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Synthesis of Benzomorphan Analogues by Intramolecular Buchwald–Hartwig Cyclization

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A new strategy toward the important class of benzomorphans is described. The key bond formation is based on an intramolecular Buchwald–Hartwig enolate arylation reaction. Thus, alkylation of piperidones with *ortho*-bromobenzyl bromides provides the necessary substrates. In the presence of a palladium catalyst, a sterically hindered phosphane ligand, and a base, carbon–carbon bond formation to tricyclic benzomorphan derivatives takes place. After removal of the *N*-protecting group, derivatization reactions are possible.

Many active drugs contain a cyclic core structure, frequently incorporating heteroatoms. In addition, other positions are decorated with groups that directly interact with matching partners on the receptor. Besides the type, the relative orientation of these groups is a key factor in determining biological activity. Prototypical cases are the opioid analgetics.[1] Morphine (**1**),[2] the natural lead structure confers its activity through an agonistic modulation at the μ-receptor (Figure 1). In the course of structure/activity studies,[3] other opiod receptors, such as the κ-, the δ-, and the ORL-1 receptor were discovered.[4] The desired analgetic properties result mainly by binding of a ligand to the μ- and the κ-receptor. Of clinical relevance are μ-agonist,[5] partial agonist (compound that shows agonistic as well as antagonistic effects at the μ-receptor) and mixed agonist/antagonists.[6] The latter type of drugs include compounds that are κ-agonists/μ-agonists or κ-agonists/μ-antagonists, respectively. For example, pentazocine is classified as κ-agonist/partial μ-agonist. The stronger the μ-agonistic part, the more a problem of dependence can occur.

As the essential structural features of morphine the phenol and the piperidine ring were identified. In order to find analgetics with improved properties and reduced side effects a range of morphine analogs were prepared. These variations include the synthesis of truncated systems. Thus, opening of the cyclohexene ring (ring C) yields the benzomorphans, such as **2** and **3**.[7–9] Also the nitrogen atoms can be repositioned, as illustrated with structures **4** and **5**.[10] In addition, variations in the ring size have been performed in the benzomorphan series.[11] Another important core structure is represented by the 5-arylmorphan skeleton **6**.[12] Finally, a range of μ-selective opioids without morphinan structure were discovered over the years.[5] Among the simpler morphine analogs, the benzomorphan and benzazocine tricyclic ring system are the most important ones.[8] Classical routes to such compounds include S_N2 reactions with a nucleophilic amine, formation of amides, intramolecular Friedel–Crafts alkylation, or iminium ion cyclizations.[3] However, due to the reactions employed, the type of substituents is restricted at certain positions.

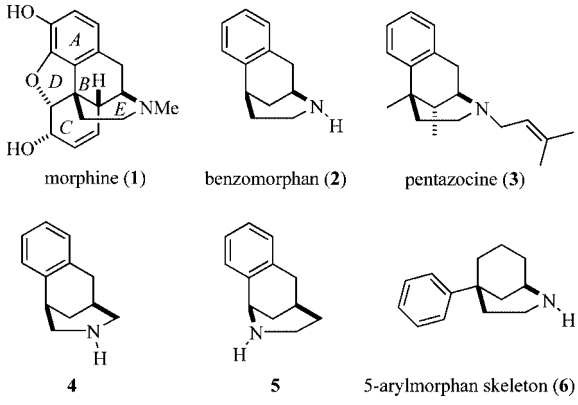

Figure 1. Structures of morphine (**1**), and prominent analogs derived from it.

With the advent of new powerful organometallic transformations, such as cross-coupling or C–H insertions, the chemistry of classical drugs might be substantially broadened. Thus, structures that previously seemed difficult to prepare might now be more easily accessible. A case in point is the Buchwald–Hartwig arylation of enolates in the presence of a palladium catalyst [Equation (1)].[13–15]

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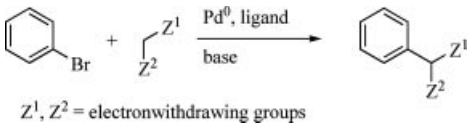


(1)

Our goal was to apply this reaction in an intramolecular setting towards the synthesis of new benzomorphan scaffolds.[16] After adding suitable functional groups, compound **7** appeared as an initial target (Figure 2). Further disconnection leads to the piperidones **9** and the *ortho*-bromobenzyl bromides **10**. Alkylation between the two carbonyl groups (cf. **8**) or at the terminus (cf. **12**) by Weiler alkylation[17] should provide the substrates for the intramolecular ketone arylation. A related strategy has been described for the bridging of some carbocyclic ketones.[16h]

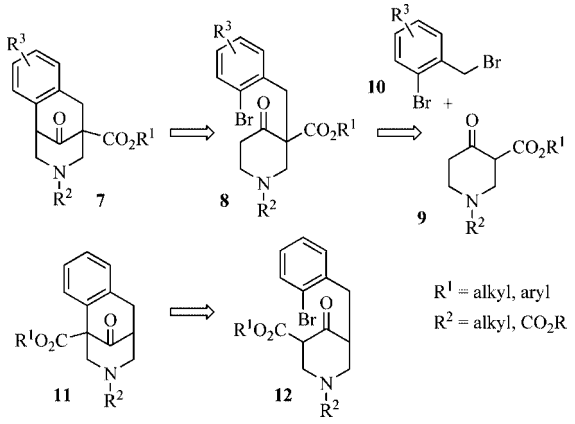
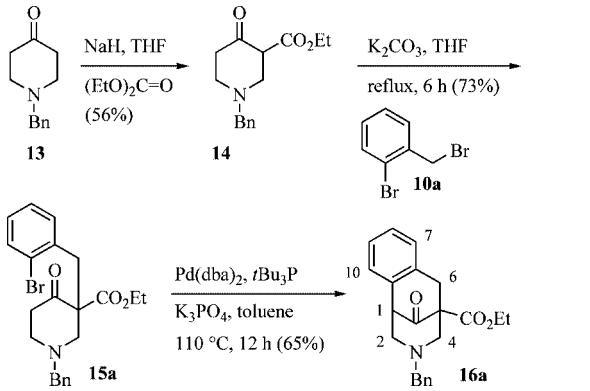


Figure 2. Synthetic strategy towards benzomorphans based on an intramolecular Buchwald–Hartwig arylation.



Scheme 1. Alkylation of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**14**) and palladium-catalyzed intramolecular ketone arylation of **15a** to yield the benzomorphan derivative **16a**.

