Palladium-Catalyzed Synthesis of Cephalotaxine Analogues

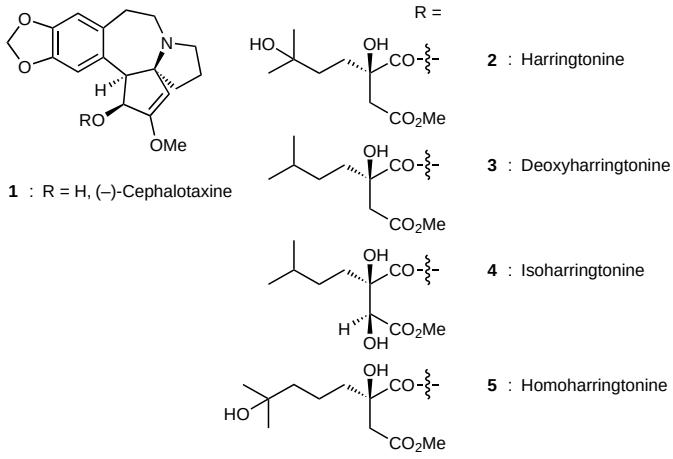
Lutz F. Tietze,* Hartmut Schirok, and Michael Wöhrmann[a]

Abstract: The synthesis of cephalotaxine ring analogues **10** was achieved by two successive intramolecular palladium-catalyzed reactions of **12** via **11**, namely an allylic amination and a Heck reaction. The substrates **12** were obtained by alkylation of primary amines **13** with tosylates **14**.

Keywords: alkaloids · antitumor agents · cephalotaxine · natural products · palladium · spiro compounds

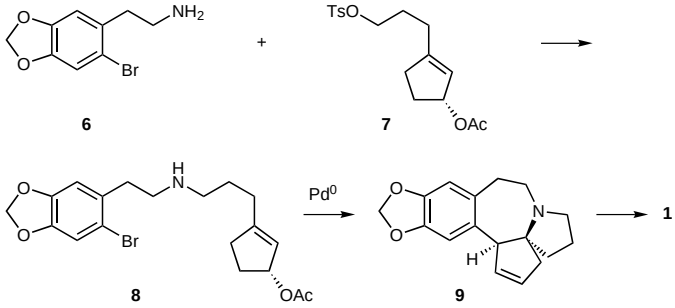
Introduction

The development of highly efficient syntheses of natural products and their analogues is one of the goals of modern organic chemistry. One way to improve the efficiency is the use of domino reactions.[1] We have recently shown that the combination of transition metal mediated or catalyzed reactions allows a facile entry to steroids,[2] antibiotics of the CC-1065 type,[3] and the pentacyclic cephalotaxine.[4] Here we describe the synthesis of analogues of cephalotaxine (**1**) by variation of the size of the different rings by means of two Pd-catalyzed reactions.



Cephalotaxine (**1**), which itself shows no pronounced biological activity, is the parent compound of the harringtonines, for example harringtonine (**2**), deoxyharringtonine (**3**), isoharringtonine (**4**), and homoharringtonine (**5**). These substances, which are found in south-east Asian plum yews of the genus *Cephalotaxus* (Cephalotaxaceae)[5] are esters of **1** and show a pronounced antileukemic activity;[5, 6] moreover homoharringtonine (**5**) has some potency in the treatment of chloroquine-resistant malaria.[7]

Several syntheses of cephalotaxine (**1**) have already been described;[4, 8] however, only very few attempts were made to access cephalotaxine analogues.[9] In our highly efficient and as yet the shortest synthesis of cephalotaxine (**1**) the secondary amine **8**, obtained by alkylation of the primary amine **6** with the tosylate **7**, was transformed stereoselectively into the pentacyclic system **9** by a Pd-catalyzed allylation followed by a Heck reaction;[4] cephalotaxine is accessible from **9** in four steps (Scheme 1).[8i,n] We have now extended



Scheme 1. Synthesis of cephalotaxine (**1**).

this study to include substrates which have different lengths of the side chains and different ring sizes as the primary amines **13** and allylic acetates **14** to allow the synthesis of modified pentacyclic ring structures of cephalotaxine (**1**) according to Scheme 2.

Results and Discussion

The primary amines **13a–d** were synthesized from commercially available compounds in a few steps according to known procedures.[10] The best method for the regioselective bromi-

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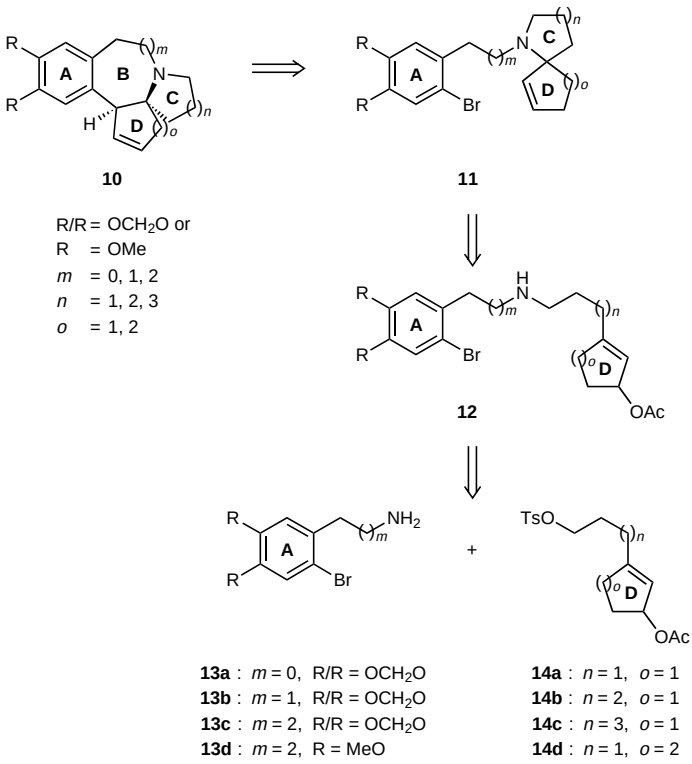
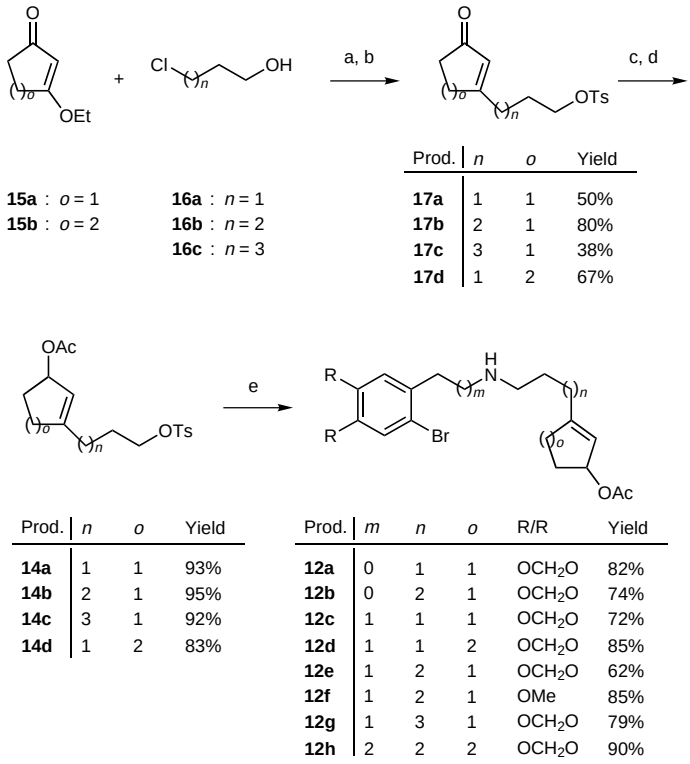


Scheme 2. Retrosynthesis of ring-size analogues **10** of cephalotaxine (**1**).



Prod.	*n*	*o*	Yield
17a	1	1	50%
17b	2	1	80%
17c	3	1	38%
17d	1	2	67%

Prod.	*n*	*o*	Yield
14a	1	1	93%
14b	2	1	95%
14c	3	1	92%
14d	1	2	83%

Prod.	*m*	*n*	*o*	R/R	Yield
12a	0	1	1	OCH_2O	82%
12b	0	2	1	OCH_2O	74%
12c	1	1	1	OCH_2O	72%
12d	1	1	2	OCH_2O	85%
12e	1	2	1	OCH_2O	62%
12f	1	2	1	OMe	85%
12g	1	3	1	OCH_2O	79%
12h	2	2	2	OCH_2O	90%

Scheme 3. Synthesis of the secondary amines **12**. a) MeMgCl (3.6 M in THF), THF, $-78\,^{\circ}C \rightarrow$room temperature; then Mg, reflux; then **15a/b**, $-10\,^{\circ}C \rightarrow$RT; then NH_4Cl solution; HCl (2 M); b) TsCl, py, $-10\,^{\circ}C$ or TsCl, DMAP, Et_3N, $-10\,^{\circ}C$; c) DIBAL (1.5 M in toluene), toluene, $-50\,^{\circ}C$; d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, $0\,^{\circ}C$; e) **13**, TBAI (1.5 equiv), THF, reflux.

nation of the aromatic ring consists of a protection of the amino function, to avoid oxidation by the formation of the hydrochloride, followed by treatment with bromine in acetic acid, and a basic workup. In all cases, the crude products obtained were clean enough to allow a further utilization without purification.

The synthesis of the allylic acetates **14a–d**[11] was found to be more demanding on account of their instability, especially in the case of the cyclopentene derivatives. The approach was similar for all four compounds. The vinylogous esters **15a**[12] and **15b**[13] were treated with a Grignard reagent obtained from the ω-chloro alkanols **16a–c**, wherein the hydroxy function is protected as a magnesium salt by means of methyl magnesium chloride. After aqueous workup, the crude alcohols were tosylated to give the slightly more stable tosylates **17a–d**.[11] For the synthesis of the necessary allylic acetates **14a–d** the enone moiety in the tosylates **17a–d** was reduced regioselectively with diisobutylaluminum hydride (DIBAL) and the corresponding alcohols were then immediately transformed into the allylic acetates by treatment with acetic anhydride in dichloromethane in nearly quantitative yield. The allylic alcohols obtained as intermediates are very unstable, whereas the allylic acetates can be kept in the refrigerator for several days without decomposition. However, after several weeks these compounds also decompose; the smell of acetic acid is evolved (Scheme 3).

The alkylation of the amines **13a–d** with the tosylates **14a–d**, after their in-situ transformation into the iodides with tetrabutylammonium iodide (TBAI), afforded the secondary amines **12a–h** in 70–90% yield (Scheme 3). Several reaction conditions for the alkylation reaction were tested; in all cases THF as the solvent was superior to DMSO. The best results were obtained with 2–3.5 equivalents of the primary amine **13** without addition of any base. Thus, with a ratio of amine **13** to tosylate **14** ranging from 0.8:1 to 1.5:1 in the presence of 1 to 5 equivalents of triethylamine or diisopropylamine, the yields of the secondary amines **12** were only 35–65%. We also used the preformed iodides obtained by a Finkelstein reaction of **14** with NaI in quantitative yield; however, this procedure did not show any advantage to the in-situ preparation of the alkylating agent.

