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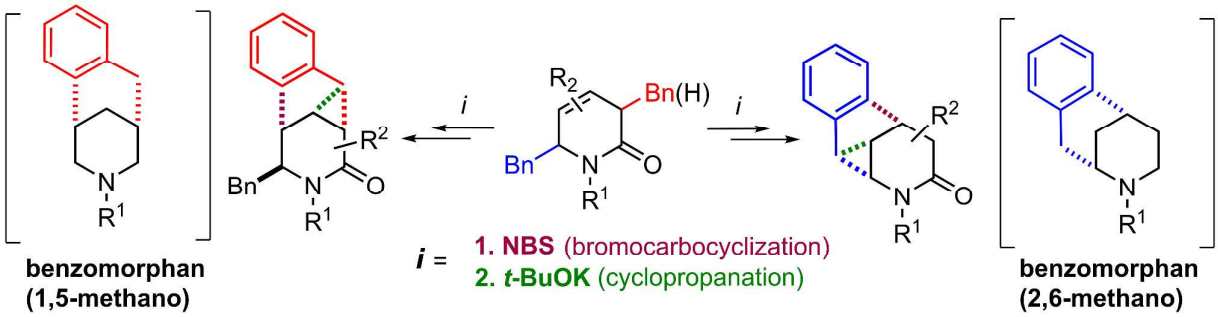
Synthesis of Polycyclic δ-Lactams with Bridged Benzomorphan Skeleton: Selectivity and Diversity Driven by Substituents

Jacek G. Sośnicki,*[†] Tomasz J. Idzik,[†] Aleksandra Borzyszkowska,[†] Gabriela Maciejewska,[‡] Łukasz Struk[†]

[†] West Pomeranian University of Technology, Szczecin, Faculty of Chemical Technology and Engineering, Department of Organic and Physical Chemistry, Al. Piastów 42, Szczecin, 71-065, Poland,

[‡] Wrocław University of Technology, Faculty of Chemistry, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

Corresponding author's e-mail address: sosnicki@zut.edu.pl



Abstract

An efficient synthesis of bromofunctionalized 2,6-methano- and 1,5-methano-benzomorphanones, starting from easily available 6-benzyl-3,6-dihydropyridin-2(1*H*)-ones, is described. Furthermore, the synthesis of bridged benzomorphanones with hitherto not known polycyclic systems containing 2- or 3-azabicyclo[4.1.0]heptane units is developed upon treatment of both 2,6- and 1,5-methanobromobenzomorphans with *t*-BuOK. The effects of substituents on the diversity and stereoselectivity of both transformations are studied.

Introduction

Polycyclic organic compounds with piperidine core constitute useful drugs or their naturally occurring precursors. A couple of synthetic benzomorphan and natural morphine (as an archetype)

are prominent examples.[1,2] The main interest in benzomorphans **1** (1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine, Figure 1), which have the ring system matching the part of morphine skeleton and which could be represented by (*R*)-pentazocine – clinically used drug[3] (Figure 1), results from their structural simplicity and new profiles of analgesic activity[4] giving hope for nonaddictive medication that could replace morphine. Apart from the opioid receptor activity, benzomorphans have also been recognized as sodium channel blockers for the treatment of stroke[5] and as potential drugs for the treatment of cocaine addiction and overdose.[6] The construction of benzomorphan analogues in terms of positional variation of nitrogen have been also carried out to determine their pharmacological utility.[2] Amongst a few ring-connections variants, benzomorphan analogues based on the skeleton of **2** (1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine, Figure 1) have attracted attention as potential drugs supporting smoking cessation (similarly to natural cytisine, Figure 1)[7] and as tyrosine analogue, which could be used as a potential ligand for SH2 inhibition.[8]

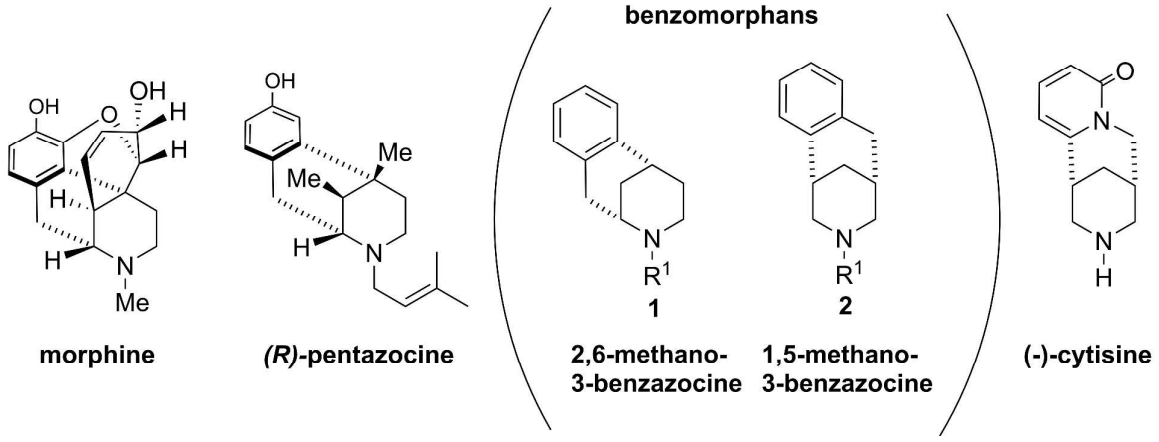


FIGURE 1. Naturally occurring morphine, cytisine and clinically used (*R*)-pentazocine as representative of synthetic benzomorphans

A number of methodologies have been developed for the synthesis of benzomorphans **1** and **2** (2,6-methano-3-benzazocines and 1,5-methano-3-benzazocines, respectively).[2] One of interesting strategies comprises the cyclization of benzyl-functionalized piperidines. Within this strategy, the sequence with intramolecular Friedel-Crafts cyclization as a key step, involving benzylpiperidines

with hydroxyl or C=C double moieties (capable to create carbocationic, electrophilic site) is a dominant approach.[2,4a,5a,9] Among other methods noteworthy is the cyclization of benzyl-piperidinones in the Buchwald-Hartwig reaction.[10] Unsaturated benzyl-δ-lactams were sparingly applied as substrates towards benzomorphans. Only recently 6-benzyl α,β-unsaturated δ-lactams have been cyclized in acidic[11] and radical[12] conditions. It should be also emphasized that amongst the reagents able to induce electrophilic site in the double C=C bond of unsaturated piperidines, only acids gave benzomorphans as cyclization products, while the attempt to use bromine led to *trans*-dibromo adduct,[13] not to bromo-substituted benzomorphans. Despite that failure, the investigation toward the synthesis of bromo-substituted benzomorphans is a hot subject of research because these compounds could reveal new pharmacological properties, as inferred from the properties of natural bioactive compounds containing bromine atom in their structure.[14] Besides, the introduction of reactive bromine atom into benzomorphan skeleton could open new synthetic possibilities. Therefore, the synthesis of halogen-functionalized benzomorphans is an ongoing challenge.

The past decades have witnessed great progress in the field of induced by halonium ions stereoselective cyclofunctionalization of alkenes equipped with a nucleophilic arm.[15] However, halocarbocyclizations, in which halonium intermediate is quenched intramolecularly by π-electrons of the aromatic ring have been less studied. As representative examples, the treatment of 3-benzyl cycloalkenes with bromine, providing bromo-cyclized product should be mentioned.[16] Amongst other reagents capable of forming halonium ion: *N*-halosuccinimide (NXS) in the presence of $Sm(OTf)_3$[17] and IPy_2BF_4–HBF_4,[18] has been used. BDSB (bromodiethylsulfonium bromopentachloroantimonate) has been recently found as one of the most convenient reagent for carbocyclization.[19] Besides, catalytic enantioselective bromocyclization of aromatic polyenes has also been successfully discovered.[20]

Recently, we have developed a straightforward synthesis of 6-benzyl β,γ-unsaturated δ-lactams through the addition of lithium di*sec*-butylbenzylmagnesiate to 2-pyridones[21] and now we

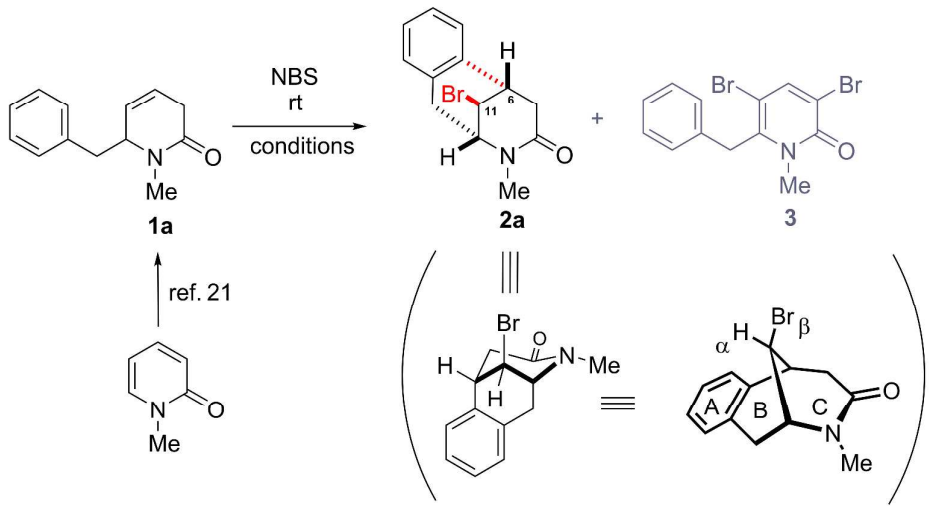
decided to use these adducts as starting material in the synthesis of bromobenzomorphans. Herein, we report results of our effort towards the synthesis of bromo-benzomorphans through the halocarbocyclization process, starting from 6-benzyl β,γ-unsaturated δ-lactams and their further transformation to the novel polycyclic systems which may be regarded as bridged benzomorphan derivatives. Hitherto, 6-benzyl β,γ-unsaturated δ-lactams have not been used for the synthesis of benzomorphans.

Results and Discussion

The initial experiments to obtain cyclized product (*via* 6-*endo trig* process) were started with 6-benzyl, N-methyl β,γ-unsaturated δ-lactam (**1a**), as well as BDSB and NBS as easy to use electrophilic sources of bromine. As a result, the use of BDSB led to total failure, while the application of NBS in THF premised success because it led to 11-bromobenzomorphanone product **2a**, unfortunately only in 30% yield (Table 1, entry 1). Because the yield of **2a** was not satisfactory and additional undesired product **3** was also formed in 28% yield, further optimization was required. The relevant results are collected in Table 1. Happily, from among solvents tested nitromethane was disclosed as the best one, allowing improvement of yield of **2a** up to 66% (Table 1, entry 7). Furthermore, triphenoxyphosphine (0.175 equiv.) was found as the best phosphine-derived additive. It allowed enhancement of the productivity of **2a** up to 97% yield and its use prevented the formation of **3** (Table 1, entry 16). Successful use of phosphorous(III) additives, in particular triphenylphosphite, indicated that reactive bromophosphonium ion (**BPI**) was formed, leading to product **2** as depicted in Scheme 1.[20c] Nitromethane as a polar solvent probably stabilized this ion and subsequently formed a bromocarbonium ion, facilitating the cyclization instead of dibromination.

TABLE 1. Optimization at the reaction conditions for bromocarbocyclization of 1a using NBS.

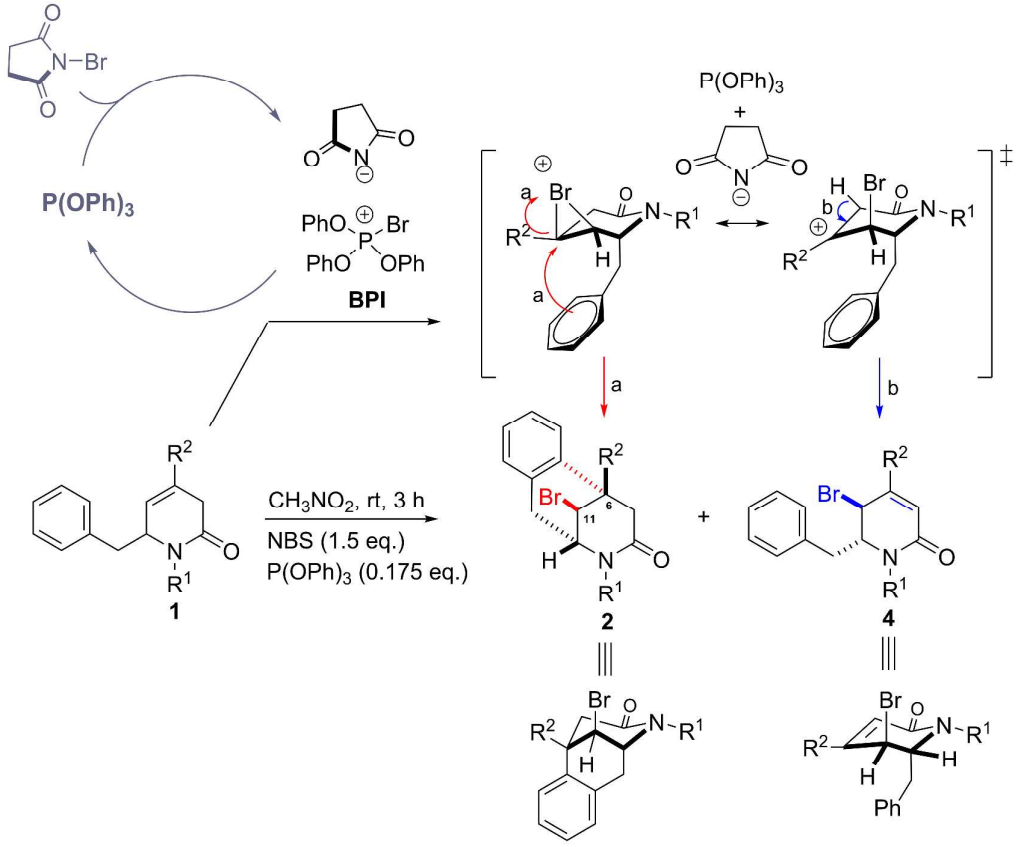
The effect of varying solvents and R_3P as additives



Entry	Solvent	R_3P additives (equiv.)	NBS (eqiv.) / Time (h)	Conv.[a] [%]	Yields[a] [%] **2a**	Yields[a] [%] **3**
1	THF	-	up to 5.8 / up to 96	>99	30	28
2	MeCN	-	up to 1.7 / up to 24	>99	33	4
3	DMF	-	up to 2.2 / up to 59	89	8	-[b]
4	CH_2Cl_2	-	2.2 / 48	98	17	48(48[e])
5	acetone	-	~2.8 / 264	>99	35	12
6[c]	PhCl	-	up to 2.2 / up to 96	98	42	16
7[c]	$MeNO_2$	-	up to 2.0 / up to 96	>99	66	3
8[c]	CH_2Cl_2	Ph_3P (0.2)	up to 1.8 / up to 92	99	26	26
9[c]	MeCN	Ph_3P (0.2)	1.2/3	89	63	0
10[c]	$MeNO_2$	Ph_3P (0.2)	1.5/3	96	81	0
11[c]	$MeNO_2$	Ph_3P (0.25)	1.5/3	96	85	0
12[c]	$MeNO_2$	Ph_3P (0.3)	1.5/3	95	88	0
13[c]	$MeNO_2$	Ph_3P (0.3)	1.5/3[d]	94	92	0
14[c]	$MeNO_2$	Ph_3P (0.4)	1.5/3	86	76	0
15[c]	$MeNO_2$	$(PhO)_3P$ (0.1)	1.5/3	86	85	0
16[c]	**$MeNO_2$**	**$(PhO)_3P$ (0.175)**	**1.5/3**	**98**	**97**	**0**
17[c]	$MeNO_2$	$(PhO)_3P$ (0.2)	1.5/3	98	84	0

18[c]	$MeNO_2$	$((o\text{-}tol)_3P)$ (0.175)	1.5/3	97	85	0
19[c]	$MeNO_2$	$((o\text{-}tol)_3P)$ (0.2)	1.5/3	97	86	0
20[c]	$MeNO_2$	$((o\text{-}tol)_3P)$ (0.3)	1.5/3	96	84	0

[a] – by GC-FID (calibration curve), [b] – unidentified product was present, [c]- the reactions were conducted in the dark; [d] – the reaction was conducted at 0°C, [e] – isolated yield



SCHEME 1. C4-substituent dependent reactivity of 1 under bromocyclization conditions (results in Table 2)

At the next step, the influence of substituents at the nitrogen atom and at C4 of 6-benzyl β,γ-unsaturated δ-lactams was tested under optimized bromocyclization conditions. As a result, C4-unsubstituted *N*-Me, *N*-Pr, *N*-Bn, and *N*-Ph derivatives gave sole bromobenzomorphans products **2** in high isolated yields, while 4-Me and 4-Ph derivatives led also to product **4** besides benzomorphans **2** (Scheme 1, Table 2). Notably, the amounts of compound **4** were depended on the nature of 4-substituent and were high for 4-phenyl and low for 4-methyl derivatives. This result indicates that for

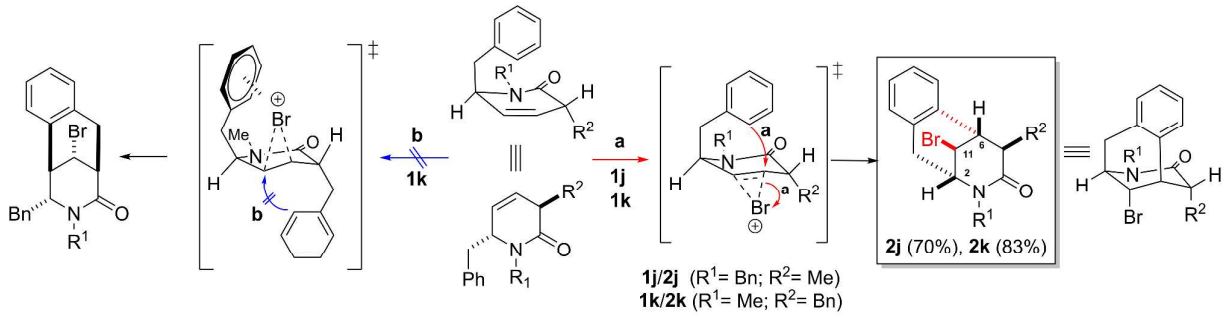
4-substituted substrates, in the transition state, carbocation formation at C4 is possible which is better stabilized by C4-Ph in comparison to C4-Me group, resulting in increasing the amounts of elimination products **4**. It is worth mentioning that compounds **2e-i** and **4e-i** were laboriously separated using 120-cm long chromatographic column and that 4-methyl derivatives of **4** were unstable, making their analysis difficult.

