Efficient Synthesis of Six-Membered Ring D Analogues of the Pentacyclic Alkaloid Cephalotaxine by Two Palladium-Catalyzed Reactions

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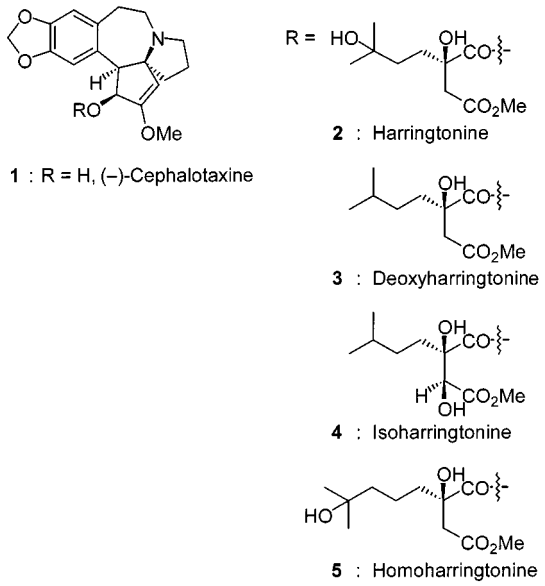
Dedicated to Professor Franz Effenberger on the occasion of his 70th birthday

Keywords: Nucleophilic allylation / Antitumor agents / Cephalotaxine / Heck reaction / Palladium / Spiro compounds

D-*homo*-Cephalotaxine analogues **19** and **23** have been prepared by intramolecular Heck reactions of **12** and **22**. The substrates **12** and **22** were obtained by alkylation and acylation, respectively, of the spirocyclic amines **17**, which, in turn, were generated by intramolecular palladium-catalyzed allylic amination.

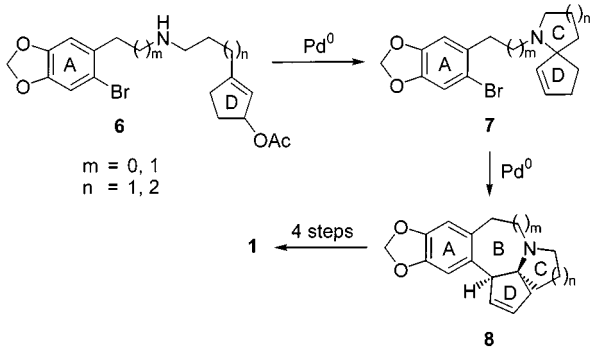
Introduction

Natural products are important lead structures in drug development. However, for a variety of reasons the parent compounds often prove unsuitable, e.g. due to low activity, side effects, instability, complexity, etc. It is therefore important to prepare analogues and to explore their biological activities. In recent years, we have developed a highly efficient access to several families of natural products based on two transition-metal-mediated or -catalyzed transformations.[1]



Scheme 1. (−)-Cephalotaxine (**1**) and harringtonines **2**−**5**

In this way, we synthesized the unique pentacyclic alkaloid cephalotaxine (**1**) through Pd-catalyzed amination of the secondary amine **6** and a Heck reaction via the spirocyclic tertiary amine **7** and the pentacyclic core **8**. Esters of cephalotaxine (**1**), namely harringtonine (**2**), deoxyharringtonine (**3**), isoharringtonine (**4**), and homoharringtonine (**5**), show high antileukemic activity and clinical trials have reached phases II−III (Scheme 1).[2] More recently, homoharringtonine (**5**) has been investigated for the treatment of chloroquine-resistant malaria.[3] Our two-step Pd-catalyzed process could also be used for the synthesis of ring analogues of the pentacyclic core of **1** with (6,5,5)-, (6,6,5)-, and (7,6,5)-BCD rings (Scheme 2).[4] In this paper, we describe an access to D-6-ring analogues of cephalotaxine (**1**), again using two Pd-catalyzed transformations. However, in this case, a sequential approach had to be employed.



