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Total Synthesis of Olivacine and Ellipticine via a Lactone Ring-Opening and Aromatization Cascade

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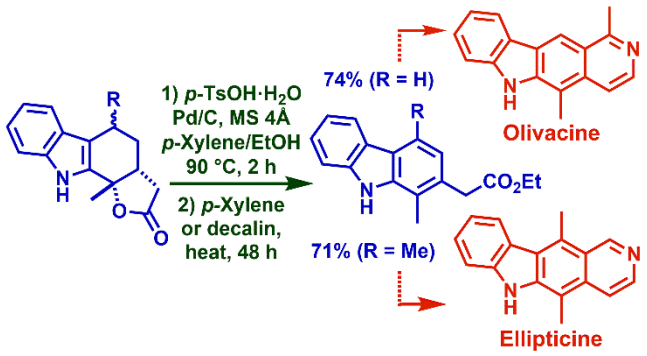
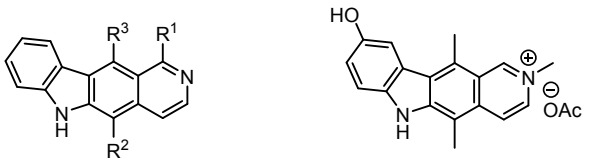


ABSTRACT: Effective preparation of olivacine and ellipticine via late-stage D-ring cyclization is described. Key features of the synthetic routes include trifluoroacetic acid-mediated formation of a lactone that is fused to a tetrahydrocarbazole derivative and its one-pot two-step ring opening and aromatization mediated by *para*-toluenesulfonic acid and palladium on carbon, respectively.

INTRODUCTION

Natural products have historically been the main arsenal of medicines.[1,2] In the same way, carbazole alkaloids continue to play an important role in the drug development.[3,4] They have also become a source of inspiration for the design of potential drugs, so that carbazole skeleton itself is regarded as a privileged building block for identification of new pharmacophores.[5] Olivacine[6] and ellipticine[7] (Figure 1), the most prominent representatives of the pyrido[4,3-*b*]carbazole alkaloids, are still attracting much attention from both medicinal and synthetic standpoints although their isolations date back to the late 1950s.[8] This is because these structural isomers and their derivatives exhibit diverse biological activities, by topoisomerase II inhibition, intercalation with DNA, affecting cell-cycles etc.[9] Consequently, a number of their derivatives have found application in clinical use. For instance, *N*-2-methyl-9-hydroxy-ellipticinium acetate (Figure 1) has been used for the treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors.



Olivacine: $R^1 = R^2 = Me$; $R^3 = H$
Ellipticine: $R^2 = R^3 = Me$; $R^1 = H$

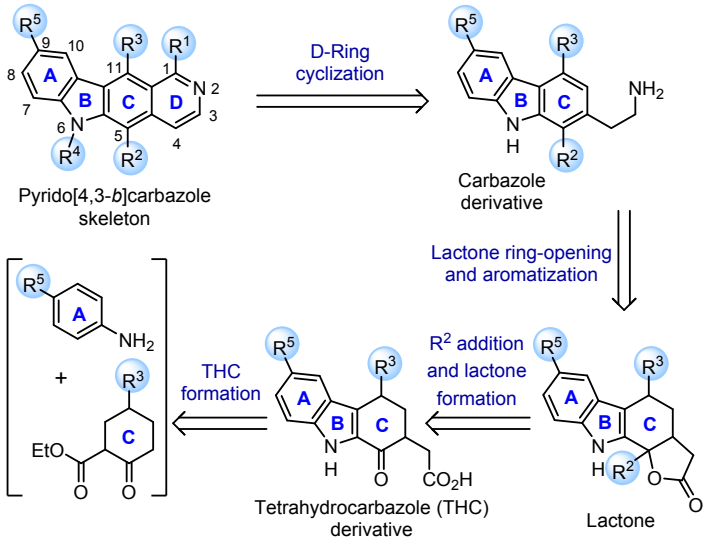
***N*-2-Methyl-9-hydroxy-ellipticinium acetate**

Figure 1. Structures of olivacine and ellipticine as well as a biologically important ellipticine derivative.

Since 1960s, total synthesis of olivacine and ellipticine has been a subject of many publications, as discussed in several review articles.[3,4,8,10–12] The majority of the methods for their syntheses rely on the late-stage D-ring cyclization,[13–22] whereas the late-stage C-ring[23–29] and B-ring cyclization strategies[30] have been rarely reported. In their report in 1962, Cranwell and Saxton presented an effective and concise synthesis of ellipticine through the late-stage cyclization of the D-ring from lower rim.[15] Cranwell–Saxton synthesis of ellipticine was later frequently utilized for the generation of ellipticine derivatives.[8,22] However, the scope of Cranwell–Saxton methodology is limited to the synthesis of ellipticine and its some derivatives, because it depends on the use of hexane-2,5-dione as the starting material. On the other hand, Schmutz and Wittwer[13] as well as Wenkert and Dave[14] introduced the late-stage cyclization of D-ring from upper rim for the synthesis of olivacine, in early 1960s. A closer and deeper evaluation of those works hinted that the late-stage cyclization of D-ring from upper rim can not only be effective, but also allow access to of pyrido[4,3-*b*]carbazole derivatives conveniently. Accordingly, our retrosynthetic analysis for pyrido[4,3-*b*]carbazoles was formulated as depicted in Scheme 1. The key steps were the lactone formation after R^2 addition to the THC compound and a lactone ring-opening and aromatization cascade giving the

desired carbazole derivative. Then, the D-ring cyclization of the carbazol-2-yl-ethaneamine would eventually afford the pyrido[4,3-*b*]carbazole skeleton as described by Schmutz and Wittwer.[13] Although our synthetic proposal at first glance seemed to have drawbacks inherent in any linear synthesis, it could make the synthesis of a specific carbazole derivative possible, by allowing step-by-step installation of the substituents. It should be mentioned that some of us recently used a lactone similar to that shown in Scheme 1 as an intermediate for the synthesis of dasycarpidol and dasycarpidone.[31,32]

Scheme 1. Retrosynthesis of pyrido[4,3-*b*]carbazole alkaloids.

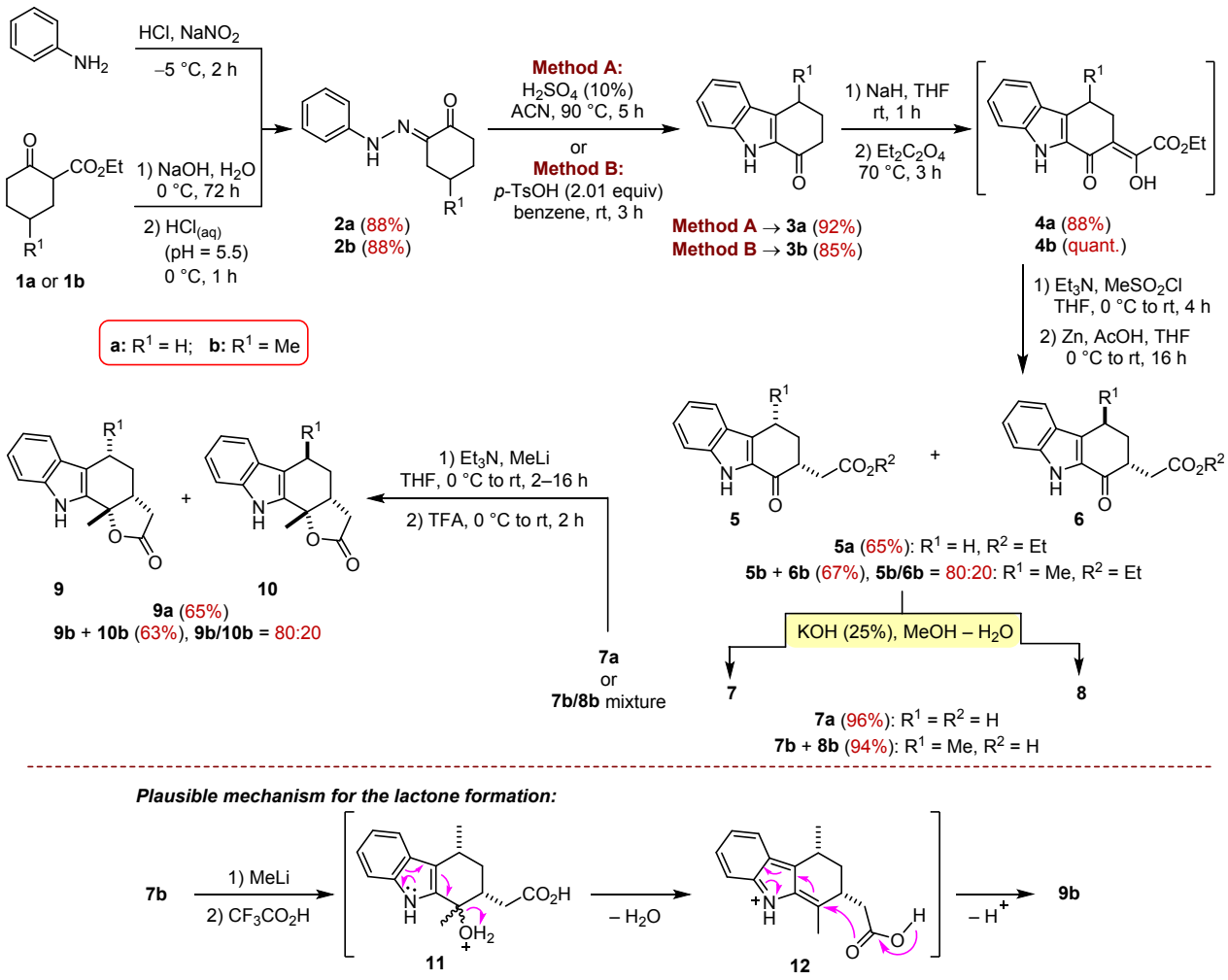


RESULTS AND DISCUSSION

Our route to olivacine and ellipticine started with the Japp-Klingemann condensation of aniline with ethyl 2-oxocyclohexanecarboxylate (**1a**) and ethyl 5-methyl-2-oxocyclohexanecarboxylate (**1b**), respectively (Scheme 2). Both keto-hydrazones **2a** and **2b** were obtained in 88% yield. The Fischer cyclization of **2a** mediated by aqueous sulfuric acid in acetonitrile (ACN) occurred to give tetrahydrocarbazole-1-one (**3a**) with high yield (92%), according to the procedure of Hillier and co-workers.[33] However, cyclization of **2b** under the same reaction conditions gave a mixture of isomers consisting of 4-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3b**) and 3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, based on NMR spectroscopy. Fortunately, Fischer indolization of the keto-hydrazone **2b** could be achieved by *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) in anhydrous benzene, thus furnishing 4-methyl-tetrahydrocarbazole-1-one (**3b**) selectively.[20] The ketones **3a** and **3b** were subjected to the aldol condensation with diethyl oxalate to give enols **4a** and **4b** that were then mesylated with methanesulfonyl chloride and reduced with zinc-acetic acid couple, consecutively, to give the ester **5a** and **5b**/**6b**-esters mixture, respectively. Structural elucidations of the esters **5b** and **6b** were made on the basis of ^{1}H, ^{13}C,

COSY, HSQC spectral data (see Exp. Sect. as well as Table S2). All ^{1}H NMR signals were assigned with the aid of COSY and HSQC. At this point, we examined possible conformations of the structures **5b** and 6**b** which are actually tetrahydrocarbazole derivatives. As is well known, tetrahydrocarbazoles usually assume half-chair conformation, depending on the type of substituents. Strong correlations between the methine proton at δ 3.22–3.17 (m, *H*-2) and the methine proton at δ 3.46–3.41 (m, *H*-4), one of the methylene protons at δ 2.30 (td, J = 12.9, 4.3 Hz, H_a-3), and one of the methylene protons at δ 3.10 (dd, J = 16.4, 5.5 Hz, *H*-10) were determined by NOE-DIFF experiments. Thus, *cis*-configuration for the major diastereomer (**5b**) was deduced from NOE-DIFF spectra. The 80:20 *cis/trans* diastereomeric ratio (**5b/6b**) could be easily calculated from ^{1}H NMR spectra as usual. The carboxylic acid **7a** and **7b**/**8b**-mixture were readily obtained from the corresponding esters through saponification with KOH in aqueous methanol. Methylation and the Brønsted acid-catalyzed cyclization cascade to the lactone **9a** was achieved by methyllithium addition to the carboxylic acid **7a** in the presence of Et_3N and quenching the reaction mixture with trifluoroacetic acid. Note that the use of hydrochloric acid instead of CF_3CO_2H did not afford **9a**. Under the same conditions, the **7b/8b** mixture could also be converted into the corresponding mixture of lactones **9b/10b**. The relative stereochemistry of **9a** (*cis*-configuration of the lactone ring) was explicitly determined by NOE-DIFF spectroscopy. The diastreomers **9b** and **10b** could be individually separated by column chromatography on silica gel. Assignment of correct skeletons of **9b** and **10b** as well as chemical shifts of all protons were in turn made by ^{1}H, ^{13}C, COSY and HSQC NMR spectra. Relative stereochemistries of **9b** and **10b** were also elucidated by NOE-DIFF experiments (see Exp. Sect., as well as Table S3 and Table S4). All in all, *syn*-configuration for **9b** and *anti*-configuration for **10b** were assigned. It is noteworthy that the configuration of the lactone ring was determined to be *cis*. Formation of **9b** and **10b** from **7b** and **8b** mixture is a three-step reaction, i.e. methyllithium addition, acid-catalyzed elimination, and ring-closure. After all these processes, however, the stereochemistry of the starting materials (**7b** and **8b**) are preserved, i.e. the lactone formation proceeds in a stereospecific manner. Approx. 80:20 diasteromeric ratio of **9b/10b** was determined. Accordingly, we might give a mechanistic proposal for the transformation of **7b** to **9b** which sequentially includes (i) the formation of the addition product **11**, (ii) the acid-catalyzed dehydration of **11** to give the 1,6-conjugated iminium cation **12**, and (iii) the ring-closure of **12** to deliver **9b** (at the bottom of Scheme 2).