TABLE 2. Bromocarbocyclization of 6-benzyl, NR^1 and C4-R^2 substituted β,γ-unsaturated δ-lactams 1 under optimized conditions (Scheme 1)

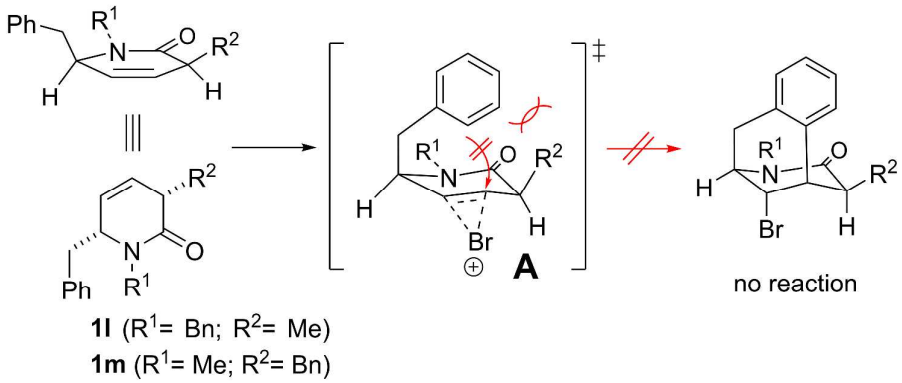
Entry	Compounds **1**, **2**, **4**	NR^1	C4-R^2	Selectivity[a] **2** : **4**	Isolated yields [%] **2**	Isolated yields [%] **4**
1	**a**	Me	H	100 : 0	97	-
2	**b**	*n*Pr	H	100 : 0	84	-
3[b]	**c**	Bn	H	100 : 0	93	-
4[b]	**d**	Ph	H	100 : 0	81	-
5	**e**	Me	Me	86 : 14	91	0
6	**f**	Bn	Me	85 : 15	83	14
7	**g**	Ph	Me	93 : 7	89	0
8	**h**	Me	Ph	19 : 81	24	75
9	**i**	Bn	Ph	21 : 79	19	76

[a] - assigned by ^1H NMR of the crude reaction mixture; [b] – PPh_3 (0.3 mole) was used.

We then evaluated the influence of substituents at C-3 of 6-benzyl-3,6-dihydropyridin-2(1*H*)-one on bromocarbocyclization, at first using C-3 monosubstituted compounds, both *trans* and *cis* derivatives, bearing benzyl substituent at C-6 and methyl or benzyl substituents at C-3 (Scheme 2 and 3). Surprisingly, only *trans*-derivatives **1j**, **1k** gave benzomorphans **2j** and **2k**, respectively (Scheme 2), while *cis*-derivatives **1l** and **1m** were unreactive (Scheme 3).

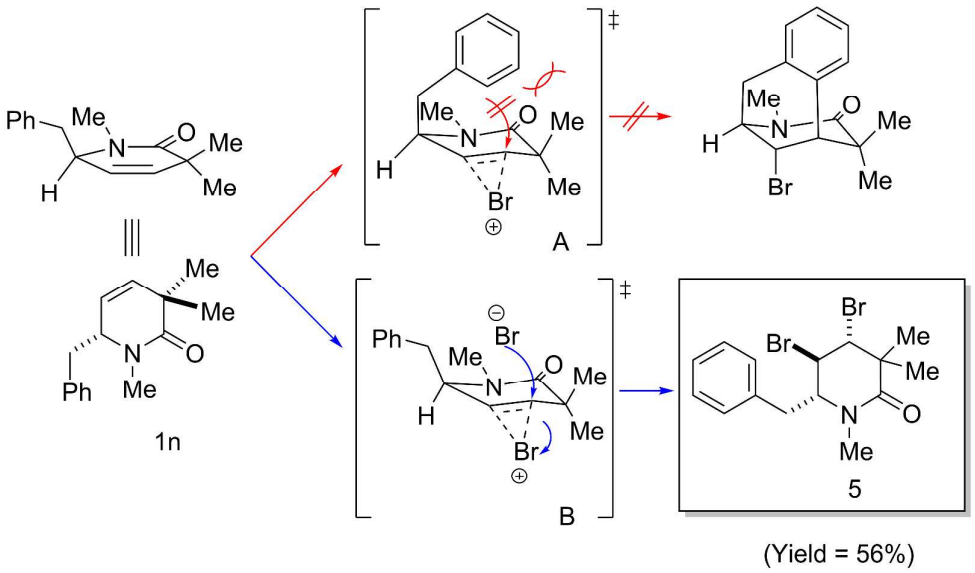


SCHEME 2. Bromocarbocyclization of 3,6-*trans* substituted 3,6-dihydropyridin-2(1*H*)-ones 1j and 1k

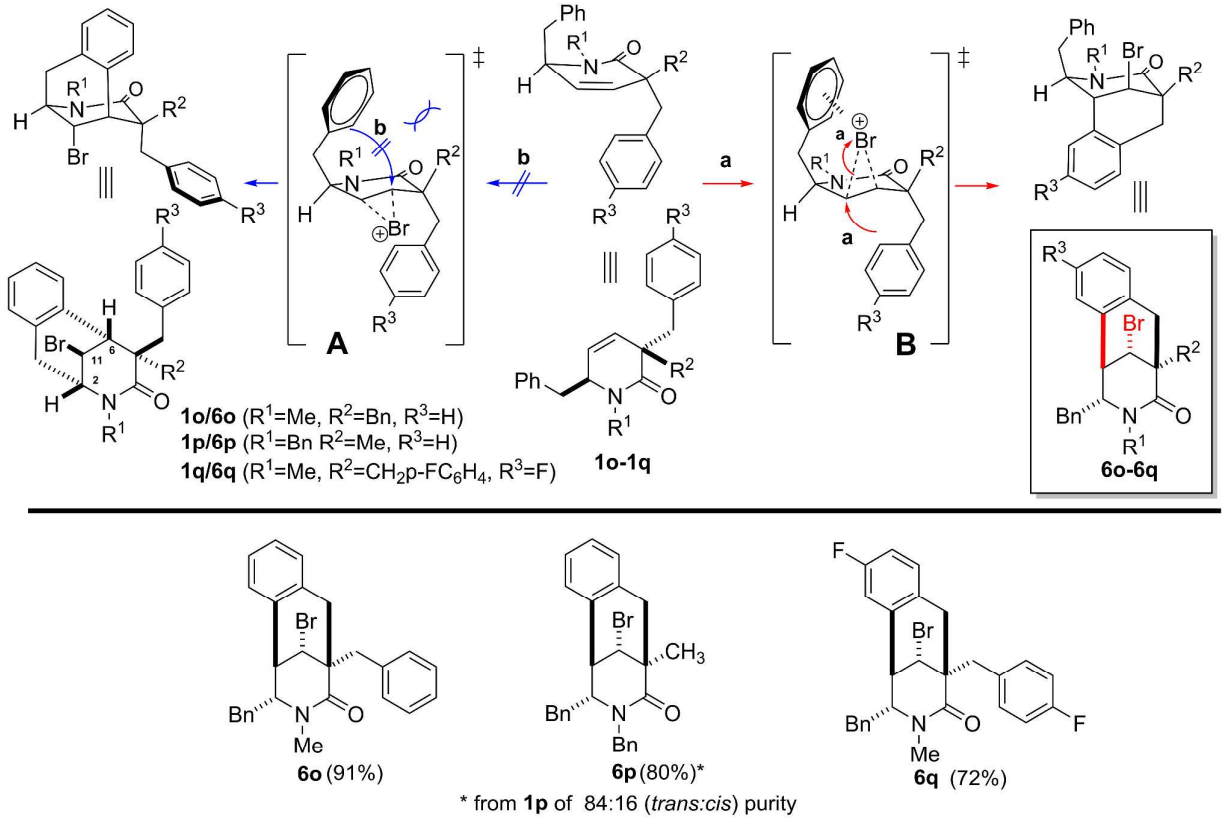


SCHEME 3. The attempts at bromocarbocyclization of 3,6-*cis* substituted 3,6-dihydropyridin-2(1*H*)-ones 1l and 1m

It should be emphasized that from the two *trans*-oriented benzyl groups in **1k**, only 6-benzyl group was involved in the cyclization process (Scheme 2, path a), while the 3-benzyl group remained intact (Scheme 2, path b). Next, 6-benzyl, 3,3-disubstituted derivatives were studied including 3,3-dimethyl- (**1n**) (Scheme 4), 3,3-dibenzyl- (**1o**), *trans*-3-benzyl-3-methyl- (**1p**) and *trans*-3,6-dibenzyl- (**1q**) substituted derivatives (Scheme 5). As a result, bromine underwent an addition to 6-benzyl-3,3-dimethyl δ–lactam **1n** yielding dibromolactam **5** (Scheme 4), instead of carbocyclized product, while for **1o-q** the 3-benzyl group (being in *trans* relation to benzyl group at C-6) was involved in carbocyclization leading to 1,5-methanobenzomorphan **6o-6q** in good yields (Scheme 5, path a). The above results indicated the steric hindrance of C6-benzyl group *vs cis*-oriented C3-methyl/benzyl substituents in the transition state **A** for the lack of carbocyclization of **1l-1n** (Scheme 3 and 4) and reactivity of **1o-q** towards 2,6-methanobenzomorphans (Scheme 5, path b).



SCHEME 4. The attempts at bromocarbocyclization of 6-benzyl-3,3-dimethyl-3,6-dihydro-pyridin-2(1*H*)-one 1n

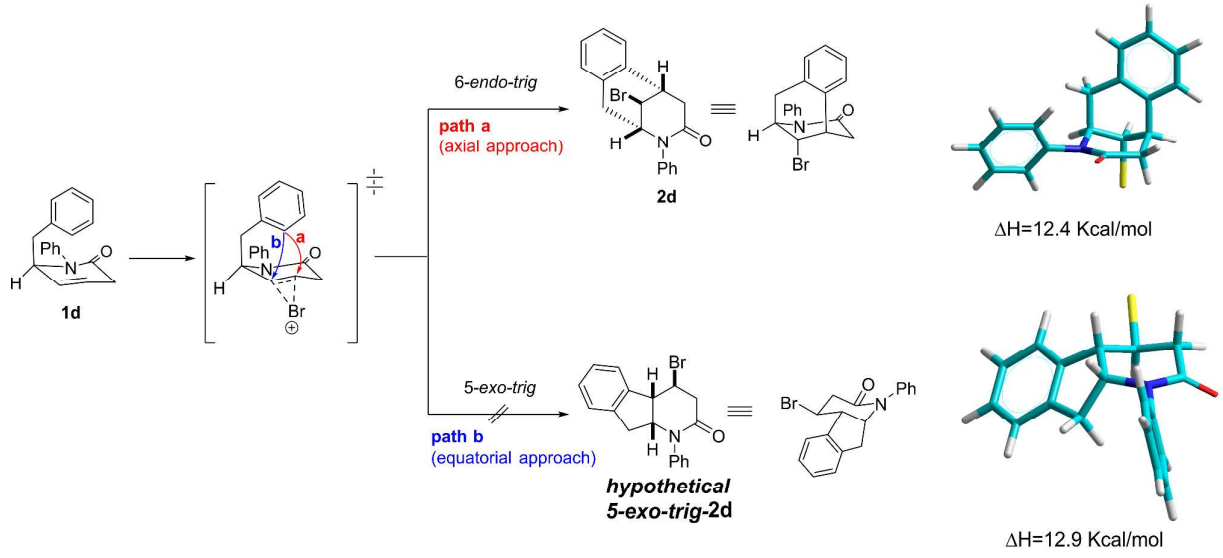


SCHEME 5. Bromocarbocyclization of 1o, 1p and 1q

In this context the preference of cyclization of **1k** towards 2,6-methano derivative **2k** with the participation of C6-Bn instead of C3-Bn group (Scheme 2) could not be easily explained. It seemed

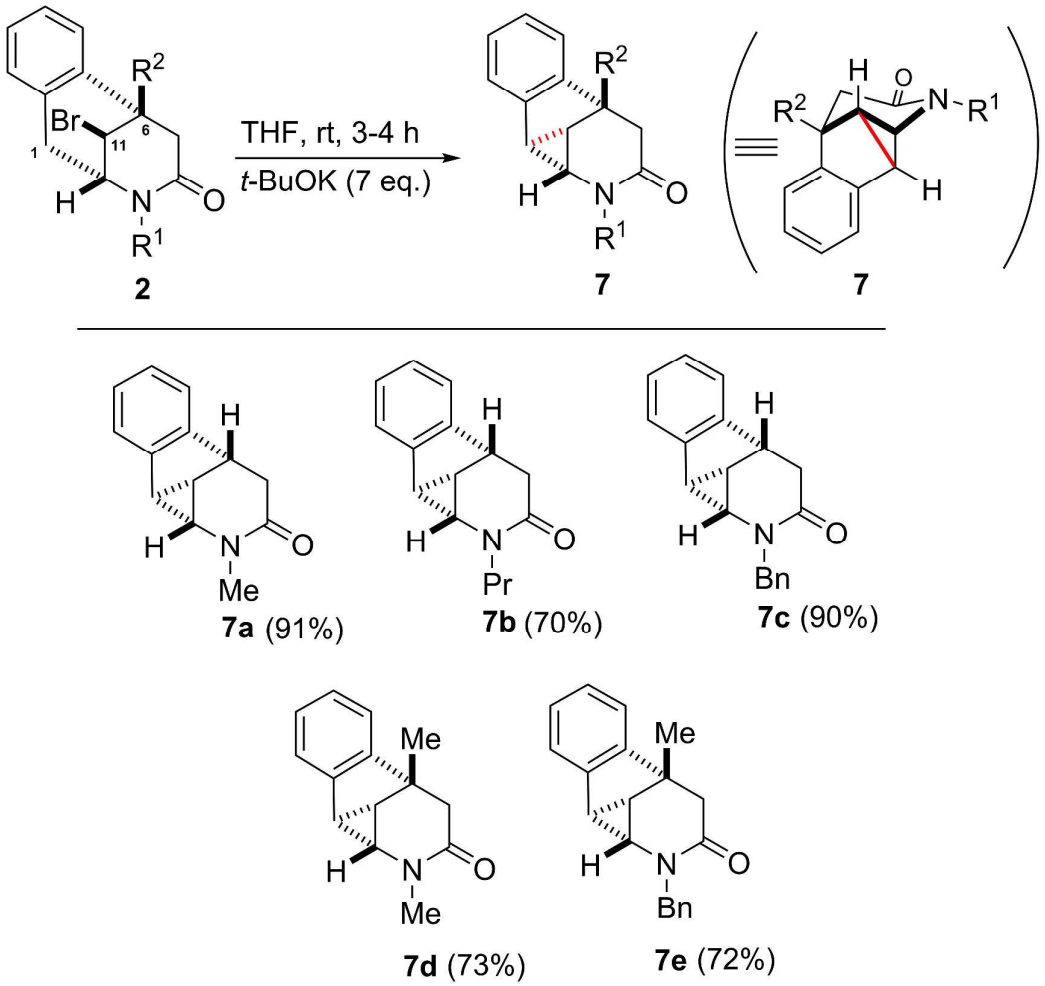
that electron distribution in the transition state and conformational preference of C6-Bn and C3-Bn groups determined by one substituent at C-3, enabling the 2,6-methanobenzomorphan formation, while two substituents at C-3, could change the conformation of lactam ring thus allowing to cyclize with the participation of C-3Bn leading do 1,5-methanobenzomorphan. However, in order to completely clarify this issue, further research is required.

It should be strongly emphasized that in all carbocyclizations showed above, only 6-*endo-trig* cyclization products were formed, even if Baldwin's rules permit both 5-*exo-trig* and 6-*endo-trig* processes and even though both products are located at similar energetic levels, as suggested by heats of formations calculated for obtained **2d** and hypothetical **5-*exo-trig*-2d** products, for example (Scheme 6). The regioselectivity of cyclization observed can be easily explained on the basis of stereoelectronic effect, which assumed axial attack relative to the electrophilic carbon atom,[22] here involved in bromonium ion. The axial approach of the benzene ring to C-4 of lactam is only possible when 6-benzyl group takes the axial orientation, thus allowing 1,3-bridge formation (Scheme 6, path a).



SCHEME 6. Example of bromocarbocyclization of 1d through 6-*endo-trig* vs 5-*exo-trig* processes

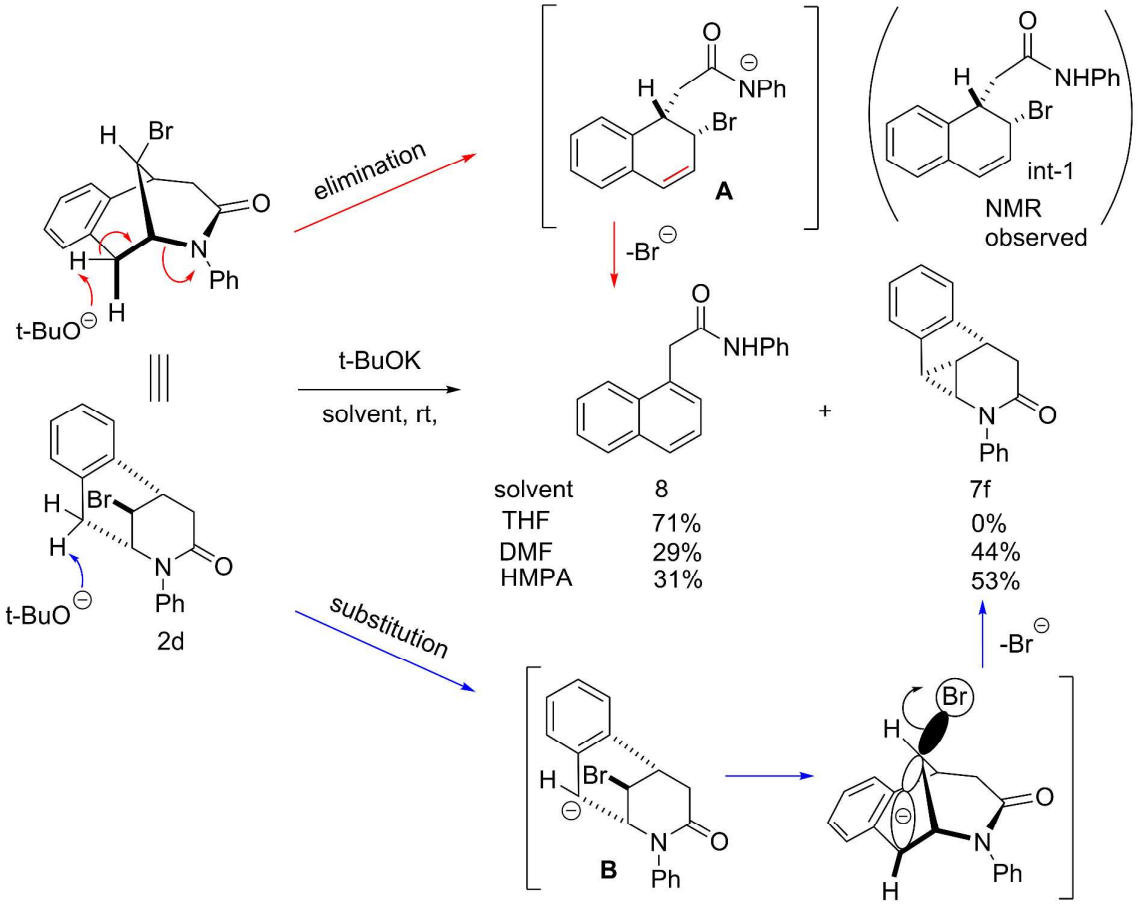
Subsequently, we checked the behavior of bromobenzomorphans **2** upon treatment with strong bases, expecting anion formation, which could react intramolecularly through substitution of bromine, yielding cyclopropane ring. The anticipated transformation involving cyclopropanation was successful because it led to the polycyclic lactam **7** by the connection of C-1 and C-11 atoms of the corresponding benzomorphan (Scheme 7, Scheme 8 - lower part). The ring system obtained has been hitherto unknown and may be considered as a novel bridged benzomorphan skeleton.