Scheme 2. Synthesis of cephalotaxine and analogues

Results and Discussion

For the synthesis of the cephalotaxine analogues containing a six-membered ring D, we first prepared several secondary amines **11** by alkylation of the primary amines **9**[5] with iodides, which, in turn, were generated in situ from tosylates **10**.[6] However, all attempts to convert amines **11** into spirocyclic compounds with a cyclohexene moiety as ring D through Pd-catalyzed intramolecular amination according to our strategy failed, irrespective of whether a five- or six-membered ring was to be formed (Scheme 3). We assume that this may be attributed to the lower reactivity of the cyclohexenyl acetate compared with the corresponding

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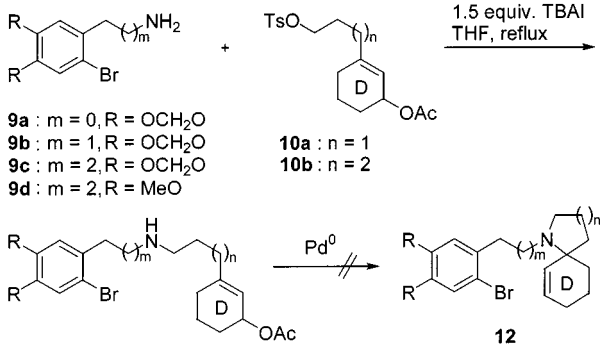
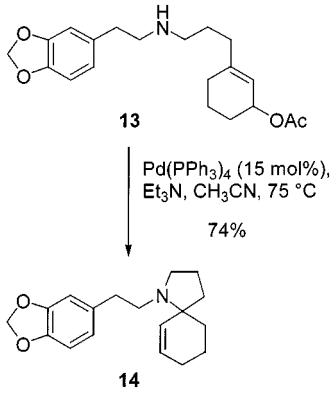


Prod.	m	n	R	Yield
11a	0	1	OCH_2O	64%
11b	1	1	OCH_2O	85%
11c	1	1	OMe	90%
11d	1	2	OCH_2O	74%
11e	2	1	OCH_2O	76%

Scheme 3. Synthesis of secondary amines **11a−e**

cyclopentenyl compound. Thus, the oxidative addition of palladium to the bromoarene moiety becomes the preferred reaction, resulting in termination of the desired transformation. We have previously encountered the same problem with iodoarenes connected to a cyclopentenyl acetate moiety. Here again, the process comes to a halt, since the allylic acetate is less reactive than the iodoarene group in this type of double-functionalized substrate.[1j]

This assumption was verified by the fact that **13**, lacking a bromo substituent on the arene moiety, provided the desired spirocyclic amine **14** in 74% yield using $[Pd(PPh_3)_4]$ as catalyst at 75 °C (Scheme 4).

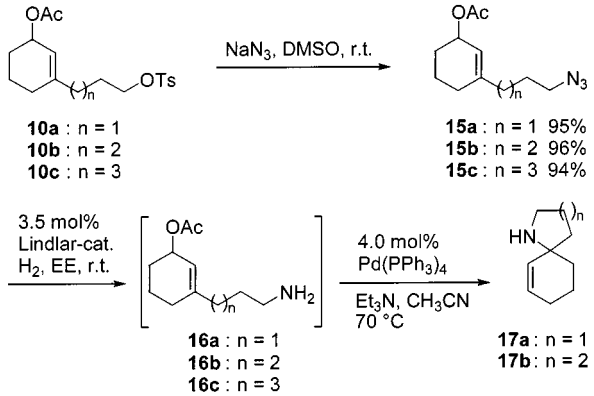


Scheme 4. Synthesis of the tertiary amine **14**

To circumvent the problem of the lack of chemoselectivity, we decided to prepare the spiroazacycle first, which was then alkylated with *ortho*-iodo- or *ortho*-bromoarylalkyl halides and nosylates **18**, respectively. The tertiary amines thus obtained could then be employed in intramolecular Heck reactions.

