

## Supporting Information

### Synthetic Studies towards Marmycins A and B: development of the vinylogous Aldol – aza-Michael domino reaction

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#### General Remarks.

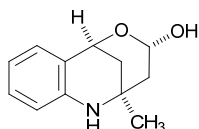
<sup>1</sup>H NMR spectra were recorded on a *Bruker* AM 400 (400 MHz) spectrometer as solutions in CDCl<sub>3</sub> or Acetone-*d*<sub>6</sub>. Chemical shifts are expressed in parts per million (ppm,  $\delta$ ) downfield from tetramethylsilane (TMS,  $\delta = 0$ ) and are referenced to residual undeuterated chloroform (7.26 ppm) or acetone (2.05 ppm) as internal standard. All coupling constants are absolute values and *J* values are expressed in Hertz (Hz). The description of signals include: s = singlet, bs = broad singlet, d = doublet, m = multiplet, dd = doublet of doublets. The spectra were analyzed according to first order. – <sup>13</sup>C NMR spectra were recorded on a *Bruker* AM 400 (100 MHz) spectrometer as solutions in CDCl<sub>3</sub>, or acetone-*d*<sub>6</sub>. Chemical shifts are expressed in parts per million (ppm,  $\delta$ ) downfield from tetramethylsilane (TMS,  $\delta = 0$ ) and are referenced to residual undeuterated chloroform (77.0 ppm) or acetone (29.8 ppm) as internal standard. The signal structure was analyzed by DEPT90 and DEPT135 spectra and is described as follows: + = primary or tertiary C-atom (positive signal), – = secondary C-atom (negative signal) and C<sub>quart.</sub> = quaternary C-atom (no signal). – MS (EI, electron impact mass spectrometry) and HRMS spectra were recorded with a *Finnigan* MAT 90 spectrometer. The molecular fragments are quoted as the relation between mass and charge (*m/z*), the intensities as a percentage value relative to the intensity of the base signal (100%). The molecular ion obtains the abbreviation [M<sup>+</sup>]. – Analytical thin layer chromatography (TLC) was carried out on *Merck* silica gel coated aluminum plates (silica gel 60, F<sub>254</sub>), detected under UV-light at 254 nm. Solvent mixtures are understood as volume/volume. – Solvents, reagents and chemicals were purchased from *Acros*, *ABCR*, *Alfa Aesar* or *Sigma-Aldrich*. Dry THF was

distilled from sodium using benzophenone as indicator. All other solvents, reagents and chemicals were used as purchased. All reactions involving moisture sensitive reactants were executed under an argon atmosphere using oven dried glassware.

*General Procedure for the vinylogous aldol – aza-Michael domino reaction:*

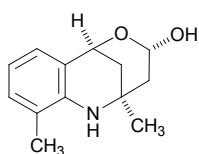
A solution of the 2-aminobenzaldehyde (1.00 mmol), prenal (2.00 mmol, 2.0 eq.) and *i*Pr<sub>2</sub>NH (0.50 mmol, 0.5 eq.) in dioxane/H<sub>2</sub>O (3:1, 1 mL) was stirred for 3 d at 55 °C. The reaction was quenched by addition of sat. aqueous NH<sub>4</sub>Cl (3 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with brine (5 mL), dried over MgSO<sub>4</sub> and evaporated. The crude products were purified by flash chromatography.

