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Note

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Convergent strategy to dizocilpine MK-801 and derivatives

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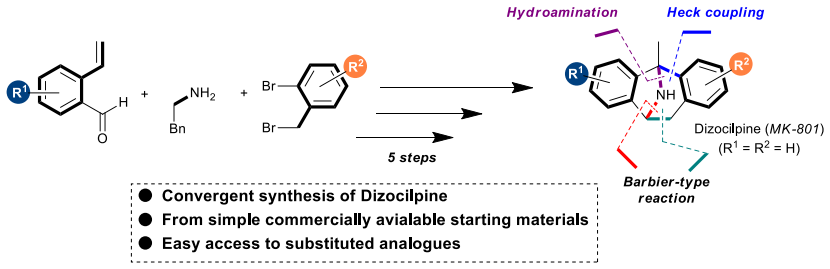
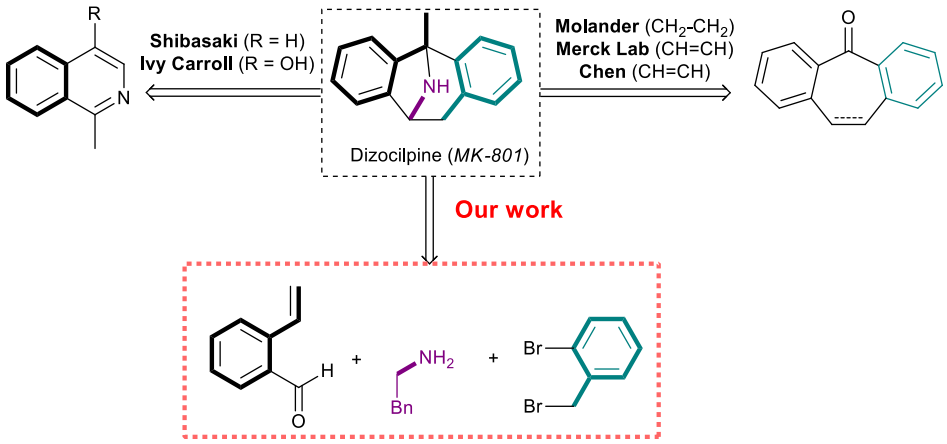


A convergent total synthesis of MK-801 has been achieved. Key synthetic transformations include multi-component Barbier-type reaction to construct the α-branched amine, a selective Heck α-coupling tactic to generate the exocyclic alkene skeleton, and a late-stage intramolecular hydroamination reaction between the exocyclic alkene and the secondary protected amine. The

efficacy of this method was demonstrated by the synthesis of two news analogues substituted on the aromatic rings.

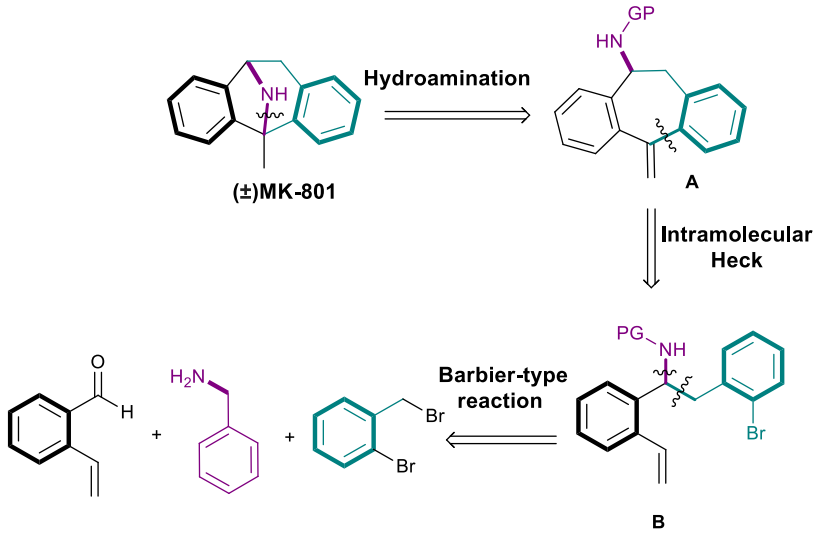
MK-801 is an original nortropane derivative whose core is fused with two benzene rings. One of its two isomers, the (+)-MK-801,[1] also called Dizocilpine, is a highly potent non-competitive antagonist of the *N*-methyl- *D*-aspartate (NMDA) receptor which acts by binding to a site located within the NMDA associated ion channel and thus prevents Ca^{2+} flux. This biological property gives it potential as drug to treat CNS disorders, confirmed by its well-known use as anticonvulsant. The therapeutic potency combined with the synthetic challenge triggered several groups attention. The principal syntheses developed are summarized in Scheme 1. *via* a catalytic Reissert-type reaction starting from the 1-methylisoquinoline using an aluminium-BINOL complex. Ivy Carroll and co-workers[3] described a rapid synthesis of the racemic version of MK-801 based on a 1,3-dipolar cycloaddition between the betaine, generated *in situ* from the 4-hydroxy-1-methylisoquinoline, and a benzyne ring. The first partner could be prepared *via* a four-step route described by the same group. Molander et *al*.[4] developed a synthetic pathway involving an original lanthanide-promoted intramolecular hydroamination reaction from the commercially available dibenzosuberone. Merck lab[5] approach consisted on the 1,2-addition of a Grignard on the dibenzosuberenone followed by a base-induced intramolecular cyclization and a final hydroxyl removal. Recently, Chen et *al*.[6] depicted a five-step synthetic route starting from the dibenzosuberenone with a key Lewis acid-catalyzed cyclization and a final magnesium desulfonylation. Although all these strategies are efficient, their main limitation is the introduction of substituents on both aromatic rings which limits the pharmacomodulation of these parts of the molecules. Our group took up the challenge to develop a new pathway to synthesize this pharmaceutical agent and various analogues *via* a key multicomponent Barbier-type reaction that could tolerate a great diversity of modulations (Scheme 1).

SCHEME 1.



The retrosynthetic approach we envisioned is depicted in Scheme 2. The nitrogen bridged core of Dizocilpine could be obtained by an hydroamination reaction between the exocyclic alkene and the secondary protected amine of compound **A** which could be obtained through an intramolecular selective α-Heck reaction. The major milestone of our strategy was to obtain the pre-organized vinyl/halide containing moiety **B** starting from the easily accessible 2-vinylbenzaldehyde,[7] the commercially available benzylamine and 2-bromobenzylbromide. Herein we report our preliminary results of this study.

