{H-NMR}$ (500 MHz, CDCl_3 , 4:1 *endo:exo* mixture): δ 6.38-6.32 (m, 0.2 H), 6.29 (dd, 3J = 5.5 Hz, 3J = 2.0 Hz, 0.8 H), 6.27-6.23 (m, 0.2 H), 5.87 (dd, 3J = 4.7 Hz, 3J = 2.8 Hz, 0.8 H), 3.99 (bs, 1 H), 3.83 (d, 3J = 3.2 Hz, 0.8 H), 3.39 (bs, 0.8 H), 3.17 (bs, 0.2 H), 2.87-2.73 (m, 0.2 H), 1.81 (bd, 2J = 8.2 Hz, 0.2 H), 1.75 (bd, 2J = 8.2 Hz, 0.2 H), 1.62 (bd, 2J = 8.5 Hz, 0.8 H), 1.43 (s, 9 H), 1.42-1.39 (m, 0.8 H); $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz, *endo:exo*

³ (a) Kobayashi, T.; Ono, K.; Kato, H. *Bull. Chem. Soc. Jpn.* **1992**, 65, 61-65; (b) Ward, S. E.; Holmes, A. B.; McCague, R. *Chem. Comm.* **1997**, 2085-2086.

mixture): δ 136.6, 135.7, 135.1, 130.0, 81.4, 65.7, 61.3, 61.0, 58.0, 49.7, 48.3, 48.0, 46.5, 28.2.

General procedure for the acylation of azabicycloalkenes with DCC/HOBt:

In a typical experiment 1 mmol of the indicated azabicycloalkene was dissolved in 10 ml abs THF and 1.1 equivalents of the appropriate carboxylic acid, 0.23 g DCC (1.1 mmol) and 0.15 g HOBt (1.1 mmol) were added. The resulting suspension was stirred at rt for 12 h, filtered and the solvent was removed *in vacuo*. The residue was dissolved in 50 ml EtOAc and washed two times with each 20 ml aqueous saturated NaHCO₃ and three times with each 20 ml aqueous saturated KHSO₄. The organic phase was dried over NaSO₄ and the solvent was removed *in vacuo*. This crude product was purified by column chromatography on silica gel with a PE/EtOAc gradient.

Bisolefines *endo*-**10** and *exo*-**10**

According to the general procedure for the acylation of azabicycloalkenes with DCC/HOBt, 3.0 g azabicycloalkene **9** (15.4 mmol) and 1.45 g vinylacetic acid (16.9 mmol) were converted to 0.73 g of bisolefine *exo*-**10** as a yellow oil (18 %) and 1.90 g of bisolefine *endo*-**10** as a yellow oil (47 %).

exo-**10**: R_f = 0.55 (PE / EtOAc 1:1; cerammonium molybdate stain); ¹H-NMR (500 MHz, CDCl₃, 7:3 rotameric mixture): δ 6.54-6.51 (m, 0.3 H), 6.44-6.40 (m, 0.7 H), 6.39-6.35 (m, 1 H), 5.99-5.83 (m, 1 H), 5.23-5.15 (m, 1.4 H), 5.14 (bs, 0.3 H), 5.11 (bd, ³ J = 10.1 Hz, 0.3 H), 5.03 (bd, ³ J = 17.0 Hz, 0.3 H), 4.66 (s, 0.7 H), 3.57 (s, 0.7 H), 3.47 (s, 0.3 H), 3.37 (bs, 0.3 H), 3.27 (bs, 0.7 H), 3.20 (bdd, ² J = 15.8 Hz, ³ J = 6.3 Hz, 0.7 H), 3.08 (bdd, ² J = 15.8 Hz, ³ J = 6.3 Hz, 0.7 H), 2.95 (m, 0.3 H), 2.79 (m, 0.3 H), 2.14 (bd, ² J = 8.5 Hz, 0.7 H), 1.90 (bd, ² J = 8.5 Hz, 0.3 H), 1.57 (bd, ² J = 8.5 Hz, 0.7 H), 1.51-1.45 (m, 0.3 H), 1.50 (s, 2.7 H), 1.47 (s, 6.3 H); ¹³C-NMR (CDCl₃, 125.8 MHz, mixture of rotamers): δ 170.7, 170.4, 170.0, 169.5, 138.4, 138.1, 137.0, 135.5, 131.5, 131.2, 118.0, 118.0, 82.5, 81.6, 62.3, 60.4, 59.9, 59.0, 49.8, 47.7, 46.0, 44.3, 40.4, 39.8, 28.2; HRMS (FAB): calcd. for C₁₅H₂₂NO₃ (MH⁺): 264.1600; found: 264.1586.

