DOI: 10.1002/ejoc.200700263

Eight-Membered-Ring Lactams – New Scaffolds for Combinatorial Chemistry Prepared by Ring-Expansion of 1,4-Diketones with Primary Amines

Rebekka Pflantz,[a] Patrick Tielmann,[b] Michael Rössle,[a] Christoph Hoenke,[b] and Jens Christoffers*[a]

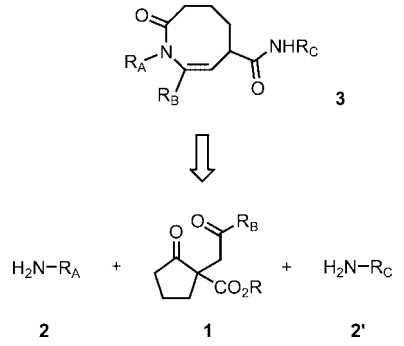
Keywords: Ketones / Lactams / Ring expansion / Heterocycles / Combinatorial chemistry

Eight-membered-ring lactams were prepared by the Bi-catalyzed reaction of 1,4-diketones with primary amines. These lactams define a new type of non-planar molecular scaffold with three points allowing for diversification, which were evaluated as the basis for combinatorial library synthesis. For this reason, reaction conditions were optimized, and the scope and limitations were investigated. After the Bi-catalyzed reaction, further diversification was achieved by ester saponification and subsequent amide formation with HATU and another primary amine. Representative examples of a model library showed sufficient stability in DMSO and solubility in aqueous buffer, which are mandatory prerequisites due to our in-house combinatorial chemistry criteria for library production.

Introduction

In contrast to their congeners with a smaller ring size, eight-membered-ring lactams (2-azocanones) are relatively rare structural motifs in natural products.[1] Nevertheless, these heterocycles are significant from a medicinal chemistry perspective. Tailored biologically active compounds of this type are mostly benzo-annulated or fused with other heterocycles.[2] With at least one endocyclic C–C double bond (i.e. hexahydroazocinones), they adopt a conformation that makes them attractive peptide building blocks, since they are known to mimic a dipeptide β-turn.[3]

Common routes to these medium-ring lactams either start from acyclic compounds or utilize sigmatropic rearrangements[4] or C–C cleavage reactions in azabicyclo[3.3.0]octanone systems.[5] However, elaborated synthetic precursors are generally required for all the syntheses published so far. As a result of attempted syntheses of pyrrole-derivatives from 1,4-diketones **1** and primary amines **2** (Paal–Knorr synthesis),[6] we have recently observed a new, elegant and relatively simple route to unsaturated 2-azocanone derivatives **3** (1,4,5,6,7,8-hexahydroazocin-8-ones, Scheme 1) by the transformation of readily available starting materials **1** and **2**.[7]



Scheme 1. Eight-membered-ring lactams **3** as molecular scaffolds for combinatorial chemistry.

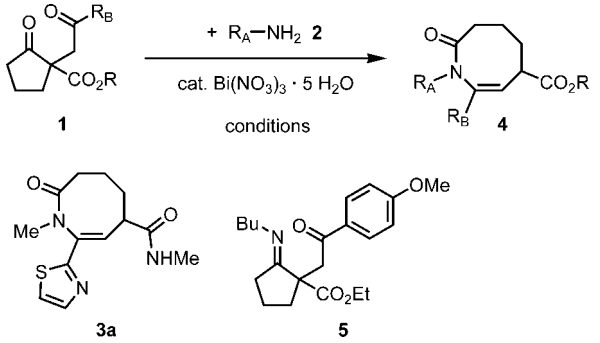
Since hexahydroazocinones were reported to exist in a folded conformation,[8] compounds **3** represent an attractive molecular scaffold for combinatorial chemistry. In our continuing efforts to identify sophisticated structural motifs as a basis for combinatorial library synthesis in drug discovery, we are interested in such non-planar and easily accessible scaffolds, which provide several points of diversification.[9] Such three-dimensional scaffolds open additional possibilities for adapting the shape of drug molecules to the requirements of binding sites on biological targets.[9a] Herein, we wish to report on studies exploring scaffolds **3** as the basis of library synthesis. Two points of diversity in structures **3** are the residues R_A at N-1 and R_B at C-2 originating from diketones **1** and primary amines **2**, respectively. As an additional site for further diversifying functionalization (R_C) we considered the carboxylate moiety at C-4, which could be converted with another amine **2′** to carboxamides after saponification (Scheme 1).

[a] Institut für Reine und Angewandte Chemie der Universität Oldenburg,
Carl von Ossietzky-Strasse 9–11, 26111 Oldenburg, Germany
Fax: +49-441-798-3873
E-Mail: jens.christoffers@uni-oldenburg.de
[b] Boehringer Ingelheim Pharma GmbH & Co. KG, Abteilung Chemische Forschung,
Birkendorfer Strasse 65, 88397 Biberach an der Riß, Germany

Results and Discussion

Synthesis of Lactams

The starting point of this project was our interest in carbonyl compounds **1**. We have recently developed a new route to these 1,4-diketones by the oxidative coupling of β-keto esters with styrene, applying a cerium catalyst.[10] The key feature of this process is the use of molecular oxygen to regenerate the catalytically active Ce^{IV}/Ce^{III} redox system. In order to prove the utility of our products **1**, we have aimed to convert them into highly substituted dihydropyrrole derivatives bearing at least one quaternary C atom within the five-membered ring. The most challenging aspect of this work seemed to be the acid-catalyzed reaction of primary amines, yielding *N*-substituted dihydropyrroles. $BuNH_2$ (**2a**) was chosen as a model amine to search for suitable reaction conditions, and we have investigated its reaction with some 1,4-diketones **1** (e.g. the six- and seven-membered-ring congener of compound **1a**). Unfortunately, only the cyclopentanone starting material **1a** gave a unique product, which surprisingly, turned out not to be a pyrrole derivative but a new eight-membered-ring lactam **4aa** (Scheme 2 and Table 1, Entry 1). All other diketone substrates investigated led to hardly separable mixtures consisting mostly of known compounds. After experimentation with several Brønsted- or Lewis-acid catalysts to optimize the reaction conditions leading to compound **4aa**, we finally worked out a protocol using THF as the solvent, an excess of amine **2a** (5 equiv.) and a substoichiometric amount of $Bi(NO_3)_3{\cdot}5H_2O$ as the catalyst, which has previously been reported to be effective in Paal–Knorr pyrrole syntheses.[11] With 5 mol-% of Bi catalyst, the mixture was kept for 2 d at 70 °C in a tightly closed reaction flask. After work-up and chromatographic purification on basic Al_2O_3 (decomposition was observed on SiO_2), **4aa** was isolated in 61% yield (Entry 1). Using more catalyst and higher temperatures applying microwave irradiation did not improve the results (Table 1, Entry 2 and Scheme 2).



Scheme 2. Synthesis of 8-oxo-1,4,5,6,7,8-hexahydroazocin-4-carboxylates **4** and structures of byproducts **3a** and **5**. For starting materials, conditions and yields, see Table 1.

With the less sterically demanding methylamine (**2b**), the yield of the reaction with ester **1a** was significantly higher (Entry 3). Under the same conditions, benzyl (**2c**), allyl (**2d**) and substituted benzylamine (**2e**) gave lower yields (e.g. 37% yield of **4ac**, Table 1, Entry 4); however, an increase in yield (57–71%) was achieved by applying an excess (10 equiv.) of the amine (Table 1, Entries 5, 7, and 8). A higher reaction temperature (100 °C, microwave irradiation, Table 1, Entry 6) gave no further improvement. The method turned out to be tolerant to a *tert*-butyl carboxylate group like in β-alanine derivative **2f**. However, the yield in this case dropped somewhat (Table 1, Entry 9). The conversion of diketone **1a** with amines having a secondary α-carbon like cyclohexylamine (**2g**), which required 100 °C, 4 d, 10 equiv. of amine and 10 mol-% of Bi catalyst to achieve a 40% yield, seemed to be particularly challenging (Table 1, Entry 10). With 2-aminopentane or cyclopropylamine, no positive result was obtained. Other amines investigated were 2-aminomethylthiazole, propargylamine, aniline, and 2,2,2-trifluoroethylamine, the latter with reaction temperatures up to 150 °C (45 min, microwave irradiation), but either no conversion and/or unspecified decomposition was observed.

Next, we investigated the reaction of benzyl ester **1b** (R = Bn, R_B = Ph) and 2-(methylthio)ethyl ester **1c** (R = Mte, R_B = Ph) with amines **2c**, **2d**, and **2e** (Table 1, Entries 11–20). The yields were generally lower (up to 47% with 10 equiv. of amine and 10 mol-% of Bi salt), but a 72% yield was reached with 20 mol-% catalyst (product **4bc**, Table 1, Entry 12). Thus, the variation of the ester moiety did not result in an improved eight-membered-ring lactam synthesis.

We were interested further in the variation of the benzoyl moiety in starting materials **1**. Therefore, electron-rich (R_B = 4-$MeOC_6H_4$, **1d**, Table 1, Entries 21–23) and electron-poor, sterically demanding (R_B = 2-ClC_6H_4, **1e**, Table 1, Entries 24 and 25) phenyl groups, as well as electron-rich (R_B = 2-thiazolyl, **1f**, Table 1, Entries 26–28) and electron-poor (R_B = 4-pyridyl, **1g**, Table 1, Entry 29) heteroaromatics were chosen. Yields were generally moderate, except for the reaction with methylamine (**2b**, Table 1, Entries 22 and 26). Interestingly, **1f** gave amidated product **3a** with 5 equiv. of the small amine **2b** (Table 1, Entry 27). If a smaller excess of **2b** (2 equiv.) was used, the expected product **4fb** was obtained (Table 1, Entry 26). *p*-Methoxy derivative **1d** did not react with butylamine **2a** at 70 °C, and the temperature had to be raised to 100 °C (1 h, microwave irradiation) to yield **4da** (21%). However, imine **5** was isolated as a byproduct (22% yield) under these conditions (Table 1, Entry 21). Product **4ga** was obtained in moderate yield (45%, Table 1, Entry 29) from pyridine derivative **1g** and butylamine **2a**, and could not be completely purified by HPLC.

If aromatic residues R_B were replaced in the starting materials by the *tert*-butyl (**1h**, R_B = *t*Bu) or methyl (**1i**, R_B = Me) groups, no conversion with benzylamine **2c** was observed in this aliphatic series, even at temperatures up to 150 °C (microwave irradiation).

In summary, eight-membered-ring lactams **4** are accessible from α-phenacyl-β-oxo esters **1** and primary alkyl, allyl and benzylamines. For these amines, some functionalization was tolerated as was shown for alkoxy- and ester-substituted derivatives. For α-branched primary amines like cy-

Table 1. Starting materials, reaction conditions, and yields for products **4xy**[a] [Mte = 2-(methylthio)ethyl].

Entry	**1**	R	R_B	**2** (equiv.)	R_A	$Bi(NO_3)_3 \cdot 5H_2O$ [mol-%]	Conditions	Product **4** (yield)
1	**1a**	Et	Ph	**2a** (5)	Bu	5	70 °C, 2 d	**4aa** (61%)
2				**2a** (5)		10	100 °C, 0.5 h[b]	**4aa** (30%)[b]
3	**1a**	Et	Ph	**2b** (5)	Me	10	70 °C, 2 d	**4ab** (84%)
4	**1a**	Et	Ph	**2c** (5)	Bn	5	70 °C, 2 d	**4ac** (37%)
5				**2c** (10)		5	70 °C, 3 d	**4ac** (67%)
6				**2c** (5)		10	100 °C, 6 h[b]	**4ac** (37%)
7	**1a**	Et	Ph	**2d** (10)	allyl	5	70 °C, 3 d	**4ad** (71%)
8	**1a**	Et	Ph	**2e** (10)	4-$MeOC_6H_4CH_2$	5	70 °C, 2 d	**4ae** (57%)
9	**1a**	Et	Ph	**2f** (5)	$tBuO_2CCH_2CH_2$	10	70 °C, 2 d	**4af** (41%)
10	**1a**	Et	Ph	**2g** (10)	*c*Hex	10	100 °C, 4 d	**4ag** (40%)
11	**1b**	Bn	Ph	**2c** (10)	Bn	10	70 °C, 2 d	**4bc** (47%)
12				**2c** (5)		20	70 °C, 2 d	**4bc** (72%)
13	**1b**	Bn	Ph	**2d** (10)	allyl	5	70 °C, 3 d	**4bd** (35%)
14				**2d** (10)		10	70 °C, 4 d	**4bd** (39%)
15	**1b**	Bn	Ph	**2e** (10)	4-$MeOC_6H_4CH_2$	5	70 °C, 2 d	**4be** (10%)
16				**2e** (10)		10	70 °C, 3 d	**4be** (13%)
17	**1c**	Mte	Ph	**2c** (10)	Bn	5	70 °C, 2 d	**4cc** (23%)
18	**1c**	Mte	Ph	**2d** (10)	allyl	5	70 °C, 3 d	**4cd** (28%)
19				**2d** (10)		10	70 °C, 2 d	**4cd** (47%)
20	**1c**	Mte	Ph	**2e** (10)	4-$MeOC_6H_4CH_2$	10	70 °C, 3 d	**4ce** (47%)
21	**1d**	Et	4-$MeOC_6H_4$	**2a** (5)	Bu	10	100 °C, 1 h[b]	**4da** (21%)[b,c]
22	**1d**	Et	4-$MeOC_6H_4$	**2b** (5)	Me	10	80 °C, 3 d	**4db** (51%)
23	**1d**	Et	4-$MeOC_6H_4$	**2c** (5)	Bn	10	70 °C, 3 d	**4dc** (32%)[d]
24	**1e**	Et	2-ClC_6H_4	**2b** (5)	Me	10	80 °C, 3 d	**4eb** (46%)
25	**1e**	Et	2-ClC_6H_4	**2c** (5)	Bn	10	70 °C, 3 d	**4ec** (49%)[e]
26	**1f**	Et	2-thiazolyl	**2b** (2)	Me	10	70 °C, 2 d	**4fb** (66%)
27				**2b** (5)		10	70 °C, 2 d	**3a**[f]
28	**1f**	Et	2-thiazolyl	**2c** (5)	Bn	10	70 °C, 3 d	**4fc** (25%)
29	**1g**	Et	4-pyridyl	**2a** (5)	Bu	10	70 °C, 4 d	**4ga** (45%)[e]