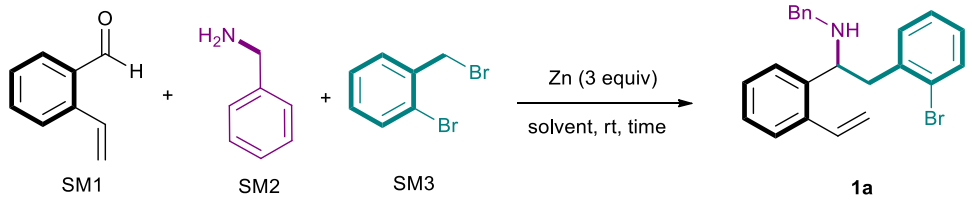
SCHEME 2. Retrosynthesis



Multicomponent reactions are very seducing for the synthesis of highly complex molecules because of the multiple bond formation usually achieved in one step.[8] Wu et *al.*[9] and later Le

Gall et *al*,[10] developped an efficient zinc-promoted Barbier-like reaction that allows the access to α-branched amines involving three partners: benzaldehyde, cyclic or alicyclic amine and benzylbromide. As their methodology seems to tolerate a wide range of substituents we decided to apply this three components strategy to our building blocks. Wu's methodology only led to **1a** with a low yield of 18% (Table 1, entry 1). Le Gall's method instead provided the desired compound with an improved yield of 41% (Table 1, entry 2). A small modification of these conditions, *i.e.* an increase of benzylamine equivalents pleasingly rose the yield up to 49%.

TABLE 1. Synthesis of 1a through zinc-promoted Barbier-like reaction[a]

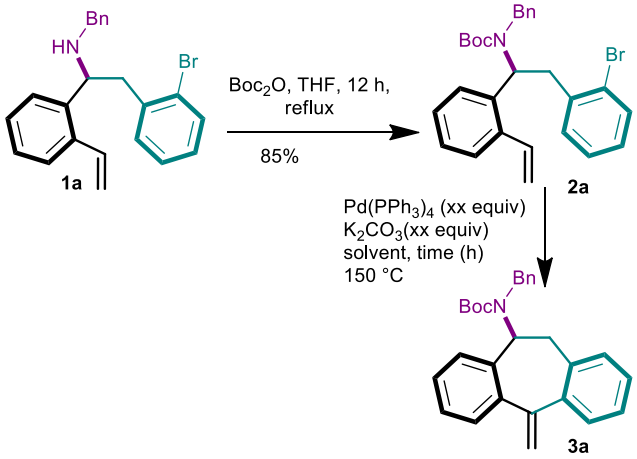


Entry	SM1 (equiv)	SM2 (equiv)	SM3(equiv)	Solvent	Time (h)	Yield (%)[b]
1	1	2	3	THF	15	18
2	1.1	1	2.5	MeCN	1	41
3	**1**	**1.4**	**2.2**	**MeCN**	**1**	**49**

[a] Conditions: Under inert atmosphere, a suspension of zinc dust (3 equiv.), trifluoroacetic acid (0.3 equiv.) and benzyl bromide (0.4 equiv.) in dry acetonitrile was stirred 5min at room temperature. Then, benzylamine (1.4 equiv.), vinylbenzaldehyde (1 equiv.) and 2-bromobenzyl bromide (2.2 equiv.) were added to the solution and the reaction mixture was stirred at room temperature for 1 h. [b]Yield of isolated product.

The next step consists in the formation of a 7-membered ring compound **3a** through an intramolecular α-Heck reaction. To prevent the formation of an indoline side-product during this step, it was necessary to protect the nitrogen atom through a carbamate group (**2a** obtained in 85% yield, Table 2). This last could result from a Buchwald coupling during the palladium-catalyzed C-C bond formation.

TABLE 2. Synthesis of 7-membered ring compound 3a through an intramolecular *α*-Heck reaction



Entry	Pd (mol%)	Base (equiv)	Solvent	Time (h)	Yield (%)[b]
1	$Pd(PPh_3)_4$ (50)	1.2	MeCN	15	10[c]
2	$Pd(PPh_3)_4$ (10)	2	DMSO	30	68
3	**$Pd(PPh_3)_4$ (20)**	**3**	**DMSO**	**2**	**90**

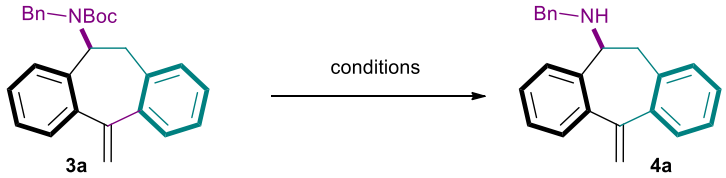
[a] Under inert atmosphere, to compound **2a** (1 equiv.) and K_2CO_3 (x equiv.) in the solvent was added Pd (x mol%) and was stirred for the suitable time. [b]Yield of isolated product. [c] heated at 85°C.

To favor the formation of the exocyclic alkene, we then optimized the Heck reaction (Table 2). Based on the conditions described by Danishefsky et *al.*[11] to generate the exocyclic Taxol alkene, the first catalytic system used consisted in $Pd(PPh_3)_4$ (0.5 equiv) in MeCN at 85°C. Despite the high catalyst loading (0.5 equiv), only 10% of **3a** has been obtained. Changing the solvent from MeCN to DMSO, in order to carry out the reaction at higher temperature, resulted in a major improvement with 68% yield (Table 2, entry 3). With 0.2 equivalent of $Pd(PPh_3)_4$ and 3 equivalents of K_2CO_3 as the base the reaction proceeded with an excellent yield of 90% in only 2 hours.