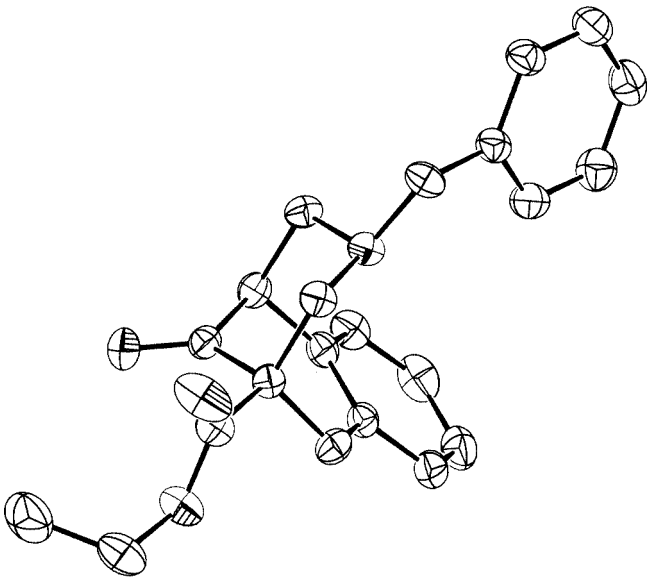


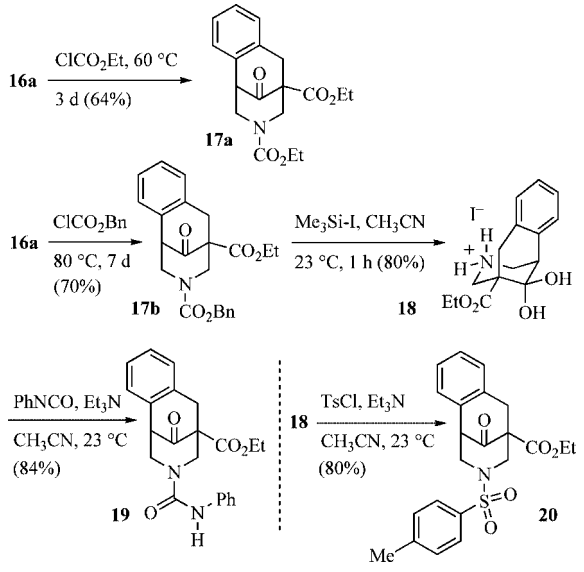
Figure 3. X-ray structure of benzomorphan **16a**. The crystal sample was obtained by crystallization from hot heptane.

Results

The commercially available 1-benzyl-4-oxopiperidine (**13**) was first converted into the keto ester **14** using diethyl carbonate in the presence of NaH (Scheme 1). The alkylation of the keto ester **14** was performed in THF with potassium carbonate as the base.[18] Under these conditions a reasonable yield for the alkylation product **15a** could be obtained. Other bases like KO*t*Bu in THF or NaH in toluene were tried, but the K_2CO_3/THF system gave the best results. The intramolecular ketone α-arylation was performed using K_3PO_4 (3 equiv.), tBu_3P (4 mol-%) and $Pd(dba)_2$ (2 mol-%) in refluxing toluene (Scheme 1).[13–15] This way, the tricyclic compound **16a** was obtained in 65% yield. The reaction was also run on a multigram scale. In this case the product was isolated by precipitation from the reaction mixture after filtration of inorganic material. The structure of the tricyclic ring system **16a** was additionally proven by an X-ray analysis (Figure 3).

It seemed appropriate to remove the *N*-benzyl protecting group by palladium-catalyzed hydrogenation to obtain the strategic benzomorphan derivative. However, under various conditions (H_2, Pd/C, EtOH, 23 °C, 12 h; EtOH/AcOH, 60 °C, 72 h) formation of the desired product was not observed. Most likely, steric hindrance interferes with the hydrogenation step. Therefore, we tried to convert the benzyl group into an urethane protecting group.[19] In the event, stirring of the tricyclic compound **16a** with ethoxycarbonyl chloride at elevated temperature for 3 d provided the ethoxycarbonyl compound **17a** in good yield. Again, attempts to cleave the ethyl carbamate under acidic conditions (concd. HCl, reflux) or with trimethylsilyl iodide (TMSI) were not successful in our hands – the starting material remained unchanged. A solution could be found by using Cbz chloride instead. Thus, heating of the tricyclic compound **16a** with Cbz chloride for several days led to the Cbz-protected tricyclic piperidone **17b** in 70% yield (Scheme 2). Deprotection was achieved by stirring of the

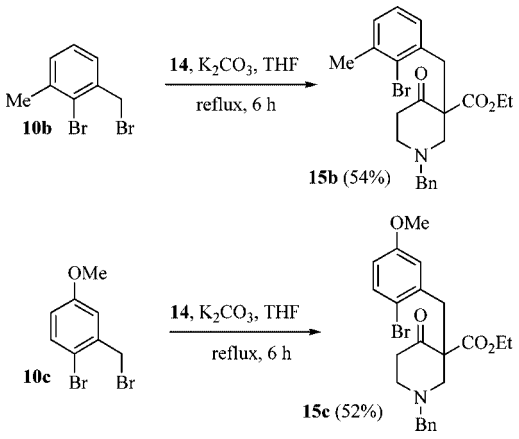
Cbz compound **17b** with trimethylsilyl iodide in acetonitrile for 1 h.[20] The deprotected compound **18** was isolated as the hydrate and the corresponding ammonium salt. The presence of the hydrate is evident from a characteristic peak in the ^{13}C NMR spectrum at δ = 91.5 ppm. With the amine **18** in hand, two representative *N*-derivatization reactions were performed in order to show the potential of **18** as a useful scaffold. Thus, reaction of the amine **18** with phenyl isocyanate in the presence of triethylamine gave a high yield of the urea **19**. Reaction of **18** was also possible with tosyl chloride under comparable conditions yielding the sulfonamide **20**.



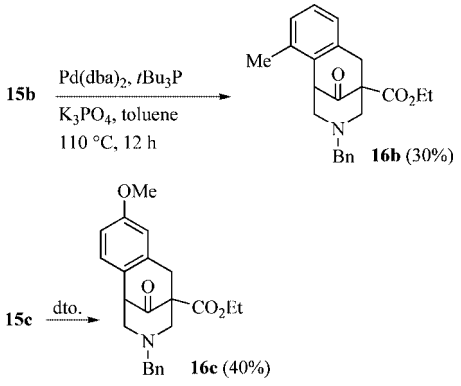
Scheme 2. Conversion of the *N*-benzyl compound **16a** to the urethanes **17a** and **17b**. Cleavage of the Cbz group to yield the ammonium iodide **18** followed by derivatization reactions on the tricyclic amino ketone.

Using the two benzyl bromides **10b** and **10c**, substrate **15b** which features a sterically demanding methyl group next to the bromo substituent, and substrate **15c** with an electron-donating methoxy substituent (Scheme 3) were prepared. The benzyl bromides **10a**–**c** were obtained from commercial sources or prepared according to the literature.[21–23] These derivatives were then subjected to the palladium-catalyzed cyclization under the same conditions as for **15a** resulting successfully in benzomorphans **16b** and **16c** (Scheme 4).