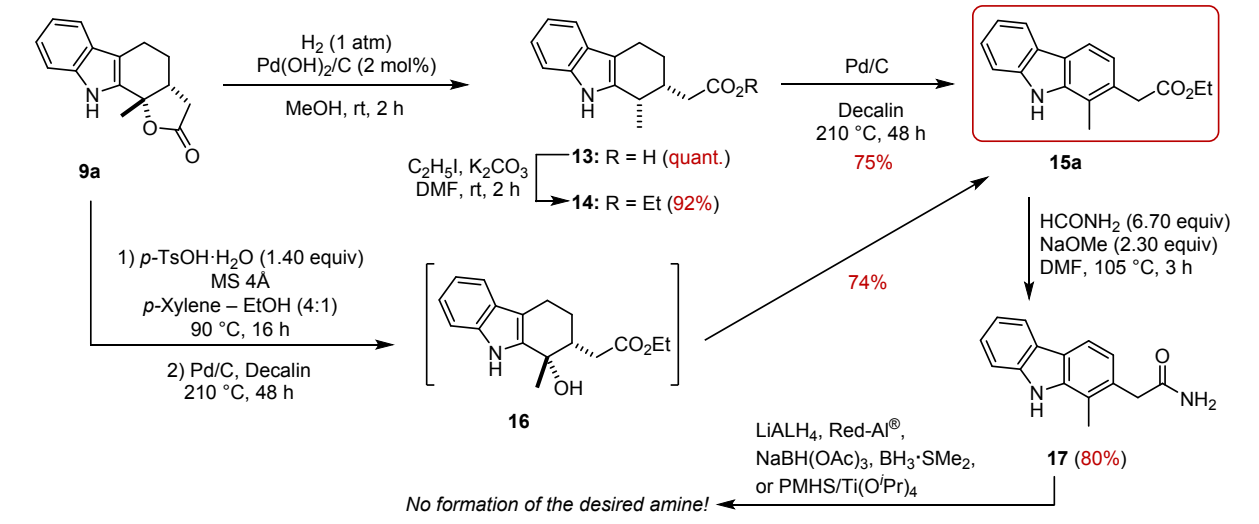
Scheme 2. Synthesis of the lactone intermediates 9a for olivacine and 9b/10b for ellipticine.



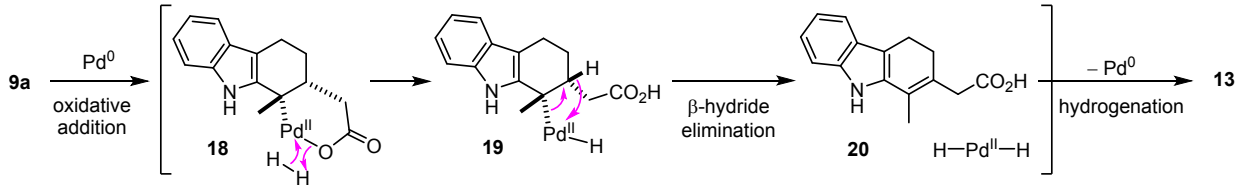
The next obstacle to overcome was the lactone ring-opening (Scheme 3). We first treated the lactone **9a** with dimethylaluminum amide (Me_2AlNH_2), hoping the formation of the ring-opened product (a carboxylic acid amide) as happened to a very similar lactone in our previous work.[31] But, no formation of the expected product was observed in this case. To our delight, catalytic hydrogenation over palladium hydroxide on carbon (Pearlman's catalyst) yielded the carboxylic acid **13** quantitatively. To the best of our knowledge, this is one of the rare examples of the lactone ring-opening through hydrogenolysis.[34–36] The high reactivity of the lactone **9a** in the hydrogenolysis can in turn be attributed to the presence of the benzylic carbon atom attached to the lactone ring. Extensive structural investigation by NMR spectroscopy (^1H, ^{13}C, COSY, HSQC and NOE-DIFF; see Exp. Sec. and Table S1) showed that the carboxylic acid **13** is *cis*-configured. A plausible mechanism for the formation of the *cis*-product (**13**) is also depicted in Scheme 3 (at the bottom): Similar to the established mechanism of the debenzylation reaction through hydrogenolysis,[36] an oxidative addition of palladium(0) to the lactone ring can take place, which lead to the formation of the palladacycle **18**. Coordination of hydrogen and subsequent

protonation might give the organopalladium **19** which must be prone to beta-hydride elimination to form alkene **20**. Then, hydrogenation of **20** delivers the *cis*-product **13** exclusively. Treatment of **13** with ethyl iodide in the presence of K_2CO_3 gave the ester **14** (92%) which was then converted into the carbazole **15a** through aromatization over palladium carbon in boiling decalin. As an alternative to the lactone ring-opening via the hydrogenation, **9a** could be directly converted into **15a** via a one-pot two-step reaction cascade: The lactone **9a** was first treated with EtOH in the presence of an over-stoichiometric amount of *p*-TsOH·H_2O (1.40 equiv) in *p*-xylene to give likely the intermediate **16**, and **16** was then converted to the carbazole-ester **15a** through aromatization on Pd/C. This furnished **15a** from **9a** directly, in 74% yield. Interestingly, the lactone ring-opening with EtOH (**9a** → **16**) took place only in *p*-xylene among the solvents employed which include mixture of xylenes, mesitylene, toluene, and decalin. Thereafter, **15a** was converted into the corresponding carboxamide **17** in 80% yield, by applying the sodium methoxide-mediated amidation procedure of esters with formamide.[37] We aimed at reducing **17** to the corresponding amine, the well-known precursor for olivacine. However, all the hydridic reducing agents ($LiAlH_4$, Red-Al, $NaBH(OAc)_3$, and $BH_3{\cdot}SMe_2$) employed for this purpose were determined to be inadequate because product mixtures were obtained in all cases. When **17** was treated with the polymethylhydrosiloxane–Ti(O*i*Pr)$_4$[38] couple, no conversion was observed.

Scheme 3. Ring-opening of the lactone 9a.

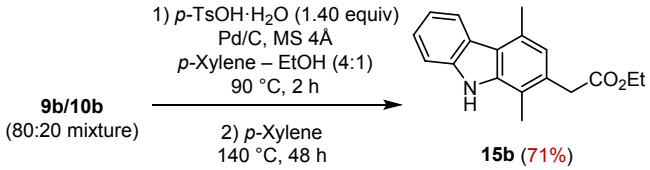


Plausible mechanism for the palladium-catalyzed hydrogenolysis of the lactone 9a:



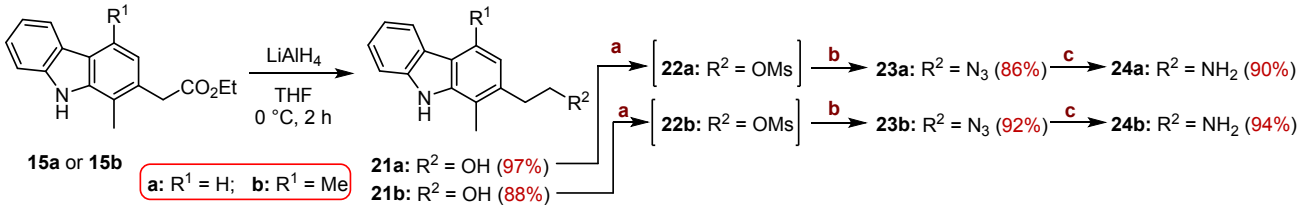
On the other hand, the lactones **9b** and **10b** did not undergo the ring-opening through hydrogenation over $Pd(OH)_2/C$ catalyst. No conversion was detected at all. The presence of an extra methyl group at the C-4 carbon of the tetrahydrocarbazole moiety in **9b** and **10b** would disturb alignment of the C–O bond in question with the indole pi-system, which might preclude the hydrogenolysis of **9b** and **10b**. Fortunately, the alternative procedure via one-pot two-step reaction cascade afforded the desired carbazole ester **15b** in 71% yield (Scheme 4).

Scheme 4. Ring-opening of the lactones 9b and 10b.



Next, reduction of the esters **15a** and **15b** were effected with lithium aluminum hydride, to give the alcohols **21a** and **21b** in high yields (Scheme 5). Alcohols **21a** and **21b** were then converted into the azides **23a** and **23b** by exploiting the conventional techniques, i.e. the mesylation with methanesulfonyl chloride and the azidation with sodium azide through an S_N2 reaction. Reduction of the azides by catalytic hydrogenation over platinum allowed to isolate the primary amines **24a** and **24b** after simple filtration through celite. It should be mentioned that reductions of the azides **23a** and **23b** to **24a** and **24b** with comparable yields were also achieved with lithium aluminum hydride in Et_2O at ambient temperatures. However, the former was practically more favorable.

Scheme 5. Synthesis of olivacine and ellipticine.[a]



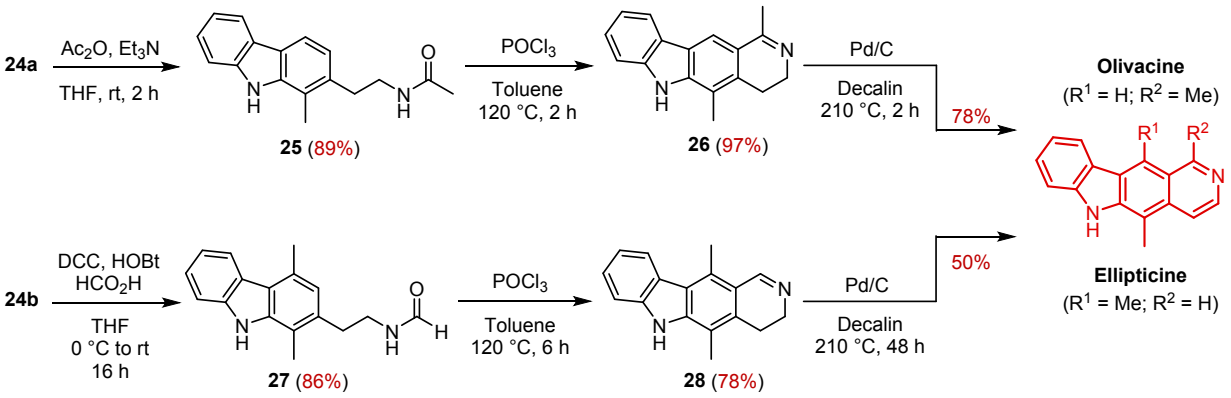
[a]Reagents and conditions: (a) MsCl, Et_3N, THF, rt, 1 h; (b) NaN_3, DMF, 50 °C, 16 h; (c) H_2 (1 atm), PtO_2, MeOH, rt, 6 h.

Having prepared the key intermediates **24a** and **24b** for olivacine and ellipticine, respectively, we focused to investigate the last steps (Scheme 6). **24a** was easily converted into the acetamide **25** in 89% yield, by treating it with acetic anhydride in the presence of Et_3N. The Bischler-Napieralski cyclization of **25** mediated by phosphorus(V) oxychloride delivered dihydroolivacine (**26**) with nearly quantitative yield (97%). Aromatization of **26** was carried out over Pd/C at 210 °C in decalin. Thus, olivacine was obtained in 78% yield. The crude olivacine was purified by reactive extraction, instead of the usual Soxhlet extraction with chloroform: The reaction mixture

of the last step was cooled down to 0 °C and filtered. The solid residue was washed with 20% aqueous acetic acid and the filtrate that contained the acetate salt of olivacine was then made alkaline by the addition of aqueous ammonia (28%). The resulting mixture was extracted with warm chloroform. By such means, NMR-pure olivacine was obtained in a straightforward manner. From the practical point of view it is also noteworthy that all the intermediates for olivacine prepared herein, save the lactone **9a**, did not require any column chromatographic purification; they could be obtained in their NMR-pure forms either by simple precipitation, washing, or recrystallization.

The primary amine **24b** that was already used as an intermediate of ellipticine by Bäckvall and Plobeck[21] was formylated with formic acid mediated by DCC and HOBt, in 86% yield (Scheme 6). The Bischler-Napieralski cyclization of **27** with the aid of phosphorus(V) oxychloride as usual furnished dihydroellipticine (**28**) in 78% yield. For its aromatization, **28** needed to be heated at 210 °C for 48 h, over Pd/C in decalin. The yield of the last step was 50%.

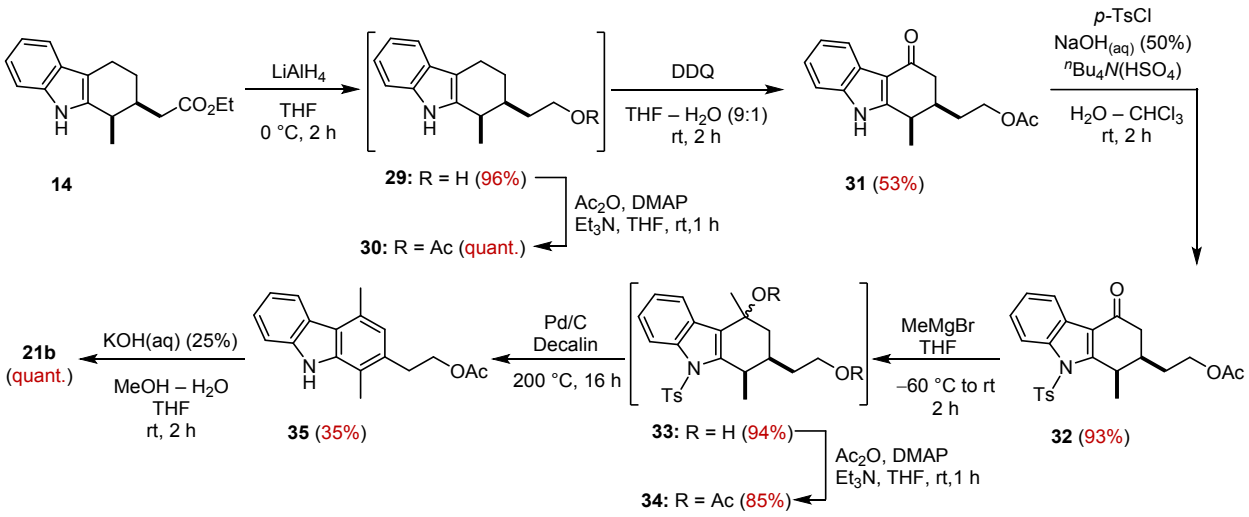
Scheme 6. Synthesis of olivacine and ellipticine.



After the synthesis of olivacine and ellipticine, we turned our attention to identify a common intermediate for their synthesis. The olivacine intermediate **14** seemed to be the most suitable for this purpose (Scheme 7). **14** was reduced with $LiAlH_4$ to the alcohol **29** which was then acylated with acetic anhydride mediated by 4-dimethylaminopyridine (DMAP), thus providing the ester **30** in 96% overall yield after two steps. It should be noted that **29** and **30** are not stable on silica gel. **30** was oxidized to **31** in 53% yield by treatment with 2.00 equivalents of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in aqueous THF. *N*-Tosyl-derivative **32** was obtained from **31** in 93% yield under the phase-transfer conditions. Note that the *N*-unprotected 4-oxotetrahydrocarbazoles generally behave like amides; therefore, addition of main group organometallics to those compounds is not possible, i.e. deprotonation of *N*-hydrogen takes place. However, a tosyl substituent at the

nitrogen atom increases the electrophilicity of the 4-oxo functionality, thus causing the carbonyl group to exhibit a more ketone-like character. So, addition of MeMgBr to **32** proceeded smoothly to yield the dihydroxy compound **33** which was then immediately acylated with acetic anhydride in the presence of Et_3N as the base and DMAP as the catalyst, thereby giving **34** in high yield. Note that treatment of **32** with MeLi resulted in the formation of **33** in lower yields than that of achieved with MeMgBr. Upon heating of **34** at 200 °C over Pd/C in decalin for 16 h, the carbazole **35** was obtained in 35% yield. Surprisingly, aromatization and detosylation took place at the same time. After saponification of the carbazole ester **35** with KOH in aqueous methanol, **21b** that was herein already identified to be a useful precursor for ellipticine was produced in quantitative yield. As a result, a divergent total synthesis of olivacine and ellipticine was accomplished.

Scheme 7. A common intermediate (14) for the synthesis of olivacine and ellipticine.