SCHEME 7. Synthesis of bridged benzomorphans 7

In a more detailed study, we found that LDA and DBU was not effective and that in optimized conditions the addition of 7eq. of *t*-BuOK to THF solution of bromobenzomorphan led to desired product in high yields within 2-7 h, at room temperatures, however, only for *N*-alkyl substituted

benzomorphans (Scheme 7), while *N*-Ph bromobenzomorphan **2d** gave at these conditions 1-carboxyamidomethyl~~o~~-substituted naphthalene **8** (Scheme 8). Switching solvent from THF to DMF or HMPA allowed us to obtain also a novel *N*-phenyl bridged derivative **7f** in 44% and 53 % yields, respectively, however, still together with naphthalene **8** (Scheme 8).

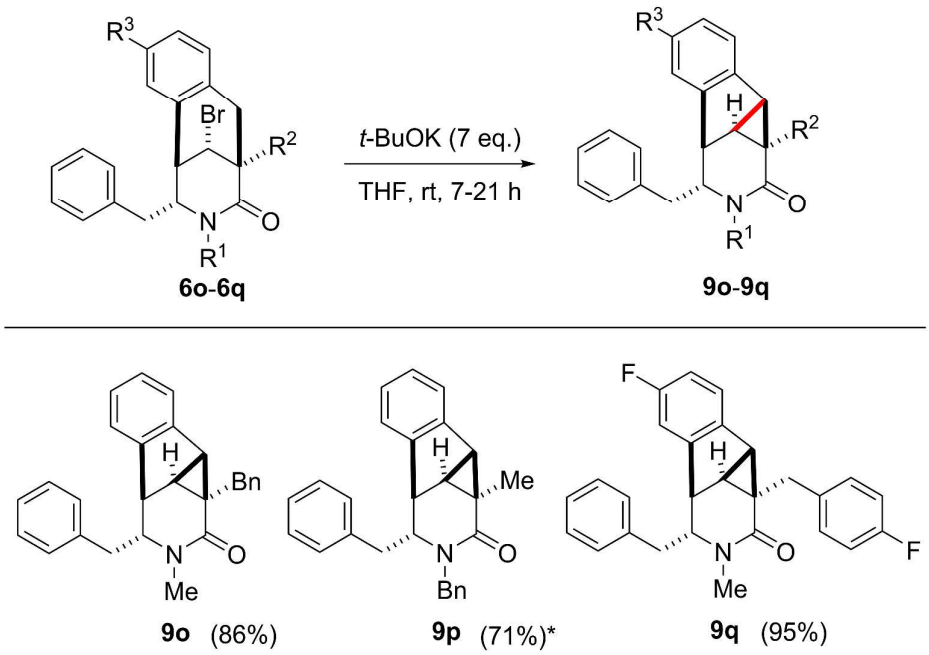


SCHEME 8. Effect of *N*-Ph substituent in 2d on distribution of product 8 and 7f

Although the formation of cyclopropane ring in **2** can be easily rationalized by the geometrically defined approach of benzyl anion in **B** to C11-Br from the opposite side with respect to the living bromine atom (Scheme 8, lower part), the unexpected formation of naphthalene derivative **8** prompted us to perform additional kinetic-like NMR study. Conducting the reaction in an NMR tube in THF-d_8 solution by mixing of **2d** with different quantities of *t*-BuOK and recording the ^{1}H NMR spectra in equal time intervals allowed us to observe the formation of intermediate **(int-1)** and to establish the dependence of the rates of both elimination processes on the quantity of the

base (see Supporting Information). A plausible mechanism of both transformation is depicted in Scheme 8. The structure of intermediate **int-1** was evidenced by the recording of 1D NMR spectra at their highest concentration reached during the reaction, conducted in an NMR tube (details see Supporting Information).

In further studies, we found that the procedure of cyclopropanation is more general because it was also successfully applied for 1,5-methanobromobezomorphan **6o-q** leading to corresponding cyclopropane-fused benzomorphans **9o-q** in satisfactory yields (Scheme 9).



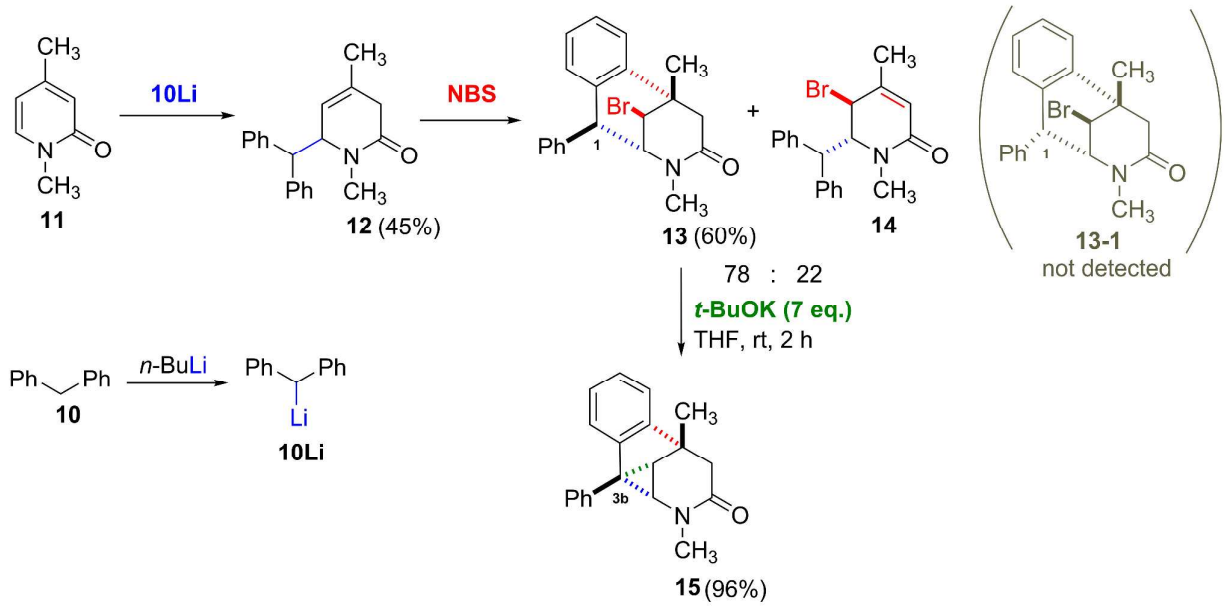
* NH deprotected derivative of substrate (**6pNH**) was also isolated

SCHEME 9. Synthesis of bridged benzomorphans 9

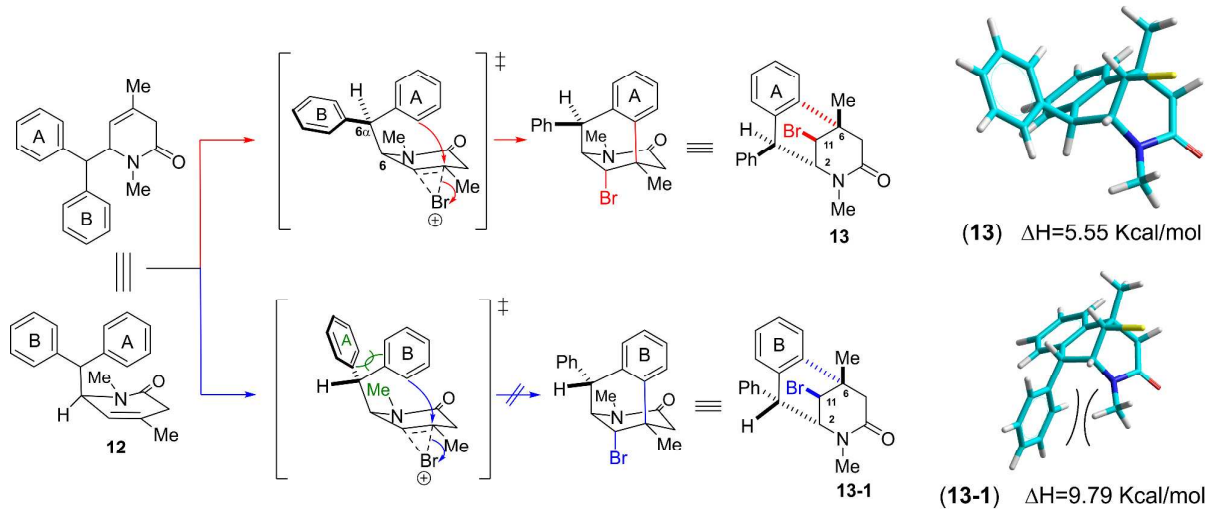
Next, we decided to apply the developed procedures in the synthesis of bridged 2,6-methano-benzomorphan **15**, having phenyl substituent in the cyclopropane ring at C3b. Synthesis of such compound implies the formation of additional asymmetric center at C1 in bromobenzomorphan and at C3b in bridged derivative (Scheme 10). Initially, 6-(diphenylmethyl)-4-methyl-3,6-dihydropyridin-2(1*H*)-one (**12**) was prepared as a starting compound in the reaction between diphenylmethyllithium[23] (**10Li**) and 4-methyl-2-pyridone in 45% yield (Scheme 10). Subsequently,

carbocyclization led to product **13**, isolable in 60% yields and by-product **14** which was difficult to purify. Products **13** : **14** were obtained at the molar ratio 78 : 22. Cyclopropanation of **13** led to product **15** in 96% yield.

Despite incomplete regioselectivity of carbocyclization, the formation of lactams **13** was fully stereoselective because the second isomer (**13-1**) possibly formed was not detected in the crude reaction mixture (checked by ^{1}H NMR) (Scheme 10). Judging by the heat of formation (ΔH), calculated at PM3 level of theory for the structure of obtained isomer **13**, which is less about 4.24 kcal/mol in relation to ΔH of possibly formed structure **13-1**, one could conclude that in transition state the steric interaction between the phenyl group of benzhydryl substituent and *N*-Me moiety determine the stereochemical course of this reaction, as depicted in Scheme 11.



SCHEME 10. Synthesis of bridged benzomorphans 15 with C3b-phenyl substituent



SCHEME 11. Stereoselective carbocyclization of 12

As azabicyclo[4.1.0]heptane ring systems, present in both obtained bridged benzomorphans **7** and **9**, consist of the central cores of some biologically active compounds, e.g. of piperidine: **(-)-GSK1360707** (developed by GlaxoSmithKline as potent dopamine reuptake inhibitor for the treatment of the major depressive disorder (MDD)[24] and amidine: **ONO-1714** (acting as a potent inhibitor of inducible nitric oxide synthase[25] and as a potential neuroprotective agent in stroke patients,[26] (Figure 2), finally, we converted two representatives of bridged benzomorphans **7a** and **9o** into amidine and piperidine derivatives, respectively, according to scheme 12. The results of not optimized transformations indicate high stability of obtained ring systems present in compounds **16-18** and designate starting lactams as prospect derivatives for further functionalizations toward bridged benzomorphans.

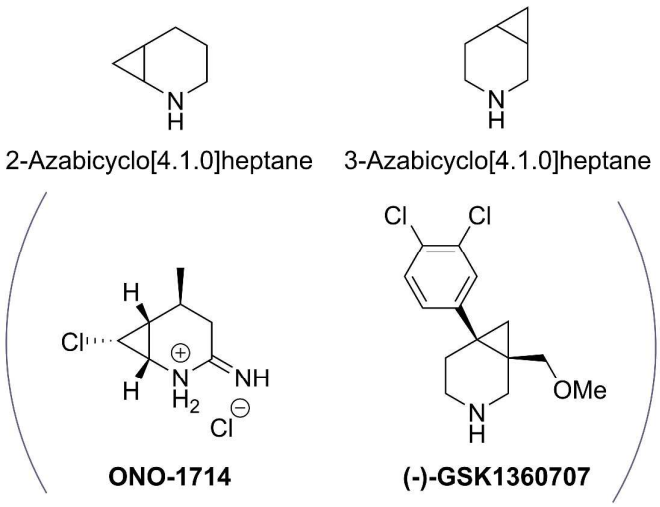
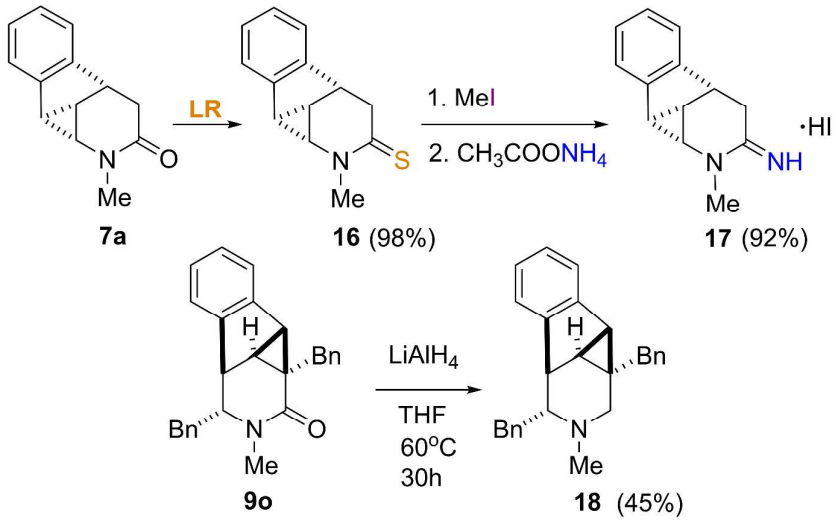


FIGURE 2. Biologically active compounds with azabicyclo[4.1.0]heptane ring systems



SCHEME 12. The attempts at derivatization of bridged benzomorphanones *via* transformations of amide group

The structures of all compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C, ^{13}C-DEPT-135) and 2D NMR (^{1}H,^{1}H DFQ-COSY, ^{13}C,^{1}H COSY, ^{1}H,^{1}H NOESY, ^{1}H,^{13}C HMBC) spectroscopy. The routine NMR spectra were taken in $CDCl_3$ solutions, although perdeuterated toluene was used in some cases in order to get a better separation of the signals. In the assignment of structures, the conformational analysis was applied. It consisted in unequivocal assignment of the maximum number of ^{1}H NMR signals to the appropriate proton in the molecule (using correlation

methods), refinement of $J_{H,H}$(exp) coupling constants, and their comparison with theoretical values of coupling constants [$J_{H,H}$(calc)] calculated using Karplus like equations[27] based on dihedral angles found in PM3[28] optimized structures. The theoretical values of coupling constants matched the coupling constants obtained from the spectra, confirming the correctness of the proposed structures. Additionally, in order to be absolutely sure that 5-*exo-trig* cyclization products were not formed, theoretical values of coupling constants of hypothetical **5-*exo-trig*-2d** (Scheme 6) were calculated for the PM3 optimized structure for comparison. The results, included in Supplementary Information, showed a large difference between the coupling constants calculated and those refined from the ^{1}H NMR spectrum of **2d**, thus unambiguously indicating benzomorphanone as the obtained product. Finally, the refined structures were additionally supported by the ^{1}H,^{1}H NOESY through-space interactions between the juxtaposed hydrogen atoms. The observed NOE effects in NOESY spectra for selected representatives are shown in Figure 3 and in Supplementary Information.

Conclusion

In conclusion, we have demonstrated that stereoselective carbocyclization of 6(3)-benzyl-β,γ-unsaturated δ-lactams using NBS with $P(OPh)_3$ as an additive, followed by treatment of the obtained 11-bromobenzomorphanones (2,6-methano- and 1,5-methano-3-benzazocinones) with *t*-BuOK as a base, provides easy access to novel and unique benzomorphanones with internal azabicyclo[4.1.0]heptane unit. In spite the fact that in both transformations the presence of substituents at the 3,6-dihydropyridin-2-one ring influenced the regioselectivity the high synthetic potential of the proposed approach is pronounced by the possible far-reaching functionalization of bromo and amide groups in the products. Besides, in the light of great interest in the synthesis of piperidine derivatives as potential pharmaceuticals, the successful synthesis of bromobenzomorphanones and its bridged derivatives, capable of further functionalization may gain considerable importance in drug development area.

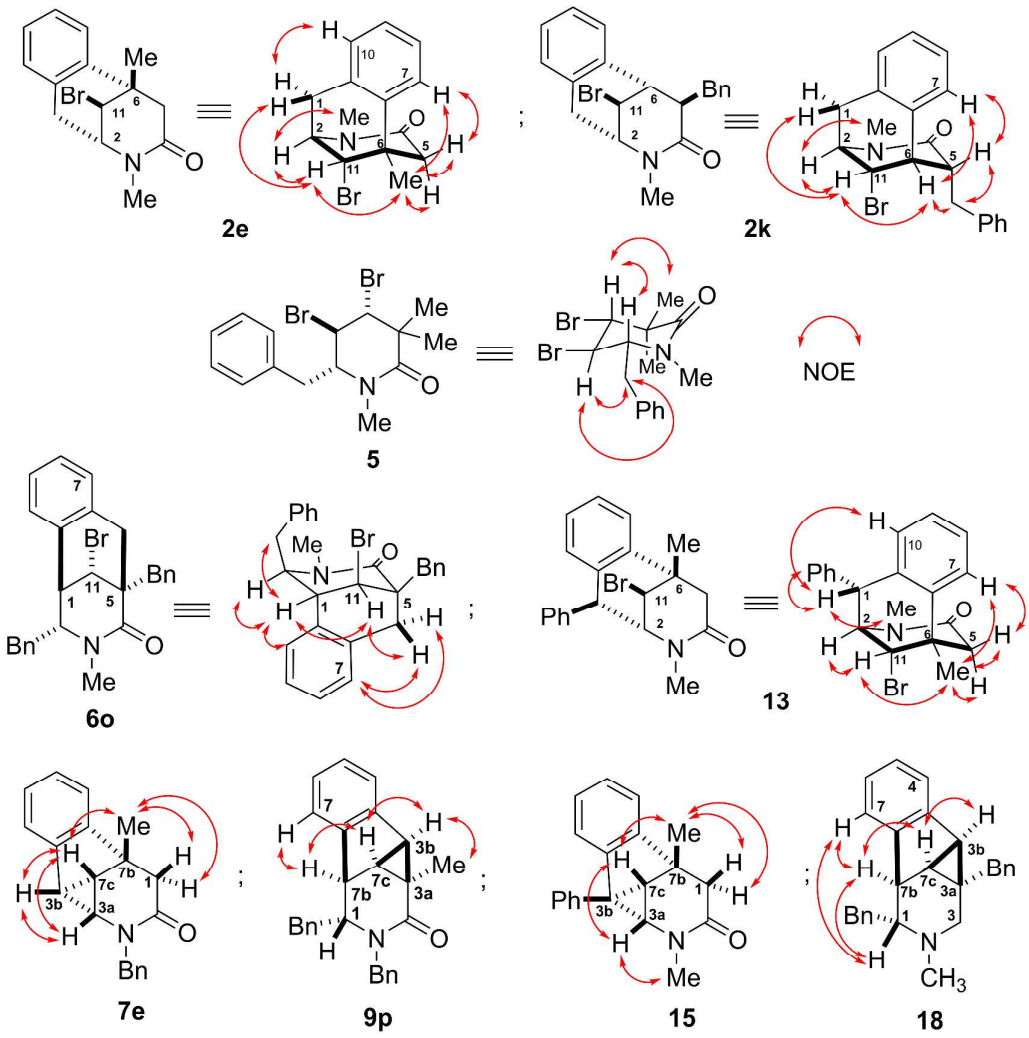


FIGURE 3. Diagnostic NOE effects found in ^{1}H,^{1}H NOESY spectra of representative compounds

Experimental section

Melting points were determined on a Boetius hot stage apparatus. ^{1}H, ^{13}C NMR spectroscopic measurements were performed on a Bruker DPX 400 Avance III HD spectrometer, operating at 400.1 and 100.6 MHz, respectively. TMS was used as internal reference and spectra were acquired in 5 mm probes. For NMR analyses ACD/SpecManager (version 12.01) and MestReNova (version 10.0.1) programs were used. For detailed peak assignments, 2D spectra were acquired using Bruker software (^{1}H,^{1}H DFQ-COSY, ^{13}C,^{1}H COSY, ^{1}H,^{1}H NOESY, ^{1}H,^{13}C HMBC). In the ^{1}H,^{1}H NOESY spectra the optimized mixing time, varied from 0.65 s to 0.95 s, was used. The ^{1}H,^{13}C HMBC long-

range correlations were acquired for $J_{C,H}$=10 Hz. The standard abbreviation for multiplicities were used (s = singlet, d = doublet, t = triplet, q =quartet, quint = quintet, m = multiplet, sxt = sextet, spt = septet, etc.). Gas chromatography-mass spectrometry (GC-MS) measurements were carried out on a Hewlett-Packard instrument model HP 6890 equipped with a mass detector HP 5973 and on an Agilent 7820A GC system equipped with a mass (Agilent 5977E MSD) and FID detectors. Infrared spectra were taken with a Specord M80 instrument and Alfa spectrometer with ATR-adapter (Bruker). The standard abbreviation for IR band intensities description was used (s – strong, m – medium, w – weak). HRMS analyses (ESI+) were performed on a Waters LCT premier XE (TOF) using acetonitrile as solvent. Elemental analysis was performed on an Elementar model Vario EL III analyzer.