**(2*S*\*,4*S*\*,6*S*\*)-2-Methyl-2,3,4,6-tetrahydro-1*H*-2,6-methanobenzo[*c*][1,5]oxazocin-4-ol**  
**(11a)**



Yellow solid; *R*<sub>f</sub>: 0.26 (CH/EtOAc 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.29 (s, 3H, CH<sub>3</sub>), 1.53 (dd, <sup>2</sup>*J* = 12.8 Hz, <sup>3</sup>*J* = 9.6 Hz, 1H, CH<sub>2</sub>), 1.64 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 1.84 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 2.00 (dd, <sup>2</sup>*J* = 12.4 Hz, <sup>3</sup>*J* = 3.6 Hz, 1H, CH<sub>2</sub>), 3.89 (bs, 1H, OH), 4.01 (bs, 1H, NH), 4.83–4.90 (m, 2H, 2 × CH), 6.42 (d, *J* = 8.0 Hz, 1H, H<sub>arom.</sub>), 6.59 (ddd, <sup>3</sup>*J* = 7.6, 7.2 Hz, <sup>4</sup>*J* = 1.2 Hz, 1H, H<sub>arom.</sub>), 7.03–7.09 (m, 2H, H<sub>arom.</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 29.3 (+, CH<sub>3</sub>), 35.4 (–, CH<sub>2</sub>), 48.5 (–, CH<sub>2</sub>), 49.0 (C<sub>quart.</sub>, CCH<sub>3</sub>), 70.6 (+, CHO), 89.9 (+, CHOH), 112.4 (+, C<sub>arom.</sub>), 116.5 (+, C<sub>arom.</sub>), 118.8 (C<sub>quart.</sub>, C<sub>arom.</sub>), 129.5 (+, C<sub>arom.</sub>), 129.9 (+, C<sub>arom.</sub>), 145.0 (C<sub>quart.</sub>, C<sub>arom.</sub>) ppm; MS (EI): *m/z* (%): 206 (7, [M<sup>+</sup>+2]), 205 (53, [M<sup>+</sup>+H]), 160 (26), 146 (16), 145 (10), 144 (100), 143 (17), 132 (23), 130 (11); HRMS: calc. 205.1103, found 205.1099.

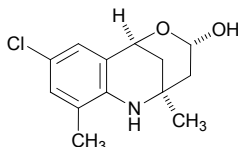
**(2*S*\*,4*S*\*,6*S*\*)-2,10-Dimethyl-2,3,4,6-tetrahydro-1*H*-2,6-methanobenzo[*c*][1,5]oxazocin-4-ol (11 b)**



Yellow solid; *R*<sub>f</sub>: 0.24 (CH/EtOAc 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.35 (s, 3H, CH<sub>3</sub>), 1.56 (dd, <sup>2</sup>*J* = 12.8 Hz, <sup>3</sup>*J* = 9.6 Hz, 1H, CH<sub>2</sub>), 1.64 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 1.84 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 2.03 (dd, <sup>2</sup>*J* = 12.8 Hz, <sup>3</sup>*J* = 3.6 Hz, 1H, CH<sub>2</sub>), 2.07 (s, 1H, Ar-CH<sub>3</sub>), 3.58 (bs, 1H, NH), 4.01 (d, *J*

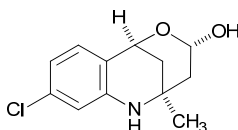
= 6.0 Hz, 1H, OH), 4.78 (m<sub>c</sub>, 1H, CH), 4.86 (m<sub>c</sub>, 1H, CHOH), 6.53 (dd, <sup>3</sup>J = 7.6, 7.2 Hz, 1H, H<sub>arom.</sub>), 6.92–6.99 (m, 2H, H<sub>arom.</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 17.0 (+, Ar-CH<sub>3</sub>), 29.6 (+, CH<sub>3</sub>), 35.3 (–, CH<sub>2</sub>), 48.5 (–, CH<sub>2</sub>), 49.1 (C<sub>quart.</sub>, CCH<sub>3</sub>), 70.8 (+, CHO), 89.9 (+, CHOH), 116.0 (+, C<sub>arom.</sub>), 118.8 (C<sub>quart.</sub>, C<sub>arom.</sub>), 119.4 (C<sub>quart.</sub>, C<sub>arom.</sub>), 127.8 (+, C<sub>arom.</sub>), 130.5 (+, C<sub>arom.</sub>), 142.9 (C<sub>quart.</sub>, C<sub>arom.</sub>) ppm; MS (EI): m/z (%): 220 (9, [M<sup>+</sup>+2]), 219 (62, [M<sup>+</sup>+H]), 174 (29), 160 (25), 159 (13), 158 (100), 157 (11), 144 (12), 132 (34); HRMS: calc. 219.1259, found 219.1263.

