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A New Synthesis of Sulfur-, Nitrogen- and Oxygen-Containing Eight-Membered Ring Lactams

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$Bi(NO_3)_3$-catalyzed ring expansion of five-membered ring 1,4-diketones in the presence of primary amines leads to eight-membered ring lactams. When applied to starting materials with a tetrahydrothiophene or pyrrolidine moiety, tetrahydro-2*H*-1,4-thiazocin-3-ones and hexahydro-1,4-diazocin-2-ones are obtained as representatives of these very rare heterocyclic systems. In the case of tetrahydrofuran derivatives, other reaction conditions are required and yields of tetrahydro-2*H*-1,4-oxazocin-3-ones are very low.

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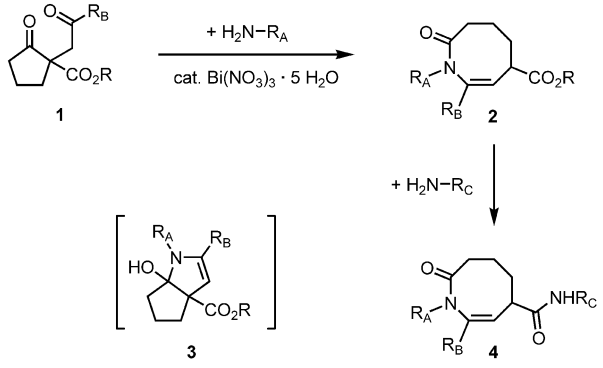
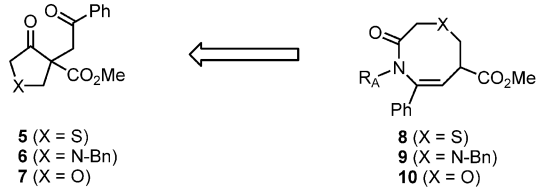
Introduction

Eight-membered ring lactams **2** are new scaffolds for combinatorial chemistry and can be prepared by bismuth nitrate catalyzed ring expansion of 1,4-diketones **1** in the presence of primary amines R_A–NH_2 (Scheme 1).[1] We have recently used this transformation for the preparation of amides **4** with three points of diversification (R_A, R_B, and R_C). Aromatic residue R_B originated from the starting material **1**. After ring expansion, the ester moieties were saponified and amidated with another set of primary amines R_C–NH_2 to give products **4**.[2] A mechanistic rationale for the ring expanding transformation considers nucleophilic attack of the amine to both carbonyl groups of the 1,4-diketone moiety with formation of the bicyclic intermediate **3**, as proposed for the Paal–Knorr pyrrole synthesis.

We considered β-oxo esters with a tetrahydrothiophene ring (**5**), pyrrolidine ring (**6**) or tetrahydrofuran ring (**7**) to be appropriate starting materials for the synthesis of nitrogen, sulfur or oxygen containing eight-membered ring lactams **8**, **9** and **10** (Scheme 2). Whereas benzo- and dibenzo-annulated 1,4-diazocanes,[3] 1,4-thiazocanes[4] and 1,4-oxazocanes[5] frequently appeared in the literature, only very few synthetic pathways to monocyclic 1,4-diazocanes,[6] 1,4-thiazocanes[7] and 1,4-oxazocanes[8] have been reported so far. Therefore, the $Bi(NO_3)_3$-catalyzed ring expanding reaction is interesting as it allows a straightforward access to these rare eight-membered heterocycles.



Scheme 1. Preparation of a model library of eight-membered ring lactams **4** from 1,4-diketones **1** and primary amines R_A–NH_2 and R_C–NH_2.



Scheme 2. Synthetic plan for tetrahydro-2*H*-1,4-thiazocin-3-ones **8**, hexahydro-1,4-diazocin-2-ones **9**, and tetrahydro-2*H*-1,4-oxazocin-3-ones **10**.

Results and Discussion

The hitherto unknown tetrahydrothiophene, pyrrolidine and tetrahydrofuran derivatives **5**, **6** and **7** with a 1,4-diketone motif were accessed starting from the corresponding β-oxo esters **11**, **12** and **13** (Scheme 3). The pyrrolidine derivative **12** was prepared from *tert*-butyl bromoacetate,

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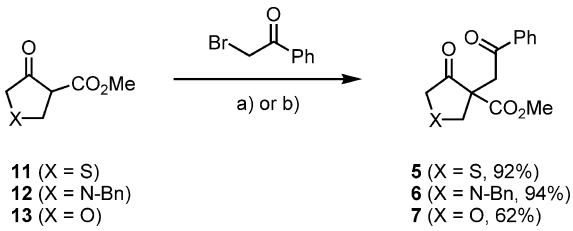
benzylamine and methyl acrylate according to a literature procedure.[9] The tetrahydrothiophene and -furan derivatives **11** and **13** were accessed from methyl acrylate and methyl thioglycolate[10] or methyl glycolate,[11] respectively, both as reported in the literature. Alkylations of these three β-oxo esters **11**–**13** with phenacyl bromide and K_2CO_3 in acetone or NaH in THF were unproblematic and proceeded with good yields.



11 (X = S)
12 (X = N-Bn)
13 (X = O)

5 (X = S, 92%)
6 (X = N-Bn, 94%)
7 (X = O, 62%)

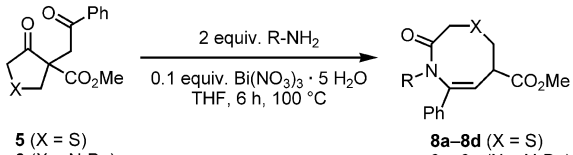
Scheme 3. Synthesis of 1,4-diketones **5**–**7** from heterocyclic β-oxo esters **11**–**13**, conditions a) for **5** and **6**: 1.1 equiv. K_2CO_3, acetone, 1 h, 65 °C; b) for **7**: 1.2 equiv. NaH, THF, 16 h, 70 °C.