As reported in Table 3, the deprotection of the amine did not occur as smoothly as we thought in classical acidic condition, *i.e.* 20% (v/v) TFA in DCM. In these conditions we observed, in a significant amount, a by-product resulting from the elimination of the

benzylamine moiety. We then turned our attention to milder conditions as the one reported by Qu et *al*.[12] Indeed, they described the use of water, at elevated temperature, as an efficient reagent to remove the Boc protecting group from a large variety of amine. Applying this attractive method to compound **3a** was vain since only the starting material was recovered. Treatment of **3a** with sodium carbonate (1.2 equiv) in a mixture of water and DME as depicted by Guillaumet et *al*.,[13] was not successful in our case. Eventually, using dry HCl in solution in dioxane followed by a quick basic treatment with potassium carbonate gave **4a** with 89% yield.[14]

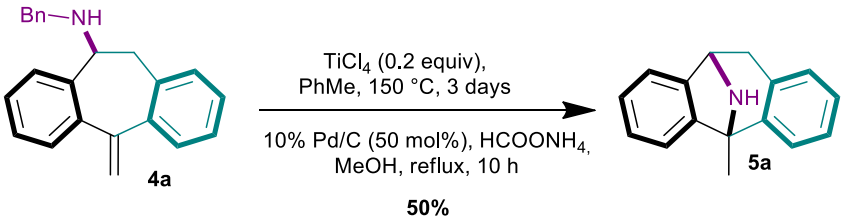
TABLE 3. Boc deprotection of 3a[a]



Entry	Reagent	Solvent	Temperature	Time (h)	Yield (%)[a]
1	TFA	DCM	rt	14	52
2	/	H_2O	100 °C	2	0
3	Na_2CO_3	H_2O/DME	100 °C	14	0
3	**HCl/Dioxane**	**/**	**rt**	**5**	**89**

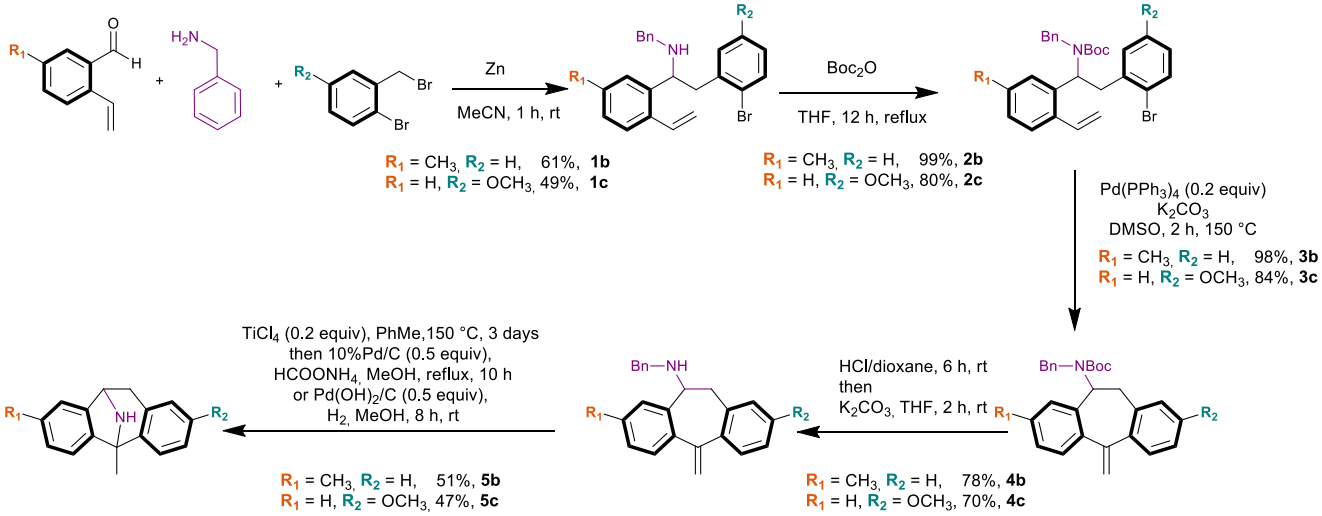
With pure compound **4a** in hand, we then focused on the final cyclization/deprotection reaction sequence. The hydroamination reaction has been widely studied and a rapid optimization, based on Ackermann et *al*.'s work[15] on $TiCl_4$-catalyzed hydroamination of vinylarene, resulted in the bridged-protected compound. This intermediate directly without any purification, underwent an hydrogenation catalyzed by 10% palladium on carbon with ammonium formate as hydrogene source.[16] This reaction required high catalyst loading (0.5 equiv) but afforded the targeted (±)-MK-801 (compound **5a**) with 50% yield over two steps (Scheme 3).

SCHEME 3. $TiCl_4$-catalyzed hydroamination



To demonstrate the robustness of our strategy, we explored the possibility to extend it to other substrates such as 5-methyl-2-vinylbenzaldehyde and 2-bromo-1-(bromomethyl)-4-methoxybenzene. To the best of our knowledge, only few examples of modified MK-801 are described in the litterature.[5,17] With our methodology, for both substrates, the sequence MCR-protection-Heck coupling-deprotection resulted in the desired compounds **4b** and **4c** with a satisfying yield of respectively 46% and 23% over 4 steps (Scheme 4). In the case of compound **4b**, it appeared that hydrogenation with Pearlman's catalyst gave a better result that the former method with $HCOONH_4$ and Pd/C, providing compound **5b** with 51% over 2 steps. For compound **4c,** the sequence previously described allowed to afford compound **5c** with 47% yield over the two steps.

SCHEME 4. Synthesis of substituted MK-801 through the described strategy



Conclusion

In conclusion, we successfully developed an original and practical synthesis of Dizocilpine and two of its analogues. This method could tolerate more modifications and presents the

advantage of requiring simple and commercially available starting material over the one existing. Efforts are now in progress to synthesis a large library of MK-801 analogues through this strategy to study their biological activity as antagonist of the *N*-methyl- D-aspartate (NMDA) receptor.

Experimental Section

General Information. All reactions were conducted under argon atmosphere. Solvents: cyclohexane, dichloromethane, 1,4-dioxane, ethyl acetate and methanol for extraction and chromatography were technical grade. THF was distilled over Na/benzophenone

Instrumentation. These compounds were all identified by usual physical methods, e.g., ^{1}H NMR, ^{13}C NMR (J-MOD), IR, HR-MS (ESI). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker Avance-300. ^{1}H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.26 ppm) or methanol (3.32 ppm). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets). ^{13}C chemical shift are reported in ppm from central peak of deuteriochloroform (77.16 ppm) or deuteriomethanol (49.00 ppm). IR spectra were measured on a Bruker Vector 22 spectrophotometer and are reported in wave numbers (cm^{-1}). The angels of rotation were measured on a Perkin Elmer Polarimeter 341 and denoted as specific rotations: $[\alpha]_D$. High resolution mass spectra (HR-MS) were recorded on a Bruker MicroTOF spectrometer, using ESI with methanol as the carrier solvent. Nominal and exact *m/z* values are reported in Daltons. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (0.015-0.040 mm) was used for column chromatography. Flash chromatography was performed on silica gel 60 (0.040-0.063 mm) at medium pressure (200 mbar). Compounds were visualized under a UVP Mineralight UVGL-58 lamp (254 nm) and with vanillin/Δ or phosphomolybdic acid/Δ. Unless otherwise noted, other materials are obtained from commercial

suppliers and were used without further purification.