The palladium-catalyzed intramolecular amination[11a, 14] of **12a–h** was performed with $[Pd(PPh_3)_4]$ and tetramethylguanidine as the base at 40–50 °C. In this way, the spirocyclic tertiary amines **11a–c**,**e**,**f**,**h** could be obtained from **12a–c**,**e**,**f**,**h** in 43–88% yield (Scheme 4, Table 1). However, it was not possible to transform the secondary amine **12d**, which contains a cyclohexenylacetate moiety, into the corresponding spirocyclic compounds. This can be explained by the lower reactivity of the cyclohexenyl compared to the cyclopentenyl acetate which results in a preferred oxidative addition of the Pd to the bromoarene moiety thus terminating the reaction. In addition, **12g** also failed to give a spirocyclic azepine moiety; here again the activation energy seems to be too high so that an oxidative addition takes place preferentially. To prove this assumption, we prepared **18** without a halogen at the arene moiety. Indeed, the reaction at 75 °C with $[Pd(PPh_3)_4]$ gave the desired spirocyclic amine **19** in 74% yield after 20 hours (Scheme 5).

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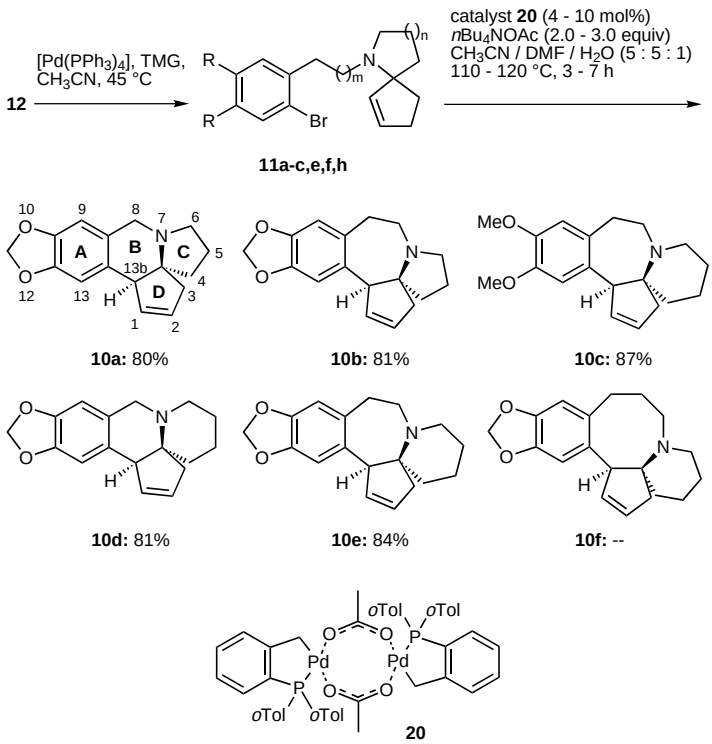
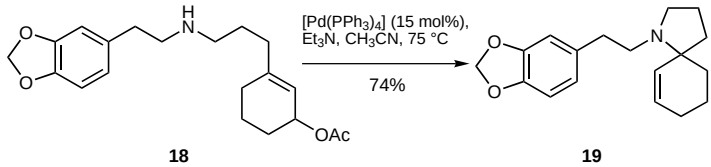


Scheme 4. Synthesis of the pentacyclic compounds **10** by intramolecular Heck reaction of **11**.

Table 1. Synthesis of the spirocyclic compounds **11** by palladium-catalyzed allylic amination of **12**.

Substrate	*m*	*n*	*o*	R/R	Product	Yield [%]
12a	0	1	1	OCH_2O	**11a**	65
12b	0	2	1	OCH_2O	**11b**	59
12c	1	1	1	OCH_2O	**11c**	88
12d	1	1	2	OCH_2O	**11d**	–
12e	1	2	1	OCH_2O	**11e**	57
12f	1	2	1	MeO	**11f**	43
12g	1	3	1	OCH_2O	**11g**	–
12h	2	2	1	OCH_2O	**11h**	67



Scheme 5. Synthesis of spirocyclic amine **19**.

The final Heck reaction of the spirocyclic amines **11** was performed under the conditions which were optimized for our cephalotaxine synthesis.[4] The substrates were stirred in a degassed solvent mixture containing acetonitrile, dimethylformamide, and water (ratio 5:5:1) in the presence of tetra-*n*-butylammonium acetate (2.1 equiv), and catalytic amounts of the palladacycle *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (**20**).[15] The transformations proceeded in all cases except one (**10f**) to give the desired products **10a–e** stereoselectively and in high yields. Thus, only one diastereomer is formed by a *Re* attack of the bromoarene moiety to the cyclopentene system *syn* to the nitrogen. We assume that this can be attributed to steric reasons; however, a coordinative influence of the nitrogen cannot be excluded. From these reactions we obtained analogues of cephalotaxine in which the pentacyclic core had different sizes of the rings BCD, that is **10a** (6,5,5), **10c** (7,6,5), **10d** (6,6,5), and **10e** (7,6,5). As expected, the formation of the analogue **10f**, with a (8,6,5) pattern, did not take place. So far we have not yet succeeded in obtaining an eight-membered ring by a Heck reaction with a variety of substrates.

The structures of the newly formed compounds were determined by NMR spectroscopy. For example, the spectroscopic data of **10a** show signals of the aromatic hydrogens at $\delta = 6.55$ and $\delta = 6.60$, whereas the hydrogens of the double bond resonate as a dddd at $\delta = 5.68$ with $J = 6.0$, 2.3, 2.3, 2.3 Hz for 1-H and at $\delta = 6.75$ as a dddd with $J = 6.0$, 2.3, 2.1, 2.0 Hz for 2-H. For 13b-H a broad singlet is observed at $\delta =$ 3.41. Significant signals in the ^{13}C NMR spectrum are found at $\delta = 129.6$ for C1 and $\delta = 132.8$ for C2, while C13b resonates at $\delta = 50.29$ and C3a at $\delta = 69.30$.

For all compounds **10a–e**, molecular peaks are found in the high-resolution mass spectra.

Conclusions

A new and highly efficient synthesis has been established for analogues **10a**,**c–e** of the pentacyclic core of cephalotaxine (**1**) by means of two successive Pd-catalyzed transformations. Cyclopentenylacetates were found to be much more reactive in the palladium-catalyzed allylic aminations than the corresponding cyclohexenyl compounds. In the Heck reactions, the cyclopentene moiety reacts smoothly and with high yield to give the final tetra- or pentacyclic products **10a–e**. Analogues with a six-membered ring D and an eight-membered ring B could not be obtained by the described process.

Experimental Section

All reactions were performed under a nitrogen or argon atmosphere in flame-dried flasks, and the reactants were introduced by syringe. All solvents were dried by standard methods. Solvents used in Pd-catalyzed reactions were degassed by pump and freeze methodology. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography was performed on precoated silica gel plates (SIL G/UV_{254}, Macherey-Nagel GmbH & Co. KG). Silica gel 32–63 (0.032–0.064 mm) (Macherey-Nagel GmbH & Co. KG) was used for column chromatography.

UV/Vis spectra were recorded in CH_3CN on a Mettler Lambda 2 spectrometer. IR spectra were recorded as KBr pellets or as films on a Bruker IFS 25 or Vector 22 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian XL 200, VXR 200 and VXR 500 or a Bruker AM 300 with tetramethylsilane (TMS) as the internal standard in [D]chloroform or [D_6]benzene. Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were measured at 70 eV on a Varian MAT 311A, high-resolution mass spectra on a Varian MAT 731 instrument. Melting points were measured on a Mettler FP 61.

3-(6-Bromo-benzo[1,3]dioxol-5-yl)-propylamine (13c): The hydrochloride of 3-benzo[1,3]dioxol-5-yl-propylamine[16] (4.01 g, 18.5 mmol) was dissolved in acetic acid (50 mL) and treated with bromine (4.01 g, 25.1 mmol, 1.4 equiv). After 3 h, Na_2SO_3 solution (5%) was added, and the mixture

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was basified with aqueous NaOH solution (20%). After extraction with CH_2Cl_2 (4×) the combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo to give the amine **13c** (4.68 g, 18.1 mmol, 98%) as a pale yellow oil. An analytical probe was purified via the hydrochloride, which was then recrystallized from MeOH/*tert*-butyl methyl ether (MTBE). IR (KBr): $\tilde{\nu}$ = 3314 (N–H), 2932 (C–H), 1572 (NH_3^+), 1478, 1232, 1113, 1038, 933 (C-O-C), 860, 826 cm^{-1} (hydrochloride); UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 202.0 (4.597), 237.0 (3.690), 294.5 (3.661) nm (hydrochloride); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 2H, NH_2), 1.71 (tt, J = 7.7, 7.1 Hz, 2H, CH_2), 2.64–2.72 (m, 2H, $ArCH_2$), 2.75 (t, J = 7.1 Hz, 2H, NCH_2), 5.94 (s, 2H, OCH_2O), 6.71 (s, 1H, 4-H), 6.98 (s, 1H, 7-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 33.31 ($ArCH_2$), 34.11 (CH_2), 41.61 (NCH_2), 101.4 (OCH_2O), 109.7 (C4), 112.6 (C7), 114.1 (C6), 134.3 (C5), 146.4 (C3a), 147.2 (C7a); MS (70 eV, EI): *m*/*z* (%): 258 (6) [M^+], 213 (8) [$M^+ - C_2H_6N$], 178 (100) [$M^+ - Br$], 150 (51) [$C_9H_{10}O_2^+$], 131 (21); $C_{10}H_{12}BrNO_2$ (258.1): calcd C 40.63, H 4.77; found C 40.93, H 4.52 (hydrochloride).