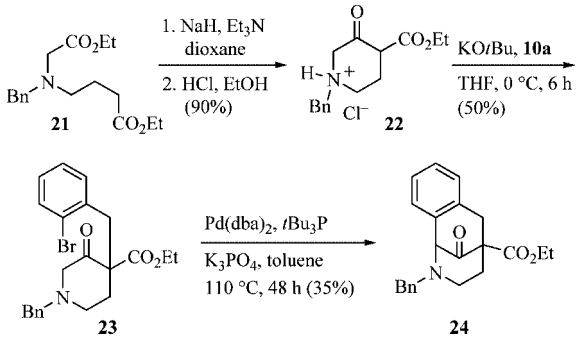
In another venture, by changing the position of the nitrogen atom in the piperidone ring, the isomeric benzomorphan derivative **24** was synthesized as shown in Scheme 5. The piperidone **22** was prepared from ethyl 2-bromoacetate and benzylamine, followed by alkylation of the resulting compound with ethyl γ-bromobutyrate to give the diester **21**. Treatment of the latter with NaH in dioxane furnished the piperidone **22** by Dieckmann condensation, according to a known procedure.[24] Alkylation of the keto ester **22** with the benzyl bromide **10a** provided the substrate **23**. Palladium-catalyzed cyclization of **23** was performed under similar conditions as for **15a**.



Scheme 3. Alkylation of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**14**) with benzyl bromides **10b** and **10c**.



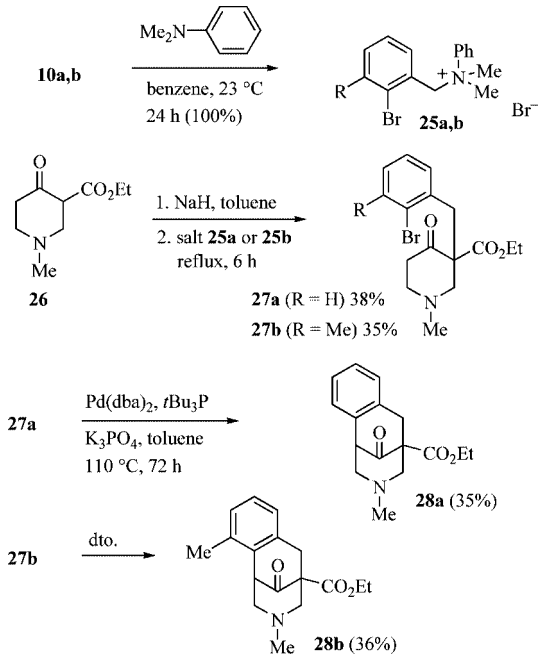
Scheme 4. Palladium-catalyzed intramolecular ketone arylation to yield the benzomorphan derivatives **16b** and **16c**.



Scheme 5. Synthesis of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate (**23**) and its Pd-catalyzed cyclization to **24**.

Because the *N*-methyl group is rather common in natural products as well as synthetic drugs, it was of interest to see whether compounds of type **7** could be accessed with an *N*-methyl instead of an *N*-benzyl group. These compounds might be prepared from the N–H derivative (cf. **18**) or directly from *N*-methyl-4-oxopiperidine3-carboxylate. In the latter route (Scheme 6), it was required to use the ammonium salt[25] **25a** for the alkylation of **26**,[26] because with the benzyl bromide **10a** the nitrogen atom in the piperidone ring reacts first.[27] The crucial cyclization was run under the same conditions that had proven useful with the *N*-ben-

zyl derivatives (**15a** → **16a**), but required longer reaction times. While the yield for the tricyclic compound **28a** was not very high, this reaction provides the desired compound in a very efficient way (Scheme 6). Compound **27b** was prepared in an analogous fashion. Under identical conditions as for the cyclization of substrate **15a**, the cyclization of **27a** and **27b** proceeds slower and requires longer reaction times. The use of other bases, such as KO*t*Bu or NaO*t*Bu did not lead to an improvement.



Scheme 6. Alkylation of the *N*-methyl piperidone **26** with the ammonium salts **25a** and **25b** followed by cyclization to the *N*-methyl-substituted benzomorphan derivatives **28a** and **28b**.

Conclusion

We could show that the tactical sequence of alkylation of a cyclic keto ester with an *ortho*-bromobenzyl bromide, followed by an intramolecular ketone arylation reaction (Buchwald–Hartwig palladium-catalyzed cyclization) provides an efficient access to novel bicyclic benzomorphan scaffolds. From the *N*-benzyl compound **16a** the amine **18** (hydroiodide) could be obtained, which was subjected to some derivatization reactions. Other targets that contain an aryl or hetaryl ring in a complex structure should be accessible as well.

Experimental Section

General: Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide, methanol, ethyl acetate, benzene, and triethylamine were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under nitrogen. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used without purification. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz): spectra were recorded at 295 K either in $CDCl_3$ or [D_6]DMSO; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H = 7.25 ppm, δ_C = 77.0 ppm), [D_6]DMSO (δ_H = 2.49 ppm, δ_C = 39.5 ppm). HRMS (FT-ICR): Electron spray ionization (ESI) combined with a fourier transform ion cyclotron resonance mass detector. Analytical LC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C; positive mode with fragmentor voltage of 40 eV; column: Nucleosil 100-5, C-18 HD, 5 μm, 70 × 3 mm, Macherey–Nagel; eluent: NaCl solution (5 mM)/acetonitrile; gradient: 0–10–15–17–20 min with 20–80–80–99–99% acetonitrile; flow: 0.5 mL min^{-1}. Flash chromatography: silica gel 43–60 μm. Thin-layer chromatography: silica gel plates Sil G/UV254.

Ethyl *N*-Benzyl-3-(2-bromobenzyl)-4-oxopiperidine-3-carboxylate (15a): To a suspension of anhydrous K_2CO_3 (8.01 g, 58 mmol) and ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (**14**) (3.93 g, 15 mmol) in anhydrous THF (25 mL) was added under nitrogen a solution of 2-bromobenzyl bromide (**10a**) (4.5 g, 18.0 mmol) in anhydrous THF (25 mL). The mixture was refluxed for 6 h. Then the inorganic materials were filtered and washed with THF. The combined filtrates were concentrated to give an oily residue. The product was isolated by flash chromatography (petroleum ether/ethyl acetate, 20:1; R_f = 0.05), yield 4.73 g (73%), slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 8.0 Hz, 1 H, ar.), 7.28–7.02 (m, 7 H, ar.), 7.05–7.00 (m, 1 H, ar.), 4.15–4.00 (m, 2 H, $CO_2CH_2CH_3$), 3.62 (d, J = 13.1 Hz, 1 H, $PhCH_2NR_2$), 3.56 (dd, J = 11.6, 2.8 Hz, 1 H, 2-H), 3.47 (d, J = 13.1 Hz, 1 H, $PhCH_2NR_2$), 3.45 (d, J = 14.4 Hz, 1 H, *o*-$BrC_6H_4CH_2$), 3.15 (d, J = 14.4 Hz, 1 H, *o*-$BrC_6H_4CH_2$), 3.01–2.95 (m, 1 H, 5-H), 2.91–2.81 (m, 1 H, 5-H), 2.80 (ddd, J = 14.4, 3.3, 2.0 Hz, 1 H, 6-H), 2.32 (d, J = 11.5 Hz, 1 H, 2-H), 2.30–2.23 (m, 1 H, 6-H), 1.09 (t, J = 7.0 Hz, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3 (C=O), 170.7 (CO_2Et), 137.7, 136.3, 132.8, 132.1, 128.9, 128.2, 128.1, 127.2, 127.0, 125.9 (ar.), 62.2 (C-3, quat.), 61.8, 61.4, 61.0, 52.6, 40.5, 35.8 (6 C, sec.), 13.8 ($CO_2CH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{22}H_{24}BrNO_3$ [M + H]$^+$ 430.1012, found 430.1013.