1,4-Diketones **5** and **6** were converted with an excess of primary amines in the presence of sub-stoichiometric amounts of $Bi(NO_3)_3 \cdot 5H_2O$. Initial optimization of this transformation was carried out with the tetrahydrothiophene derivative **5** and Bn–NH_2 (Table 1, entry 1, product **8a**). The reaction conditions given in Scheme 4 were adopted for all four amines R–NH_2 (Table 1). Reactions were performed with THF as solvent at 100 °C, thus, tightly closed vials were used as flasks. For larger volumes (>20 mL), the reaction mixture was split up into several vials for the reaction and recombined for workup and purification. Yields of thiazocine products **8a**–**8d** are in the range of 50–70%. Correlations between yields and steric or electronic influence of the amine cannot be identified. Yields of diazocine products **9a**–**9c** (Table 1) are significantly lower. Moreover, in the case of a primary amine with secondary alkyl residue (Cy–NH_2) the formation of product **9d** failed completely.

Table 1. Amines used for the ring expansion reactions and yields of thiazocines **8** and diazocines **9**.

Entry	Amine R–NH_2	Yield of **8** (X = S)	Yield of **9** (X = NBn)
1	$PhCH_2NH_2$	56% (**8a**)	35% (**9a**)
2	Me–NH_2[a]	68% (**8b**)	20% (**9b**)
3	Allyl–NH_2	51% (**8c**)	31% (**9c**)
4	Cy–NH_2	62% (**8d**)	– (**9d**)[b]

[a] Solution (2 mol dm^{-3}) in THF was used. [b] No product detectable.

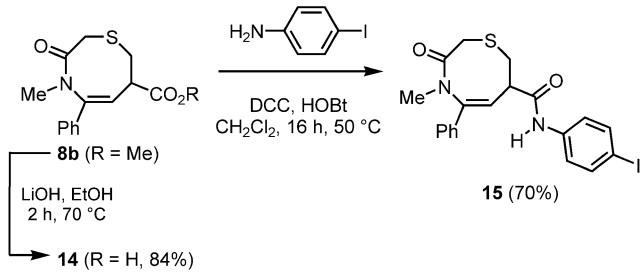


5 (X = S)
6 (X = N-Bn)

8a–**8d** (X = S)
9a–**9c** (X = N-Bn)

Scheme 4. Synthesis of 1,4-thiazocin-3-ones **8a**–**8d** and 1,4-diazocin-3-ones **9a**–**9c**. For residues R and yields see Table 1.

We planned to obtain a X-ray single-crystal structure in order to proof the constitution of our lactams, but we failed to obtain single crystals of compounds **8** and **9**. Therefore, we have prepared *p*-iodophenylamide **15** from *N*-methylthiazocinone **8b** by ester saponification and amidation of the carboxylic acid **14** with DCC, HOBt (Scheme 5). Compound **15** with iodine as heavy atom showed good crystallinity and suitable single crystals were obtained and investigated.[12] Figure 1 shows the structure in the solid state. The eight-membered ring is in a folded, crown-shaped conformation. The enamine C–C double bond and the amide N–C–O plane are almost perpendicular (dihedral angle C5–C6–N1–C7: 114.18°).



Scheme 5. Ester saponification and amidation.

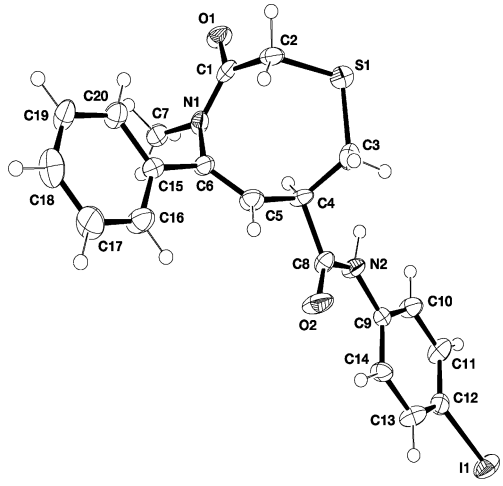


Figure 1. ORTEP-representation of the structure of amide **15** in the solid state.

We of course tried to convert tetrahydrofuran derivative **7** with primary amines and catalytic amounts of Bi salt in order to access tetrahydrooxazocines, but even under different reaction conditions, we were never able to detect eight-membered ring products like **10**. Therefore, we attempted other Lewis acids [$Sc(OTf)_3$, $FeCl_3 \cdot 6H_2O$, $CeCl_3 \cdot 7H_2O$, $ZnCl_2$] as well as Brönsted acids (H_2SO_4, HCl/H_2O, $KHSO_4$, AcOH) as catalysts, but remained unsuccessful. To our surprise and after extensive experimentation, we were able to obtain compound **10** in low yield together with byproduct **16** when using 2 equiv. of $MeNH_2$ and 1 equiv. *p*TosOH as an additive, if all starting materials are mixed at 0 °C (Scheme 6). The open-chain product **16** is clearly resulting from retro-Dieckmann reaction of intermediate