4-(3-Oxocyclopent-1-enyl)butyl toluene-4-sulfonate (17b): A solution of 4-chlorobutan-1-ol (**16b**) (6.44 g, 59.3 mmol) in THF (60 mL) was cooled to –78 °C and methylmagnesium chloride (3.8 M in THF, 15.6 mL, 59.3 mmol, 1.0 equiv) was added dropwise. After the addition was complete the solution was allowed to warm to room temperature. When the gas production ceased, magnesium turnings (1.59 g, 65.4 mmol, 1.1 equiv) were added, and the solution was heated to reflux for 3 h. Subsequently, the reaction mixture was cooled to –10 °C, 3-ethoxy-cyclopent-2-enone (**15a**)[12] (5.05 g, 40.0 mmol) was added, and the mixture was stirred for 1.5 h. The mixture was warmed to 0 °C, and saturated NH_4Cl solution (10 mL) was added. The mixture was partitioned between cold ethyl acetate (100 mL) and HCl (50 mL, 2 N). The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and evaporated. The crude product was dissolved in CH_2Cl_2 (80 mL) and cooled to –10 °C. Tosyl chloride (8.31 g, 43.6 mmol, 1.1 equiv), triethylamine (7.40 mL, 53.0 mmol, 1.3 equiv), and 4-dimethylaminopyridine (DMAP) (242 mg, 1.98 mmol, 0.05 equiv) were added, and the mixture was stirred at –10 °C for 18 h, then partitioned between ethyl acetate and a saturated solution of $NaHCO_3$. After separation, the organic layer was washed with HCl (1 N) and brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography (1000 g SiO_2, petroleum ether/ethyl acetate = 2:3) afforded **17b** (9.82 g, 31.8 mmol, 80%) as a colorless oil. R_f = 0.34 (PE/EtOAc = 2:3); IR (KBr): $\tilde{\nu}$ = 2961 (=C–H), 1708 (C=O), 1617 (C=C), 1597, 1356 (SO_2), 1188, 1174 (SO_2), 942, 817, 665 cm^{-1}; UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 194.0 (4.687), 224.0 (4.433), 255.0 (2.813), 261.5 (2.859), 266.5 (2.829), 272.5 (2.777), 302.0 nm (2.395); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.54–1.76 (m, 4H, 2-H_2, 3-H_2), 2.32–2.42 (m, 4H, 4-H_2, 5′-H_2), 2.44 (s, 3H, CH_3), 2.55 (m, 2H, 4′-H_2), 4.07 (t, J = 6.4 Hz, 2H, OCH_2), 5.87 (s, 1H, 2′-H), 7.36 (d, J = 8.0 Hz, 2H, Ar-2-H, Ar-6-H), 7.78 (d, J = 8.0 Hz, 2H, Ar-3-H, Ar-5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.57 (CH_3), 22.90 (C3), 28.35 (C2), 31.33 (C5′), 32.58 (C4), 35.17 (C4′), 69.81 (OCH_2), 127.7 (Ar-C3, Ar-C5), 129.5 (C2′), 129.8 (Ar-C2, Ar-C6), 132.8 (Ar-C4), 144.8 (Ar-C1), 181.6 (C1′), 209.7 (C3′); MS (70 eV, EI): *m*/*z* (%): 308 (100) [M^+], 206 (12), 155 (14) [Ts^+], 153 (48) [$M^+ - Ts$], 136 (74) [$M^+ - TsOH$], 109 (80), 91 (87) [CH_3Ph^+]; $C_{16}H_{20}O_4S$ (308.4); calcd C 62.32, H 6.54; found C 62.38, H 6.48; HRMS calcd 308.1082; found 308.1082.

5-(3-Oxocyclopent-1-enyl)pentyl toluene-4-sulfonate (17c): Analogous to **17b**, 5-chloropentan-1-ol (**16c**) (7.30 g, 59.6 mmol) was deprotonated with methylmagnesium chloride solution (3.8 M in THF, 16.0 mL, 60.8 mmol, 1.0 equiv) and treated with magnesium turnings (1.60 g, 65.8 mmol, 1.1 equiv) in THF (120 mL). Subsequently, 3-ethoxycyclopent-2-enone (**15a**)[12] (4.95 g, 39.2 mmol) was added. After aqueous workup, the crude product was tosylated in CH_2Cl_2 with tosyl chloride (8.31 g, 43.6 mmol, 1.1 equiv), triethylamine (7.40 mL, 53.0 mmol, 1.3 equiv), and DMAP (250 mg, 2.05 mmol, 0.05 equiv). Purification by column chromatography (900 g SiO_2, petroleum ether/ethyl acetate = 1:1) afforded **17c** (4.86 g, 15.1 mmol, 38%) as a colorless oil. R_f = 0.30 (PE/EtOAc = 1:1); IR (neat): $\tilde{\nu}$ = 2933 (=C–H), 1705 (C=O), 1615 (C=C), 1599, 1357 (SO_2), 1188, 1176 (SO_2), 947, 817, 665 cm^{-1}; UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 194.0 (4.706), 224.5 (4.416), 261.5 (2.898), 266.5 (2.876), 272.5 (2.843), 304.0 nm (2.653); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (tt, J = 7.7, 7.6 Hz, 2H, 3-H_2), 1.52 (tt, J = 7.7, 7.6 Hz, 2H, 4-H_2), 1.66 (tt, J = 7.6, 6.4 Hz, 2H, 2-H_2), 2.34 (t, J = 7.6 Hz, 2H, 5-H_2), 2.36 (m, 2H, 5′-H_2), 2.42 (s, 3H, CH_3), 2.51–2.54 (m, 2H, 4′-H_2), 4.00 (t, J = 6.4 Hz, 2H, OCH_2), 5.87 (s, 1H, 2′-H), 7.33 (d, J = 8.0 Hz, 2H, Ar-2-H, Ar-6-H), 7.76 (d, J = 8.0 Hz, 2H, Ar-3-H, Ar-5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.56 (CH_3), 25.07 (C3), 26.27 (C4), 28.47 (C2), 31.39 (C5′), 33.13 (C5), 35.19 (C4′), 70.11 (OCH_2), 127.7 (Ar-C3, Ar-C5), 129.4 (C2′), 129.8 (Ar-C2, Ar-C6), 132.9 (Ar-C4), 144.7 (Ar-C1), 182.3 (C1′), 209.9 (C3′); MS (70 eV, EI): *m*/*z* (%): 322 (96) [M^+], 167 (90) [M^+ – Ts], 155 (16) [Ts^+], 151 (31) [$M^+ - TsO$], 109 (100) [$C_7H_9O^+$], 91 (91) [$PhCH_3^+$]; $C_{17}H_{22}O_4S$ (322.4): calcd C 63.33 H 6.88; found C 63.03, H 6.74.

3-[5-(Toluene-4-sulfonyloxy)pentyl]cyclopent-2-enyl acetate (14c): Cyclopentenone **17c** (4.57 g, 14.2 mmol) was dissolved in toluene (70 mL) and cooled to –50 °C. A DIBAL solution in toluene (1.5 M, 11.5 mL, 17.3 mmol, 1.2 equiv) was added dropwise with the aid of a syringe pump. After the addition of celite (4 g), a 1:1 mixture of methanol and water (4 mL) was added, and the mixture was warmed to room temperature, filtered, and flushed again with ethyl acetate. The filtrate was dried over Na_2SO_4 and evaporated. The crude allylic alcohol, as a 0.3 M solution in CH_2Cl_2, was acetylated at 0 °C with acetic anhydride (1.53 g, 15.0 mmol, 1.06 equiv), triethylamine (1.65 g, 16.3 mmol, 1.2 equiv), and DMAP (173 mg, 1.42 mmol, 0.1 equiv). The mixture was stirred for 1.5 h and then poured into a cold, half-saturated solution of $NaHCO_3$. The organic layer was extracted with CH_2Cl_2 (3×) and the combined organic fractions were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel (220 g SiO_2, petroleum ether/ethyl acetate = 7:2) to give the allylic acetate **14c** (4.76 g, 13.0 mmol, 92%) as a colorless oil. R_f = 0.32 (PE/EtOAc = 7:2); IR (neat): $\tilde{\nu}$ = 2931 (C–H), 1713 (C=O), 1598, 1359 (SO_2), 1268 (C–O), 1176 (SO_2), 1098, 947, 816 (arene), 664 cm^{-1}; UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 224.5 (4.079), 255.0 (2.800), 261.5 (2.837), 272.5 nm (2.707); ^1H NMR (200 MHz, C_6D_6): δ = 0.85–1.16 (m, 4H, 2′-H_2, 3′-H_2), 1.25 (tt, J = 6.8, 6.8 Hz, 2H, 4′-H_2), 1.66–1.89 (m, 4H, 1′-H_2, 5-H_2), 1.74 (s, 3H, $COCH_3$), 1.89 (s, 3H, Ar-CH_3), 2.03–2.24 (m, 2H, 4-H_2), 3.80 (t, J = 6.5 Hz, 2H, OCH_2), 5.50 (br s, 1H, 2-H), 5.70–5.82 (m, 1H, 1-H), 6.77 (d, J = 8.1 Hz, 2H, Ar-2-H, Ar-6-H), 7.78 (d, J = 8.1 Hz, 2H, Ar-3-H, Ar-5-H); ^{13}C NMR (50.3 MHz, C_6D_6): δ = 20.99 ($COCH_3$), 21.15 (Ar-CH_3), 25.30 (C3′), 26.86 (C2′), 28.83 (C4′), 30.84 (C5), 31.03 (C1′), 33.59 (C4), 70.15 (OCH_2), 80.89 (C1), 123.3 (C2), 128.1 (Ar-C3, Ar-C5), 129.8 (Ar-C2, Ar-C6), 134.5 (Ar-C4), 144.2 (Ar-C1), 151.7 (C3), 170.2 (CO); $C_{19}H_{26}O_5S$ (366.5).

3-(3-Iodopropyl)cyclohex-2-enyl acetate: The tosylate **14d** (5.11 g, 14.5 mmol) was dissolved in acetone (500 mL). After addition of sodium iodide (10.2 g, 68.1 mmol, 4.7 equiv) the mixture was refluxed for 1.5 h. Water and MTBE were added and, after separation, the aqueous layer was extracted with MTBE (3×). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (200 g SiO_2, petroleum ether/ethyl acetate = 14:1) to afford the title compound (4.33 g, 14.1 mmol, 97%) as a colorless oil. R_f = 0.37 (PE/EtOAc = 14:1); IR (neat): $\tilde{\nu}$ = 2937 (=C–H), 1729 (C=O), 1666 (C=C), 1242 (C–O), 1019 cm^{-1}; UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 252.0 nm (2.855); ^1H NMR (200 MHz, C_6D_6): δ = 1.43–1.77 (m, 10H, 1′-H_2, 2′-H_2, 4-H_2, 5-H_2, 6-H_2), 1.77 (s, 3H, CH_3), 2.68 (t, J = 6.9 Hz, 2H, 3′-H_2), 5.34–5.44 (m, 1H, 1-H), 5.55 (m, 1H, 2-H); ^{13}C NMR (50.3 MHz, C_6D_6): δ = 5.99 (C3′), 19.41 (C5), 21.03 (CH_3), 28.25, 28.48 (C4, C6), 31.35 (C2′), 38.18 (C1′), 68.44 (C1), 121.4 (C2), 142.0 (C3), 169.9 (CO); MS (70 eV, EI): *m*/*z* (%): 308 (5) [M^+], 266 (38) [M^+ – Ac+H], 248 (100) [M^+ – AcOH], 139 (19) [$C_9H_{14}O^+$], 121 (17) [$C_9H_{13}^+$], 97 (50) [$C_6H_9O^+$], 93 (78) [$C_7H_9^+$], 79 (54) [$C_6H_7^+$]. $C_{11}H_{17}IO_2$ (308.2): calcd C 42.87, H 5.56; found C 43.05; H 5.57; HRMS calcd 308.0273; found 308.0273.

General procedure I: alkylation of primary amines 13: A 1 M solution of the amine **13** (2.5 equiv) in THF was heated with TBAI (1.5 equiv) to reflux and a 0.5 M solution of the tosylate **14** was added dropwise with an infusion pump over a period of 8 h. The mixture was heated for additional 2 h, poured into MTBE, and basified with cold 5% NaOH solution. The aqueous layer was extracted with MTBE (4×). The combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography.