Ethyl *N*-Benzyl-3-(2-bromo-3-methylbenzyl)-4-oxopiperidine-3-carboxylate (15b): The reaction was performed with piperidone **14** (1.31 g, 5.0 mmol) and the benzyl bromide **10b** (1.32 g, 5.0 mmol) as described above. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate, 20:1; R_f = 0.05) gave the alkylated product **15b** (1.2 g, 54%) as colorless crystals, m.p. 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.25 (m, 5 H, ar.), 7.05–6.93 (m, 3 H, ar.), 4.12–3.97 (m, 2 H, $CO_2CH_2CH_3$), 3.60 (d, J = 13.1 Hz, 1 H, $PhCH_2NR_2$), 3.52 (dd, J = 11.4, 3.0 Hz, 1 H, 2-H), 3.49 (d, J = 14.4 Hz, 1 H, $ArCH_2$), 3.43 (d, J = 13.1 Hz, 1 H, $PhCH_2NR_2$), 3.16 (d, J = 14.4 Hz, 1 H, $ArCH_2$), 2.98–2.91 (m, 1 H, 5-H), 2.87–2.78 (m, 1 H, 5-H), 2.38–2.32 (m, 4 H, CH_3Ar and 6-H), 2.30 (d, J = 11.4 Hz, 1 H, 2-H), 2.27–2.20 (m, 1 H, 6-H), 1.05 (t, J = 7.0 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3 (C=O), 170.8 (CO_2Et), 138.4, 137.8, 136.7 (3 C, quat. ar.), 129.4, 129.2, 128.9 (4 C, tert. ar.), 128.7 (quat. ar.), 128.2, 127.2, 126.3 (4 C, tert. ar.), 62.2 (C-3, quat.), 61.8, 61.4, 61.1, 52.5, 40.5, 36.5 (6 C, sec.), 24.5 (CH_3Ar), 13.8 ($CO_2CH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{23}H_{27}BrNO_3$ [M + H]$^+$ 444.1169, found 444.1174.

Ethyl *N*-Benzyl-3-(2-bromo-5-methoxybenzyl)-4-oxopiperidine-3-carboxylate (15c): The reaction was performed with piperidone **14** (2.61 g, 10.0 mmol) and benzyl bromide **10c** (2.95 g, 11.0 mmol) as described above. Purification of the crude product by flash

chromatography (petroleum ether/diethyl ether, 9:1; R_f = 0.1) gave the alkylated product **15c** (2.4 g, 52%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.8 Hz, 1 H, 3′-H, ar.), 7.31–7.21 (m, 5 H, *N*-benzyl, ar.), 6.78 (d, J = 3.0 Hz, 1 H, 6′-H, ar.), 6.62 (dd, J = 8.8, 3.0 Hz, 1 H, 4′-H, ar.), 4.16–4.03 (m, 2 H, $CO_2CH_2CH_3$), 3.72 (s, 3 H, CH_3OAr), 3.66–3.58 (m, 2 H, $PhCH_2NR_2$ and 2-H), 3.50 (d, J = 13.3 Hz, 1 H, $PhCH_2NR_2$), 3.41 (d, J = 14.4 Hz, 1 H, $ArCH_2$), 3.13 (d, J = 14.4 Hz, 1 H, $ArCH_2$), 3.03–2.97 (m, 1 H, 5-H), 2.93–2.83 (m, 1 H, 5-H), 2.40 (ddd, J = 14.4, 3.3, 2.0 Hz, 1 H, 6-H), 2.33–2.24 (m, 2 H, 2-H and 6-H), 1.12 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3 (C=O), 170.8 (CO_2Et), 158.4 (MeO*C*, quat. ar.), 137.7, 137.2 (2 C, quat. ar.), 133.1, 128.9, 128.2, 127.2, 117.5 (7 C, tert. ar.), 116.4 (quat. ar.), 114.3 (tert. ar.), 62.3 (C-3, quat.), 61.8, 61.4, 60.9 (3 C, sec.), 55.4 (CH_3OAr), 52.6 ($PhCH_2NR_2$), 40.5 (C-5), 36.0 ($ArCH_2$) 13.8 ($CO_2CH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{23}H_{27}BrNO_4$ [M + H]$^+$ 460.1118, found 460.1125.

Ethyl *N*-Benzyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (16a): An oven-dried Schlenk tube fitted with a rubber septum was purged with nitrogen and charged with ethyl 1-benzyl-3-(2-bromobenzyl)-4-oxopiperidine-3-carboxylate (**15a**) (4.30 g, 10 mmol), anhydrous toluene (50 mL), K_3PO_4 (4.25 g, 20 mmol), and $Pd(dba)_2$ (115 mg, 2 mol%). Then the tube was purged with nitrogen, and tBu$_3$P (10 mL of 0.04 N in toluene, 4 mol%) was added. The mixture was vigorously stirred in an oil bath at 110 °C for 12 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (100 mL), filtered through Celite and concentrated in vacuo. The crude material was dissolved in diethyl ether and then the solvent was evaporated. This procedure was repeated three times which results in the precipitation of the crude product. The solids were washed with a mixture of pentane/diethyl ether (5:1), filtered and dried in vacuo. Alternatively, the crude material may be purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 9:1; R_f = 0.2). The precipitation method provided the tricyclic compound **16a** (2.3 g, 65%) as a yellow solid, m.p. 117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 1 H, ar.), 7.22–7.12 (m, 5 H, ar.), 6.95–6.87 (m, 3 H, ar.), 4.25 (dd, J = 14.1, 7.1 Hz, $CO_2CH_2CH_3$), 4.01 (d, J = 17.1 Hz, 1 H, 6-H), 3.57 (dd, J = 14.5 Hz, 2 H, $PhCH_2NR_2$), 3.42 (dd, J = 2.5 Hz, 1 H, 1-H), 3.41 (d, J = 17.2 Hz, 1 H, 6-H), 3.19 (dd, J = 11.2, 2.8 Hz, 1 H, 4-H), 3.11 (d, J = 11.2 Hz, 1 H, 4-H), 3.00 (ddd, J = 10.6, 2.8 Hz, 1 H, 2-H), 2.75 (dd, J = 10.6, 2.5 Hz, 1 H, 2-H), 1.30 (t, J = 7.1 Hz, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.4 (C=O), 170.2 (CO_2Et), 138.2, 137.3, 136.3 (3 C, quat. ar.), 128.2, 128.1, 127.5, 127.1, 127.0, 126.2, 126.2 (*C*H, ar.), 63.5, 61.8, 61.5, 60.2 (4 C, sec.), 59.1 (C-5, quat.), 52.7 (C-1, tert.), 41.0 (C-6), 14.1 ($CO_2CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2985, 2816, 1724, 1450, 1256, 744 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{23}NO_3$ [M + H]$^+$ 350.1751, found 350.1752; methanol adduct (hemiacetal): calcd. for $C_{23}H_{28}NO_4$ [M + CH_3OH + H]$^+$ 382.2013, found 382.2008. CCDC-624497 contains 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.