Typical procedure for the MCR[2]:

A suspension of zinc dust (3 equiv.), trifluoroacetic acid (0.3 equiv.) and benzyl bromide (0.4 equiv.) in dry acetonitrile was stirred 5min at room temperature. Then, benzylamine (1.4 equiv.), vinylbenzaldehyde (1 equiv.) and 2-bromobenzyl bromide (2.2 equiv.) were added to the solution and the reaction mixture was stirred at room temperature for 1 h (exothermic reaction). After completion of reaction, the resulting solution was poured to a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness and the desired compound was purified by column chromatography.

N-benzyl-2-(2-bromophenyl)-1-(2-vinylphenyl)ethanamine (1a)

Following the general procedure for MCR compound **1a** was obtained starting from benzylamine (1.71 g, 16 mmol), 2-vinylbenzaldehyde (1.45 g, 11 mmol) and 2-bromobenzyl bromide. Light yellow oil (2.11 g, 5.3 mmol, 49%); **TLC**: R_f 0.28 (*c*-hexane/EtOAc 90/10); **IR** (neat): ν (cm^{-1}) 628, 660, 696, 749, 773, 912, 986, 1024, 1112, 1158, 1205, 1361, 1440, 1469, 1495, 1567, 1625, 3026, 3062; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 1H), 7.64 – 7.54 (m, 1H), 7.53 – 6.89 (m, 12H), 5.52 (dd, J = 17.3, 1.2 Hz, 1H), 5.24 (dd, J = 10.9, 1.2 Hz, 1H), 4.51 (t, J = 7.0 Hz, 1H), 3.77 (d, J = 13.5 Hz, 1H), 3.59 (d, J = 13.5 Hz, 1H), 3.22 (dd, J = 13.4, 7.8 Hz, 1H), 3.10 (dd, J = 13.4, 6.3 Hz, 1H), 1.80 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.6 (C), 140.5(C), 138.2(C), 137.8(C), 134.7(CH), 132.8(CH), 131.8(CH), 128.3(2CH), 128.1(2CH), 128.0(2CH), 127.2(CH), 127.1(CH), 126.8(CH), 126.3(CH), 125.1(C), 116.0(CH_2), 57.2(CH), 51.5(CH_2), 44.5(CH_2); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **Calcd for** $C_{23}H_{22}{}^{79}BrN$ 392.1015, **found**: 392.1018. and *m/z*: $(M+H)^+$ **calcd for** $C_{23}H_{22}{}^{81}BrN$ 394.0993, **found**: 394.0995.

N-benzyl-2-(2-bromophenyl)-1-(5-methyl-2-vinylphenyl)ethanamine (1b)

Following the general procedure for MCR, compound **1b** was obtained starting from benzylamine (0.4 mL, 3.66 mmol), 5-methyl-2-vinylbenzaldehyde (297 mg, 2 mmol) and 2-bromobenzyl bromide (1.19 g, 4.76 mmol). Colorless oil (512 mg, 1.26 mmol, 61%); **TLC** : R_f 0.2 (*c*-hexane / EtOAc 20/1); **IR** (neat): ν (cm^{-1}) 630, 660, 697, 749, 823, 909, 986, 1025, 1120, 1158, 1199, 1357, 1411, 1439, 1469, 1566, 1609, 1734, 2922, 3027, 3062; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.6 Hz, 1H), 7.50 – 7.00 (m, 12H), 5.53 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 4.60 – 4.45 (m, 1H), 3.81 (d, *J* = 13.5 Hz, 1H), 3.62 (d, *J* = 13.5 Hz, 1H), 3.41 – 3.00 (m, 2H), 2.51 (s, 3H), 1.83 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.7(C), 140.3(C), 138.2(C), 137.7(C), 134.8(C), 134.4(CH), 132.8(CH), 131.8(CH), 128.3(2CH), 128.1(CH), 127.9(2CH), 127.2(2CH), 127.2(CH), 126.7(CH), 126.1(CH), 125.0(C), 115.1(CH_2), 57.0(CH), 51.5(CH_2), 44.5(CH_2), 21.5(CH_3); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{24}H_{24}{}^{79}BrN$ 406.1170, **found**: 406.1173 and *m/z*: $(M+H)^+$ **calcd for** $C_{24}H_{24}{}^{81}BrN$ 408.1150, **found:** 408.1164.

N-benzyl-2-(2-bromo-5-methoxyphenyl)-1-(2-vinylphenyl) ethanamine (1c)

Following the general procedure for MCR compound **1c** was obtained starting from benzylamine (1.71 g, 16 mmol), 2-vinylbenzaldehyde (1.45 g, 11 mmol) and 1-bromo-2-(bromomethyl)-4-methoxybenzene (7.0 g, 25 mmol). Colorless oil (2.2 g, 5.39 mmol, 49%) **TLC**: R_f 0.44 (*c*-hexane/EtOAc 80/20); **IR** (neat): ν (cm^{-1}) 644, 698, 733, 763, 774, 801, 856, 874, 912, 986, 1015, 1047, 1057, 1116, 1133, 1240, 1278, 1313, 1414, 1440, 1464, 1478, 1572,`1595, 2834, 2933, 3026, 3061; **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.67 – 7.62 (m, 1H), 7.42 – 7.30 (m, 3H), 7.30 – 7.13 (m, 7H), 6.95 (dd, *J* = 17.3, 10.9 Hz, 1H), 6.59 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.40 (d, *J* = 3.1 Hz, 1H), 5.41 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.12 (dd, *J* = 11.0, 1.6 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 1H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.55 (d, *J* = 10.3 Hz, 4H), 3.10 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.93 (dd, *J* = 13.3, 6.5 Hz, 1H), 1.73 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 158.6(C), 140.6(C), 140.4(C), 138.9(C), 137.9(C), 134.6(CH), 133.2(CH), 128.3(2CH),

128.1(CH), 128.0(2CH), 127.1(CH), 126.8(2CH), 126.3(CH), 116.8(CH), 116.0(CH_2), 115.5(C), 114.4(CH_2), 57.2(CH), 55.4(CH_3), 51.5(CH_2), 44.7(CH_2); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{24}H_{24}{}^{79}BrNO$ 422.1120, **found**: 422.1116 and *m/z*: $(M+H)^+$ **calcd. for** $C_{24}H_{24}{}^{81}BrNO$ 424.1099**, found**: 424.1095.