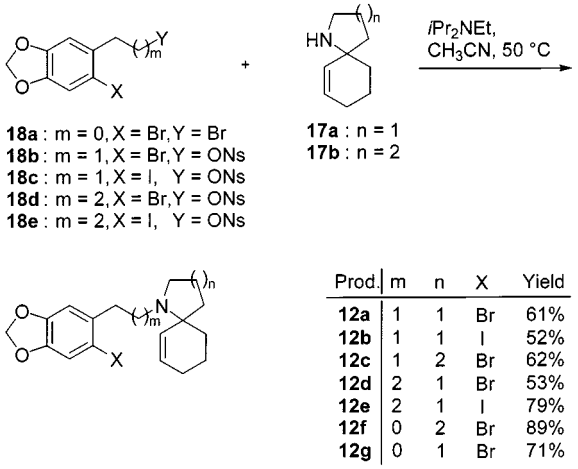
The *o*-bromobenzyl bromide **18a**[7] was prepared in one step from piperonyl alcohol and bromine in 98% yield. Clearly, the HBr produced in the aromatic substitution reaction served as the reagent for the generation of the benzyl bromide. The corresponding phenylethyl alcohol, which was synthesized in 90% yield from bromomethylenedioxybenzene by a Grignard reaction with oxirane,[8] did not react in the same way. After bromination of the arene moiety, the hydroxy group was thus transformed into a nosylate to give **18b**. In a similar way, **18c** was obtained.[9,10] For the syntheses of **18d** and **18e**, the corresponding phenylpropanol derivatives were prepared from safrol applying a procedure described by Kabalka et al.[11] Bromination and iodination, respectively, followed by conversion to the nosylates led to the desired substrates.

The requisite primary amines **16** were obtained from the tosylates **10a−c**[6] via the azides **15a−c** (Scheme 5). The latter were prepared in almost quantitative yield by stirring **10a−c** at room temperature in DMSO with sodium azide. Several methods for reducing the azides were tested, but of these only the catalytic hydrogenation proved applicable due to the instability of the resulting primary amines **16a**,**b**. Staudinger reduction[12] led to the desired amines, as indicated by TLC, but they could not be separated from the byproducts. Similar problems were encountered when reducing agents containing sulfur, such as propane-1,3-dithiol were employed.[13] However, hydrogenation using 3−4 mol-% Lindlar's catalyst in ethyl acetate for 1 h (longer stirring resulted in an overreduction) led to crude and unstable **16a** and **16b**, which were usually employed for the allylic amination without prior purification. The reactions were performed in acetonitrile with triethylamine as base and 4 mol-% of $[Pd(PPh_3)_4]$ as catalyst and were allowed to proceed for 18 h at 70 °C, thereby affording the desired spirocyclic amines **17a** and **17b** as volatile liquids. The 6,7-spirocyclic amine **17c** could not be obtained in this way. For the synthesis of the tertiary amines **12a−e**, it was found to be most efficient to use the crude amines **17a**,**b** as substrates for the alkylation with various nosylates **18b−e**; the yields over the three steps ranged from 52 to 79% (Scheme 6).



Scheme 5. Synthesis of secondary spirocyclic amines **17**

For the preparation of **12f**, the amine **17b** as its hydrochloride was alkylated with the benzyl bromide **18a**[7] in 89% yield. In the same manner, **12g** was prepared from the amine **17a** and benzyl bromide **18a** in 71% yield. The structure of the hydrochloride of the tertiary spirocyclic amine **12f** was verified by an X-ray analysis, as depicted in Fig-



Prod.	m	n	X	Yield
12a	1	1	Br	61%
12b	1	1	I	52%
12c	1	2	Br	62%
12d	2	1	Br	53%
12e	2	1	I	79%
12f	0	2	Br	89%
12g	0	1	Br	71%