Ethyl *N*-Benzyl-10-methyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (16b): This compound was prepared as described above using 455 mg (1.02 mmol) of the alkylated compound **15b**. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1; R_f = 0.1), yield 95 mg (30%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.14 (m, 4 H, ar.), 7.07–7.01 (m, 2 H, ar.), 6.96–6.88 (m, 2 H, ar.), 4.24 (dd, J = 14.4, 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 3.99 (d, J = 17.3 Hz, 1 H, 6-H), 3.65 (dd, J = 2.5 Hz, 1 H, 1-H), 3.57 (s, 2 H, $PhCH_2NR_2$), 3.41 (d, J = 17.3 Hz, 1 H, 6-H), 3.16 (dd, J = 11.2, 2.8 Hz, 1 H, 4-H), 3.10 (d, J = 11.2 Hz, 1 H, 4-H), 3.02 (ddd, J = 10.6, 2.8 Hz, 1 H, 2-H), 2.71 (dd, J = 10.6, 2.5 Hz, 1 H, 2-H), 2.16 (s, 3 H, CH_3Ar), 1.29 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0 (C=O), 170.3 (CO_2Et), 138.2, 136.2, 134.6 (4 C, quat. ar.), 128.2, 128.0, 127.8, 127.0, 126.7, 124.3 (4 C, tert. ar.), 63.2, 61.5, 60.2, 59.4 (4 C, sec.), 58.9 (C-5, quat.), 49.0 (C-1, tert.), 41.1 (C-6, sec.), 18.4 (CH_3Ar), 14.1 ($CO_2CH_2CH_3$) ppm. IR (film): $\tilde{\nu}$ = 2951, 2812, 1728, 1458, 1261, 1107, 744 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NO_3$ [M + H]$^+$ 364.1907, found 364.1917.

Ethyl *N*-Benzyl-8-methoxy-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (16c): This compound was prepared as described above using the alkylated compound **15c** (577 mg, 1.25 mmol). The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 20:1; R_f = 0.1), yield 144 mg (40%), yellow oil which crystallizes within several days, m.p. 84–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.15 (m, 3 H, ar.), 6.97–6.93 (m, 2 H, ar.), 6.86–6.82 (m, 1 H, ar.), 6.75–6.72 (m, 2 H, ar.), 4.27–4.20 (m, 2 H, $CO_2CH_2CH_3$), 3.97 (d, J = 17.4 Hz, 1 H, 6-H), 3.84 (s, 3 H, CH_3OAr), 3.57 (s, 2 H, $PhCH_2NR_2$), 3.39 (dd, J = 2.5 Hz, 1 H, 1-H), 3.38 (d, J = 17.4 Hz, 1 H, 6-H), 3.15 (dd, J = 11.2, 2.8 Hz, 1 H, 4-H), 3.08 (d, J = 11.2 Hz, 1 H, 4-H), 2.97 (ddd, J = 10.6, 2.8 Hz, 1 H, 2-H), 2.71 (dd, J = 10.5, 2.5 Hz, 1 H, 2-H), 1.29 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5 (C=O), 170.3 (CO_2Et), 158.8 (MeO*C*, quat. ar.), 138.2, 137.4, 129.6 (3 C, quat. ar.), 128.5, 128.2, 128.1, 127.1, 112.3, 111.4 (8 C, tert. ar.), 63.4, 62.0, 61.5, 60.3 (4 C, sec.), 58.8 (C-5, quat.), 55.3 (CH_3OAr), 52.0 (C-1, tert.), 41.1 (C-6), 14.1 ($CO_2CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2943, 2816, 1724, 1608, 1454, 1265, 1088, 741 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NO_4$ [M + H]$^+$ 380.18563, found 380.18573; methanol adduct (hemiacetal) calcd. for $C_{24}H_{30}NO_5$ [M + CH_3OH + H]$^+$ 412.2119, found 412.2111.

Diethyl 11-Oxo-1,6-dihydro-1,5-methano-3-benzazocine-3,5(2*H*)-dicarboxylate (17a): The *N*-benzyl-protected substrate **16a** (225 mg, 0.64 mmol) was mixed with ethoxycarbonyl chloride (5 mL) and the mixture was heated at 60 °C for 3 d. Then, the excess of ethyl chloroformate was removed by distillation in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 5:1; R_f = 0.1–0.2) of the residue gave the product **17a** (135 mg, 64%) as an oil. Conversion of starting material was around 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.14 (m, 2 H), 7.13–7.00 (m, 2 H), 4.79 (dd, J = 13.6, 3.3 Hz, 0.6 H), 4.60–4.37 (m, 0.5 H), 4.32–4.22 (m, 2.6 H), 4.05–3.87 (m, 1.6 H), 3.77–3.51 (m, 4 H), 3.47–3.30 (m, 1.3 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.13 (t, J = 7.1 Hz, 1 H), 0.77 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.3, 169.3, 155.8, 134.8, 134.4, 128.2, 127.7, 127.3, 126.8, 61.8, 61.6, 59.7, 53.9, 53.2, 52.5, 39.0, 14.1 ppm. According to the NMR spectroscopic data, **17a** is a mixture of rotamers. HRMS (ESI): calcd. for $C_{18}H_{22}NO_5$ [M + H]$^+$ 332.1493, found 332.1491.

3-Benzyl 5-Ethyl 11-Oxo-1,6-dihydro-1,5-methano-3-benzazocine-3,5(2*H*)-dicarboxylate (17b): The *N*-benzyl compound **16a** (1.0 g, 2.8 mmol) was mixed with benzyloxycarbonyl chloride (5 mL). The resulting mixture was then heated at 80 °C until the reaction was finished (up to 7 d). During this time, every day, additional Cbz chloride (1 mL) was added. The progress of this reaction was monitored by LC-MS. After completion, the liquid part was removed by distillation in vacuo at 80 °C. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1; R_f = 0.1–0.2), yield 0.78 g (70%) of **17b** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.03 (m, 7 H), 7.02–6.85 (m, 2 H), 4.98–4.72 (m, 2 H), 4.62–4.39 (m, 1.5 H), 4.32–4.22 (m, 2.5 H),

4.03–3.90 (m, 1 H), 3.77–3.63 (m, 1 H), 3.59–3.52 (m, 1.5 H), 3.46–3.28 (m, 1.5 H), 1.35–1.27 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.2, 169.3, 169.2, 155.6, 154.9, 136.0, 135.8, 134.8, 134.6, 134.3, 133.5, 128.5, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 127.2, 126.9, 126.8, 67.6, 67.5, 61.9, 59.6, 59.1, 54.1, 53.9, 53.2, 52.4, 52.4, 39.2, 39.0, 14.1 ppm. According to the NMR spectroscopic data, **17b** is a mixture of rotamers. IR (film): $\tilde{\nu}$ = 3440, 2931, 1713, 1443, 1227, 748 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}NO_5$ $[M + H]^+$ 394.1649, found 394.1651.