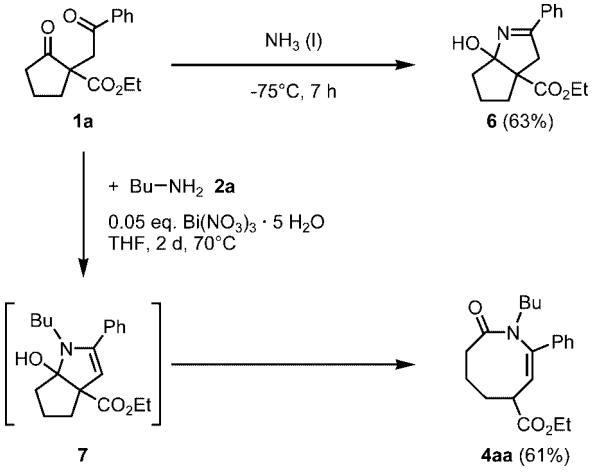
[a] Letter **x** indicates the 1,4-diketone **1x**, letter **y** indicates the amine **2y**. [b] Microwave irradiation. [c] Compound **5** (22% yield, 70% purity by LCMS) was formed as a byproduct. [d] 95% pure by LCMS. [e] 90% pure by LCMS. This compound could not be further purified by HPLC. [f] When 5 equiv. of amine **2b** were employed, **3a** (10% yield, purity 70% by LCMS) was isolated exclusively.

clohexylamine, higher reaction temperatures and larger amounts of the catalyst were required, or they did not give a single reaction product, as in the case for 2-aminopentane and cyclopropylamine. Furthermore, the reaction seems to be limited to amines of sufficient nucleophilicity since the more electron-deficient and less nucleophilic amines like propargylamine, aniline, and 2,2,2-trifluoroethylamine did not lead to the desired products.

Besides the amine part, the influence of the substituents of the 1,4-dicarbonyl substrates has been investigated. Here, different ester groups (R = Et, Bn or Mte) worked equally well, resulting in comparable product yields in the lactam formation. Furthermore, the reaction was tolerant to the variation of the aryl residue R_B, which could be phenyl, *p*-methoxyphenyl, *o*-chlorophenyl, 2-thiazolyl or 4-pyridyl. However, if R_B was an alkyl group like Me or *t*Bu, no product was obtained.

Mechanistic Considerations

When reacted with aqueous ammonia at ambient or higher temperatures, starting material **1a** led to complex product mixtures. When the reaction was performed at –75 °C with an excess of liquid ammonia in the presence of molecular sieves (4 Å), a single product was obtained. The constitution of the crystalline product **6** (Scheme 3) was previously established by single-crystal X-ray crystallography.[10b] Its 2-azabicyclo[3.3.0]octane skeleton provides strong evidence for a mechanistic proposal of the formation of eight-membered-ring lactams **4**. The primary amine **2** seems to react with both ketone moieties of diketone **1a** and forms a bicyclic hemiaminal-enamine **7** as a reaction

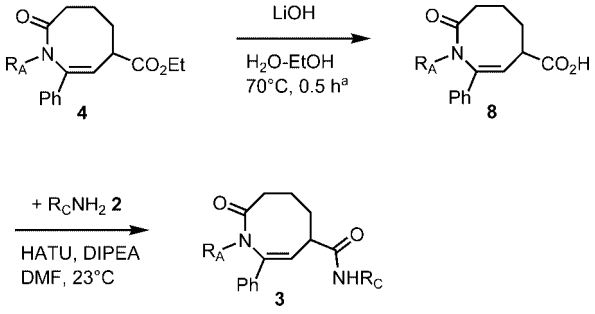


Scheme 3. Mechanistic proposal for eight-membered-ring lactam formation.

intermediate with the C–C double bond in a fixed (*Z*) configuration. A subsequent retro-Claisen reaction cleaves the central bond (between C-1 and C-5) of bicyclic **7** and forms a monocyclic eight-membered-ring product **4**. Similar retro-Claisen reactions of bicyclic intermediates were recently reported for the formation of heterocyclic seven-membered rings[12] (Scheme 3).

Derivatization of Lactams

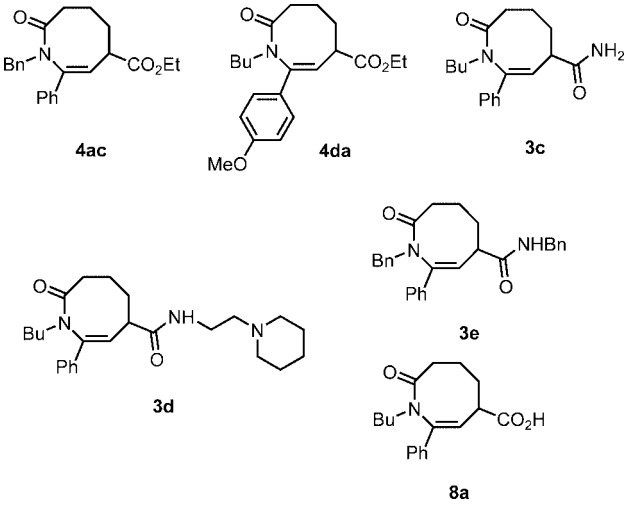
In order to explore the third point of diversification within this compound class, we submitted lactams **4aa** (R_A = Bu and R_B = Ph) and **4ac** (R_A = Bn and R_B = Ph) to ester saponification with LiOH under microwave irradiation (Scheme 4, Table 2). Carboxylic acid **8a** was obtained in quantitative yield from ester **4aa**. For compound **8b** (from ester **4ac**) the yield was moderate (47%). Both carboxylic acids were purified by HPLC. Amide formation was performed with phenyl-substituted ethylamine **2h**, ammonia (**2i**), piperidine derivative **2j**, and benzylamine (**2c**) using HATU-DIPEA as the coupling reagents.[13] Yields of amides **3b**–**3e** after purification by HPLC were good (65–99%, Scheme 4). A fifth compound, *N*-methylamide **3a**, was obtained earlier (Scheme 2, Table 1, Entry 27).



Scheme 4. Ester saponification and amide formation.

Stability and Solubility

Due to our in-house criteria for library production, we investigated the solubility and stability of the small set of synthesized library representatives. Since libraries of single compounds are commonly used for activity screening in physiological buffer and stored over a longer period of time as solutions in frozen DMSO, the prerequisites of high stability in DMSO and sufficient solubility in water are mandatory. We were therefore interested in the stability of our lactams **4** in DMSO under ambient conditions in order to simulate long-term storage in DMSO at –18 °C. For this reason, we exposed wet DMSO solutions of compounds **4ac** and **4da** (Scheme 5) for two weeks to air at 23 °C. In both cases, no decomposition was detectable by LCMS. Therefore, we conclude that lactams **4** fulfil our stability criteria so that the corresponding DMSO solutions are well suited for storage and handling during screening for biological activity (Scheme 5).



Scheme 5. Compounds for stability and solubility tests.

Furthermore, the solubility of compounds under physiological conditions should be an essential precondition for studying biological activity in screening programs. To obtain a good estimation about some general solubility issues of a broad range of library members, we have chosen a hydrophilic (**3c**, neutral), basic (**3d**, protonated at pH 7.4), acidic (**8a**, deprotonated at this pH), and lipophilic candidate (**3e**) from our compounds. After dilution of a DMSO stock solution with PBS buffer (pH 7.4),[14] filtration or centrifugation and reextraction into organic solvent, the recovery was determined by LC. At concentrations of 10^{-6} and 10^{-5} mol dm^{-3} the recovery of all four compounds was quantitative within experimental error. At 10^{-4} mol dm^{-3} only the lipophilic triphenyl-substituted derivative **3e** was not completely solubilized. Since this is, to our experience, not a critical issue, we can conclude that all four compounds show sufficient experimental solubility in order to perform bioactivity studies in a buffered aqueous environment. Thus, no limitations have to be considered for the selection of substituents in the final library of eight-membered-ring lactams.

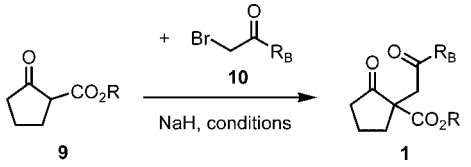
Table 2. Results of ester saponification and amidation.

Entry	Lactam **4**	R_A	Acid **8** (yield)	**2**, R_C (amine)	Amide **3** (yield)
1	**4aa**	Bu	**8a** (97%)	**2h**, 2-$ClC_6H_4CH_2CH_2$	**3b** (87%)
				2i, H (ammonia)	**3c** (84%)
				2j, cyclo-$(CH_2)_5NCH_2CH_2$	**3d** (65%)[a]
2	**4ac**	Bn	**8b** (47%)	**2c**, Bn	**3e** (99%)

[a] Isolated as the TFA salt.

Synthesis of Starting Materials

As mentioned in the introduction, 1,4-diketone **1a** can be prepared by the cerium-catalyzed oxidative coupling of β-oxo ester **9a** with styrene.[10] Since this procedure is hardly adopted to other styrene derivatives or vinyl-substituted heteroaromatic compounds, we decided to access a series of 1,4-diketones **1a**–**1i** by the S_N2 reaction of β-oxo esters **9a**–**9c** with α-bromoacetophenones **10a**–**10c** or their heteroaromatic analogues **10d** and **10e** (Scheme 6).[15] Moreover, we used α-bromopinacolone **10f** in order to prepare aliphatic congener **1h**. However, attempts to prepare compound **1i** (R = Et and R_B = Me) by the reaction of β-oxo ester **9a** with α-bromoacetone resulted in low conversions. Thus, diketone **1i** was synthesized by a known[16] two-step sequence consisting of the propargylation of β-oxo ester **9a** and the subsequent HgO-catalyzed addition of water to the C–C triple bond.



Scheme 6. Alkylation of β-keto esters **9** with α-bromo ketones **10** to give 1,4-diketones **1**. For conditions and yields, see Table 3.

Products **1a**–**1c** were obtained by the reaction of β-oxo esters **9a**–**9c** with phenacyl bromide **10a** with NaH (60% in mineral oil) as the base in THF at 70 °C in 65–80% yield after chromatographic purification. For the preparation of **1d**–**1g**, we used NaH without oil (95%) and Et_2O as the solvent, and the reactions proceeded readily at 23 °C with full conversion after 16 h. The same was true for compound **1h**, which was prepared in DMF applying NaH (60% in mineral oil) as the base. In three cases (**1d**, **1e**, and **1g**) products were isolated by extraction and used without further purification. Compounds **1f** and **1h** were purified by preparative HPLC and column chromatography, respectively (Scheme 6).

Conclusions

The bismuth nitrate catalyzed reaction of 1-phenacyl-2-oxocyclopentane-1-carboxylates **1** with primary amines **2** yielded eight-membered-ring lactams **4** with one enamide moiety. These lactams **4** constitute a new type of nonplanar molecular scaffold and could be applied as a basis for combinatorial library synthesis. Therefore, we optimized the conditions and evaluated the scope and limitations of this reaction. The amines **2**, the aromatic ring and the ester groups in the carbonyl compounds **1** have been varied. Optimum reaction conditions were determined to be 2–4 d, 70–100 °C, 5–10 equiv. of amine **2** and 0.05–0.1 equiv. of the catalyst. Yields were highly dependent on the constitution of the starting materials and were as large as 84%. Performing the reactions under microwave irradiation did not generally improve the results.

