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Synthesis of 1,5-methano-3-benzazocines by intramolecular Buchwald–Hartwig arylation of 2-piperidinones

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Abstract

A conceptually novel route to 1,5-methano-3-benzazocines based on an intramolecular Buchwald–Hartwig arylation was developed. The reaction required the use of the zinc enolate of the piperidinone substrates. These substrates, piperidin-2-ones with a 2-bromobenzyl substituent in the 5-position were prepared by reductive amination of 4-formyl esters. The latter could be obtained via Michael addition of enamines, derived from 3-arylpropanals, to ethyl acrylate.

Keywords: Cyclization; Pd catalysis; Arylation; Benzazocines; Scaffolds

1. Introduction

Many polycyclic alkaloids are useful drugs or serve as interesting lead compounds. In this regard morphine (**1**) and cytisine (**2**) are prominent examples (Fig. 1). Whereas the analgetic morphine is an agonist for the μ-receptor,[1] cytisine acts as a potent agonist at nicotinic acetylcholine receptors.[2–4] Disregarding the nitrogen atoms, these two natural products have in common a 5,6,7,8,9,10-hexahydro-5,9-methanobenzo[8]annulene substructure **3**. Using this tricyclic ring system a number of nitrogen-containing analogs were designed and synthesized over the years. For example, a range of benzomorphans [1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines (**4**)], such as pentazocine (**6**) were developed as useful analgetics.[5] Quite recently the isomeric 1,5-methano-3-benzazocines **5** served as a lead structure in the development of varenicline (**7**) as a drug for smoking cessation.[6,7] One should also mention that 1,5-methano-3-benzazocines derivatives have been used as constrained tyrosine analogs in the search for SH2 (Src homology 2) ligands.[8] Typically, tricyclic structures such as **4** or **5** are produced by using classical key reactions like Grewe cyclization, Mannich reaction, or Michael addition.[5] Furthermore, lactam intermediates are frequently used.[9]

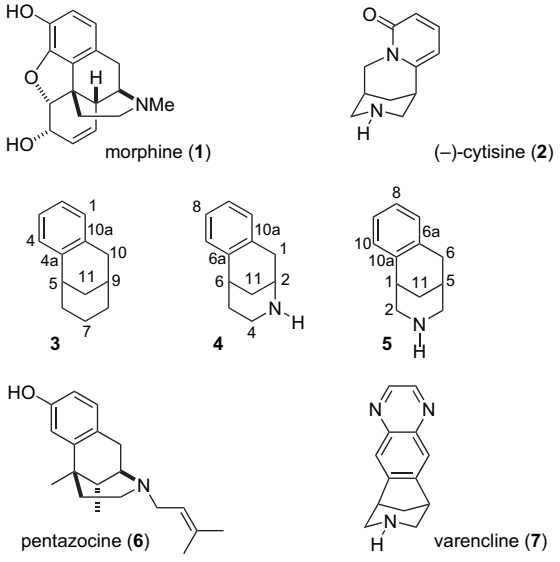

Figure 1. Structure of morphine (**1**) and cytisine (**2**), their common core **3**, the nitrogen-containing core structures **4** and **5**, as well as derived pharmaceuticals.

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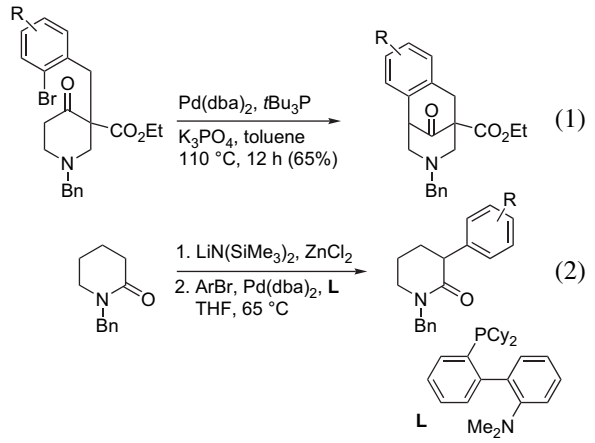
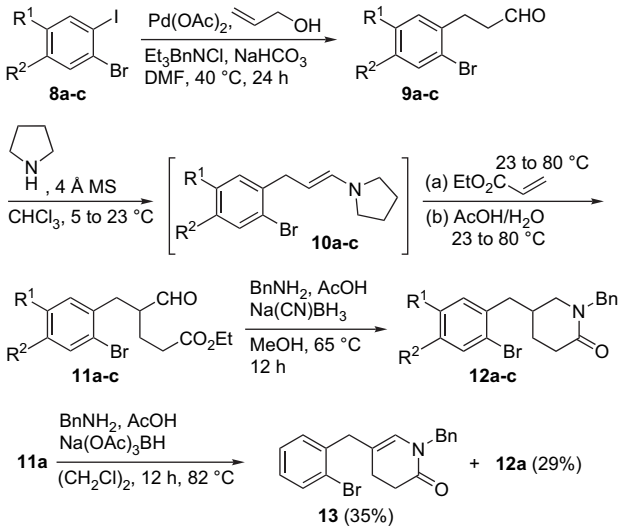


Figure 2. Intramolecular Buchwald–Hartwig arylation of ketones yielding 3-benzazocines (Eq. 1) and intermolecular lactam arylation (Eq. 2).

In order to broaden the range of accessible polycyclic amines, we initiated a program aimed at the use of metal catalyzed transformations as key steps. For example, we recently disclosed the synthesis of various 1,5-methano-3-benzazocines based on a Buchwald–Hartwig cyclization.[10] In this approach, piperidinone derivates containing a 2-bromobenzyl group were converted under palladium catalysis to tricyclic products (Fig. 2, Eq. 1). As can be seen, a ketone was arylated during this process, positioning the keto function in the methano bridge. We reasoned that it might be possible to employ a lactam for the intramolecular arylation to reach 3-benzazocines as well. The literature contains a number of arylation reactions for activated methylene and methine groups. Thus, intermolecular arylation reactions of ketones,[11] esters,[12] nitriles,[13] and amides[14,15] have been described.[16] Furthermore, examples of intramolecular processes for the arylation of amides[17] and other compounds[18,19] are known. In general, sterically hindered, electron-rich phosphine or *N*-heterocyclic carbene ligands are required. Moreover, the counterion for the enolate can be crucial. Thus, zinc enolates seem to provide a broader scope in the arylation of esters, imides, and piperidinones. In this regard, the group of Cossy reported on the arylation of *N*-protected 2-piperidinones using the corresponding zinc enolates and the Buchwald ligand **L** (Fig. 2, Eq. 2).[15] These arylations were performed with 2 equiv of piperidinone. In this paper we illustrate a concise route of the corresponding cyclizations substrates as well as the realization of the intramolecular Buchwald–Hartwig arylation.