**(2*S*\*,4*S*\*,6*S*\*)-8-Chloro-2,10-dimethyl-2,3,4,6-tetrahydro-1*H*-2,6-methanobenzo[*c*][1,5]oxazocin-4-ol (11 c)**



Pale yellow solid; *R*<sub>f</sub>: 0.34 (*n*-pentane/Et<sub>2</sub>O 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.34 (s, 3H, CH<sub>3</sub>), 1.53–1.62 (m, 2H, CH<sub>2</sub>), 1.84 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 2.03 (dd, <sup>2</sup>J = 12.8 Hz, <sup>3</sup>J = 3.6 Hz, 1H, CH<sub>2</sub>), 2.06 (s, 1H, Ar-CH<sub>3</sub>), 3.58 (bs, 1H, NH), 4.40 (bs, 1H, OH), 4.63 (m<sub>c</sub>, 1H, CH), 4.77 (m<sub>c</sub>, 1H, CHOH), 6.87 (d, <sup>4</sup>J = 2.4 Hz, 1H, H<sub>arom.</sub>), 6.91 (d, <sup>4</sup>J = 2.4 Hz, 1H, H<sub>arom.</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 16.9 (+, Ar-CH<sub>3</sub>), 29.5 (+, CH<sub>3</sub>), 35.1 (–, CH<sub>2</sub>), 48.0 (–, CH<sub>2</sub>), 49.2 (C<sub>quart.</sub>, CCH<sub>3</sub>), 70.3 (+, CHO), 90.0 (+, CHOH), 119.4 (C<sub>quart.</sub>, C<sub>arom.</sub>), 120.1 (C<sub>quart.</sub>, C<sub>arom.</sub>), 121.4 (C<sub>quart.</sub>, C<sub>arom.</sub>), 127.0 (+, C<sub>arom.</sub>), 130.0 (+, C<sub>arom.</sub>), 141.6 (C<sub>quart.</sub>, C<sub>arom.</sub>) ppm; MS (EI): m/z (%): 253/255 (52/18, M<sup>+</sup>), 210 (14), 208 (29), 194 (51), 193 (21), 192 (100), 191 (29), 178 (20), 166 (28), 113 (20), 95 (33), 85 (22), 71 (29), 59 (25), 43 (47); HRMS: calc. 253.0870, found 253.0868.

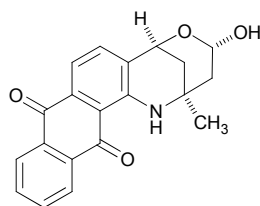
**(2*S*\*,4*S*\*,6*S*\*)-9-Chloro-2-methyl-2,3,4,6-tetrahydro-1*H*-2,6-methanobenzo[*c*][1,5]oxazocin-4-ol (11d)**



Pale yellow solid; *R*<sub>f</sub>: 0.17 (CH/EtOAc 2:1); <sup>1</sup>H NMR (400 MHz, Acetone-*d*<sub>6</sub>): δ = 1.28 (s, 3H, CH<sub>3</sub>), 1.48 (dd, <sup>2</sup>J = 12.8 Hz, <sup>3</sup>J = 9.6 Hz, 1H, CH<sub>2</sub>), 1.54 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 1.81 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 1.95 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 4.76 (m<sub>c</sub>, 1H, CH), 4.83 (m<sub>c</sub>, 1H, CHOH), 5.09 (d, <sup>3</sup>J = 6.8 Hz, 1H, OH), 5.61 (bs, 1H, NH), 6.48 (dd, <sup>3</sup>J = 8.0 Hz, <sup>4</sup>J = 2.0 Hz, 1H, H<sub>arom.</sub>), 6.54 (d, *J* = 8.0 Hz,