We identified three points of diversification, with one resulting from the primary amines applied in the lactam formation and the second arising from the aromatic residue of the starting carbonyl compound. To diversify the third position, we cleaved the ethyl ester group with LiOH and coupled the resulting carboxylic acids **8** with HATU and further primary amines to give amides **3**.

Stability and solubility tests have been performed with representative examples of our small model library. As a result, compounds **3**, **4** and **8** turned out to be suitable for long-term storage as DMSO solutions and screening in aqueous buffer. Thus, these compounds fulfil our preconditions for library synthesis so that no limitations within the final library design have to be considered. In summary, the eight-membered-ring lactams proved to be well suited for library production.

Experimental Section

General Methods: Preparative column chromatography was carried out using Merck SiO_2 60 or basic Al_2O_3 with hexanes (PE, b.p. 40–60 °C) and ethyl acetate (EA) as eluents. Preparative HPLC was performed with an Agilent 1100 Series HPLC system (gradient elution with MeCN/H_2O, 0.1% TFA) equipped with a Gilson 215 Liquid Handler and ESI-MS detection (Thermo Finnigan Surveyor MSQ). ^1H and ^{13}C-NMR spectra were recorded on a Bruker Avance 500, Avance 400 and Avance 300. Multiplicities were determined with DEPT experiments. MS and HRMS spectra with EI and CI were obtained with a Finnigan MAT 95 spectrometer. IR spectra (ATR) were recorded on a Bruker Tensor 27 spectrometer. Elemental analyses were measured with an EA 1108 from Fisons Instruments. A Biotage Initiator microwave reactor with autosampler was used for heating with microwaves, P_{max} = 400 W. Compounds **1i**,[16] **2f**,[17] **9b**,[18] **9c**,[19] **10d**,[20] and **10e**[21] were prepared

Table 3. Phenacylation of β-keto esters **9** [Mte = 2-(methylthio)ethyl].

Entry	β-Keto ester **9**	Acyl bromide **10**	Conditions	Product **1** (yield)
1	**9a** (R = Et)	**10a** (R_B = Ph)	70 °C, 16 h, THF[a]	**1a** (80%)[b]
2	**9b** (R = Bn)	**10a** (R_B = Ph)	70 °C, 16 h, THF[a]	**1b** (71%)[b]
3	**9c** (R = Mte)	**10a** (R_B = Ph)	70 °C, 16 h, THF[a]	**1c** (65%)[b]
4	**9a** (R = Et)	**10b** (R_B = 4-$MeOC_6H_4$)	23 °C, 16 h, Et_2O[c]	**1d** (99%)[d]
5	**9a** (R = Et)	**10c** (R_B = 2-ClC_6H_4)	23 °C, 16 h, Et_2O[c]	**1e** (99%)[d]
6	**9a** (R = Et)	**10d** (R_B = 2-thiazolyl)	23 °C, 16 h, Et_2O[c]	**1f** (55%)[e]
7	**9a** (R = Et)	**10e** (R_B = 4-pyridyl)	23 °C, 16 h, Et_2O[c]	**1g** (83%)[d]
8	**9a** (R = Et)	**10f** (R_B = *t*Bu)	23 °C, 16 h, DMF[a]	**1h** (58%)[b]

[a] NaH (60% in mineral oil) was used. [b] Purified by column chromatography. [c] NaH (95%) was used. [d] Used without further purification. [e] Purified by preparative HPLC.

according to literature procedures. All other starting materials were commercially available. $MeNH_2$ (**2b**) was used as solution in THF (2 mol dm^{-3}), ammonia (**2i**) as solution in 1,4-dioxane (0.5 mol dm^{-3}). Spectra of compounds **1a**,[10c] and **3aa**[7] were in accordance with the literature. Compound **1h** appeared several times in the literature before, but no experimental details were so far published.[22] The preparation and data of compound **6** were reported before.[7]

Ethyl 2-Oxo-1-(2-oxo-2-phenylethyl)cyclopentane-1-carboxylate (1a). Typical Procedure: NaH (0.32 g, 7.7 mmol, 1.2 equiv., 60% dispersion in mineral oil) was added to a solution of β-oxo ester **9a** (1.0 g, 6.4 mmol) and phenacyl bromide **10a** (1.53 g, 7.69 mmol, 1.2 equiv.) in abs. THF (15 mL). The resulting mixture was heated to reflux for 16 h and then cooled to ambient temperature. Brine (10 mL) was added, and the layers were separated. The aqueous layer was extracted with EA (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by chromatography (SiO_2, PE/EA, 3:1, R_f = 0.33) to give compound **1a** (1.41 g, 5.14 mmol, 80%) as a colorless solid, m.p. 31 °C. HRMS (EI, 70 eV): calcd. 274.1205 (for $C_{16}H_{18}O_4$), found 274.1205 [M$^+$]. $C_{16}H_{18}O_4$ (274.31): calcd. C 70.06, H 6.61; found C 70.04, H 6.86.

Benzyl 2-Oxo-1-(2-oxo-2-phenylethyl)cyclopentane-1-carboxylate (1b): According to the procedure reported for compound **1a**, a mixture of β-oxo ester **9b** (2.0 g, 9.2 mmol), phenacyl bromide **10a** (2.19 g, 11.0 mmol, 1.2 equiv.) and NaH (0.44 g, 11.0 mmol, 1.2 equiv., 60% dispersion in mineral oil) in THF (20 mL) was converted to give compound **1b** (2.20 g, 6.54 mmol, 71%) as a colorless solid after chromatography (SiO_2, PE/EA, 3:1, R_f = 0.21), m.p. 68 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.04–2.20 (m, 3 H), 2.51–2.68 (m, 3 H), 3.50 (part A of an AB system, J = 18.5 Hz, 1 H), 3.86 (part B of an AB system, J = 18.5 Hz, 1 H), 4.77 (part A of an AB system, J = 16.4 Hz, 1 H), 5.53 (part B of an AB system, J = 16.4 Hz, 1 H), 7.26–7.36 (m, 5 H), 7.42–7.93 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 19.83 (CH_2), 33.37 (CH_2), 37.74 (CH_2), 43.52 (CH_2), 57.55 (C), 67.28 (CH_2), 127.85 (2 CH), 128.04 (2 CH), 128.24 (CH), 128.55 (2 CH), 128.62 (2 CH), 133.45 (CH), 135.45 (C), 136.29 (C), 170.55 (C), 196.64 (C), 214.70 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3029 (w), 2956 (w), 2920 (w), 1748 (s), 1715 (s), 1678 (s), 1595 (s), 1449 (s), 1352 (m), 1221 (m), 1180 (m), 1103 (s), 961 (s), 853 (s), 755 (vs), 696 (vs) cm^{-1}. MS (EI, 70 eV: *m*/*z* (%) = 336 (1) [M$^+$], 245 (53), 227 (35), 202 (18), 185 (51), 105 (70), 91 (100), 77 (24). HRMS (EI, 70 eV): calcd. 336.1362 (for $C_{21}H_{20}O_4$), found 336.1362 [M$^+$].

2-(Methylthio)ethyl 2-Oxo-1-(2-oxo-2-phenylethyl)cyclopentane-1-carboxylate (1c): According to the procedure reported for compound **1a**, a mixture of β-oxo ester **9c** (3.00 g, 14.8 mmol), phenacyl bromide **10a** (3.54 g, 17.8 mmol, 1.2 equiv.) and NaH (0.712 g, 17.8 mmol, 1.2 equiv., 60% dispersion in mineral oil) in THF (30 mL) was converted to give compound **1c** (3.08 g, 9.62 mmol, 65%) as a red oil after chromatography (SiO_2, PE/EA, 3:1, R_f = 0.29). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.07–2.09 (m, 1 H), 2.12 (s, 3 H), 2.18–2.35 (m, 2 H), 2.54–2.74 (m, 5 H), 3.47 (part A of an AB system, J = 18.5 Hz, 1 H), 3.85 (part B of an AB system, J = 18.5 Hz, 1 H), 4.28 (t, J = 6.9 Hz, 2 H), 7.43–7.95 (m, 5 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 15.61 (CH_3), 19.84 (CH_2), 32.37 (CH_2), 33.44 (CH_2), 37.77 (CH_2), 43.60 (CH_2), 57.59 (C), 63.73 (CH_2), 128.05 (2 CH), 128.60 (2 CH), 133.48 (CH), 136.34 (C), 170.47 (C), 196.61 (C), 214.59 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2961 (w), 2917 (w), 1750 (s), 1721 (vs), 1596 (s), 1448 (s), 1402 (m), 1353 (m), 1219 (s), 1150 (m), 1105 (m), 1001 (s), 854 (w), 753 (vs), 691 (vs) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 320 (1) [M$^+$], 247 (6) 201 (4), 173 (2), 105 (50), 74 (100). $C_{17}H_{20}O_4S$ (320.40): calcd. C 63.73, H 6.29; found C 64.02, H 6.42.

Ethyl 2-Oxo-1-[2-oxo-2-(4-methoxyphenyl)ethyl]cyclopentane-1-carboxylate (1d). Typical Procedure: NaH (702 mg, 27.8 mmol, 1.2 equiv., 95%) was added in small portions to a solution of β-oxo ester **9a** (3.78 g, 23.2 mmol) and phenacyl bromide **10b** (6.70 g, 27.8 mmol, 1.2 equiv.) in abs. Et_2O (80 mL). The resulting mixture was stirred at 23 °C for 16 h. Brine (40 mL) and EA (40 mL) were added and the resulting biphasic mixture slightly basified with aqueous NaOH (1 mol dm^{-3}, controlled by pH paper). After phase separation the aqueous layer was extracted with EA (2 × 40 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated. The crude compound **1d** (7.0 g, 23.0 mmol, 99%, 90% purity by LCMS) was obtained as yellow liquid and used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.23 (t, J = 6.9 Hz, 3 H), 2.07–2.18 (m, 3 H), 2.49–2.53 (m, 1 H), 2.59–2.63 (m, 2 H), 3.45 (part A of an AB system, J = 18.3 Hz, 1 H), 3.80 (part B of an AB system, J = 18.3 Hz, 1 H), 3.87 (s, 3 H), 4.17 (q, J = 6.6 Hz, 2 H), 6.91–6.93 (m, 2 H), 7.91–7.93 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 14.01 (CH_3), 19.86 (CH_2), 33.46 (CH_2), 37.79 (CH_2), 43.20 (CH_2), 55.50 (CH_3), 57.52 (C), 61.61 (CH_2), 113.77 (2 CH), 129.49 (C), 130.34 (2 CH), 163.74 (C), 170.85 (C), 195.19 (C), 215.22 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2976 (m), 2841 (w), 1749 (vs), 1719 (s), 1675 (s), 1599 (vs), 1510 (s), 1463 (m), 1403 (m), 1352 (m), 1258 (s), 1222 (s), 1167 (vs), 1111 (m), 1027 (s), 987 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 304 (4) [M$^+$], 259 (5), 231 (29), 203 (8), 150 (34), 135 (100), 92 (7), 77 (9). MS (ESI, positive mode), *m*/*z*: 305.2 [M + H$^+$]. HRMS (EI, 70 eV): calcd. 304.1310 (for $C_{17}H_{20}O_5$), found 304.1311 [M$^+$].

Ethyl 2-Oxo-1-[2-oxo-2-(2-chlorophenyl)ethyl]cyclopentane-1-carboxylate (1e): According to the procedure reported for compound **1d**, a mixture of β-oxo ester **9a** (3.24 g, 19.8 mmol), phenacyl bromide **10c** (5.52 g, 23.7 mmol, 1.2 equiv.) and NaH (601 mg, 23.8 mmol, 1.2 equiv., 95%) in Et_2O (80 mL) was converted to give compound **1e** (6.1 g, 19.8 mmol, 99%, 95% purity by LCMS) as a yellow liquid which was used without further purification. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.13–1.16 (t, J = 7.1 Hz, 3 H), 1.97–2.07 (m, 3 H), 2.39–2.44 (m, 2 H), 2.58–2.64 (m, 1 H), 3.38 (part A of an AB system, J = 18.7 Hz, 1 H, partially hidden by H_2O peak), 3.60 (part B of an AB system, J = 18.7 Hz, 1 H), 4.07 (q, J = 7.0 Hz, 2 H), 7.42–7.67 (m, 4 H) ppm. MS (ESI, positive mode), *m*/*z*: 309.1 [M + H$^+$]. $C_{16}H_{17}ClO_4$ (308.76).