endo-10: R_f = 0.34 (PE / EtOAc 1:1; cerammonium molybdate stain); $^1\text{H-NMR}$ (500 MHz, CDCl_3 , 6:4 rotameric mixture): δ 6.46 (dd, $^3J = 2.5$ Hz, $^3J = 5.4$ Hz, 0.4 H), 6.42 (dd, $^3J = 2.5$ Hz, $^3J = 5.4$ Hz, 0.6 H), 6.14 (dd, $^3J = 2.5$ Hz, $^3J = 5.4$ Hz, 0.6 H), 6.11 (dd, $^3J = 2.5$ Hz, $^3J = 5.4$ Hz, 0.4 H), 5.98-5.87 (m, 1 H), 5.29 (bs, 0.4 H), 5.20-5.12 (m, 1.2 H), 5.10 (dd, $^2J = 1.6$ Hz, $^3J = 10.4$ Hz, 0.4 H), 5.05 (dd, $^2J = 1.6$ Hz, $^3J = 17.3$ Hz, 0.4 H), 4.64 (bs, 0.6 H), 4.31 (d, $^3J = 3.5$ Hz, 0.6 H), 4.30 (d, $^3J = 3.5$ Hz, 0.4 H), 3.55 (bs, 0.4 H), 3.43 (bs, 0.6 H), 3.14-3.10 (m, 1.2 H) 2.94 (dddd, $^2J = 15.8$ Hz, $^3J = 1.6$ Hz, $^3J = 5.7$ Hz, 0.4 H), 2.82 (bdd, $^2J = 15.8$ Hz, $^3J = 7.6$ Hz, 0.4 H), 1.71 (bd, $^2J = 8.2$ Hz, 0.6 H), 1.65-1.61 (m, 1.0 H), 1.54 (bd, $^2J = 8.2$ Hz, 0.4 H), 1.42 (s, 3.6 H), 1.40 (s, 5.4 H); $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz, mixture of rotamers): δ 169.5, 169.3, 168.3, 167.7, 136.4, 135.5, 134.7, 134.5, 131.7, 131.5, 118.0, 117.8, 82.2, 81.2, 63.4, 61.0, 58.9, 58.1, 50.0, 49.1, 49.0, 46.7, 41.1, 40.1, 28.1, 28.0; HRMS (FAB): calcd. for $\text{C}_{15}\text{H}_{22}\text{NO}_3$ (MH^+): 264.1600; found: 236.1584.

Bisolefine-12

A solution of 0.87 g (S)-vinylglycine (3.74 mmol) in 50 ml abs THF was treated at 0°C with 0.29 g pyridine (3.74 mmol) and 0.51 mg isobutyl chloroformate (3.74 mmol). The reaction mixture was stirred for 15 min at rt under nitrogen. Azabicycloalkene **11** (0.73 g, 3.74 mmol) was added and the solution was stirred for 12 h under nitrogen. The solvent was removed *in vacuo* and the resulting residue was purified by column chromatography on silica (PE / EtOAc, 2:1) to give the title compound as a yellow oil in 0.77 g (50 %) yield; R_f = 0.22 (PE / EtOAc 2:1; cerammonium molybdate stain); $^1\text{H-NMR}$ (500 MHz, CDCl_3 , 4:1 rotameric mixture): δ 7.27-7.33 (m, 5 H), 6.51-6.57 (m, 0.2 H), 6.40-6.46 (m, 0.8 H), 6.36-6.40 (m, 0.2 H), 6.29-6.35 (m, 0.8 H), 6.06 (d, 0.8 H, $^3J = 6.9$ Hz), 5.82-5.94 (m, 0.2 H), 5.72 (ddd, 0.8 H, $^3J_{\text{trans}} = 17.3$ Hz, $^3J_{\text{cis}} = 10.1$ Hz, $^3J = 7.3$ Hz), 5.58 (d, 0.2 H, $^3J = 7.9$ Hz), 5.41 (d, 0.8 H, $^3J_{\text{trans}} = 17.3$ Hz), 5.33-5.36 (m, 0.2 H), 5.30 (d, 0.8 H, $^3J_{\text{cis}} = 10.1$ Hz), 5.25 (d, 0.2 H, $^3J_{\text{cis}} = 10.4$ Hz), 5.02-5.18 (m, 3 H, Cbz- CH_2 -), 4.81 (br s, 0.8 H), 4.58-4.63 (m, 0.2 H), 3.86 (br s, 0.2 H), 3.54 (br s, 0.8 H), 3.40 (br s, 0.2 H), 3.26 (br s, 0.8 H), 2.16 (d, 0.8 H, $^2J = 8.5$ Hz), 1.94 (d, 0.2 H, $^2J = 9.1$ Hz), 1.61 (d, 0.8 H, $^2J = 8.5$ Hz), 1.40-1.53 (m, 9.2 H); $^{13}\text{C-NMR}$ (CDCl_3 , 100.6 MHz, mixture of rotamers): δ 169.6, 167.2, 155.7, 138.8, 138.3, 137.6, 136.8, 136.2, 134.0, 133.29 (C-10), 128.9, 128.9, 128.6, 128.5, 128.4, 128.4, 119.6, 118.2, 82.9, 82.2, 67.3, 67.2, 62.7, 61.6, 60.3, 59.4, 56.2,

55.9, 50.0, 47.6, 46.2, 44.4, 28.4, 28.3; HRMS (FAB): calcd. for $C_{15}H_{22}NO_3$ (MH^+): 264.1600; found: 264.1590.