Typical procedure for Boc protection

A solution of compound **1** (1 equiv.) and Boc_2O (1.5 equiv.) in THF was stirred at 60°C for 12 h. The mixture was then quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

Tert-butyl benzyl (2-(2-bromophenyl)-1-(2-vinylphenyl) ethyl)carbamate(2a)

Following the general procedure for Boc protection, compound **2a** was obtained starting from compound **1a** (392 mg, 1 mmol), Boc_2O (327 mg, 1.5 mmol), THF (2 mL). White solid (418 mg, 0.85 mmol, 85%); **mp**: 85-87°C; **TLC** : R_f 0.71(*c*-hexane/EtOAc 80/20); **IR** (neat): ν (cm^{-1}) 630, 661, 695, 731, 750, 781, 823, 868, 914, 930, 951, 964, 983, 1027, 1074, 1123, 1145, 1160, 1222, 1252, 1277, 1324, 1361, 1401, 1428, 1470, 1570, 1679, 2928, 2969, 3032; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 (d, J = 7.9 Hz, 1H), 7.50-7.44 (m, 1H), 7.36 (s, 1H), 7.31-7.13 (m, 5H), 7.1-7.05 (m, 4H), 6.90 (br s, 2H), 5.98 (s, 1H), 5.46 (d, J = 17.1 Hz, 1H), 5.23 (d, J = 10.2 Hz, 1H), 4.34 (d, J = 15.5 Hz, 1H), 4.20 (d, J = 15.4 Hz, 1H), 3.33 (d, J = 7.1 Hz, 2H), 1.22 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.3(C), 139.3(C), 138.9(C), 138.2(C), 136.9(C), 134.8(CH), 132.8(CH), 131.6(CH), 128.2(CH), 127.8(3CH), 127.7(2CH), 127.4(1CH), 126.6(CH), 126.5(CH), 126.3(CH), 125.5(CH_2), 116.4(CH_2), 79.8(C), 54.6(CH), 38.4(CH_2), 28.2($3CH_3$); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{28}H_{30}{}^{79}BrNO_2$ 492.1538, **found**: 492.1545, and *m/z*: $(M+H)^+$ **calcd for** $C_{28}H_{30}{}^{81}BrNO_2$ 494.1518, found: 494.1536.

Tert-butyl benzyl (2-(2-bromophenyl)-1-(5-methyl-2-vinylphenyl)ethyl)carbamate(2b)

Following the general procedure for Boc protection, compound **2b** was obtained starting from compound **1b** (510 mg, 1.25 mmol), Boc_2O (360 mg, 1.65 mmol), THF (6 mL). Colorless oil (602 mg, 1.19 mmol, 79%), **TLC** : R_f 0.28 (*c*-hexane/EtOAc 20/1); **IR** (neat): ν (cm^{-1}) 662, 698, 751, 825, 844, 868, 910, 967, 1028, 1059, 1115, 1160, 1212, 1252, 1321, 1369, 1397, 1432, 1455, 1474, 1495, 1688, 1755, 1811, 2932, 2982; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 1H), 7.45 – 6.84 (m, 12H), 5.95 (s, 1H), 5.43 (d, *J* = 16.7 Hz, 1H), 5.18 (d, *J* = 13.1 Hz, 1H), 4.26 (dd, *J* = 41.6, 26.7 Hz, 2H), 3.32 (s, 2H), 2.36 (d, *J* = 36.6 Hz, 3H), 1.21 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.2(C), 139.3(C), 138.2(C), 137.2(C), 136.6(C), 135.9(C), 134.5(2CH), 132.7(2CH), 131.6(CH), 128.7(2CH), 128.1(CH), 127.6(2CH), 127.3(2CH), 126.3(2CH), 125.4(CH_2), 115.4(CH_2), 79.6(C), 54.4(CH), 38.1(CH_2), 28.1($3CH_3$), 21.4(CH_3). **HRMS** (ESI-TOF) *m/z*: $(M+Na)^+$ **calcd for** $C_{29}H_{32}BrNO_2Na$ 528.1514, **found:** 528.1506.

Tert-butyl benzyl (2-(2-bromo-5-methoxyphenyl)-1-(2-vinylphenyl) ethyl) carbamate (2c)

Following the general procedure for Boc protection, compound **2c** was obtained (starting from compound **1c** (422 mg, 1 mmol), Boc_2O (327 mg, 1.5 mmol), THF (2 mL) White solid (418 mg, 0.8 mmol, 80%); **mp**: 67-69°C; **TLC** : R_f 0.52 (*c*-hexane/EtOAc 80/20); **IR** (neat): ν (cm^{-1}); 680, 696, 729, 750, 802, 826, 865, 903, 921, 942, 973, 991, 1009, 1023, 1060, 1113, 1132, 1163, 1219, 1254, 1278, 1301, 1326, 1363, 1403, 1424, 1456, 1474, 1572, 1599, 1673, 2834, 2930, 2969, 3010; **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.57 – 6.90 (m, 12H), 6.80 – 6.62 (m, 1H), 6.00 (s, 1H), 5.57 (t, *J* = 28.0 Hz, 1H), 5.31 (t, *J* = 14.1 Hz, 1H), 4.31 (q, *J* = 15.5 Hz, 2H), 3.73 (s, 3H), 3.45 – 3.16 (m, 2H), 1.29 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 158.8(C), 155.3(C), 139.3(C), 139.1(C), 138.8(C), 136.8(C), 134.7(CH), 133.1(CH), 128.1(2CH), 127.8(2CH), 127.6(2CH), 127.0(CH), 126.5(CH), 126.4(2CH), 116.8(CH), 116.3(CH_2), 115.8(C), 114.3(CH_2), 79.7(C), 55.53(OCH_3), 54.6 (CH), 38.2 (CH_2), 28.1($3CH_3$). **HRMS** (ESI-TOF) *m/z*: $(M+Na)^+$ **calcd for** $C_{29}H_{32}{}^{79}BrNO_3Na$ 544.1463, **found**: 544.1467 and *m/z*: $(M+Na)^+$ **calcd for** $C_{24}H_{15}{}^{81}BrNO_3Na$ 546.1443, **found**: 546.1457.