2. Results

In order to produce 1,5-methano-3-benzazocines by intramolecular arylation of piperidinones, a 2-bromobenzyl group would have to be installed in the 5-position of a 2-piperidinone. There are a few reports in the literature for such structures.[20,21] We sought a more flexible route and considered 5-(2-bromophenyl)-4-formyl-pentanoic acid esters as precursors for the desired piperidinones. The synthesis started from bromoiodobenzenes **8a–c**, which were subjected to a Jeffery–Heck coupling with allylalcohol (Scheme 1, Table 1).[19,22] The resulting aldehydes **9a–c** were then converted to the enamines **10a–c** using pyrrolidine in $CHCl_3$ together with molecular sieves.[23] Treatment of the crude enamines with ethyl acrylate[24] provided the 4-formyl esters **11a–c**. It was then planned to perform a reductive amination with benzylamine followed by lactam formation. If the reduction was performed with sodium cyanoborohydride,[25] the desired piperidinones **12a–c** were the only product. Under otherwise typical conditions,[26,27] that is, stirring the aldehyde ester **11a** with benzylamine, acetic acid, and sodium triacetoxyborohydride a mixture of the enamide **13** and the lactam **12a** was formed. The yields for the individual steps of the sequence shown in Scheme 1 are given in Table 1. Compound **9b** was prepared as described in the literature from 3-bromo-4-iodotoluene.[28,29] As a further advanced starting material we targeted 3-(2-bromo-5-methoxyphenyl)propanal (**9c**) (Scheme 1, Table 1). This aldehyde is available from 3-methoxybenzaldehyde[30] or from 3-iodophenyl methyl ether.[31] The latter route involves bromination to give 4-bromo-3-iodophenyl methyl ether[31] **8c**, which was then subjected to the Jeffery–Heck reaction[22] with allylalcohol.



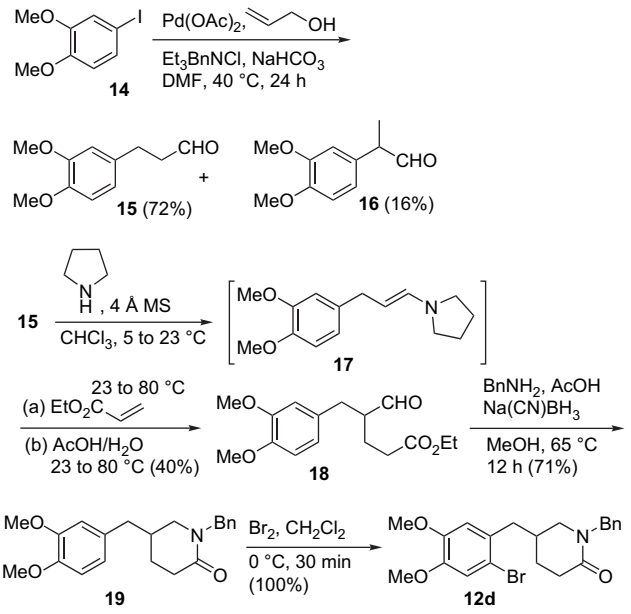
Scheme 1. Synthesis of the cyclization substrates **12a–c** via reductive amination of the formyl esters **11a–c**.

In order to prepare the piperidinone **12d**, which features a 2-bromo-4,5-dimethoxybenzyl substituent at the 5-position a late stage bromination was chosen (Scheme 2). Thus, veratrole was converted to 1,2-dimethoxy-4-iodobenzene (**14**) by iodination in presence of HgO.[32] A subsequent Jeffery–Heck reaction of **14** with allylalcohol led to the propanal[33]

Table 1
Yields for the individual steps in the synthesis of the piperidinones **12a–c**

R^1	R^2	Coupling step compound (%)	Michael addition compound (%)	Reductive amination compound (%)
H	H	**9a** (80)	**11a** (50)	**12a** (82)
H	Me	**9b** (70)	**11b** (40)	**12b** (72)
OMe	H	**9c** (70)	**11c** (46)	**12c** (71)

15 in 72% yield along with the isomeric aldehyde **16** (16%). After separation of the two isomers by chromatography, enamine formation on aldehyde **15** was followed by Michael addition of the intermediate enamine to ethyl acrylate. This allowed the isolation of the 4-formyl ester **18** in reasonable yield. Reaction with benzylamine under reductive conditions provided the substituted piperidinone **19**. Due to the electron-rich aromatic ring bromination to give **12d** was rather facile, taking place within 30 min at 0 °C.

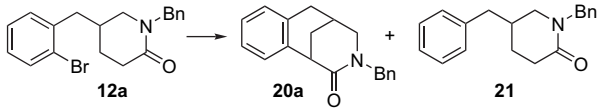


Scheme 2. Synthesis of piperidinone **12d** from iodobenzene **14**.

With the substrates in hand we screened a range of conditions using **12a** for achieving the Buchwald–Hartwig cyclization (Table 2). Using the rather weak *t*-BuONa as base, *t*-Bu_3P as ligand, and $Pd(OAc)_2$ as palladium source[18] the only product formed was the debrominated lactam **21** (entry 1) in 50% yield. We then turned to the use of zinc enolates.[15] With a stronger base [$NaN(SiMe_3)_2$], the same ligand *t*-Bu_3P but $Pd(dba)_2$ as palladium source and with added ZnF_2 in THF as solvent there was also no cyclized product (entry 2). Not even the debrominated 2-piperidinone **21** could be identified by LC–MS. If, however, the additive was changed to $ZnCl_2$ (4 equiv) the tricyclic lactam **20** was formed, even though the yield was not too high (entry 3). Also higher temperatures (entry 4) did not result in a better yield. Since the Cossy group had successfully employed the biphenyl ligand **L** (Fig. 2, Eq. 2) in bimolecular lactam arylations, we tried this ligand as well. While the product **20** was formed the yield was still in the 30% range (entry 5). The highest yield could be realized using lithium tetramethylpiperidide (LiTMP) as base, which led to the product **20** in 40% isolated yield. Since the conditions explained in Table 2 (entry 3) were simple and reliable we used those for larger scale runs and for other substrates.