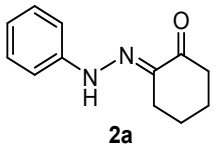
CONCLUSIONS

The procedures disclosed here are high yielding and practical, thus allow effective synthesis of olivacine and ellipticine. For instance, 1.2 g of olivacine and 700 mg of ellipticine were prepared at a one-batch cycle. Additionally, both alkaloids could be prepared from a common intermediate, whereby a divergent synthesis of them was exemplified. *En-route* to them, a number of carbazole compounds having interesting substitution patterns were generated. We believe that our synthetic route enables the synthesis of particular carbazole compounds. Furthermore, we might note that by following the procedures detailed herein we have also successfully synthesized 9-trifluoromethylellipticine, a hitherto unknown derivative of ellipticine, which will be the subject of a prospective publication on medicinal chemistry soon. This can be regarded as a true indication of the utility of our syntheses.

EXPERIMENTAL SECTION

General Information. All air-sensitive reactions were performed under an inert atmosphere of dry nitrogen (N_2) using oven-dried glassware. All reagents and solvents were transferred using gas-tight syringe and cannula techniques under N_2. Reactions were monitored by thin layer chromatography (TLC) on aluminum sheets that were pre-coated with silica gel *SIL G/UV*$_{254}$ from MN GmbH & Co., in which the spots were visualized in UV-light (λ = 254 nm) and/or by staining with phosphomolybdic acid solution in EtOH (10%, w/v). Chromatographic separations were performed using silica gel (230–400 mesh). All melting points were determined in open glass capillary tube and values are uncorrected. Infrared (FT-IR) spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer, $\tilde{\nu}_{max}$ in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a 500 MHz or 600 MHz NMR spectrometer. Chemical shifts δ are reported in parts per million (ppm) relative to the residual protons in the NMR solvent ($CHCl_3$: δ 7.26) and carbon resonance of the solvent ($CDCl_3$: δ 77.00). NMR peak multiplicities were given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained with MeOH on a Bruker micrOTOF-Q.

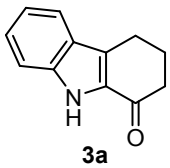
Tetrahydrofuran (THF) was freshly distilled under N_2 from sodium/benzophenone prior to use under nitrogen atmosphere. *N,N*-Dimethylformamide (DMF) was distilled under reduced pressure from calcium hydride (CaH_2). Dichloromethane (DCM) and triethylamine (TEA) were dried by distillation over CaH_2 under N_2. All other chemicals were purchased from the commercial suppliers and used as received. 2-(2-Phenylhydrazono)cyclohexan-1-one (**2a**)[33], 4-methyl-2-(2-phenylhydrazono)cyclohexan-1-one (**2b**)[33], 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3a**)[33], 4-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3b**)[20], ethyl 2-(1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate (**5a**)[14,32], and 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetic acid (**7a**)[14,32] were prepared according to the literature procedures. All chiral compounds are in their racemic forms. The directions of the wedged bonds and hashed wedged bonds in the drawings are used to denote just the relative stereochemistries of the chiral molecules.



2a

*2-(2-Phenylhydrazono)cyclohexan-1-one (**2a**).*[33] Ethyl 2-oxocyclohexanecarboxylate (**1a**; 44.8 g, 0.25 mol, 1.00 equiv) and 600 mL water were added into 1 L two-jacketed reactor that was equipped with a mechanical stirrer

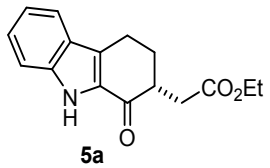
and a thermo-circulator. The mixture was cooled down to 2 °C with the aid of the thermo-circulator and 110 mL of a 2.50 M aqueous NaOH solution were added dropwise into the reactor. After the addition was completed, the mixture was stirred at 2 °C for 2 hours and left in a refrigerator at 4 °C for 72 hours. Then, the mixture was extracted with *tert*-butyl methyl ether (MTBE) and the organic phase was discharged. The pH value of the aqueous phase was adjusted to 5.50 by adding 18% aqueous HCl at 5–10 °C and the mixture was stirred at 5–10 °C for 2 hours. Aniline (23.28 g, 22.78 mL, 0.25 mol, 1.00 equiv), 37% aqueous HCl (62.70 mL, 0.75 mol, 3.00 equiv) and 600 mL water were added into a 1 L two-jacketed reactor that was equipped with a mechanical stirrer and a thermo circulator. A solution of sodium nitrite ($NaNO_2$, 17.25 g, 0.25 mol, 1.00 equiv) in water (165 mL) was added into the reactor dropwise. After the addition was completed, the mixture was stirred 2 hours at −5 °C and so, the formation of the diazonium salt was accomplished. The already prepared carboxylic acid solution of **1a** was added into a 5 L beaker containing crushed ice for maintaing cooling and equipped with a mechanical stirrer. Then, the diazonium salt solution was carefully added dropwise into the 5 L beaker. After the addition was completed, the mixture was stirred 3 hours at 0 °C. The precipitate was filtered and dried in air. The title compound (**2a**) was obtained as an orange solid (44.50 g, 0.22 mol, 88%). Mp: 185–186 °C. TLC: R_f = 0.6 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) =3466 (br, w, N-H), 3245 (s), 3124 (s), 3048 (s), 3008 (s), 2942 (s), 1661 (s, C=O), 1604 (s, C=N). ^1H NMR (600 MHz, $CDCl_3$): δ= 13.79 (s, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 2H), 7.02 – 6.96 (m, 1H), 2.70 (dd, J = 6.5, 2.4 Hz, 2H), 2.54 – 2.46 (m, 2H), 1.84 (dt, J = 6.9, 3.5 Hz, 4H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, $CDCl_3$): δ= 197.2 (C=O), 143.2 (C), 132.4 (C), 129.3 (CH), 122.7 (CH), 114.3 (CH), 39.8 (CH_2), 32.0 (CH_2), 23.5 (CH_2), 22.3 (CH_2). GCMS: t_R = 17.79 min, *m/z* (%): 202 ($[M]^+$, 100), 93 (35). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{15}N_2O$ 203.1179; Found 203.1178.



3a

*2,3,4,9-Tetrahydro-1H-carbazol-1-one (**3a**).*[33] An oven-dried 2 L round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with 2-(2-phenylhydrazono)cyclohexan-1-one (**2a**; 40.45 g, 0.2 mol, 1.00 equiv). The flask was evacuated for 15 minutes, and back-filled with N_2. Then, CH_3CN (500 mL) and aqueous H_2SO_4 (334 mL, 10%) were added into flask consequtively, by means of a dropping funnel. The reaction flask was heated to 90 °C and stirred at this temperature for 5 h. After the conversion was completed (TLC), the mixture was poured into a 5 L beaker containing 2 L cold water. The precipitate was filtered, washed with distilled water, and dried. The title compound

(**3a**) was obtained as a pale pink solid (34.04 g, 0.184 mol, 92%). Mp: 170–171 °C. TLC: R_f = 0.32 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3386 (br, s, N-H), 3284 (s), 2928 (s), 1647 (s, C=O). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.89 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.16 (dd, J = 7.8, 7.2 Hz, 1H), 3.02 (t, J = 6.1 Hz, 2H), 2.73 – 2.69 (m, 2H), 2.31 – 2.25 (m, 2H). ^{13}C{^{1}H} NMR (APT, 150 MHz, $CDCl_3$): δ = 191.7 (C=O), 138.2 (C), 131.2 (C), 129.6 (C), 126.9 (CH), 125.7 (C), 121.2 (CH), 120.2 (CH), 112.8 (CH), 38.2 (CH_2), 25.0 (CH_2), 21.4 (CH_2). GCMS: t_R = 30.67 min, *m/z* (%): 185 ($[M]^+$, 100), 125 (84). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{11}NNaO$ 208.0733; Found 208.0732.

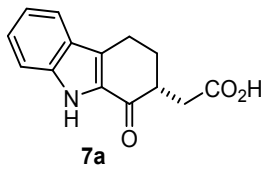


5a

*Ethyl 2-(1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate (**5a**).*[14,32] A 2 L two-jacketed reactor that was equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser was charged with 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3a**; 30.0 g, 0.162 mol, 1.00 equiv). The reactor was evacuated for 15 minutes, back-filled with dry N_2. Then, dry THF (600 mL) was added into the reactor by means of a funnel under positive pressure of dry nitrogen. Upon addition of THF, the starting material was dissolved. Then, NaH (16.2 g of 60% dispersion in mineral oil, 0.402 mol, 2.50 equiv NaH) was added into the solution within 1 hour and the mixture was stirred at room temperature for 1 hour. Diethyl oxalate (35.51 g, 32.90 mL, 0.243 mol, 1.50 equiv) was dropwise added into the reaction mixture at room temperature, by means of a dropping funnel. After the addition of diethyl oxalate was completed, the mixture was heated to 70 °C by means of thermo-circulator and stirred at this temperature for 3 h. The conversion was followed by TLC. The reactor was cooled down to room temperature and the reaction mixture was poured into 2 L beaker containing 250 mL 10% HCl. THF was removed by rotary evaporation under reduced pressure. The precipitate was filtered, washed with distilled water, dried and washed with some methyl *tert*-butyl ether. Thus, the compound **4a** was obtained as a yellow solid (40.67 g, 0.142 mol, 88%). This compound was used directly in the next step without further purification.

An oven-dried 1 L round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with **4a** (57.00 g, 0.2 mol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2 and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Solid particles were dissolved by adding dry THF (600 mL) and triethylamine (TEA; 40.48 g, 55.45 mL, 0.40 mol, 2.00 equiv). The flask was cooled down to 0 °C in an ice-bath and methanesulfonyl chloride ($MeSO_2Cl$; 45.82 g, 30.96 mL, 0.40 mol, 2.00 equiv) was added into the flask dropwise at this temperature. The mixture was then

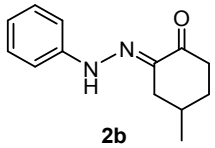
stirred for 16 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. The flask was cooled down to 0 °C and zinc dust (130.8 g, 2.0 mol, 10.00 equiv) was added into flask at this temperature and the resulting mixture was stirred for 1 hour. Then, AcOH (168,14 g, 160.13 mL, 2.80 mol, 14.00 equiv) was dropwise added into the flask at 0 °C. After completion of the reaction (at room temperature for 2h), the mixture was filtered and solid particles were removed. THF was removed by rotary evaporation under reduced pressure. The precipitate was filtered, washed with distilled water, dried and purified by column chromatography to give 35.23 g (0.13 mol, 65%) of the title compound (**5a**) as a white solid. Mp: 143–144 °C. TLC: R_f = 0.34 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3430 (br, w, N-H), 3257 (s), 2977 (s), 2929 (s), 1728 (s, C=O), 1649 (s, C=O). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.63 (s, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.42 – 7.34 (m, 1H), 7.20 – 7.11 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.27 – 2.97 (m, 4H), 2.48 (dd, J = 16.3, 7.4 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.19 – 2.05 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, $CDCl_3$): δ = 191.7 (C=O), 172.6 (C=O), 138.4 (C), 130.7 (C), 129.2 (C), 127.0 (CH), 125.7 (C), 121.2 (CH), 120.4 (CH), 112.7 (CH), 60.6 (CH_2), 44.0 (CH), 34.8 (CH_2), 31.2 (CH_2), 21.1 (CH_2), 14.2 (CH_3). GCMS: t_R = 35.91 min, *m/z* (%): 271 ([M]$^+$, 74), 184 (100). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{17}NNaO_3$ 294.1101; Found 294.1106.



7a

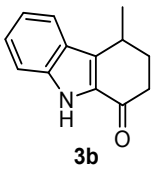
*2-(1-Oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetic acid (**7a**).*[14,32] An oven-dried 500 mL round-bottomed one necked flask that was equipped with a magnetic stirring bar was charged with ethyl 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate (**5a**; 20.3 g, 75.0 mmol, 1.00 equiv). Then, THF (100 mL) and 150 g of 25% KOH (37.5 g KOH + 82.5 g MeOH + 30 g H_2O) solution were added into the flask consecutively. The resulting mixture was stirred at room temperature for 1 h. After the conversion was completed (TLC), the pH value of the mixture was adjusted to 1.5 with 10% HCl solution. The precipitate was filtered, washed with distilled water, and dried. Recrystallization from MTBE afforded 17.50 g (72.0 mmol, 96%) of the title compound **7a** as a white solid. Mp: 237-238 °C. TLC: R_f = 0.58 (silica gel; EtOAc/MeOH, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) =3281 (s, O-H), 2938 (m), 1708 (s, C=O), 1617 (s, C=O). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.12 (s, 1H), 11.51 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.30 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.08 (ddd, J = 7.9, 7.0, 0.9 Hz, 1H), 3.06 (ddd, J = 16.5, 4.8, 3.0 Hz, 1H), 3.02 – 2.87 (m, 2H), 2.79 (dd, J = 16.5, 5.2 Hz, 1H), 2.42 (dd, J = 16.5, 7.0 Hz, 1H), 2.33 – 2.21 (m, 1H), 2.06 (dt, J = 12.5, 7.5 Hz, 1H). ^{13}C{^{1}H} NMR (APT, 125 MHz, DMSO-d_6): δ = 190.9 (C=O), 173.3 (C=O), 138.2 (C), 130.7 (C), 127.6 (C), 126.0

(CH), 125.1 (C), 121.0 (CH), 119.6 (CH), 112.7 (CH), 43.7 (CH), 34.2 (CH_2), 30.5 (CH_2), 20.4 (CH_2). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{14}NO_3$ 244.0968; Found 244.0957.