Typical procedure for Heck coupling[3]

A sealed tube was equipped with a septum and purged with argon. The tube was charged with compound **2** (1 equiv.), K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (0.2 equiv.) and dry DMSO. The resulting mixture was flushed with argon and was stirred for 2 h at 150 °C. The resulting slurry was allowed to cool to room temperature, diluted with EtOAc and washed with a large amount of brine solution. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash chromatography.

Tert-butylbenzyl (5-methylene-10, 11-dihydro-5H-dibenzo [a,d][7]annulen-10-yl) carbamate (3a)

Following the general procedure for Heck coupling, compound **3a** was obtained starting from compound **2a** (492 mg, 1.0 mmol), K_2CO_3 (414 mg, 3.0 mmol), $Pd(PPh_3)_4$ (231 mg, 0.2 mmol), DMSO (5 mL). Compound **3a** was isolated as a mixture of rotamers. White solid (370 mg, 0.9 mmol, 90%); **mp**: 127-129°C; **TLC**: R_f 0.41 (*c*-hexane/EtOAc 80/20); **IR** (neat): ν (cm^{-1}) 663, 697, 710, 740, 752, 769, 784, 858, 876, 902, 959, 1033, 1060, 1106, 1125, 1154, 1166, 1210, 1252, 1271, 1298, 1314, 1364, 1396, 1460, 1485, 1626, 1683, 2933, 2976; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 – 7.07 (m, 13H), 5.91 (br s, 0.4H), 5.67 (br s, 1H), 5.36 (m, 1.2H), 4.5 (m, 0.5H), 4.01 (m, 1H), 3.53 (m, 0.6H), 3.1 (m, 0.5H), 2.75 (sl, 0.4H) 1.50 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.1(C), 151.8(C), 144.2(C), 140.4(C), 136.4(C), 135.5(C), 135.1(C), 129.5(CH), 128.2(CH), 128.0(CH), 128.0(CH), 127.0(2CH), 127.0(2CH), 126.7(2CH), 126.4(CH), 117.0(CH_2), 80.3(C), 58.4(CH), 38.2(CH_2), 37.6(CH_2), 28.6($3CH_3$). **HRMS** (ESI-TOF) *m/z*: $(M+Na)^+$ **calcd for** $C_{28}H_{29}NO_2Na$ 434.2096, **found**: 434.2089.

Tert-butyl benzyl(8-methyl-5-methylene-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-yl)carbamate (3b)

Following the general procedure for Heck coupling, compound **3b** was obtained starting from compound **2b** (192 mg, 0.38 mmol), K_2CO_3 (173.5 mg, 1.25 mmol), $Pd(PPh_3)_4$ (45 mg, 0.03 mmol), DMSO (0.9 mL). Compound **3b** was isolated as a mixture of rotamers. Colorless oil (160 mg, 0.37 mmol, 98%), **TLC**: R_f 0.42 (*c*-hexane/EtOAc 20/1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 6.84 (m, 13H), 5.84 (br s, 0.5H), 5.62 (br s, 0.5H), 5.28 (m, 1H), 4.36 (m, 0.6H), 3.92 (br s, 1H), 3.5 (m, 0.7H), 3.11 (m, 0.5H), 2.2 (s, 3H) 1.50 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.4(C), 151.7(C), 144.5(C), 140.3(C), 137.8(C), 135.7(C), 135.0(C), 129.6(CH), 129.4(CH), 128.6(CH), 128.0(2CH), 127.0(2CH), 126.6(2CH), 116.5(CH_2), 80.2(C), 58.4(CH), 48.6 (CH_2), 38.1(CH_2), 37.3(CH_2), 28.6($3CH_3$). IR (neat): ν (cm^{-1})1042, 1053, 1078, 1228, 1253, 1381, 1407, 1452, 1964, 2208, 2340, 2362, 2902, 2970, 2988; **HRMS** (ESI-TOF) *m/z*: $(M+Na)^+$ **calcd for** $C_{29}H_{31}NO_2Na$ 448.2252, **found**: 448.2254.

Tert-butyl benzyl(2-methoxy-5-methylene-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-yl)carbamate (3c)

Following the general procedure for Heck coupling, compound **3c** was obtained starting from compound **2c** (522 mg, 1 mmol), K_2CO_3 (414 mg, 3 mmol), $Pd(PPh_3)_4$ (231 mg, 0.2 mmol), DMSO (5 mL). Compound **3a** was isolated as a mixture of rotamers. White solid (371 mg, 0.8 mmol, 84%); **mp**: 46-48°C; **TLC** : R_f 0.26 (*c*-hexane/EtOAc 90/10); **IR** (neat): ν (cm^{-1}) 621, 643, 706, 741, 774, 792, 815, 858, 872, 894, 910, 935, 963, 1028, 1077, 1090, 1116, 1157, 1261, 1281, 1295, 1314, 1332, 1365, 1390, 1424, 1447, 1496, 1608, 1684, 2839, 2973; **^{1}H NMR** (300 MHz, $CDCl_3$) *δ* 7.32 – 6.94 (m, 12H), 6.75-6.55 (m, 1.7H), 6.4 (br s, 0.4H), 5.65 (br s, 0.4H), 5.48 (s, 1H), 5.15 (s, 1H), 4.32 (m, 0.5H), 3.94 (m, 1H), 3.94-3.58 (m, 4H), 3.37 (m, 0.7H), 2.93 (m, 0.5H), 1.34 (br s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 159.5(C), 156.3(C), 151.3(C), 140.3(C), 136.7(C), 136.3(C), 131.1(CH), 129.4(2CH), 128.6(CH), 128.0(2CH), 127.8(CH), 127.0(2CH), 127.0(CH), 126.5(CH), 116.7(CH_2), 114.2(CH), 112.4(CH), 111.8(CH), 80.2(C), 58.4(CH), 48.6(CH), 38.5(CH_2), 37.9(CH_2), 28.5($3CH_3$). **HRMS** (ESI-

TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{29}H_{32}NO_3$ 442.2382, **found:** 442.2381.