Bisolefine-14

A solution of 579 mg (2.69 mmol) *rac*-allylglycine and 242 mg (1.79 mmol) HOBt in 5 ml dry DMF was added to a solution of 283 mg (0.26 mmol) of 2-azabicycloalkene **13** in 10 ml DMF. After cooling to 0 °C 555 mg (2.69 mmol) DCC was added and the reaction was stirred under a nitrogen atmosphere at room temperature for 16 h. The solid precipitate was filtered off and the solvent was removed *in vacuo*. The residue was dissolved in 20 ml ethyl acetate and washed with each 10 ml saturated aqueous $KHSO_4$ - $NaHCO_3$ - and brine. The organic layer was dried over $NaSO_4$, filtered and the solvent was removed *in vacuo*. The product was purified by column chromatography using PE / EtOAc 2:1 as eluent. Drying *in vacuo* gave 366 mg bisolefine **14** as a colourless wax (59 %). R_f = 0.4 (PE / EtOAc 2:1; Mo/Ce); 1H -NMR (500 MHz, $CDCl_3$, mixture of two diastereoisomers, some signals are broadened or doubled due to rotational isomerism): δ 6.35 – 6.53 (m, 2H), 5.79 – 5.91 (m, 0.3H), 5.60 – 5.77 (m, 1.1H), 5.27 (d, 0.35H, J = 8.8 Hz), 5.01 – 5.19 (m, 2.5H), 4.81 (br s, 0.35H), 4.58 – 4.64 (m, 0.4H), 4.50 – 4.57 (m, 0.35H), 4.33 – 4.39 (m, 0.13H), 4.16 – 4.26 (m, 2H), 4.13 (br s, 0.25H), 3.92 – 3.97 (m, 0.12H), 3.70 (br s, 0.35H), 3.61 (br s, 0.25H), 3.46 (br s, 0.25H), 3.32 (br s, 0.35H), 3.28 (br s, 0.4H), 2.39 – 2.56 (m, 1.3H), 2.23 – 2.35 (0.7H), 2.14 (d, 0.4H, J = 8.5 Hz), 2.07 (d, 0.35H, J = 8.5 Hz), 1.80 – 1.92 (m, 0.4H), 1.60-1.65 (m, 0.4H), 1.41 (s, 4.8H), 1.40 (s, 3H), 1.35 (s, 1.2H), 1.32–1.22 (m, 3H); ^{13}C -NMR (100.6 MHz, $CDCl_3$, mixture of two diastereoisomers, some signals are broadened or doubled due to rotational isomerism): δ 170.7, 169.4, 139.1, 138.4, 138.1, 137.5, 136.3, 136.3, 134.0, 133.1, 132.9, 119.4, 119.2, 119.0, 118.4, 80.1, 62.9, 62.6, 62.2, 61.8, 59.7, 58.7, 58.6, 53.1, 52.0, 51.8, 49.8, 47.8, 47.7, 46.7, 46.2, 44.8, 38.4, 37.9, 37.1, 36.9, 34.1, 28.7, 28.6, 14.6; HRMS (FAB): calcd. for $C_{19}H_{29}N_2O_5$ (MH^+): 365.2076; found: 365.2078; Anal. calcd. for $C_{19}H_{28}N_2O_5$: C, 65.61; H, 7.29; N, 6.29; found: C, 65.50; H, 7.37; N, 6.27.

• **General procedure for tandem metatheses under an ethylene atmosphere:**

In a typical experiment a 0.01 molar solution of the indicated bisolefine was dissolved in abs CH₂Cl₂ and the indicated quantity of ruthenium catalyst was added under nitrogen. The reaction vessel was evacuated, flushed with ethylene and stirred at the indicated temperature for 12 h. After removal of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel.

• **Azabicycloalkane **15****

According to the general procedure for tandem metathesis of azabicycloalkenes under an ethylene atmosphere, 88 mg bisolefine **endo-10** (0.33 mmol) and 28 mg ruthenium catalyst **7** (33 μmol, 10 mol %) were heated to reflux. This gave 63 mg of azabicycloalkane **15** along with ~5 % pyridone **16** as a yellow oil (73 % overall yield).