3-{3-[(6-Bromobenzo[1,3]dioxol-5-ylmethyl)amino]propyl}cyclopent-2-enyl acetate (12a): According to general procedure I, **13a** (1.01 g, 4.37 mmol, 2.5 equiv) in THF (5 mL) was alkylated with **14a** (582 mg, 1.72 mmol) in THF (3 mL) in the presence of TBAI (1.00 g, 2.71 mmol, 1.6 equiv). Purification by column chromatography (70 g SiO_2, gradient column: 300 mL ethyl acetate; then ethyl acetate/MeOH = 20:1, 1% Et_3N) afforded **12a** (562 mg, 1.42 mmol, 82%) as a pale yellow oil. R_f = 0.59

(EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3341 (N–H), 2933 (C–H), 1726 (C=O), 1651 (C=C), 1478, 1244 (C–O), 1120, 1037, 932 (C-O-C), 877, 831 (arene) cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.609), 240.5 (3.758), 293.5 nm (3.587); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.78 (tt, J = 7.6, 7.4 Hz, 2H, 2′-H_2), 1.83 (dddd, J = 14.2, 9.0, 4.0, 3.2 Hz, 5-H_{cis}), 2.02 (s, 3H, CH_3), 2.16–2.25 (m, 3H, 1′-H_2, 4-H), 2.31 (dddd, J = 14.2, 9.0, 7.5, 5.0 Hz, 1H, 5-H_{trans}), 2.41–2.49 (m, 1H, 4-H), 2.68 (t, J = 7.2 Hz, 2H, 3′-H_2), 2.85 (br s, 1H, NH), 3.85 (s, 2H, 1″-H_2), 5.47 (m, 1H, 2-H), 5.61–5.66 (m, 1H, 1-H), 5.97 (s, 2H, OCH_2O), 6.99 (s, 1H, Ar–H), 7.01 (s, 1H, Ar–H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.36 (CH_3), 27.33 (C2′), 28.82 (C1′), 30.30 (C5), 33.46 (C4), 48.36 (C3′), 53.12 (C1″), 80.87 (C1), 101.7 (OCH_2O), 110.3 (C4‴), 112.7 (C7‴), 114.2 (C6‴), 122.6 (C2), 131.4 (C5‴), 147.3 (C3a‴), 147.5 (C7a‴), 151.9 (C3), 171.1 (CO); MS (70 eV, CI (NH_3)): m/z (%): 396/394 (4) [M+H$^+$], 338/336 (13/14) [M^+ – AcO], 318 (20) [M^+ – Br+2H], 280/278 (8/11), 258 (27), 184/182 (42), 169 (100), 152/150 (93/90), 124 (56) [$C_8H_{14}N^+$]; $C_{18}H_{22}BrNO_4$ (396.3).

3-{4-[(6-Bromobenzo[1,3]dioxol-5-ylmethyl)amino]butyl}cyclopent-2-enyl acetate (12b): According to general procedure I, the amine **13a** (2.61 g, 11.4 mmol, 2.5 equiv) was alkylated with tosylate **14b** (1.63 g, 4.63 mmol) in the presence of TBAI (2.56 g, 6.93 mmol, 1.5 equiv). Purification by column chromatography (80 g AloxB, petroleum ether/MTBE = 1:3) afforded **12b** (1.40 g, 3.41 mmol, 74%) as pale yellow oil. R_f = 0.63 (PE/EtOAc/MeOH = 10:5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3338 (N–H), 2930 (C–H), 1727 (C=O), 1651 (C=C), 1478, 1245 (C–O), 1119, 1037, 933 (C-O-C), 875, 830 (arene) cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.623), 236.0 (3.714), 293.5 nm (3.622); ^1H NMR (500 MHz, C_6D_6): δ = 0.83 (br s, 1H, NH), 1.23–1.36 (m, 4H, 2′-H_2, 3′-H_2), 1.73 (s, 3H, CH_3), 1.81–1.93 (m, 4H, 1′-H_2, 5-H_2), 2.13 (dddd, J = 14.8, 8.7, 7.6, 5.7 Hz, 1H, 4-H), 2.19–2.26 (m, 1H, 4-H), 2.37 (t, J = 6.8 Hz, 2H, 4′-H_2), 3.66 (s, 2H, 1″-H_2), 5.22 (s, 2H, OCH_2O), 5.60 (m, 1H, 2-H), 5.79–5.83 (m, 1H, 1-H), 6.94 (s, 1H, Ar–H), 7.01 (s, 1H, Ar–H); ^{13}C NMR (50.3 MHz, C_6D_6): δ = 20.99 (CH_3), 25.37 (C2′), 30.23 (C5), 30.70 (C3′), 31.27 (C1′), 33.63 (C4), 49.11 (C4′), 53.61 (C1″), 80.96 (C1), 101.6 (OCH_2O), 110.0 (C4‴), 112.8 (C7‴), 114.0 (C6‴), 123.3 (C2), 133.8 (C5‴), 147.6 (C3a‴), 147.9 (C7a‴), 151.9 (C3), 170.2 (CO); MS (70 eV, CI (NH_3)): m/z (%): 412/410 (87/92) [M+H$^+$], 352/350 (73/75) [M^+ – AcO], 332 (37) [M^+ – Br+2H], 249/247 (34/35) [$C_8H_9BrNO_2^+$+NH_3], 232/230 (13/16) [$C_8H_9BrNO_2^+$], 198/196 (31/27), 169 (100) [$C_{10}H_{18}N^+$+NH_3], 152 (36) [$C_{10}H_{18}N^+$], 150 (43) [$C_{10}H_{16}N^+$], 138 (49) [$C_9H_{16}N^+$]; $C_{19}H_{24}BrNO_4$ (410.3): calcd C 55.62, H 5.90; found C 55.76, H 5.95.

3-{3-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethylamino]propyl}cyclopent-2-enyl acetate (12c): According to general procedure I, the amine **13b** (741 mg, 3.04 mmol, 2.0 equiv) was alkylated with tosylate **14a** (505 mg, 1.49 mmol) in the presence of TBAI (804 mg, 2.18 mmol, 1.5 equiv). Purification by column chromatography (90 g SiO_2, gradient column: 150 mL ethyl acetate; 300 mL ethyl acetate/MeOH = 15:1, 1% Et_3N; then ethyl acetate/MeOH = 5:1, 1% Et_3N) afforded **12c** (438 mg, 1.07 mmol, 72%) as a pale yellow oil. R_f = 0.54 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3330 (N–H), 2932 (C–H), 1726 (C=O), 1650 (C=C), 1478, 1246 (C–O), 1116, 1038, 934 (C-O-C), 862, 834 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.633), 236.5 (3.677), 294.0 nm (3.628); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.7 (br s, 1H, NH), 1.71 (tt, J = 7.3, 7.2 Hz, 2H, 2′-H_2), 1.83 (dddd, J = 14.0, 8.7, 3.9, 3.2 Hz, 1H, 5-H_{cis}), 2.02 (s, 3H, CH_3), 2.12–2.26 (m, 3H, 1′-H_2, 4-H), 2.32 (dddd, J = 14.0 Hz, 8.7 Hz, 7.6 Hz, 5.1 Hz, 1H, 5-H_{trans}), 2.41–2.49 (m, 1H, 4-H), 2.68 (t, J = 7.2 Hz, 2H, 3′-H_2), 2.86 (m, 4H, 1″-H_2, 2″-H_2), 5.47 (m, 1H, 2-H), 5.95 (s, 2H, OCH_2O), 6.62–6.66 (m, 1H, 1-H), 6.74 (s, 1H, 4‴-H), 6.99 (s, 1H, 7‴-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.40 (CH_3), 27.82 (C2′), 28.97 (C1′), 30.35 (C5), 33.50 (C4), 36.51 (C2″), 49.42, 49.59 (C1″, C3′), 80.93 (C1), 101.6 (OCH_2O), 110.2 (C4‴), 112.7 (C7‴), 114.4 (C6‴), 122.5 (C2), 132.3 (C5‴), 146.8 (C3a‴), 147.3 (C7a‴), 152.2 (C3), 171.1 (CO); MS (70 eV, CI (NH_3)): m/z (%): 412/410 (100/98) [M+H$^+$], 352/350 (18/19) [M^+ – AcO], 332 (27) [M^+ – Br+2H]; $C_{19}H_{24}BrNO_4$ (410.3): calcd C 55.62, H 5.90; found C 55.31, H 5.80.

3-{3-[2-(6-Bromo-benzo[1,3]dioxol-5-yl)ethylamino]propyl}cyclohex-2-enyl acetate (12d): According to general procedure I, the amine **13b** (234 mg, 959 μmol, 3.7 equiv) was alkylated with tosylate **14d** (92.0 mg, 261 μmol) in the presence of TBAI (144 mg, 390 μmol, 1.5 equiv). Purification by column chromatography (45 g SiO_2, gradient column: 200 mL ethyl acetate/MeOH = 15:1, 1% Et_3N; then ethyl acetate/MeOH = 5:1, 1% Et_3N) afforded **12d** (93.8 mg, 221 μmol, 85%) as a pale yellow oil. R_f = 0.45 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3322 (N–H), 2936 (C–H), 1728 (C=O), 1666 (C=C), 1480, 1370, 1246 (C–O), 1116, 1040, 934 (C-O-C), 910, 860, 834 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.659), 235.0 (3.720), 294.0 nm (3.661); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59–1.82 (m, 7H, 2′-H_2, 5-H_2, 6-H_2, NH), 1.89–2.05 (m, 4H, 1′-H_2, 4-H_2), 2.04 (s, 3H, CH_3), 2.66 (t, J = 7.4 Hz, 2H, 3′-H_2), 2.82–2.90 (m, 4H, 1″-H_2, 2″-H_2), 5.23–5.27 (m, 1H, 1-H), 5.46 (m, 1H, 2-H), 5.96 (s, 2H, OCH_2O), 6.75 (s, 1H, 4‴-H), 7.00 (s, 1H, 7‴-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.05 (C5), 21.40 (CH_3), 27.62 (C2′), 28.13, 28.21 (C4, C6), 35.19 (C1′), 43.63 (C2″), 48.57 (C3′), 53.49 (C1″), 68.67 (C1), 101.6 (OCH_2O), 110.0 (C4‴), 112.6 (C7‴), 113.9 (C6‴), 119.6 (C2), 132.5 (C5‴), 144.1 (C3), 147.2 (C3a‴, C7a‴), 170.8 (CO); MS (70 eV, EI): m/z (%): 425/423 (<1) [M^+], 210 (15) [$C_{12}H_{20}NO_2^+$], 150 (100) [$C_{10}H_{16}N^+$], 121 (6) [$C_9H_{13}^+$]; $C_{20}H_{26}BrNO_4$ (424.3): calcd C 56.61, H 6.18, Br 18.83; found C 56.69, H 6.30, Br 18.87; HRMS calcd 423.1045; found 423.1045.