As can be seen from Table 3, the crucial palladium-mediated cyclizations on substrates **12b–d** did take place with comparable yields. For substrate **12d** featuring a rather electron-rich aromatic ring (entry 4), the chemical yield (30%) of the tricyclic compound **20d** was somewhat lower than that in the other cases. The IR spectra of the tricyclic compounds show a prominent band between 1640 and 1651 cm^{-1} due to the amide C=O stretching. These values are typical for *N*,*N*-disubstituted amides. In the ^1H NMR spectra each of the three methylene groups of the polycyclic ring system appears as doublet of doublet (AB system). The 4-H pair is deshielded most, followed by the 6-H pair. The hydrogen atoms of the methano bridge (H-11) resonate at higher field at around 2.1 and 1.9 ppm, respectively. The methine signals 1-H and 5-H appear at around 3.5 and 2.5 ppm, respectively. According to Chem3D force field calculations (see Supplementary data), the piperidinone ring adopts an envelope-like conformation to allow for planarity around the amide bond.

Table 2
Reaction of the piperidinone with base, palladium source, and a phosphine ligand under various conditions[a]



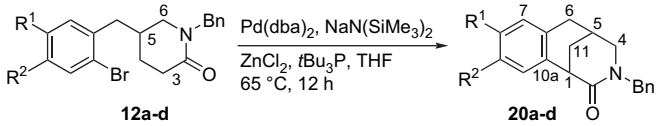
Entry	Base	Ligand	Additive	Solvent	Temp [°C]	Yield **20a** (%)	Yield **21** (%)
1[b]	*t*-BuONa	*t*-Bu_3P	—	Toluene	110	—	50
2	NaHMDS	*t*-Bu_3P	ZnF_2	THF	65	—	—
3	NaHMDS	*t*-Bu_3P	$ZnCl_2$	THF	65	36	—
4	NaHMDS	*t*-Bu_3P	$ZnCl_2$	Dioxane	100	35	—
5	NaHMDS	L	$ZnCl_2$	THF	65	33	—
6	LiTMP	*t*-Bu_3P	$ZnCl_2$	THF	65	40	—

Palladium source=$Pd(dba)_2$ (7–10 mol %), except for entry 1.
[a] Typical amounts of reagents: NaHMDS (4 equiv), $ZnCl_2$ (4 equiv), *t*-Bu_3P (15 mol %), $Pd(dba)_2$ (10 mol %).
[b] Palladium source=$Pd(OAc)_2$.

3. Conclusion

In summary we could illustrate a novel strategy to 3-benzazocines. The key step in this strategy is the intramolecular Buchwald–Hartwig arylation of piperidinones that carry a 2-bromobenzyl substituent in the 5-position. It turned out that this lactam arylation requires formation of the intermediate zinc enolates. While the yields are moderate this concept

Table 3
Buchwald–Hartwig arylation of piperidinones to give 3-benzazocines **20a–d**



Entry	R^1	R^2	Substrate	Product	Yield (%)
1	H	H	**12a**	**20a**	36
2	H	Me	**12b**	**20b**	33
3	OMe	H	**12c**	**20c**	34
4	OMe	OMe	**12d**	**20d**	30

allows for the formation of pharmaceutically interesting tricyclic compounds that might be difficult to access by standard methods. We also note that the 5-substituted piperidinones, which are of interest itself are easily accessible from aldehydes by a sequence of Michael addition followed by reductive amination and lactam formation.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K in $CDCl_3$. Chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). 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 mm, 70×3 mm Machery-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: J.T. Baker silica gel 43–60 μm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV$_{254}$. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under a nitrogen atmosphere.

4.2. Ethyl 5-(2-bromophenyl)-4-formylpentanoate (*11a*)

To a cooled (0 °C), stirred solution of the aldehyde **9a** (770 mg, 3.6 mmol) in $CHCl_3$ (5 mL) were added molecular sieves (4 Å, 4.2 g) followed by pyrrolidine (0.59 mL, 7.2 mmol). The reaction mixture was stirred for 4 h at room temperature. Then the mixture was filtered, with washing of the molecular sieves using diethyl ether (3×10 mL). The combined filtrates were washed with aqueous $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the crude enamine **10**. To the crude enamine in CH_3CN (8 mL) at 5 °C was added ethyl acrylate (0.59 mL, 5.4 mmol). The resultant mixture was stirred for 2 h at room temperature, and then refluxed for 2 h. After cooling the mixture to room temperature, AcOH (1 mL) in H_2O (4 mL) was added followed by refluxing the mixture for 2 h. After cooling to ambient temperature, the mixture was treated with 3 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Concentration of the filtrate and purification of the residue by flash chromatography (ethyl acetate/hexane, 1:9) furnished the aldehyde ester **11a** (566 mg, 50% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=9.67 (1H, s, CH=O), 7.52 (1H, d, J=8.1 Hz, Ar–H), 7.25–7.16 (2H, m, Ar–H), 7.10–7.03 (1H, m, Ar–H), 4.09 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 3.17–3.06 (1H, m, 4-H), 2.90–2.70 (2H, m, 5-H), 2.48–2.20 (2H, m, 2-H), 2.10–1.90 (1H, m, 3-H), 1.90–1.70 (1H, m, 3-H), 1.21 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=203.0 (CH, CH=O), 172.7 (C, OC=O), 137.8 (C, C-1′), 133.0 (CH), 131.3 (CH), 128.3 (CH), 127.5 (CH), 124.5 (C, C-2′), 60.5 (CH$_2$, OCH_2CH$_3$), 50.8 (CH, C-4), 35.2 (CH$_2$, C-5), 31.4 (CH$_2$, C-2), 23.6 (CH$_2$, C-3), 14.1 (CH$_3$, OCH$_2$CH_3).