Reactions in tetrahydrofuran (THF) solution was performed under argon in flame-dried flasks and liquid components were added from a syringe. THF was purified in argon atmosphere according to a standard procedure prior to use. Products were purified by flash column chromatography on silica gel (63-200 μm, Merck) using appropriate solvents. Nitromethane was used such as purchased. NBS was recrystallized before use.

Syntheses of substrates used

Compounds **1c**, **1d**, **1e**, **1h**, **1i**, **1n**, **1q** were obtained according to procedure described earlier.[21] Compounds **1e**, **1h**, **1i** are new, their spectroscopic data are as follows:

(±)-6-Benzyl-1,4-dimethyl-3,6-dihydropyridin-2(1*H*)-one (**1e**): Yield 80% (0.377g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 3) gave colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 1.60 (t, *J*=1.3 Hz, 3 H, 4-CH_3), 1.95 (dt, *J*=21.3, 2.7 Hz, 1 H, C<u>H</u>H-3), 2.47 (dd, *J*=21.3, 2.0 Hz, 1 H, CH<u>H</u>-3), 2.82 (dd, *J*=13.3, 3.5 Hz, 1 H, 6-C<u>H</u>H), 2.92 (dd, *J*=13.3, 6.1 Hz, 1 H, 6-CH<u>H</u>), 3.08 (s, 3 H, NCH_3), 4.03-4.11 (m, 1 H, CH-6), 5.37 (ddq, *J*=4.2, 2.7, 1.3 Hz, 1 H, =CH-5), 7.01-7.05 (m, 2 H, C_6H_5), 7.20-7.28 (m, 3 H, C_6H_5). ^{13}C NMR (100 MHz,

$CDCl_3$, 23°C): δ = 21.6 (4-CH_3), 32.9 (NCH_3), 36.5 (CH_2-3), 39.7 (6-CH_2), 61.3 (CH-6), 119.0 (=CH-5), 126.7, 128.1, 130.0, 135.9 (C_6H_5), 132.3 (=CH-4), 168.7 (C=O). GC-MS (EI, 70eV): *m/z* = 124 (100), 91 (13). IR (ATR): ν = 1637 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{18}NO[M+H]^+$, 216.1388; found 216.1394.

(±)-6-Benzyl-1-methyl-4-phenyl-3,6-dihydropyridin-2(1*H*)-one (**1h**): Yield 85% (0.517g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 2) gave white solid, m.p. 94-96 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.32 (dt, *J*=20.5, 2.9 Hz, 1 H, C<u>H</u>H-3), 2.95 (dd, *J*=13.3, 3.5 Hz, 1 H, 6-C<u>H</u>H), 2.99 (d, *J*=20.5 Hz, 1 H, CH<u>H</u>-3), 3.05 (dd, *J*=13.3, 6.1 Hz, 1 H, 6-CH<u>H</u>), 3.16 (s, 3 H, NCH_3), 4.27-4.34 (m, 1 H, CH-6), 6.02 (dd, *J*=4.8, 2.9 Hz, 1 H, =CH-5), 7.03-7.07 (m, 2 H, ArH), 7.21-7.35 (m, 8 H, ArH). ^{13}C NMR (100 MHz, CDCl3, 23°C): δ = 32.8 (NCH_3), 34.0 (CH_2-3), 39.6 (6-CH_2), 61.7 (CH-6), 120.6 (=CH-5), 125.0, 126.9, 127.9, 128.2, 128.6, 130.0 (ArH), 134.7, 135.5, 138.4 (Ar, =C-4), 168.5 (C=O). GC-MS (EI, 70eV): 186 (100), 91 (12). IR (ATR): ν = 1635 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{20}NO[M+H]^+$, 278.1545; found 278.1545.

(±)-1,6-Dibenzyl-4-phenyl-3,6-dihydropyridin-2(1*H*)-one (**1i**): Yield 77% (0.601g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave white solid, m.p. 134-136 °C (petroleum ether : ethyl acetate).^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.39 (ddd, *J*=20.6, 3.3, 2.9 Hz, 1 H, C<u>H</u>H-3), 2.90 (dd, *J*=13.5, 3.3 Hz, 1 H, 6-C<u>H</u>H), 3.07 (dd, *J*=13.5, 6.5 Hz, 1 H, 6-CH<u>H</u>), 3.11 (dd, *J*=20.6, 1.7 Hz, 1 H, CH<u>H</u>-3), 4.07 (d, *J*=15.0 Hz, 1 H, NC<u>H</u>H), 4.25 (dqt, *J*=6.5, 3.3, 2.9, 1.7 Hz, 1 H, CH-6), 5.71 (d, *J*=15.0 Hz, 1 H, NCH<u>H</u>), 5.99 (dd, *J*=5.1, 2.9 Hz, 1 H, =CH-5), 7.03-7.06 (m, 2 H, ArH), 7.21-7.37 (m, 13 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 34.3 (CH_2-3), 39.2 (6-CH_2), 46.6 (NCH_2), 57.7 (CH-6), 120.9 (=CH-5), 125.0, 126.9, 127.5, 127.95, 127.98, 128.3, 128.6, 128.8, 130.1 (ArH), 134.8, 135.6, 136.8, 138.2 (Ar, =C-4), 168.9

(C=O). GC-MS (EI, 70eV): 262 (100), 91 (98); IR (ATR): ν = 1633 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{24}NO[M+H]^+$, 354.1858; found 354.1848.

Synthesis and spectroscopic data for compound 12

A stirred solution of diphenylmethane (1.679g; 10mmol) in dry THF (20mL) in a Schlenk flask was cooled to 0°C under argon, and *n*-BuLi (1.6 M in hexane; 6.55mL, 10.05mmol) was added by syringe. The resulting solution was stirred for 30 min, at 0°C and then was slowly transferred by syringe to a precooled (-80°C) solution of 1,4-dimethylpyridin-2(1*H*)-one (0.819g; 6.65mmol) in THF (50mL), prepared in another Schlenk flask. The resulting solution was stirred for 1h at -80°C. After this time, the mixture was carefully quenched with saturated aqueous NH_4Cl (15mL), then it was allowed to warm up to room temp and diluted with water (ca. 10 mL). The aqueous layer was extracted with ethyl acetate (3 x 70mL), and the combined organic layers were dried with $MgSO_4$. The mixture was filtered and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using *n*-hexane : ethyl acetate (1: 3), yielding 0.865g of pale yellow solid.

(±)-6-Benzhydryl-1,4-dimethyl-3,6-dihydropyridin-2(1*H*)-one (**12**): Yield 45% (0.865g), m.p. 75-78 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.59 (s, 3 H, 4-CH_3), 1.80 (d, *J*=21.0 Hz, 1 H, C<u>H</u>H-3), 2.44 (dd, *J*=21.0, 1.4 Hz, 1 H, CH<u>H</u>-3), 2.98 (s, 3 H, NCH_3), 4.42 (d, *J*=4.7 Hz, 1 H, $CHPh_2$), 4.62-4.68 (m, 1 H, CH-6), 5.59 (ddq, *J*=4.7, 2.8, 1.4 Hz, 1 H, =CH-5), 7.10-7.17 (m, 2 H, ArH), 7.22-7.36 (m, 8 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.8 (4-CH_3), 33.7 (NCH_3), 36.6 (CH_2-3), 54.2 (CH-Ph_2), 64.2 (CH-6), 117.6 (=CH-5), 126.7, 127.1, 128.0, 128.5, 128.5, 130.1 (one signal overlaps), 134.1 (=C-4), 138.8, 140.4 (Ar), 169.0 (C=O). GC-MS (EI, 70eV): *m/z* = 124 (100). IR (ATR): ν = 1638 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{22}NO[M+H]^+$, 292.1701; found 292.1709.

Synthesis of compound 1k and 1m according to procedure described earlier[29]

To a solution of **1a** (0.510g, 2.53 mmol) in dry THF (20mL) in a Schlenk flask at -80°C commercially available (Sigma Aldrich) 2.0M solution of LDA in THF/heptane/ethylbenzene (1.30mL, 2.57 mmol) was added dropwise and stirred at that temperature for 1h. After this time, benzyl bromide was added dropwise for about 5 minutes, and the reaction mixture was allowed to slowly warm to 0°C for 1h. After completion of the reaction (GC-MS control) the mixture was carefully quenched with saturated aqueous NH_4Cl (10 mL), then allowed to warm to rt and diluted with water (ca. 10mL). The aqueous layer was extracted with ethyl acetate (3 x 70 mL), and the combined organic layers were dried with $MgSO_4$. The mixture was filtered and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (column length 120cm) on silica gel using *n*-hexane:ethyl acetate (3:1) to give desired product **1k** as colorless oil with 80% yield (0.591g, 2.03mmol) and product **1m** as pale yellow oil with 8% yield (0.059g, 0.2mmol).

(±)-*trans*-3,6-Dibenzyl-1-methyl-3,6-dihydropyridin-2(1*H*)-one (**1k**)[30]: Yield 80% (0.591g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1; 1.2 m column lenght) gave colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 2.35-2.42 (m, 1 H, CH-3), 2.72 (dd, *J*=13.6, 9.4 Hz, 1 H, 3-C<u>H</u>H), 2.83-2.92 (m, 2 H, 6-CH_2), 3.08 (s, 3 H, NCH_3), 3.24 (dd, *J*=13.6, 4.3 Hz, 1 H, 3-CH<u>H</u>), 4.00 (ttd, *J*=4.8, 4.2, 0.8 Hz, 1 H, CH-6), 5.50 (ddd, *J*=10.1, 2.3, 0.6 Hz, 1 H, CH-4), 5.58 (ddd, *J*=10.1, 4.2, 2.7 Hz, 1 H, =CH-5), 7.01-7.09 (m, 4 H, C_6H_5), 7.14-7.19 (m, 1 H, C_6H_5), 7.20-7.26 (m, 5 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$, 23^{o}C): δ = 33.2 (NCH_3), 37.5 (3-CH_2), 39.5 (6-CH_2), 41.4 (CH-3), 61.4 (CH-6), 124.6 (=CH-5), 127.0 (=CH-4), 126.1, 126.7, 128.15, 128.21, 129.3, 129.9, 135.8, 139.2 (2 x C_6H_5); 170.5 (C=O). ^{1}H and ^{13}C NMR data for this product matched those reported previously.[30]

(±)-*cis*-3,6-Dibenzyl-1-methyl-3,6-dihydropyridin-2(1*H*)-one (**1m**)[30]: Yield 8% (0.059g) The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1; 1.2 m column lenght) gave pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 1.94 (dd, *J*=13.0, 9.3 Hz, 1 H, 3-C<u>H</u>H), 2.12 (dd, *J*=13.4, 7.6 Hz, 1 H, 6-C<u>H</u>H), 2.70 (dd, *J*=13.4, 3.7 Hz, 1 H, 6-CH<u>H</u>), 2.90 (dd, *J*=13.0, 4.1 Hz, 1 H, 3-CH<u>H</u>), 3.04-3.11 (m, 4 H, CH-3, NCH_3), 3.97 (dq, *J*=7.4, 3.6 Hz, 1 H, CH-6), 5.47 (dd, *J*=10.3, 3.3 Hz, 1 H, =CH-4), 5.51 (dd, 1 H, *J*=10.3, 3.5 Hz, =CH-5), 6.98-7.06 (m, 4 H, C_6H_5), 7.15-7.33 (m, 6 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$, 23^{o}C): δ = 33.2 (NCH_3), 39.6 (3-CH_2), 40.0 (6-CH_2), 43.4 (CH-3), 61.6 (CH-6), 124.5 (=CH-5), 126.3 (=CH-4), 126.3, 126.8, 128.1, 128.3, 129.6, 129.9, 136.2, 138.6 (2 x C_6H_5); 170.2 (C=O). ^{1}H and ^{13}C NMR data for this product matched those reported previously.[30]

Synthesis of compound 1p

A stirred solution of BnMgCl (2.0 M in THF; 1.77cm^3, 2.95mmol) in dry THF (12mL) in a Schlenk flask was cooled to 0°C under argon, and *s*-BuLi (1.4 M in cyclohexane, 5.06mL, 7.08mmola) was added by syringe over 5 min. The resulting solution was stirred for 5 min, and then it was cooled to –80°C. The solution containing lithium benzyldi(*sec*-butyl)magnesate and LiCl was then transferred by syringe to a precooled (-80°C) solution of 1-benzyl-3-methyl-2-pyridone (0.59g, 2.95mmol) in THF (32mL) in another Schlenk flask. The resulting solution was stirred for 60 min at –80 °C. After this time benzyl bromide (0.53mL; 0.757g; 4.426mmol) was added and the mixture was stirred 15 min at -80^{o}C, then 2 h at 0^{o}C and then 80 min at rt. After this time, saturated aqueous NH_4Cl (10mL), was added and the aqueous layer was extracted with ethyl acetate (3 x 60mL), and the combined organic layers were dried with $MgSO_4$. The mixture was filtered, and the solvents were evaporated under reduced pressure. The crude product was purified by 1.2-m long column chromatography on silica gel using a mixture of *n*-hexane and ethyl acetate (9 : 1) to give the by-product **19** in 20% yield (0.224g) as thick oil and desired product **1p** in 84:16 mixture of *trans* : *cis* products, in total yields of 50% as colourless oil (0.564g).

(3*SR*,6*SR*)-1,3,6-Tribenzyl-3-methyl-3,6-dihydropyridin-2(1*H*)-one (**1p**). Yield 50% (0.564g), ^{1}H NMR (400 MHz, $CDCl_3$, 23°C, major isomer (*trans*) from 84:16 mixture of trans and cis isomers): δ = 0.84-0.90 (m, 3 H, 3-CH_3), 2.51 (d, *J*=13.0 Hz, 1 H, 3-CHH), 2.75-2.86 (m, 2 H, 6-CH_2), 3.30 (d, *J*=13.0 Hz, 1 H, 3-CHH), 3.70-3.76 (m, 1 H, CH-6), 3.95 (d, *J*=15.2 Hz, 1 H, NCHH), 5.43 (dd, *J*=10.1, 4.0 Hz, 1 H, =CH-5), 5.58 (dd, *J*=10.1, 1.2 Hz, 1 H, =CH-4), 5.71 (d, *J*=15.3 Hz, 1 H, NCHH), 6.70-6.75 (m, 2 H, Ph), 6.96-7.01 (m, 2 H, Ph), 7.12-7.34 (m, 11 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 27.9 (3-CH_3), 39.5 (6-CH_2), 44.5 (C-3), 46.0 (NCH_2), 46.7 (3-CH_2), 56.9 (CH-6), 123.3 (=CH-5), 126.1, 126.8, 127.1, 127.7, 127.8, 128.2, 128.5, 129.9, 130.6 (Ph), 132.0 (=CH-4), 136.1, 136.5, 138.2 (Ph), 172.8 (C=O). HRMS (ESI-TOF): *m*/*z* calcd for $C_{27}H_{28}NO[M+H]^+$, 382.2171; found: 382.2161.

(4*SR*,5*RS*)-1,3,4-Tribenzyl-3-methyl-3,4-dihydropyridin-2(1*H*)-one (**19**). Yield 20% (0.224g), ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.28 (s, 3 H, 3-CH_3), 2.24 (t, *J*=12.5 Hz, 1 H, 4-CHH), 2.37 (ddd, *J*=12.5, 5.0, 3.9 Hz, 1 H, CH-4), 2.76 (d, *J*=13.2 Hz, 1 H, 3-CHH), 2.87 (dd, *J*=12.5, 3.9 Hz, 1 H, 4-CHH), 3.29 (d, *J*=13.2 Hz, 1 H, 3-CHH), 4.65 (d, *J*=14.9 Hz, 1 H, NCHH), 4.79 (d, *J*=14.9 Hz, 1 H, NCHH), 4.82 (dd, *J*=7.8, 4.9 Hz, 1 H, =CH-5), 6.02 (d, *J*=7.8 Hz, 1 H, =CH-6), 6.90-6.94 (m, 2 H, Ph), 7.12-7.37 (m, 13 H, 3 xPh). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 19.1 (3-CH_3), 35.1 (4-CH_2), 40.3 (CH-4), 42.0 (3-CH_2), 46.2 (C-3), 49.7 (NCH_2), 109.3 (=CH-5), 126.0, 126.6 (Ph), 126.0, 126.6 (Ph), 127.5 (=CH-6), 127.8, 128.1, 128.1, 128.7, 129.2, 130.5, 137.1, 137.5, 139.8 (Ph), 174.0 (C=O). GC-MS (EI, 70eV): *m/z* = 290 (70), 91 (100); IR (ATR): ν = 1656 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{27}H_{28}NO[M+H]^+$, 382.2171; found: 382.2169.

Synthesis and spectroscopic data of compound 1q

A stirred solution of BnMgCl (2.0 M in THF; 3.26 cm^3, 6.51 mmol) in dry THF (10 mL) in a Schlenk flask was cooled to 0°C under argon, and *s*-BuLi (1.4 M in cyclohexane, 9.30 cm^3, 13.02 mmol) was added by syringe over 5 min. The resulting solution was stirred for 5 min, and then it was

cooled to –80°C. The solution containing lithium benzyldi(*sec*-butyl)magnesate and LiCl was then transferred by syringe to a precooled (-80 °C) solution of *N*-methyl-2-pyridone (0.592 g, 5.43 mmol) in THF (20 mL) in another Schlenk flask. The resulting solution was stirred for 60 min at -80 °C. After this time, 2.5 fold excess of *p*-fluorobenzyl bromide (1.69cm^3, 2.564g, 13.56 mmol) was added and the mixture was stirred 15 minut at -80^{o}C, then 4.5 h at 0^{o}C. After this time, saturated aqueous NH_4Cl (15 mL), was added and the aqueous layer was extracted with ethyl acetate (3 x 70 mL), and the combined organic layers were dried with $MgSO_4$. The mixture was filtered, and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a mixture of *n*-hexane and ethyl acetate in 6:1 ratio to give the desired product **1q** with 75% yield (1.699g) as white solid (crystalized from AcOEt : petroleum ether).