3-{4-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethylamino]butyl}cyclopent-2-enyl acetate (12e): According to general procedure I, the amine **13b** (1.73 g, 7.09 mmol, 2.5 equiv) was alkylated with tosylate **14b** (995 mg, 2.82 mmol) in the presence of TBAI (1.71 mg, 4.64 mmol, 1.6 equiv). Purification by column chromatography (120 g SiO_2, gradient column: 300 mL ethyl acetate; then ethyl acetate/MeOH = 15:1, 1% Et_3N) afforded **12e** (739 mg, 1.74 mmol, 62%) as a pale yellow oil. R_f = 0.67 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3322 (N–H), 2931 (C–H), 1727 (C=O), 1651 (C=C), 1478, 1245 (C–O), 1115, 1039, 933 (C-O-C), 861, 834 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.622), 237.5 (3.714), 294.0 nm (3.641); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.51 (m, 5H, 2′-H_2, 3′-H_2, NH), 1.78–1.92 (m, 1H, 5-H_{cis}), 2.03 (s, 3H, CH_3), 2.14 (m, 2H, 1′-H_2), 2.19–2.54 (m, 3H, 4-H_2, 5-H_{trans}), 2.65 (m, 2H, 4′-H_2), 2.83 (m, 4H, 1″-H_2, 2″-H_2), 5.44–5.50 (br s, 1H, 2-H), 5.60–5.68 (m, 1H, 1-H), 5.95 (s, 2H, OCH_2O), 6.74 (s, 1H, 4‴-H), 6.99 (s, 1H, 7‴-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.37 (CH_3), 25.14 (C2′), 29.84 (C3′), 30.29 (C5), 31.05 (C1′), 33.45 (C4), 36.48 (C2″), 49.54, 49.63 (C1″, C4′), 80.96 (C1), 101.5 (OCH_2O), 110.1 (C4‴), 112.7 (C7‴), 114.4 (C6‴), 122.3 (C2), 132.3 (C5‴), 146.7 (C3a‴), 147.2 (C7a‴), 152.4 (C3), 171.1 (CO); MS (70 eV, EI): m/z (%): 426/424 (<1) [M+H$^+$], 425/423 (<1) [M^+], 366/364 (9/10) [M^+ – AcO], 284 (4) [M^+ – Br – AcOH], 210 (17) [$C_{12}H_{20}NO_2^+$], 150 (100) [$C_{10}H_{16}N^+$]; $C_{20}H_{26}BrNO_4$ (424.3): calcd C 56.61, H 6.18; found C 56.37, H 6.00; HRMS calcd 423.1045; found 423.1045.

3-{4-[2-(2-Bromo-4,5-dimethoxyphenyl)ethylamino]butyl}cyclopent-2-enyl acetate (12f): According to general procedure I, the amine **13d** (1.87 g, 7.29 mmol, 2.5 equiv) was alkylated with tosylate **14b** (1.00 g, 2.84 mmol) in the presence of TBAI (1.58 g, 4.28 mmol, 1.5 equiv). Purification by column chromatography (140 g AloxB, gradient column: 300 mL petroleum ether/MTBE = 1:3; then ethyl acetate/MeOH = 30:1, 1% Et_3N) afforded **12f** (1.06 g, 2.41 mmol, 85%) as a pale yellow oil. R_f = 0.46 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3324 (N–H), 2933 (C–H), 1727 (C=O), 1651 (C=C), 1508, 1380, 1255 (C–O), 1164, 1024 (Ar-O-C), 877, 800 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 203.0 (4.684), 229.5 (3.993), 286.5 nm (3.515); ^1H NMR (200 MHz, C_6D_6): δ = 0.69 (br s, 1H, NH), 1.25–1.45 (m, 4H, 2′-H_2, 3′-H_2), 1.72 (s, 3H, $COCH_3$), 1.74–1.98 (m, 4H, 1′-H_2, 4-H, 5-H_{cis}), 2.15 (dddd, J = 14.0, 9.0, 7.5, 5.0 Hz, 1H, 4-H), 2.15–2.35 (m, 1H, 5-H_{trans}), 2.49 (t, J = 6.5 Hz, 2H, 4′-H_2), 2.87 (m, 4H, 1″-H_2, 2″-H_2), 3.36 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 5.60 (m, 1H, 2-H), 5.80 (m, 1H, 1-H), 6.64 (s, 1H, 6‴-H), 6.95 (s, 1H, 3‴-H); ^{13}C NMR (75.5 MHz, C_6D_6): δ = 20.95 (CH_3), 25.46 (C2), 30.36 (C5), 30.67 (C3′), 31.33 (C1′), 33.63 (C4), 36.96 (C2″), 49.87 (C4′), 50.38 (C1″), 55.54 (OCH_3), 55.70 (OCH_3), 80.94 (C1), 114.6 (C2‴), 116.5 (C3‴, C6‴), 123.3 (C2), 132.0 (C1‴), 149.3 (C5‴), 149.5 (C4‴), 152.0 (C3), 170.2 (CO); MS (70 eV, EI): m/z (%): 441/439 (<1) [M^+], 382/380 (3) [M^+ – AcO], 300 (3) [M^+ – AcOH – Br], 231/229 (3) [$C_9H_{10}BrO_2^+$], 210 (10) [$C_{12}H_{20}NO_2^+$], 150 (100) [$C_{10}H_{16}N^+$], 44 (22) [CO_2^+]; $C_{21}H_{30}BrNO_4$ (440.4).

3-{5-[2-(6-Bomobenzo[1,3]dioxol-5-yl)ethylamino]pentyl}cyclopent-2-enyl acetate (12g): According to general procedure I, the amine **13b** (1.67 g, 6.82 mmol, 2.6 equiv) was alkylated with tosylate **14c** (943 mg, 2.57 mmol) in the presence of TBAI (1.70 g, 4.61 mmol, 1.8 equiv). Purification by column chromatography (120 g SiO_2, gradient column: 300 mL ethyl acetate; then ethyl acetate/MeOH = 15:1, 1% Et_3N) afforded **12g** (894 mg, 2.04 mmol, 79%) as a pale yellow oil. R_f = 0.57 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3325 (N–H), 2930 (C–H), 1727 (C=O), 1650 (C=C), 1478, 1245 (C–O), 1115, 1039, 934 (C-O-C), 861, 834 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 200.5 (4.636), 236.5 (3.712), 294.0 nm (3.643); ^1H NMR (200 MHz, C_6D_6): δ = 0.58 (br s, 1H, NH), 1.13–1.42 (m, 6H,

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2′-H_2, 3′-H_2, 4′-H_2), 1.73 (s, 3H, CH_3), 1.80–2.00 (m, 3H, 1′-H_2, 5-H_{cis}), 2.06–2.34 (m, 3H, 4-H_2, 5-H_{trans}), 2.44 (t, J = 6.3 Hz, 2H, 5′-H_2), 2.74 (m, 4H, 1″-H_2, 2″-H_2), 5.19 (s, 2H, OCH_2O), 5.62 (br s, 1H, 2-H), 5.76–5.87 (m, 1H, 1-H), 6.62 (s, 1H, 4‴-H), 6.93 (s, 1H, 7‴-H); ^{13}C NMR (125.7 MHz, C_6D_6): δ = 20.96 (CH_3), 27.42 (C2′), 27.66 (C3′), 30.36 (C5), 30.68 (C4′), 31.40 (C1′), 33.65 (C4), 37.03 (C2″), 49.90, 50.08 (C1″, C5′), 80.97 (C1), 101.5 (OCH_2O), 110.6 (C4‴), 112.9 (C7‴), 114.9 (C6‴), 123.2 (C2), 133.3 (C5‴), 147.2 (C3a‴), 147.7 (C7a‴), 152.1 (C3), 170.2 (CO); MS (70 eV, CI (NH_3)): m/z (%): 442/440 (15) [M+H$^+$], 380/378 (56) [M^+ – AcO], 360 (33) [M^+ – Br+2H], 300 (100) [$C_{19}H_{26}NO_2^+$], 263/261 (14/16) [$C_9H_{11}BrNO_2^+$+NH_3], 246/244 (37/40) [$C_9H_{11}BrNO_2^+$], 183 (42) [$C_{11}H_{20}N^+$+NH_3], 166 (93) [$C_{11}H_{20}N^+$], 152 (52) [$C_{10}H_{18}N^+$]; $C_{21}H_{28}BrNO_4$ (438.4): calcd C 57.65, H 6.46; found C 57.76, H 6.53.

3-{4-[3-(6-Bromobenzo[1,3]dioxol-5-yl)propylamino]butyl}cyclopent-2-enyl acetate (12h): According to general procedure I, the amine **13c** (2.77 g, 10.7 mmol, 2.5 equiv) was alkylated with tosylate **14b** (1.50 g, 4.26 mmol) in the presence of TBAI (2.40 g, 6.50 mmol, 1.5 equiv). Purification by column chromatography (100 g AloxB, petroleum ether/MTBE = 1:3) afforded **12h** (1.68 g, 3.83 mmol, 90%) as a pale yellow oil. R_f = 0.37 (PE/EtOAc/MeOH = 10:5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3348 (N–H), 2930 (C–H), 1726 (C=O), 1651 (C=C), 1477, 1229 (C–O), 1112, 1040, 937 (C-O-C), 860, 833 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 200.5 (4.644), 236.5 (3.710), 294.0 nm (3.632); ^{1}H NMR (500 MHz, C_6D_6): δ = 0.6 (br s, 1H, NH), 1.32 (tt, J = 7.5, 7.1 Hz, 2H, 2′-H_2), 1.39 (tt, J = 7.1, 7.1 Hz, 2H, 3′-H_2), 1.66 (tt, J = 7.6, 7.1 Hz, 2H, 2″-H_2), 1.73 (s, 3H, CH_3), 1.82–1.98 (m, 2H, 5-H_2), 1.92 (t, J = 7.5 Hz, 2H, 1′-H_2), 2.14 (dddd, J = 14.0, 9.0, 7.5, 5.0 Hz, 1H, 4-H), 2.21–2.29 (m, 1H, 4-H), 2.41 (t, J = 7.1 Hz, 2H, 1″-H_2), 2.47 (t, J = 7.1 Hz, 2H, 4′-H_2), 2.68 (t, J = 7.6 Hz, 2H, 3″-H_2), 5.21 (s, 2H, OCH_2O), 5.63 (m, 1H, 2-H), 5.80–5.84 (m, 1H, 1-H), 6.60 (s, 1H, 4‴-H), 6.94 (s, 1H, 7‴-H); ^{13}C NMR (125.7 MHz, C_6D_6): δ = 20.97 (CH_3), 25.48 (C2′), 30.34 (C5), 30.68 (C3″), 30.84 (C3′), 31.34 (C1′), 33.65 (C4), 33.96 (C2″), 49.32, 49.91 (C1″, C4′), 80.96 (C1), 101.5 (OCH_2O), 110.3 (C4‴), 112.9 (C7‴), 114.6 (C6‴), 123.3 (C2), 135.1 (C5‴), 147.1 (C3a‴), 147.8 (C7a‴), 152.0 (C3), 170.2 (CO); MS (70 eV, CI (NH_3)): m/z (%): 440/438 (8/9) [M+H$^+$], 380/378 (8/9) [M^+ – AcO], 360 (14) [M^+ – Br+2H], 300 (6) [$C_{19}H_{26}NO_2^+$], 277/275 (5) [$C_{10}H_{13}BrNO_2^+$+NH_3], 260/258 (4/5) [$C_{10}H_{13}BrNO_2^+$], 213 (26), 198 (57), 180 (15) [$C_{12}H_{22}N^+$], 155 (44) [$C_9H_{16}N^+$+NH_3], 138 (100) [$C_9H_{16}N^+$]; $C_{21}H_{28}BrNO_4$ (438.4): calcd C 57.65, H 6.46; found C 57.59, H 6.58.