Scheme 6. Alkylation of spirocyclic amines **17**

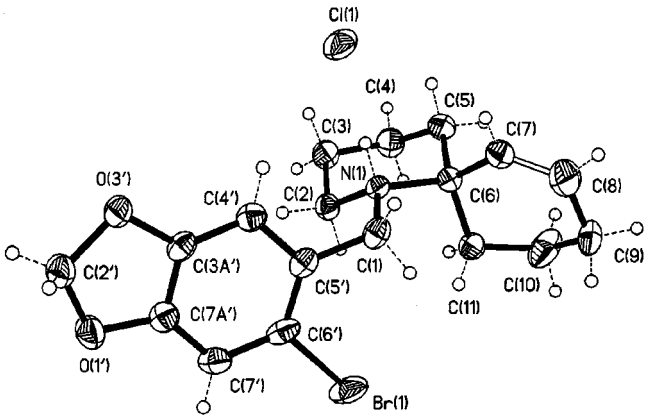
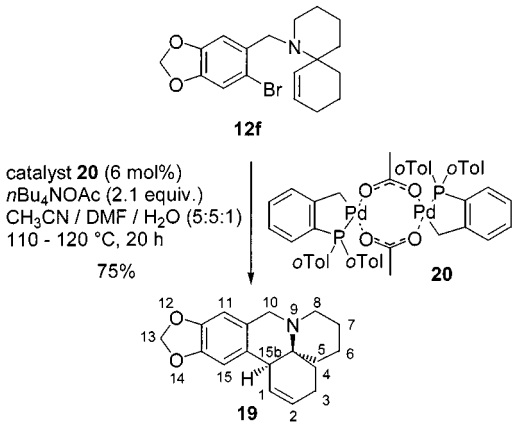


Figure 1. X-ray crystal structure of tertiary spirocyclic amine **12f**

ure 1.[14] As expected, the alkene moiety is equatorially disposed.

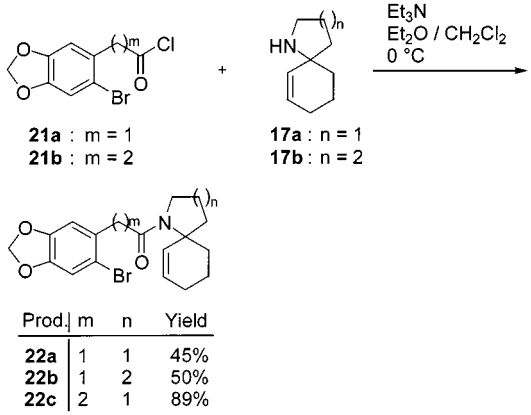
The final Heck reactions of **12a−g** were performed using the optimized conditions for our cephalotaxine synthesis.[1i,1j] For these transformations, the bromoarenes **12a−g** were stirred in a degassed solvent mixture consisting of acetonitrile, dimethylformamide, and water (ratio 5:5:1) in the presence of 2.1 equiv. of tetra-*n*-butylammonium acetate with catalytic amounts of the palladacycle *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium(II)[15] (**20**). However, compared to the Heck reactions of the analogous cyclopentene derivatives,[4] the substrates **12a−g** possessing a cyclohexene moiety proved to be much less reactive. Thus, only in the case of the benzylic compound **12f** could a Heck reaction be achieved. This gave the all-6-ring system **19** in 75% yield after a reaction time of 20 h, three times longer than needed for the corresponding cyclopentene derivative (Scheme 7). The other substrates **12a−e**,**g** could not be converted to the expected Heck products, despite examining a multitude of different reaction conditions. For example, the reaction of compound **12b** in the presence of 20 mol-% of palladium(II) acetate as catalyst led to the deiodinated compound **14** in 20% yield after work-up, indicating that the alkene insertion did not take place. We have often found cyclohexene derivatives to be less reactive in Heck reactions than cyclopentene systems,



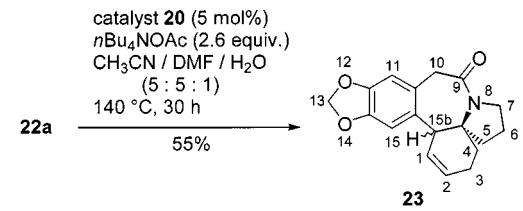
Scheme 7. Synthesis of the (5,6,6,6,6)-ring cephalotaxine analogue **19**

but in most cases this problem has been overcome by using higher temperatures. However, in the case of **12a−e**,**g**, use of higher temperatures resulted in decomposition of the substrates. We therefore prepared the corresponding amides **22a−c**, which indeed allowed us to synthesize the (5,6,7,6,6)-cephalotaxine analogue **23**.