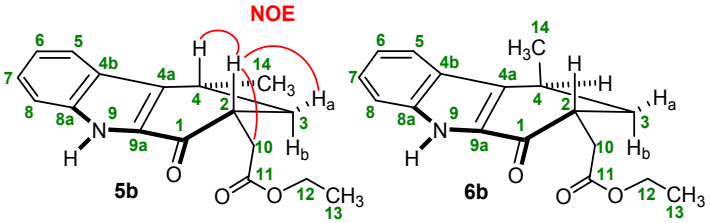
2b

*4-Methyl-2-(2-phenylhydrazono)cyclohexan-1-one (**2b**).*[33] Ethyl 5-methyl-2-oxocyclohexanecarboxylate (**1b**) (55.2 g, 0.3 mol, 1.00 equiv) and 720 mL water were added into a 1 L two-jacketed reactor that was equipped with a mechanical stirrer and a thermo-circulator. The mixture was cooled down to 2 °C with the aid of the thermo-circulator and 132 mL of a 2.50 M aqueous NaOH solution were added dropwise into the reactor. After the addition was completed, the mixture was stirred at 2 °C for 2 hours and was left in a refrigerator at 4 °C for 72 hours. Then, the mixture was extracted with MTBE and the organic phases were discharged. The pH value of the aqueous phase was adjusted to 5.5 by adding 18% aqueous HCl at 5–10 °C and the mixture was stirred at 5–10 °C for 2 hours. Aniline (28.00 g, 27.45 mL, 0.3 mol, 1.00 equiv), 37% aqueous HCl (75.2 mL, 0.9 mol, 3.00 equiv) and 720 mL water were added into a 1 L two-jacketed reactor that was equipped with a mechanical stirrer and thermo circulator. The resulting mixture in the reactor was cooled down to −5 °C and $NaNO_2$ (20.7 g, 0.3 mol, 1.00 equiv) solution in 200 mL water was added into the reactor dropwise. After the addition was completed, the mixture was stirred 2 hours at −5 °C and so, formation of the diazonium salt was accomplished. The already prepared carboxylic acid solution of **1b** was added into a 5 L beaker containing crushed ice for maintaing cooling and equipped with a mechanical stirrer. Then, the diazonium salt solution was carefully added dropwise into the 5 L beaker. After the addition was completed, the mixture was stirred at 0 °C for 3 hours. The precipitate was filtered and dried in air. The title compound (**2b**) was obtained as an yellow solid (57.0 g, 0.26 mol, 88%). Mp: 144–145 °C. TLC: R_f = 0.73 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3436 (br, w, N-H), 3241 (s), 2955 (m), 2928 (m), 1666 (m), 1601 (s, C=N). ^1H NMR (600 MHz, $CDCl_3$): δ = 13.80 (s, 1H), 7.29 (ddd, *J* = 9.0, 5.6, 1.8 Hz, 2H), 7.26 – 7.22 (m, 2H), 6.99 (tt, *J* = 7.3, 1.2 Hz, 1H), 2.79 (ddd, *J* = 16.0, 4.5, 2.4 Hz, 1H), 2.58 (ddd, *J* = 18.8, 5.8, 3.4 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.33 (dd, *J* = 16.0, 11.2 Hz, 1H), 1.97 (dddd, *J* = 9.7, 7.7, 5.5, 2.8 Hz, 1H), 1.89 (dddd, *J* = 12.4, 9.7, 6.2, 3.2 Hz, 1H), 1.51 (dtd, *J* = 13.3, 11.1, 5.8 Hz, 1H), 1.10 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, $CDCl_3$): δ = 197.0 (C=O), 143.2 (C), 131.8 (C), 129.3 (CH), 122.7 (CH), 114.3 (CH), 40.4 (CH_2), 38.8 (CH_2), 30.3 (CH_2), 29.9 (CH), 21.3 (CH_3). GCMS: t_R = 30.44 min, *m/z* (%): 216 ($[M]^+$, 100), 93 (42). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{17}N_2O$ 217.1335; Found 217.1315.



3b

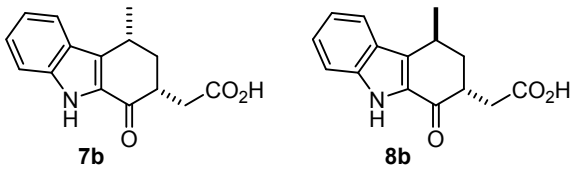
*4-Methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3b**).*[20] An oven-dried 2 L round-bottomed two necked flask that was equipped with a magnetic stirring bar and a Dean-Stark apparatus was charged with *p*-TsOH·H_2O (107.00 g, 0.56 mol, 2.01 equiv), capped with a glass stopper was evacuated for 15 min and back-filled with dry nitrogen. The glass stopper was replaced with a rubber septum, under a positive pressure of nitrogen. Dry benzene (1.2 L) was added into the flask and the mixture was heated to reflux in an oil bath under N_2 and stirred under reflux for 24 hours. After the mixture was cooled down to ambient temperature, 600 mL of 0.463 M 4-methyl-2-(2-phenylhydrazono)cyclohexan-1-one (**2b**) in dry benzene (60.0 g, 0.278 mol, 1.00 equiv of hydrazone) were added into the flask at ambient temperature and the resulting mixture was stirred at ambient temperatures for 3 hours. The conversion was followed by TLC. Then, the resulting mixture was poured into 5 L beaker containing 2 L of aqueous $NaHCO_3$ (7.5%) stirred 15 minutes with a mechanical stirrer. The phases were seperated by means of a separatory funnel and the aqueous phase was shaken with $CHCl_3$ (3 × 250 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The residue was then purified by column chromatography to afford 47.0 g (0.236 mol, 85%) of the title compound (**3b**) as a white solid. Mp: 134–136 °C. TLC: R_f = 0.42 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3467 (br, w, N-H), 3268 (s), 2931 (w), 1635 (s, C=O). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.45 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 7.20 – 7.12 (m, 1H), 3.47 – 3.37 (m, 1H), 2.81 (ddd, *J* = 17.1, 9.5, 4.5 Hz, 1H), 2.61 (ddd, *J* = 17.1, 7.6, 4.6 Hz, 1H), 2.39 (ddd, *J* = 18.3, 9.5, 4.8 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.52 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, $CDCl_3$): δ = 191.4 (C=O), 138.2 (C), 133.7 (C), 130.4 (C), 126.7 (CH), 125.5 (C), 121.9 (CH), 120.3 (CH), 112.8 (CH), 35.4 (CH_2), 32.7 (CH_2), 27.8 (CH), 19.8 (CH_3). GCMS: t_R = 30.97 min, *m/z* (%): 199 ([M]$^+$, 73), 184 (100). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{14}NO$ 200.1070; Found 200.1056.



*cis- and trans-ethyl 2-(4-methyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate (**5b** [cis] and **6b** [trans]).* An oven-dried 1 L two-jacketed reactor that was equipped with a mechanical stirrer, dropping funnel and reflux

condenser was charged with 4-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3b**) (19.9 g, 0.1 mol, 1.00 equiv). The reactor was evacuated for 15 minutes, back-filled with dry N_2. Then, dry THF (400 mL) was added into the reactor by means of a funnel under positive pressure of dry nitrogen. Upon addition of THF, the starting material was dissolved. Then, NaH (10.2 g of 60% dispersion in mineral oil, 0.25 mol, 2.50 equiv) was added into the solution within 1 hour and the mixture was stirred 1 hour at room temperature. Diethyl oxalate (21.92 g, 20.30 mL, 0.15 mol, 1.50 equiv) was dropwise added into the reaction mixture at room temperature, by means of a dropping funnel. After the addition of diethyl oxalate was completed, the reactor was heated to 70 °C by means of a thermo-circulator and was stirred at this temperature for 3 h. The conversion was followed by TLC. The reactor was cooled down to room temperature and the reaction mixture was poured into 2 L beaker containing 200 mL 10% HCl. THF was removed by rotary evaporation under reduced pressure. Then, the organic components were extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. The remaining solid was filtered, washed with *n*-hexane and dried. Thus, the compound **4b** was obtained as a green solid (29.9 g, 0.1 mol, quant.) and it was used directly in the next step without further purification. An oven-dried 1 L round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with **4b** (29.9 g, 0.1 mol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2 and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Solid particles were dissolved by adding dry THF (300 mL) and TEA (30.36 g, 41.58 mL, 0.30 mol, 3.00 equiv). The flask was cooled down to 0 °C in an ice-bath and $MeSO_2Cl$ (34.37 g, 23.22 mL, 0.30 mol, 3.00 equiv) was added into the flask dropwise at this temperature. The mixture was then stirred for 16 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. The flask was cooled down to 0 °C and zinc dust (32.7 g, 0.50 mol, 5.00 equiv) was added into flask at this temperature and it was stirred for 1 hour. Then, AcOH (84.0 g, 80.0 mL, 1.40 mol, 14.00 equiv) was dropwise added into the flask at 0 °C. After completion of the reaction, the mixture was filtered and solid particles were removed. THF was removed by rotary evaporation under reduced pressure. The precipitate was filtered, washed with distilled water, dried and purified by column chromatography to give 19.0 g (0.065 mol, 67%) of a mixture the title compounds (**5b**/**6b** diastereomeric ratio: 80:20) as a white solid. **5b** and **6b** could not be sepatared from each other by column chromatography. Mp: 146–147 °C. TLC: R_f = 0.34 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3452 (br, w, N-H), 3298 (s), 2981 (w), 2959 (w), 1736 (s, C=O), 1638 (s, C=O). ^{1}H NMR of the major diastereomer **5b** (600 MHz, $CDCl_3$): δ = 9.70 (s, 1H, N-*H*), 7.87 (d, *J* = 8.2 Hz, 1H, *H*-7), 7.49 (dd, *J* =11.2, 3.6 Hz, 1H, *H*-8), 7.36 (t, *J* = 7.8 Hz, 1H, *H*-6), 7.13 (t, *J* = 7.5 Hz, 1H, *H*-5), 4.22 (q, *J* = 7.1 Hz, 2H, *H*-12), 3.46 – 3.41 (m, 1H, *H*-4), 3.22 – 3.17 (m, 1H, *H*-2), 3.10 (dd, *J* = 16.4, 5.5 Hz, 1H, *H*-10), 2.44 (dd, *J* = 16.4, 7.2 Hz, 1H, *H*-10), 2.30 (td, *J* = 12.9, 4.3 Hz, 1H, H_a-

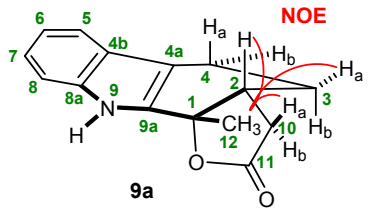
3), 1.84 (m, 1H, H_b-3), 1.61 (d, J = 6.8 Hz, 3H, H-14), 1.30 (t, J = 7.1 Hz, 3H, H-13). $^{13}C\{^1H\}$ NMR of the major diastereomer **5b** (APT, 150 MHz, $CDCl_3$): δ = 192.0 (C, C=O, C-1), 172.8 (C, C=O, C-11), 138.77 (C, C-8a or C-9a), 132.9 (C, C-8a or C-9a), 130.4 (C, C-4b), 126.7 (CH, C-6), 125.7 (C, C-4a), 122.8 (CH, C-7), 120.4 (CH, C-5), 113.1 (CH, C-8), 60.76 (CH_2, C-12), 43.7 (CH, C-2), 41.0 (CH_2, C-3), 34.8 (CH_2, C-10), 30.1 (CH, C-4), 20.9 (CH_3, C-14), 14.4 (CH_3, C-13). ^1H NMR of the minor diastereomer **6b** (600 MHz, $CDCl_3$): δ = 9.70 (s, 1H, N-H), 7.67 (d, J = 8.2 Hz, 1H, H-7), 7.48 (m, 1H, H-8), 7.39 (t, J = 7.8 Hz, 1H, H-6), 7.15 (t, J = 7.5 Hz, 1H, H-5), 4.22 (q, J = 7.1 Hz, 2H, H-12), 3.51 – 3.46 (m, 1H, H-2), 3.46 – 3.41 (m, 1H, H-4), 3.06 (dd, J = 16.4, 5.6 Hz, 1H, H-10), 2.44 (dd, J = 16.4, 7.2 Hz, 1H, H-10), 2.35 (td, J = 13.0, 5.3 Hz, 1H, H_a-3 of H_b-3), 2.12 (ddd, J = 13.2, 4.3, 2.4 Hz, 1H, H_a-3 of H_b-3), 1.50 (d, J = 7.2 Hz, 3H, H-14), 1.30 (t, J = 7.1 Hz, 3H, H-13). $^{13}C\{^1H\}$ NMR of the minor diastereomer **6b** (APT, 150 MHz, $CDCl_3$): δ = 191.7 (C, C=O, C-1), 172.7 (C, C=O, C-11), 138.72 (C, C-8a or C-9a), 133.9 (C, C-8a or C-9a), 129.7 (C, C-4b), 127.1 (CH, C-6), 125.4 (C, C-4a), 121.4 (CH, C-7), 120.5 (CH, C-5), 113.0 (CH, C-8), 60.75 (CH_2, C-12), 39.5 (CH, C-2), 38.2 (CH_2, C-3), 35.0 (CH_2, C-10), 26.4 (CH, C-4), 19.5 (CH_3, C-14), 14.4 (CH_3, C-13). GCMS (**6b**): t_R = 35.26 min, *m/z* (%): 285 ($[M]^+$, 48), 198 (100). GCMS (**5b**): t_R = 35.67 min, *m/z* (%): 285 ($[M]^+$, 100), 196 (88). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_3$ 286.1443; Found 286.1428.



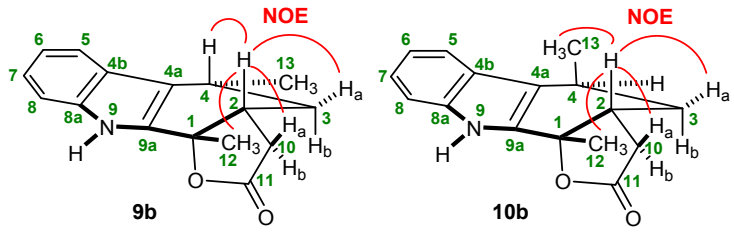
7b **8b**

*Diastereomeric mixture of 2-(4-methyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetic acid (**7b** and **8b**).* An oven-dried 500 mL round-bottomed one necked flask that was equipped with a magnetic stirring bar was charged with diastereomeric mixture of ethyl 2-(4-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate (**5b/6b**) (17.5 g, 61.4 mmol, 1.00 equiv). Then, THF (100 mL) and 150 g of 25% KOH (37.5 g KOH + 82.5 g MeOH + 30 g H_2O) solution were added into the flask respectively and the resulting mixture was stirred at rt for 1 h. The conversion was followed by TLC. After the conversion was completed, the pH value of the mixture was adjusted to 1.5 with 10% HCl solution. The precipitate was filtered, washed with distilled water, dried and afforded 14.85 g (57.72 mmol, 94%) of the title compound (diastereomeric mixture of **7b/8b**, 80:20) as a white solid. Mp: 225–226 °C. TLC: R_f = 0.58 (silica gel; EtOAc/MeOH, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) =3307 (br, s, O-H), 2909 (m), 1708 (s, C=O), 1642 (s, C=O). ^1H NMR (600 MHz, DMSO-d_6): 20% minor isomer, 80% major ısomer. $^{13}C\{^1H\}$ NMR (Minor Isomer, APT, 150 MHz, DMSO-d_6): δ = 190.8 (C=O), 173.4 (C=O), 138.3 (C), 131.9 (C), 129.6 (C), 126.0 (CH), 124.7 (C), 121.1 (CH), 119.7 (CH), 112.9 (CH), 39.0 (CH), 37.2 (CH_2), 34.2 (CH_2), 25.5 (CH_3), 19.5 (CH_3). $^{13}C\{^1H\}$ NMR (Major Isomer, APT, 150 MHz, DMSO-d_6): δ = 191.2 (C=O), 173.4 (C=O), 138.4 (C), 130.9 (C), 130.4 (C), 125.7 (CH), 125.0 (C), 122.4

(CH), 119.6 (CH), 113.0 (CH), 43.2 (CH), 40.2 (CH_2), 34.0 (CH_2), 29.3 (CH_3), 20.7 (CH_3). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{16}NO_3$ 258.1130; Found 258.1155.