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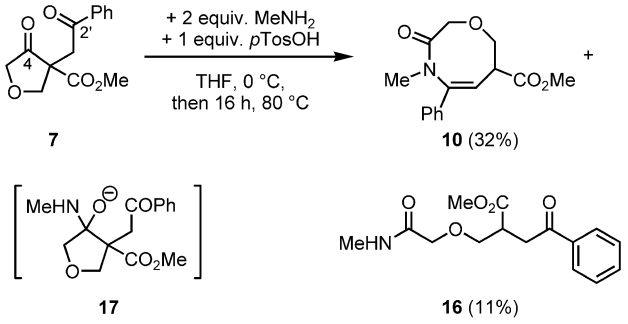
hemi-aminal anion **17** after addition of the amine to the carbonyl group C-4. Compared with the sulfur and nitrogen cogeners **5** and **6**, the addition of $MeNH_2$ to the more electrophilic carbonyl group C-4 of compound **7** might be favoured by the –I-effect of the ether oxygen. Even after extensive variation of stoichiometry and other reaction conditions, we were not able to raise the amount of formed eight-membered ring product **10** and minimize the formation of amide **16** in the reaction mixtures. Even worse, we completely failed to obtain any product of type **10** when using other amines than $MeNH_2$. Finally, we conclude that ring expansion of diketone **7** is not a suitable method for the preparation of oxazocines like compound **10** on a preparative useful scale. Nevertheless, we were able to grow single crystals of compound **10** and obtained a X-ray structure, which is shown in Figure 2. It shows the same key features like compound **15**: crown-shaped conformation of the eight-membered ring and almost perpendicular C–C-double bond and amide moiety (dihedral angle C5–C6–N1–C7: 118.96°).



Scheme 6. Attempts on preparation of oxazocine **10**.

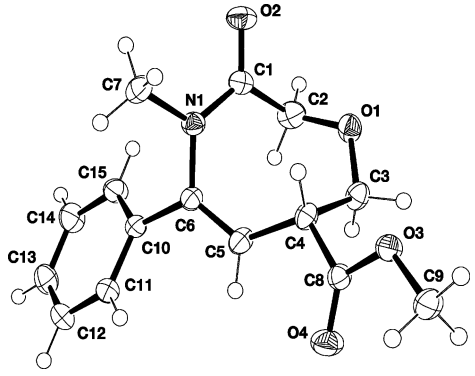


Figure 2. ORTEP representation of the structure of lactam **10** in the solid state.

Experimental Section

General Methods: Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexane and ethyl acetate (EA) or *tert*-butyl methyl ether (MTBE) as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 500 and Avance DPX 300. Multiplicities were determined with DEPT experiments. EI-MS, CI-MS and HRMS spectra were obtained with a Finnigan MAT 95 spectrometer, ESI-MS (HRMS) spectra with a Waters Q-TOF Premier. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. Elemental analyses were measured with a Euro EA-CHNS from HEKAtech. Oxo esters **11**,[10] **12**[9] and **13**[11] were prepared according to literature protocols. All other starting materials were commercially available. $MeNH_2$ in THF was obtained from Aldrich.

Methyl 4-Oxo-3-(2-oxo-2-phenylethyl)tetrahydrothiophene-3-carboxylate (5): K_2CO_3 (7.10 g, 72.1 mmol, 1.1 equiv.) and phenacyl bromide (15.7 g, 78.7 mmol, 1.2 equiv.) were added successively to a solution of compound **11** (10.5 g, 65.5 mmol, 1.0 equiv.) in acetone (65 mL). The resulting mixture was stirred for 1 h at 65 °C, then cooled to ambient temperature and diluted with H_2O (65 mL). The layers were separated and the aqueous layer extracted with MTBE (3 × 65 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to give compound **5** (16.8 g, 60.3 mmol, 92%) after chromatography (SiO_2, hexane/MTBE, 2:1, R_f = 0.20) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.30 (A-part of an AB-system, J = 12.1 Hz, 1 H), 3.48 (A-part of an AB-system, J = 17.3 Hz, 1 H), 3.58 (B-part of an AB-system, J = 17.3 Hz, 1 H), 3.63 (B-part of an AB-system, J = 11.9 Hz, 1 H), 3.64 (A-part of an AB-system, J = 18.6 Hz, 1 H), 3.75 (s, 3 H), 3.78 (B-part of an AB-system, J = 18.3 Hz, 1 H), 7.44–7.47 (m, 2 H), 7.56–7.59 (m, 1 H), 7.91–7.92 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 34.79 (CH_2), 37.79 (CH_2), 42.66 (CH_2), 53.27 (CH_3), 58.48 (C), 128.06 (2 CH), 128.70 (2 CH), 133.74 (CH), 135.89 (C), 169.85 (C), 195.84 (C), 207.52 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2953 (w), 1727 (vs), 1682 (vs), 1596 (m), 1448 (s), 1398 (m), 1351 (m), 1285 (m), 1218 (vs), 1098 (m), 1046 (m), 1000 (m), 775 (s), 688 (vs) cm^{-1}. MS (EI, 70 eV): m/z (%) = 278 (9) [M$^+$], 173 (17), 159 (46), 120 (34), 105 (100). HRMS (EI, 70 eV): calcd. 278.0613 (for $C_{14}H_{14}O_4S$); found 278.0611 [M$^+$]. $C_{14}H_{14}O_4S$ (278.32).