Reaction of the readily available acid chlorides **21a** and **21b**[16,17] with the spirocyclic secondary amines **17a** and **17b** furnished the amides **22a−c** in reasonable yields. The ^{1}H- and ^{13}C-NMR spectra of **22a** and **22b** showed double sets of signals, clearly due to a high inversion barrier at the amide nitrogen atom. Heck reaction of **22a** with the palladacycle **20** as catalyst using a reaction temperature of 140 °C and a reaction time of 30 h gave the desired product **23** in 55% yield as a 1:1.1 mixture of two diastereomers (Scheme 8). The low stereoselectivity associated with formation of the second stereogenic center was unexpected since in the syntheses of cephalotaxine **1** and its analogues



Prod.	m	n	Yield
22a	1	1	45%
22b	1	2	50%
22c	2	1	89%



Scheme 8. Synthesis of the (5,6,7,5,6)-ring cephalotaxine analogue **23**

with (7,5,5)-, (7,6,5)-, (6,5,5)-, (6,6,5)-, and (6,6,6)-BCD rings, only one diastereomer was obtained. One must therefore assume that the partial planarization of the nitrogen atom due to the presence of the amide moiety renders the on-side attack less favorable. One of the two diastereomers of **23** could be separated by chromatography, but the spectral data did not allow an unambiguous assignment of the two isomers. Reactions of the amides **22b** and **22c** led to unidentifiable products. The negative result in the case of **22c** was not unexpected since all our attempts to prepare eight-membered rings by a Heck reaction have hitherto met with little success.

The structures of the newly formed compounds were mainly established by NMR spectroscopy. However, for **12f** an X-ray analysis has been performed.[14] The ^{1}H- and ^{13}C-NMR spectra of the azaspirocycle **17a** and the compounds **12f** and **19** are discussed here as representative cases. In the ^{1}H-NMR spectrum of the azaspirocycle **17a**, signals are found at δ = 5.54 due to 6-H and 5.66 due to 7-H as a dt with J = 9.8, 1.7 Hz (6-H) and J = 9.8, 3.4 Hz (7-H), and at δ = 2.94 and 3.04 as a dt (J = 10.3, 6.6 Hz) due to the CH_2 group attached to the nitrogen atom (2-H). Significant signals in the ^{13}C-NMR spectrum are observed at δ = 126.7 due to C-7 and at δ = 134.0 due to C-6, while C-5 resonates at δ = 59.7. The ^{1}H-NMR spectrum of the alkylated compound **12f** features a doublet (J = 10.0 Hz) due to the olefinic protons at δ = 5.46 and a dt at δ = 5.75 with J = 10.0 and 3.7 Hz. In the pentacyclic compound **19**, the olefinic protons resonate at δ = 5.66 as a broad doublet (J = 10.0 Hz, 1-H) and at δ = 6.09 as a dddd with J = 10.0, 5.6, 2.0, and 2.0 Hz for 2-H. The corresponding signals in the ^{13}C-NMR spectrum are found at δ = 126.4 (C-1) and δ = 128.6 (C-2).

Conclusion

In our attempts to improve the pharmacological activity of cephalotaxine and its esters, we have prepared novel ring-size analogues of this pentacyclic alkaloid. Recently, we showed that the combination of a Pd-catalyzed nucleophilic addition of an amine to an allyl acetate with a subsequent Heck reaction allows highly efficient access to cephalotaxine and several ring-size analogues with a five-membered ring D, but that analogues with a six-membered ring D could not be prepared in this way. However, by preforming the spiroazacycles and then subjecting them to *N*-alkylation and *N*-acylation, respectively, with a bromoarene derivative and subsequent Heck reaction, we have now succeeded in preparing ring-size analogues of cephalotaxine with (5,6,6,6,6)- and (5,6,7,5,6)-ring systems.