Typical procedure for the amine deprotection: [4]

Under an inert atmosphere, at 0 °C, HCl (80 equiv., 4M in dioxane) was added compound **3** (1 equiv.). The mixture was then stirred at room temperature for 5h. The solvent was removed by rotary evaporation and the crude reaction was used directly to the next step without any purification. Dry THF and K_2CO_3 (2 equiv.) were added to the residue and the stirring was maintained for 2h at room temperature. The resulting suspension was filtered through a celite pad and rinsed with EtOAc. The filtrate was concentrated *in vacuo* and the crude was purified by silica gel chromatography.

N-benzyl-5-methylene-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-amine(4a)

Following the general procedure for the amine deprotection, compound **4a** was obtained starting from compound **3a** (411 mg, 1.0 mmol). White solid (277 mg, 0.89 mmol, 89%); **mp**: 264-266°C; **TLC**: R_f 0.25(*c*-hexane/EtOAc 90/10); **IR** (neat): ν (cm^{-1}) 697, 727, 753, 779, 904, 975, 1028, 1037, 1073, 1093, 1118, 1158, 1202, 1254, 1269, 1328, 1452, 1486, 1601, 1616, 1668, 1695, 1723, 2920, 3026, 3062; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 4H), 7.37 – 7.13 (m, 9H), 5.45 (dd, J = 14.3, 1.6 Hz, 2H), 4.25 (dd, J = 7.4, 3.2 Hz, 1H), 3.76 (s, 2H), 3.41 – 3.26 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.8(C), 140.7(C), 140.2(C), 139.8 (C), 135.1(2C), 130.6(CH), 128.5(2CH), 128.4(CH), 128.4(CH), 128.3(CH), 127.9(CH), 127.9(CH), 127.2(CH), 127.1(CH), 126.6(CH), 117.4(CH_2), 58.5(CH), 51.4(CH_2), 39.2(CH_2); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{23}H_{21}N$ 312.1728, **found**: 312.1723.

N-benzyl-8-methyl-5-methylene-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-amine(4b)

Following the general procedure for the amine deprotection, compound **4b** was obtained starting from compound **3b** (300 mg, 0.7 mmol). Yellowish oil (180 mg, 0.55 mmol, 78%); **TLC** : R_f 0.17 (*c*-hexane/EtOAc 80/20); **IR** (neat): ν (cm^{-1})804, 880, 1045, 1088, 1274,

1326, 1380, 1408, 1453, 2361, 2901, 2974; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.07 (m, 12H), 5.46 (d, *J* = 9.1 Hz, 2H), 4.23 (dd, *J* = 7.3, 3.1 Hz, 1H), 3.84 (s, 2H), 3.44 – 3.28 (m, 2H), 2.41 (s, 3H), 1.79 (s, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.6(C), 140.6(C), 140.4(C), 139.9(C), 137.7(C), 137.6(C), 135.1(C), 130.5(CH), 128.7(CH), 128.4(2CH), 128.4(2CH), 128.2(CH), 127.8(CH), 127.7(CH), 127.0(CH), 126.5(CH), 117.1(CH_2), 58.6(CH), 51.5(CH_2), 39.2(CH_2), 21.0(CH_3); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{24}H_{23}N$ 326.1909, **found:** 326.1918.

N-benzyl-2-methoxy-5-methylene-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-amine(4c)

Following the general procedure for the amine deprotection, compound **4c** was obtained starting from compound **3c** (441.6mg, 1.0 mmol). White solid (239 mg, 0.7 mmol, 70%); **mp**: 264-266°C; **TLC** : R_f 0.35 (*c*-hexane/EtOAc:80/20); **IR** (neat): ν (cm^{-1}) 634, 650, 667, 697, 717, 731, 750, 761, 783, 801, 824, 847, 865, 881, 902, 919, 944, 973, 944, 973, 1016, 1041, 1068, 1081, 1101, 1124, 1231, 1270, 1306,1323,1343,1375, 1409, 1434, 1460, 1499, 1604, 1650, 1698, 2327, 2341, 2361, 2902, 2989; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 10H), 6.73 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.67 (d, *J* = 2.7 Hz, 1H), 5.39 (dd, *J* = 26.2, 1.8 Hz, 2H), 4.21 (dd, *J* = 7.5, 3.4 Hz, 1H), 3.76 (s, 5H), 3.36 – 3.18 (m, 2H), 1.83 (s, 1H).**^{13}C NMR** (75 MHz, $CDCl_3$) *δ* 159.3(C), 151.2(C), 141.2(C), 140.6(C), 140.0(C), 136.6(C), 132.4(C), 129.6(CH), 128.5(2CH), 128.4(2CH), 128.2(CH), 127.8(CH), 127.4(CH), 127.2(CH), 127.0(CH), 116.5(CH_2), 115.7(C), 112.2(CH), 58.6(CH), 55.4(CH), 51.6(CH_3), 40.1(CH_2); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{24}H_{23}NO$ 342.1858, **found**: 342.1865.

Typical procedure for the cyclization/hydrogenation[5]:

A sealed tube was charged with dry toluene, compound **4** (1 equiv.) and $TiCl_4$ (0.2 equiv.). The tube was flushed with argon, and the resulting mixture was stirred for 3 days at 150°C. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude reaction was used directly to the next step without any purification. 10% Pd/C (0.5 equiv.),

anhydrous ammonium formate (15 equiv.) and dry methanol were added in a single portion under nitrogen. The resulting reaction mixture was stirred at reflux temperature. After completion of reaction, the catalyst was removed by filtration through a celite pad and rinsed with chloroform. The filtrate was evaporated under reduced pressure and the resulting crude was purified by flash chromatography.