Azabicycloalkane **15**: *R*_f = 0.19 (PE / EtOAc 1:1; KMnO₄); ¹H-NMR (500 MHz, CDCl₃): δ 5.95-5.82 (m, 2 H), 5.81-5.73 (m, 1 H), 5.21 (ddd, ³*J* = 17.0 Hz, ³*J* = 1.3 Hz, ²*J* = 1.3 Hz, 1 H), 5.15 (ddd, ³*J* = 10.4 Hz, ³*J* = 1.3 Hz, ²*J* = 1.3 Hz, 1 H), 4.34 (d, ³*J* = 9.1 Hz, 1 H), 4.29-4.22 (m, 1 H), 3.10-3.02 (m, 1 H), 2.96-2.92 (m, 2 H), 2.15-2.09 (m, 1 H), 1.98 (ddd, ²*J* = 12.0 Hz, ³*J* = 12.0 Hz, 1 H), 1.42 (s, 9 H); ¹³C-NMR (100.6 MHz, CDCl₃): δ 169.1, 167.5, 134.3, 126.0, 123.6, 117.9, 81.9, 62.4, 58.8, 44.0, 35.1, 33.3, 28.2.

Pyridone **16**: *R*_f = 0.13 (PE / EtOAc 1:1; KMnO₄); ¹H-NMR (500 MHz, CDCl₃): δ 7.32 (dd, ³*J* = 6.6 Hz, ³*J* = 9.2 Hz, 1 H), 6.38 (d, ³*J* = 9.2 Hz, 1 H), 6.09 (d, ³*J* = 6.6 Hz, 1

H), 5.90-5.82 (m, 1 H), 5.27-5.24 (m, 2 H), 5.04 (d, $^3J = 8.8$ Hz, 1 H), 3.42-3.34 (m, 1 H), 3.18 (dd, $^2J = 16.1$ Hz, $^3J = 11.4$ Hz, 1 H), 3.08 (dd, $^2J = 16.1$ Hz, $^3J = 8.0$ Hz, 1 H), 1.45 (s, 9 H); ^{13}C -NMR (100.6 MHz, CDCl_3): δ 150.1, 140.8, 133.5, 118.9, 117.7, 101.1, 83.1, 65.0, 42.8, 35.7, 28.2 (carbonyl carbons not detectable).

Azabicycloalkane **17**

According to the general procedure for tandem metathesis of azabicycloalkenes under an ethylene atmosphere, 107 mg bisolefine **exo-10** (0.41 mmol) and 35 mg ruthenium catalyst **7** (41 μmol , 10 mol %) were heated to reflux. This gave 76 mg of azabicycloalkane **17** (70 %) as a yellow oil; $R_f = 0.31$ (PE / EtOAc 1:1; KMnO_4); ^1H -NMR (500 MHz, CDCl_3): δ 5.87-5.77 (m, 3 H, 8-H, 7-H und 13-H), 5.17 (bd, $^3J = 17.0$ Hz, 1 H, 14-Hb), 5.12 (bd, $^3J = 10.1$ Hz, 1 H, 14-Ha), 4.40-4.33 (m, 1 H, 8a-H), 4.20 (d, $^3J = 8.5$ Hz, 1 H, 3-H), 3.07-2.99 (m, 1 H, 6-H), 2.94-2.86 (m, 1 H, 6-H), 2.85-2.77 (m, 1 H, 2-H), 2.28-2.23 (m, 1 H, 1-Hb), 1.55-1.48 (m, 1 H, 1-Ha), 1.47 (s, 9 H, 12-H); ^{13}C -NMR (100.6 MHz, CDCl_3): δ 171.0, 166.4, 137.4, 124.7, 123.2, 116.8, 81.8, 63.1, 59.3, 46.3, 38.7, 32.6, 28.2; MS (EI): $m/z = 207$ ($[\text{M} + \text{H} - \text{C}_4\text{H}_9]^+$), 162 ($[\text{M} - \text{C}_4\text{H}_9 - \text{CO}_2]^+$); HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{22}\text{NO}_3$ (MH^+): 264.1600; found: 264.1583.

Dipeptide mimetic **19**

According to the general procedure for tandem metathesis of azabicycloalkenes under an ethylene atmosphere, 50 mg bisolefine **12** (0.12 mmol) and 10 mg ruthenium catalyst **7** (12 μmol , 10 mol %) were heated to reflux. This gave 29 mg of