Experimental Section

General Remarks: All reactions were performed in flame-dried flasks under nitrogen or argon; the reactants were introduced by means of syringes. All solvents were dried by standard methods. Solvents used for 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 SIL G/UV_{254} plates (Macherey−Nagel GmbH & Co. KG), while silica gel 32−63 (0.032−0.063 mm) (Macherey−Nagel GmbH & Co. KG) was used for column chromatography. − UV/Vis spectra of samples in CH_3CN solution were recorded with a Mettler Lambda 2 spectrophotometer. − IR spectra were recorded from samples in KBr pellets or as films with Bruker IFS 25 or Vector 22 spectrometers. − ^{1}H- and ^{13}C-NMR spectra were recorded with Varian XL 200, VXR 200, and VXR 500 spectrometers or a Bruker AM-300 spectrometer with samples in [D]chloroform or [D_6]benzene using tetramethylsilane (TMS) as an internal standard. The multiplicities of ^{13}C-NMR peaks were determined using the APT pulse sequence. Mass spectra were measured at 70 eV with a Varian MAT 311A spectrometer, high-resolution mass spectra with a Varian MAT 731 instrument. − Melting points were measured with a Mettler FP 61 apparatus and are uncorrected. The following abbreviations are used in the text: MTBE = *tert*-butyl methyl ether, PE = petroleum ether, TBAI = tetra-*n*-butylammonium iodide, TFA = trifluoroacetic acid.

3-[5-(Tolyl-4-sulfonyloxy)pentyl]cyclohex-2-enyl Acetate (10c). − 5-(3-Oxocyclohex-1-enyl)pentyl Toluene-4-sulfonate: A solution of 5-chloropentan-1-ol[18] (10.0 g, 81.6 mmol) in THF (160 mL) was cooled to −78 °C and methylmagnesium chloride (3.8 M in THF, 21.5 mL, 81.6 mmol) was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature. Once gas production had ceased, magnesium turnings (2.38 g, 97.9 mmol) were added, and the mixture was heated under reflux for 3 h. The reaction mixture was subsequently cooled to −10 °C, 3-ethyloxycyclohex-2-enone[19] (7.19 g, 51.3 mmol) was added, and the resulting mixture was stirred for 3 h. It was then allowed to warm to 0 °C, whereupon saturated aq. NH_4Cl solution (20 mL) was added. The resulting mixture was partitioned between cold ethyl acetate (200 mL) and 2 N HCl (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were dried with Na_2SO_4 and concentrated to dryness in vacuo. The crude product was redissolved in cold (−10 °C) pyridine (50 mL), and tosyl chloride (14.7 g, 77.0 mmol) was added. The resulting mixture was stirred for 18 h at −10 °C, then poured into ethyl acetate (200 mL) and extracted twice with cold 2 N HCl. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated to dryness in vacuo. Purification of the residue by column chromatography (500 g SiO_2; PE/EtOAc, 1:1 → 1:2) gave the tosylate (4.96 g, 14.7 mmol) in 29% yield; R_f = 0.28 (PE/MTBE, 1:3). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (m, 4 H, 3-H_2, 4-H_2), 1.67 (tt, J = 7.0, 6.4 Hz, 2 H, 2-H_2), 1.90−2.06 (m, 2 H, 5′-H_2), 2.18 (t, J = 6.7 Hz, 2 H, 5-H_2), 2.26 (t, J = 6.0 Hz, 2 H, 6′-H_2), 2.36 (t, J = 6.7 Hz, 2 H, 4′-H_2), 2.46 (s, 3 H, CH_3), 4.02 (t, J = 6.4 Hz, 2 H, OCH_2), 5.82 (br. s, 1 H, 2′-H), 7.35 (d, J = 8.0 Hz, 2 H, Ar-2-H, Ar-6-H), 7.78 (d, J = 8.0 Hz, 2 H, Ar-3-H, Ar-5-H). − The cyclohexenone (1.68 g, 5.00 mmol) was dissolved in toluene (25 mL) and the resulting solution was cooled to −50 °C. A solution of DIBAL in toluene (1.5 M, 4.00 mL, 6.00 mmol, 1.2 equiv.) was then added dropwise by means of a syringe pump. After the addition of Celite (1.5 g), a 1:1 mixture of methanol and water (4 mL) was added, and the resulting mixture was allowed to warm to room temperature. It was then filtered, rinsing with ethyl acetate. The combined filtrate and washings were dried with Na_2SO_4 and the solvents were evaporated. The allylic alcohol thus obtained was treated with acetic anhydride (535 mg, 5.24 mmol, 1.05 equiv.), triethylamine (607 mg, 6.00 mmol, 1.2 equiv.), and DMAP (61.1 mg, 500 μmol, 0.1 equiv.) in CH_2Cl_2 at 0