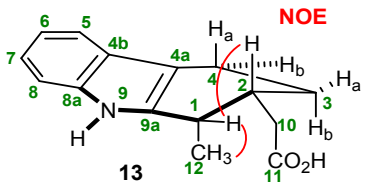


*10b-Methyl-3,3a,4,5,10,10b-hexahydro-2H-furo[2,3-a]carbazol-2-one (**9a**).* An oven-dried 250 mL two-jacketed reactor that was equipped with a magnetic stirrer and dropping funnel was charged with 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetic acid (**7a**) (5.28 g, 21.67 mmol, 1.00 equiv). The reactor was evacuated for 15 minutes, back-filled with dry N_2. Then, dry THF (90 mL) and TEA (2.19 g, 3.00 mL, 21.67 mmol, 1.00 equiv) were added into reactor respectively by means of a gas-tight syringe. Solid particles were dissolved upon addition of THF and TEA. The reaction mixture was cooled down to 0 °C by means of a thermo circulator and 20.97 mL of 3.10 M methyllithium solution in diethoxymethane (65.0 mmol, 3.30 equiv of MeLi) were dropwise added into the mixture. After the addition of MeLi was completed, the mixture was stirred at 0 ˚C for 2 hours. The conversion was followed by TLC. After the conversion was completed, 11 mL of CF_3COOH were dropwise added into the reaction mixture via gas-tight syringe and it was stirred for 2 h while the temperature was allowed to rise to room temperature. After the conversion was completed, the mixture poured into 500 mL beaker containing 250 mL 10% aqueous K_2CO_3. THF was removed by rotary evaporation under reduced pressure. The precipitate was filtered, washed with distilled water, dried and recrystallization from methanol afforded 3.40 g (14.1 mmol, 65%) of the title compound (**9a**) as a white solid. Mp: 199–201 °C. TLC: R_f = 0.2 (silica gel; hexanes/EtOAc 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3319 (br, s, N-H), 2921 (s), 2892 (s), 2848 (s), 1756 (s, C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.21 (s, 1H, N*H*), 7.47 (d, *J* = 7.8 Hz, 1H, *H*-7), 7.34 (d, *J* = 8.1 Hz, 1H, *H*-8), 7.15 – 7.07 (m, 1H, *H*-6), 6.99 (t, *J* = 7.4 Hz, 1H, *H*-5), 2.82 (dd, *J* = 17.5, 8.4 Hz, 1H, H_a-10), 2.77 (ddd, *J* = 15.8, 8.0, 5.1 Hz, 1H, H_a-4), 2.70 (qd, *J* = 7.6, 4.0 Hz, 1H, *H*-2), 2.65 (dt, *J* = 15.9, 5.5 Hz, 1H, H_b-4), 2.42 (dd, *J* = 20.6, 10.3 H, 1H, H_b-10), 1.97 (m, 1H, H_a-3), 1.82 – 1.72 (m, 1H, H_b-3), 1.72 (s, 3H, *H*-12). ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6): δ = 175.7 (C, *C*=O), 136.6 (C, *C*-8a or *C*-9a), 133.0 (C, *C*-8a or *C*-9a), 125.6 (C, *C*-4), 122.1 (CH, *C*-6), 118.9 (CH, *C*-7), 118.6 (CH, *C*-5), 111.4 (CH, *C*-8), 110.5 (C, *C*-4a), 81.6 (C, *C*-1), 40.7 (CH, *C*-2), 32.9 (CH_2, *C*-10), 25.4 (CH_3, *C*-12), 24.4 (CH_2, *C*-3), 17.0 (CH_2, *C*-4). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1181; Found 242.1168.



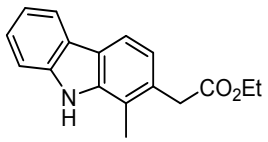
*syn- and anti-5,10b-dimethyl-3,3a,4,5,10,10b-hexahydro-2H-furo[2,3-a]carbazol-2-one (**9b** [syn] and **10b** [anti]).* An oven-dried 250 mL two-jacketed reactor that was equipped with a magnetic stirrer and dropping funnel was charged with diastereomeric mixture of 2-(4-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetic acid (**7b/8b**) (5.14 g, 20.0 mmol, 1.00 equiv). The reactor was evacuated for 15 minutes, back-filled with dry N_2. Then dry THF (80 mL) and TEA (2.02 g, 2.77 mL, 20.0 mmol, 1.00 equiv) were consecutively added into the reactor by means of a gas-tight syringe. Solid particles were dissolved upon addition of THF and TEA. The homogenous mixture was cooled down to 0 ˚C with a thermo circulator and 21.30 mL of 3.10 M methyllithium solution in diethoxymethane (66.0 mmol, 3.30 equiv of MeLi) were dropwise added into the mixture by means of a dropping funnel. After the addition of MeLi was completed, the mixture was stirred at 0 ˚C for 16 hours. After the conversion was completed, 11 mL of CF_3COOH were dropwise added into the reaction mixture via gas-tight syringe and it was stirred for 2 h while the temperature was allowed to rise to room temperature. After the conversion was completed, the mixture poured into 500 mL beaker containing 250 mL 10% aqueous K_2CO_3. THF was removed by rotary evaporation under reduced pressure. The aqueous residue was extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Then, the residue was purified by column chromatography, which afforded 2.5 g (10.0 mmol, 50%) of **9b** and 0.7 g (2.75 mmol, 13%) of **10b**. **Compound 9b:** White solid, mp: 225–227 °C. TLC: R_f = 0.49 (silica gel; hexanes/EtOAc, 7:3). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3350 (br, s, N-H), 2972 (m), 2931 (m), 1745 (s, C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.28 (s, 1H, N-*H*), 7.67 (d, *J* = 8.0 Hz, 1H, *H*-7), 7.36 (t, *J* = 8.1 Hz, 1H, *H*-8), 7.11 (t, *J* = 7.3 Hz, 1H, *H*-6), 6.97 (t, *J* = 7.3 Hz, 1H, *H*-5), 3.23 (dd, *J* = 17.6, 7.8 Hz, 1H, H_a-10), 2.99 –2.95 (m, 1H, *H*-4), 2.56 –2.50 (m, 1H, *H*-2), 2.25 (d, *J* = 17.5 Hz, 1H, H_b-10), 1.92 (td, *J* = 13.3, 4.4 Hz, H_a-3), 1.69 (s, 3H, *H*-12), 1.43 (d, *J* = 6.8 Hz, 3H, *H*-13), 1.22 – 1.16 (m, 1H, H_b-3). ^{13}C{^{1}H} NMR (APT, 150 MHz, DMSO-d_6): δ = 175.8 (C, C=O, *C*-11), 136.9 (C, *C*-8a or *C*-9a), 132.2 (C, *C*-8a or *C*-9a), 125.2 (C, *C*-4b), 121.8 (CH, *C*-6), 120.6 (CH, *C*-7), 118.6 (CH, *C*-5), 116.3 (C, *C*-4a), 111.6 (CH, *C*-8), 80.5 (C, *C*-1), 40.0 (CH, *C*-2), 37.5 (CH_2, *C*-3), 35.4 (CH_2, *C*-10), 27.4 (CH, *C*-4), 25.1 (CH_3, *C*-12), 20.7 (CH_3, *C*-13). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}NO_2$ 256.1338; Found 256.1326. **Compound 10b:** White solid, mp: 200–202 °C. TLC: R_f = 0.58 (silica gel; hexanes/EtOAc, 7:3). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3314 (br, s, N-H), 2978 (w), 2959 (w), 2916 (m), 1752 (s, C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.22 (s, 1H, N-*H*), 7.57 (d, *J* = 7.9 Hz, 1H, *H*-7), 7.34 (d, *J* = 8.1 Hz, 1H, *H*-8), 7.11 (t, *J* = 7.4 Hz, 1H, *H*-6), 6.99 (t, *J* = 7.5 Hz, 1H, *H*-5), 3.17 – 3.14 (m, 1H, *H*-4),

2.91 (dd, *J* = 17.6, 8.3 Hz, 1H, H_a-10), 2.75 (m, 1H, *H*-2), 2.36 (dd, *J* = 17.6, 6.4 Hz, 1H, H_b-10), 1.85 – 1.81 (m, 1H, H_b-3), 1.76 (s, 3H, *H*-12), 1.71 – 1.67 ((m, 1H, H_a-3), 1.31 (d, *J* = 6.9 Hz, 3H, *H*-13). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, DMSO-d_6): δ = 175.8 (C=O), 136.8 (C, *C*-8a or *C*-9a), 132.3 (C, *C*-8a or *C*-9a), 125.2 (C, *C*-4b), 121.9 (CH, *C*-6), 119.6 (CH, *C*-7), 118.6, CH, *C*-5), 115.4 (C, *C*-4a), 111.5 (CH, *C*-8), 81.2 (C, *C*-1), 38.5 (CH, *C*-2), 33.6 (CH_2, *H*-10), 33.4 (CH_2, *C*-3), 25.3 (CH_3, *C*-12), 24.1 (CH, *C*-4), 20.6 (CH_3, *C*-13). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}NO_2$ 256.1338; Found 256.1326.



13

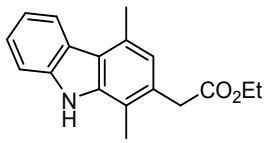
*cis-2-(-1-Methyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetic acid (**13**).* An oven-dried 500 mL round-bottomed three necked flask that was equipped with a magnetic stirring bar, a punch balloon containing hydrogen gas, and a vacuum adaptor was charged with (3a,10b)-10b-methyl-3,3a,4,5,10,10b-hexahydro-2*H*-furo[2,3-a]carbazol-2-one (**9a**) (2.41 g, 10.0 mmol, 1.00 equiv), 400 mg $Pd(OH)_2/C$ and capped with a glass stopper. The flask was evacuated for 15 minutes, back-filled with dry N_2, then the flask was evacuated for 15 minutes again and back-filled with H_2. The glass stopper was replaced with a rubber septum under positive pressure of dry hydrogen. Anhydrous methanol (150 mL) was added by means of a gas-tight syringe and the resulting heterogenous dark mixture was vigorously stirred at ambient temperatures for 2 hours, under hydrogen aymosphere (ca. 1 atm). The conversion was followed by TLC. After the conversion was completed, the mixture was filtered through a short plug of celite. After metanol was removed by rotary evaporation under reduced pressure, the title compound (**13**) (2.43 g, 10.0 mmol, quant.) was obtained as a white solid. Note that this compound is extremely instable. It decomposes not only in solution in a couple of days, but also in its solid state within a month. Mp: 167–168 °C. TLC: R_f = 0.28 (silica gel; hexanes/EtOAc 3:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3400 (br, w, N-H), 2965 (s), 2929 (s), 1555 (s, C=O). ^1H NMR (600 MHz, DMSO-d_6): δ = 10.70 (s, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.95 (dd, *J* = 11.2, 3.9 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 3.04 (qd, *J* = 12.4, 6.3 Hz, 1H, *H*-1), 2.69 – 2.60 (m, 1H, *H*-4), 2.57 – 2.51 (m, 1H, *H*-4), 2.34 (d, *J* = 3.7 Hz, 1H, *H*-2), 2.11 (dd, *J* = 14.3, 7.1 Hz, 1H, *H*-10), 2.01 (dd, *J* = 14.3, 7.8 Hz, 1H, *H*-10), 1.75 – 1.68 (m, 1H, *H*-3), 1.59 (dd, *J* = 10.9, 4.3 Hz, 1H, *H*-3), 1.11 (d, *J* = 7.0 Hz, 3H, *H*-12). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, DMSO-d_6): δ = 176.7 (C=O), 140.6 (C, C_{aryl}), 135.9 (C, C_{aryl}), 127.0 (C, C_{aryl}), 119.8 (CH, C_{aryl}), 117.7 (CH, C_{aryl}), 117.2 (CH, C_{aryl}), 110.6 (CH, C_{aryl}), 106.9 (C, C_{aryl}), 41.0 (CH_2, *C*-10), 35.7 (CH, *C*-2), 30.7 (CH, *C*-1), 24.8 (CH_2, *C*-3), 20.6 (CH_2, *C*-4), 15.6 (CH_3, *C*-12). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_2$ 244.1338; Found 244.1326.



15a

*Ethyl 2-(1-methyl-9H-carbazol-2-yl)acetate (**15a**) from **14**.* An oven-dried 250 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with 2-(-1-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetic acid (**13**) (2.43 g, 10.0 mmol, 1.00 equiv) and K_2CO_3 (2.76 g, 20.0 mmol, 2.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2 and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Anhydrous DMF (50 mL) and ethyl iodide (3.12 g, 1.61 mL, 20.00 mol, 2.00 equiv) were added sequentially by means of gas-tight syringes and the resulting heterogenous mixture was stirred ambient temperature for 2 hours. The conversion was followed by TLC. After the conversion was completed, 50 mL water were added into the flask. The organic components were extracted with Et_2O (3 × 75 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo and the compound **14** was obtained. This compound was used directly in the next step without further purification. An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with 1.0 g Pd/C (containing 5% Pd) and the compound **14**. The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen and decalin (50 mL) was added by means of gas-tight syringes. The resulting mixture was heated to 210 °C in an oil-bath and stirred at this temperature for 48 h. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to the ambient temperatures and 50 mL $CHCl_3$ were added into the flask. The mixture was filtered through a short plug of celite. The filtrate was concentrated by rotary evaporation under reduced pressure. The precipitate was filtered, washed with hexanes, and dried under vacuum. Thus, the title compound (**15a**) (1.87 g, 7.0 mmol, 70%) was obtained as a white solid. Mp: 143–145 °C. TLC: R_f = 0.32 (silica gel; hexanes/EtOAc 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3346 (br, s, N-H), 2987 (s), 2954 (w), 1708 (s, C=O). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 7.9 Hz, 1H). 7.40 (ddd, J = 9.7, 9.1, 4.3 Hz, 2H), 7.22 (ddd, J = 7.9, 6.7, 1.4 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.83 (s, 2H), 2.48 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, $CDCl_3$): δ = 171.9 (C=O), 139.7 (C), 139.4 (C), 129.8 (C), 125.5 (CH), 123.8 (C), 122.1 (CH), 120.3 (CH), 119.4 (CH), 118.5 (C), 117.7 (CH), 110.6 (CH), 60.8 (CH_2), 39.4 (CH_2), 14.2 (CH_3), 13.4 (CH_3). GCMS: t_R = 35.77 min, *m/z* (%): 267 ([M]$^+$,54), 194 (100). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1338; Found 268.1334.

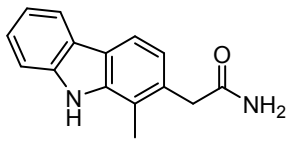
*Ethyl 2-(1-methyl-9H-carbazol-2-yl)acetate (**15a**) from **9a**.* An oven-dried 500 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with (3a,10b)-10b-methyl-3,3a,4,5,10,10b-hexahydro-2*H*-furo[2,3-*a*]carbazol-2-one (**9a**) (2.41 g, 10.0 mmol, 1.00 equiv), *p*-TsOH·H_2O (2.66 g, 14.0 mmol, 1.40 equiv), and 5.0 g of active molecular sieve (4 Å). The flask was evacuated for 15 minutes, back-filled with dry N_2. Absolute ethanol (40 mL) and *p*-xylene (160 mL) were added into the flask by means of a funnel under positive pressure of dry nitrogen. The mixture was heated to 90 °C under N_2 and was stirred at this temperature for 16 h. The conversion was followed by TLC. After the conversion was completed, the flask cooled down to ambient temperature. Solid particles were filtered off. Ethanol and *p*-xylene were removed by rotary evaporation under reduced pressure and the intermediate **16** was obtained. An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, glass stopper was charged with 1.0 g Pd/C (containing 5% Pd) and the intermediate **16**. The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen and decalin (50 mL) was added by means of gas-tight syringes. The flask was heated to 210 °C in an oil-bath and was stirred at this temperature for 48 h. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to the ambient temperatures and 50 mL $CHCl_3$ were added into the flask. The mixture was filtered through a short plug of celite. Chloroform was removed by rotary evaporation under reduced pressure. The precipitate was filtered, dried and purified by column chromatography to afford 1.98 g (7.4 mmol, 74%) of the title compound (**15a**) as a white solid.