azabicycloalkane **19** (59 %) as a yellow oil; R_f = 0.54 (PE / EtOAc 1:1; KMnO₄); ¹H-NMR (500 MHz, CDCl₃): δ 7.28-7.40 (m, 5 H), 6.02 (d, 1 H, ³*J* = 7.5 Hz), 5.87-5.94 (m, 0.8 H), 5.74-5.86 (m, 1.6 H), 5.51-5.56 (m, 0.2 H), 5.38-5.44 (m, 0.2 H), 5.27-5.32 (m, 0.2 H), 5.05-5.22 (m, 4.2 H), 5.00 (t, 0.2 H, ³*J* = 7.6 Hz), 4.65-4.77 (m, 1 H), 4.35-4.47 (m, 0.8 H), 4.16-4.23 (m, 0.2 H), 4.12 (d, 0.8 H, ³*J* = 9.2 Hz), 3.02-3.10 (m, 0.2 H), 2.84-2.94 (m, 0.8 H), 2.24-2.43 (m, 0.8 H), 1.55-1.72 (m, 1.2 H), 1.40-1.52 (m, 9 H); ¹³C-NMR (100.6 MHz, CDCl₃): δ 172.4, 136.5, 128.8, 128.7, 128.6, 128.6, 128.2, 128.2, 126.4, 125.5, 117.4, 82.2, 67.1, 63.5, 59.9, 58.8, 46.9, 37.8, 28.2, 28.1; HRMS (ESI): calcd. for C₂₃H₂₉N₂O₅ (MH⁺): 413.2076; found: 413.2068.

Dipeptide mimetic 20

To a solution of 250 mg (0.69 mmol) of bisolefine **14** in 30 ml abs CH₂Cl₂ 60 mg (0.07 mmol) of ruthenium catalyst **7** were added and the reaction mixture was stirred for 20 h at 50 °C under an atmosphere of ethylene. After the solvent was removed *in vacuo*, the product was purified by column chromatography using PE / EtOAc 2:1 as eluent. Drying *in vacuo* yielded 142 mg of a colourless wax (57 %). R_f = 0.6 (PE / EtOAc 1:1; Mo/Ce); ¹H-NMR (500 MHz, CDCl₃, two diastereoisomers): δ 5.65 – 5.82 (m, 3H), 5.49 – 5.53 (m, 1H), 5.09 – 5.19 (m, 2H), 4.78 (br s, 1H), 4.65 – 4.71 (m, 1H), 4.19 – 4.25 (m, 3.2H), 3.01 – 3.06 (m, 0.05H), 2.81 – 2.89 (m, 0.95H), 2.62 – 2.68 (m, 1H), 2.47 – 2.54 (m, 1H), 2.17 – 2.26 (m, 1H), 1.80 – 1.87 (m, 0.1H), 1.71 – 1.79 (m, 1H), 1.43 (s, 9H), 1.27 (t, 3H, *J* = 7.3 Hz); ¹³C-NMR (101 MHz, CDCl₃, two diastereoisomers): δ 136.5, 129.2, 128.8, 127.5, 126.4, 117.3, 79.7, 65.9, 61.4, 56.5, 51.3, 45.3, 40.2, 32.7, 28.5, 14.4 (carbonyl carbons not detectable); HRMS (FAB): calcd. for C₁₉H₂₉N₂O₅ (MH⁺): 365.2076; found: 365.2069.

Bisolefine **22**

Deprotection of azabicycloalkene **21** was performed as described in the literature.⁴ According to the general procedure for acylation of azabicycloalkenes with DCC/HOBt, 0.43 g of the resulting deprotected azabicycloalkene (3 mmol) and 0.28 g (0.28 ml) vinylacetic acid (3.3 mmol) were converted to 0.51 g of bisolefine **22** (72 %) as a colourless oil; R_f = 0.29 (PE / EtOAc 3:1; KMnO₄); ¹H-NMR (500 MHz, CDCl₃): δ 7.31-7.27 (m, 1 H), 7.25-7.22 (m, 1 H), 7.07-7.05 (m, 1 H), 6.99-6.95 (m, 3 H), 5.90 (bs, 1 H), 5.89-5.78 (m, 1 H), 5.56 (bs, 1 H), 5.16-5.07 (m, 2 H), 3.08-2.97 (m, 2 H); ¹³C-NMR (100.6 MHz, CDCl₃): δ 166.7, 148.3, 148.1, 144.4, 142.4, 130.7, 125.4, 125.2, 121.5, 120.5, 118.5, 65.7, 63.5, 39.4; HRMS (FAB): calcd. for C₁₄H₁₄NO (MH⁺): 212.1075; found: 212.1084.

Pyridones **23** and **24**

According to the general procedure for tandem metathesis of azabicycloalkenes under an ethylene atmosphere 78 mg bisolefine **22** (0.37 mmol) and 36 mg ruthenium catalyst **7** (0.42 mmol, 10 mol %) were heated to reflux. This gave overall 11 mg of azabicycloalkane **24** (10 %). The two isomers of **24** were separated to give 7 mg of *Z*-**24** (7 %, yellow oil) and 3 mg of *E*-**24** (3 %, yellow oil). In addition 19 mg (25 %) pyridone **23** as a yellow oil.

⁴ Carpino, L. A.; Barr, D. E. *J. Org. Chem.* **1966**, *31*, 764–767.