Ethyl 2-Oxo-1-[2-oxo-2-(2-thiazolyl)ethyl]cyclopentane-1-carboxylate (1f): According to the procedure reported for compound **1d**, a mixture of β-oxo ester **9a** (216 mg, 1.32 mmol), phenacyl bromide **10d** (337 mg, 1.59 mmol, 1.2 equiv.) and NaH (40 mg, 1.59 mmol, 1.2 equiv., 95%) in Et_2O (10 mL) was converted to give compound **1f** (207 mg, 0.73 mmol, 55%) as a pale brown liquid after preparative HPLC. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.11 (t, J = 7.3 Hz, 3 H), 1.95–2.15 (m, 3 H), 2.39–2.45 (m, 2 H), 2.55–2.61 (m, 1 H), 3.43 (part A of an AB system, J = 18.7 Hz, 1 H), 3.91 (part B of an AB system, J = 18.7 Hz, 1 H), 4.06 (q, J = 7.3 Hz, 2 H), 8.16 (d, J = 3.1 Hz, 1 H), 8.24 (d, J = 3.1 Hz, 1 H) ppm. MS (ESI, positive mode), *m*/*z*: 282.1 [M + H$^+$]. $C_{13}H_{15}NO_4S$ (281.32).

Ethyl 2-Oxo-1-[2-oxo-2-(4-pyridyl)ethyl]cyclopentane-1-carboxylate (1g): According to the procedure reported for compound **1d**, a mixture of β-oxo ester **9a** (3.24 g, 19.8 mmol), phenacyl bromide **10e** (6.76 g, 23.8 mmol, 1.2 equiv., used as HBr-salt) and NaH (1.20 g, 47.6 mmol, 2.4 equiv., 95%) in Et_2O (100 mL) was converted to give compound **1e** (4.79 g, 16.5 mmol, 83%, 95% purity by LCMS) as a red liquid which was used without further purification. ^{1}H

NMR ($CDCl_3$, 500 MHz): δ = 1.24 (t, J = 7.1 Hz, 3 H), 2.07–2.14 (m, 2 H), 2.17–2.25 (m, 1 H), 2.55–2.58 (m, 2 H), 2.63–2.70 (m, 1 H), 3.40 (part A of an AB system, J = 18.7 Hz, 1 H), 3.81 (part B of an AB system, J = 18.7 Hz, 1 H), 4.18 (t, J = 7.1 Hz, 2 H), 7.71–7.73 (m, 2 H), 8.81–8.83 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 13.95 (CH_3), 19.79 (CH_2), 33.34 (CH_2), 37.57 (CH_2), 43.39 (CH_2), 57.38 (C), 61.83 (CH_2), 120.90 (2 CH), 142.14 (C), 150.94 (2 CH), 170.33 (C), 196.43 (C), 214.46 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2979 (m), 2909 (w), 2360 (w), 1751 (s), 1721 (vs), 1699 (s) 1557 (w), 1407 (m), 1224 (s), 1107 (m), 812 (m) cm^{-1}. HRMS (CI, isobutane): calcd. 276.1236 (for $C_{15}H_{18}NO_4$), found 276.1236 (100) [M + H^+]. $C_{15}H_{17}NO_4$ (275.30).

Ethyl 1-(3,3-Dimethyl-2-oxobutyl)-2-oxocyclopentane-1-carboxylate (1h): NaH (4.0 g, 100 mmol, 1 equiv., 60% dispersion in mineral oil) was portionwise added to a solution of β-oxo ester **9a** (15.6 g, 100 mol) in abs. DMF (200 mL) at 0 °C. After stirring for 15 min at this temperature α-bromo ketone **10f** was added dropwise and the resulting mixture was warmed to ambient temperature overnight. After removal of the solvent in vacuo the residue was agitated in water at 0 °C. Then, the resulting aqueous layer was threefold extracted with chloroform. The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was evaporated. The residue was purified by chromatography (SiO_2, PE/EA, 5:2, R_f = 0.48) to give compound **1h** (14.8 g, 58.2 mmol, 58%) as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.14 (s, 9 H), 1.23 (t, J = 7.0 Hz, 3 H), 1.89–1.95 (m, 1 H), 2.00–2.02 (m, 1 H), 2.07–2.15 (m, 1 H), 2.43–2.59 (m, 3 H), 2.82 (part A of an AB system, J = 18.6 Hz, 1 H), 3.51 (part B of an AB system, J = 18.6 Hz, 1 H), 4.14 (q, J = 7.0 Hz, 2 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.43 (CH_3), 20.20 (CH_2), 26.85 (3 CH_3), 33.74 (CH_2), 38.08 (CH_2), 42.42 (CH_2), 44.34 (C), 57.75 (C), 61.98 (CH_2), 171.15 (C), 213.46 (C), 215.51 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2967 (m), 2873 (w), 1751 (s), 1721 (vs), 1465 (m), 1366 (m), 1280 (m), 1225 (m), 1145 (m), 1111 (s), 1065 (s), 1002 (m), 865 (m) cm^{-1}. MS (EI, 70 eV), m/z (%): 254 (3) [M^+], 197 (58), 169 (42), 147 (5), 141 (17), 123 (31), 97 (26), 67 (19), 57 (100), 41 (56). HRMS (CI, isobutane): calcd. 255.1596 (for $C_{14}H_{23}O_4$), found 255.1596 (100) [M + H^+]. $C_{14}H_{22}O_4$ (254.32).

***N*,1-Dimethyl-8-oxo-2-(2-thiazolyl)-1,4,5,6,7,8-hexahydroazocine-4-carboxamide (3a):** With the same procedure given for compound **4fb**, but using 5 equiv. of amine **2b**, no product **4fb** could be obtained, but only compound **3a** was isolated (49 mg, 123 μmol, 10%, 70% purity by LCMS). ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.41–1.63 (m, 2 H), 1.82–1.95 (m, 2 H), 2.27–2.30 (m, 2 H), 2.58 (d, J = 4.5 Hz, 3 H), 2.86 (t, J = 10.1 Hz, 1 H), 2.98 (s, 3 H), 6.58 (d, J = 9.6 Hz, 1 H), 7.79 (d, J = 3.0 Hz, 1 H), 7.88 (d, J = 3.0 Hz, 1 H), 7.97 (br. q, J = 4.6 Hz, 1 H) ppm. MS (ESI, positive mode), m/z: 280.1 [M + H^+]. $C_{13}H_{17}N_3O_2S$ (279.36).

1-Butyl-*N*-[2-(2-chlorophenyl)ethyl]-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxamide (3b). Typical Procedure: DIPEA (40 μL, 29 mg, 0.22 mmol, 2 equiv.) and HATU (43 mg, 0.11 mmol, 1 equiv.) were added to a solution of carboxylic acid **8a** (34 mg, 0.11 mmol) in DMF (2 mL). After stirring the resulting mixture for 5 min at 23 °C the amine **2h** (17 mg, 0.11 mmol, 1 equiv.) was added followed by continued stirring for 16 h. Preparative chromatography using HPLC gave compound **3b** (43 mg, 97 μmol, 87%) as a brownish oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 0.76 (t, J = 7.1 Hz, 3 H), 1.09–1.48 (m, 5 H), 1.54–1.62 (m, 1 H), 1.78–1.90 (m, 2 H), 2.24–2.34 (m, 2 H), 2.53–2.59 (m, 1 H), 2.76 (t, J = 10.3 Hz, 1 H), 2.80–2.93 (m, 2 H), 3.30–3.39 (m, 2 H), 3.85–3.93 (m, 1 H), 6.04 (d, J = 9.4 Hz, 1 H), 7.24–7.27 (m, 2 H), 7.29–7.33 (m, 3 H), 7.35–7.44 (m, 4 H), 8.03 (t, J = 5.5 Hz, 1 H) ppm. MS (ESI, positive mode), m/z: 439.2 [M + H^+]. $C_{26}H_{31}ClN_2O_2$ (439.00).

1-Butyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxamide (3c): According to the procedure given for compound **3b** a mixture of acid **8a** (30 mg, 0.10 mmol), DIPEA (35 μL, 26 mg, 0.20 mol, 2 equiv.), HATU (38 mg, 0.10 mmol, 1 equiv.) and ammonia **2i** (5.0 mg, 0.30 mol, 3 equiv., 0.6 mL of a solution in 1,4-dioxane, c = 0.5 mol dm^{-3}) in DMF (2 mL) was stirred for 16 h at 23 °C. Preparative chromatography using HPLC gave compound **3c** (32 mg, 75 μmol, 84%) as a colorless solid. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 0.77 (t, J = 7.3 Hz, 3 H), 1.11–1.47 (m, 5 H), 1.58–1.67 (m, 1 H) 1.88–1.91 (m, 2 H), 2.26–2.35 (m, 2 H), 2.54–2.59 (m, 1 H), 2.80 (t, J = 10.8 Hz, 1 H), 3.89–3.96 (m, 1 H, hidden by H_2O peak), 6.09 (d, J = 9.2 Hz, 1 H), 6.87 (br. s, 2 H), 7.33–7.44 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ([D_6]DMSO, 100 MHz): δ = 13.6 (CH_3), 19.7 (CH_2), 23.7 (CH_2), 28.8 (CH_2), 30.8 (CH_2), 33.1 (CH), 43.6 (CH_2), 43.9 (CH_2), 125.8 (2 CH), 126.0 (CH), 128.6 (CH), 128.9 (2 CH), 135.9 (C), 138.5 (C), 172.7 (C), 174.9 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3423 (w), 3315 (w), 3198 (w), 2951 (w), 2875 (w), 1775 (w), 1665 (vs), 1631 (s), 1447 (m), 1407 (m), 1206 (s), 1152 (vs), 1082 (m), 1026 (m), 960 (m), 864 (w), 815 (m), 768 (vs), 695 (s), 628 (s) cm^{-1}. HRMS (ESI, positive mode): calcd. 301.1916 (for $C_{18}H_{25}N_2O_2$), found 301.1919 [M + H^+]. $C_{18}H_{24}N_2O_2$ (300.40).

1-Butyl-8-oxo-2-phenyl-*N*-[2-(1-piperidyl)ethyl]-1,4,5,6,7,8-hexahydroazocine-4-carboxamide, Trifluoroacetate (3d·TFA): According to the procedure given for compound **3b** a mixture of acid **8a** (30 mg, 0.10 mmol), DIPEA (35 μL, 26 mg, 0.20 mol, 2 equiv.), HATU (38 mg, 0.10 mmol, 1 equiv.) and amine **2j** (12.8 mg, 0.10 mol, 1 equiv.) in DMF (2 mL) was stirred for 16 h at 23 °C. Preparative chromatography using HPLC gave compound (**3d**·TFA) (34 mg, 64 μmol, 65%) as a brown oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 0.78 (t, J = 7.1 Hz, 3 H), 1.10–1.20 (m, 2 H), 1.22–1.49 (m, 4 H), 1.59–1.71 (m, 4 H), 1.88–1.93 (m, 4 H), 2.27–2.37 (m, 2 H), 2.55–2.62 (m, 1 H), 2.81 (t, J = 10.0 Hz, 1 H), 2.90–2.95 (m, 2 H), 3.10–3.15 (m, 2 H), 3.38–3.49 (m, 4 H), 3.85–3.93 (m, 1 H), 6.06 (d, J = 9.4 Hz, 1 H), 7.33–7.36 (m, 2 H), 7.39–7.46 (m, 3 H), 8.22 (t, J = 5.7 Hz, 1 H), 9.15 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ([D_6]-DMSO, 100 MHz): δ = 13.5 (CH_3), 19.7 (CH_2), 21.1 (CH_2), 22.5 (2 CH_2), 23.6 (CH_2), 28.8 (CH_2), 30.5 (CH_2), 33.1 (CH), 33.8 (CH_2), 43.8 (CH_2), 44.1 (CH_2), 52.3 (2 CH_2), 54.7 (CH_2), 116.0 (CF_3), 125.1 (CH), 125.9 (2 CH), 128.7 (CH), 128.9 (2 CH), 135.7 (C), 139.0 (C), 158.2 (C), 172.6 (C), 173.4 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3282 (w) 3057 (w), 3028 (w), 2937 (m), 2864 (w), 1666 (s), 1546 (w), 1446 (m), 1405 (m), 1198 (vs), 1175 (s), 1128 (vs), 885 (w), 830 (m), 798 (m), 771 (m), 719 (s), 698 (m) cm^{-1}. HRMS (ESI, positive mode): calcd. 412.2964 (for $C_{25}H_{38}N_3O_2$), found 412.2955 [M + H^+]. $C_{25}H_{37}N_3O_2$ (411.59). $C_{27}H_{38}F_3N_3O_4$ (525.61).