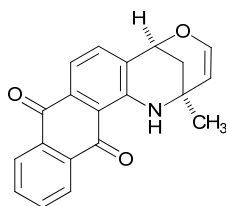
1H, H<sub>arom.</sub>), 7.01 (d,  $J = 8.0$  Hz, 1H, H<sub>arom.</sub>) ppm; <sup>13</sup>C NMR (100 MHz, Acetone-*d*<sub>6</sub>):  $\delta = 29.2$  (+, CH<sub>3</sub>), 36.4 (-, CH<sub>2</sub>), 49.3 (-, CH<sub>2</sub>), 49.7 (C<sub>quart.</sub>, CCH<sub>3</sub>), 70.2 (+, CHO), 90.4 (+, CHOH), 112.3 (+, C<sub>arom.</sub>), 115.7 (+, C<sub>arom.</sub>), 119.3 (C<sub>quart.</sub>, C<sub>arom.</sub>), 131.8 (+, C<sub>arom.</sub>), 134.8 (C<sub>quart.</sub>, C<sub>arom.</sub>), 148.3 (C<sub>quart.</sub>, C<sub>arom.</sub>) ppm; MS (EI):  $m/z$  (%): 239/241 (46/14, M<sup>+</sup>), 194 (29), 196 (12), 180 (100), 178 (49), 166 (24), 164 (10); HRMS: calc. 239.0713, found 239.0715.

**(2*S*\*,4*S*\*,6*S*\*)-4-Hydroxy-2-methyl-3,4-dihydro-1*H*-2,6-methanoanthra[2,1-*c*][1,5]oxazocine-9,14(2*H*,6*H*)-dione (11e)**



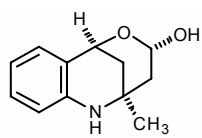
Red solid;  $R_f$ : 0.28 (*n*-pentane/Et<sub>2</sub>O 2:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.49$  (s, 3H, CH<sub>3</sub>), 1.61 (dd, <sup>2</sup> $J = 12.8$  Hz, <sup>3</sup> $J = 9.6$  Hz, 1H, CH<sub>2</sub>), 1.69 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 2.03 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 2.12 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 3.64 (s, 1H, OH), 4.88 (m<sub>c</sub>, 1H, CH), 4.94 (m<sub>c</sub>, 1H, CHOH), 7.40 (d,  $J = 7.6$  Hz, 1H, H<sub>arom.</sub>), 7.46 (d,  $J = 7.6$  Hz, 1H, H<sub>arom.</sub>), 7.67 (ddd, <sup>3</sup> $J = 7.6$ , 7.2 Hz, <sup>4</sup> $J = 1.6$  Hz, 1H, H<sub>arom.</sub>), 7.74 (ddd, <sup>3</sup> $J = 7.6$ , 7.2 Hz, <sup>4</sup> $J = 1.6$  Hz, 1H, H<sub>arom.</sub>), 8.15 (dd, <sup>3</sup> $J = 7.6$  Hz, <sup>4</sup> $J = 1.2$  Hz, 1H, H<sub>arom.</sub>), 8.21 (dd, <sup>3</sup> $J = 7.6$  Hz, <sup>4</sup> $J = 1.2$  Hz, 1H, H<sub>arom.</sub>), 9.75 (bs, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 28.8$  (+, CH<sub>3</sub>), 34.7 (-, CH<sub>2</sub>), 47.0 (-, CH<sub>2</sub>), 49.3 (C<sub>quart.</sub>, CCH<sub>3</sub>), 70.4 (+, CHO), 90.3 (+, CHOH), 111.4 (C<sub>quart.</sub>, C<sub>arom.</sub>), 115.4 (+, C<sub>arom.</sub>), 126.5 (+, C<sub>arom.</sub>), 126.8 (+, C<sub>arom.</sub>), 127.5 (C<sub>quart.</sub>, C<sub>arom.</sub>), 132.9 (C<sub>quart.</sub>, C<sub>arom.</sub>), 133.1 (+, C<sub>arom.</sub>), 134.0 (+, C<sub>arom.</sub>), 134.6 (C<sub>quart.</sub>, C<sub>arom.</sub>), 134.7 (C<sub>quart.</sub>, C<sub>arom.</sub>), 135.5 (+, C<sub>arom.</sub>), 148.9 (C<sub>quart.</sub>, C<sub>arom.</sub>), 183.2 (C<sub>quart.</sub>, C=O), 185.0 (C<sub>quart.</sub>, C=O) ppm; MS (EI):  $m/z$  (%): 336.2 (10, [M<sup>+</sup>+H]), 335.2 (40, [M<sup>+</sup>]), 290.1 (28), 276.1 (19), 275.1 (29), 274.1 (100), 262.1 (14), 260.1 (12); HRMS: calc. 335.1158, found 335.1156.