3-{3-[(2-Benzo[1,3]dioxol-5-yl)ethylamino]propyl}cyclohex-2-enyl acetate (18): According to general procedure I, 2-benzo[1,3]dioxol-5-yl-ethylamine (540 mg, 3.23 mmol, 2.0 equiv) was alkylated with 3-(3-iodopropyl)-cyclohex-2-enyl acetate (503 mg, 1.63 mmol). Purification by column chromatography (100 g SiO_2, gradient column: 100 mL ethyl acetate; 300 mL ethyl acetate/MeOH = 15:1, 1% Et_3N; then ethyl acetate/MeOH = 5:1, 1% Et_3N) afforded **18** (450 mg, 1.30 mmol, 80%) as a pale yellow oil. R_f = 0.53 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3328 (N–H), 2936 (C–H), 1726 (C=O), 1664 (C=C), 1490, 1442, 1246 (C–O), 1122, 1040, 934 (C-O-C), 912, 860, 810 cm^{-1} (arene); UV (CH_3CN): λ_{max} (lg ε) = 198.5 (4.680), 234.0 (3.603), 287.0 nm (3.565); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (br s, 1H, NH), 1.50–1.85 (m, 6H, 2′-H_2, 5-H_2, 6-H_2), 1.90–2.05 (m, 4H, 1′-H_2, 4-H_2), 2.04 (s, 3H, CH_3), 2.59 (t, J = 7.2 Hz, 2H, 3′-H_2), 2.65–2.86 (m, 4H, 1″-H_2, 2″-H_2), 5.19–5.29 (m, 1H, 1-H), 5.43 (br s, 1H, 2-H), 5.92 (s, 2H, OCH_2O), 6.65 (dd, J = 7.8, 1.7 Hz, 1H, 6‴-H), 6.69 (d, J = 1.7 Hz, 1H, 4‴-H), 6.74 (d, J = 7.8 Hz, 1H, 7‴-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.07 (C5), 21.42 (CH_3), 27.65 (C2′), 28.16, 28.21 (C4, C6), 35.27 (C1′), 36.02 (C2″), 49.43 (C3′), 51.22 (C1″), 68.68 (C1), 100.7 (OCH_2O), 108.1 (C4‴), 108.9 (C7‴), 119.6 (C2), 121.4 (C6‴), 133.8 (C5‴), 144.2 (C3), 145.8 (C7a‴), 147.6 (C3a‴), 170.8 (CO); MS (70 eV, CI (NH_3)): m/z (%): 346 (100) [M+H$^+$], 286 (10) [M^+ – AcO], 183 (11), 166 (13) [$C_{11}H_{20}N^+$]; $C_{20}H_{27}NO_4$ (345.4): calcd C 69.54, H 7.88; found C 69.63, H 7.99.

General procedure II: palladium-catalyzed allylic amination of 12: A solution of the secondary amine (0.25–0.05 M) in acetonitrile was degassed by pump and freeze methodology. Then of [Pd(PPh_3)$_4$] (5–10 mol%) and triethylamine or tetramethylguanidine (2.5 equiv) was added. The mixture was degassed a second time and heated to 45 °C until the reaction was complete (TLC). The mixture was diluted with MTBE and extracted twice with cold HCl (1M). The aqueous phase was washed twice with MTBE and basified with cold NaOH solution (10%). The mixture was extracted with MTBE (4×), the organic layer dried over Na_2SO_4, evaporated, and the residue purified by column chromatography.

1-(6-Bromobenzo[1,3]dioxol-5-ylmethyl)-1-aza-spiro[4.4]non-6-ene (11a): According to general procedure II, the amine **12a** (205 mg, 517 µmol) was cyclized with [Pd(PPh_3)$_4$] (54.0 mg, 47.0 µmol, 7 mol%) and tetramethylguanidine (138 mg, 1.20 mmol, 2.3 equiv). Column chromatography (50 g SiO_2, EtOAc) furnished **11a** (112 mg, 334 µmol, 65%) as a colorless oil. R_f = 0.61 (EtOAc); IR (neat): $\tilde{\nu}$ = 3048 (Ar–H), 2956 (C–H), 1477, 1235, 1101, 1039, 936 (C-O-C), 869, 831 (arene), 720 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 202.0 (4.596), 233.5 (3.790), 293.0 nm (3.619); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60–2.10 (m, 6H, 3-H_2, 4-H_2, 9-H_2), 2.38 (m, 2H, 8-H_2), 2.50–2.83 (m, 2H, 2-H_2), 3.46 (m, 2H, 1′-H_2), 5.60–5.66 (m, 1H, 6-H), 5.83–5.91 (m, 1H, 7-H), 5.94 (s, 2H, OCH_2O), 6.95 (s, 1H, 4″-H), 7.02 (s, 1H, 7″-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.56 (C3), 30.09 (C8), 31.56 (C9), 38.17 (C4), 51.11 (C2), 52.59 (C1′), 101.5 (OCH_2O), 110.2 (C4″), 112.3 (C7″), 113.9 (C6″), 135.1 (C6), 146.9 (C3a″), 147.4 (C7a″); MS (70 eV, EI): m/z (%): 338/336 (100/98) [M+H$^+$], 258 (61) [M^+ – Br+2H], 150 (29) [$C_8H_8NO_2^+$], 124 (58) [$C_8H_{14}N^+$]; $C_{16}H_{18}BrNO_2$ (336.22): calcd C 57.16, H 5.40; found C 57.38, H 5.30.

6-(6-Bromobenzo[1,3]dioxol-5-ylmethyl)-6-aza-spiro[4.5]dec-1-ene (11b): According to general procedure II, the amine **12b** (700 mg, 1.71 mmol) was cyclized with [Pd(PPh_3)$_4$] (130 mg, 112 µmol, 7 mol%) and tetramethylguanidine (441 mg, 3.83 mmol, 2.3 equiv). Column chromatography (20 g SiO_2, EtOAc) afforded **11b** (353 mg, 1.01 mmol, 59%) as a colorless oil. R_f = 0.77 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (KBr): $\tilde{\nu}$ = 3053 (Ar–H), 2957, 2925 (C–H), 1464, 1367, 1236, 1100, 1037, 937 (C-O-C), 881, 854, 831 (arene), 743 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 202.0 (4.650), 232.0 (3.834), 293.5 nm (3.665); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45–2.00 (m, 8H, 4-H_2, 8-H_2, 9-H_2, 10-H_2), 2.19–2.56 (m, 4H, 3-H_2, 7-H_2), 3.20 (d, J = 15.4 Hz, 1H, 1′-H), 3.57 (d, J = 15.4 Hz, 1H, 1′-H), 5.53–5.59 (m, 1H, 1-H), 5.73–5.79 (m, 1H, 2-H), 5.94 (s, 2H, OCH_2O), 6.94 (s, 1H, 4″-H), 7.19 (s, 1H, 7″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.93 (C9), 26.08 (C3), 26.42 (C8), 31.68 (C4), 37.80 (C10), 48.90 (C1′), 54.52 (C7), 72.60 (C5), 101.4 (OCH_2O), 109.8 (C4″), 112.1 (C7″), 113.7 (C6″), 131.0 (C2), 133.6 (C5″), 137.8 (C1), 146.5 (C3a″), 147.3 (C7a″); MS (70 eV, EI): m/z (%): 351/349 (12) [M^+], 322/320 (6) [M^+ – C_2H_5], 294/292 (6) [$C_{13}H_{11}BrNO_2^+$], 270 (100) [M^+ – Br], 242 (7) [$C_{15}H_{16}NO_2^+$], 238 (7) [$C_{14}H_{14}NO_2^+$], 215/213 (29/31) [$C_8H_6BrO_2^+$], 136 (10) [$C_9H_{14}N^+$], (hydrochloride); $C_{17}H_{20}BrNO_2$ (350.3): HRMS calcd 349.0677, found 349.0677.

1-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethyl]-1-aza-spiro[4.4]non-6-ene (11c): According to general procedure II, the amine **12c** (625 mg, 1.52 mmol) was cyclized with [Pd(PPh_3)$_4$] (130 mg, 112 µmol, 7 mol%) and tetramethylguanidine (230 mg, 1.99 mmol, 1.3 equiv). Column chromatography (70 g SiO_2, EtOAc) furnished **11c** (471 mg, 1.35 mmol, 88%) as a colorless oil. R_f = 0.57 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3048 (Ar–H), 2954 (C–H), 1478, 1230, 1112, 1040, 936 (C-O-C), 860, 834 (arene), 748 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.592), 294.0 nm (3.639); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (dt, J = 13.6, 6.8 Hz, 1H, 4-H), 1.74–1.98 (m, 5H, 3-H_2, 4-H, 9-H_2), 2.30 (tdd, J = 7.1, 2.2, 2.1 Hz, 2H, 8-H_2), 2.38, 2.56 (m, 2H, 2′-H_2*), 2.69–2.85 (m, 3H, 1′-H_2*, 2-H*), 2.88–3.02 (m, 1H, 2-H*), 5.56 (dt, J = 5.6, 2.1 Hz, 1H, 6-H), 5.80 (dt, J = 5.6, 2.2 Hz, 1H, 7-H), 5.93 (s, 2H, OCH_2O), 6.71 (s, 1H, 4″-H), 6.96 (s, 1H, 7″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.32 (C3), 29.56 (C8), 31.45 (C9), 36.39 (C2′), 38.19 (C4), 49.65 (C1′), 51.22 (C2), 101.5 (C2″), 110.2 (C4″), 112.5 (C7″), 114.3 (C6″), 132.1 (C7), 133.1 (C5″), 134.7 (C6), 146.6 (C3a″), 147.1 (C7a″); MS (70 eV, CI (NH_3)): m/z (%): 352/350 (98/100) [M+H$^+$], 272 (8) [M^+ – Br+2H], 136 (10) [$C_9H_{14}N^+$], (hydrochloride); $C_{17}H_{20}BrNO_2$ (350.3): HRMS calcd 349.0677; found 349.0677.

6-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethyl]-6-aza-spiro[4.5]dec-1-ene (11e): According to general procedure II, the amine **12e** (474 mg, 1.12 mmol) was cyclized with [Pd(PPh_3)$_4$] (112 mg, 96.9 µmol, 9 mol%) and tetramethylguanidine (320 mg, 2.80 mmol, 2.5 equiv). Column chromatography (50 g SiO_2, EtOAc) furnished **11e** (233 mg, 640 µmol, 57%) as a colorless oil. R_f = 0.66 (EtOAc/MeOH = 5:1, 1% Et_3N); UV (CH_3CN): λ_{max} (lg ε) = 201.5 (4.558), 294.0 nm (3.648); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42–1.50 (m, 2H, 9-H, 10-H), 1.53–1.65 (m, 4H, 8-H_2, 9-H, 10-H), 1.74–1.80 (m, 2H, 3-H_2), 2.11 (ddd, J = 12.1, 10.5, 4.8 Hz, 1H, 7-H_{ax}), 2.24–2.30 (m, 2H, 4-H_2), 2.35 (m, 1H, 1′-H), 2.56–2.64 (m, 1H, 7-H_{eq}), 2.65–2.69 (m, 1H, 2′-H), 2.77–2.81 (m, 1H, 2′-H), 2.81–2.85 (m, 1H, 1′-H), 5.50 (dt, J = 5.6, 2.0 Hz, 1H, 1-H), 5.69 (dt, J = 5.6, 2.4 Hz, 1H, 2-H), 5.91 (s, 2H, OCH_2O), 6.67 (s, 1H, 4″-H), 6.94 (s, 1H, 7″-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.79 (C9), 26.30 (C3, C8), 31.56 (C4), 35.76 (C2′), 37.69 (C10), 49.04 (C1′), 51.66 (C7), 72.92 (C5), 101.5 (OCH_2O), 110.5 (C4″), 112.5

(C7″), 114.4 (C6″), 130.7 (C2), 133.3 (C5″), 137.4 (C1), 146.6 (C3a″), 147.1 (C7a″); MS (70 eV, EI): *m/z* (%): 365/363 (<1) [M^+], 284 (<1) [M^+ – Br+2H], 215/213 (3) [$C_8H_6BrO_2^+$], 150 (100) [$C_{10}H_{16}N^+$]; $C_{18}H_{22}BrNO_2$ (364.3): calcd C 53.95, H 5.78 (hydrochloride); found C 54.18, H 6.12; HRMS calcd 363.0834; found 363.0834.