Methyl 1-Benzyl-4-oxo-3-(2-oxo-2-phenylethyl)pyrrolidine-3-carboxylate (6): K_2CO_3 (3.47 g, 25.1 mmol, 1.05 equiv.) and phenacyl bromide (5.00 g, 25.1 mmol, 1.05 equiv.) were added successively to a solution of compound **12** (5.57 g, 23.9 mmol, 1.0 equiv.) in acetone (30 mL). The resulting mixture was stirred for 2 h at 65 °C, then cooled to ambient temperature and diluted with H_2O (30 mL). The layers were separated and the aqueous layer extracted with MTBE (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to give compound **6** (7.91 g, 22.5 mmol, 94%) as a yellow brown oil, which could be used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.11 (d, J = 10.0 Hz, 1 H), 3.18 (A-part of an AB-system, J = 17.1 Hz, 1 H), 3.26 (B-part of an AB-system, J = 17.1 Hz, 1 H), 3.49 (d, J = 18.1 Hz, 1 H), 3.67 (d, J = 10.0 Hz, 1 H), 3.69 (A-part of an AB-system, J = 13.1 Hz, 1 H), 3.72 (s, 3 H), 3.79 (d, J = 18.2 Hz, 1 H), 3.82 (B-part of an AB-system, J = 13.2 Hz, 1 H), 7.28–7.30 (m, 5 H), 7.41–7.46 (m, 2 H), 7.53–7.57 (m, 1 H), 7.90–7.93 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 41.50 (CH_2), 52.78 (CH_3), 58.68 (C), 59.04 (CH_2), 59.70 (CH_2), 60.47 (CH_2), 127.25 (CH), 127.94 (2 CH), 128.30 (2 CH), 128.43 (2 CH), 128.56 (2 CH), 133.45 (CH), 136.03 (C), 137.23 (C), 169.28 (C), 196.01 (C), 208.57 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3063 (w), 2952 (w), 1766 (m), 1728 (vs), 1682 (vs), 1597 (m), 1449 (m), 1434 (m), 1354 (m), 1215 (vs), 1177 (s), 1076 (s), 1044 (m), 1028 (m), 1001 (m), 754 (s), 689 (vs) cm^{-1}. MS (EI, 70 eV): m/z (%) = 351 (13) [M$^+$], 292 (18), 232 (36), 200 (48), 105 (16), 91 (100). HRMS (EI, 70 eV): calcd. 351.1471 (for $C_{21}H_{21}NO_4$); found 351.1468 [M$^+$]. $C_{21}H_{21}NO_4$ (351.40).

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Methyl 4-Oxo-3-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carboxylate (7): NaH (60% dispersion in mineral oil, 1.36 g, 34.0 mmol) and phenacyl bromide (6.8 g, 34 mmol) were added to a solution of compound **13** (4.0 g, 28 mmol) in THF (30 mL) and the mixture was stirred for 16 h at 70 °C. After cooling to ambient temperature, it was diluted with H_2O (30 mL) and washed with brine (30 mL). The layers were separated and the aqueous layer extracted with MTBE (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. The residue was chromatographed (SiO_2, hexane/MTBE, 1:1, R_f = 0.21) to give compound **7** (4.56 g, 17.4 mmol, 62%) as a light pink oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.42 (A-part of an AB-system, J = 18.5 Hz, 1 H), 3.70 (s, 3 H), 3.83 (B-part of an AB-system, J = 18.4 Hz, 1 H), 4.13 (A-part of an AB-system, J = 16.9 Hz, 1 H), 4.17 (A-part of an AB-system, J = 9.9 Hz, 1 H), 4.19 (B-part of an AB-system, J = 16.9 Hz, 1 H), 4.79 (B-part of an AB-system, J = 9.9 Hz, 1 H), 7.39–7.42 (m, 2 H), 7.51–7.54 (m, 1 H), 7.87–7.88 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 41.17 (CH_2), 53.29 (CH_3), 56.73 (C), 70.70 (CH_2), 74.63 (CH_2), 128.14 (2 CH), 128.77 (2 CH), 133.87 (CH), 135.71 (C), 168.82 (C), 195.90 (C), 209.85 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2954 (w), 1729 (vs), 1683 (s), 1597 (m), 1449 (m), 1355 (m), 1220 (vs), 1001 (m), 756 (vs), 689 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (3) [M$^+$], 232 (10), 143 (25), 120 (22), 105 (100). HRMS (EI, 70 eV): calcd. 262.0841 (for $C_{14}H_{14}O_5$); found 262.0836 [M$^+$]. $C_{14}H_{14}O_5$ (262.26).

General Procedure A. Bismuth-Catalyzed Preparation of Lactams: The respective amine R–NH_2 (2–3 equiv.) was added to a mixture of $Bi(NO_3)_3{\cdot}5H_2O$ (0.1 equiv.) and compound **5** or **6** (1.0 equiv.) in THF (c = 0.7 mol dm^{-3}). The resulting mixture was stirred for 4–6 h at 100 °C in a tightly closed reaction vial. After cooling to ambient temperature, the reaction mixture was diluted with EA (ca. 5–10 dm^3 mol^{-1}) and extracted with H_2O (ca. 5–10 dm^3 mol^{-1}). After phase separation, the aqueous layer was again extracted with EA (2 × 5–10 dm^3 mol^{-1}). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to give products **8** or **9** as crude materials, which were purified by chromatography on SiO_2.

Methyl 4-Benzyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-thiazocin-7-carboxylate (8a): According to general procedure A, reaction of benzylamine (3.86 g, 36.0 mmol), compound **5** (5.0 g, 18 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (870 mg, 1.80 mmol) gave product **8a** (3.71 g, 10.1 mmol, 56%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.23) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.53 (dd, J = 10.0, J = 13.8 Hz, 1 H), 2.72 (t, J = 9.9 Hz, 1 H), 2.84 (d, J = 13.9 Hz, 1 H), 3.23 (A-part of an AB-system, J = 13.6 Hz, 1 H), 3.50 (B-part of an AB-system, J = 13.6 Hz, 1 H), 3.56 (s, 3 H), 3.62 (A-part of an AB-system, J = 13.7 Hz, 1 H), 5.57 (B-part of an AB-system, J = 13.7 Hz, 1 H), 5.88 (d, J = 9.9 Hz, 1 H), 7.29–7.36 (m, 5 H), 7.42–7.44 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 30.97 (CH_2), 31.71 (CH_2), 47.15 (CH), 48.27 (CH_2), 52.11 (CH_3), 124.46 (CH), 126.34 (2 CH), 127.58 (CH), 128.42 (2 CH), 129.19 (2 CH), 129.56 (CH), 129.66 (2 CH), 135.13 (C), 135.78 (C), 140.22 (C), 169.76 (C), 172.19 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3028 (w), 2948 (w), 1731 (s), 1650 (vs), 1493 (m), 1433 (m), 1391 (m), 1317 (m), 1244 (m), 1167 (s), 1076 (m), 1028 (m), 913 (m), 867 (m), 761 (s), 730 (s), 696 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 367 (9) [M$^+$], 234 (42), 220 (12), 91 (100). $C_{21}H_{21}NO_3S$ (367.46): calcd. C 68.64, H 5.76, N 3.81; found C 68.74, H 5.91, N 4.20. HRMS (EI, 70 eV): calcd. 367.1242; found 367.1243 [M$^+$].