Pyridone **Z-24**: R_f = 0.38 (PE / EtOAc 1:1; KMnO_4); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.79 (d, 3J = 7.6 Hz, 2 H), 7.67-7.72 (m, 1 H), 7.50 (dd, 3J = 9.1 Hz, 3J = 6.9 Hz, 1 H), 7.40-7.46 (m, 4 H), 7.34-7.37 (m, 1 H), 7.30 (t, 3J = 7.4 Hz, 1 H), 6.91 (d, 3J = 11.4 Hz, 1 H), 6.67 (d, 3J = 6.9 Hz, 1 H, 1-H), 6.48-6.55 (m, 2 H, 3-H, 6-H), 5.36 (dd, 3J = 11.4 Hz, 3J = 9.7 Hz, 1 H); $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3): δ 161.0, 146.8, 140.6, 138.9, 132.3, 131.8, 131.0, 129.5, 128.0, 127.8, 127.6, 126.3, 126.1, 123.0, 120.1, 117.7, 97.3, 62.0; MS (FAB): 286.1 ($\text{M} + \text{H}^+$).

Pyridone **E-24**: R_f = 0.31 (PE / EtOAc 1:1; KMnO_4); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.74-7.78 (m, 1 H), 7.49-7.55 (m, 4 H), 7.36 (d, 3J = 6.9 Hz, 2 H), 7.24-7.29 (m, 2 H), 7.19-7.23 (m, 1 H), 6.83 (d, 3J = 15.8 Hz, 1 H), 6.71 (d, 3J = 6.6 Hz, 1 H), 6.52 (d, 3J = 9.1 Hz, 1 H), 6.30 (dd, 3J = 15.8 Hz, 3J = 7.6 Hz, 1 H), 6.11 (d, 3J = 7.6 Hz, 1 H); $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3): δ 161.9, 147.4, 141.1, 139.9, 136.2, 134.2, 133.4, 130.4, 128.9, 128.4, 128.0, 127.1, 124.3, 123.8, 121.3, 118.9, 98.3, 66.5; MS (FAB): 286.1 ($\text{M} + \text{H}^+$).

Pyridone **23**: R_f = 0.28 (PE / EtOAc 1:2; KMnO_4); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.71-7.74 (m, 1 H), 7.47-7.53 (m, 4 H), 6.68 (d, 3J = 6.9 Hz, 1 H), 6.48-6.55 (d, 3J = 9.1 Hz, 1 H), 5.91-5.99 (m, 2 H), 5.52 (bd, 3J = 16.1 Hz, 1 H), 5.39 (bd, 3J = 10.1 Hz, 1 H); $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3): δ 160.9, 146.8, 139.9, 138.9, 131.9, 131.9, 129.4, 127.8, 123.1, 120.2, 118.0, 117.9, 97.3, 65.9; MS (FAB): 210.0 ($\text{M} + \text{H}^+$).

Bisolefine 25

The title compound was prepared according to a protocol from Lautens and coworkers² from Boc-protected azabicycloalkene **21** to give 0.11 g of bisolefine **25** (68 %) as a colourless oil; R_f = 0.46 (PE / EtOAc 3:1; KMnO_4); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.31-7.27 (m, 1 H), 7.26-7.22 (m, 1 H), 7.08-7.05 (m, 1 H), 6.99-6.94 (m, 3 H), 5.90 (bs, 1 H), 5.85-5.73 (m, 1 H), 5.55 (bs, 1 H), 4.99 (dd, 3J = 16.8 Hz, 2J = 1.5 Hz, 1 H), 4.95 (dd, 3J = 9.9 Hz, 2J = 1.5 Hz, 1 H), 2.33-2.25 (m, 4 H); $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3): δ 168.7, 148.4, 148.2, 144.5, 142.4, 137.3, 125.4, 125.1, 121.5, 120.4, 115.4, 65.7, 63.5, 33.3, 28.7; HRMS (FAB): calcd. for $\text{C}_{15}\text{H}_{16}\text{NO}$ (MH^+): 226.1232; found: 226.1225.