Ethyl 11-Oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate Hydroiodide Hydrate (18): A solution of the Cbz-protected compound **17b** (350 mg, 0.9 mmol) in CH_3CN (35 mL) was placed in a water bath at room temperature and treated with Me_3SiI (1 mL, 7.3 mmol) in a dropwise fashion. The mixture was stirred for 1 h, before the CH_3CN was evaporated in vacuo [longer reaction time (up to 24 h) causes complete decomposition of the product]. The residue was treated with water (35 mL) and this solution was washed with CH_2Cl_2. The aqueous phase was then concentrated to dryness resulting in yellow crystals of pure product **18**, yield 290 mg (80%), m.p. 170–172 °C. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 9.19 (br. s, 1 H), 7.50–7.30 (m, 1 H), 7.30–7.17 (m, 4 H, ar.), 4.25–4.13 (m, 2 H, $CO_2CH_2CH_3$), 3.64 (d, J = 17.7 Hz, 1 H, 6-H), 3.53–3.30 (m, 3 H), 3.15–3.08 (m, 3 H), 3.04 (d, J = 17.7 Hz, 1 H, 6-H), 1.25 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.0, 134.7, 134.3 (2 C, quat. ar.), 129.1, 127.9, 127.0, 126.3 (4 C, tert. ar.), 91.5 [$C(OH)_2$], 61.4 ($CO_2CH_2CH_3$), 48.5, 48.3, 47.0, 44.2, 35.6 (5 C, aliph.), 13.9 ($CO_2CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3903, 3325, 2924, 2816, 1724, 1458, 1238, 1053, 771 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}NO_3$ $[M]^+$ 260.1281, found 260.1286; methanol adduct (hemiacetal): calcd. for $C_{16}H_{22}NO_4$ $[M + CH_3OH]^+$ 292.1543, found 292.1543.

Ethyl *N*-(Anilinocarbonyl)-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (19): Et_3N (25 μL, 0.18 mmol) was added to a solution of the salt **18** (45 mg, 0.11 mmol) in acetonitrile (15 mL) and the mixture was stirred for 1 h. Then, phenyl isocyanate (20 μL, 0.18 mmol) was added and stirring was continued at room temperature for 24 h. The solvent was evaporated and the residue treated with hot CCl_4. Non-soluble material, which mainly consists of triethylammonium salt, was removed by filtration and the filtrate concentrated in vacuo. The urea derivative **19** was obtained as a light yellow powder, yield 35 mg (84%), m.p. 199–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 2 H, ar.), 7.17–7.08 (m, 4 H, ar.), 6.97–6.91 (m, 1 H, ar.), 6.75 (d, J = 7.8 Hz, 2 H, ar.), 5.47 (br. s, 1 H, N*H*Ph), 4.88 (dd, J = 13.6, 3.0 Hz, 1 H, 4-H), 4.33–4.23 (m, 2 H, $CO_2CH_2CH_3$), 4.03–3.93 (m, 2 H, 6-H and 4-H), 3.69–3.62 (m, 3 H), 3.52 (d, J = 17.8 Hz, 1 H, 6-H), 1.30 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6 (C=O), 169.2 (CO_2Et), 155.1 [R_2NC(=O)-NHPh], 138.1, 135.1, 134.9 (3 C, quat. ar.), 128.7, 128.5, 128.1, 127.4, 127.3, 123.4, 120.5 (9 C, tert. ar.), 62.0, 59.8, 54.6, 53.5, 52.4 (5 C, aliph.), 39.0 (C-6, sec.), 14.0 ($CO_2CH_2CH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3348, 2920, 1743, 1635, 1535, 1446, 1234, 1026, 752 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_4$ $[M + H]^+$ 379.1652, found 379.1656; calcd. for $C_{22}H_{22}N_2NaO_4$ $[M + Na]^+$ 401.1472, found 401.1475.

Ethyl 11-Oxo-*N*-tosyl-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (20): Et_3N (25 μL, 0.18) was added to a solution of the salt **18** (48 mg, 0.12 mmol) in acetonitrile (15 mL) and the mixture stirred for 1 h. Then, tosyl chloride (35 mg, 0.18 mmol) was added and stirring was continued at room temperature for additional 24 h. Then, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 3:1; R_f = 0.1 and 0.3, both spots are the product, compound is in equilibrium with adduct of water addition to the ketone), providing the tosylate **20** as a light yellow oil, yield 42 mg (80%). This compound contains some hydrate. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.3 Hz, 2 H, ar.), 7.26–7.10 (m, 4 H, ar.), 7.11 (d, J = 7.6 Hz, 1 H, ar.), 6.95 (d, J = 7.6 Hz, 1 H, ar.), 4.26 (dd, J = 14.2, 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.13 (dd, J = 12.1, 3.3 Hz, 1 H, 4-H), 4.03 (d, J = 17.6 Hz, 1 H, 6-H), 3.93 (ddd, J = 11.6, 2.8 Hz, 1 H, 4-H), 3.51 (dd, J = 2.5 Hz, 1 H, 1-H), 3.46 (d, J = 17.6 Hz, 1 H, 6-H), 3.40 (d, J = 12.1 Hz, 1 H, 4-H), 3.12 (dd, J = 11.6, 2.5 Hz, 1 H, 4-H), 2.40 (s, 3 H, p-$CH_3C_6H_4SO_2N$), 1.29 (m, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.2 (C=O), 169.0 (CO_2Et), 143.9, 134.8, 134.7, 134.2 (4 C, quat. ar.), 129.8, 128.0, 127.9, 127.2, 127.2, 127.1 (8 C, tert. ar.), 62.1 (sec.), 58.1 (quat.), 55.9, 54.9, 51.3 (3 C, aliph.), 34.0 (C-6, sec.), 21.5 (p-$CH_3C_6H_4SO_2N$), 14.1 ($CO_2CH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{22}H_{24}NO_5S$ $[M + H]^+$ 414.1370, found 414.1366; calcd. for $C_{22}H_{23}NNaO_5S$ $[M + Na]^+$ 436.1174, found 436.1174.