Methyl 4-Methyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-thiazocin-7-carboxylate (8b): According to general procedure A, reaction of methylamine (14.4 mmol, 7.20 mL of a 2.00 mol dm^{-3} solution in THF), compound **5** (2.0 g, 7.2 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (340 mg, 0.720 mmol) gave product **8b** (1.43 g, 4.90 mmol, 68%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.16) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.53 (dd, J = 9.8, J = 13.9 Hz, 1 H), 2.81 (s, 3 H), 2.88 (d, J = 13.9 Hz, 1 H), 3.00 (A-part of an AB-system, J = 13.6 Hz, 1 H), 3.27 (d, J = 9.8 Hz, 1 H), 3.31 (B-part of an AB-system, J = 13.5 Hz, 1 H), 3.62 (s, 3 H), 5.79 (d, J = 10.0 Hz, 1 H), 7.21–7.23 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 30.94 (CH_2), 31.16 (CH_2), 33.68 (CH_3), 47.33 (CH), 52.47 (CH_3), 121.82 (CH), 125.99 (2 CH), 128.93 (2 CH), 129.38 (CH), 134.71 (C), 142.50 (C), 170.27 (C), 172.34 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3082 (w), 2950 (m), 1732 (s), 1647 (vs), 1426 (m), 1375 (s), 1324 (m), 1246 (m), 1160 (s), 1065 (w), 866 (m), 766 (s), 696 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 291 (30) [M$^+$], 234 (100), 205 (24), 186 (50), 158 (40), 133 (39), 118 (81), 91 (23). HRMS (EI, 70 eV): calcd. 291.0929 (for $C_{15}H_{17}NO_3S$); found 291.0927 [M$^+$]. $C_{15}H_{17}NO_3S$ (291.37).

Methyl 4-Allyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-thiazocin-7-carboxylate (8c): According to general procedure A, reaction of allylamine (205 mg, 3.40 mmol), compound **5** (500 mg, 1.70 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (88 mg, 0.19 mmol) gave product **8c** (290 mg, 0.913 mmol, 51%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.27) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.69 (dd, J = 9.9, J = 14.0 Hz, 1 H), 3.02 (d, J = 13.9 Hz, 1 H), 3.20 (A-part of an AB-system, J = 13.6 Hz, 1 H), 3.24 (dd, J = 14.2, J = 8.1 Hz, 1 H), 3.45 (t, J = 10.0 Hz, 1 H), 3.48 (B-part of an AB-system, J = 13.6 Hz, 1 H), 3.78 (s, 3 H), 4.81 (dd, J = 14.2, J = 5.8 Hz, 1 H), 5.04 (d, J = 17.0 Hz, 1 H), 5.11 (d, J = 10.0 Hz, 1 H), 5.80 (dddd, J = 17.0, J = 10.0, J = 8.1, J = 5.8 Hz, 1 H), 5.99 (d, J = 9.9 Hz, 1 H), 7.36–7.38 (m, 2 H), 7.40–7.41 (m, 3 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 31.16 (CH_2), 31.54 (CH_2), 47.65 (CH_2), 47.93 (CH), 52.58 (CH_3), 119.75 (CH_2), 123.65 (CH), 126.18 (2 CH), 129.00 (2 CH), 129.47 (CH), 131.18 (CH), 135.05 (C), 140.83 (C), 169.81 (C), 172.58 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2951 (w), 1732 (vs), 1650 (s), 1390 (m), 1316 (m), 1249 (m), 1154 (s), 1115 (m), 924 (m), 866 (m), 766 (s), 696 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 317 (22) [M$^+$], 270 (16), 258 (34), 231 (38), 212 (31), 191 (50), 170 (38), 144 (52), 115 (34), 41 (100). $C_{17}H_{19}NO_3S$ (317.40): calcd. C 64.33, H 6.03, N 4.41; found C 64.29, H 6.29, N 4.79. HRMS (EI, 70 eV): calcd. 317.1086 (for $C_{17}H_{19}NO_3S$); found 317.1088 [M$^+$].