(±)-6-Benzyl-3,3-bis-(4-fluorobenzyl)-1-methyl-3,6-dihydropyridin-2(1*H*)-one (**1q**). Yield 75% (1.699g), ^{1}H NMR (400 MHz): δ = 1.12 (dd, *J*=13.0, 9.8 Hz, 1 H, 6-C<u>H</u>H), 2.54 (d, *J*=13.0 Hz, 1 H, 3-C<u>H</u>H), 2.59 (dd, *J*=13.0, 4.4 Hz, 1 H, 6-CH<u>H</u>), 2.60 (d, *J*=13.0 Hz, 1 H, 3-CH<u>H</u>), 2.82 (s, 3 H, NCH_3), 3.14 (d, *J*=13.0 Hz, 1 H, 3-C<u>H</u>H), 3.42 (d, *J*=13.0 Hz, 1 H, 3-CH<u>H</u>), 3.41-3.47 (m, 1 H, CH-6), 5.29 (dd, *J*=10.4, 3.5 Hz, 1 H, =CH-5), 5.41 (dd, *J*=10.4, 1.0 Hz, 1 H, =CH-6), 6.81-6.87 [m, 4 H, 2xCH-3', 2xCH(Bn)], 6.96 - 7.05 (m, 4 H, 2xCH-2', 2xCH-3'), 7.07-7.26 [m, 5 H, 2xCH-2', 2xCH(Bn)] ppm. ^{13}C NMR (100 MHz, CDCl3, 23^{o}C): δ = 33.2 (NCH_3), 41.1 (6-CH_2), 45.1 (2x3-CH_2), 50.6 (C-3), 61.4 (CH-6), 114.4 (d, $^2J_{CF}$=21.3 Hz, 2xCH-3'), 114.7 (d, $^2J_{CF}$=21.3 Hz, 2xCH-3'), 125.3 (=CH-5), 126.6 [ArH, (6-Bn)], 128.3 (=CH-4), 128.4, 129.2 [ArH, (6-Bn)], 131.6 (d, $^3J_{CF}$=7.9 Hz, 2xCH-2'), 132.1 (d, $^3J_{CF}$=7.9 Hz, 2xCH-2'), 133.3 (d, $^4J_{CF}$=3.7 Hz, C-1'), 136.7 [Ar, (Bn)], 161.6 (d, $^1J_{CF}$=243.6 Hz, CH-4'), 162.9 (d, $^1J_{CF}$=243.6 Hz, CH-4'), 170.6 (C=O). GC-MS (EI, 70eV): *m/z* = 326 (44), 109 (100), 91 (18). IR (ATR): ν = 1620 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{26}F_2NO[M+H]^+$, 418.1982, found: 418.1990.

*A typical procedure for the bromocarbocyclization of N-substituted 6-benzyl-3,6-dihydropyridin-2(1H)-ones. Synthesis of bromobenzomorphans **2**, **6, 13,** bromolactams **4**, **5**, **14**.*

To a stirred solution of *N*-substituted 6-benzyl-3,6-dihydropyridin-2(1*H*)-one (1.7 mmol) in $MeNO_2$ (35 mL) triphenyl phosphite 0.175 equiv. (0.297 mmol, 0.092g,) and then *N*-bromosuccinimide 1.5 equiv (2.55 mmol, 0.454 g) were added. The resulting orange - yellow solution was stirred for 2-3h (TLC control, products **2**, **4**, **13** and **14**) or 24-100h (TLC control, products **5** and **6**) at room temperature in the dark. After this time 2% solution of Na_2SO_3 (10mL) and then saturated aqueous solution of $NaHCO_3$ (10mL) were added and the mixture was stirred for additional 10 min. The aqueous layer was extracted with ethyl acetate (3 x 70mL) and the combined organic layers were dried over $MgSO_4$. The mixture was filtered and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a mixture of appropriate solvents to give the desired product.

(*2RS,6SR,11SR*)-11-Bromo-3-methyl-2,3,5,6-tetrahydro-2,6-methanobenzo[d]azocin-4(*1H*)-one (**2a**): Yield 97% (0.462g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 2) gave white solid, m.p. 149-151 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.48 (ddd, *J*=17.8, ~1.8, ~1.5 Hz, 1 H, CH<u>H</u>-5$_\alpha$), 3.02 (s, 3 H, NCH_3), 3.15-3.17 (m, 2 H, CHH-1), 3.24 (dd, *J*=17.8, 5.9 Hz, 1 H, CH<u>H</u>-5$_\beta$), 3.41 (dddd, *J*=5.9, 3.9, 1.8, 1.5 Hz, 1 H, CH-6), 4.00 (tt, *J*=3.1, 3.1, 1.8, 1.8 Hz, 1 H, CH-2), 4.70 (dt, *J*=3.9, 1.8, 1.8 Hz, 1 H, CH-11), 7.05-7.11 (m, 2 H, ArH-7,10), 7.17-7.23 (m, 2 H, C_6H_4). ^{13}C NMR (100.6 MHz $CDCl_3$): δ = 34.1 (NCH_3), 35.4 (CH_2-1), 37.6 (CH_2-5), 40.1 (CH-6), 48.6 (CH-11), 61.4 (CH-2), 127.3, 127.8, (C-8, C-9) 128.7, 129.5 (C-7, C-10), 129.7, 138.3 (C-6a, C-10a), 167.5 (C=O). GC-MS: (EI, 70eV): *m/z* = 281 (64), [M+2], 279 (64), [M^+], 200 (100); IR (KBr pellet): ν = 1638 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd. for $C_{13}H_{15}BrNO[M+H]^+$, 280.0337, found: 280.0340.

(*2RS,6SR,11SR*)-11-Bromo-3-propyl-2,3,5,6-tetrahydro-2,6-methanobenzo[d]azocin-4(*1H*)-one (**2b**): Yield 84% (0.440g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 93-95 °C (*n*-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 0.96 (t, *J*=7.4 Hz, 3 H, CH_3), 1.56-1.72 (m, 2 H, C<u>H$_2$</u>CH_3), 2.46 (ddd,

J=17.7, ~1.8, ~1.5 Hz, 1 H, CHH-5$_\alpha$), 2.63 (ddd, *J*=13.6, 8.6, 5.6 Hz, 1 H, NCHH), 3.08-3.19 (m, 2 H, m, 2 H, CHH-1), 3.22 (dd, 1 H, *J*=17.7, 5.9 Hz, CHH-5$_\beta$), 3.38 (dddd, *J*=5.9, 3.9, 1.8, 1.5 Hz, 1 H, CH-6), 4.01 (ddd, *J*=13.6, 9.0, 6.7 Hz, 1 H, NCHH), 4.02-4.05 (m, 1 H, CH-2), 4.71 (dt, *J*=3.9, 1.8, 1.8 Hz, 1 H, CH-11), 7.04-7.09 (m, 2 H, ArH-7,10), 7.16-7.21 (m, 2 H, ArH-7,10). ^{13}C NMR (100.6 MHz $CDCl_3$): δ = 11.4 (CH_3), 20.2 (CH_2CH_3), 36, 1 (CH_2-1), 37.9 (CH_2-5), 39.9 (CH-6), 47.1 (NCH_2), 48.8 (CH-11), 58.5 (CH-2), 127.2, 127.8, (C-8, C-9) 128.6, 129.5 (C-7, C-10), 129.9, 138.5 (C-6a, C-10a), 167.1 (C=O). GC-MS (EI, 70eV): *m/z* = 309 (52), [M+2], 307 (52), [M^+], 228 (100); IR (ATR): ν = 1633 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{19}BrNO[M+H]^+$, 308.0650, found: 308.0661.

(*2RS,6SR,11SR*)-3-Benzyl-11-bromo-3-2,3,5,6-tetrahydro-2,6-methano-benzo[d]azocin-4(1*H*)-one (**2c**): Yield 93% (0.563g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 5 : 1, then 3 : 1) gave white solid, m.p. 134-136 °C (*n*-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.59 (br d, *J*=17.6 Hz, 1 H, CHH-5$_\alpha$), 3.05 (dd, *J*=17.4, 3.9 Hz, 1 H, CHH-1$_\beta$), 3.12 (dd, *J*=17.4, 2.2 Hz, 1 H, CHH-1$_\alpha$), 3.35 (dd, *J*=17.6, 6.1 Hz, 1 H, CHH-5$_\beta$), 3.39-3.43 (m, 1 H, CH-6), 3.96 (dq, *J*=3.9, ~2.0, 2.0, 2.0 Hz, 1 H, CH-2), 3.99 (d, *J*=15.1 Hz, 1 H, NCHH), 4.65 (dt, *J*=3.9, 2.0, 2.0 Hz, 1 H, CH-11), 5.39 (d, *J*=15.1 Hz, 1 H, NCHH), 7.01-7.06 (m, 1 H, ArH), 7.06-7.11 (m, 1 H, ArH), 7.17-7.24 (m, 2 H, ArH), 7.26-7.36 (m, 5 H, ArH). ^{13}C NMR (100.6 MHz $CDCl_3$): δ = 35.5 (CH_2-1), 38.0 (CH_2-5), 40.0 (CH-6), 48.1 (NCH_2), 48.6 (CH-11), 57.6 (CH-2), 127.3, 127.6, 127.9, 128.4, 128.5, 129.7, 129.5, (ArH), 130.0, 136.3, 138.4 (Ar), 167.6 (C=O). GC-MS (EI, 70eV): *m/z* = 357 (34), [M+2], 355 (33), [M^+], 276 (16), 91 (100); IR (ATR): ν = 1634 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{19}BrNO[M+H]^+$, 356.0650; found 356.0645.

(*2RS,6SR,11SR*)-11-Bromo-3-phenyl-2,3,5,6-tetrahydro-2,6-methanobenzo[d]azocin-4(1*H*)-one (**2d**): Yield 81% (0.471g, reaction time: 3h). The crude product purified by column chromatography

(SiO_2, *n*-hexane : ethyl acetate, 5 : 1 then 3 : 1) gave white solid, m.p. 164-166 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.66 (ddd, *J*=18.0, 1.8, 1.4 Hz, 1 H, CH<u>H</u>-5$_\alpha$), 3.04 (dd, *J*=17.6, 4.0 Hz, 1 H, CH<u>H</u>-1$_\beta$), 3.16 (dd, *J*=17.6, 2.2 Hz, 1 H, CH<u>H</u>-1$_\alpha$), 3.39 (dd, *J*=18.0, 6.0 Hz, 1 H, C<u>H</u>H-5$_\beta$), 3.52 (dddd, *J*=6.0, 3.9, 1.8, 1.4 Hz, 1 H, CH-6), 4.40 (dq, *J*=4.0, ~2.0, 2.0, 2.0 Hz, 1 H, CH-2), 4.85 (dt, *J*=3.9, 1.8, 1.8 Hz, 1 H, CH-11), 7.10-7.16 (m, 2 H, ArH), 7.18-7.22 (m, 2 H, ArH), 7.23-7.27 (m, 2 H, ArH), 7.31-7.36 (m, 1 H, ArH), 7.41-7.46 (m, 2 H, ArH). ^{13}C NMR (100.6 MHz $CDCl_3$): δ = 36.0 (CH_2-1), 38.3 (CH_2-5), 40.1 (CH-6), 49.0 (CH-11), 63.3 (CH-2), 127.5, 127.8, 128.0, 128.1, 128.9, 129.6, 129.8, 138.4, 141.5 (C_6H_5, C_6H_4), 167.5 (C=O); (one signal is overlapped). GC-MS (EI, 70eV): *m/z* = 343 (72), [M+2], 341 (64), [M^+], 262 (38), 234 (100), 77 (54); IR (ATR): ν = 1647 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{17}BrNO[M+H]^+$, 342.0494; found: 342.0493.

(*2SR,6RS,11RS*)-11-Bromo-3,6-dimethyl-2,3,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-4(1*H*)-one (**2e**): Yield 91% (0.455g, reaction time: 2h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave white solid, m.p. 128-130 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.57 (s, 3 H, 4-CH_3), 2.42 (dd, *J*=17.5, 1.3 Hz, 1 H, CH<u>H</u>$_\beta$-5), 2.87 (d, *J*=17.5 Hz, 1 H, CH<u>H</u>$_\alpha$-5), 2.99 (s, 3 H, NCH_3), 3.13 (dd, *J*=17.1, 2.2 Hz, 1 H, CH<u>H</u>$_\alpha$-1), 3.22 (dd, *J*=17.1, 3.9 Hz, 1 H, CH<u>H</u>$_\beta$-1), 4.10 (ddd, *J*=3.9, 2.2, 2.0 Hz, 1 H, CH-2), 4.59 (dd, *J*=2.0, 1.3 Hz, 1 H, CH-11), 7.04 (d, *J*=7.5 Hz, 1 H, CH-10), 7.18 (tt, *J*=7.3, 1.4 Hz, 1 H, CH-9), 7.21-7.26 (m, 1 H, CH-8), 7.37 (dd, *J*=7.9, 1.3 Hz, 1 H, CH-7). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 25.9 (6-CH_3), 33.7 (NCH_3), 35.8 (CH_2-1), 39.4 (C-6), 44.5 (CH_2-5), 58.6 (CH-11), 62.4 (CH-2), 126.6 (CH-7), 127.4 (CH-8), 127.6 (CH-9), 129.5 (CH-10), 130.0 (C-10a), 140.7 (C-6a), 168.1 (C=O). GC-MS (EI, 70eV): *m/z* = 295 (27) [M^++2], 293 (28) [M^+], 280 (12), 278 (12), 214 (100). IR (ATR): ν = 1638 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{17}BrNO[M+H]^+$, 294.0494, found: 294.0488.

(*2SR,6RS,11RS*)-3-Benzyl-11-bromo-6-methyl-2,3,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-4(1*H*)-one (**2f**): Yield 83% (0.522g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 145-147 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ =2.53 (dd, *J*=17.6, 1.3 Hz, 1 H, CH<u>H</u>-5$_\alpha$), 2.98 (d, *J*=17.6 Hz, 1 H, CH<u>H</u>-5$_\beta$), 3.03-3.15 (m, 2 H, CH_2-1), 4.00-4.07 (m, 2 H, CH-2, NC<u>H</u>H), 4.55 (t, *J*=1.3 Hz, 1 H, CH-11), 5.31 (d, *J*=15.0 Hz, 1 H, NCH<u>H</u>), 6.98 (d, *J*=7.5 Hz, 1 H, ArH), 7.18 (td, *J*=7.4, 1.3 Hz, 1 H, ArH), 7.22-7.35 (m, 7 H, ArH), 7.40 (dd, *J*=7.9, 1.0 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 25.9 (6-CH_3), 35.9 (CH_2-1), 39.2 (C-6), 44.8 (CH_2-5), 47.8 (NCH_2), 58.6 (CH-11), 58.7 (CH-2), 126.7, 127.4, 127.5, 127.6, 128.3, 128.4, 129.4 (ArH), 130.2 (C-10a), 136.4(Ar), 140.8 (C-6a), 168.2 (C=O). GC-MS (EI, 70eV): *m/z* = 371 (35) [M^++2], 369 (33) [M^+], 290 (31), 91 (100). IR (ATR): ν = 1634 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}BrNO[M+H]^+$, 370.0807, found: 370.0816.

(*5SR,6RS*)-1,6-Dibenzyl-5-bromo-4-methyl-5,6-dihydropyridin-2(1*H*)-one (**4f**): Yield 14% (0.088g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave colorless solid, which during storage in a refrigerator converted itself into 6-benzyl-4-methylpyridin-2-one. ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.97 (d, *J*=1.3 Hz, 3 H, 4-CH_3), 2.65 (dd, *J*=13.8, 9.8 Hz, 1 H, 6-C<u>H</u>H), 2.92 (dd, *J*=13.8, 5.4 Hz, 1 H, 6-CH<u>H</u>), 3.79 (ddd, *J*=9.9, 5.4, 1.3 Hz, 1 H, CH-6), 3.97 (d, *J*=14.7 Hz, 1 H, NC<u>H</u>H), 4.23 (d, *J*=1.0 Hz, 1 H, CH-5), 5.28 (d, *J*=14.8 Hz, 1 H, NCH<u>H</u>), 5.93 (q, *J*=1.3 Hz, 1 H, =CH-3), 6.98-7.02 (m, 2 H, C_6H_5), 7.23-7.40 (m, 8 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 20.4 (4-CH_3), 38.4 (6-CH_2), 47.3 (CH-5), 48.3 (NCH_2), 63.5 (CH-6), 123.2 (=CH-3), 127.3, 127.8, 128.5, 128.9, 129.1, 129.2, 136.4, 136.4 (2 x C_6H_5), 146.5 (=C-4), 162.3 (C=O).

(*2SR,6RS,11RS*)-11-Bromo-6-methyl-3-phenyl-2,3,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-4(1*H*)-one (**2g**): Yield 89% (0.539g, reaction time: 3h). The crude product purified by column

chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave white solid, m.p. 155-157 °C (hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.65 (s, 3 H, CH_3), 2.58 (dd, *J*=17.7, 1.7 Hz, 1 H, CH<u>H</u>-5$_\alpha$), 3.02 (d, *J*=17.7 Hz, 1 H, CH<u>H</u>-5$_\alpha$), 3.09 (m, 2 H, CH_2-1), 4.47 (ddd, *J*=3.5, 2.9, 1.7 Hz, 1 H, CH-2), 4.73 (dd, *J*=2.9, 1.7 Hz, 1 H, CH-11), 7.08 (dd, *J*=7.3, 1.0 Hz, 1 H, ArH), 7.14-7.18 (m, 2 H, ArH), 7.21-7.35 (m, 3 H, ArH), 7.39-7.47 (m, 3 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 25.9 (CH_3), 36.3 (CH_2-1), 39.5 (C-6), 45.1 (CH_2-5), 58.9 (CH-11), 64.9 (CH-2), 126.8, 127.6, 127.7, 127.8, 128.2, 29.5, 129.6, 130.2, 140.8, 141.3 (Ar), 168.1 (C=O). GC-MS (EI, 70eV): *m/z* = 357 (55), [M+2], 355 (59), [M^+], 276 (33),91 (14), 77 (46). IR (ATR): ν = 1641 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{19}BrNO[M+H]^+$, 356.0650; found 356.0664.

(*2SR,6RS,11SR*)-11-Bromo-3-methyl-6-phenyl-2,3,5,6-tetrahydro-2,6-methano-benzo[*d*]azocin-4(1*H*)-one (**2h**): Yield 24% (0.145g, reaction time: 3h). The crude product purified by 1.2 m long column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave colorless solid, m.p. 232-235 °C (hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.84 (dd, *J*=16.8, 1.7 Hz, 1 H, CH<u>H</u>$_\alpha$-5), 3.05 (s, 3 H, NCH_3), 3.23 (dd, *J*=17.4, 2.2 Hz, 1 H, CH<u>H</u>$_\alpha$-1), 3.39 (dd, *J*=17.4, 3.6 Hz, 1 H, CH<u>H</u>$_\beta$-1), 3.66 (d, *J*=16.8 Hz, 1 H, CH<u>H</u>$_\beta$-5), 4.21 (dt, *J*=3.6, 2.2 Hz, 1 H, CH-2), 4.99 (t, *J*=1.7 Hz, 1 H, CH-11), 6.58 (dd, *J*=7.9, 0.7 Hz, 1 H, ArH), 6.97-7.04 (m, 2 H, ArH), 7.05-7.09 (m, 1 H, ArH), 7.10-7.15 (m, 1 H, ArH), 7.27-7.35 (m, 2 H, ArH), 7.40-7.51 (m, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 33.7 (NCH_3), 35.7 (CH_2-1), 41.7 (CH_2-5), 48.2 (C-6), 57.5 (CH-11), 62.0 (CH-2), 126.6, 127.2, 127.4, 127.4, 127.5, 128.1, 129.1, 129.1 (ArH), 130.0 (C-10a), 130.3 (ArH), 141.7 (C-6a), 144.3 (Ph), 167.8 (C=O). GC-MS (EI, 70eV): *m/z* = 357 (4) [M^++2], 355 (5) [M^+], 276 (100), 91 (8). IR (ATR): ν = 1641 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{19}BrNO[M+H]^+$, 356.0650, found 356.0648.