**(2*S*\*,6*S*\*)-2-Methyl-1*H*-2,6-methanoanthra[2,1-*c*][1,5]oxazocine-9,14(2*H*,6*H*)-dione (13)**



MsCl (0.18 mL, 2.4 mmol, 2.5 eq.) was added to a solution of lactol **11e** (320 mg, 0.954 mmol) and Et<sub>3</sub>N (1.06 mL, 7.63 mmol, 8.0 eq.) in THF (10 mL) at 0 °C. The mixture was stirred for 3 h at RT. The reaction was quenched by addition of sat. aqueous NH<sub>4</sub>Cl (10 mL). The phases were separated and extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over MgSO<sub>4</sub> and evaporated. Purification by flash chromatography (*n*-pentane/Et<sub>2</sub>O 20:1) gave the product as a red solid (263 mg, 0.829 mmol, 87%).

*R*<sub>f</sub>: 0.48 (*n*-pentane/Et<sub>2</sub>O 9:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 1.59 (s, 3H, CH<sub>3</sub>), 1.89 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 2.16 (m<sub>c</sub>, 1H, CH<sub>2</sub>), 4.78 (dd, <sup>3</sup>*J* = 6.0 Hz, <sup>4</sup>*J* = 2.4 Hz, 1H, OCH=CH), 5.24 (m<sub>c</sub>, 1H, CH), 6.45 (d, <sup>3</sup>*J*<sub>cis</sub> = 6.0 Hz, 1H, OCH=CH), 7.54–7.57 (m, 2H, H<sub>arom.</sub>), 7.68 (ddd, <sup>3</sup>*J* = 7.6, 7.2 Hz, <sup>4</sup>*J* = 1.6 Hz, 1H, H<sub>arom.</sub>), 7.73 (ddd, <sup>3</sup>*J* = 7.6, 7.2 Hz, <sup>4</sup>*J* = 1.6 Hz, 1H, H<sub>arom.</sub>), 8.21 (m<sub>c</sub>, 2H, H<sub>arom.</sub>), 9.84 (bs, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 26.1 (+, CH<sub>3</sub>), 33.8 (–, CH<sub>2</sub>), 44.6 (C<sub>quart.</sub>, CCH<sub>3</sub>), 70.3 (+, CHO), 109.0 (+, OCH=CH), 113.6 (C<sub>quart.</sub>, C<sub>arom.</sub>), 115.6 (+, C<sub>arom.</sub>), 126.6 (+, C<sub>arom.</sub>), 126.7 (+, C<sub>arom.</sub>), 129.4 (C<sub>quart.</sub>, C<sub>arom.</sub>), 132.9 (C<sub>quart.</sub>, C<sub>arom.</sub>), 133.0 (+, C<sub>arom.</sub>), 133.9 (+, C<sub>arom.</sub>), 134.8 (C<sub>quart.</sub>, C<sub>arom.</sub>), 134.9 (C<sub>quart.</sub>, C<sub>arom.</sub>), 137.0 (+, C<sub>arom.</sub>), 143.3 (+, OCH=CH), 148.6 (C<sub>quart.</sub>, C<sub>arom.</sub>), 183.3 (C<sub>quart.</sub>, C=O), 184.6 (C<sub>quart.</sub>, C=O) ppm; MS (EI): *m/z* (%): 318.1 (M<sup>+</sup>+H, 22), 317.1 (M<sup>+</sup>, 100), 316.1 (33), 303.1 (17), 302.1 (85), 289.1 (11), 288.1 (49), 279.2 (19), 275.1 (17), 274.1 (96), 273.1 (17), 167.1 (19), 149.0 (56), 77.0 (10), 71.1 (11), 57.1 (17), 43.0 (34); HRMS: calc. 317.1052, found 317.1053.



11a