Methyl 4-Cyclohexyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-thiazocin-7-carboxylate (8d): According to general procedure A, reaction of cyclohexylamine (4.27 g, 14.4 mmol), compound **5** (6.00 g, 21.6 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (1.05 g, 2.16 mmol) gave product **8d** (4.82 g, 13.4 mmol, 62%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.28) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.88 (tq, J = 3.6, J = 13.1 Hz, 1 H), 0.95 (dq, J = 3.6, J = 12.4 Hz, 1 H), 1.17–1.31 (m, 2 H), 1.37 (dq, J = 3.4, J = 12.4 Hz, 1 H), 1.51 (d, J = 13.0 Hz, 1 H), 1.57 (dd, J = 2.4, J = 13.4 Hz, 1 H), 1.70 (dt, J = 2.3, J = 11.8 Hz, 2 H), 1.72 (d, J = 11.8 Hz, 1 H), 2.68 (dd, J = 9.9, J = 14.0 Hz, 1 H), 3.00 (d, J = 13.9 Hz, 1 H), 3.16 (A-part of an AB-system, J = 13.9 Hz, 1 H), 3.51 (B-part of an AB-system, J = 13.5 Hz, 1 H), 3.54 (t, J = 9.6 Hz, 1 H), 3.80 (s, 3 H), 4.12 (tt, J = 3.5, J = 12.1 Hz, 1 H), 5.91 (d, J = 10.1 Hz, 1 H), 7.36–7.39 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 25.17 (CH_2), 25.82 (2 CH_2), 30.12 (CH_2), 30.78 (CH_2), 31.51 (CH_2), 32.16 (CH_2), 47.61 (CH), 52.60 (CH_3), 56.05 (CH), 126.04 (CH), 126.16 (2 CH), 128.54 (2 CH), 129.11 (CH), 137.94 (C), 140.57 (C), 169.68 (C), 172.39 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2933 (m), 2856 (m), 1735 (vs), 1639 (vs), 1447 (m), 1357 (m), 1248 (m), 1165 (s), 766 (s), 645 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 359 (36) [M$^+$], 300 (25), 277 (45), 234 (100), 228 (33), 191

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(26), 172 (59), 156 (27), 120 (16), 104 (17). HRMS (EI, 70 eV): calcd. 359.1555 (for $C_{20}H_{25}NO_3S$); found 359.1553 [M^+]. $C_{20}H_{25}NO_3S$ (359.48).

Methyl 1,4-Dibenzyl-2-oxo-8-phenyl-1,2,3,4,5,6-hexahydro-1,4-diazocin-6-carboxlate (9a): According to general procedure A, reaction of benzylamine (0.90 g, 8.4 mmol), compound **6** (1.00 g, 2.85 mmol) and $Bi(NO_3)_3·5H_2O$ (136 mg, 0.280 mmol) gave compound **9a** (432 mg, 0.981 mmol, 35%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.50) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.34 (dd, J = 13.2, J = 8.9 Hz, 1 H), 2.50 (t, J = 9.1 Hz, 1 H), 3.01 (d, J = 13.3 Hz, 1 H), 3.41 (d, J = 13.0 Hz, 1 H), 3.45 (d, J = 13.6 Hz, 1 H), 3.47 (s, 3 H), 3.60 (d, J = 12.9 Hz, 1 H), 3.59 (d, J = 13.7 Hz, 1 H), 4.09 (d, J = 13.9 Hz, 1 H), 5.47 (d, J = 13.7 Hz, 1 H), 5.93 (d, J = 9.3 Hz, 1 H), 7.20–7.35 (m, 15 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 41.64 (CH), 48.05 (CH_2), 51.87 (CH_3), 53.44 (CH_2), 55.50 (CH_2), 57.42 (CH_2), 124.62 (CH), 126.39 (2 CH), 127.32 (CH), 127.54 (CH), 128.24 (4 CH), 128.98 (2 CH), 129.14 (CH), 129.27 (4 CH), 135.30 (C), 136.04 (2 C), 139.43 (C), 167.78 (C), 172.40 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3060 (w), 2950 (w), 1733 (s), 1644 (s), 1494 (m), 1447 (m), 1435 (m), 1397 (m), 1304 (m), 1254 (m), 1223 (m), 1198 (m), 1170 (m), 1114 (m), 1075 (m), 1028 (m), 913 (m), 767 (m), 755 (m), 732 (s), 697 (vs) cm^{-1}. HRMS (ESI): calcd. 441.2178 (for $C_{28}H_{29}N_2O_3$); found 441.2187 [M + H^+]. $C_{28}H_{28}N_2O_3$ (440.53).

Methyl 4-Benzyl-1-methyl-2-oxo-8-phenyl-1,2,3,4,5,6-hexahydro-1,4-diazocin-6-carboxylate (9b): According to general procedure A, reaction of methylamine (8.4 mmol, 4.2 mL of a 2.00 mol dm^{-3} solution in THF), compound **6** (1.00 g, 2.85 mmol) and $Bi(NO_3)_3·5H_2O$ (136 mg, 0.280 mmol) gave compound **9b** (204 mg, 0.560 mmol, 20%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.40) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.47 (dd, J = 13.6, J = 8.8 Hz, 1 H), 2.88 (s, 3 H), 3.17–3.21 (m, 2 H), 3.41 (A-part of an AB-system, J = 13.2 Hz, 1 H), 3.56 (B-part of an AB-system, J = 13.2 Hz, 1 H), 3.58 (d, J = 13.9 Hz, 1 H), 3.64 (s, 3 H), 4.10 (d, J = 13.9 Hz, 1 H), 5.98 (d, J = 9.3 Hz, 1 H), 7.16–7.33 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 33.61 (CH_3), 42.08 (CH), 52.20 (CH_3), 54.32 (CH_2), 55.32 (CH_2), 57.36 (CH_2), 122.05 (CH), 126.19 (2 CH), 127.14 (CH), 128.18 (2 CH), 128.84 (2 CH), 129.03 (CH), 129.07 (2 CH), 135.27 (C), 138.28 (C), 141.60 (C), 168.88 (C), 173.00 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3061 (w), 2953 (w), 1734 (s), 1647 (s), 1449 (m), 1436 (m), 1386 (m), 1347 (m), 1312 (m), 1252 (m), 1204 (m), 1168 (m), 1072 (m), 1030 (m), 859 (m), 769 (s), 740 (m), 699 (vs) cm^{-1}. MS (EI, 70 eV): m/z (%) = 364 (27) [M^+], 307 (60), 278 (35), 244 (10), 216 (17), 204 (49), 158 (26), 144 (19), 118 (27), 91 (100). HRMS (EI, 70 eV): calcd. 364.1787 (for $C_{22}H_{24}N_2O_3$); found 364.1791 [M^+]. $C_{22}H_{24}N_2O_3$ (364.44).