5-methyl-10,11-dihydro-5H-5,10-epiminodibenzo[a,d][7]annulene (5a)

Following the general procedure for cyclization/hydrogenation, compound **5a** was obtained starting from compound **4a** (312 mg, 1.0 mmol). Colorless oil (110 mg, 0.50 mmol, 50%) **TLC**: R_f 0.24 (MeOH/DCM, 5/95); **IR** (neat): ν (cm^{-1})631, 691, 713, 725, 741, 754, 772, 799, 844, 1014, 1032, 1048, 1061, 1095, 1117, 1202, 1244, 1296, 1344, 1375, 1423, 1458, 1488, 1731, 2928, 2961, 3065; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.14 – 7.03 (m, 5H), 6.96 – 6.92 (m, 1H), 4.70 (d, J = 5.6 Hz, 1H), 3.45 (dd, J = 16.8, 5.7 Hz, 1H), 2.73 (d, J = 16.8 Hz, 1H), 2.54 (s, 1H), 1.92 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.2(C), 144.7(C), 144.4(C), 132.4(C), 130.3(CH), 127.2(CH), 127.1(CH), 126.7(CH), 125.8(CH), 121.7(CH), 121.5(CH), 118.7(CH), 64.3(C), 58.5(CH), 34.6(CH_2), 20.2(CH_3); **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{16}H_{15}N$ 222.1283, **found**: 222.1275.

2-methoxy-5-methyl-10,11-dihydro-5H-5,10-epiminodibenzo[a,d][7]annulene (5c)

Following the general procedure for cyclization/hydrogenation, compound **5c** was obtained starting from compound **4c** (341 mg, 1.0 mmol). Colorless oil (118 mg, 0.47 mmol, 47%); **TLC** : R_f 0.17 (MeOH/DCM, 3/97); **IR** (neat): ν (cm^{-1}) 651, 695, 732, 760, 799, 817, 842, 895, 980, 1030, 1069, 1143, 1193, 1253, 1273, 1311, 1342, 1377, 1407, 1455, 1496, 1576, 1606, 2360, 2901, 2970, 2988; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 6.96 (m, 6H), 6.61 (d, J = 3 Hz, 1H), 6.49 (s, 1H), 4.87 (s, 1H), 4.71 (d, J = 2.1 Hz, 1H), 3.68 (s, 3H), 3.45 (dd, J = 16.8, 5.0 Hz, 1H), 2.72 (d, J = 17.1 Hz, 1H), 1.91 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9, 151.7,

143.6, 136.2, 133.5, 127.3, 127.1, 126.8, 122.6, 121.8, 118.5, 115.5, 111.2, 64.1, 58.2, 55.2, 34.6,19.9. **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{17}H_{17}NO$ 252.1388, **found**: 252.1385.

5,8-dimethyl-10,11-dihydro-5H-5,10-epiminodibenzo[a,d][7]annulene (5b)

In a sealed tube, under argon, to a solution of N-benzyl-8-methyl-5-methylene-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-amine (144 mg, 0.44 mmol) in dry toluene (1 mL) was added $TiCl_4$ (0.09 mL, 0.09 mmol, 1M in DCM) was added. The resulting mixture was stirred for 3 days at 150 °C. After completion of the reaction, solvent was evaporated under reduced pressure. The crude reaction was used directly to the next step without any purification. 10~15% $Pd(OH)_2/C$ (200 mg, 0.16 mmol, 50% in H_2O) was added to the crude solubilized in dry methanol (4 mL). The mixture was stirred under hydrogen atmosphere for 8h. After completion of reaction, the catalyst was removed by filtration through a celite pad, which was then rinsed with DCM. The filtrate was evaporated to dryness and purified by flash chromatography to afford the desired product 5,8-dimethyl-10,11-dihydro-5H-5,10-epiminodibenzo[a,d][7]annulene as a yellowish oil (40.4 mg, 0.17 mmol, 51%); **TLC** : R_f 0.31 (DCM/MeOH, 95:5); **IR** (neat): ν (cm^{-1}) 630, 665, 711, 742, 773, 810, 836, 853, 880, 904, 929, 966, 989, 1034, 1070, 1103, 1117, 1229, 1266, 1293, 1321, 1341, 1375, 1425, 1451, 1484, 1615, 1713, 2854, 2921, 2968 **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 – 7.14 (m, 1H), 7.04 – 6.97 (m, 3H), 6.88 – 6.83 (m, 3H), 4.62 (d, J = 5.6 Hz, 1H), 3.54 – 3.35 (m, 3H), 2.65 (d, J = 16.9 Hz, 1H), 2.21 (s, 3H), 1.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.9(C), 144.2(C), 144.0(C), 136.7(C), 132.1(C), 130.3(CH), 127.8(CH), 125.9(CH), 122.6(CH), 121.5(CH), 118.5(CH), 64.3(C), 58.4(CH_3), 34.4(CH_2), 21.4(CH), 20.0(CH_3). **HRMS** (ESI-TOF) *m/z*: $(M+H)^+$ **calcd for** $C_{17}H_{17}N$ 236.1439, **found:** 236.1436.

Supporting Information Available: Spectroscopic data of all compounds. This material is available free of charge via the the Internet at http://pubs.acs.org.

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REFERENCES

(1) Wong, E. H.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. *Proc. Natl. Acad. Sci.* **1986**, *83*, 7104-7108.

(2) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784-10785.

(3) Constable, K. P.; Blough, B. E.; Carroll, F. I. *Chem. Commun.* **1996**, 717-718.

(4) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515-6517.

(5) Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. a; Thies, J. E.; Magill, C. a; Varga, S. L.; Schwering, J. E.; Lyle, P. a; Christy, M. E. *J. Med. Chem.* **1990**, *33*, 789-808.

(6) Chang, M. Y.; Huang, Y. P.; Lee, T. W.; Chen, Y. L. *Tetrahedron* **2012**, *68*, 32833287.

(7) Vautravers, N. R.; Regent, D. D.; Breit, B. *Chem. Commun.* **2011**, *47*, 6635-6637.

(8) Domling, A. *Chem. Rev.* **2006**, *106*, 17-89.

(9) Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* **2007**, *72*, 3149-3151.

(10) Le Gall, E.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem.* **2009**, *74*, 7970-9973.

(11) Young, W. B.; Masters, J. J.; Danishefsky, S. *J. Am. Chem. Soc.* **1995**, *117*, 5228-5234.

(12) Wang, J.; Liang, Y.-L.; Qu, J. *Chem. Commun.* **2009**, *14*, 5144-5146.

(13) El Kazzouli, S.; Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 8575-8578.

(14) Han, G.; Tamaki, M.; Hruby, V. J. *J. Pept. Res.* **2001**, *58*, 338-341.

(15) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chemie Int. Ed.* **2005**, *44*, 5972-5974.

(16) Ram, S.; Spicer, L. *Tetrahedron Lett.* **1987**, *28*, 515-516.

(17) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2962-2965.