15b

*Ethyl 2-(1,4-dimethyl-9H-carbazol-2-yl)acetate (**15b**).* An oven-dried 500 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with diastereomeric mixtures of (3a,10b)-5,10b-dimethyl-3,3a,4,5,10,10b-hexahydro-2*H*-furo[2,3-*a*]carbazol-2-one (**9b/10b**, 80:20) (7.85 g, 30.8 mmol, 1.00 equiv), *p*-TsOH·H_2O (2.66 g, 14.0 mmol, 1.40 equiv), 10.0 g molecular sieves (4 A°) and 6.16 g Pd/C (contain 10% Pd). The flask was evacuated for 15 minutes, back-filled with dry N_2. Absolute ethanol (123 mL) and *p*-xylene (492 mL) were added into the flask by means of a funnel under positive pressure of dry nitrogen. The flask was heated to 90 ˚C and was stirred at this temperature for 2 h. The conversion was followed by TLC. After the conversion was completed, ethanol was removed by distillation under nitrogen atmosphere. Then the flask was heated to 140 ˚C for 48 h. The conversion was followed by TLC. After the

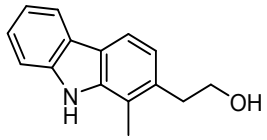
conversion was completed, the flask was cooled down to the ambient temperatures and 50 mL $CHCl_3$ were added into the flask. The mixture was filtered through a short plug of celite. $CHCl_3$ and *p*-xylene were removed by rotary evaporation under reduced pressure. The precipitate was filtered, dried and purified by column chromatography to afford 6.14 g (21.85 mmol, 71%) of the title compound (**15b**) as a white solid. Mp: 134–136 °C. TLC: R_f = 0.38 (silica gel; hexanes/EtOAc, 8:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3380 (br, s, N-H), 2967 (m), 2955 (m), 1709 (s, C=O). ^1H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.9 Hz, 1H), 8.08 (s, 1H), 7.40 (ddd, *J* = 11.1, 8.8, 4.3 Hz, 2H), 7.25 – 7.20 (m, 1H), 6.89 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 2.78 (s, 3H), 2.45 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, $CDCl_3$): δ = 172.1 (C=O), 139.7 (C), 139.4 (C), 130.5 (C), 129.4 (C), 124.8 (CH), 124.4 (C), 123.4 (CH), 122.3 (CH), 120.7 (C), 119.3 (CH), 115.7 (C), 110.4 (CH), 60.8 (CH_2), 39.2 (CH_2), 20.3 (CH_3), 14.2 (CH_3), 13.1 (CH_3). GCMS: t_R = 36.36 min, *m/z* (%): 281 ($[M]^+$, 71), 208 (100). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_2$ 282.1494; Found 282.1475.



17

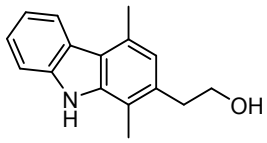
*2-(1-Methyl-9H-carbazol-2-yl)acetamide (**17**).* An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, glass stopper and reflux condenser was charged with ethyl 2-(1-methyl-9*H*-carbazol-2-yl)acetate (**15a**) (1.07 g, 4.0 mmol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. 16 mL dry DMF were added by means of a gas-tight syringe. Upon dissolution of the solid particles, formamide (1.21 g, 1.07 mL, 26.8 mmol, 6.70 equiv) was added into the flask flask by means of a gas-tight syringe. The flask was heated to 105 ˚C in an oil-bath and was stirred at this temperature for 1 hour. Then, 4 mL of 2.31 M NaOMe in methanol (9.24 mmol, 2.31 equiv of NaOMe) were dropwise added into the flask at 105 ˚C, within 15 minutes. The resulting mixture was stirred at this temperature for 3 hours. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to the ambient temperatures and 50 mL water were added. The organic components were extracted with EtOAc (3 × 75 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. The precipitate was washed with Et_2O and dried in vacuo overnight, which afforded 763 mg (3.2 mmol, 80%) of the title compound (**17**) as a white solid. Mp: 267–268 °C. TLC: R_f = 0.25 (silica gel; EtOAc). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3433 (s, N-H), 3365 (s, N-H), 2921 (s), 1631 (s, C=O). ^1H NMR (500 MHz, DMSO-d_6): δ = 11.08 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.13 (dd, *J* = 11.0, 3.8 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 3.60 (s, 2H), 2.51 (s,

3H). $^{13}C\{^1H\}$ NMR (APT, 125 MHz, DMSO-d_6): δ= 172.5 (C=O), 140.0 (C), 139.7 (C), 131.8 (C), 125.0 (CH), 122.9 (C), 121.4 (CH), 120.7 (C), 119.9 (CH), 118.9 (C), 118.3 (CH), 117.0 (CH), 110.9 (CH), 40.1 (CH_2), 13.5 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2O$ 239.1184; Found 239.1172.



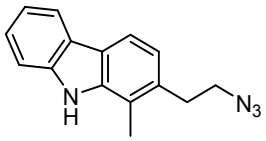
21a

*2-(1-Methyl-9H-carbazol-2-yl)ethan-1-ol (**21a**).* An oven-dried 100 mL Schlenk flask that was equipped with a magnetic stirring bar and a glass stopper was evacuated for 15 minutes, back-filled with dry N_2. The glass stopper opened, $LiAlH_4$ (570 mg, 15.0 mmol, 2.50 equiv) was added into flask and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. 10 mL dry THF were added into flask by means of a gas-tight syringe and the flask was cooled down to 0 ˚C in an ice-bath, 25 mL of 0.24 M ethyl 2-(1-methyl-9*H*-carbazol-2-yl)acetate (**15a**) (1.60 g, 6.0 mmol, 1.00 equiv) in THF were dropwise added into the flask. The resulting mixture was then stirred for 1 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. After the conversion was completed, 20 mL of 3.0 M KOH were dropwise added into the flask at ambient temperatures. Organic components were extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave 1.31 g (5.82 mmol, 97%) of the title compound (**21a**) as a white solid. Mp: 116–117 °C. TLC: R_f = 0.28 (silica gel; hexanes/EtOAc, 1:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3434 (s, N-H), 3305 (br, s, O-H), 2945 (m), 2873 (m), 1928 (s). ^1H NMR (500 MHz, $CDCl_3$): δ= 8.05 (d, *J* = 7.8 Hz, 1H), 8.00 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.42 (ddd, *J* = 10.7, 9.1, 4.5 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 3.90 (t, *J* = 6.8 Hz, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 2.50 (s, 3H). $^{13}C\{^1H\}$ NMR (APT, 125 MHz, $CDCl_3$): δ= 139.69 (C), 139.65 (C), 133.6 (C), 125.5 (CH), 123.9 (C), 121.8 (CH), 121.6 (C), 120.2 (CH), 119.5 (CH), 118.1 (C), 117.7 (CH), 110.6 (CH), 63.4 (CH_2), 36.5 (CH_2), 13.0 (CH_3). GCMS: t_R = 35.07 min, *m/z* (%): 225 ($[M]^+$,34), 194 (100). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}NO$ 226.1232; Found 226.1220.



21b

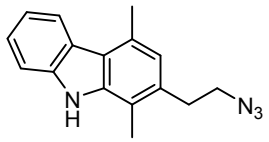
*2-(1,4-Dimethyl-9H-carbazol-2-yl)ethan-1-ol (**21b**).* An oven-dried 250 mL Schlenk flask that was equipped with a magnetic stirring bar and a glass stopper was evacuated for 15 minutes, back-filled with dry N_2. The glass stopper was opened, $LiAlH_4$ (3.80 g, 0.10 mol, 5.00 equiv) was added into the flask and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. 20 mL dry THF was added by means of a gas-tight syringe and the flask cooled down to 0 °C in an ice-bath. 60 mL of 0.33 M ethyl 2-(1,4-dimethyl-9*H*-carbazol-2-yl)acetate (**15b**) (5.62 g, 20.0 mmol, 1.00 equiv) in THF were dropwise added into the flask. The mixture was then stirred for 1 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. After the conversion was completed, 50 mL 3.0 M KOH were dropwise added into the flask at ambient temperatures. Organic components were extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave 4.21 g (17.6 mmol, 88%) of the title compound (**21b**) as a white solid. Mp: 153–155 °C. TLC: R_f = 0.3 (silica gel; hexanes/EtOAc, 3:2). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3532 (s, N-H), 3269 (s, O-H), 2936 (w), 2880 (w). ^1H NMR (600 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 6.87 (s, 1H), 3.90 (t, *J* = 6.8 Hz, 2H), 3.06 (t, *J* = 6.8 Hz, 2H), 2.83 (s, 3H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, $CDCl_3$): δ = 139.6 (C), 139.5 (C), 133.2 (C), 130.5 (C), 124.8 (CH), 124.4 (C), 123.1 (CH), 122.3 (CH), 120.1 (C), 119.3 (CH), 115.3 (C), 110.4 (CH), 63.4 (CH_2), 36.4 (CH_2), 20.3 (CH_3), 12.8 (CH_3). GCMS: t_R = 36.36 min, *m/z* (%): 239 ($[M]^+$, 32), 208 (100). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1373.



23a

*2-(2-Azidoethyl)-1-methyl-9H-carbazole (**23a**).* An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar and the glass stopper was charged with 2-(1-methyl-9*H*-carbazol-2-yl)ethan-1-ol (**21a**) (1.13 g, 5.0 mmol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Upon addition of 50 mL dry THF by means of a gas-tight syringe, the solid particles were dissolved. The flask was cooled down to 0 °C in an ice-bath. TEA (1.01 g, 1.39 mL, 10.0 mmol, 2.00 equiv) and $MeSO_2Cl$ (601 mg, 406.0 µL, 5.25 mmol, 1.05 equiv) were consecutively added into the flask by using gas-tight syringes. The mixture was then stirred for 1 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. After the conversion was completed, 50 mL aqueous saturated $NaHCO_3$ were dropwise added into the flask at ambient temperatures.

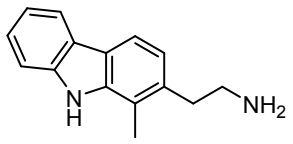
Organic components were extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo and the intermediate **22a** was obtained. An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar and a glass stopper was charged with the intermediate **22a** and NaN_3 (1.63 g, 25.0 mmol, 5.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. 40 mL dry DMF were added into the flask by means of a gas-tight syringe and the resulting heterogenous mixture was stirred at 50 °C in an oil bath for 16 hours. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to the ambient temperatures and 40 mL water were added. Organic components were extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave 1.08 g (4.3 mmol, 86%) of the title compound (**23a**) as a white solid. Mp: 70–71 °C. TLC: R_f = 0.23 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3441 (s, N-H), 2935 (m), 2090 (s, N_3). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.48 – 7.38 (m, 2H), 7.26 (ddd, J = 8.0, 5.0, 1.4 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 3.55 (t, J = 7.6 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H), 2.52 (s, 3H). $^{13}C\{^1H\}$ NMR (APT, 125 MHz, $CDCl_3$): δ = 139.8 (C), 139.6 (C), 133.3 (C), 125.6 (CH), 124.0 (C), 122.0 (C), 121.5 (CH), 120.3 (CH), 119.6 (CH), 117.9 (CH), 117.8 (C), 110.7 (CH), 52.3 (CH_2), 32.8 (CH_2), 12.9 (CH_3).



23b

*2-(2-Azidoethyl)-1,4-dimethyl-9H-carbazole (**23b**).* An oven-dried 500 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar and a glass stopper was charged with 2-(1,4-dimethyl-9*H*-carbazol-2-yl)ethan-1-ol (**21b**) (4.60 g, 19.2 mmol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Upon addition of 190 mL dry THF by means of a gas-tight syringe, the solid particles were dissolved. The flask cooled down to 0 ˚C in an ice-bath. TEA (3.89 g, 5.33 mL, 38.4 mmol, 2.00 equiv) and $MeSO_2Cl$ (2.31 g, 1.56 mL, 20.16 mmol, 1.05 equiv) were consecutively added into the flask by using gas-tight syringes. The mixture was then stirred for 1 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. After the conversion was completed, 50 mL aqueous saturated $NaHCO_3$ were dropwise added into the flask at ambient temperatures. Organic components were extracted with EtOAc (3 × 150 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo and the intermediate **22b** was obtained.

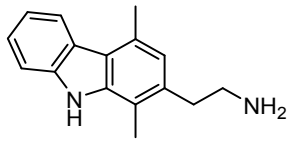
An oven-dried 500 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar and a glass stopper was charged with the intermediate **22b** and NaN_3 (6.24 g, 96.00 mmol, 5.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. 150 mL dry DMF were added into the flask by means of a gas-tight syringe and the resulting heterogenous mixture was stirred 50 ˚C in an oil-bath for 16 hours. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to ambient temperatures and 40 mL water were added into the flask. Organic components were extracted with Et_2O (3 × 200 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave 4.67 g (17.66 mmol, 92%) of the title compound (**23b**) as a white solid. Mp: 74–75 °C. TLC: R_f = 0.32 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3359 (s, N-H), 2921 (m), 2090 (s, N_3). ^1H NMR (600 MHz, $CDCl_3$): δ = 8.16 (d, J = 7.9 Hz, 1H), 7.98 (s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 3.53 (t, J = 7.7 Hz, 2H), 3.09 (t, J = 7.7 Hz, 2H), 2.85 (s, 3H), 2.49 (s, 3H). $^{13}C\{^1H\}$ NMR (APT, 125 MHz, $CDCl_3$): δ = 139.6 (C), 139.4 (C), 132.9 (C), 130.7 (C), 124.9 (CH), 124.4 (C), 122.8 (CH), 122.3 (CH), 120.4 (C), 119.5 (CH), 115.0 (C), 110.4 (CH), 52.2 (CH_2), 32.7 (CH_2), 20.3 (CH_3), 12.7 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}N_4$ 263.1297; Found 263.1321.