Methyl 1-Allyl-4-benzyl-2-oxo-8-phenyl-1,2,3,4,5,6-hexahydro-1,4-diazocin-6-carboxylate (9c): According to general procedure A, reaction of allylamine (479 mg, 8.40 mmol), compound **6** (1.00 g, 2.85 mmol) and $Bi(NO_3)_3·5H_2O$ (136 mg, 0.280 mmol) gave compound **9c** (339 mg, 0.868 mmol, 31%) after chromatography (SiO_2, hexane/EA, 2:1, R_f = 0.43) as a yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.56 (dd, J = 13.4, J = 8.8 Hz, 1 H), 3.22–3.34 (m, 3 H), 3.50 (A-part of an AB-system, J = 13.2 Hz, 1 H), 3.66 (d, J = 13.9 Hz, 1 H), 3.67 (B-part of an AB-system, J = 13.0 Hz, 1 H), 3.74 (s, 3 H), 4.21 (d, J = 14.0 Hz, 1 H), 4.78 (dd, J = 14.3, J = 5.6 Hz, 1 H), 5.05 (d, J = 17.1 Hz, 1 H), 5.14 (d, J = 10.0 Hz, 1 H), 5.81 (dddd, J = 17.1, J = 10.0, J = 7.9, J = 5.8 Hz, 1 H), 6.13 (d, J = 9.4 Hz, 1 H), 7.30–7.45 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 41.94 (CH), 47.48 (CH_2), 52.29 (CH_3), 53.92 (CH_2), 55.34 (CH_2), 57.53 (CH_2), 199.43 (CH_2), 123.68 (CH), 126.37 (3 CH), 127.48 (CH), 128.21 (2 CH), 128.85 (3 CH), 129.14 (CH), 129.35 (CH), 131.38 (C), 137.28 (C), 140.15 (C), 167.57 (C), 172.60 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3060 (w), 2950 (w), 1733 (s), 1644 (s), 1447 (m), 1435 (m), 1396 (m), 1335 (m), 1306 (m), 1254 (m), 1197 (m), 1166 (s), 1134 (m), 1097 (m), 1076 (m), 1028 (m), 1000 (m), 926 (m), 767 (s), 741 (m), 696 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 390 (28) [M^+], 307 (19), 230 (17), 202 (76), 170 (13), 134 (16), 91 (100). HRMS (EI, 70 eV): calcd. 390.1943 (for $C_{24}H_{26}N_2O_3$); found 390.1947 [M^+]. $C_{24}H_{26}N_2O_3$ (390.48).

4-Methyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-thiazocin-7-carboxylic Acid (14): A solution of LiOH in H_2O (c = 2 mol dm^{-3}, 16.8 mmol, 8.40 mL) was added to compound **8b** (490 mg, 1.68 mmol) in EtOH (8.5 mL) and the resulting mixture was stirred for 2 h at 70 °C. After cooling to ambient temperature, it was diluted with H_2O (12 mL) and washed with CH_2Cl_2 (30 mL). The aqueous layer was acidified with concentrated hydrochloric acid (ca. 5 mL) and extracted with MTBE (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated to give compound **14** (390 mg, 1.41 mmol, 84%) as an analytically pure product without purification and as beige solid, mp. 148 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.73 (dd, J = 9.7, J = 14.0 Hz, 1 H), 3.04 (s, 3 H), 3.15 (A-part of an AB-system, J = 13.9 Hz, 1 H), 3.32 (B-part of an AB-system, J = 13.8 Hz, 1 H), 3.51 (t, J = 9.6 Hz, 2 H), 6.04 (d, J = 9.9 Hz, 1 H), 7.38–7.44 (m, 5 H), 11.31 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 30.93 (CH_2), 31.20 (CH_2), 34.15 (CH_3), 47.40 (CH), 122.14 (CH), 126.10 (2 CH), 129.10 (2 CH), 129.65 (CH), 134.40 (C), 142.39 (C), 171.32 (C), 175.75 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2969 (w), 2925 (w), 1737 (s), 1712 (vs), 1608 (s), 1433 (m), 1380 (s), 1317 (m), 1192 (s), 1109 (w), 881 (m), 767 (s), 697 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 277 (19) [M^+], 230 (16), 220 (51), 186 (23), 158 (14), 118 (33), 89 (51), 45 (100). $C_{14}H_{15}NO_3S$ (277.34): calcd. C 60.63, H 5.45, N 5.05; found C 60.82, H 5.11, N 5.18. HRMS (EI, 70 eV): calcd. 277.0773 (for $C_{14}H_{15}NO_3S$); found 277.0776 [M^+].