°C. The crude product was purified by chromatography on silica gel (100 g SiO_2; PE/EtOAc, 3:1) to give the allylic acetate **10c** (1.69 g, 4.45 mmol, 89%) as a colorless oil; R_f = 0.40 (PE/EtOAc, 3:1). − IR (neat): $\tilde{\nu}$ = 2936 cm^{-1} (=C−H), 1727 (C=O), 1665 (C=C), 1598, 1362 (SO_2), 1243 (C−O), 1188, 1177 (SO_2), 953, 816, 664. − UV (CH_3CN): λ_{max} (lg ε) = 194 nm (4.77), 225 (4.09), 256 (2.72), 262 (2.79), 267 (2.75), 273 (2.67). − ^1H NMR (200 MHz, C_6D_6): δ = 0.87−1.12 (m, 4 H, 2′-H_2, 3′-H_2), 1.26 (tt, *J* = 6.6, 6.6 Hz, 2 H, 4′-H_2), 1.30−1.50 (m, 2 H, 5-H_2), 1.56−1.70 (m, 6 H, 1′-H_2, 4-H_2, 6-H_2), 1.75 (s, 3 H, $COCH_3$), 1.90 (s, 3 H, Ar−CH_3), 3.80 (t, *J* = 6.3 Hz, 2 H, OCH_2), 5.35−5.45 (m_c, 1 H, 1-H), 5.54 (br. s, 1 H, 2-H), 6.79 (d, *J* = 8.3 Hz, 2 H, Ar-2-H, Ar-6-H), 7.78 (d, *J* = 8.3 Hz, 2 H, Ar-3-H, Ar-5-H). − ^{13}C NMR (50.3 MHz, C_6D_6): δ = 19.5 (C-5), 21.1 (CO*C*H_3), 21.2 (Ar−CH_3), 25.2 (C-3′), 26.8 (C-2′), 28.4, 28.6 (C-4, C-6), 28.9 (C-4′), 37.5 (C-1′), 68.7 (C-1), 70.2 (OCH_2), 120.5 (C-2), 128.1 (Ar-C-3, Ar-C-5), 129.8 (Ar-C-2, Ar-C-6), 134.5 (Ar-C-4), 143.7 (C-3), 144.2 (Ar-C-1), 170.0 (CO). − MS (70 eV, EI): *m/z* (%) = 380 (< 1) [M^+], 337 (100) [M^+ − Ac], 320 (13) [M^+ − AcOH], 166 (13), 148 (21) [$C_{11}H_{16}^+$], 155 (4) [Ts^+], 97 (25) [$C_8H_9O^+$], 91 (45) [CH_3Ph^+]. − $C_{20}H_{28}O_5S$ (380.5): calcd. C 63.13, H 7.42; found C 63.34, H 7.26.

General Procedure I. − Synthesis of the Secondary Amines 11a−e by Alkylation of Primary Amines 9a−d: A 1 M solution of the amine **9** (2.5 equiv.) in THF was refluxed with TBAI (1.5 equiv.) and a 0.5 M solution of the tosylate **10** was added dropwise by means of an infusion pump over a period of 8 h. No TBAI was added when 3-(3-iodopropyl)cyclohex-2-enyl acetate[4] was used instead of tosylate **10**. The reaction mixture was heated for a further 2 h, poured into MTBE, and made basic with cold 5% aq. NaOH solution. After separation of the layers, the aqueous layer was extracted four times with MTBE. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness in vacuo. The crude product was purified by column chromatography.