6-[2-(2-Bromo-4,5-dimethoxy-phenyl)ethyl]-6-aza-spiro[4.5]dec-1-ene (11f): According to general procedure II, the amine **12f** (576 mg, 1.31 mmol) was cyclized with [Pd(PPh$_3$)$_4$] (147 mg, 127 μmol, 10 mol%) and tetramethylguanidine (372 mg, 3.23 mmol, 2.5 equiv). Column chromatography (18 g SiO_2, EtOAc) furnished **11f** (213 mg, 560 μmol, 43%) as a colorless oil. R_f = 0.60 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3048 (Ar–H), 2931 (C–H), 1508, 1440, 1217 (Ar-O-C), 1098, 1034 (Ar-O-C), 854, 798 (arene), 731 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 204.0 (4.613), 286.5 nm (3.545); ^{1}H NMR (500 MHz, C_6D_6): δ = 1.33 – 1.44 (m, 2H, 10-H$_2$), 1.49 – 1.66 (m, 5H, 4-H, 8-H$_2$, 9-H$_2$), 1.70 – 1.76 (m, 1H, 4-H), 2.17 (m, 2H, 7-H$_2$), 2.28 – 2.38 (m, 2H, 3-H$_2$), 2.82 – 3.00 (m, 4H, 1′-H$_2$, 2′-H$_2$), 3.19 (s, 3H, OCH$_3$), 3.38 (s, 3H, OCH$_3$), 5.54 (dt, *J* = 5.7, 2.0 Hz, 1H, 1-H), 5.60 (dt, *J* = 5.7, 2.2 Hz, 1H, 2-H), 6.70 (s, 1H, 6″-H), 6.96 (s, 1H, 3″-H); ^{13}C NMR (125.7 MHz, C_6D_6): δ = 22.38 (C9), 27.04 (C3, C8), 31.80 (C4), 36.00 (C2′), 37.99 (C10), 49.20 (C1′), 51.98 (C7), 55.68 (2 OCH$_3$), 73.08 (C5), 114.7 (C2″), 115.2 (C6″), 116.3 (C3″), 130.4 (C2), 132.7 (C1″), 138.6 (C1), 149.1 (C4″, C5″); MS (70 eV, EI): *m/z* (%): 382/380 (<1) [M+H$^+$], 231/229 (2) [$C_9H_{10}BrO_2^+$], 189 (7), 150 (100) [$C_{10}H_{16}N^+$], (hydrochloride); $C_{19}H_{26}BrNO_2$ (380.3): calcd C 60.00, H 6.89; found C 59.70, H 6.86.

6-[3-(6-Bromobenzo[1,3]dioxol-5-yl)propyl]-6-aza-spiro[4.5]dec-1-ene (11h): According to general procedure II, the amine **12h** (80.0 mg, 182 μmol) was cyclized with [Pd(PPh$_3$)$_4$] (21 mg, 18.0 μmol, 10 mol%) and tetramethylguanidine (52.0 mg, 454 μmol, 2.5 equiv). Column chromatography (8 g SiO_2, EtOAc) furnished **11h** (45.8 mg, 121 μmol, 67%) as a colorless oil. R_f = 0.54 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3048 (Ar–H), 2929 (C–H), 1477, 1408, 1354, 1229, 1112, 1040, 936 (C-O-C), 858, 833 (arene), 720 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 201.0 (4.574), 294.5 nm (3.620); ^{1}H NMR (500 MHz, C_6D_6): δ = 1.31 – 1.46 (m, 2H, 9-H, 10-H), 1.48 – 1.61 (m, 4H, 8-H$_2$, 9-H, 10-H), 1.61 – 1.79 (m, 4H, 2-H$_2$, 4-H$_2$), 2.00 (ddd, *J* = 13.0, 6.9, 5.0 Hz, 1H, 1′-H), 2.11 (ddd (*J* = 11.2, 11.2, 3.0 Hz, 1H, 7-H$_{ax}$), 2.21 (ddt, *J* = 7.0, 1.8, 1.4 Hz, 2H, 3-H$_2$), 2.57 (ddd, *J* = 14.0, 10.0, 6.0 Hz, 1H, 3′-H), 2.60 (ddd, *J* = 14.0, 7.8, 7.8 Hz, 1H, 3′-H), 2.68 (ddd, *J* = 11.2, 3.2, 0.6 Hz, 1H, 7-H$_{eq}$), 2.79 (ddd, *J* = 13.0, 10.1, 5.7 Hz, 1H, 1′-H), 5.21 (s, 2H, OCH$_2$O), 5.61 (m, 2H, 1-H, 2-H), 6.60 (s, 1H, 4″-H), 6.95 (s, 1H, 7″-H); ^{13}C NMR (125.7 MHz, C_6D_6): δ = 22.37 (C9), 26.93 (C3, C8), 29.45 (C2′), 31.95 (C4), 34.39 (C3′), 38.07 (C10), 48.60 (C1′), 50.34 (C7), 73.02 (C5), 101.4 (OCH$_2$O), 110.2 (C4″), 112.9 (C7″), 114.7 (C6″), 130.1 (C2), 135.7 (C5″), 139.0 (C1), 146.9 (C3a″), 147.7 (C7a″); MS (70 eV, EI): *m/z* (%): 379/377 (24/25) [M^+], 324/322 (9/10) [$C_{15}H_{17}BrNO_2^+$], 298 (80) [M^+ – Br], 242/240 (8) [$C_{10}H_9BrO_2^+$], 215/213 (13) [$C_8H_6BrO_2^+$], 164 (100) [$C_{11}H_{18}N^+$], 150 (92) [$C_{10}H_{16}N^+$], 136 (46) [$C_9H_{14}N^+$]; $C_{19}H_{24}BrNO_2$ (378.3): calcd C 60.32, H 6.39; found C 60.51, H 6.44; HRMS calcd 377.0990; found 377.0990.

1-(2-Benzo[1,3]dioxol-5-yl-ethyl)-1-aza-spiro[4.5]dec-6-ene (19): Analogous to general procedure II; however, at 75 °C, the amine **18** (20.3 mg, 58.8 μmol) was cyclized with [Pd(PPh$_3$)$_4$] (10.0 mg, 8.70 μmol, 15 mol%) and triethylamine (18.2 mg, 179 μmol, 3.0 equiv). Column chromatography (20 g SiO_2, EtOAc) gave **19** (12.4 mg, 43.5 μmol, 74%) as a colorless oil. R_f = 0.45 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (KBr): $\tilde{\nu}$ = 3013 (Ar–H), 2936 (C–H), 1490, 1247, 1109, 1042, 931 (C-O-C), 863, 808 (arene), 742 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 198.5 (4.627), 230.5 (3.718), 287.0 nm (3.577); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 – 1.90 (m, 8H, 3-H$_2$, 4-H$_2$, 9-H$_2$, 10-H$_2$), 1.93 (m, 2H, 8-H$_2$), 2.56 – 2.72 (m, 4H, 1′-H$_2$, 2′-H$_2$), 2.82 (br s, 1H, 2-H), 2.99 (m, 1H, 2-H), 5.46 (d, *J* = 10.1 Hz, 1H, 6-H), 5.76 (dt, *J* = 10.1, 4.1 Hz, 1H, 7-H), 5.91 (s, 2H, OCH$_2$O), 6.65 (dd, *J* = 8.0, 1.6 Hz, 1H, 6″-H), 6.71 (d, *J* = 1.6 Hz, 1H, 7″-H), 6.72 (d, *J* = 8.0 Hz, 1H, 4″-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.09, 21.21 (C3, C9), 25.13 (C8), 28.32 (C4), 36.24 (C2′), 38.28 (C10), 50.63 (C2), 51.75 (C1′), 63.71 (C5), 100.6 (OCH$_2$O), 108.0 (C4″), 109.1 (C7″), 121.3 (C6″), 128.9 (C7), 133.2 (C6), 134.7 (C5″), 145.5 (C7a″), 147.3 (C3a″); MS (70 eV, EI): *m/z* (%): 285 (<1) [M^+], 150 (100) [$C_{10}H_{16}N^+$], 135 (8) [$C_8H_7O_2^+$]; $C_{18}H_{23}NO_2$ (285.4): calcd C 75.76, H 8.12; found C 75.62, H 7.89; HRMS calcd 285.1729; found 285.1728.

General procedure III: intramolecular Heck reaction of 11: To a 0.05 M solution of the bromoarenes **11** in a mixture of acetonitrile, dimethylformamide, and water (5:5:1) were added the catalyst **20** (5 mol%) and tetra-*n*-butylammonium acetate (2.1 equiv). The mixture was degassed by pump and freeze methodology and then heated to 120 °C until the reaction was completed (TLC), diluted with MTBE, and extracted with diluted NaOH solution. Subsequently, the organic layer was extracted with HCl (1 M, 3×). The aqueous layer was basified with NaOH solution and extracted with MTBE (3×). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography.

3,5,6,7,8,13b-Hexahydro-4*H*-cyclopenta[*c*][1,3]dioxolo[4,5-*g*]pyrrolo[1,2-*b*]-isoquinoline (10a): According to general procedure III, the tertiary amine **11a** (29.0 mg, 86.0 μmol), the palladium catalyst **20** (6.2 mg, 6.6 μmol, 8 mol%), and tetra-*n*-butylammonium acetate (55.0 mg, 182 μmol, 2.1 equiv) were reacted in the solvent mixture (1.5 mL). The crude product was purified via its hydrochloride by recrystallization from CH_2Cl_2/MTBE to afford **10a** (20.0 mg, 68.7 μmol, 80%). R_f = 0.28 (EtOAc/MeOH = 5:1, 1% Et_3N); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72 – 1.91 (m, 4H, 4-H$_2$, 5-H$_2$), 2.30 (br d, *J* = 17.2 Hz, 1H, 3-H), 2.69 (ddd, *J* = 10.6, 10.6, 5.7 Hz, 1H, 6-H), 2.72 (br d, *J* = 17.2 Hz, 1H, 3-H), 2.92 (m, 1H, 6-H), 3.41 (br s, 1H, 13b-H), 3.67 (d, *J* = 15.6 Hz, 1H, 8-H), 3.92 (d, *J* = 15.6 Hz, 1H, 8-H), 5.68 (dddd, *J* = 6.0, 2.3, 2.3, 2.3 Hz, 1H, 1-H), 5.75 (dddd, *J* = 6.0, 2.3, 2.1, 2.0 Hz, 1H, 2-H), 5.87 (d, *J* = 1.5 Hz, 1H, 11-H), 5.90 (d, *J* = 1.5 Hz, 1H, 11-H), 6.55 (s, 1H, 13-H), 6.60 (s, 1H, 9-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.06 (C5), 39.80, 40.61 (C3, C4), 48.39 (C6), 50.29 (C13b), 50.68 (C8), 69.30 (C3a), 100.5 (C11), 107.5 (C13), 108.0 (C9), 125.6 (C8a), 129.6 (C1), 130.8 (C13a), 132.8 (C2), 145.4 (C9a), 146.3 (C12a); MS (70 eV, EI): *m/z* (%): 255 (70) [M^+], 254 (100) [M^+ – H], 214 (28) [M^+ – C_3H_5], (hydrochloride); $C_{16}H_{17}NO_2$ (255.3): calcd 255.1259; found 255.1259.