***N*,1-Dibenzyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxamide (3e):** According to the procedure given for compound **3b** a mixture of acid **8b** (30 mg, 89 μmol), DIPEA (31.5 μL, 23.1 mg, 178 μmol, 2 equiv.), HATU (34 mg, 89 μmol, 1 equiv.) and amine **2c** (9.5 mg, 89 μmol, 1 equiv.) in DMF (2 mL) was stirred for 16 h at 23 °C. Preparative chromatography using HPLC gave compound **3c** (29 mg, 89 μmol, 99%) as a colorless solid. ^1H NMR ([D_6]-DMSO, 400 MHz): δ = 1.24–1.36 (m, 1 H), 1.60–1.71 (m, 1 H), 1.83 (dd, J = 5.1 Hz, J = 13.6 Hz, 1 H), 1.88–1.93 (m, 1 H), 2.32–2.49 (m, 3 H), 3.65 (part A of an AB system, J = 14.4 Hz, 1 H), 4.11 (dd, J = 5.7 Hz, J = 15.2 Hz, 1 H), 4.22 (dd, J = 6.0 Hz, J = 15.2 Hz, 1 H), 5.29 (part B of an AB system, J = 14.1 Hz, 1 H), 6.00 (d, J = 9.4 Hz, 1 H), 7.05–7.07 (m, 2 H), 7.09–7.17 (m, 5 H), 7.22–7.47 (m, 8 H), 7.66 (t, J = 5.7 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ([D_6]DMSO, 100 MHz): δ = 23.7 (CH_2), 30.6 (CH_2), 33.2 (CH), 42.0 (CH_2), 43.7 (CH_2), 47.1 (CH_2), 126.0 (2 CH), 126.2 (CH), 126.68 (CH), 126.71 (CH), 127.1 (2 CH), 128.1 (2 CH), 128.2 (2 CH), 128.6 (CH), 128.7 (2 CH), 128.9 (2 CH), 135.7 (C), 136.5 (C),

138.0 (C), 139.2 (C), 172.3 (C), 172.9 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3252 (w), 3076 (w), 3029 (w), 2935 (w), 1778 (w), 1653 (s), 1638 (m), 1568 (m) 1435 (w), 1395 (w), 1208 (w), 1197 (m), 1155 (m), 1070 (w), 1027 (w), 970 (w), 772 (w), 752 (m), 698 (vs) cm^{-1}. HRMS (ESI, positive mode): calcd. 425.2229 (for $C_{28}H_{29}N_2O_2$), found 425.2232 [M + H^+]. $C_{28}H_{28}N_2O_2$ (424.54).

Ethyl 1-Butyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4aa). Typical Procedure: A suspension of ester **1a** (100 mg, 365 μmol), *n*-$BuNH_2$ **2a** (133 mg, 1.83 mmol, 5 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (9 mg, 18 μmol, 0.05 equiv.) in THF (1.0 mL) was stirred in a closed reaction vial for 2 d at 70 °C. After cooling to ambient temperature, the reaction mixture was chromatographed on basic Al_2O_3 [PE/EA, 2:1, $R_f(SiO_2)$ = 0.32] to give the lactam **4aa** (74 mg, 223 μmol, 61%) as a yellowish oil. $C_{20}H_{27}NO_3$ (329.44): calcd. C 72.92, H 8.26, N 4.25; found C 73.07, H 8.35, N 4.31. All spectroscopic data are in accordance with the literature.[7]

Ethyl 1-Methyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ab): According to the procedure given for compound **4aa** a mixture of ester **1a** (100 mg, 346 μmol), amine **2b** (54 mg, 1.73 mmol, 5 equiv., 870 μL of a solution in THF, c = 2 mol dm^{-3}), and $Bi(NO_3)_3{\cdot}5H_2O$ (16.8 mg, 35.0 μmol, 0.1 equiv.) in THF (1.5 mL) was stirred for 2 d at 70 °C. Preparative chromatography using HPLC gave compound **4ab** (84 mg, 290 μmol, 84%) as a yellowish oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.23 (t, J = 7.1 Hz, 3 H), 1.37–1.47 (m, 1 H), 1.52–1.63 (m, 1 H), 1.92–1.98 (m, 1 H), 2.08 (dd, J = 5.0 Hz, J = 13.8 Hz, 1 H), 2.28–2.38 (m, 2 H), 2.79 (s, 3 H), 2.84 (t, J = 10.0 Hz, 1 H), 4.12–4.16 (m, 2 H), 5.98 (d, J = 9.4 Hz, 1 H), 7.36–7.47 (m, 5 H) ppm. MS (ESI, positive mode), m/z: 288.1 [M + H^+]. $C_{17}H_{21}NO_3$ (287.35).

Ethyl 1-Benzyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ac): According to the procedure given for compound **4aa** a mixture of ester **1a** (200 mg, 730 μmol), amine **2c** (781 mg, 7.30 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (18 mg, 36 μmol, 0.05 equiv.) in THF (1.5 mL) was stirred for 3 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 2:1, $R_f(SiO_2)$ = 0.43] gave compound **4ac** (165 mg, 486 μmol, 67%) as a yellowish oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (t, J = 7.1 Hz, 3 H), 1.23–1.39 (m, 1 H), 1.66–1.81 (m, 1 H), 1.98 (dd, J = 12.8 Hz, J = 4.5 Hz, 2 H), 2.31 (dd, J = 10.4 Hz, J = 9.8 Hz, 1 H), 2.42–2.55 (m, 2 H), 3.63 (part A of an AB system, J = 13.7 Hz, 1 H), 3.94–4.07 (m, 2 H), 5.48 (part B of an AB system, J = 13.7 Hz, 1 H), 5.96 (d, J = 9.5 Hz, 1 H), 7.18–7.25 (m, 5 H), 7.38–7.45 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 14.15 (CH_3), 24.24 (CH_2), 29.46 (CH_2), 33.51 (CH_2), 43.21 (CH), 47.82 (CH_2), 60.58 (CH_2), 125.42 (CH), 126.39 (2 CH), 127.39 (CH), 128.18 (2 CH), 128.94 (3 CH), 129.49 (2 CH), 135.61 (C), 136.24 (C), 139.17 (C), 173.44 (C), 173.53 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3030 (w), 2963 (m), 2861 (w), 1729 (vs), 1650 (vs), 1444 (m), 1395 (s), 1305 (s), 1180 (s), 1028 (s), 759 (vs), 699 (vs) cm^{-1}. MS (EI, 70 eV), m/z (%): 363 (71) [M^+], 290 (20), 262 (19), 244 (46), 220 (6), 91 (100). $C_{23}H_{25}NO_3$ (363.45): calcd. C 76.01, H 6.93, N 3.85; found C 76.04, H 7.17, N 3.68.

Ethyl 1-Allyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ad): According to the procedure given for compound **4aa** a mixture of ester **1a** (200 mg, 730 μmol), amine **2d** (416 mg, 7.30 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (18 mg, 36 μmol, 0.05 equiv.) in THF (1.5 mL) was stirred for 3 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 2:1, $R_f(SiO_2)$ = 0.28] gave compound **4ad** (163 mg, 520 μmol, 71%) as a yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.30 (t, J = 7.1 Hz, 3 H), 1.41–1.50 (m, 1 H), 1.77–1.86 (m, 1 H), 1.99–2.05 (m, 1 H), 2.15 (dd, J = 4.8, J = 13.9 Hz, 1 H), 2.44–2.53 (m, 2 H), 2.98 (t, J = 10.3 Hz, 1 H), 3.25 (dd, J = 14.2 Hz, J = 8.0 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 4.73 (dd, J = 14.2 Hz, J = 5.7 Hz, 1 H), 4.95 (d, J = 17.1 Hz, 1 H), 5.07 (d, J = 10.0 Hz, 1 H), 5.79 (dddd, J = 17.2 Hz, J = 9.8 Hz, J = 8.0 Hz, J = 6.1 Hz, 1 H), 6.07 (d, J = 9.5 Hz, 1 H), 7.36–7.38 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.13 (CH_3), 24.14 (CH_2), 29.62 (CH_2), 33.46 (CH_2), 43.71 (CH), 47.48 (CH_2), 60.9 (CH_2), 119.06 (CH_2), 124.68 (CH), 126.27 (CH), 128.78 (2 CH), 128.91 (2 CH), 131.7 (CH), 135.61 (C), 139.71 (C), 173.65 (C), 173.71 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2975 (w), 2909 (w), 2876 (w), 1735 (s), 1646 (s), 1441 (m), 1393 (s), 1229 (vs), 1174 (s), 1032 (s), 926 (s), 863 (s), 780 (vs), 704 (vs) cm^{-1}. MS (EI, 70 eV), m/z (%): 313 (100) [M^+], 284 (33), 244 (69), 212 (67), 184 (18), 157 (34), 144 (60), 91 (17), 77 (11), 55 (12), 41 (52). $C_{19}H_{23}NO_3$ (313.38): calcd. C 72.82, H 7.40, N 4.47; found C 72.58, H 7.51, N 4.69.

Ethyl 1-(4-Methoxybenzyl)-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ae): According to the procedure given for compound **4aa** a mixture of ester **1a** (200 mg, 730 μmol), amine **2e** (1.0 g, 7.3 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (18 mg, 36 μmol, 0.05 equiv.) in THF (1.5 mL) was stirred for 2 d at 70 °C. Chromatography on basic Al_2O_3 [PE–EA, 3:1, $R_f(SiO_2)$ = 0.15] gave compound **4ae** (163 mg, 420 μmol, 57%) as a yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.18 (t, J = 7.1 Hz, 3 H), 1.37–1.45 (m, 2 H), 1.67–1.81 (m, 1 H), 1.97 (dd, J = 4.9 Hz, J = 13.6 Hz, 1 H), 2.28 (t, J = 10.3 Hz, 1 H), 2.40–2.55 (m, 2 H), 3.57 (part A of an AB system, J = 13.8 Hz, 1 H), 3.74 (s, 3 H), 3.97–4.05 (m, 2 H), 5.42 (part B of an AB system, J = 13.8 Hz, 1 H), 5.99 (d, J = 9.4 Hz, 1 H), 6.73–7.15 (m, 4 H), 7.42–7.44 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.01 (CH_3), 24.26 (CH_2), 29.47 (CH_2), 33.53 (CH_2), 43.18 (CH), 47.16 (CH_2), 55.03 (CH_3), 60.56 (CH_2), 113.52 (2 CH), 125.44 (CH), 126.39 (2 CH), 128.52 (C), 128.94 (3 CH), 130.72 (2 CH), 135.66 (C), 139.14 (C), 158.92 (C), 173.46 (C), 173.53 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2936 (m), 2861 (w), 1729 (vs), 1650 (vs), 1511 (vs), 1444 (s), 1396 (s), 1302 (vs), 1245 (s), 1176 (s), 1032 (m), 848 (s), 772 (vs), 699 (vs) cm^{-1}. MS (EI, 70 eV), m/z (%): 393 (17) [M^+], 365 (3), 320 (2), 279 (4), 244 (2), 167 (6), 149 (16), 121 (100). $C_{24}H_{27}NO_4$ (393.19): calcd. C 73.26, H 6.92, N 3.56; found C 73.08, H 7.09, N 3.30.

Ethyl 1-[2-(*tert*-Butyloxycarbonyl)ethyl]-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4af): According to the procedure given for compound **4aa** a mixture of ester **1a** (500 mg, 1.81 mmol), amine **2f** (1.31 g, 9.03 mmol, 5 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (88 mg, 0.18 mmol, 0.1 equiv.) in THF (4 mL) was stirred for 2 d at 70 °C. Preparative chromatography using HPLC gave compound **4af** (298 mg, 735 μmol, 41%) as a yellowish oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.23 (t, J = 7.1 Hz, 3 H), 1.33 (s, 9 H), 1.36–1.44 (m, 1 H), 1.48–1.61 (m, 1 H), 1.82–1.91 (m, 1 H), 2.08 (dd, J = 4.1 Hz, J = 13.7 Hz, 1 H), 2.21–2.41 (m, 4 H), 2.79–2.86 (m, 1 H), 2.91 (t, J = 9.9 Hz, 1 H), 4.13 (m, 3 H), 6.03 (d, J = 9.7 Hz, 1 H), 7.36–7.52 (m, 5 H) ppm. MS (ESI, positive mode), m/z: 402.0 [M + H^+], 346.3 [M – *t*Bu + H^+]. $C_{23}H_{31}NO_5$ (401.50).