(*5SR,6RS*)-6-Benzyl-5-bromo-1-methyl-4-phenyl-5,6-dihydropyridin-2(1*H*)-one (**4h**): Yield 75% (0.454g, reaction time: 3h). The crude product purified by 1.2 m long column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave colorless solid, m.p. 133-135 °C (*n*-hexane : ethyl acetate). ^{1}H

NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.77 (dd, *J*=13.7, 9.4 Hz, 1 H, 6-C<u>H</u>H), 3.09 (3 H, s, NCH_3), 3.11 (dd, *J*=13.7, 6.0 Hz, 1 H, 6-CH<u>H</u>), 4.01 (ddd, *J*=9.3, 6.0, 1.5 Hz, 1 H, CH-6), 4.97 (br d, *J* =~1.0 Hz, 1 H, CH-5), 6.46 (s, 1 H, =CH-3), 7.08-7.12 (m, 2 H, ArH), 7.26-7.36 (m, 3 H, ArH), 7.41-7.46 (m, 3 H, ArH), 7.49-7.53 (m, 2 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.1 (NCH_3), 38.3 (6-CH_2), 44.3(CH-5), 68.3 (CH-6), 121.3 (=CH-3), 126.1, 127.4, 129.1, 129.1, 129.1, 130.2, 134.5, 136.2 (2 x C_6H_5), 146.3 (=C-4), 162.6 (C=O). IR (ATR): ν = 1649 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{19}BrNO[M+H]^+$, 356.0650, found: 356.0641.

(*2SR,6RS,11SR*)-3-benzyl-11-Bromo-6-phenyl-2,3,5,6-tetrahydro-*1H*-2,6-methanobenzo[*d*]azocin-4(1*H*)-one (**2i**): Yield 19% (0.140g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave white solid, m.p. 153-156 °C (n-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.95 (dd, *J*=16.9, 1.7 Hz, 1 H, CH<u>H</u>$_\alpha$-5), 3.16 (dd, 1 H, *J*=17.2, 2.4 Hz, CH<u>H</u>$_\alpha$-1), 3.29 (dd, *J*=17.2, 3.7 Hz, 1 H, CH<u>H</u>$_\beta$-1), 3.79 (d, *J*=16.9 Hz, 1 H, CH<u>H</u>$_\beta$-5), 4.12 (d, *J*=15.3 Hz, 1 H, NC<u>H</u>H), 4.15-4.18 (m, 1 H, CH-2), 4.95 (t, *J*=1.7 Hz, 1 H, CH-11), 5.36 (d, *J*=15.3 Hz, 1 H, NCH<u>H</u>), 6.61 (d, *J*=7.6 Hz, 1 H, ArH), 6.97-7.06 (m, 3 H, ArH), 7.14 (td, *J*=7.6, 1.0 Hz, 1 H, ArH), 7.27-7.36 (m, 7 H, ArH), 7.45 (t, *J*=6.1 Hz, 1 H, ArH), 7.51 (d, *J*=7.3 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, CDCl3, 23°C): δ = 35.9 (CH_2-1), 42.0 (CH_2-5),47.9 (NCH_2), 48.1 (C-6), 57.6 (CH-11), 58.5 (CH-2), 126.6, 127.2, 127.4, 127.4, 127.5, 127.6, 128.1, 128.2, 128.6, 129.1, 129.1 (ArH), 130.2 (C-10a), 130.3 (ArH), 136.3 (Ar), 141.8 (C-6a), 144.4 (Ar), 168.0 (C=O). GC-MS (EI, 70eV): *m/z* = 433 (50) [M^++2], 431 (50) [M^+], 352 (32), 91 (100), 77 (19). IR (ATR): ν = 1632 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{19}BrNO[M+H]^+$, 356.0650, found: 356.0665.

(*2SR,6RS,11SR*)- 1,6-Dibenzyl-5-bromo-4-phenyl-5,6-dihydropyridin-2(1*H*)-one (**4i**): Yield 76% (0.559g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave colorless solid, m.p. 51-53 °C (*n*-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.72 (dd, *J*=13.7, 10.3 Hz, 1 H, 6-C<u>H</u>H), 2.98 (dd, *J*=13.7, 5.3 Hz, 1 H, 6-

CHH), 3.95 (ddd, *J*=10.1, 5.3, 1.5 Hz, 1 H, CH-6), 4.13 (d, *J*=14.7 Hz, 1 H, NCHH), 4.88 (d, *J*=1.2 Hz, 1 H, CH-5), 5.32 (d, *J*=14.7 Hz, 1 H, NCHH), 6.53 (s, 1 H, =CH-3), 6.98 (dd, *J*=7.5, 1.6 Hz, 2 H, C_6H_5), 7.24-7.52 (m, 13 H, C_6H_5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 38.3 (6-CH_2), 43.6 (CH-5), 48.5 (NCH_2), 64.1 (CH-6), 121.3 (=CH-3), 126.1, 127.4, 127.9, 128.6, 128.9, 129.0, 129.1, 129.3, 130.3, 134.4, 136.1, 136.3 (3 x C_6H_5), 146.4 (=C-4), 162.6 (C=O). IR (ATR): ν = 1646 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{23}BrNO[M+H]^+$ 432.0963, found: 432.0968.

(*2SR,5SR,6RS,11RS*)-3-Benzylo-11-bromo-5-methyl-2,3,5,6-tetrahydro-2,6-methanobenzo[d]azocin-4(1*H*)-one (**2j**). Yield 70% (0.441g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 10 : 1) gave white solid, m.p. 115-117 °C (*n*-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 1.77 [d, *J*=7.7 Hz, 3 H, 5-(CH_3)], 2.63 (q, *J*=7.7 Hz, 1 H, CH-5), 3.07 (dd, *J*=17.5, 4.5 Hz, 1 H, CHH-1$_\beta$), 3.14 (dd, *J*=17.5, 1.8 Hz, 1 H, CHH-1$_\alpha$), 3.37 (dd, *J*=3.2, 2.2 Hz, 1 H, CH-6), 4.03 (dq, *J*=4.4, 2.2 Hz, 1 H, CH-2), 4.07 (d, *J*=14.8 Hz, 1 H, NCHH), 4.64 (dd, *J*=3.2, 2.2 Hz, 1 H, CH-11), 5.36 (d, *J*=14.8 Hz, 1 H, NCHH), 7.01-7.05 (m, 1 H, Ar, H-10), 7.05-7.09 (m, 1 H, ArH-7), 7.15-7.23 (m, 2H, ArH-8, ArH-9), 7.27-7.39 (m, 5 H, C_6H_5). ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 21.0 (5-CH_3), 35.4 (CH_2-1), 44.6 (CH-5), 46.5 (CH-6), 46.6 (CH-11), 48.9 (NCH_2), 58.3 (CH-2), 127.4, 127.6, 127.6, 127.9, 128.5, 128.7, 129.4, 129.5, 136.5, 141.1 (C_6H_4, C_6H_5), 171.1 (C=O). GC-MS (EI, 70eV): *m/z* = 371 (50) [M+2], 369 (51), [M^+], 290 (35), 91 (100). IR (KBr pellet): ν = 1631 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{21}BrNO[M+H]^+$, 370.0807, found: 370.0807.

(*2SR,5SR,6RS,11RS*)-5-Benzyl-11-bromo-3-methyl-2,3,5,6-tetrahydro-2,6-methanobenzo[*d*]azocin-4(1*H*)-one (**2k**): Yield 83% (0.522g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 6 : 1) gave white solid, m.p. 160-162 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 2.67 (dd, *J*=12.6, 4.4 Hz, 1 H, CH-5$_\alpha$), 3.11 (m, 3 H, NCH_3), 3.14-3.23 (m, 2 H, CH_2-1), 3.35 (dd, *J*=3.1, 2.2 Hz, 1 H, CH-6), 3.43 (dd,

J=13.7, 12.6 Hz, 1 H, 5-CHH), 3.60 (dd, *J*=13.7, 4.4 Hz, 1 H, 5-CHH), 4.05 (dq, *J*=4.3, 2.2 Hz, 1 H, CH-2), 4.65 (dd, *J*=3.1, 2.2 Hz, 1 H, CH-11), 6.11 (d, *J*=7.6 Hz, 1 H, CH-7), 6.95-7.02 (m, 2 H, ArH), 7.06-7.11 (m, 1 H, ArH), 7.27-7.33 (m, 1 H, ArH), 7.36-7.43 (m, 4 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.9 (NCH_3), 35.2 (CH_2-1), 38.6 (5-CH_2), 40.0 (CH-6), 47.2 (CH-11), 51.6 (CH-5), 61.9 (CH-2), 126.5, 127.3, 127.5, 128.7 129.3 (ArH), 129.3 (Ar), 129.8 (ArH), 140.3, 140.8 (Ar), 169.6 (C=O). GC-MS (EI, 70eV): *m/z* = 371 (6) [M^++2], 369 (6) [M^+], 290 (7), 91 (12). IR (ATR): ν = 1630 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}BrNO[M+H]^+$, 370.0807, found: 370.0813.

(*4RS,5RS,6RS*) 6-Benzyl-4,5-dibromo-1,3,3-trimethylpiperidin-2(1*H*)-one (**5**): Yield 56% (0.370g, reaction time: 24h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 112-114 °C (petrolem ether). ^{1}H NMR (400 MHz, Toluene-d_8, 23^{o}C): δ = 0.45 (s, 3 H, 3-CH_{3ax}), 1.33 (s, 3 H, 3-CH_{3eq}), 2.62 (s, 3 H, NCH_3), 2.73 (d, *J*=3.4 Hz, 2 H, 6-CH_2), 3.49 (dt, *J*=8.6, 3.4 Hz, 1 H, CH-6), 3.74 (d, *J*=12.2 Hz, 1 H, CBrH-4), 4.06 (dd, *J*=12.2, 8.6 Hz, 1 H, CBrH-5), 6.83-6.88 (m, 2 H, C_6H_5), 6.94-6.98 (m, 3 H, C_6H_5). ^{13}C NMR (100 MHz, Toluene-d_8,, 23^{o}C): 21.1 (3-CH_3), 27.5 (3-CH_3), 33.6 (NCH_3), 35.5 (6-CH_2), 45.2 (C-3), 52.4 (CH-5), 63.3 (CH-4), 65.4 (CH-6), 127.7, 129.0, 130.2, 135.0 (C_6H_5), 170.6 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 0.44-0.51 (m, 3 H, 3-CH_3), 1.36 (s, 3 H, 3-CH_3), 3.11 (s, 3 H, N-CH_3), 3.13 (dd, 1 H, *J*=14.9, 3.2 Hz, NCHH), 3.32 (dd, 1 H, *J*=14.8, 3.3 Hz, NCHH), 4.08-4.17 (m, 2 H, CH-5, CH-6), 4.31 (d, *J*=11.7 Hz, 1 H, CH-4), 7.10-7.14 (m, 2 H, C_6H_5), 7.26-7.36 (m, 3 H, C_6H_5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.9 (3-CH_3), 27.3 (3-CH_3), 34.1 (NCH_3), 35.4 (6-CH_2), 45.0 (C-3), 51.5 (CH-5), 63.0 (CH-4), 65.6 (CH-6), 127.7, 129.0, 129.9, 134.3 (C_6H_5), 171.7 (C=O). GC-MS (EI, 70eV): *m/z* = 91. IR (KBr pellet): ν = 1648 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{20}Br_2NO[M+H]^+$, 387.9912; found: 387.9902.

(*1RS,2RS,5SR,11SR*)-11-Bromo-2,5-dibenzyl-3-methyl-2,3,5,6-tetrahydro-1,5-methano-3-benzoazocin-4(1*H*)-one: (**6o**) Yield 90% (0.704g, reaction time: 24h). The crude product purified by

column chromatography (SiO_2, *n*-hexane : ethyl acetate, 6 : 1) gave white solid, m.p. 199-201 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, Toluene-d_8, 23°C): δ = 2.70 (s, 3 H, NCH_3), 2.89 (d, *J*=17.4 Hz, 1 H, CHH-6), 2.92 (dd, *J*=13.3, 4.6 Hz, 2 H, 2-CHH), 3.04 (d, *J*=17.5 Hz, 1 H, CHH-6), 3.25 (d, *J*=3.7 Hz, 1 H, CH-1), 3.30 (dd, *J*=11.7, 4.6 Hz, 1 H, CH-2), 3.60 (d, *J*=14.3 Hz, 1 H, 5-CHH), 3.76 (dd, *J*=13.2, 11.7 Hz, 1 H, 2-CHH), 3.94 (d, *J*=14.3 Hz, 1 H, 5-CHH), 4.09 (d, *J*=3.7 Hz, 1 H, CH-11), 6.14-6.19 (m, 1 H, CH-10), 6.48-6.53 (m, 1 H, CH-6), 6.69-6.77 (m, 2 H, CH-8, CH-9), 7.07 (d, *1* H, *J*=7.3 Hz, ArH), 7.11-7.19 (m, 5 H, ArH), 7.21-7.26 (m, 2 H, ArH), 7.47-7.51 (m, 2 H, ArH). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 3.01-3.10 (m, 5 H, NCH_3, CH_2-6), 3.32 (dd, *J*=13.4, 4.6 Hz, 1 H, 2-CHH), 3.47-3.57 (m, 3 H, CH-1, CH-2, 5-CHH), 3.64 (d, *J*=14.2 Hz, 1 H, 5-CHH), 3.91 (dd, *J*=13.3, 11.8 Hz, 1 H, 2-CHH), 4.46 (d, *J*=3.7 Hz, 1 H, CH-11), 6.22 (d, *J*=7.1 Hz, 1 H, ArH), 6.87-6.98 (m, 2 H, ArH), 7.04 (td, *J*=7.6, 1.5 Hz, 1 H, ArH), 7.21 (tt, *J*=7.3, 1.2 Hz, 1 H, ArH), 7.26-7.46 (m, 7 H, ArH), 7.51-7.55 (m, 2 H, ArH). ^{13}C NMR (100 MHz, toluene-d8, 23°C): δ = 34.3 (NCH_3), 38.7 (2-CH_2), 39.7 (CH_2-6), 40.9 (CH-1), 41.6 (5-CH_2), 47.2 (C-5), 55.3 (CH-11), 70.9 (CH-2), 126.6, 127.0, 127.0, 127.2, 127.4, 128.5, 128.6, 128.9, 130.3, 131.9 (ArH), 133.2, 137.6, 139.1, 140.1 (Ar), 171.2 (C=O). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.8 (NCH_3), 38.5 (2-CH_2), 38.9 (CH_2-6), 40.5 (CH-1, 5-CH_2), 46.8 (C-5), 53.9 (CH-11), 70.4 (CH-2), 126.6, 126.7, 126.8, 126.9, 127.3, 128.3, 128.3, 128.6, 128.8, 129.8, 131.4, (ArH), 132.7, 136.7, 138.2, 139.4 (Ar), 171.9 (C=O). GC-MS (EI, 70eV): *m/z* = 370 (94), 368 (94), 91 (100). IR (ATR): ν = 1638 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{27}BrNO[M+H]^+$, 460.1276; found: 460.1277.

(*1RS,2RS,5SR,11SR*)-11-Bromo-2,3-dibenzyl-5-methyl-2,3,5,6-tetrahydro-1,5-methano-3-benzoazocin-4(1*H*)-one): (**6p**) Yield 80% (0.783g, reaction time: 27h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 8 : 1) gave white solid, m.p. 144-146 °C (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.61 (s, 3 H, 5-CH3), 2.97 (d, *J*=17.5 Hz, 1 H, CHH-6), 3.18 (dd, *J*=13.4, 4.6 Hz, 1 H, 2-CHH), 3.37 (d, *J*=17.5 Hz, 1 H, CHH-6), 3.44 (d, 1 H, *J*=3.4 Hz, CH-1), 3.49 (dd, 1 H, *J*=11.9, 4.6 Hz, CH-2), 3.85 (dd, 1 H, *J*=13.3, 11.9 Hz, 2-CHH),

4.28 (d, 1 H, *J*=15.4 Hz, NCHH), 4.63 (d, *J*=3.3 Hz, 1 H, CH-11), 5.30 (d, *J*=15.4 Hz, 1 H, NCHH), 6.22 (d, *J*=7.6 Hz, 1 H, CH-10), 6.72 (d, *J*=7.2 Hz, 2 H, ArH), 6.95 (t, *J*=7.5 Hz, 1 H, ArH), 6.99-7.15 (m, 5 H, ArH), 7.18 (d, *J*=7.0 Hz, 2 H, ArH), 7.24-7.30 (m, 1 H, ArH), 7.32-7.37 (m, 2 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.8 (5-CH_3), 37.8 (2-CH_2), 40.5 (CH-1), 43.6 (C-5), 45.1 (CH_2-6), 47.9 (NCH_2), 55.9 (CH-11), 67.5 (CH-2), 126.7, 126.8, 126.9, 126.9, 127.1, 127.4, 127.9, 128.3, 128.8, 129.6 (ArH), 133.0, 136.7, 138.3, 139.6 (Ar), 172.5 (C=O). GC-MS (EI, 70eV): *m/z* = 370 (59), 368 (62), 91 (100). IR (ATR): ν = 1638 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{27}BrNO[M+H]^+$, 460.1276, found: 460.1277.

(*1RS,2RS,5SR,11SR*)-11-Bromo-2,3-dibenzyl-5-methyl-2,3,5,6-tetrahydro-1,5-methano-3-benzoazocin-4(1*H*)-one (**6pNH**): Yield 7% (0.044g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 232-234 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, , $CDCl_3$, 23°C): δ = 1.55 (s, 3 H, 5-CH_3), 2.97 (d, *J*=17.8 Hz, 1 H, CHH-6), 3.32 (d, *J*=17.8 Hz, 1 H, CHH-6), 3.43 (dd, *J*=13.3, 8.7 Hz, 1 H, 2-CHH), 3.49 (dd, *J*=13.3, 7.5 Hz, 1 H, 2-CHH), 3.57 (d, *J*=3.3 Hz, 1 H, CH-1), 3.66 (ddd, *J*=8.7, 7.5, 2.8 Hz, 1 H, CH-2), 4.61 (d, *J*=3.3 Hz, 1 H, CH-11), 5.69 (br. s., 1 H, NH), 6.74 (dd, *J*=7.3, 1.7 Hz, 1 H, CH-10), 7.01 (d, *J*=7.2 Hz, 1 H, CH-7), 7.10-7.14 (m, 1 H, CH-8(9)), 7.17 (td, *J*=7.3, 7.3, 1.7 Hz, 1 H, CH-9(8)), 7.24-7.31 (m, 3 H, C_6H_5), 7.34-7.40 (m, 2 H, C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 26.1 (5-CH_3), 42.9 (C-5), 43.1 (2-CH_2), 43.2 (CH-1), 43.3 (CH_2-6), 55.1 (CH-11), 63.4 (CH-2), 127.1 [C_6H_5, CH-8(9)], 127.2 (CH-10), 127.7 [CH-9(8)], 128.4 (CH-7), 129.0, 129.5 (C_6H_5), 132.6 (C-6a), 137.6 (C_6H_5), 140.0 (C-10a), 173.4 (C=O). GC-MS (EI, 70eV): *m/z* = 280 (98), 278 (100), 199 (11), 198 (12), 91 (21). IR (ATR): ν = 3117 br, 3051 br, 1657 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}BrNO[M+H]^+$, 370.0807, found: 370.0812.