24a

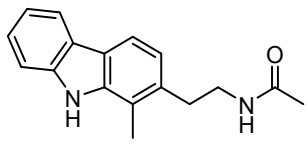
*2-(1-Methyl-9H-carbazol-2-yl)ethan-1-amine (**24a**).*[13,14,21] An oven-dried 100 mL round-bottomed three necked flask that was equipped with a magnetic stirring bar, a punch balloon that was containing hydrogen gas, and a vacuum adaptor was charged with 2-(2-azidoethyl)-1-methyl-9*H*-carbazole (**23a**) (1.50 g, 6.0 mmol, 1.00 equiv), 68 mg PtO_2 (5%) and capped with a glass stopper. The flask was evacuated for 15 minutes, back-filled with dry N_2, then the flask was evacuated for 15 minutes again and back-filled with H_2. The glass stopper was replaced with a rubber septum under positive pressure of hydrogen. Anhydrous methanol (48 mL) was added by means of a gas-tight syringe and the resulting heterogenous mixture was vigorously stirred for 6 hours at ambient temperatures under hydrogen atmosphere (ca. 1 atm). The conversion was followed by TLC. After the conversion was completed, the mixture was carefully filtered through a short plug of celite. Methanol was removed by rotary evaporation under reduced pressure and the remaining solid was dried overnight in vacuo. Thus, the title compound (**24a**) (1.21 g, 5.4 mmol, 90%) was obtained as a white solid. Mp: 168–171 °C. TLC: R_f = 0.6 (silica gel; TEA/MeOH, 1:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3437 (br, w, N-H), 3350 (s, N-H), 2882 (m). ^1H NMR (500 MHz, DMSO-d_6): δ = 10.92 (s),

8.01 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.24 (m, 1H), 7.18 – 7.06 (m, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 2.94 – 2.76 (m, 4H), 2.52 (s, 3H). $^{13}C\{^{1}H\}$ NMR (APT, 125 MHz, DMSO-d_6): δ = 139.9 (C), 139.8 (C), 135.4 (C), 124.8 (CH), 123.0 (C), 120.8 (CH), 120.2 (C), 119.8 (CH), 118.3 (CH), 117.9 (C), 117.1 (CH), 110.9 (CH), 43.4 (CH_2), 37.7 (CH_2), 13.1 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}N_2$ 225.1392; Found 225.1387.



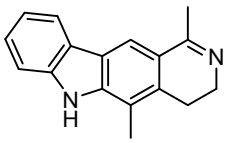
24b

*2-(1,4-Dimethyl-9H-carbazol-2-yl)ethan-1-amine (**24b**).* An oven-dried 250 mL round-bottomed three necked flask that was equipped with a magnetic stirring bar, a punch balloon that was containing hydrogen gas, and a vacuum adaptor was charged with 2-(2-azidoethyl)-1,4-dimethyl-9*H*-carbazole (**23b**) (4.28 g, 16.20 mmol, 1.00 equiv), 184 mg PtO_2 (5%) and capped with a glass stopper. The flask was evacuated for 15 minutes, back-filled with dry N_2, then the flask was evacuated for 15 minutes again and back-filled with H_2. The glass stopper was replaced with a rubber septum under positive pressure of hydrogen. Anhydrous methanol (130 mL) was added by means of a gas-tight syringe and the resulting heterogenous mixture was vigorously stirred at ambient temperatures for 6 hours under hydrogen atmosphere (ca. 1atm). The conversion was followed by TLC. After the conversion was completed, the mixture was carefully filtered through a short plug of celite. Methanol was removed by rotary evaporation under reduced pressure and the remaining solid was dried overnight in vacuo. Thus, the title compound(**24b**) (3.47 g, 14,6 mmol, 90%) was obtained as a white solid. Mp: 195–200 °C (Decomp.). TLC: R_f = 0.6 (silica gel; TEA/MeOH, 1:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3410 (br, w, N-H), 3348 (s, N-H), 3288 (w), 3153 (m), 3086 (m), 2927 (m). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.05 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.77 (s, 1H), 2.78 (td, *J* = 11.2, 6.9 Hz, 4H), 2.72 (s, 3H), 2.47 (s, 3H). $^{13}C\{^{1}H\}$ NMR (APT, 150 MHz, DMSO-d_6): δ = 139.9 (C), 139.8 (C), 135.1 (C), 128.9 (C), 124.2 (CH), 123.5 (C), 122.2 (CH), 121.6 (CH), 118.8 (C), 118.4 (CH), 115.2 (C), 110.7 (CH), 43.5 (CH_2), 37.6 (CH_2), 20.1 (CH_3), 12.9 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2$ 239.1548; Found 239.1538.



25

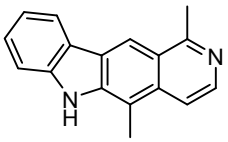
*N-[2-(1-Methyl-9H-carbazol-2-yl)ethyl]acetamide (**25**)*[13,21,26] An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with 2-(1-methyl-9*H*-carbazol-2-yl)ethan-1-amine (**24a**) (1.2 g, 5.3 mmol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2. Upon addition of dry THF (25 mL) by means of a gas-tight syringe, solid particles were dissolved. Then, TEA (1.07 g, 1.47 mL, 10.6 mmol, 2.00 equiv) and Ac_2O (2.16 g, 2.00 mL, 21.2 mmol, 4.00 equiv) were consecutively added into the flask by using gas-tight syringes. The resulting mixture was stirred at ambient temperatures for 1 h. Conversion was followed by TLC. After the conversion was completed, THF was removed by rotary evaporation under reduced pressure. Purification of the residue by flash column chromatography on silica gel gave 1.26 g (4.73 mmol, 89%) of the title compound (**25**) as a white solid. Mp: 159–160 °C. TLC: R_f = 0.2 (silica gel; EtOAc). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3410 (s, N-H), 3254 (s, N-H), 3089 (w), 2939 (w), 1641 (s, C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 5.67 (s, 1H), 3.51 (dd, *J* = 13.2, 7.0 Hz, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 1.94 (s, 3H). ^{13}C{^{1}H} NMR (APT, 125 MHz, $CDCl_3$): δ= 170.3 (C=O), 139.7 (C), 139.7 (C), 134.0 (C), 125.4 (CH), 123.7 (C), 121.5 (C), 121.3 (CH), 120.1 (CH), 119.4 (CH), 118.0 (C), 117.7 (CH), 110.7 (CH), 40.4 (CH_2), 33.1 (CH_2), 23.3 (CH_3), 13.0 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}N_2O$ 267.1497; Found 267.1481.



26

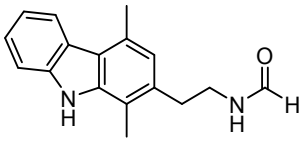
*1,5-Dimethyl-4,6-dihydro-3H-pyrido[4,3-b]carbazole (**26**)*.[13] An oven-dried 250 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with *N*-(2-(1-methyl-9*H*-carbazol-2-yl)ethyl)acetamide (**25**) (1.0 g, 3.75 mmol, 1.00 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2. 187.5 mL dry toluene and $POCl_3$ (9.20 g, 5.60 mL, 60.0 mmol, 16.00 equiv) were added into the flask consecutively by means of a gas-tight syringe under positive pressure of dry nitrogen. The flask was heated to 120 ˚C in an oil-bath and stirred at this temperature for 2 hours. The conversion was followed by TLC. After the conversion was completed, toluene was removed by rotary evaporation under reduced pressure. 400 mL of 0.2 M HCl were added into the crude product, the resulting mixture was stirred for 30 minutes and then filtered off under vacuo. The pH value of the filtrate was adjusted to range of 9.0–9.50 with aqueous ammonia (26%). Organic components were extracted with hot $CHCl_3$ (2 × 250 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. The remaining solid was dried

overnight in vacuo. Thus, the title compound (**26**) (900 mg, 3.64 mmol, 97%) was obtained as a yellow solid. Mp: 298–321 °C (Decomp.). TLC: R_f = 0.35 (silica gel; EtOAc/TEA, 4:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3466 (br, w, N-H), 2917 (m), 1605 (m, C=N). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.27 (s, 1H), 8.22 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 3.55 (t, J = 7.1 Hz, 2H), 2.77 – 2.70 (m, 2H), 2.48 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (APT, 125 MHz, DMSO-d_6): δ = 163.7 (C=N), 140.6 (C), 140.0 (C), 132.7 (C), 125.2 (CH), 123.2 (C), 121.5 (C), 119.9 (CH), 119.7 (C), 118.8 (CH), 116.1 (C), 115.6 (CH), 111.0 (CH), 46.3 (CH_2), 23.4 (CH_3), 23.0 (CH_2), 12.5 (CH_3). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{17}N_2$ 249.1392; Found 249.1388.



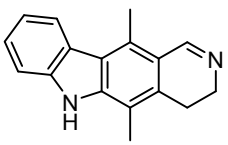
Olivacine

*1,5-Dimethyl-6H-pyrido[4,3-b]carbazole (**Olivacine**).*[13,14,21,26] An oven-dried 250 mL round-bottomed two-necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with 1,5-dimethyl-4,6-dihydro-3*H*-pyrido[4,3-*b*]carbazole (**26**) (0.99 g, 4.0 mmol, 1.00 equiv) and 0.625 g Pd/C (contains 10% Pd). The flask was evacuated for 15 minutes, back-filled with dry N_2. Then, decalin (100 mL) was added into the flask by means of a gas-tight syringe under positive pressure of dry nitrogen. The flask was heated to 210 ˚C in an oil-bath and was stirred at this temperature for 2 hours. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to 0 ˚C with an ice-bath and was stirred 30 minutes at this temperature. The precipitate was filtered off and the solid particles were put into a 500 mL beaker. 250 mL 10% AcOH were added into the beaker and the mixture was stirred 30 minutes at ambient temperatures. The aqueous mixture was filtered off and the pH value of the filtrate was adjusted to 9.0–9.5 by adding aqueous ammonia (26%). Then, organic components were extracted with hot $CHCl_3$ (2 × 250 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. After drying the remaining solid under high vacuum overnight, 770 mg (3.12 mmol, 78%) of the title compound (**olivacine**) were obtained as a pale yellow solid. Mp: 312–329 °C (Decomp.). TLC: R_f = 0.57 (silica gel; EtOAc/MeOH, 4:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3436 (br, w, N-H), 3064 (m), 3015 (m), 2968 (m), 2915 (m), 2848 (m), 2769 (m), 1886 (w), 1634 (m), 1615 (m), 1598 (m, C=N). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.35 (s, 1H), 8.92 (s, 1H), 8.37 (d, J = 7.7 Hz, 1H), 8.25 (d, J = 6.1 Hz, 1H), 7.79 (d, J = 6.1 Hz, 1H), 7.52 (ddd, J = 12.3, 8.9, 4.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 3.04 (s, 3H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, DMSO-d_6): δ = 158.7 (C=N), 142.5 (C), 140.5 (C), 139.5 (CH), 132.4 (C), 127.6 (CH), 124.7 (C), 122.7 (C), 121.8 (C), 121.4 (CH), 119.0 (CH), 114.9 (CH), 114.7 (CH), 111.0 (C), 110.8 (CH), 23.0 (CH_3), 12.4 (CH_3). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{15}N_2$ 247.1235; Found 247.1251.



27

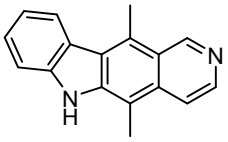
*N-[2-(1,4-Dimethyl-9H-carbazol-2-yl)ethyl]formamide (**27**).*[21] An oven-dried 250 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar and a glass stopper was charged with 2-(1,4-dimethyl-9*H*-carbazol-2-yl)ethan-1-amine (1.43 g, 6.0 mmol, 1.00 equiv) (**24b**). The flask was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Upon addition of dry THF (60 mL) by means of a gas-tight syringe, the solid particles were dissolved. Formic acid (1.1 g, 0.91 mL, 24.0 mmol, 4.00 equiv) was added into the flask by means of a gas-tight syringe. After the flask was cooled down to 0 ˚C in an ice-bath, *N,N'*-dicyclohexylcarbodiimide (**DCC**; 1.24 g, 6.00 mmol, 1.00 equiv) and 1-hydroxybenzotriazole hydrate (**HOBt**; 0.81 g, 6.00 mmol, 1.00 equiv) were added into the mixture under positive nitrogen. The resulting mixture was then stirred for 16 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. After the conversion was completed, The mixture was filtered off, so the side product (*N,N'*-dicyclohexylurea) was removed from the mixture. THF was removed by rotary evaporation under reduced pressure. Purification of the residue by flash column chromatography on silica gel gave 1.37 g (5.16 mmol, 86%) of the title compound (**27**) as a white solid. Mp: 193–194 °C. TLC: R_f = 0.5 (silica gel; EtOAc). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3325 (s, N-H), 2941 (w), 2895 (w), 1630 (s, C=O). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.09 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 6.81 (s, 1H), 3.35 (dd, J = 14.7, 6.4 Hz, 2H), 2.92 – 2.88 (m, 2H), 2.75 (s, 3H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, DMSO-d_6): δ = 161.1 (C=O), 139.9 (C), 139.8 (C), 133.9 (C), 129.1 (C), 124.4 (CH), 123.4 (C), 122.1 (CH), 121.7 (CH), 119.1 (C), 118.4 (CH), 115.5 (C), 110.7 (CH), 38.6 (CH_2), 33.0 (CH_2), 20.1 (CH_3), 12.8 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}N_2O$ 267.1497; Found 267.1481.



28

*5,11-Dimethyl-4,6-dihydro-3H-pyrido[4,3-b]carbazole (**28**).*[21] An oven-dried 500 mL round-bottomed two-necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with *N*-(2-(1,4-dimethyl-9*H*-carbazol-2-yl)ethyl)formamide (**27**) (1.38 g, 5.19 mmol, 1.00 equiv). The flask was evacuated

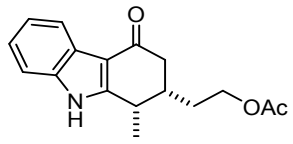
for 15 minutes, back-filled with dry N_2. 250 mL dry toluene and $POCl_3$ (12.72 g, 7.76 mL, 83.0 mmol, 16.00 equiv) were consecutively added into the flask by means of a gas-tight syringe under positive pressure of dry nitrogen. The flask was heated to 120 ˚C in an oil-bath and was stirred at this temperature for 2 hours. The conversion was followed by TLC. After the conversion was completed, toluene was removed by rotary evaporation under reduced pressure. 400 mL of 0.2 M HCl were added into the crude product, the resulting mixture was stirred for 30 minutes and then filtered off under vacuo. The pH value of the filtrate was adjusted to range of 9.0-9.50 with aqueous ammonia (26%). Organic components were extracted with hot $CHCl_3$ (2 × 250 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. The remaining solid was dried overnight in vacuo. Thus, the title compound (**28**) (1.0 g, 4.05 mmol, 78%) was obtained as a yellow solid. Mp: 275–278 °C. **TLC:** R_f = 0.16 (silica gel; EtOAc/TEA, 4:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3434 (br, w, N-H), 3033 (m), 2950 (m), 2860 (m), 1925 (w),1623 (s), 1601 (s, C=N). ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.37 (s, 1H), 8.79 (s, 1H), 8.17 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 3.58 (t, J = 6.5 Hz, 2H), 2.91 (s, 1H), 2.74 (t, J = 6.5 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, DMSO-d_6): δ = 157.7 (C=N), 140.7 (C), 140.1 (C), 132.6 (C), 129.3 (C), 124.8 (CH), 123.7 (C), 122.3 (CH), 119.1 (CH), 119.0 (C), 118.8 (C), 114.0 (C), 111.1 (CH), 46.4 (CH_2), 23.1 (CH_2), 14.5 (CH_3), 12.4 (CH_3). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2$ 249.1392; Found 249.1397.