Ethyl 1-Benzyl-4-(2-bromobenzyl)-3-oxopiperidine-4-carboxylate (23): A mixture of potassium *tert*-butoxide (7.5 g, 65.0 mmol) and absolute tetrahydrofuran (150 mL) was stirred at room temperature for 0.5 h. The resulting milky solution was cooled to 0 °C, and then ethyl *N*-benzyl-3-oxo-4-piperidinecarboxylate hydrochloride[24] (**22**) (10.0 g, 33.6 mmol) was added through a powder dropping funnel whereby the temperature was kept below 5 °C. The mixture was then warmed to room temperature and further stirred for 1 h, resulting in a yellow solution. After cooling to 0 °C, a solution of 2-bromobenzyl bromide (8.8 g, 35.2 mmol) in absolute THF (40.0 mL) was added dropwise within 0.5 h. A maximum temperature of 2 °C was observed. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction solution was cooled to 0 °C, before saturated NH_4Cl solution (100 mL) was added. After separation of the layers, the aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed twice with saturated NaCl solution, dried with Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 10:1; R_f = 0.2) to yield 7.4 g (50%) of the product **23** as a slightly yellow oil. This compound should be used immediately after isolation, or can be kept under an inert gas at –20 °C for a longer time. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.1 Hz, 1 H, ar.), 7.37–7.22 (m, 7 H, ar.), 7.15–7.08 (m, 1 H, ar.), 4.25–4.15 (m, 2 H, $CO_2CH_2CH_3$), 3.57 (s, 2 H, $PhCH_2NR_2$), 3.51 (d, J = 14.1 Hz, 1 H, 2-H), 3.31 (d, J = 14.1 Hz, 1 H, 2-H), 3.24 (d, J = 15.9 Hz, 1 H, $ArCH_2$), 3.12 (d, J = 15.9 Hz, 1 H, $ArCH_2$), 2.80–2.70 (m, 1 H, CH_2CH_2), 2.65–2.55 (m, 2 H, CH_2CH_2), 1.87–1.77 (m, 1 H, CH_2CH_2), 1.22 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.9 (C=O), 169.8 (CO_2Et), 137.1 (quat. ar.), 136.2 (quat. ar.), 132.9, 132.3, 128.8, 128.3, 128.2, 127.3, 127.0 (9 C, tert. ar.), 125.9 (quat. ar.), 62.2 (C-4, quat.), 61.5, 61.4, 58.7, 48.7, 37.4, 30.0 (6 C, sec.), 13.9 ($CO_2CH_2CH_3$) ppm.

Ethyl 2-Benzyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-2-benzazocine-5(2*H*)-carboxylate (24): An oven-dried Schlenk tube fitted with a rubber septum was purged with nitrogen and charged with **23** (430 mg, 1 mmol) in 5 mL of anhydrous toluene, K_3PO_4 (425 mg, 2 mmol), and $Pd(dba)_2$ (34.5 mg, 6 mol%). Then the tube was purged with nitrogen, and tBu$_3$P (3 mL of 0.04 N in toluene, 12 mol%) was added. The mixture was vigorously stirred in an oil bath at 110 °C for 48 h [if starting material is still present in the reaction mixture, additional $Pd(dba)_2$ (34.5 mg) and tBu$_3$P (3 mL of 0.04 N in toluene) should be added and heating continued until completion]. The reaction mixture was then cooled to room temperature and filtered through Celite. Then, the solvent was evapo-

rated and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 5:1; R_f = 0.5), providing the compound **24** as a light yellow oil, yield 125 mg (35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 5 H, ar.), 7.28–7.21 (m, 3 H, ar.), 6.98 (d, J = 7.6 Hz, 1 H, ar.), 4.29 (dd, J = 14.4, 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.08 (s, 1 H, 1-H), 4.07 (d, J = 17.6 Hz, 1 H, 6-H), 3.69 (d, J = 13.4 Hz, 1 H, $PhCH_2NR_2$), 3.42 (d, J = 13.4 Hz, 1 H, $PhCH_2NR_2$), 3.27 (d, J = 17.6 Hz, 1 H, 6-H), 2.87 (dddd, J = 13.2, 5.5, 1.8 Hz, 1 H, 3-H), 2.61 (ddd, J = 12.5, 5.5, 1.8 Hz, 1 H, 4-H), 2.49 (ddd, J = 12.8, 3.1 Hz, 1 H, 4-H), 1.98 (ddd, J = 13.4, 3.0, 1.8 Hz, 1 H, 3-H), 1.33 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.0 (C=O), 171.2 (CO_2Et), 137.8 (quat. ar.), 136.4 (quat. ar.), 130.4 (tert. ar.), 129.9 (quat. ar.), 128.7, 128.6, 128.5, 127.3, 127.1, 126.2 (8 C, tert. ar.), 67.9 (C-1, tert.), 61.7 ($CO_2CH_2CH_3$), 57.7 ($PhCH_2NR_2$), 57.1 (C-5, quat.), 42.8 (C-4, sec.), 40.2 (C-6, sec.), 37.3 (C-2, sec.), 14.2 ($CO_2CH_2CH_3$) ppm. IR (film): $\tilde{\nu}$ = 2974, 2831, 1732, 1450, 1227, 737 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.1751, found 350.1749.

(*ortho*-Bromobenzyl)dimethylanilinium Bromide (25a): This compound was prepared by a modified literature procedure.[25] *N*,*N*-Dimethylaniline (12.2 g, 0.1 mol) and *ortho*-bromobenzyl bromide (**10a**) (25.0 g, 0.1 mol) were mixed and diluted with benzene (100 mL). The resulting solution was stirred at room temperature for 48 h, and then concentrated to dryness. The solids were treated with a 1:1 mixture of petroleum ether/diethyl ether and the slurry was heated before it was filtered. The yield was quantitive. The salt **25a** should be kept under nitrogen. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.7 Hz, 2 H), 7.54–7.40 (m, 5 H), 7.24–7.14 (m, 2 H), 5.52 (s, 2 H), 3.93 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 135.4, 133.6, 132.4, 130.7, 130.4, 127.9, 127.7, 127.3, 121.5, 71.7, 53.7 ppm.

Ethyl 3-(2-Bromobenzyl)-*N*-methyl-4-oxopiperidine-3-carboxylate (27a): To a suspension of NaH (235 mg, 5.85 mmol, 60% in mineral oil) was added ethyl 1-methyl-4-oxopiperidine-3-carboxylate[27] (**26**) (1.07 g, 5.8 mmol) in toluene (20 mL). The mixture was then kept at 80 °C for 1 h. Then, powdered (*ortho*-bromobenzyl)dimethylanilinium bromide (**25a**) (2.06 g, 5.55 mmol) was added in one portion to the suspension of the sodium salt at room temperature. This mixture was refluxed for 6 h. After cooling, the mixture was poured carefully into water (30 mL). The organic layer was separated, washed with saturated aqueous NaCl solution (2 × 20 mL), dried with Na_2SO_4, filtered, and concentrated to give an oily residue. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1; R_f = 0.25) to give 0.74 g (38%) of **27a** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 7.9 Hz, 1 H, ar.), 7.20–7.17 (m, 2 H, ar.), 7.09–7.03 (m, 1 H, ar.), 4.17–4.08 (m, 2 H, $CO_2CH_2CH_3$), 3.47 (d, J = 14.4 Hz, 1 H, *o*-$BrC_6H_4CH_2$), 3.43 (dd, J = 11.6, 3.0 Hz, 1 H, 2-H), 3.17 (d, J = 14.4 Hz, 1 H, *o*-$BrC_6H_4CH_2$), 3.04–2.97 (m, 1 H, 5-H), 2.94–2.84 (m, 1 H, 5-H), 2.42 (ddd, J = 14.4, 3.0, 2.0 Hz, 1 H, 6-H), 2.32–2.25 (m, 4 H, NCH_3 and 6-H), 2.20 (d, J = 11.6 Hz, 1 H, 2-H), 1.15 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9 (C=O), 170.3 (CO_2Et), 136.1 (quat. ar.), 132.9, 132.2, 128.4, 127.1 (4 C, tert. ar.), 125.9 (quat. ar.), 62.9 (C-3, quat.), 61.6, 55.8 (2 C, sec.), 45.6 (NCH_3), 40.5, 36.0 (2 C, sec.), 14.0 ($CO_2CH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{16}H_{21}BrNO_3$ $[M + H]^+$ 354.0699, found 354.0701.