4.3. Ethyl 5-(2-bromo-4-methylphenyl)-4-formylpentanoate (*11b*)

The reaction was performed with aldehyde[29] **9b** (1.4 g, 4.9 mmol), pyrrolidine (0.8 mL, 9.8 mmol), and ethyl acrylate (0.75 mL, 6.85 mmol) as described above. Purification of the crude product by flash chromatography (ethyl actate/hexane, 1:8) furnished the aldehyde ester **11b** (800 mg, 40% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=9.67 (1H, s, CH=O), 7.36 (1H, s, 3′-H), 7.08 (1H, d, J=7.9 Hz, 5′-H), 7.02 (1H, d, J=7.9 Hz, 6′-H), 4.10 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 3.15–3.00 (1H, m, 4-H), 2.88–2.70 (2H, m, 5-H), 2.48–2.20 (2H, m, 2-H), 2.28 (3H, s, ArCH$_3$), 2.10–1.98 (1H, m) and 1.88–1.70 (1H, m) [3-H], 1.22 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=203.2 (CH, CH=O), 172.8 (C, OC=O), 138.5 (C), 134.6 (C), 133.5 (CH, C-3′), 131.1 (CH, C-5′), 128.3 (CH, C-6′), 124.2 (C, C-2′), 60.5 (CH$_2$, OCH_2CH$_3$), 51.0 (CH, C-4), 34.9 (CH$_2$, C-5), 31.5 (CH$_2$, C-2), 23.7 (CH$_2$, C-3), 20.6 (CH$_3$, ArCH$_3$), 14.2 (CH$_3$, OCH$_2$CH_3).

4.4. Ethyl 5-[2-bromo-5-(methyloxy)phenyl]-4-formylpentanoate (*11c*)

The reaction was performed with aldehyde[31] **9c** (1.7 g, 7.0 mmol), pyrrolidine (1.16 mL, 14.1 mmol), and ethyl acrylate (1.07 mL, 9.87 mmol) as described above. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:6) furnished the aldehyde ester **11c** (1.2 g, 46% for two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=9.68 (1H, s, CH=O), 7.41 (1H, d, J=8.9 Hz, 3′-H), 6.77 (1H, d, J=3.1 Hz, 6′-H), 6.65 (1H, dd, J=8.9 and 3.1 Hz, 4′-H), 4.10 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 3.76 (3H, s, OCH$_3$), 3.08 (1H, dd, J=12.7, 6.9 Hz, 4-H), 2.90–2.65 (2H, m, 5-H), 2.50–2.25 (2H, m, 2-H), 2.20–1.90 (1H, m) and 1.90–1.73 (1H, m) [3-H], 1.22 (3H, t, J=7.1 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=203.0 (CH, CH=O), 172.8 (C, OC=O), 158.9 (C, C-5′), 138.8 (C, C-1′), 133.6 (CH, C-3′), 117.1 (CH, C-6′), 114.8 (C, C-2′), 114.0 (CH, C-4′), 60.5 (CH$_2$, OCH_2CH$_3$), 55.4 (CH$_3$, OCH$_3$), 50.8 (CH, C-4), 35.4 (CH$_2$, C-5), 31.5 (CH$_2$, C-2), 23.7 (CH$_2$, C-3), 14.2 (CH$_3$, OCH$_2$CH_3).

4.5. 1-Benzyl-5-(2-bromobenzyl)-2-piperidinone (*12a*) and 1-benzyl-5-(2-bromobenzyl)-3,4-dihydro-2(1*H*)-pyridinone (*13*)

To a stirred solution of the aldehyde ester **11a** (300 mg, 0.96 mmol) in CH_2ClCH_2Cl (5 mL) at room temperature, were added sequentially benzylamine (0.2 mL, 1.9 mmol), AcOH (0.1 mL), and Na(OAc)$_3$BH (609 mg, 2.87 mmol),

followed by refluxing the mixture for 12 h. After cooling to ambient temperature, saturated $NaHCO_3$ solution was added, and the mixture extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with saturated NaCl solution, dried with Na_2SO_4, and filtered. Evaporation of the filtrate and purification of the residue by flash chromatography (ethyl acetate/hexane, 1:2) furnished the cyclic enamide **13** (120 mg, 35%) (first fraction) as brown viscous oil. Further elution of the column with ethyl acetate/hexane (1:1) provided the required cyclic amide **12a** (100 mg, 29%) as light brownish viscous oil.

*4.5.1. Data for enamide **12***

IR (neat): ν_{max}/cm^{-1}=2925, 1668, 1407, 1211, 752; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.44 (1H, d, J=8.1 Hz, Ar–H), 7.30–7.09 (6H, m, Ar–H), 7.06 (1H, d, J=8.1 Hz, Ar–H), 7.05–6.95 (1H, m, Ar–H), 5.72 (1H, s, CH=C), 4.57 (2H, s, NCH_2Ph), 3.35 (2H, s, CH_2Ar), 2.48 (2H, t, J=8.4 Hz, 4-H), 2.16 (2H, t, J=8.4 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=168.6 (C, NC=O), 138.0 (C), 137.1 (C), 132.9 (CH), 130.5 (CH), 128.5 (2C, CH), 128.0 (CH), 127.5 (2C, CH), 127.3 (2C, CH), 126.3 (CH), 124.9 (C, C-2′), 117.4 (C), 48.9 (CH_2, NCH_2Ph), 39.8 (CH_2, CH_2Ar), 31.1 (CH_2, C-3), 24.0 (CH_2, C-4); HRMS (ESI): calcd for $C_{19}H_{19}NBrO$ $[M+H]^+$ 356.0644, found 356.0644.