(*1RS,2RS,5SR,11SR*)- 11-Bromo-2-benzyl-9-fluoro-5-(4-fluorobenzyl)-3-methyl-2,3,5,6-tetrahydro-1,5-methano-3-benzoazocin-4(1*H*)-one (**6q**): Yield 72% (0.608g, reaction time: 100h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 6 : 1) gave white solid,

m.p. 217-220 °C (petroleum ether: ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.90 (d, *J*=17.7 Hz, 1 H, CHH-6), 3.00 (d, *J*=17.7 Hz, 1 H, CHH-6), 3.08 (s, 3 H, NCH_3), 3.33 (dd, *J*=13.3, 4.6 Hz, 1 H, 2-CHH), 3.42 (d, *J*=14.5 Hz, 1 H,5-CHH), 3.47 (d, *J*=3.7 Hz, 1 H, CH-1), 3.53 (dd, *J*=11.8, 4.6 Hz, 1 H, CH-2), 3.61 (d, *J*=14.5 Hz, 1 H, 5-CHH), 3.88 (dd, *J*=13.3, 11.8 Hz, 1 H, 2-CHH), 4.39 (d, *J*=3.7 Hz, 1 H, CH-11), 5.91 (dd, *J*=9.0, 2.6 Hz, 1 H, CH-10), 6.76 (td, *J*=8.5, 2.6 Hz, 1 H, CH-8), 6.87 (dd, *J*=8.6, 5.6 Hz, 1 H, CH-7), 6.94-7.03 (m, 2 H, 2xCH-3'), 7.32-7.41 (m, 3 H, Bn), 7.42-7.53 (m, 4 H, Bn, 2xCH-2'). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 34.7 (NCH_3), 38.3 (CH_2-6), 38.5 (2-CH_2), 39.8 (5-CH_2), 40.3 (CH-1), 46.7 (C-5), 53.2 (CH-11), 70.2 (CH-2), 113.0 (d, $^2J_{CF}$=21.3 Hz, CH-10), 114.9 (d, $^2J_{CF}$=21.3 Hz, CH-8), 115.2 (d, $^2J_{CF}$=21.3 Hz, 2xCH-3'), 127.1 (2-Bn), 128.2 (d, $^4J_{CF}$=2.9 Hz, C-6a), 129.0, 129.7 (2-Bn), 130.1 (d, $^3J_{CF}$=8.1 Hz, CH-7), 132.2 (d, $^4J_{CF}$=2.9 Hz, CH-1'), 132.8 (d, $^3J_{CF}$=7.3 Hz, 2xCH-2'), 137.9 (Bn), 141.01 (d, $^2J_{CF}$=7.2 Hz, C-10a), 161.0 (d, $^1J_{CF}$=245.8 Hz, CH-9), 161.9 (d, $^1J_{CF}$=245.8 Hz, C4'), 171.6 (C=O). GC-MS (EI, 70eV): *m/z* = 406 (99), 404 (98), 109 (100), 91 (26). IR (ATR): ν = 1642 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{24}BrF_2NONa[M+Na]^+$, 518.0907, found: 518.0897.

(1*SR*,2*SR*,6*SR*,11*SR*)-11-Bromo-3,6-dimethyl-1-phenyl-2,3,5,6-tetrahydro-2,6-methano-benzo[d]azocin-4(1*H*)-one (**13**): Yield 60% (0.378g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 237-239 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.61 (s, 3 H, 6-CH_3), 2.46 (dd, *J*=17.5, 1.6 Hz, 1 H, CHH_α-5), 2.90 (d, *J*=17.5 Hz, 1 H, CHH_β-5), 3.18 (s, 3 H, N-CH_3), 3.98 (dd, *J*=2.1, 1.9 Hz, 1 H, CH-2), 4.53 (d, *J*=1.8 Hz, 1 H, CH-1), 4.66 (dd, 1 H, *J*=2.1, 1.6 Hz, CH-11), 6.93-6.99 (m, 3 H, ArH-10, 1-Ph), 7.19 (td, *J*=7.5, 1.2 Hz, 1 H, ArH), 7.24-7.36 (m, 4 H, ArH), 7.47 (dd, *J*=8.0, 0.9 Hz, 1 H, ArH-7). ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 25.9 (6-CH_3), 34.0 (NCH_3), 39.4 (C-6), 44.8 (CH_2-5), 51.0 (CH-1), 54.5 (CH-11), 69.7 (C-2), 126.6, 127.3, 127.8, 128.3, 128.8, 128.9, 131.2, 131.9, 141.6, 142.3 (Ar), 167.9 (C=O). GC-MS (EI, 70eV): *m/z* = 290 (100). IR (ATR): ν = 1653 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{21}BrNO[M+H]^+$, 370.0807, found: 370.0816.

Synthesis of compound 3

To a stirred solution of *N*-methyl 6-benzyl-3,6-dihydropyridin-2(1*H*)-one (**1a**) (0.45mmol, 0.09g) in CH_2Cl_2 (5mL) *N*-bromosuccinimide (0.5mmol, 0.088g) was added. The resulting orange - yellow solution was stirred for 24h at room temperature. After this time additional portion of NBS (0.5 mmol, 0.088 g) was added and the mixture was stirred another 24h. Subsequently, 2% solution of Na_2SO_3 (1mL) and then saturated aqueous solution of $NaHCO_3$ (1mL) were added and the mixture was stirred for additional 10 min. The aqueous layer was extracted with ethyl acetate (3 x 25mL) and the combined organic layers were dried over $MgSO_4$. The mixture was filtered and the solvents were evaporated under reduced pressure. The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave **3** as pale yellow solid (0.077g, 48% yield).

6-Benzyl-3,5-dibromo-1-methylpyridin-2(1*H*)-one (**3**). Yield 48% (0.077g), m.p. 98-100 °C (hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23^{o}C): δ = 3.52 (s, 3 H, NCH_3), 4.30 (s, 2 H, 6-CH_2), 7.09 (d, *J*=7.0 Hz, 2 H, C_6H_5), 7.25-7.37 (m, 3 H, C_6H_5), 7.95 (s, 1 H, =CH-4). ^{13}C NMR (100.6 MHz $CDCl_3$): δ = 34.2 (NCH_3), 39.2 (6-CH_2), 100.3 (C-5), 114.9 (C-3), 127.5, 127.5, 129.3, 134.1 (C_6H_5), 143.7 (=CH-4), 145.5 (C-6), 159.3 (C=O). GC-MS: (EI, 70eV): *m/z* = 355 (36), [M^+], 276 (16), 197 (100), 91 (88). IR (ATR): ν = 1644 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd. for $C_{13}H_{12}Br_2NO[M+H]^+$, 355.9286, found: 355.9286.

*A typical procedure for the intramolecular cyclopropanation of bromobenzomorphans. Synthesis of bridged benzomorphans 7, **9, 11** and 2-naphthalen-1-yl-N-phenylacetamide **8***

A solution of bromobenzomorphan **2**, **6** or **13** (0.8mmol) in dry THF (15mL) in a Schlenk flask was stirred at room temperature under argon and 7.0 equiv. of *t*-BuOK (5.6 mmol, 0.628g) was added. The resulting yellow to the brown solution was stirred for 2-7h for compounds **2**, **15** and 7-21h for compounds **6**, (GC-MS control) and after this time the mixture was quenched with a saturated aqueous solution of NH_4Cl (10mL). The aqueous layer was extracted with ethyl acetate (3x50mL),

and the combined organic layers were dried over $MgSO_4$. The mixture was filtered, and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a mixture of appropriate solvents to give the desired product.

(3a*SR*,7b*RS*,7c*SR*)-3-Methyl-1,3,3a,3b,7b,7c-hexahydro-3-azacyclopro-pa[jk]fluoren-2-one (**7a**): Yield 91% (0.145g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 88-90 °C (*n*-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.48 (ddd, *J*=8.1, 7.6, 6.4 Hz, 1 H, CH-7c), 2.51 (dd, *J*=15.9, 3.2 Hz, 1 H, C<u>H</u>H-1), 2.65 (s, 3 H, NCH_3), 2.66 (dd, *J*=6.4, 5.9 Hz, 1 H, CH-3b), 2.91 (dd, *J*=15.9, 3.4 Hz, 1 H, CH<u>H</u>-1), 3.00 (dd, *J*=8.1, 5.9 Hz, 1 H, CH-3a), 3.80 (ddd, *J*=7.6, 3.4, 3.2 Hz, 1 H, CH-7b), 7.04-7.08 (m, 1 H, ArH), 7.11-7.18 (m, 2 H, ArH), 7.23-7.27 (m, 1 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.0 (CH-7c), 31.8 (CH-3b), 32.5 (NCH_3), 36.6 (CH_2-1), 40.3 (CH-7b), 41.5 (CH-3a), 123.7, 124.4, 127.0, 127.1 (ArH), 139.4, 145.2, (Ar), 170.6 (C=O). GC-MS (EI, 70eV): *m/z* = 199 (100), [M^+], 198 (45). IR (ATR): ν = 1634 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{14}NO[M+H]^+$, 200.1075; found: 200.1083.

(3a*SR*,7b*RS*,7c*SR*)-3-Propyl-1,3,3a,3b,7b,7c-hexahydro-3-azacyclopropa[jk]fluoren-2-one (**7b**): Yield 70% (0.127g, reaction time: 3h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave pale yellow oil. ^{1}H NMR (400 MHz): δ = 0.60 (t, *J*=7.4 Hz, 3 H, CH_3), 1.13-1.22 (m, 1 H, C<u>H</u>H), 1.30-1.42 (m, 1 H, CH<u>H</u>), 2.46 (ddd, *J*=8.1, 7.6, 6.4 Hz, 1 H, CH-7c), 2.51 (dd, *J*=16.0, 3.1 Hz, 1 H, CHH-1), 2.63 (dd, *J*=6.4, 5.9 Hz, 1 H, CH-3b), 2.91 (dd, *J*=16.0, 3.4 Hz, 1 H, CH<u>H</u>-1), 2.95-3.01 (m, 1 H, NC<u>H</u>H), 3.00 (dd, *J*=8.1, 5.9 Hz, 1 H, CH-3a), 3.27 (ddd, *J*=13.3, 9.1, 6.5 Hz, 1 H, NCH<u>H</u>), 3.76 (ddd, *J*=7.6, 3.4, 3.1 Hz, 1 H, CH-7b), 7.03-7.09 (m, 1 H, ArH), 7.11-7.17 (m, 2 H, ArH), 7.19-7.24 (m, 1 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.3 (CH_3), 20.1 (CH_2), 24.1 (CH-7c), 32.2 (CH-3b), 36.3 (CH_2-1), 39.9 (CH-7b), 40.1 (CH-3a), 47.4 (NCH_2), 123.7, 124.5, 126.8, 127.1 (ArH), 140.0, 145.0 (Ar), 170.3 (C=O). GC-MS (EI, 70eV):

m/z = 227 (100), [M^+]. IR (ATR): ν = 1649, 1630 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{15}H_{18}NO[M+H]^+$, 228.1388; found: 228.1381.

(3a*SR*,7b*RS*,7c*SR*)-3-Benzyl-1,3,3a,3b,7b,7c-hexahydro-3-aza-cyclopropa[jk]fluoren-2-one (**7c**): Yield 90% (0.198g, reaction time: 4h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave colorless solid, m.p. 114-116 °C (hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.43 (ddd, *J*=8,1, 7.6, 6.4 Hz, 1 H, CH-7c), 2.53 (t, *J*=6.2 Hz, 1 H, CH-3b), 2.59 (dd, *J*=16.1, 3.1 Hz, 1 H, C<u>H</u>H-1), 2.93-3.00 (m, 2 H, CH<u>H</u>-1, CH-3a), 3.78 (ddd, *J*=7.6, 3.4, 3.2 Hz, 1 H, CH-7b), 3.96 (d, *J*=14.4 Hz, 1 H, NC<u>H</u>H), 4.60 (d, *J*=14.4 Hz, 1 H, NCH<u>H</u>), 6.93 (d, 1 H, *J*=7.3 Hz, ArH), 7.03-7.17 (m, 5 H, ArH), 7.21-7.26 (m, 3 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.5 (CH-7c), 32.0 (CH-3b), 36.3 (CH_2-1), 39.4 (CH-3a), 40.0 (CH-7b), 48.9 (NCH_2), 123.6, 124.6, 126.8, 127.1, 127.2. 128.4, 128.6 (ArH), 136.8, 139.6, 144.8 (Ar), 170.5 (C=O). GC-MS (EI, 70eV): *m/z* = 275 (68), [M^+], 274 (31), 184 (45), 191(100). IR (ATR): ν = 1634 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{18}NO[M+H]^+$, 276.1388; found: 276.1394.

(3a*SR*,7b*RS*,7c*SR*)-3,7b-dimethyl-1,3,3a,3b,7b,7c-hexahydro-3-aza-cyclopropa[jk]fluoren-2-one (**7d**): Yield 73% (0.125g, reaction time: 7h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 3) gave white solid, m.p. 120-122 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.41 (s, 3 H, 7b-CH_3), 2.19 (dd, 1 H, *J*=8.1, 6.4 Hz, CH-7c), 2.43 (d, 1 H, *J*=15.8 Hz, C<u>H</u>H-1), 2.62 (s, 3 H, NCH_3), 2.70 (dd, 1 H, *J*=6.4, 6.0 Hz, CH-3b), 2.74 (d, 1 H, *J*=15.8 Hz, CH<u>H</u>-1), 3.00 (dd, 1 H, *J*=8.1, 6.0 Hz, CH-3a), 7.01-7.05 (m, 1 H, ArH), 7.15 (pseudo quint, 2 H, *J*=7.1, 1.5 Hz, ArH), 7.21-7.25 (m, 1 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.8 (7b-Me), 31.0 (CH-3b), 31.3 (CH-7c), 32.3 (NCH_3), 42.1 (CH-3a), 43.9 (CH_2-1), 45.7, (C-7b), 122.2, 124.2, 127.1, 127.2 (ArH), 138.6, 148.7 (Ar), 170.9 (C=O). GC-MS (EI, 70eV): *m/z* = 213 (17) [M^+], 198 (100). IR (ATR): ν = 1635 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{16}NO[M+H]^+$, 214.1232; found: 214.1238.

(3a*SR*,7b*RS*,7c*SR*)-3-benzyl-7b-methyl-1,3,3a,3b,7b,7c-hexahydro-3-aza-cyclopropa[jk]fluoren-2-one (**7e**): Yield 72% (0.167g, reaction time: 7h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 3) gave white solid, m.p. 112-114 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.40 (s, 3 H, 7b-CH_3), 2.13 (dd, *J*=8.2, 6.4 Hz, 1 H, CH-7c), 2.52 (d, *J*=15.7 Hz, 1 H, CHH-1), 2.57 (dd, *J*=6.4, 6.0 Hz, 1 H, CH-3b), 2.79 (d, *J*=15.7 Hz, 1 H, CHH-1), 2.95 (dd, *J*=8.2, 6.0 Hz, 1 H, CH-3a), 3.92 (d, *J*=14.4 Hz, 1 H, NC<u>H</u>H), 4.58 (d, *J*=14.4 Hz, 1 H, NCH<u>H</u>), 6.92 (d, *J*=7.3 Hz, 1 H, ArH), 7.01-7.10 (m, 4 H, ArH), 7.15 (td, *J*=7.5, 1.0 Hz, 1 H, ArH), 7.20-7.25 (m, 3 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.9 (7b-Me), 30.8 (CH-7c), 31.2 (CH-3b), 40.1 (CH-3a), 43.6 (CH_2-1), 45.3, (C-7b), 48.7 (NCH_2), 122.0, 124.4, 126.8, 127.1, 127.2, 128.4, 128.6 (ArH), 136.8, 138.7, 148.4 (Ar), 170.7 (C=O). GC-MS (EI, 70eV): *m/z* = 289 (60) [M^+], 274 (70), 198 (28), 91 (100). IR (ATR): ν = 1633 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{20}NO[M+H]^+$, 290.1545; found: 290.1545.

(3a*SR*,7b*RS*,7c*SR*)-3-Phenyl-1,3,3a,3b,7b,7c-hexahydro-3-aza-cyclopropa[jk]fluoren-2-one (**7f**): (Note: DMF or HMPA was used as solvent instead of THF). Yield 44% (0.092g, reaction time: 2h in DMF or in HMPA). The crude product purified by column chromatography (SiO_2, 1.2 m-long column, *n*-hexane : ethyl acetate, 6 : 1) gave colorless solid, m.p. 134-135 °C (*n*-hexane : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.60 (ddd, 1 H, *J*=8.3, 7.8, 6.4 Hz, CH-7c), 2.68 (dd, 1 H, *J*=16.1, 3.2 Hz, C<u>H</u>H-1), 2.97 (dd, 1 H, *J*=6.4, 5.9 Hz, CH-3b), 3.10 (dd, 1 H, *J*=16.1, 3.4 Hz, CH<u>H</u>-1), 3.37 (dd, 1 H, *J*= 8.3, 5.9 Hz, CH-3a), 3.91 (ddd, 1 H, *J*=7.6, 3.4, 3.2 Hz, CH-7b), 6.86-6.91 (m, 2 H, ArH), 7.14-7.30 (m, 7 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.1 (CH-7c), 31.7 (CH-3b), 35.8 (CH_2-1), 39.1 (CH-7b), 41.9 (CH-3a), 122.9, 123.7, 125.1, 125.7, 126.2, 126.3, 127.9 (ArH), 138.9, 140.3, 143.9 (Ar), 169.3 (C=O). ^{1}H NMR (400 MHz, toluene-d_8, 23°C): δ = 1.82 (ddd, *J*=8.3, 7.8, 6.4 Hz, 1 H, CH-7c), 2.09 (dd, *J*=6.4, 5.9 Hz, 1 H, CH-3b), 2.45 (dd, *J*=15.9, 3.2 Hz, 1 H, C<u>H</u>H-1), 2.59 (dd, *J*=15.9, 3.4 Hz, 1 H, CH<u>H</u>-1), 2.75 (dd, *J*=8.3, 5.9 Hz, 1 H, CH-3a), 3.22 (ddd, *J*=7.8, 3.4, 3.2 Hz, 1 H, CH-7b), 6.75-6.80 (m, 1 H, ArH), 6.87 (tt, 1 H, *J*=7.3, 1.2 Hz,

ArH), 6.92-7.11 (m, 7 H, ArH). ^{13}C NMR (100 MHz, toluene-d_8, 23°C): δ = 25.3 (CH-3), 32.9 (CH-2), 37.1 (CH_2-7), 40.4 (CH-8), 42.5 (CH-4), 124.0, 124.8, 125.8, 125.9, 127.2, 127.3, 128.6 (ArH), 140.2, 142.5, 145.3 (Ar), 168.5 (C=O). GC-MS (EI, 70eV): *m/z* = 261 (100), [M^+], 77 (92). IR (ATR): ν = 1668 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{16}NO[M+H]^+$, 262.1232; found 262.1234.