Ethyl 1-Cyclohexyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ag): According to the procedure given for compound **4aa** a mixture of ester **1a** (500 mg, 1.84 mmol), amine **2g** (1.82 g, 18.4 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (89 mg, 0.18 mmol, 0.1 equiv.) in THF (3 mL) was stirred for 4 d at 100 °C. Chromatography on basic Al_2O_3 [PE/EA, 5:1, $R_f(SiO_2)$ = 0.12] gave compound **4ag** (259 mg, 731 μmol, 40%) as a yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.02–1.09 (m, 1 H), 1.16–1.26 (m, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.39–1.51 (m, 3 H), 1.57 (d, J = 13.2 Hz, 1 H), 1.66–1.75 (m, 3 H), 1.78–1.87 (m, 1 H), 1.97–2.00 (m, 1 H), 2.13 (dd, J = 13.8 Hz, J = 5.5 Hz, 1 H), 2.42–2.51 (m, 2 H), 3.07 (t, J = 10.5 Hz, 1 H), 4.09–4.15 (m, 1 H), 4.17–4.22 (m, 2 H), 5.96 (d, J = 9.6 Hz, 1 H), 7.35–7.38 (m, 5 H) ppm. $^{13}C\{^1H\}$

NMR ($CDCl_3$, 125 MHz): δ = 14.15 (CH_3), 24.40 (CH_2), 25.33 (CH_2), 25.98 (CH_2), 26.02 (CH_2), 29.52 (CH_2), 30.08 (CH_2), 31.60 (CH_2), 34.09 (CH_2), 43.78 (CH), 55.84 (CH), 60.94 (CH_2), 126.33 (2 CH), 127.04 (CH), 128.43 (2 CH), 128.63 (CH), 138.52 (C), 139.78 (C), 173.64 (C), 173.70 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2931 (m), 2856 (w), 1731 (vs), 1645 (vs), 1445 (s), 1366 (s), 1176 (s), 1027 (m), 881 (m), 698 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 355 (13) [M^+], 326 (8), 282 (18), 273 (100), 227 (9), 200 (39), 172 (14), 157 (11), 104 (23). $C_{22}H_{29}NO_3$ (355.48): calcd. C 74.33, H 8.22, N 3.94; found C 74.08, H 8.61, N 3.69.

Benzyl 1-Benzyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4bc): According to the procedure given for compound **4aa** a mixture of ester **1b** (200 mg, 594 μmol), amine **2c** (319 mg, 2.97 mmol, 5 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (60 mg, 120 μmol, 0.2 equiv.) in THF (2 mL) was stirred for 2 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 3:1, $R_f(SiO_2)$ = 0.26] gave compound **4bc** (182 mg, 427 μmol, 72%) as a yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.29–1.38 (m, 1 H), 1.63 (dq, *J* = 13.5 Hz, *J* = 5.9 Hz, 1 H), 1.94–2.02 (m, 2 H), 2.38 (t, *J* = 10.3 Hz, 1 H), 2.46 (t, *J* = 12.0 Hz, 1 H), 2.53–2.57 (m, 1 H), 3.61 (part A of an AB system, *J* = 13.8 Hz, 1 H), 4.94 (part A of an AB system, *J* = 12.3 Hz, 1 H), 5.04 (part B of an AB system, *J* = 12.3 Hz, 1 H), 5.51 (part B of an AB system, *J* = 13.8 Hz, 1 H), 5.97 (d, *J* = 9.4 Hz, 1 H), 7.04–7.10 (m, 3 H), 7.16–7.17 (m, 2 H), 7.26–7.27 (m, 3 H), 7.35–7.42 (m, 7 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 24.22 (CH_2), 29.47 (CH_2), 33.52 (CH_2), 43.21 (CH), 47.87 (CH_2), 66.40 (CH_2), 125.14 (CH), 126.45 (2 CH), 127.44 (CH), 128.15 (2 CH), 128.22 (2 CH), 128.29 (CH), 128.51 (2 CH), 128.99 (2 CH), 129.05 (CH), 129.42 (2 CH), 135.58 (C), 135.76 (C), 136.18 (C), 139.43 (C), 173.30 (C), 173.54 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3032 (w), 2938 (m), 2863 (w), 1723 (s), 1651 (s), 1496 (s), 1447 (m), 1397 (s), 1282 (w), 1171 (m), 1077 (m), 760 (s), 699 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 425 (36) [M^+], 396 (8), 334 (10), 306 (26), 262 (9), 91 (100). HRMS (EI, 70 eV): calcd. 425.1991 (for $C_{28}H_{27}NO_3$), found 425.1991 [M^+]. $C_{28}H_{27}NO_3$ (425.52): calcd. C 79.03, H 6.40, N 3.29; found C 78.58, H 6.24, N 3.28.

Benzyl 1-Allyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4bd): According to the procedure given for compound **4aa** a mixture of ester **1b** (200 mg, 594 μmol), amine **2d** (339 mg, 5.94 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (30 mg, 60 μmol, 0.1 equiv.) in THF (1 mL) was stirred for 4 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 2:1, $R_f(SiO_2)$ = 0.28] gave compound **4bd** (86 mg, 230 μmol, 39%) as a yellowish oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.39–1.53 (m, 1 H), 1.72–1.88 (m, 1 H), 1.96–2.06 (m, 1 H), 2.17 (dd, *J* = 5.1 Hz, *J* = 13.9 Hz, 1 H), 2.41–2.57 (m, 2 H), 3.05 (t, *J* = 10.3 Hz, 1 H), 3.23 (dd, *J* = 8.1 Hz, *J* = 14.2 Hz, 1 H), 4.73 (dd, *J* = 5.7 Hz, *J* = 14.1 Hz, 1 H), 4.93–5.01 (m, 2 H), 5.18 (s, 2 H), 5.77 (dddd, *J* = 5.8 Hz, *J* = 8.0 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1 H), 6.05 (d, *J* = 9.5 Hz, 1 H), 7.32–7.41 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 24.11 (CH_2), 29.47 (CH_2), 33.48 (CH_2), 43.74 (CH), 47.49 (CH_2), 66.65 (CH_2), 119.23 (CH_2), 124.47 (CH), 126.35 (2 CH), 127.91 (2 CH), 128.30 (CH), 128.59 (2 CH), 128.86 (2 CH), 129.02 (CH), 131.68 (CH), 135.56 (C), 135.58 (C), 139.95 (C), 173.54 (C), 173.67 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3032 (w), 2931 (m), 2861 (w), 1733 (s), 1650 (s), 1445 (s), 1394 (s), 1307 (m), 1258 (m), 1171 (s), 1151 (s), 1080 (m), 996 (m), 923 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 375 (80) [M^+], 346 (15), 306 (31), 240 (35), 212 (31), 157 (21), 144 (33), 91 (100), 41 (30). $C_{24}H_{25}NO_3$ (375.47): calcd. C 76.77, H 6.71, N 3.73; found C 76.43, H 6.97, N 4.02.

Benzyl 1-(4-Methoxybenzyl)-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4be): According to the procedure given for compound **4aa** a mixture of ester **1b** (200 mg, 594 μmol), amine **2e** (803 mg, 5.94 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (30 mg, 60 μmol, 0.1 equiv.) in THF (2 mL) was stirred for 3 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 3:1, $R_f(SiO_2)$ = 0.13] gave compound **4be** (31 mg, 79 μmol, 13%) as a yellowish oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.26–1.40 (m, 1 H), 1.64–1.80 (m, 1 H), 1.91–2.03 (m, 1 H), 2.37–2.57 (m, 2 H), 3.58 (part A of an AB system, *J* = 13.8 Hz, 1 H), 3.66 (s, 3 H), 3.72–3.81 (m, 2 H), 5.01 (s, 2 H), 5.40 (part B of an AB system, *J* = 13.8 Hz, 1 H), 5.98 (d, *J* = 9.4 Hz, 1 H), 6.67–6.70 (m, 2 H), 7.10–7.14 (m, 2 H), 7.25–7.43 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 24.22 (CH_2), 29.44 (CH_2), 33.55 (CH_2), 43.20 (CH), 47.32 (CH_2), 55.09 (CH_3), 66.40 (CH_2), 113.59 (2 CH), 125.08 (CH), 126.44 (2 CH), 127.85 (2 CH), 128.22 (CH), 128.57 (2 CH), 128.92 (CH), 128.96 (2 CH), 129.49 (C), 130.37 (C), 130.71 (2 CH), 135.63 (C), 139.49 (C), 158.95 (C), 173.38 (C), 173.52 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2935 (m), 1733 (s), 1650 (s), 1511 (vs), 1445 (m), 1396 (m), 1301 (s), 1244 (s), 1173 (s), 1031 (m), 915 (w), 821 (w), 734 (m), 697 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 455 (13) [M^+], 427 (2), 121 (100) [$C_8H_9O^+$], 91 (6). $C_{29}H_{29}NO_4$ (455.55): calcd. C 76.46, H 6.42, N 3.07; found C 76.45, H 6.61, N 3.23.

2-(Methylthio)ethyl 1-Benzyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4cc): According to the procedure given for compound **4aa** a mixture of ester **1c** (200 mg, 624 μmol), amine **2c** (669 mg, 6.24 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (15 mg, 30 μmol, 0.05 equiv.) in THF (1.5 mL) was stirred for 2 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 2:1, $R_f(SiO_2)$ = 0.23] gave compound **4cc** (56 mg, 140 μmol, 23%) as a yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.26–1.40 (m, 1 H), 1.58–1.82 (m, 1 H), 1.94–2.04 (m, 2 H), 2.14 (s, 3 H), 2.34 (t, *J* = 10.2 Hz, 1 H), 2.42–2.55 (m, 2 H), 2.59–2.64 (m, 2 H), 3.62 (part A of an AB system, *J* = 13.7 Hz, 1 H), 4.08–4.14 (m, 2 H), 5.48 (part B of an AB system, *J* = 13.7 Hz, 1 H), 5.96 (d, *J* = 9.5 Hz, 1 H), 7.21–7.43 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 15.72 (CH_3), 24.25 (CH_2), 29.44 (CH_2), 32.44 (CH_2), 33.53 (CH_2), 43.20 (CH), 47.86 (CH_2), 62.90 (CH_2), 125.12 (CH), 126.46 (2 CH), 127.41 (CH), 128.26 (2 CH), 129.00 (2 CH), 129.07 (CH), 129.57 (2 CH), 135.56 (C), 136.31 (C), 139.38 (C), 173.26 (C), 173.56 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3029 (w), 2936 (m), 2861 (w), 1731 (vs), 1650 (vs), 1493 (vs), 1445 (s), 1396 (s), 1305 (m), 1172 (s), 1001 (m), 930 (w), 759 (vs), 699 (vs), 631 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 409 (7) [M^+], 335 (15), 318 (21), 290 (13), 91 (100). HRMS (EI, 70 eV): calcd. 409.1712 (for $C_{24}H_{27}NO_3S$), found 409.1712 [M^+].

2-(Methylthio)ethyl 1-Allyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4cd): According to the procedure given for compound **4aa** a mixture of ester **1c** (200 mg, 624 μmol), amine **2d** (356 mg, 6.24 mmol, 10 equiv.), and $Bi(NO_3)_3{\cdot}5H_2O$ (30 mg, 60 μmol, 0.1 equiv.) in THF (1.5 mL) was stirred for 2 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 2:1, $R_f(SiO_2)$ = 0.25] gave compound **4cd** (106 mg, 295 μmol, 47%) as a yellowish oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.39–1.54 (m, 1 H), 1.73–1.89 (m, 2 H), 1.98–2.03 (m, 1 H), 2.17 (s, 3 H), 2.41–2.53 (m, 2 H), 2.73–2.78 (m, 2 H), 3.00 (t, *J* = 9.7 Hz, 1 H), 3.25 (dd, *J* = 7.9 Hz, *J* = 14.5 Hz, 1 H), 4.29–4.34 (m, 2 H), 4.73 (dd, *J* = 5.8 Hz, *J* = 14.2 Hz, 1 H), 5.03 (dd, *J* = 17.1 Hz, *J* = 10.0 Hz, 2 H), 5.78 (dddd, *J* = 17.0 Hz, *J* = 10.1 Hz, *J* = 7.9 Hz, *J* = 6.1 Hz, 1 H), 6.06 (d, *J* = 9.4 Hz, 1 H), 7.38 (s, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 15.78 (CH_3), 24.15 (CH_2), 29.67 (CH_2), 32.67 (CH_2), 33.49 (CH_2), 43.73 (CH), 47.54 (CH_2), 63.29 (CH_2), 119.19 (CH_2), 124.41 (CH), 126.36 (2 CH), 128.85 (2 CH), 129.01 (CH), 131.74 (CH), 135.59 (C), 139.94 (C), 173.56 (C), 173.64 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3029 (w), 2936 (m), 2861 (w), 1731 (vs), 1650 (vs), 1493 (s), 1445 (s), 1396 (s), 1305 (m), 1172 (s), 1074 (m), 1001 (w), 877

(w), 759 (vs), 699 (vs) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 359 (7) [M^+], 330 (8), 312 (10), 285 (21), 256 (6), 240 (22), 212 (23), 157 (12), 144 (28), 75 (100). $C_{20}H_{25}NO_3S$ (359.48): calcd. C 66.82, H 7.01, N 3.90; found C 66.49, H 7.02, N 3.90.