*4.6. 1-Benzyl-5-(2-bromobenzyl)-2-piperidinone (**12a**) by reductive amination with Na(CN)BH$_3$*

To a stirred solution of the aldehyde ester **11a** (350 mg, 1.12 mmol) in MeOH (3 mL) were added sequentially benzylamine (0.24 mL, 2.23 mmol), AcOH (0.1 mL), and $Na(CN)BH_3$ (140 mg, 2.2 mmol) at room temperature. Then the mixture was refluxed for 12 h. After cooling to room temperature, saturated $NaHCO_3$ solution was added, and the mixture extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with saturated NaCl solution, dried with Na_2SO_4, and filtered. Concentration of the filtrate and purification of the residue by flash column chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic amide **12a** (330 mg, 82%) as a light brownish viscous oil. IR (neat): ν_{max}/cm^{-1}=2925, 1641, 1492, 1261, 1022, 754, 701; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.44 (1H, dd, J=8.1 and 1.0 Hz, Ar–H), 7.34–7.12 (5H, m, Ar–H), 7.12–7.05 (1H, m, Ar–H), 7.02–6.93 (1H, m, Ar–H), 6.88 (1H, dd, J=7.6, 1.5 Hz, Ar–H), 4.65 and 4.34 (2H, 2d, J=14.5 Hz, NCH_2Ph), 3.12 (1H, ddd, J=12.0, 4.8, 1.3 Hz) and 2.91 (1H, dd, J=12.0, 9.6 Hz) [6-H], 2.70–2.40 (3H, m), 2.38–2.23 (1H, m), 2.20–2.03 (1H, m), 1.85–1.70 (1H, m) and 1.57–1.40 (1H, m) [4-H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=169.5 (C, NC=O), 138.5 (C), 137.0 (C), 133.0 (CH), 131.0 (CH), 128.5 (2C, CH), 128.1 (3C, CH), 127.3 (2C, CH), 124.6 (C, C-2′), 52.0 (CH_2, NCH_2Ph), 50.2 (CH_2, C-6), 39.2 (CH_2, CH_2Ar), 34.0 (CH, C-5), 31.2 (CH_2, C-3), 26.7 (CH_2, C-4); HRMS (ESI): calcd for $C_{19}H_{21}NBrO$ $[M+H]^+$ 358.0801, found 358.0800.

*4.7. 1-Benzyl-5-(2-bromo-4-methylbenzyl)-2-piperidinone (**12b**)*

As described for compound **12a**, the formyl ester **11b** (1.0 g, 3.06 mmol) in MeOH (8 mL) was reacted with benzylamine (0.67 mL, 6.1 mmol), AcOH (0.3 mL), and $Na(CN)BH_3$ (192 mg, 3.06 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) furnished the cyclic amide **12b** (818 mg, 72%) as light brownish viscous oil. IR (neat): ν_{max}/cm^{-1}=2922, 1643, 1492, 1453, 1259, 701; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.25–7.05 (6H, m, Ar–H), 6.83 (1H, d, J=7.9 Hz, 5′-H), 6.70 (1H, d, J=7.9 Hz, 6′-H), 4.59 and 4.28 (2H, 2d, J=14.8 Hz, NCH_2Ph), 3.05 (1H, ddd, J=12.0, 4.8, 1.3 Hz) and 2.84 (1H, dd, J=12.0 and 9.7 Hz) [6-H], 2.57–2.34 (3H, m), 2.33–2.15 (1H, m), 2.13 (3H, s, $ArCH_3$), 2.12–1.94 (1H, m), 1.71 (1H, br s), 1.50–1.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=169.5 (C, NC=O), 138.0 (C), 137.1 (C), 135.3 (C), 133.3 (CH), 130.6 (CH), 128.5 (2C, CH), 128.1 (3C, CH), 127.2 (CH), 124.3 (C, C-2′), 52.0 (CH_2, NCH_2Ph), 50.7 (CH_2, C-6), 38.7 (CH_2, CH_2Ar), 34.1 (CH, C-5), 31.2 (CH_2, C-3), 26.6 (CH_2, C-4), 20.5 (CH_3, $ArCH_3$); HRMS (ESI): calcd for $C_{20}H_{23}NBrO$ $[M+H]^+$ 372.0957, found 372.0957.

*4.8. 1-Benzyl-5-(2-bromo-5-methoxybenzyl)-2-piperidinone (**12c**)*

As described for compound **12a**, the formyl ester **11c** (1.0 g, 3.06 mmol) in MeOH (8 mL) was reacted with benzylamine (0.48 mL, 4.4 mmol), AcOH (0.3 mL), and $Na(CN)BH_3$ (180 mg, 2.9 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 1:1) as eluent furnished the cyclic amide **12c** (800 mg, 71%) as light brownish viscous oil. IR (neat): ν_{max}/cm^{-1}=2932, 1643, 1493, 1474, 1242, 701; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.23 (1H, d, J=8.7 Hz, 3′-H), 7.20–7.00 (5H, m, Ar–H), 6.52–6.33 (2H, m, Ar–H), 4.51 and 4.30 (2H, 2d, J=14.5 Hz, NCH_2Ph), 3.55 (3H, s, OCH_3), 3.01 (1H, dd, J=12.0, 4.8 Hz), 2.81 (1H, dd, J=12.0, 9.6 Hz) [6-H], 2.50 (1H, dd, J=13.5, 6.4 Hz), 2.46–2.30 (2H, m), 2.30–2.13 (1H, m), 2.02 (1H, br s), 1.69 (1H, br s), 1.48–1.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=169.5 (C, NC=O), 158.7 (C), 139.4 (C), 137.0 (C), 133.4 (CH, C-3′), 128.5 (2C, CH), 127.9 (2C, CH), 127.2 (CH), 116.7 (CH, C-6′), 114.9 (C, C-2′), 113.4 (CH, C-4′), 55.3 (CH_3, OCH_3), 52.2 (CH_2, NCH_2Ph), 50.2 (CH_2, C-6), 39.4 (CH_2, CH_2Ar), 34.1 (CH, C-5), 31.3 (CH_2, C-3), 26.6 (CH_2, C-4); HRMS (ESI): calcd for $C_{20}H_{23}NBrO$ $[M+H]^+$ 388.0907, found 388.0909.