2-Naphthalen-1-yl-N-phenyl-acetamide[31] (**8**): Yield 71% (0.148g, reaction time: 2h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 5 : 1) gave colorless solid, m.p. 161-162°C (*n*-hexane : ethyl acetate). Lit.162-164°C (Ethanol).[31] ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 4.17 (s, 2 H, CH_2), 7.01-7.06 (t, *J*=7.7 Hz, 1 H, C_6H_5), 7.07 (br. s., 1H, NH), 7.21 (t, *J*=8.3 Hz, 2 H, C_6H_5), 7.27-7.31 (m, 2 H, C_6H_5), 7.47-7.58 (m, 4 H, ArH), 7.85-7.93 (m, 2 H, ArH), 7.99–8.05 (m, 1 H ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 42.8 (CH_2), 119.9 (C_6H_5), 123.7 (naph), 124.4 (C_6H_5), 125.7, 126.3, 127.1, 128.5 (naph), 128.8 (C_6H_5), 128.9, 130.6, 132.0, 134.0 (naph), 137.5 (C_6H_5), 169.1 (C=O). GC-MS (EI, 70eV): *m/z* = 261 (41), [M^+], 168 (35), 142 (100), 141 (92), 77 (9). IR (KBr pellet): ν = 1662 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{16}NO[M+H]^+$, 262.1232; found: 262.1234.

(1*RS*,3a*SR*,3b*SR*,7c*RS*,7b*RS*)-1,3a-Dibenzyl-2-methyl-1,2,3a,3b,7b,7c-hexahydro-2-aza-cyclopropa[jk]fluoren-3-one (**9o**): Yield 74% (0.225g, reaction time: 7h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 3 : 1) gave white solid, m.p. 158-160 °C (ethyl acetate : petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.19 (d, *J*=13.3 Hz, 2 H, 3a-C<u>H</u>H), 2.21-2.22 (m, 3 H, NCH_3), 2.29 (dd, *J*=13.4, 7.0 Hz, 1 H, 1-C<u>H</u>H), 2.50 (dd, *J*=13.4, 7.9 Hz, 1 H, 1-CH<u>H</u>), 2.65 (dd, *J*=7.3, 6.3 Hz, 1 H, CH-7c), 2.70 (d, *J*=6.2 Hz, 1 H, CH-3b), 3.23 (ddd, *J*=7.9, 7.0, 2.8 Hz, 1 H, CH-1), 3.42 (dd, *J*=7.3, 2.8 Hz, 1 H, CH-7b), 4.03 (d, *J*=13.3 Hz, 1 H, 3a-CH<u>H</u>), 6.74-6.79 (m, 2 H, ArH(1-Bn)), 6.97 (d, *J*=7.3 Hz, 1 H, ArH-7), 7.08 (td, *J*=7.3, 1.5 Hz, 1 H, ArH-6), 7.13 (td, J=7.3, 1.5 Hz, 1 H, ArH-5), 7.16-7.28 (m, 4 H, ArH), 7.33 (d, *J*=7.3 Hz, 1 H, ArH-

4), 7.35-7.39 (m, 4 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 29.5 (CH-7c), 35.4 (NCH_3), 35.6 (C-3a), 39.9 (CH-3b), 40.4 (3a-CH_2), 41.0, (1-CH_2), 44.5 (CH-7b), 67.7 (CH-1), 122.6 (CH-7), 124.8 (CH-4), 126.5, 126.6 (ArH), 126.8 (CH-6), 127.4 (CH-5), 128.5, 128.6, 128.9, 129.8 (ArH), 138.1 (Ar), 139.2 (Ar), 142.1 (C-3c), 145.3 (C-7a), 167.7 (C=O). GC-MS (EI, 70eV): *m/z* = 379 (100), [M^+], 288 (65), 91 (37). IR (ATR): ν = 1640 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{26}NO[M+H]^+$, 380.2014; found: 380.2026.

(1*RS*,3a*SR*,3b*SR*,7c*RS*,7b*RS*)-1,2-Dibenzyl-3a-methyl-1,2,3a,3b,7b,7c-hexahydro-2-aza-cyclopropa[jk]fluoren-3-one (**9p**): Yield 71% (0.215g, reaction time: 21h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 108-110 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.49 (s, 3 H, 3a-CH_3), 2.39 (dd, 1 H, *J*=7.2, 6.2 Hz, CH-7c), 2.51 (d, 1 H, *J*=6.2 Hz, CH-3b), 3.08 (dd, 1 H, *J*=13.3, 8.1 Hz, 1-C<u>H</u>H), 3.19 (dd, 1 H, *J*=13.3, 5.4 Hz, 1-CH<u>H</u>), 3.28 (d, 1 H, *J*=14.7 Hz, NC<u>H</u>H), 3.38-3.45 (m, 2 H, CH-1, CH-7b), 5.05 (d, 1 H, *J*=14.7 Hz, NCH<u>H</u>), 6.31 (d, 1 H, *J*=7.5 Hz, CH-7), 6.52 [d, 2 H, *J*=7.2 Hz, ArH(Bn)], 6.71 (td, 1 H, *J*=7.5, 1.0 Hz, CH-6), 6.98 - 7.13 (m, 4 H, ArH), 7.23-7.31 (m, 4 H, ArH), 7.34 - 7.39 (m, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 20.9 (NCH_3), 28.6 (C-3a), 32.0 (CH-7c), 40.0 (CH-3b), 41.4 (1-CH_2), 43.7 (CH-7b), 48.5 (NCH_2), 62.8 (CH-1), 123.0 (CH-7), 124.5 (CH-4), 126.7, 126.8, 126.8, 126.9, (ArH), 128.2, 128.4, 128.9, 129.1 (ArH), 136.5, 137.8, (Ar), 141.8 (C-3c), 144.5 (C-7a), 169.4 (C=O). GC-MS (EI, 70eV): *m/z* = 379 (8), [M^+], 288 (50), 91 (58). IR (ATR): ν = 1637 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{26}NO[M+H]^+$, 380.2014; found: 380.2022.

(1*RS*,3a*SR*,3b*SR*,7c*RS*,7b*RS*)-1-Benzyl-6-fluoro-3a-(4-fluoro-benzyl)-2-methyl-1,2,3a,3b,7b,7c-hexahydro-2-aza-cyclopropa[jk]fluoren-3-one (**9q**): Yield 95% (0.316g, reaction time: 21h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 1) gave white solid, m.p. 188-189 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.15

(d, *J*=13.7 Hz, 1 H, 3a-CHH), 2.29 (s, 3 H, NCH_3), 2.29 (dd, *J*=13.4, 7.7 Hz, 1 H, 1-CHH), 2.55 (dd, *J*=13.4, 7.5 Hz, 1 H, 1-CHH), 2.61-2.67 (m, 2 H, CH-3b, CH-7c), 3.21 (ddd, *J*=7.7, 7.5, 2.9 Hz, 1 H, CH-1), 3.38-3.44 (m, 1 H, CH-7b), 3.98 (d, *J*=13.7 Hz, 1 H, 3a-CHH), 6.68 (dd, *J*=8.7, 2.3 Hz, 1 H, CH-7), 6.78 - 6.85 (m, 3 H, CH-5, 1-Bn), 7.02-7.08 (m, 2 H, 2xCH-3'), 7.18-7.27 (m, 4 H, CH-4, 1-Bn), 7.29-7.35 (m, 2 H, 2 x CH-2'). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 29.9 (CH-7c), 35.4 (NCH_3), 35.5 (C-3a), 38.9 (CH-3b), 39.5 (3a-CH_2), 40.9 (NCH_2), 44.4 (d, $^4J_{CF}$= 2.2 Hz, CH-7b), 67.5 (CH-1), 109.9 (d, $^2J_{CF}$=23.5 Hz, CH-7), 114.3 (d, $^2J_{CF}$=22.2 Hz, CH-5), 115.4 (d, $^2J_{CF}$=21.3 Hz, 2xCH-3'), 125.7 (d, $^3J_{CF}$= 8.9 Hz, CH-4), 126.8, 128.7, 128.8 (ArH, C_6H_5), 131.2 (d, $^3J_{CF}$= 7.3 Hz, 2xCH-2'), 134.8 (d, $^4J_{CF}$= 2.9 Hz, C-1'), 137.5 (d, $^4J_{CF}$= 2.9 Hz, C-3c), 137.6 (Ar, C_6H_5), 147.6 (d, $^3J_{CF}$= 8.1 Hz, C-7a), 162.0 (d, $^1J_{CF}$= 245.7 Hz), 162.1 (d, $^1J_{CF}$= 244.3 Hz), (C-4', C-6), 167.4 (C=O). GC-MS (EI, 70eV): *m/z* = 415 (19), [M^+], 324 (74), 91 (12). IR (ATR): ν = 1636 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{24}F_2NO[M+H]^+$, 416.1826; found: 416.1828.

(3a*SR*,3b*RS*,7b*RS*,7c*SR*)-3,7b-dimethyl-3b-phenyl-1,3,3a,3b,7b,7c-hexahydro-3-azacyclopro-pa[jk]fluoren-2-one (**15**): Yield 96% (0.222g, reaction time: 2h). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 1 : 3) gave white solid, m.p. 172-174 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.53 (s, 3 H, 7b-CH_3), 2.40 (d, 1 H, *J*=8.3 Hz, CH-7c), 2.52 (d, 1 H, *J*=15.5 Hz, CHH-1), 2.75 (s, 3 H, NCH_3), 2.79 (d, *J*=15.5 Hz, 1 H, CHH-1), 3.39 (d, *J*=8.3 Hz, 1 H, CH-3a), 6.95 (d, *J*=7.5 Hz, 1 H, ArH), 7.07-7.14 (m, 2 H, ArH), 7.17-7.22 (m, 1 H, ArH), 7.30-7.35 (m, 1 H, ArH), 7.37-7.45 (m, 4 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 26.9 (7b-Me), 32.5 (NCH_3), 39.0 (CH-7c), 43.7 (CH_2-1), 45.6, 47.1 (C-7b, C-3b), 47.3 (CH-3a), 122.1, 124.2, 127.4, 127.4, 128.8, 129.8 (ArH), 138.6, 141.5, 148.3 (Ar), 170.6 (C=O). GC-MS (EI, 70eV): *m/z* = 289 (41) [M^+], 274 (100). IR (ATR): ν = 1652 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{20}NO[M+H]^+$: 290.1545; found: 290.1554.

Synthesis of compounds 16, 17

Lawesson's reagent (0.2632g, 0.65mmol) was added to the solution of compound **7a** (0.2356g, 1.18mmol) in dry toluene (15mL). The resulting mixture was stirred for 1h at 80°C and then concentrated to 1/3 volume under reduced pressure and in this form was applied to a column chromatography on silica gel using a mixture of *n*-hexane and ethyl acetate in a ratio of 8:1. Subsequently, it was additionally purified by column chromatography on silica gel using chloroform to afford compound **16** in 98% yield (0.2498g, 1.16mmol) as white solid. Compound **16** (0.1057g, 0.49mmol) was dissolved in acetone (3mL), then MeI (0.04mL, 0.0839g, 0.59mmol) was added and resulting mixture was stirred for 24h at rt and the solvent was evaporated. The resulting white solid, without further purification, was dissolved in dry ethanol (3mL) then ammonium acetate (0.1892g; 2.45 mmol) was added and refluxed for 5h and the solvent was evaporated. Compound **17** was crystallized from ethyl acetate to afford a white solid in 92% (0.1472g, 0.45mmol).

(3a*SR*,7b*RS*,7c*SR*)-3-Methyl-1,3,3a,3b,7b,7c-hexahydro-3-azacyclopro-pa[jk]fluoren-2-thione (**16**): Yield 98% (0.250g). The crude product purified by column chromatography (SiO_2, *n*-hexane : ethyl acetate, 8 : 1, and SiO_2, $CHCl_3$) gave white solid, m.p. 146-149 °C (petroleum ether : ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 2.67 (td, *J*=7.7, 6.2 Hz, 1 H, CH-7c), 2.76 (t, *J*=6.2 Hz, 1 H, CH-3b), 3.16 (s, 3 H, NCH_3), 3.16 (dd, *J*=7.7, 6.2 Hz, 1 H, CH-7b), 3.28 (dd, *J*=16.6, 3.3 Hz, 1 H, C<u>H</u>H-1), 3.34 (dd, *J*=16.6, 3.3 Hz, 1 H, CH<u>H</u>-1), 3.72 (dt, *J*=7.7, 3.3 Hz,1 H, CH-3a), 7.08 (d, *J*=7.2 Hz, 1 H, ArH), 7.12 - 7.21 (m, 2 H, ArH), 7.23-7.27 (m, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, 23°C): δ = 26.7 (CH-7c), 32.3 (CH-3b), 39.9 (CH-3a), 40.8 (CH-7b), 44.0 (NCH_3), 46.0 (CH_2-1), 124.0,124.4, 127.2, 127.3 (ArH), 139.0, 144.2 (Ar), 200.4 (C=S). GC-MS (EI, 70eV): *m/z* = 215 (100) [M^+], 214 (56), 200 (10), 182 (29). IR (ATR): ν = 1499 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd. for $C_{13}H_{14}NS[M+H]^+$: 216.0847, found: 216.0845.

(3a*SR*,7b*RS*,7c*SR*)-3-Methyl-1,3,3a,3b,7b,7c-hexahydro-3-aza-cyclopro-pa[jk]fluoren-2-ylideneamine hydroiodide (**17**): Yield 92% (0.147g). White solid, decomposed above 320°C. ^{1}H

NMR (400 MHz, DMSO-d_6, 23°C): δ= 2.70-2.78 (m, 5 H, NCH_3, CH-7c, CHH-1), 2.84 (t, *J*=6.3 Hz, 1 H, CH-3b), 3.23 (dd, *J*=16.3, 3.0 Hz, 1 H, CHH-1), 3.46 (dd, *J*=7.7, 6.4 Hz, 1 H, CH-3a), 3.87 (ddd, *J*=7.7, 3.3, 3.0 Hz, 1 H, CH-7b), 7.14-7.18 (m, 1 H, ArH-7), 7.19-7.24 (m, 2 H, ArH-8,9), 7.33-7.38 (m, 1 H, ArH-10), 8.70 (br s, 2 H, 2 x NH). ^{13}C NMR (100 MHz, DMSO-d_6, 23°C): δ = 25.4 (CH-7c), 31.1 (CH-3b), 32.7 (CH_2-1), 36.3 (NCH_3), 37.3 (CH-7b), 41.9 (CH-3a), 123.6 (CH-7), 124.8, 127.0 (CH-8,9), 127.4, (CH-10), 139.1 (C-10a), 144.3 (C-7a), 165.4 (C-2). IR (ATR): ν = 3222 br., 3087 br., 1655 cm^{-1}. Anal. Calcd for $C_{13}H_{15}IN_2$: C, 47.87; H, 4.64; N, 8.59. Found: C, 47.89; H, 4.53; N, 8.39.

Synthesis of compound 18

To a solution of compound **9o** (0.142g, 0.38mmol) in dry THF (10mL) was added portionwise $LiAlH_4$ (0.043g, 1.12mmol) at 0°C and stirred for 5min, then temperature was raised to 60°C and the resulting suspension was stirred for another 30h (progress of the reaction was tested by GC-MS). After this time the suspension was diluted with diethyl ether (10mL) and cooled to 0°C. Then 1mL of distilled H_2O and 3mL of 2% NaOH were carefully added, the mixture was allowed to reach rt and stirred for an additional 15 minutes. Then 5 grams of $MgSO_4$ was added and stirred for another 15 minutes. The resulting suspension was filtered and extracted with ethyl acetate (3x50mL) and dried over anhydrous $MgSO_4$. The mixture was filtered and solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using a mixture of chloroform:$NH_{3(aq)}$ (100:3 v/v) to give the desired product **18** as orange oil with a yield of 45% (0.062g, 0.17mmol).

(1*RS*, 3a*SR*, 3b*SR*, 7c*RS*, 7b*RS*)-1,3a-Dibenzyl-2-methyl-2,3,3a,3b,7b,7c-hexahydro-1H-2-aza-cyclopropa[jk]fluorene (**18**): Yield 45% (0.062g). The crude product purified by column chromatography (SiO_2, $CHCl_3$: NH_3(aq), 100: 3) gave orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23°C): δ = 1.60 (d, *J*=12.8 Hz, 1 H, 3a-CHH), 1.72 (dd, *J*=7.2, 5.9 Hz, 1 H, CH-7c), 2.24 (s, 3 H,

NMe), 2.45 (d, *J*=15.3 Hz, 1 H, CHH-3), 2.47 (d, *J*=5.9 Hz, 1 H, CH-3b), 2.52-2.58 (m, 2 H, CH-1, 3a-CHH), 2.68 (dd, *J*=13.1, 9.5 Hz, 1 H, 1-CHH), 3.05 (dd, *J*=13.1, 3.3 Hz, 1 H, 1-CHH), 3.33 (d, *J*=15.3 Hz, 1 H, CHH-3), 3.42 (d, *J*=7.2 Hz, 1 H, CH-7b), 6.75 (dt, *J*=7.3, 1.0 Hz, 1 H, ArH-7), 7.02 (td, *J*=7.3, 1.5 Hz, 1 H, ArH-6), 7.07 (tt, *J*=7.3, 1.0 Hz, 1 H, ArH-5), 7.17-7.37 (m, 11 H, 2 x C_6H_5). ^{13}C NMR (100 MHz, $CDCl_3$, 23^{o}C), δ = 24.0 (CH-7c), 30.3 (C-3a), 35.5 (CH-3b), 42.0 (1-CH_2), 42.9 (CH_2-3), 43.2 (CH-7b), 43.9 (NCH_3), 50.1 (3a-CH_2), 66.5 (CH-1), 123.6, 123.7, 125.9, 126.05, 126.10, 126.3, 128.2, 128.3, 129.1, 129.6 (ArH), 139.6, 139.8, 142.9, 149.2 (Ar). GC-MS (EI, 70eV): *m/z* = 274 (100), 91 (23). IR (ATR): ν = 749, 697 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{28}N[M+H]^+$: 366.2222; found: 366.2221.

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ASSOCIATED CONTENT

Supporting Information.

^{1}H NMR, ^{13}C NMR, ^{13}C DEPT NMR spectra of compounds: **1e**, **1h**, **1i**, **12**, **1p**, **19**, **1q**, **2a-2k**, **4f**, **4h**, **4i**, **13**, **3**, **5**, **6o**, **6p**, **6pNH**, **6q**, **7a-7f**, **8**, **15**, **9o-9q**, **16-18.** ^{1}H, ^{1}H NOESY, ^{1}H,^{1}H COSYDQF, ^{13}C,^{1}H COSY and ^{1}H,^{13}C HMBC spectra of compounds: **2e**, **2k**, **5**, **6o**, **13**, **7e**, **9p**, **15**, **18**. Samples of conformational analyses (for compounds **2d**, **2j**), Predicted coupling constants for hypothetical structure **5-*exo-trig*-2d**, kinetic-like study of **8** formation and computational data. Schemes for the syntheses of compounds **1k**, **1m**, **1p**, **19** and **1q**.

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