Ethyl 3-(2-Bromo-3-methylbenzyl)-*N*-methyl-4-oxopiperidine-3-carboxylate (27b): The alkylation was performed as described for **27a**. For this reaction 1.07 g (5.8 mmol) of **26** and 2.22 g (5.7 mmol) of the anilinium salt **25b** were used. The product was isolated by flash chromatography (petroleum ether/diethyl ether, 1:1; R_f = 0.2), yield 0.73 g (35%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.05 (m, 2 H, ar.), 7.00–6.96 (m, 1 H, ar.), 4.19–4.06 (m, 2 H, $CO_2CH_2CH_3$), 3.53 (d, J = 14.4 Hz, 1 H, $ArCH_2$), 3.43 (dd, J = 11.6, 2.8 Hz, 1 H, 2-H), 3.22 (d, J = 14.4 Hz, 1 H, $ArCH_2$), 3.04–2.96 (m, 1 H, 5-H), 2.94–2.84 (m, 1 H, 5-H), 2.45–2.37 (m, 4 H, CH_3Ar and 6-H), 2.32–2.25 (m, 4 H, NCH_3 and 6-H), 2.2 (d, J = 11.6 Hz, 1 H, 2-H), 1.15 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9 (C=O), 170.4 (CO_2Et), 138.6, 136.5 (2 C, quat. ar.), 129.5, 129.3 (2 C, tert. ar.), 128.6 (quat. ar.), 126.4 (tert. ar.), 62.9 (sec.), 61.6 (C-3, quat.), 61.5, 55.8 (2 C, sec.), 45.6 (NCH_3), 40.6, 36.7 (2 C, sec.), 24.6 (CH_3Ar), 13.8 ($CO_2CH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{17}H_{23}BrNO_3$ $[M + H]^+$ 368.0856, found 368.0857.

Ethyl *N*-Methyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate Hydrochloride (28a): An oven-dried Schlenk tube fitted with a rubber septum was purged with argon and charged with ethyl 3-(2-bromobenzyl)-*N*-methyl-4-oxopiperidine-3-carboxylate (**27a**) (745 mg, 2.16 mmol) in 10 mL of anhydrous toluene, K_3PO_4 (1.3 g, 6.1 mmol), and $Pd(dba)_2$ (50 mg, 4 mol-%). Then the tube was purged with nitrogen, and tBu$_3$P (4 mL of a 0.04 N solution in toluene, 8 mol-%) was added. The mixture was vigorously stirred in an oil bath at 120 °C for 72 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (10 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure. The crude material was then treated with a concentrated ethanol solution of HCl (1 mL), and subsequently the solvent was evaporated. The residue was dissolved in water (5 mL), and the solution washed with diethyl ether (10 mL) and CH_2Cl_2 (10 mL). The aqueous solution was concentrated, and the residue dried in vacuo to give 206 mg (35%) of the salt **28a** as a yellow oily solid. ^{1}H NMR (400 MHz, $CDCl_3$); free base: δ = 7.25–7.12 (m, 3 H, ar.), 6.97 (d, J = 7.6 Hz, 1 H, ar.), 4.27 (dd, J = 14.4, 7.1 Hz, $CO_2CH_2CH_3$), 4.02 (d, J = 17.4 Hz, 1 H, 6-H), 3.52 (d, J = 17.45 Hz, 1 H, 6-H), 3.39 (dd, J = 2.5 Hz, 1 H, 1-H), 3.15 (dd, J = 11.2, 2.8 Hz, 1 H, 4-H), 3.02 (d, J = 11.2 Hz, 1 H, 4-H), 2.99 (ddd, J = 10.6, 2.5 Hz, 1 H, 2-H), 2.67 (dd, J = 10.6, 2.8 Hz, 1 H, 2-H), 2.25 (s, 3 H, NCH_3), 1.31 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.5 (C=O), 170.3 (CO_2Et), 137.3, 135.8 (2 C, quat. ar.), 127.5, 127.2, 126.6, 126.3 (4 C, tert. ar.), 66.6, 64.7, 61.6 (3 C, sec.), 58.6 (C-5, quat.), 52.5 (sec.), 45.0 (NCH_3), 41.0 (sec.), 14.1 ($CO_2CH_2CH_3$) ppm. IR (film): $\tilde{\nu}$ = 3378 cm^{-1} (br), 2819, 2673, 1720, 14589, 1281, 1084, 768 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1438, found 274.1432; methanol adduct (hemiacetal): calcd. for $C_{17}H_{24}NO_4$ $[M + CH_3OH + H]^+$ 306.1700, found 306.1699.

Ethyl *N*,10-Dimethyl-11-oxo-1,3,4,6-tetrahydro-1,5-methano-3-benzazocine-5(2*H*)-carboxylate (28b): The cyclization was performed as described for **28a** using 147 mg (0.4 mmol) of **27b**. The cyclized product **28b** was isolated by flash chromatography (petroleum ether/ethyl acetate, 20:1; R_f = 0.15), yield 41 mg (36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.09 (m, 1 H, ar.), 7.03–6.98 (m, 2 H, ar.), 4.30–4.23 (m, 2 H, $CO_2CH_2CH_3$), 4.01 (d, J = 17.3 Hz, 1 H, 6-H), 3.60 (dd, J = 2.5 Hz, 1 H, 1-H), 3.49 (d, J = 17.3 Hz, 1 H. 6-H), 3.14 (dd, J = 11.2, 2.8 Hz, 1 H, 4-H), 3.02 (d, J = 11.2 Hz, 1 H, 4-H), 2.99 (ddd, J = 10.6, 2.5 Hz, 1 H, 2-H), 2.63 (dd, J = 10.6, 2.8 Hz, 1 H, 2-H), 2.27 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 1.31 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.1 (C=O), 170.4 (CO_2Et), 135.7, 135.3, 134.7, 128.0, 126.8, 124.6 (6 C, ar.), 66.3, 62.4, 61.5 (3 C, sec.), 58.5 (C-5, quat.), 48.7 (C-1, tert.), 45.1 (NCH_3), 41.0 (sec.), 18.5 (CH_3Ar), 14.1 ($CO_2CH_2CH_3$) ppm.

Supporting Information (See footnote on the first page of this article): ^{1}H- and ^{13}C NMR spectra for important intermediates.

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