*4.9. 1-Benzyl-5-(2-bromo-4,5-dimethoxybenzyl)-2-piperidinone (**12d**)*

To a cooled (0 °C), stirred solution of the lactam **19** (1.1 g, 3.2 mmol) in CH_2Cl_2 (30 mL) was slowly added molecular bromine (0.17 ml, 3.4 mmol) followed by stirring the mixture at the same temperature for 30 min. Then, the reaction mixture

was washed with aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/hexane, 7:3) furnished the aryl bromide **12d** (1.36 g, 100%) as brown viscous oil. IR (neat): ν_{max}/cm^{-1}=2930, 1640, 1507, 1440, 1257, 1217, 1164, 1029, 703; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.45–7.18 (5H, m, Ar–H), 7.00 (1H, s, 3′-H), 6.55 (1H, s, 6′-H), 4.67 and 4.50 (2H, 2d, J=14.8 Hz, NCH_2Ph), 3.85 (3H, s) and 3.79 (3H, s) [2OCH_3], 3.20 (1H, ddd, J=12.0, 4.8, 1.3 Hz) and 2.99 (1H, dd, J=12.0, 9.6 Hz) [6-H], 2.78–2.50 (3H, m), 2.48–2.28 (1H, m), 2.28–2.09 (1H, m), 1.96–1.80 (1H, m), 1.67–1.44 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=169.7 (C, NC=O), 148.3 (C, C-4′), 148.2 (C, C-5′), 137.1 (C), 130.5 (C), 128.6 (2C, CH), 128.1 (2C, CH), 127.3 (CH), 115.6 (CH, C-3′), 114.4 (C, C-2′), 113.4 (CH, C-6′), 56.1 (2C, 2OCH_3), 52.3 (CH_2, NCH_2Ph), 50.3 (CH_2, C-6), 39.0 (CH_2, CH_2Ar), 34.6 (CH, C-5), 31.4 (CH_2, C-3), 26.8 (CH_2, C-4); HRMS (ESI): calcd for $C_{21}H_{25}NBrO_3$ $[M+H]^+$ 418.1012, found 418.1014.

4.10. 3-(3,4-Dimethoxyphenyl)-propan-1-al (**15**) and 2-(3,4-dimethoxyphenyl)-propan-1-al (**16**)

To a stirred solution of $Pd(OAc)_2$ (127.5 mg, 0.57 mmol), allylalcohol (2.58 mL, 37.9 mmol), triethylbenzylammonium chloride (3.88 g, 17.0 mmol), and $NaHCO_3$ (3.18 g, 37.9 mmol) in DMF (40 mL) was added iodoveratrol **14** (5.0 g, 18.9 mmol) and the resulting blackish brown solution was heated at 40 °C for 24 h. The reaction was quenched with aqueous NH_4Cl and the mixture extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent and purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:4) furnished the 2-methylacetaldehyde **16** (600 mg, 16%) as the first fraction (colorless oil). Further elution of the column with ethyl acetate/hexane, 1:3, provided the required aldehyde[33] **15** (2.6 g, 72%) as colorless oil.

4.10.1. Data for **15**

^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=9.80 (1H, s, CH=O), 6.78 (1H, d, J=8.4 Hz, 5′-H), 6.74–6.67 (2H, m, Ar–H), 3.85 (3H, s) and 3.84 (3H, s) [2OMe], 2.90 (2H, t, 3-H) and 2.75 (2H, t, 2-H) [2×J=7.4 Hz]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=201.6 (CH, CH=O), 148.9 (C), 147.5 (C), 132.9 (C, C-1′), 120.0 (CH, C-6′), 111.6 (CH), 111.3 (CH), 55.9, 55.8 (2OMe), 45.5 (CH_2, C-2), 27.7 (CH_2, C-3).

4.10.2. Data for **16**

^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=9.64 (1H, s, CH=O), 6.86 (1H, d, J=8.1 Hz, 5′-H), 6.75 (1H, dd, J=8.1, 2.0 Hz, 6′-H), 6.67 (1H, d, J=2.0 Hz, 2′-H), 3.86 (6H, s, 2OMe), 3.56 (1H, q, J=7.1 Hz, 2-H), 1.41 (3H, d, J=7.1 Hz, *sec*-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=201.0 (CH, CH=O), 149.4 (C), 148.5 (C), 130.0 (C, C-1′), 120.4 (CH), 111.6 (CH), 111.3 (CH), 55.9 (2C, OCH_3), 52.5 (CH, C-2), 14.6 (CH_3).

4.11. Ethyl 5-[2-bromo-4,5-bis(methyloxy)phenyl]-4-formylpentanoate (**18**)

The reaction was performed with aldehyde **15** (1.9 g, 9.8 mmol), pyrrolidine (1.2 mL, 14.7 mmol), and ethyl acrylate (1.49 mL, 13.7 mmol) as described above. Purification of the crude product by flash column chromatography (ethyl actate/hexane, 1:3) furnished the aldehyde ester **18** (1.13 g, 40% for two steps) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=9.65 (1H, s, CH=O), 6.77 (1H, d, J=8.1 Hz, 5′-H), 6.69 (1H, d, J=2.0 Hz, 2′-H), 6.66 (1H, dd, J=8.1, 2.0 Hz, 6′-H), 4.09 (2H, q, J=7.1 Hz, OCH_2CH_3), 3.84 (3H, s) and 3.83 (3H, s) [2OCH_3], 3.00–2.87 (1H, m, 4-H), 2.75–2.60 (2H, m, 5-H), 2.45–2.20 (2H, m, 2-H), 2.03–1.88 (1H, m) and 1.85–1.70 (1H, m) [3-H], 1.21 (3H, t, J=7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=203.8 (CH, CH=O), 172.8 (C, OC=O), 149.0 (C, C-3′), 147.7 (C, C-4′), 130.6 (C, C-1′), 120.9 (CH), 112.0 (CH), 111.3 (CH), 60.5 (CH_2, OCH_2CH_3), 55.8 (2C, 2OCH_3), 52.6 (CH, C-4), 34.8 (CH_2, C-5), 31.5 (CH_2, C-2), 23.5 (CH_2, C-3), 14.1 (CH_3, OCH_2CH_3).