Ellipticine

*5,11-Dimethyl-6H-pyrido[4,3-b]carbazole (**Ellipticine**).*[21] An oven-dried 250 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper and a reflux condenser was charged with 5,11-dimethyl-4,6-dihydro-3*H*-pyrido[4,3-*b*]carbazole (**28**) (1.40 g, 5.64 mmol, 1.00 equiv) and 1.8 g Pd/C (contains 10% Pd). The flask was evacuated for 15 minutes, back-filled with dry N_2. Then, decalin (140 mL) was added into the flask by means of a gas-tight syringe under positive pressure of dry nitrogen. The flask was heated to 210 ˚C in an oil-bath and was stirred at this temperature for 2 hours. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to 0 °C with an ice-bath and was stirred 30 minutes at this temperature. The precipitate was filtered off and solid particles and decalin were seperated. The solid particles were put into a 500 mL beaker. 250 mL 10% AcOH were added into the beaker and the mixture was stirred 30 minutes at ambient temperatures. The mixture was filtered under vacuum, thus the insoluble particles were removed from the mixture. Then, the pH avlue of the filtrate was adjusted to the range of 9.0–9.50 with aqueous

ammonia (26%). Then organic components were extracted with hot $CHCl_3$ (2 × 250 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. After drying the remaining solid under high vacuum overnight, the title compound (**ellipticine**) (700 mg, 2.82 mmol, 50%) of a pale yellow solid. Mp: 316–317 °C. TLC: R_f = 0.68 (silica gel; EtOAc/MeOH, 3.5:1.5). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3436 (br, w, N-H), 3145 (m), 3089 (m), 2976 (m), 2869 (m), 1599 (s, C=N). ^1H NMR (600 MHz, DMSO-d_6): δ = 11.34 (s, 1H), 9.66 (s, 1H), 8.41 (d, J = 6.0 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 5.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 3.20 (s, 3H), 2.75 (s, 3H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, DMSO-d_6): δ = 149.6 (C=N), 142.7 (CH), 140.5 (C), 140.4 (CH), 132.4 (C), 127.9 (C), 127.0 (CH), 123.7 (CH), 123.3 (C), 123.1 (C), 121.9 (C), 119.1 (CH), 115.8 (CH), 110.6 (CH), 107.9 (C), 14.3 (CH_3), 11.9 (CH_3). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2$ 247.1235; Found 247.1224.



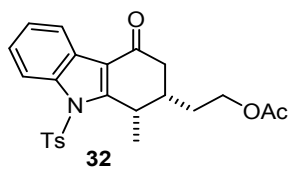
31

*2-(1-Methyl-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)ethyl acetate (**31**).* An oven-dried 250 mL Schlenk flask that was equipped with a magnetic stirring bar and a glass stopper was evacuated for 15 minutes, back-filled with dry N_2, the glass stopper opened, $LiAlH_4$ (1.42 g, 37.5 mmol, 2.50 equiv) was added into flask and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. 15 mL dry THF were added into flask by means of a gas-tight syringe and the flask was cooled down to 0 ˚C in an ice-bath. 45 mL of 0.334 M ethyl 2-(1-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetate (**14**) in THF (4.07 g, 15.00 mmol, 1.00 equiv of the ester **12**) were dropwise added into the flask. The resulting mixture was then stirred for 1 h while the temperature was allowed to rise to room temperature. The conversion was followed by TLC. After the conversion was completed, 40 mL 3.0 M aqueous KOH were dropwise added into the flask at ambient temperatures. Organic components were extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo and 2-(1-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethan-1-ol (**29**) (3.30 g, 14.4 mmol, 96%) was obtained as a white solid. This compound was used directly in the next step without further purification because it is unstable on silica gel.

An oven-dried 250 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar and a glass stopper was charged with 2-(1-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethan-1-ol (**29**) (2.95 g, 12.9 mmol, 1.00 equiv) and 4-*N,N*-dimethylaminopyridine (DMAP, 158 mg, 1.29 mmol, 0.10 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2 and the glass stopper was replaced with a rubber septum under

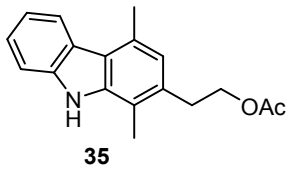
positive pressure of dry nitrogen. Dry THF (130 mL), TEA (4.30 mL, 3.14 g, 31.0 mmol, 2.40 equiv) and Ac_2O (2.69 mL, 2.90 g, 28.40 mmol, 2.20 equiv) were added sequentially by means of gas-tight syringes and the resulting homogeneous mixture was stirred at ambient temperatures for 1 hour. The conversion was followed by TLC. After the conversion was completed, 100 mL aqueous saturated $NaHCO_3$ was added into the flask. The organic components were extracted with EtOAc (3 × 75 mL). The combined organic phases were shaken with 1.0 M HCl to remove DMAP, and then were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Thus, 2-(1-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethyl acetate (**30**; 3.5 g, 12.9 mmol, quant.) was obtained as a colorless oil. This compound was used directly in the next step without further purification because it is unstable on silica gel.

An oven-dried 500 mL round-bottomed one necked flask that was equipped with a magnetic stirring bar was charged with 2-(1-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethyl acetate (**30**; 3.16 g, 11.66 mmol, 1.00 equiv). Dry THF (108 mL) and distilled water (12 mL) were added into the flask. After the flask was cooled down to 0 °C in an ice-water bath, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ; 5.3 g, 23.32 mmol, 2.00 equiv) was added into the flask portionswise. The mixture was then stirred for 2 h while the temperature was allowed to rise to ambient temperatures. The conversion was followed by TLC. After the conversion was completed, THF was removed by rotary evaporation under reduced pressure. Aqueous K_2CO_3 (250 mL, 10%, w/v) was added into the flask and organic components were extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave 1.76 g (6.18 mmol, 53%) of the title compound (**31**) as a white solid. Mp: 147–149 °C. TLC: R_f = 0.27 (silica gel; hexanes/EtOAc, 1:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3451 (br, w, N-H), 2969 (m), 2934 (m), 1742 (s, C=O), 1635 (s, C=O). ^1H NMR (600 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 8.24 – 8.18 (m, 1H), 7.38 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.28 – 3.19 (m, 1H), 2.65 – 2.48 (m, 3H), 2.04 (s, 3H), 1.83 (dq, *J* = 13.0, 6.4 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.31 (d, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, $CDCl_3$): δ = 193.3 (C=O), 171.1 (C=O), 156.6 (C), 136.1 (C), 124.6 (C), 123.4 (CH), 122.6 (CH), 121.3 (CH), 111.8 (C), 111.3 (CH), 61.9 (CH2), 40.1 (CH_2), 36.2 (CH), 31.5 (CH), 30.6 (CH_2), 20.9 (CH_3), 13.7 (CH_3). GCMS: t_R = 38.01 min, *m/z* (%): 285 ($[M]^+$, 80), 171 (100). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}NO_3$ 286.1443; Found 286.1434.



32

*2-(1-Methyl-4-oxo-9-tosyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)ethyl acetate (**32**).* An oven-dried 25 mL round-bottomed one necked flask that was equipped with a magnetic stirring bar was charged with *p*-toluenesulfonyl chloride (**TsCl**; 2.52 g, 13.52 mmol, 2.20 equiv). It was dissolved by the additon of $CHCl_3$ (30 mL). After consequtive additions of aqueous NaOH (24 mL, 50%, w/v), tetrabutylammonium hydrogensulfate (600 mg) and 2-(-1-methyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethyl acetate (**31**; 1.71 g, 6.0 mmol, 1.00 equiv) into the flask, the resulting mixture was stirred at ambient temperatures for 6 h. The pH value of the mixture was adjusted to 5–6 with 2.0 N HCl. Organic components were extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Purification of the residue by flash column chromatography on silica gel gave 2.45 g (5.58 mmol, 93%) of the title compound (**32**) as a white solid. Mp: 120–121 °C. **TLC:** R_f = 0.75 (silica gel; hexanes/EtOAc, 1:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3455 (br, w, N-H), 2978 (m), 2945 (m), 1740 (s, C=O), 1670 (s, C=O). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.23 (dd, *J* = 6.5, 2.3 Hz, 1H), 8.12 (dd, *J* = 6.9, 1.8 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.34 (pd, *J* = 7.2, 3.8 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 4.28 – 4.18 (m, 2H), 3.90 – 3.83 (m, 1H), 2.59 – 2.40 (m, 3H), 2.36 (s, 3H), 2.08 (s, 3H), 1.92 (td, *J* = 13.8, 6.9 Hz, 1H), 1.80 (td, *J* = 13.2, 6.6 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (APT, 150 MHz, $CDCl_3$): δ = 194.1 (C=O), 170.9 (C=O), 157.1 (C), 145.7 (C), 136.3 (C), 135.5 (C), 130.2 (CH), 126.4 (CH), 125.7 (C), 125.5 (CH), 125.1 (CH), 121.9 (CH), 117.1 (C), 114.3 (CH), 62.1 (CH_2), 39.6 (CH_2), 36.5 (CH), 32.0 (CH_3), 31.5 (CH_2), 21.6 (CH_3), 20.9 (CH_3), 13.8 (CH_3). GCMS: t_R = 44.06 min, *m/z* (%): 439 ([M]$^+$, 94), 224 (100). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{25}NO_5S$ 440.1532; Found 440.1527.



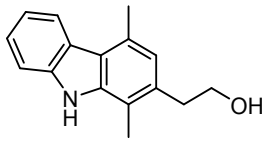
35

*2-(1,4-Dimethyl-9H-carbazol-2-yl)ethyl acetate (**35**).* An oven-dried 100 mL Schlenk tube that was equipped with a magnetic stirring bar was charged with 2-(1-methyl-4-oxo-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethyl acetate (**32**; 1.27 g, 2.90 mmol, 1.00 equiv) under nitrogen atmosphere. Dry THF (30 mL) was added into the flask. After the flask was cooled down to −60 °C by means of a thermo-circulator. 3.87 mL of 3.0 M methylmagnesium bromide solution in diethyl ether (11.60 mmol, 4.00 equiv of MeMgBr) was added into the tube. The mixture was then stirred for 2 h while the temperature was allowed to rise to ambient temperatures. The conversion was followed by TLC. After the conversion was completed, saturated aqueous NH_4Cl (30 mL) was added into the tube. Organic components were extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo and 2-(2-hydroxyethyl)-1,4-dimethyl-9-tosyl-

2,3,4,9-tetrahydro-1*H*-carbazol-4-ol (**33**; 1.13 g, 2.73 mmol, 93%) was obtained as a white solid. This compound was used directly in the next step without further purification because it is unstable on silica gel.

An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with 2-(2-hydroxyethyl)-1,4-dimethyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-4-ol (**33**, 1.22 g, 2.95 mmol, 1.00 equiv) and DMAP (72 mg, 0.59 mmol, 0.20 equiv). The flask was evacuated for 15 minutes, back-filled with dry N_2 and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Dry THF (30 mL), TEA (1.64 mL, 1.19 g, 11.8 mmol, 4.00 equiv) and Ac_2O (1.11 mL, 1.20 g, 11.8 mmol, 4.00 equiv) were added sequentially by means of gas-tight syringes and the resulting homogeneous mixture was stirred at ambient temperatures for 1 hour. The conversion was followed by TLC. After the conversion was completed, 100 mL aqueous saturated $NaHCO_3$ was added into the flask. The organic components were extracted with EtOAc (3 × 75 mL). The combined organic phases were shaken with 1.0 M HCl to remove DMAP, then were dried over Na_2SO_4, filtered, concentrated by rotary evaporation in vacuo. Thus, 2-(4-acetoxy-1,4-dimethyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)ethyl acetate (**34**; 1.24 g, 2.5 mmol, 85%) was obtained as a white solid. This compound was used directly in the next step without further purification because it is unstable on silica ge

An oven-dried 100 mL round-bottomed two necked flask that was equipped with a magnetic stirring bar, a glass stopper was charged with 2-(4-acetoxy-1,4-dimethyl-9-tosyl-2,3,4,9-tetrahydro-1H-carbazol-2-yl)ethyl acetate (**34**; 1.07 g, 2.14 mmol, 1.00 equiv) and 750 mg Pd/C (contains 10% Pd). The flask was evacuated for 15 minutes, back-filled with dry N_2 and the glass stopper was replaced with a rubber septum under positive pressure of dry nitrogen. Decalin (25 mL) was added ito the flask. The flask was heated to 210 °C in an oil-bath and was stirred for 16 h at this temperature. The conversion was followed by TLC. After the conversion was completed, the flask was cooled down to ambient temperatures and 50 mL $CHCl_3$ added into the flask. The mixture was filtered through a short plug of celite. The filtrate was concentrated by rotary evaporation under reduced pressure. Purification of the residue by flash column chromatography on silica gel gave 210 mg (0.75 mmol, 35%) of the title compound (**35**) as a white solid. Mp: 160–162 °C. TLC: R_f = 0.25 (silica gel; hexanes/EtOAc, 9:1). FTIR (KBr): $\tilde{\nu}_{max}$ (cm^{-1}) = 3324 (s, N-H), 2954 (m), 2918 (m), 1719 (s, C=O). ^1H NMR (600 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.9 Hz, 1H), 8.05 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.27 – 7.23 (m, 1H), 6.87 (s, 1H), 4.31 (t, J = 7.6 Hz, 2H), 3.12 (t, J = 7.6 Hz, 2H), 2.83 (s, 3H), 2.51 (s, 3H), 2.08 (s, 3H). $^{13}C\{^1H\}$ NMR (APT, 150 MHz, $CDCl_3$): δ = 171.1 (C=O), 139.6 (C), 139.4 (C), 132.5 (C), 130.5 (C), 124.8 (CH), 124.5 (C), 123.1 (CH), 122.3 (CH), 120.3 (C), 119.4 (CH), 115.3 (C), 110.4 (CH), 64.9 (CH_2), 32.5 (CH_2), 21.0 (CH_3), 20.3 (CH_3), 12.7 (CH_3). GCMS: t_R = 36.56 min, *m/z* (%): 281 ($[M]^+$, 32), 221 (100). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{19}NO_2$ 282.1494; Found 282.1487.



21b

*2-(1,4-Dimethyl-9H-carbazol-2-yl)ethan-1-ol (**21b**) from **35**.* An oven-dried 50 mL round-bottomed one necked flask that was equipped with a magnetic stirring bar was charged with 2-(1,4-dimethyl-9H-carbazol-2-yl)ethyl acetate (**35**; 92.8 mg, 0.33 mmol, 1.00 equiv). Then, THF (5 mL) and 5 g of 25% KOH (1.25 g KOH + 2.75 g MeOH + 1 g H_2O) solution were consecutively added into the flask and the resulting mixture was stirred at rt for 1 h. The conversion was followed by TLC. After the conversion was completed, the pH value of the mixture was adjusted to 1.5 with 10% aqueous HCl solution. The organic components were extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in vacuo. Thus, 78.9 mg (0.33 mmol, quant.) of 2-(1,4-dimethyl-9*H*-carbazol-2-yl)ethan-1-ol (**16b**) were obtained in its NMR-pure form.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Spectroscopic data for compounds described herein (PDF)

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Notes

The authors declare no competing financial interest.

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