4-Methyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-thiazocin-7-carboxylic Acid (4-Iodophenyl)amide (15): DCC (123 mg, 0.595 mmol) was added to a cooled (ice-water bath) solution of compound **14** (150 mg, 0.541 mmol) in CH_2Cl_2 (3 mL). After stirring the mixture for 1 min, HOBt (100 mg, 0.649 mmol) was added, and the mixture was stirred further for 1 min at 23 °C. 4-Iodoaniline (237 mg, 1.08 mmol) was then added and the mixture stirred for 16 h at 50 °C. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with sat. NH_4Cl solution (20 mL), sat. $NaHCO_3$ solution (20 mL) and H_2O (20 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated. The residue was chromatographed (SiO_2, hexane/EA, 2:1, R_f = 0.21) to give compound **15** (180 mg, 0.379 mmol, 70%) as a yellow solid, mp. 106 °C. Single crystals were obtained by slow diffusion of hexane into a CH_2Cl_2 solution. ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.91 (dd, J = 9.6, J = 13.8 Hz, 1 H), 3.01 (d, J = 13.9 Hz, 1 H), 3.06 (A-part of an AB-system, J = 13.6 Hz, 1 H), 3.15 (s, 3 H), 3.56 (t, J = 9.6 Hz, 1 H), 3.63 (B-part of an AB-system, J = 13.7 Hz, 1 H), 6.26 (d, J = 9.8 Hz, 1 H), 7.40–7.42 (m, 5 H), 7.53–7.56 (m, 2 H), 7.63–7.66 (m, 2 H), 10.24 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 31.16 (CH_2), 32.19 (CH_2), 34.23 (CH_3), 49.12 (CH_2), 87.20 (C), 121.61 (2 CH), 124.40 (CH), 126.06 (2 CH), 129.10 (2 CH), 129.57 (CH), 134.33 (C), 137.85 (2 CH), 138.65 (C), 141.27 (C), 170.82 (C), 171.54 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3258 (w), 3104 (w), 2927 (w), 1687 (s), 1631 (vs), 1532 (s), 1483 (s), 1389 (s), 1303 (m), 1241 (m), 1157 (m), 1061 (m), 1002 (s), 821 (vs), 762 (vs), 691 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 478 (45) [M^+], 421 (100), 374 (32), 260 (21), 232 (92), 186 (50),

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158 (36), 118 (35), 91 (17). $C_{20}H_{19}IN_2O_2S$ (478.35): calcd. C 50.22, H 4.00, N 5.86; found C 49.83, H 4.27, N 5.41.

Methyl 4-Methyl-3-oxo-5-phenyl-3,4,7,8-tetrahydro-2*H*-1,4-oxazocine-7-carboxylate (10): Methylamine (c = 2 mol dm^{-3} solution in THF, 0.5 mL, 1 mmol) was added to a cooled (ice-water bath) solution of compound **7** (135 mg, 0.516 mmol) and pTosOH (89 mg, 0.52 mmol) in THF (1 mL) and the mixture stirred in a tightly closed reaction vial for 1 h at 0 °C and then 16 h at 80 °C. After cooling to ambient temperature, the solvent was evaporated and the residue chromatographed (SiO_2, hexane/EA, 1:1). In a first fraction (R_f = 0.28) compound **10** was isolated (45 mg, 0.16 mmol, 32%) as a colorless solid, mp. 115 °C. In a second fraction (R_f = 0.03) byproduct **16** was isolated (17 mg, 0.058 mmol, 11%) as a pale yellow oil. Single crystals of product **10** were obtained by slow diffusion of hexane into a CH_2Cl_2 solution. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.91 (s, 3 H), 3.29–3.38 (m, 2 H), 3.71 (s, 3 H), 4.05 (d, J = 12.5 Hz, 1 H), 4.19 (d, J = 8.8 Hz, 1 H), 4.23 (d, J = 12.5 Hz, 1 H), 5.95 (d, J = 8.9 Hz, 1 H), 7.27–7.39 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 34.11 (CH_3), 46.35 (CH), 52.52 (CH_3), 69.57 (CH_2), 69.66 (CH_2), 120.16 (CH), 126.39 (2 CH), 128.96 (2 CH), 129.35 (CH), 135.13 (C), 142.97 (C), 169.22 (C), 171.59 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2952 (m), 1732 (vs), 1653 (vs), 1446 (s), 1388 (s), 1303 (m), 1196 (m), 1091 (s), 921 (s), 856 (m), 786 (vs), 699 (vs) cm^{-1}. MS (EI, 70 eV): m/z (%) = 275 (7) [M$^+$], 218 (100), 186 (36), 158 (22), 118 (46). HRMS (ESI): calcd. 298.1055 (for $C_{15}H_{17}NNaO_4$); found 298.1059 [M + Na$^+$]. $C_{15}H_{17}NO_4$ (275.30).

2-[2-(Methoxycarbonyl)-4-oxo-4-phenylbutoxy]-*N*-methylacetamide (16): Compound **16** (17 mg, 0.058 mmol, 11%) was isolated as a byproduct during the synthesis of compound **10** (chromatography on SiO_2, hexane/EA, 1:1, R_f = 0.03). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.85 (d, J = 5.0 Hz, 3 H), 3.25 (dd, J = 17.7, J = 6.2 Hz, 1 H), 3.42 (pent, J = 5.8 Hz, 1 H), 3.55 (dd, J = 17.7, J = 6.7 Hz, 1 H), 3.74 (s, 3 H), 3.75–3.83 (m, 2 H), 3.94 (A-part of an AB system, J = 15.4 Hz, 1 H), 3.96 (B-part of an AB system, J = 15.3 Hz, 1 H), 6.82 (br. s, 1 H; NH), 7.46–7.53 (m, 2 H), 7.56–7.63 (m, 1 H), 7.94–8.03 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 25.48 (CH_3), 37.03 (CH_2), 40.77 (CH), 52.22 (CH_3), 70.42 (CH_2), 71.41 (CH_2), 127.98 (2 CH), 128.63 (2 CH), 133.45 (CH), 136.21 (C), 169.82 (C), 173.62 (C), 197.29 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3350 (m), 2953 (m), 1733 (s), 1673 (vs), 1543 (s), 1450 (m), 1223 (s), 1170 (s), 1111 (vs), 1004 (m), 758 (s), 692 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 294 (4) [M$^+$], 221 (27), 191 (21), 174 (39), 142 (34), 120 (25), 105 (100). HRMS (ESI): calcd. 316.1161 (for $C_{15}H_{19}NNaO_5$); found 316.1153 [M + Na$^+$]. $C_{15}H_{19}NO_5$ (293.32).

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[12] CCDC-739826 (for **15**) and -741031 (for **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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