4.12. 1-Benzyl-5-(3,4-dimethoxybenzyl)-2-piperidinone (**19**)

As described for compound **12a**, the formyl ester **18** (1.08 g, 3.7 mmol) in MeOH (8 mL) was reacted with benzylamine (0.8 mL, 7.3 mmol), AcOH (0.3 mL), and $Na(CN)BH_3$ (231 mg, 3.7 mmol). Purification of the crude product by flash chromatography (ethyl acetate/hexane, 7:3) furnished the cyclic amide **19** (880 mg, 71%) as light brownish viscous oil. IR (neat): ν_{max}/cm^{-1}=2925, 1638, 1515, 1461, 1258, 700; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.60–7.34 (5H, m, Ar–H), 6.94 (1H, d, J=8.6 Hz, 6′-H), 6.77 (1H, s, 2′-H), 6.76 (1H, d, J=8.6 Hz, 5′-H), 4.79 and 4.69 (2H, 2d, J=14.5 Hz, NCH_2Ph), 4.03 (3H, s) and 4.01 (3H, s) [2OCH_3], 3.35 (1H, ddd, J=12.0, 4.8, 1.3 Hz) and 3.11 (1H, dd, J=12.0, 9.7 Hz) [6-H], 2.83–2.50 (4H, m), 2.32–2.15 (1H, m), 2.12–2.00 (1H, m), 1.77–1.58 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=169.8 (C, NC=O), 148.9 (C, C-3′), 147.5 (C, C-4′), 137.1 (C), 131.6 (C), 128.6 (2C, CH), 128.1 (2C, CH), 127.3 (CH), 120.8 (CH, C-6′), 112.0 (CH, C-5′), 111.2 (CH, C-2′), 55.9, 55.8 (2C, 2OCH_3), 52.3 (CH_2, NCH_2Ph), 50.3 (CH_2, C-6), 39.1 (CH_2, CH_2Ar), 35.8 (CH, C-5), 31.3 (CH_2, C-3), 26.9 (CH_2, C-4); HRMS (ESI): calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$ 340.1907, found 340.1907.

4.13. 3-Benzyl-3,4,5,6-tetrahydro-1,5-methano-3-benzazocin-2(1H)-one (**20a**)

In an oven dried Schlenk tube fitted with a rubber septum, a solution of the amide **12a** (160 mg, 0.45 mmol) in anhydrous THF (5 mL) was treated with NaHMDS solution (0.89 mL, 2 M in THF, 1.78 mmol) at 0 °C followed by stirring the mixture for 10 min at 0 °C. To the resulting solution of the amide enolate were added sequentially anhydrous $ZnCl_2$ (243 mg, 1.78 mmol), *t*-Bu_3P (0.56 mL, 0.12 M in toluene, 15 mol %),

and $Pd(dba)_2$ (25.7 mg, 10 mol %) at 0 °C. The reaction mixture was heated in an oil bath at 65 °C for 12 h before it was cooled to room temperature and washed with aqueous NH_4Cl solution. After separation of the layers, the aqueous layer was extracted with ethyl acetate (3×3 mL). The combined organic layers were washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate and purification of the crude material by flash chromatography (ethyl acetate/hexane, 2:3) furnished the benzazocine **20a** (45 mg, 36%) as brown viscous oil. IR (neat): ν_{max}/cm^{-1}=2925, 1648, 1489, 1452, 1258, 700; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.40–6.80 (9H, m, Ar–H), 4.43 and 4.36 (2H, 2d, J=14.8 Hz, NCH_2Ph), 3.63 (1H, s, 1-H), 3.49 (1H, dd, J=12.5, 6.4 Hz) and 2.99 (1H, d, J=12.5 Hz) [4-H], 3.15 (1H, dd, J=17.6, 6.6 Hz) and 2.64 (1H, d, J=17.6 Hz) [6-H], 2.50 (1H, s, 5-H), 2.18 (1H, d) and 2.00 (1H, d) [J=12.5 Hz, 11-H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=171.2 (C, NC=O), 137.1 (C), 136.1 (C), 134.4 (C), 128.9 (CH), 128.7 (CH), 128.4 (2C, CH), 127.6 (2C, CH), 127.1 (2C,CH), 126.2 (CH), 54.0 (CH_2, NCH_2Ph), 49.4 (CH_2, C-4), 43.4 (CH, C-1), 35.8 (CH_2, C-6), 26.7 (CH_2, C-11), 25.8 (CH, C-5); HRMS (ESI): calcd for $C_{19}H_{20}NO$ $[M+H]^+$ 278.1539, found 278.1539.

*4.14. 3-Benzyl-9-methyl-3,4,5,6-tetrahydro-1,5-methano-3-benzazocin-2(1H)-one (**20b**)*

The reaction was performed with the enolate of the amide **12b** (180 mg, 0.48 mmol) [prepared from NaHMDS (0.96 mL of 2 M in THF, 1.9 mmol)] in anhydrous THF (5 mL). Then, sequentially anhydrous $ZnCl_2$ (263 mg, 1.9 mmol), t-Bu_3P (0.6 mL of 0.12 M in toluene, 15 mol %), and $Pd(dba)_2$ (27.8 mg, 10 mol %) were added as described for compound **20a**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 2:3) furnished the benzazocine **20b** (46 mg, 33%) as brown viscous oil. IR (neat): ν_{max}/cm^{-1}= 2924, 1650, 1494, 1453, 1259, 706; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.50–6.60 (8H, m, Ar–H), 4.42 and 4.38 (2H, 2d, J=14.8 Hz, NCH_2Ph), 3.58 (1H, s, 1-H), 3.48 (1H, dd, J=12.5, 6.6 Hz) and 2.98 (1H, d, J=12.5 Hz) [4-H], 3.10 (1H, dd, J=17.6, 7.1 Hz) and 2.60 (1H, d, J=17.6 Hz) [6-H], 2.48 (1H, br s, 5-H), 2.25 (3H, s, $ArCH_3$), 2.15 and 1.97 (2H, 2d, J=12.0 Hz, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=171.3 (C, NC=O), 137.2 (C), 135.9 (C), 135.7 (C), 131.2 (C), 129.3 (CH), 128.6 (CH), 128.5 (2C, CH), 128.0 (CH), 127.6 (2C, CH), 127.1 (CH), 54.0 (CH_2, NCH_2Ph), 49.4 (CH_2, C-4), 43.4 (CH, C-1), 35.5 (CH_2, C-6), 26.8 (CH_2, C-11), 25.9 (CH, C-5), 20.9 (CH_3, $ArCH_3$); HRMS (ESI): calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1696.