2-(Methylthio)ethyl 1-(4-Methoxybenzyl)-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ce): According to the procedure given for compound **4aa** a mixture of ester **1c** (200 mg, 624 µmol), amine **2e** (856 mg, 6.24 mmol, 10 equiv.), and $Bi(NO_3)_3 \cdot 5H_2O$ (30 mg, 60 µmol, 0.1 equiv.) in THF (2 mL) was stirred for 3 d at 70 °C. Chromatography on basic Al_2O_3 [PE/EA, 5:1, $R_f(SiO_2)$ = 0.09] gave compound **4ce** (129 mg, 293 µmol, 47%) as a yellowish oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.29–1.37 (m, 1 H), 1.69–1.78 (m, 1 H), 1.95–2.02 (m, 2 H), 2.14 (s, 3 H), 2.31 (t, *J* = 10.3 Hz, 1 H), 2.42–2.47 (m, 1 H), 2.52–2.55 (m, 1 H), 2.62 (t, *J* = 7.1 Hz, 2 H), 3.57 (part A of an AB system, *J* = 13.8 Hz, 1 H), 3.76 (s, 3 H), 4.09–4.16 (m, 2 H), 5.43 (part B of an AB system, *J* = 13.8 Hz, 1 H), 5.97 (d, *J* = 9.4 Hz, 1 H), 6.74–7.14 (m, 4 H), 7.41–7.44 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 15.64 (CH_3), 24.22 (CH_2), 29.40 (CH_2), 32.25 (CH_2), 33.51 (CH_2), 43.13 (CH), 47.15 (CH_2), 55.11 (CH_3), 62.90 (CH_2), 113.56 (2 CH), 125.14 (CH), 126.42 (2 CH), 128.53 (C), 128.96 (2 CH), 129.02 (CH), 130.77 (2 CH), 135.56 (C), 139.27 (C), 158.89 (C), 173.32 (C), 173.48 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2934 (m), 2835 (w), 1731 (vs), 1649 (s), 1511 (vs), 1444 (s), 1396 (s), 1302 (s), 1244 (s), 1173 (s), 1032 (s), 974 (m), 918 (m), 771 (vs), 699 (vs) cm^{-1}. MS (EI, 70 eV), *m/z* (%): 439 (12) [M^+], 368 (4), 318 (3), 121 (100), 91 (2). $C_{25}H_{29}NO_4S$ (439.61): calcd. C 68.30, H 6.65, N 3.18; found C 68.57, H 6.73, N 3.29.

Ethyl 1-Butyl-2-(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4da): According to the procedure given for compound **4aa** a mixture of ester **1d** (117 mg, 365 µmol), amine **2a** (133 mg, 1.83 mmol, 5 equiv.), and $Bi(NO_3)_3 \cdot 5H_2O$ (8.9 mg, 18 µmol, 0.05 equiv.) in THF (1 mL) was stirred for 1 h at 100 °C in a microwave oven. Preparative chromatography using HPLC gave compound **4da** (28 mg, 77 µmol, 21%) as a colorless oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 0.78 (t, *J* = 7.3 Hz, 3 H), 1.12–1.60 (m, 9 H), 1.91–1.95 (m, 1 H), 2.05 (dd, *J* = 4.5 Hz, *J* = 13.5 Hz, 1 H), 2.30–2.33 (m, 2 H), 2.53–2.59 (m, 1 H), 2.84 (t, *J* = 10.1 Hz, 1 H), 3.78 (s, 3 H), 3.91–3.98 (m, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 5.82 (d, *J* = 9.6 Hz, 1 H), 6.96–7.00 (m, 2 H), 7.27–7.31 (m, 2 H) ppm. MS (ESI, positive mode), *m/z*: 360.2 [M + H^+]. $C_{21}H_{29}NO_4$ (359.46). In a second fraction, the byproduct **5** was isolated (42 mg, 82 µmol, 22%, 70% purity) as an impure material. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 1.12 (t, *J* = 7.7 Hz, 3 H), 1.27–1.37 (m, 3 H), 1.45–1.57 (m, 3 H), 1.94–2.01 (m, 3 H), 2.39–2.46 (m, 2 H), 2.57–2.60 (m, 1 H), 2.74–2.82 (m, 2 H), 3.84 (s, 3 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 7.01–7.04 (m, 2 H), 7.89–7.92 (m, 2 H) ppm. MS (ESI, positive mode), *m/z*: 360.2 [M + H^+]. $C_{21}H_{29}NO_4$ (359.46).

Ethyl 1-Methyl-2-(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4db): According to the procedure given for compound **4aa** a mixture of ester **1d** (750 mg, 2.34 mmol), amine **2b** (364 mg, 11.7 mmol, 5 equiv., 5.85 mL of a solution in THF, *c* = 2 mol dm^{-3}), and $Bi(NO_3)_3 \cdot 5H_2O$ (114 mg, 234 µmol, 0.1 equiv.) was stirred for 3 d at 80 °C. Preparative chromatography using HPLC gave compound **4db** (379 mg, 1.18 mmol, 51%) as a green solid. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.35–1.45 (m, 1 H), 1.50–1.62 (m, 1 H), 1.92–1.97 (m, 1 H), 2.06 (dd, *J* = 4.7 Hz, *J* = 13.6 Hz, 1 H), 2.31–2.34 (m, 2 H), 2.78 (s, 3 H), 2.80 (t, *J* = 10.5 Hz, 1 H), 3.78 (s, 3 H), 4.13–4.15 (m, 2 H), 5.84 (d, *J* = 9.8 Hz, 1 H), 6.97–7.00 (m, 2 H), 7.28–7.32 (m, 2 H) ppm. MS (ESI, positive mode), *m/z*: 318.2 [M + H^+]. $C_{18}H_{23}NO_4$ (317.38).

Ethyl 1-Benzyl-2-(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4dc): According to the procedure given for compound **4aa** a mixture of ester **1d** (750 mg, 2.34 mmol), amine **2c** (1.25 g, 11.7 mmol, 5 equiv.), and $Bi(NO_3)_3 \cdot 5H_2O$ (114 mg, 234 µmol, 0.1 equiv.) in THF (5 mL) was stirred for 3 d at 70 °C. Preparative chromatography using HPLC gave compound **4dc** (314 mg, 758 µmol, 32%) as a brownish oil. ^1H NMR ([D_6]-DMSO, 400 MHz): δ = 1.14 (t, *J* = 7.1 Hz, 3 H), 1.23–1.33 (m, 1 H), 1.44–1.52 (m, 1 H), 1.81–1.92 (m, 1 H), 2.16 (t, *J* = 11.0 Hz, 1 H), 2.30–2.40 (m, 2 H), 3.55 (part A of an AB system, *J* = 13.9 Hz, 1 H), 3.74–3.85 (m, 1 H), 3.80 (s, 3 H), 3.87–4.00 (m, 2 H), 5.27 (part B of an AB system, *J* = 14.2 Hz, 1 H), 5.77 (d, *J* = 9.3 Hz, 1 H), 7.03 (d, *J* = 8.9 Hz, 2 H), 7.10–7.12 (m, 2 H), 7.21–7.26 (m, 3 H), 7.33 (d, *J* = 8.9 Hz, 2 H) ppm. MS (ESI, positive mode), *m/z*: 394.2 [M + H^+]. $C_{24}H_{27}NO_4$ (393.48).

Ethyl 2-(2-Chlorophenyl)-1-methyl-8-oxo-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4eb): According to the procedure given for compound **4aa** a mixture of ester **1e** (700 mg, 2.15 mmol), amine **2b** (334 mg, 10.8 mmol, 5 equiv., 5.4 mL of a solution in THF, *c* = 2 mol dm^{-3}), and $Bi(NO_3)_3 \cdot 5H_2O$ (105 mg, 215 µmol, 0.1 equiv.) was stirred for 3 d at 80 °C. Preparative chromatography using HPLC gave compound **4eb** (319 mg, 981 µmol, 46%) as a greenish oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.37–1.47 (m, 1 H), 1.50–1.61 (m, 1 H), 1.95–2.02 (m, 1 H), 2.08 (dd, *J* = 4.1 Hz, *J* = 14.0 Hz, 1 H), 2.38–2.43 (m, 1 H), 2.63–2.68 (m, 4 H), 2.86 (t, *J* = 9.9 Hz, 1 H), 4.13 (d, *J* = 7.1 Hz, 2 H), 5.80 (d, *J* = 9.3 Hz, 1 H), 7.35–7.46 (m, 3 H), 7.49–7.53 (m, 1 H) ppm. MS (ESI, positive mode), *m/z*: 322.1 [M + H^+]. $C_{17}H_{20}ClNO_3$ (321.80).

Ethyl 1-Benzyl-2-(2-chlorophenyl)-8-oxo-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ec): According to the procedure given for compound **4aa** a mixture of ester **1e** (700 mg, 2.15 mmol), amine **2c** (1.15 g, 11.7 mmol, 5 equiv.), and $Bi(NO_3)_3 \cdot 5H_2O$ (104 mg, 215 µmol, 0.1 equiv.) in THF (5 mL) was stirred for 3 d at 70 °C. Preparative chromatography using HPLC gave compound **4ec** (467 mg, 1.06 mmol, 49%, 90% purity by LCMS) as a brownish oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.13 (t, *J* = 7.0 Hz, 3 H), 1.28–1.39 (m, 1 H), 1.46–1.57 (m, 1 H), 1.89–1.97 (m, 2 H), 2.37–2.50 (m, 1 H), 2.68 (t, *J* = 11.9 Hz, 1 H), 3.46 (part A of an AB system, *J* = 13.9 Hz, 1 H), 3.93–4.09 (m, 3 H), 5.15 (part B of an AB system, *J* = 14.2 Hz, 1 H), 5.77 (d, *J* = 9.2 Hz, 1 H), 7.10–7.55 (m, 9 H) ppm. MS (ESI, positive mode), *m/z*: 398.1 [M + H^+]. $C_{23}H_{24}ClNO_3$ (397.90).

Ethyl 1-Methyl-8-oxo-2-(2-thiazolyl)-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4fb): According to the procedure given for compound **4aa** a mixture of ester **1f** (350 mg, 1.23 mmol), amine **2b** (76 mg, 2.46 mmol, 2 equiv., 1.2 mL of a solution in THF, *c* = 2 mol dm^{-3}), and $Bi(NO_3)_3 \cdot 5H_2O$ (60 mg, 123 µmol, 0.1 equiv.) in THF (2.5 mL) was stirred for 2 d at 70 °C. Preparative chromatography using HPLC gave compound **4fb** (242 mg, 814 µmol, 66%) as a brownish oil. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.22 (t, *J* = 7.3 Hz, 3 H), 1.43–1.64 (m, 2 H), 1.94–1.99 (m, 1 H), 2.09–2.13 (m, 1 H), 2.28–2.35 (m, 2 H), 2.92 (t, *J* = 10.0 Hz, 1 H), 2.97 (s, 3 H), 4.14 (dq, *J* = 7.2 Hz, *J* = 2.3 Hz, 2 H), 6.57 (d, *J* = 9.7 Hz, 1 H), 7.82 (d, *J* = 3.2 Hz, 1 H), 7.91 (d, *J* = 3.2 Hz, 1 H) ppm. MS (ESI, positive mode), *m/z*: 295.2 [M + H^+]. $C_{14}H_{18}N_2O_3S$ (294.36).

Ethyl 1-Benzyl-8-oxo-2-(2-thiazolyl)-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4fc): According to the procedure given for compound **4aa** a mixture of ester **1f** (400 mg, 1.41 mmol), amine **2c** (754 mg, 7.04 mmol, 5 equiv.), and $Bi(NO_3)_3 \cdot 5H_2O$ (68 mg, 141 µmol, 0.1 equiv.) in THF (4.5 mL) was stirred for 3 d at 70 °C. Preparative chromatography using HPLC gave compound **4fc**

(129 mg, 345 μmol, 25%) as a yellowish oil. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.11 (t, J = 7.1 Hz, 3 H), 1.95–2.15 (m, 3 H), 2.39–2.45 (m, 2 H), 2.54–2.61 (m, 1 H), 3.43 (part A of an AB system, J = 18.7 Hz, 1 H), 3.91 (part B of an AB system, J = 18.8 Hz, 1 H), 4.04–4.09 (m, 4 H), 7.36–7.47 (m, 5 H), 8.15 (d, J = 3.1 Hz, 1 H), 8.23 (d, J = 3.1 Hz, 1 H) ppm. MS (ESI, positive mode), m/z: 371.3 [M + H]. $C_{20}H_{22}N_2O_3S$ (370.46).