Lactam **26**

To a solution of 200 mg (0.888 mmol) *Bisolefine* **25** in 90 ml abs. dichloromethane 83 mg (0.098 mmol) Grubbs 2 catalyst **7** was added and the reaction was stirred under a ethylene atmosphere at room temperature for 48 h. The solvent was removed and the residue was dissolved in 100 ml methanol. To this solution 10 % palladium on charcoal was added and the reaction was stirred under a hydrogen atmosphere at room temperature for 48 h. After filtration over celite, the solvent was removed *in vacuo*. The product was purified by column chromatography using PE / EtOAc 3:1 → PE / EtOAc 2:1 as eluent. Drying *in vacuo* yielded 120 mg of a yellow solid (59 %). R_f = 0.40 (PE / EtOAc 1:2; UV); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 7.27 – 7.32 (m, 2H), 7.20 – 7.25 (m, 1H), 7.16 – 7.19 (m, 1H), 5.29 (dd, 1H, J = 5.7 Hz, J = 2.7 Hz), 4.94 (d, 1H, J = 10.7 Hz), 2.64 (dd, 1H, J = 14.5 Hz, J = 7.1 Hz), 2.49 – 2.58 (m, 1H), 2.16 – 2.26 (m, 2H), 2.08– 2.16 (m, 1H), 1.91– 2.00 (m, 1H), 1.72 – 1.79 (m, 1H), 1.60 – 1.72 (m, 1H), 0.74 (t, 3H, J = 7.5 Hz); $^{13}\text{C-NMR}$ (101 MHz, CDCl_3): δ 174.9, 140.9, 139.6, 128.0, 127.7, 122.7, 122.4, 65.1, 64.2, 38.8, 36.4, 30.2, 26.9, 23.8, 9.1; HRMS (FAB): calcd. for $\text{C}_{15}\text{H}_{20}\text{NO}$ (MH^+): 230.1545; found: 230.1544.

R	[Ru], mol %	isoindole, [%]	29 [%]
CO_2Me	7 , 5	27 , 61	12
CO_2Me	8 , 3	27 , 62	9
SiMe_3	8 , 7	28 , 98	0
SiMe_3	7 , 3	28 , 100	0
SiMe_3	8 , 3	28 , 97	0
SiMe_3	8 , 1	28 , 73	0

General procedure for ROCM:

In a typical experiment a 0.01 molar solution of azabicycloalkene **21** was dissolved in abs CH_2Cl_2 and the indicated quantity of a cross metathesis reaction partner and

ruthenium catalyst were added under nitrogen. The reaction was stirred at rt for 12 h. After removal of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel.

Isoindole 27

According to the general procedure for ROCM of azabicycloalkenes 200 mg azabicycloalkene **21** (0.82 mmol), 164 mg (0.17 ml) methylbutenoat (1.64 mmol) and 16 mg ruthenium catalyst **8** (21 μ mol, 3 mol %) were converted to overall 175 mg of isoindole **27** (62 %). The *E*- and *Z*-isomers of **27** were separated with column chromatography but could not be assigned unambiguously to two fractions of 110 mg (fast eluting, colourless oil) and 65 mg (slow eluting, colourless oil) due to substantial line broadening (equilibrating rotamers of the carbamate). In addition, isoindole **29** was isolated in 26 mg (12 %) yield and educt **21** reisolated in 44 mg (22 %) yield.

Fast-27: R_f = 0.41 (PE / EtOAc 9:1; KMnO₄); ¹H-NMR (400 MHz, CDCl₃, extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ 7.23-7.19 (m, 2 H), 7.17-7.06 (bm, 2 H), 5.87-5.60 (bm, 3 H), 5.44-5.04 (bm, 4 H), 3.69 (s, 3 H), 3.65-3.20 (bm, 2 H), 1.40 (s, 9 H); ¹³C-NMR (100.6 MHz, CDCl₃, extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ 172.9, 154.6, 139.3, 128.2, 128.0, 123.5, 123.4, 115.4, 80.3, 66.4, 60.5, 52.1, 33.2, 28.6; HRMS (FAB): calcd. for C₂₀H₂₆NO₄ (MH⁺): 344.1862; found: 344.1864.

Slow-27: R_f = 0.35 (PE / EtOAc 9:1; KMnO₄); ¹H-NMR (500 MHz, CDCl₃, extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ 7.23-7.19 (m, 2 H), 7.17-7.05 (bm, 2 H), 5.89-5.68 (bm, 2 H), 5.61-5.16 (bm, 4 H), 5.10-5.07 (bm, 1 H), 3.61 (s, 3 H), 3.12-2.96 (bm, 2 H), 1.41 (s, 9 H); ¹³C-NMR (100.6 MHz, CDCl₃, extreme line broadening was observed due to slow rotation of the carbamate C-N-bond, chemical shifts were therefore extracted from HMBC and HMQC spectra): δ 171.9, 139.2, 135.4, 134.8, 127.8, 123.5, 123.3, 115.4, 79.9, 51.7, 37.4, 28.4; HRMS (FAB): calcd. for C₂₀H₂₆NO₄ (MH⁺): 344.1862; found: 344.1870.

Isoindole **29**: R_f = 0.82 (PE / EtOAc 9:1; KMnO₄); ¹H-NMR (400 MHz, CDCl₃, extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ

7.23-7.19 (m, 2 H), 7.12-7.07 (bm, 2 H), 5.84-5.69 (bm, 2 H), 5.40-5.21 (bm, 4 H), 5.09-5.07 (m, 2 H), 1.41 (s, 9 H); ^{13}C -NMR (100.6 MHz, CDCl_3 , extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ 154.7, 139.2, 128.0, 127.7, 123.5, 115.6, 80.1, 66.3, 28.6; HRMS (FAB): calcd. for $\text{C}_{17}\text{H}_{22}\text{NO}_2$ (MH^+): 272.1651; found: 272.1648.