*4.15. 3-Benzyl-8-methoxy-3,4,5,6-tetrahydro-1,5-methano-3-benzazocin-2(1H)-one (**20c**)*

The reaction was performed with the enolate of the amide **12c** (180 mg, 0.46 mmol) [prepared from NaHMDS (0.69 mL of 2 M in THF, 1.39 mmol)] in anhydrous THF (5 mL). Then, sequentially anhydrous $ZnCl_2$ (190 mg, 1.39 mmol), t-Bu_3P (0.38 mL, 0.12 M in toluene, 10 mol %), and $Pd(dba)_2$ (18.7 mg, 7 mol %) were added as described for compound **20a**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 2:3) furnished the benzazocine **20c** (47 mg, 34%) as brown viscous oil. IR (neat): ν_{max}/cm^{-1}= 2930, 1640, 1492, 1453, 1258, 701; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.35–7.08 (4H, m, Ar–H), 6.95–6.85 (2H, m, Ar–H), 6.67 (1H, dd, J=8.4, 2.5 Hz, 9-H), 6.56 (1H, d, J=2.5 Hz, 7-H), 4.42 and 4.37 (2H, 2d, J=15.0 Hz, NCH_2Ph), 3.72 (3H, s, OCH_3), 3.57 (1H, s, 1-H), 3.47 (1H, dd, J=12.7, 6.4 Hz) and 2.98 (1H, d, J=12.7 Hz) [4-H], 3.12 (1H, dd, J=17.6, 6.3 Hz) and 2.61 (1H, d, J=17.6 Hz) [6-H], 2.48 (1H, br s, 5-H), 2.16 (1H, d) and 1.97 (1H, d) [J=12.2 Hz, 11-H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=171.5 (C, NC=O), 158.7 (C, C-8), 137.2 (C), 135.6 (C), 129.8 (CH), 128.6 (C), 128.5 (2C, CH), 127.6 (2C, CH), 127.1 (CH), 113.8 (CH, C-7), 112.0 (CH, C-9), 55.3 (CH_3, OCH_3), 53.9 (CH_2, NCH_2Ph), 49.4 (CH_2, C-4), 42.5 (CH, C-1), 36.1 (CH_2, C-6), 26.9 (CH_2, C-11), 25.7 (CH, C-5); HRMS (ESI): calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$ 308.1645, found 308.1645.

*4.16. 3-Benzyl-8,9-dimethoxy-3,4,5,6-tetrahydro-1,5-methano-3-benzazocin-2(1H)-one (**20d**)*

The reaction was performed with the enolate of the amide **12d** (200 mg, 0.48 mmol) [prepared from NaHMDS (2 M in THF, 0.96 mL, 1.9 mmol)] in anhydrous THF (5 mL). Then, sequentially anhydrous $ZnCl_2$ (261 mg, 1.9 mmol), t-Bu_3P (0.6 mL, 0.12 M in toluene, 15 mol %), and $Pd(dba)_2$ (27.7 mg, 10 mol %) were added as described for compound **20a**. Purification of the crude product by flash chromatography (ethyl acetate/hexane, 6:4) furnished the benzazocine **20d** (48 mg, 30%) as brown viscous oil. IR (neat): ν_{max}/cm^{-1}= 2930, 1641, 1494, 1452, 1259, 699; ^1H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.25–7.05 (3H, m, Ar–H), 6.93–6.82 (2H, m, Ar–H), 6.80 (1H, s, 10-H), 6.46 (1H, s, 7-H), 4.38 and 4.34 (2H, 2d, J=14.8 Hz, NCH_2Ph), 3.78 (3H, s) and 3.74 (3H, s) [$2OCH_3$], 3.48 (1H, s, 1-H), 3.43 (1H, dd, J=12.5, 6.6 Hz) and 2.93 (1H, d, J=12.5 Hz) [4-H], 3.02 (1H, dd, J=17.6, 6.6 Hz) and 2.50 (1H, d, J=17.6 Hz) [6-H], 2.44 (1H, s, 5-H), 2.12 and 1.92 (2H, 2d, J=12.7 Hz, 11-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=171.5 (C, NC=O), 148.2 (C), 147.3 (C), 137.2 (C), 128.5 (2C, CH), 128.2 (C), 127.6 (2C, CH), 127.1 (CH), 126.2 (C), 111.4 (2C, CH, C-7, C-10), 55.9 (2C, $2OCH_3$), 53.9 (CH_2, NCH_2Ph), 49.4 (CH_2, C-4), 42.9 (CH, C-1), 35.7 (CH_2, C-6), 26.9 (CH_2, C-11), 25.8 (CH, C-5); HRMS (ESI): calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$ 338.1751, found 338.1750.

*4.17. 1,5-Dibenzyl-2-piperidinone (**21**)*

An oven dried Schlenk tube fitted with a rubber septum was purged with nitrogen and charged with the cyclic amide **12a** (100 mg, 0.28 mmol), anhydrous toluene (5 mL), t-BuONa (134 mg, 1.4 mmol), and t-Bu_3P (0.35 mL, 0.12 M in toluene, 15 mol %). Then the tube was purged with nitrogen, and $Pd(OAc)_2$ (6.4 mg, 10 mol %) was added. The reaction mixture was heated in an oil bath at 110 °C for 12 h. The reaction

mixture was then cooled to room temperature and filtered through Celite. The filter cake was washed with ethyl acetate. Concentration of the filtrate under reduced pressure and purification of the crude material by flash chromatography (ethyl acetate/hexane, 1:1) furnished the debrominated cyclic amide **21** (39 mg, 50%) as light yellow viscous oil. IR (neat): ν_{max}/cm^{-1}=2924, 1642, 1494, 1454, 1260, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=7.35–7.05 (8H, m, Ar–H), 6.97 (2H, d, J=6.9 Hz, Ar–H), 4.56 and 4.42 (2H, 2d, J=14.8 Hz, NCH_2Ph), 3.11 (1H, ddd, J=12.2, 5.1, 1.5 Hz) and 2.87 (1H, dd, J=12.2, 9.9 Hz) [6-H], 2.58–2.38 (3H, m), 2.38–2.23 (1H, m), 2.10–1.90 (1H, m), 1.88–1.70 (1H, m) and 1.52–1.33 (1H, m) [4-H]; ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=169.7 (C, NC=O), 139.1 (C), 137.1 (C), 128.8 (2C, CH), 128.5 (2C, CH), 128.4 (2C, CH), 128.1 (2C, CH), 127.3 (CH), 126.3 (CH), 52.3 (CH_2, NCH_2Ph), 50.2 (CH_2, C-6), 39.4 (CH_2, CH_2Ar), 35.7 (CH, C-5), 31.3 (CH_2, C-3), 26.8 (CH_2, C-4); HRMS (ESI): calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1695.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.088.

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