Ethyl 1-Butyl-8-oxo-2-(4-pyridyl)-1,4,5,6,7,8-hexahydroazocine-4-carboxylate (4ga): According to the procedure given for compound **4aa** a mixture of ester **1g** (100 mg, 360 μmol), amine **2a** (132 mg, 1.80 mmol, 5 equiv.), and $Bi(NO_3)_3 \cdot 5H_2O$ (17 mg, 36 μmol, 0.1 equiv.) in THF (1 mL) was stirred for 4 d at 70 °C. Preparative chromatography using HPLC gave compound **4ga** (59 mg, 161 μmol, 45%, 90% purity by LCMS) as a brownish oil. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 0.84 (t, J = 7.3 Hz, 3 H), 1.10–1.62 (m, 9 H), 1.91–1.97 (m, 1 H), 2.06–2.13 (m, 1 H), 2.17–2.25 (m, 1 H), 2.32–2.37 (m, 1 H), 2.53–2.58 (m, 1 H), 2.93 (t, J = 10.1 Hz, 1 H), 3.91–3.98 (m, 1 H), 4.15 (q, J = 7.0 Hz, 2 H), 6.43 (d, J = 9.7 Hz, 1 H), 7.60 (d, J = 6.4 Hz, 2 H), 8.70 (d, J = 6.3 Hz, 2 H) ppm. MS (ESI, positive mode), m/z: 331.2 [M + H$^+$]. $C_{19}H_{26}N_2O_3$ (330.42).

1-Butyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylic Acid (8a): An aqueous LiOH solution (1 mL, c = 2 mol dm^{-3}) was added to a solution of **4aa** (50 mg, 144 μmol) in ethanol (1 mL) and the resulting mixture was stirred for 30 min at 70 °C in a microwave oven. Preparative chromatography using HPLC gave compound **8a** (42 mg, 140 μmol, 97%) as a colorless solid. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 0.77 (t, J = 7.5 Hz, 3 H), 1.10–1.44 (m, 5 H), 1.51–1.61 (m, 1 H), 1.91–1.97 (m, 1 H), 2.07 (dd, J = 4.8 Hz, J = 13.9 Hz, 1 H), 2.27–2.36 (m, 2 H), 2.51–2.58 (m, 1 H), 2.80 (t, J = 10.0 Hz, 1 H), 3.91–3.98 (m, 1 H), 5.99 (d, J = 9.3 Hz, 1 H), 7.35–7.45 (m, 5 H), 12.5 (br. s, 1 H) ppm. ^{13}C{^{1}H} NMR ([D$_6$]DMSO, 100 MHz): δ = 13.6 (CH_3), 19.7 (CH_2), 23.8 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 33.0 (CH), 43.3 (CH_2), 43.6 (CH_2), 124.7 (CH), 125.9 (2 CH), 128.8 (CH), 128.9 (2 CH), 135.5 (C), 139.3 (C), 172.7 (C), 174.5 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3100 (w, very broad), 2933 (m), 2863 (w), 1724 (s), 1643 (vs), 1601 (vs), 1446 (m), 1401 (m), 1383 (m), 1175 (vs), 1155 (vs), 1083 (w), 960 (w), 866 (w), 771 (s), 698 (vs), 669 (m) cm^{-1}. MS (ESI, negative mode), m/z: 300.1 [M – H$^+$]. HRMS (ESI, positive mode): calcd. 302.1756 (for $C_{18}H_{24}NO_3$), found 302.1754 [M + H$^+$]. $C_{18}H_{23}NO_3$ (301.38).

1-Benzyl-8-oxo-2-phenyl-1,4,5,6,7,8-hexahydroazocine-4-carboxylic Acid (8b): An aqueous LiOH solution (3 mL, c = 3 mol dm^{-3}) was added to a solution of **4ac** (525 mg, 1.43 mmol) in ethanol (2 mL) and the resulting mixture was stirred for 30 min at 70 °C in a microwave oven. Preparative chromatography using HPLC gave compound **8b** (238 mg, 674 μmol, 47%) as a colorless solid. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 1.23–1.34 (m, 1 H), 1.46–1.62 (m, 1 H), 1.91–1.94 (m, 2 H), 2.21 (d, J = 10.1 Hz, 1 H), 2.31–2.43 (m, 2 H), 3.58 (part A of an AB system, J = 14.0 Hz, 1 H), 5.24 (part B of an AB system, J = 13.9 Hz, 1 H), 5.94 (d, J = 9.6 Hz, 1 H), 7.10–7.12 (m, 2 H), 7.18–7.25 (m, 3 H), 7.38–7.49 (m, 5 H), 12.20 (br. s, 1 H) ppm. ^{13}C{^{1}H} NMR ([D$_6$]DMSO, 100 MHz): δ = 24.0 (CH_2), 29.2 (CH_2), 33.0 (CH), 42.8 (CH_2), 47.4 (CH_2), 125.5 (CH), 126.1 (2 CH), 127.3 (CH), 128.1 (2 CH), 128.6 (2 CH), 128.82 (2 CH), 128.85 (CH), 135.4 (C), 136.4 (C), 138.4 (C), 172.7 (C), 174.1 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3100 (w, very broad), 3056 (w), 3030 (w), 2937 (w), 2857 (w), 1723 (m), 1648 (m), 1601 (m), 1446 (m), 1389 (w), 1175 (s), 1153 (s), 1099 (w), 1076 (w), 978 (w), 866 (w), 758 (s), 697 (vs) cm^{-1}. MS (ESI, negative mode), m/z: 334.2 [M – H$^+$]. HRMS (ESI, positive mode): calcd. 336.1600 (for $C_{21}H_{22}NO_3$), found 336.1599 [M + H$^+$]. $C_{21}H_{21}NO_3$ (335.40).

Acknowledgments

This work was generously supported by the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie. Dr. Peter Sieger is thanked for performing solubility measurements. We gratefully acknowledge EMKA-Chemie GmbH & Co. KG (Eching, Germany) for providing compounds **1h** and **1i**.

[1] a) W. H. Pearson, I. Y. Lee, Y. Mi, P. Stoy, *J. Org. Chem.* **2004**, *69*, 9109–9122; b) P. Arya, S. Couve-Bonnaire, P. Durieux, D. Laforce, R. Kumar, D. M. Leek, *J. Comb. Chem.* **2004**, *6*, 735–745; c) L. K. Hansen, F. C. Størmer, D. Petersen, A. J. Aasen, *Acta Crystallogr. Sec. E* **2001**, *57*, o909–o912.

[2] a) S. Bergemann, R. Brecht, F. Büttner, D. Guenard, R. Gust, G. Seitz, M. T. Stubbs, S. Thoret, *Bioorg. Med. Chem.* **2003**, *11*, 1269–1281; b) O. Baudoin, M. Cesario, D. Guenard, F. Gueritte, *J. Org. Chem.* **2002**, *67*, 1199–1207; c) R. Brecht, G. Seitz, D. Guenard, S. Thoret, *Bioorg. Med. Chem.* **2000**, *8*, 557–562; d) U. Berg, H. Bladh, C. Svensson, M. Wallin, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2771–2776; e) W. R. Schoen, J. M. Pisano, K. Prandergast, M. J. Wyvratt, M. H. Fisher, K. Cheng, W. W.-S. Chan, B. Butler, R. G. Smith, R. G. Ball, *J. Med. Chem.* **1994**, *37*, 897–906; f) J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz, B. M. Finn, *J. Med. Chem.* **1985**, *28*, 1511–1516; g) N. Tohru, T. Hiroshi, Y. Hirotake, A. Takeshi, T. Shuzo, EP 0465254A1 (1992).

[3] a) R. Kaul, S. Surprenant, W. D. Lubell, *J. Org. Chem.* **2005**, *70*, 3838–3844; b) Correction: R. Kaul, S. Surprenant, W. D. Lubell, *J. Org. Chem.* **2005**, *70*, 4901–4902; c) C. J. Creighton, G. C. Leo, Y. Du, A. B. Reitz, *Bioorg. Med. Chem.* **2004**, *12*, 4375–4385; d) S. Derrer, J. E. Davies, A. B. Holmes, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2943–2956; e) S. Derrer, J. E. Davies, A. B. Holmes, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957–2967; f) S. Derrer, N. Feeder, S. J. Teat, J. E. Davies, A. B. Holmes, *Tetrahedron Lett.* **1998**, *39*, 9309–9312.

[4] B. Alcaide, C. Rodríguez-Ranera, A. Rodríguez-Vicente, *Tetrahedron Lett.* **2001**, *42*, 3081–3083.

[5] a) R. Hernández, D. Melián, T. Prangé, E. Suárez, *Heterocycles* **1995**, *41*, 439–454; b) R. L. Dorta, C. G. Francisco, E. Suárez, *Tetrahedron Lett.* **1994**, *35*, 1083–1086; c) R. Hernández, J. J. Marrero, D. Melián, E. Suárez, *Tetrahedron Lett.* **1988**, *29*, 6661–6663.

[6] Recent examples: a) M. Biava, G. C. Poretta, G. Poce, S. Supino, D. Deidda, R. Pompei, P. Molicotti, F. Manetti, M. Botta, *J. Med. Chem.* **2006**, *49*, 4946–4952; b) S. Werner, P. S. Iyer, M. D. Fodor, C. M. Coleman, L. A. Twining, B. Mitasev, K. M. Brummond, *J. Comb. Chem.* **2006**, *8*, 368–380; c) I. Bianchi, R. Forlani, G. Minetto, I. Peretto, N. Regalia, M. Taddei, L. F. Raveglia, *J. Comb. Chem.* **2006**, *8*, 491–499; d) H. S. Iden, W. D. Lubell, *Org. Lett.* **2006**, *8*, 3425–3428; e) A. E. Mattson, A. R. Bharadwaj, A. M. Zuhl, K. A. Scheidt, *J. Org. Chem.* **2006**, *71*, 5715–5724; f) M. Galezowski, D. T. Gryko, *J. Org. Chem.* **2006**, *71*, 5942–5950; g) J. Chen, H. Wu, Z. Zheng, C. Jin, X. Zhang, W. Su, *Tetrahedron Lett.* **2006**, *47*, 5383–5387; h) K. Ogura, K. Ooshima, M. Akazome, S. Matsumoto, *Tetrahedron* **2006**, *62*, 2484–2491; i) H. Chochois, M. Sauthier, E. Maerten, Y. Castanet, A. Mortreux, *Tetrahedron* **2006**, *62*, 11740–11746.

[7] M. Rössle, J. Christoffers, *Synlett* **2006**, 106–108.

[8] A. Hassner, B. Amit, V. Marks, H. E. Gottlieb, *Eur. J. Org. Chem.* **2006**, 1256–1261.

[9] a) D. Weber, E. Heller, C. Hoenke, S. Hörer, P. Bäuerle, V. Austel, *Synthesis* **2005**, 2357–2366; b) P. Tielmann, C. Hoenke, *Tetrahedron Lett.* **2006**, *47*, 261–265.

[10] a) M. Rössle, T. Werner, W. Frey, J. Christoffers, *Eur. J. Org. Chem.* **2005**, 5031–5038; b) M. Rössle, T. Werner, A. Baro, W. Frey, J. Christoffers, *Angew. Chem.* **2004**, *116*, 6709–6711; *Angew. Chem. Int. Ed.* **2004**, *43*, 6547–6549; c) J. Christoffers, T. Werner, W. Frey, A. Baro, *Eur. J. Org. Chem.* **2003**, 4879–4886;

d) Review: J. Christoffers, T. Werner, M. Rössle, *Catal. Today* **2007**, *121*, 22–26.
[11] a) B. K. Banik, I. Banik, M. Renteria, S. K. Dasgupta, *Tetrahedron Lett.* **2005**, *46*, 2643–2645; b) J. S. Yadav, B. V. S. Reddy, B. Eeshwaraiah, M. K. Gupta, *Tetrahedron Lett.* **2004**, *45*, 5873–5876.
[12] Y. Coquerel, D. Bensa, A. Doutheau, J. Rodrigues, *Org. Lett.* **2006**, *8*, 4819–4822.
[13] Review: A. Speicher, T. Klaus, T. Eicher, *J. Prakt. Chem.* **1998**, *340*, 581–583.
[14] Y. Zhang, S. Lu, W. Liu, C. Zhao, R. Xi, *J. Agric. Food Chem.* **2007**, *55*, 211–218.
[15] O. Riobe, M. Lamant, L. Gouin, R. Gigault, *Comptes Rendus* **1958**, *246*, 1710–1712.
[16] D. K. Klipa, H. Hart, *J. Org. Chem.* **1981**, *46*, 2815–2816.
[17] R. Ruijtenbeek, J. A. W. Kruijtzer, W. van de Wiel, M. J. E. Fischer, M. Flück, F. A. M. Redegeld, R. M. J. Liskamp, F. P. Nijkamp, *ChemBioChem* **2001**, *2*, 171–179.
[18] J. Christoffers, N. Önal, *Eur. J. Org. Chem.* **2000**, 1633–1635.
[19] B. Kreidler, A. Baro, J. Christoffers, *Eur. J. Org. Chem.* **2005**, 5339–5348.
[20] A. Dondoni, P. Merino, J. Orduna, *Tetrahedron Lett.* **1991**, *32*, 3247–3250.
[21] W. Wunderlich, *J. Prakt. Chem.* **1955**, *2*, 302–307.
[22] W. Herz, *J. Am. Chem. Soc.* **1956**, *78*, 1485–1494.

Received: March 26, 2007
Published Online: May 8, 2007