3,5,6,8,9,14b-Hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]-pyrrolo[2,1-*b*]-[3]benzazepine (10b):[8n] According to general procedure III, the tertiary amine **11c** (179 mg, 511 μmol) was cyclized with the palladium catalyst **20** (19.0 mg, 20.0 μmol, 4 mol%) and tetra-*n*-butylammonium acetate (310 mg, 1.03 mmol, 2.0 equiv). The crude product was purified by column chromatography (25 g SiO_2, ethyl acetate) to give **10b** (112 mg, 416 μmol, 81%). R_f = 0.22 (EtOAc/MeOH = 5:1, 1% Et_3N); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.66 – 1.87 (m, 2H, 4-H$_2$), 1.91 – 2.07 (m, 3H, 3-H, 5-H$_2$), 2.34 (dd, *J* = 14.2, 6.1 Hz, 1H, 8-H), 2.43 (ddd, *J* = 9.3, 9.3, 6.8 Hz, 1H, 6-H), 2.58 (dd, *J* = 11.7, 7.3 Hz, 1H, 9-H), 2.76 (ddd, *J* = 17.8, 4.9, 2.4 Hz, 1H, 3-H), 2.96 (ddd, *J* = 12.7, 11.7, 6.1 Hz, 1H, 9-H), 3.11 (ddd, *J* = 9.3, 7.6, 4.9 Hz, 1H, 6-H), 3.20 (ddd, *J* = 14.2, 12.7, 7.3 Hz, 1H, 8-H), 3.88 (br s, 1H, 14b-H), 5.52 (dddd, *J* = 5.9, 2.4, 2.2, 2.2 Hz, 1H, 1-H), 5.79 (dddd, *J* = 5.9, 2.7, 2.7, 2.1 Hz, 1H, 2-H), 5.88 (d, *J* = 1.5 Hz, 1H, 12-H), 5.89 (d, *J* = 1.5 Hz, 1H, 12-H), 6.59 (s, 1H, 10-H), 6.65 (s, 1H, 14-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.80 (C5), 30.42 (C9), 34.89 (C4), 42.94 (C3), 48.92 (C7), 53.50 (C8), 62.13 (C14b), 68.30 (C3a), 100.7 (C12), 109.8 (C10), 110.7 (C14), 128.6 (C1), 131.6 (C14a), 132.0 (C2), 133.5 (C9a), 146.0 (C13a), 146.3 (C10a); $C_{17}H_{19}NO_2$ (269.3).

3,4,5,6,7,9,10,14b-Octahydro-12,13-dimethoxycyclopenta[*a*]pyrido[2,1-*b*]-[3]benzazepine (10c): According to general procedure III, the tertiary amine **11f** (37.0 mg, 97.0 μmol) was cyclized with the palladium catalyst **20** (5.5 mg, 5.9 μmol, 6 mol%) and tetra-*n*-butylammonium acetate (87.0 mg, 290 μmol, 3.0 equiv). The crude product was purified by column chromatography (15 g SiO_2, ethyl acetate) to give **10c** (25.2 mg, 84.2 μmol, 87%). R_f = 0.25 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (neat): $\tilde{\nu}$ = 3057 (Ar–H), 2935 (C–H) 1517, 1465, 1266 (Ar-O-C), 1127, 1022 (Ar-O-C), 733 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} (lg ε) = 203.5 (4.472), 234.0 (3.694), 282.5 nm (3.313); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 – 1.84 (m, 6H, 4-H$_2$, 5-H$_2$, 6-H$_2$), 2.17 (br d, *J* = 17.6 Hz, 1H, 3-H), 2.25 – 2.40 (m, 2H, 7-H, 10-H), 2.42 (ddd, *J* = 13.2, 7.1, 2.2 Hz, 1H, 7-H), 2.58 (ddd, *J* = 12.7, 3.9, 3.4 Hz, 1H, 9-H), 2.68 – 2.95 (m, 2H, 3-H, 9-H), 3.25 (ddd, *J* = 13.9, 9.5, 8.8 Hz, 1H, 10-H), 3.58 (br s, 1H, 14b-H), 3.87 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 5.56 (dddd, *J* = 6.0, 2.2, 2.2, 2.0 Hz, 1H, 1-H), 5.79 (dddd, *J* = 6.0, 2.5, 2.5, 2.2 Hz, 1H, 2-H), 6.62 (s, 1H, 11-H), 6.67 (s, 1H, 14-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.45 (C5), 24.89 (C6), 30.75 (C10), 34.69 (C3), 40.54 (C4), 51.94 (C9), 53.03 (C7), 55.78 (OCH$_3$), 56.07 (OCH$_3$), 64.82 (C14b), 65.09 (C3a), 112.4 (C11), 113.7 (C14), 128.4 (C2), 130.6 (C14a), 130.8 (C10a), 132.0 (C1), 147.8 (C13), 147.7 (C12); MS (70 eV, EI): *m/z* (%): 299 (100) [M^+], 284 (49) [M^+ – CH$_3$], 258 (72) [M^+ – C_3H_5], 202 (44) [$C_{12}H_{12}NO_2^+$], 134 (54) [$C_9H_{12}N^+$]; $C_{19}H_{25}NO_2$ (299.4): calcd C 67.94, H 7.80 (hydrochloride); found C 67.76, H 7.83; HRMS calcd 299.1885; found 299.1885.

3,4,5,6,7,8,9,14b-Octahydro-cyclopenta[*c*][1,3]dioxolo[4,5-*g*]pyrido[1,2-*b*]isoquinoline (10d): According to general procedure III, the tertiary amine

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11b (55.0 mg, 157 μmol) was cyclized with the palladium catalyst **20** (10 mg, 11.0 μmol, 7 mol%) and tetra-*n*-butylammonium acetate (104 mg, 345 μmol, 2.2 equiv). The crude product was purified by column chromatography (8 g SiO_2, EtOAc) to give **11d** (34.1 mg, 127 μmol, 81%). R_f = 0.56 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (KBr): $\tilde{\nu}$ = 3066 (Ar–H), 2933 (C–H), 1485, 1242, 1119, 1041, 933 (C-O-C), 874, 859 (arene), 702 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 200.5 (4.563), 293.5 nm (3.676); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.53–1.76 (m, 5H, 4-H, 5-H_2, 6-H_2), 1.84 (m, 1H, 4-H), 2.08 (ddd, J = 16.8, 2.7, 1.8 Hz, 1H, 3-H), 2.43 (ddd, J = 11.5, 11.5, 2.7 Hz, 1H, 7-H_{ax}), 2.58 (br d, J = 16.8 Hz, 1H, 3-H), 2.73 (ddd, J = 11.5, 3.7, 3.7 Hz, 1H, 7-H_{eq}), 3.34 (d, J = 15.2 Hz, 1H, 9-H), 3.44 (br s, 1H, 14b-H), 3.62 (d, J = 15.2 Hz, 1H, 9-H), 5.64 (dddd, J = 6.0, 2.8, 1.8, 1.8 Hz, 1H, 1-H), 5.76 (dddd, J = 6.0, 2.7, 2.7, 1.6 Hz, 1H, 2-H), 5.82 (d, J = 1.4 Hz, 1H, 12-H), 5.86 (d, J = 1.4 Hz, 1H, 12-H), 6.50 (s, 1H, 14-H), 6.55 (s, 1H, 10-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.81 (C5), 25.50 (C6), 30.32 (br, C3), 38.06 (C4), 51.41 (C7), 52.99 (C9), 54.85 (br, C14b), 64.05 (C3a), 100.4 (C12), 106.7 (C14), 107.6 (C10), 126.7 (C9a), 128.6 (C1), 130.5 (C14a), 133.5 (C2), 145.1 (C10a), 146.3 (C13a); MS (70 eV, EI): *m*/*z* (%): 269 (81) [M^+], 268 (95) [M^+ – H], 228 (100) [$M^+ - C_3H_5$]; $C_{17}H_{19}NO_2$ (269.3): calcd C 75.81, H 7.11; found C 75.59, H 7.05; HRMS calcd 269.1416; found 269.1415.

3,4,5,6,7,9,10,15b-Octahydrocyclopenta[*a*][1,3]dioxolo[4,5-*h*]-pyrido[2,1-*b*]-[3]benzazepine (10e): According to general procedure III, the tertiary amine **11e** (23.0 mg, 63.0 μmol) was cyclized with the palladium catalyst **20** (5.0 mg, 5.0 μmol, 8 mol%) and tetra-*n*-butylammonium acetate (47.0 mg, 156 μmol, 2.5 equiv). The crude product was purified by column chromatography (8 g SiO_2, ethyl acetate) to give **10e** (15.0 mg, 52.9 μmol, 84%): R_f = 0.29 (EtOAc/MeOH = 5:1, 1% Et_3N); IR (KBr): $\tilde{\nu}$ = 3038 (Ar–H), 2919 (C–H), 1489, 1229, 1109, 1037, 934 (C-O-C), 839, 849 (arene), 737 cm^{-1} (=C–H); UV (CH_3CN): λ_{max} ($\lg\varepsilon$) = 200.5 (4.597), 231.5 (3.602), 292.5 nm (3.654); ^1H NMR (200 MHz, $CDCl_3$): δ = 1.36–1.76 (m, 6H, 4-H_2, 5-H_2, 6-H_2), 2.15 (br d, J = 17.3 Hz, 1H, 3-H), 2.30–2.43 (m, 2H, 7-H, 10-H), 2.53 (ddd, J = 13.2, 3.9, 3.4 Hz, 1H, 7-H), 2.59 (ddd, J = 9.3, 8.6, 2.7 Hz, 1H, 9-H), 2.66–2.79 (m, 2H, 3-H, 9-H), 3.23 (ddd, J = 14.2, 9.5, 8.6 Hz, 1H, 10-H), 3.53 (m, 1H, 15b-H), 5.56 (dddd, J = 6.0, 2.2, 2.2, 2.0 Hz, 1H, 1-H), 5.79 (dddd, J = 6.0, 2.5, 2.5, 2.2 Hz, 1H, 2-H), 5.88 (s, 2H, 13-H_2), 6.58 (s, 1H, 11-H), 6.64 (s, 1H, 15-H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.53 (C5), 24.90 (br, C6), 31.06 (C10), 34.66 (br, C3), 41.00 (br, C4), 51.75 (br, C9), 52.88 (C7), 64.66, 64.98 (C3a, C15b), 100.6 (C13), 109.3 (C11), 110.2 (C15), 128.5 (C2), 131.8 (C15a), 131.8 (C1), 132.0 (C10a), 145.7 (C14a), 146.1 (C11a); MS (70 eV, EI): *m*/*z* (%): 283 (100) [M^+], 268 (23), 242 (79) [$M^+ - C_3H_5$], 186 (31) [$C_{11}H_8NO_2^+$], 134 (40) [$C_9H_{12}N^+$]; $C_{18}H_{21}NO_2$ (283.4): calcd C 67.60, H 6.93 (hydrochloride); found C 67.54, H 6.83; HRMS calcd 283.1572; found 283.1572.

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