Isoindole 28

According to the general procedure for ROCM of azabicycloalkenes, 200 mg azabicycloalkene **21** (0.82 mmol), 113 mg (0.16 ml) allyltrimethylsilan (0.99 mmol) and 21 mg ruthenium catalyst **7** (21 μmol , 3 mol %) were converted to 290 mg of isoindole **28** (quant.). Isoindole **28** was isolated as a mixture of two isomers, most likely due to *E*- and *Z*-configuration at the olefine. However, the isomers could not be assigned due to substantial line broadening (equilibrating rotamers of the carbamate); R_f = 0.44 (PE / EtOAc 9:1; KMnO_4); ^1H -NMR (500 MHz, CDCl_3 , extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ 7.14-7.12 (m, 2 H), 7.07-6.99 (bm, 2 H), 5.79-5.56 (bm, 2 H), 5.49-5.38 (bm, 0.5 H), 5.32-4.97 (m, 4.5 H), 2.08-1.96 (bm, 0.5 H), 1.62-1.53 (bm, 0.5 H), 1.35 (brs, 10 H), 0.00 (s, 4.5 H), 0.12 (s, 4.5 H); ^{13}C -NMR (100.6 MHz, CDCl_3 , extreme line broadening was observed due to slow rotation of the carbamate C-N-bond): δ 154.7, 140.7, 139.5, 127.9, 127.8, 127.6, 123.5, 123.4, 123.3, 123.3, 115.2, 79.7, 66.2, 66.1, 28.8, 28.6, 22.7, 18.7, -1.3, -1.8; HRMS (FAB): calcd. for $\text{C}_{21}\text{H}_{32}\text{NO}_2\text{Si}$ (MH^+): 358.2202; found: 358.2205.

Azabicycloalken 9

Azabicycloalken 9

Bisolefin exo-10

Current DRX500 Data

DU
NAME 0529jun
EXPNO 136
PROCNO 1

F2 - Acquisition Parameters

Date_ 20050629
Time 22.16
INSTRUM drx500
PROBHD 5 mm 1H/13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 640
DS 2
SWH 39682.539 Hz
FIDRES 0.605507 Hz
AQ 0.6258036 sec
RG 11585.2
DW 12.600 usec
DE 6.00 usec
TE 300.0 K
d11 0.03000000 sec
d12 0.00002000 sec
PL13 20.00 dB
D1 1.00000000 sec
CPDPRG2 waltz16
PCPD2 100.00 usec
SFO2 500.1320005 MHz
NUC2 1H
PL2 0.00 dB
PL12 20.00 dB
P1 10.50 usec
SFO1 125.7736214 MHz
NUC1 13C
PL1 -2.00 dB

F2 - Processing parameters

SI 32768
SF 125.7577390 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters

CX 20.00 cm
F1P 215.000 ppm
F1 27037.92 Hz
F2P -5.000 ppm
F2 -628.79 Hz
PPMCM 11.00000 ppm/cm
HZCM 1383.33508 Hz/cm

Bisolefin endo-10

Bisolefin endo-10

Bisolefin 12

Bisolefin 12

Bisolefin 14

Bisolefin 14

15 + 16

15 + 16

Azabicycloalkane 17

Azabicycloalkane 17

Dipeptide mimetic 19

Dipeptide mimetic 19

Dipeptide mimetic 20

Dipeptide mimetic 20

Bisolefin 22

Bisolefin 22

Pyridone Z-24

Pyridone E-24

Integral

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

(ppm)

7.7801
7.7403
7.5500
7.4907
7.3621
7.3483
7.2903
7.2606
7.2398
7.2304
7.1900
6.8433
6.8118
6.7135
6.7002
6.5332
6.5149
6.3214
6.3063
6.2899
6.2747
6.1171
6.1020

4.1271
4.1126

2.1685

1.2570

0.9274
0.9141
0.8977

Pyridone E-24

Bisolefin 25

Bisolefin 25

Lactam 26

Lactam 26

— 174.8498

— 140.9166
— 139.5896

— 127.9727
— 127.6618
— 122.7102
— 122.4448

— 77.4785
— 77.1600
— 76.8415

— 65.0578
— 64.2161

— 38.8287
— 36.3795

— 30.2222
— 26.3928
— 23.8071

— 9.0964

(ppm)

fast-27

fast-27

slow 27

slow-27

slow-27

(ppm)

isoindole 28

isoindole 28

Isoindole 29

Isoindole 29