3-{3-[(6-Bromobenzo[1,3]dioxol-5-ylmethyl)amino]propyl}cyclohex-2-enyl Acetate (11a): A solution of amine **9a**[5] (251 mg, 1.09 mmol), 3-(3-iodopropyl)cyclohex-2-enyl acetate[4] (410 mg, 1.33 mmol, 1.2 equiv.), and diisopropylethylamine (450 mg, 3.50 mmol, 3.2 equiv.) in THF (6 mL) was refluxed for 23 h. After work-up according to General Procedure I, the crude product was purified by column chromatography (100 g SiO_2; PE/EtOAc, 1:1, + 1% Et_3N) to give **11a** (287 mg, 700 μmol, 64%) as a pale-yellow oil; R_f = 0.57 (EtOAc/MeOH, 15:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3338 cm^{-1} (N−H), 2936 (C−H), 1726 (C=O), 1664 (C=C), 1476, 1240 (C−O), 1118, 1038, 932 (C−O−C), 912, 866, 832 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 201 nm (4.61), 237 (3.68), 294 (3.61). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.57−1.83 (m, 7 H, 2′-H_2, 5-H_2, 6-H_2, NH), 1.90−2.10 (m, 4 H, 1′-H_2, 4-H_2), 2.04 (s, 3 H, CH_3), 2.59 (t, *J* = 7.0 Hz, 2 H, 3′-H_2), 3.75 (s, 2 H, 1′′-H_2), 5.20−5.30 (m_c, 1 H, 1-H), 5.46 (m_c, 1 H, 2-H), 5.96 (s, 2 H, OCH_2O), 6.90 (s, 1 H, 4′′′-H), 6.99 (s, 1 H, 7′′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.5 (CH_3), 27.7 (C-2′), 28.2, 28.3 (C-4, C-6), 35.3 (C-1′), 48.6 (C-3′), 53.5 (C-1′′), 68.7 (C-1), 101.6 (OCH_2O), 110.1 (C-7′′′), 112.7 (C-4′′′), 114.0 (C-6′′′), 119.7 (C-2), 132.4 (C-5′′′), 144.2 (C-3), 147.3 (C-3a′′′, C-7a′′′), 170.8 (CO). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 412/410 (97/100) [M + H^+], 352/350 (10) [M^+ − AcO], 332 (75) [M^+ − Br + 2 H], 249/247 (15) [$C_8H_9BrNO_2^+$ + NH_3], 232/230 (20/22) [$C_8H_9BrNO_2^+$], 198 (70) [$C_{11}H_{20}NO_2$], 169 (49) [$C_{10}H_{18}N^+$ + NH_3], 152 (54) [$C_{10}H_{18}N^+$], 138 (31) [$C_9H_{16}N^+$]. − $C_{19}H_{24}BrNO_4$ (410.3): calcd. C 55.62, H 5.90; found C 55.85, H 5.96. − HRMS: calcd. 409.0889; found 409.0889.

3-{3-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethylamino]propyl}cyclohex-2-enyl Acetate (11b): According to General Procedure I, amine **9b**[5] (234 mg, 959 μmol, 3.7 equiv.) was alkylated with tosylate **10a**[6] (92.0 mg, 261 μmol) in the presence of TBAI (144 mg, 390 μmol, 1.5 equiv.). Purification of the crude product by column chromatography (45 g SiO_2; gradient column: 200 mL EtOAc/MeOH, 15:1, + 1% Et_3N; then EtOAc/MeOH, 5:1, + 1% Et_3N) afforded **11b** (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 cm^{-1} (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(arene). − UV (CH_3CN): λ_{max} (lg ε) = 201 nm (4.66), 235 (3.72), 294 (3.66). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59−1.82 (m, 7 H, 2′-H_2, 5-H_2, 6-H_2, NH), 1.89−2.05 (m, 4 H, 1′-H_2, 4-H_2), 2.04 (s, 3 H, CH_3), 2.66 (t, *J* = 7.4 Hz, 2 H, 3′-H_2), 2.82−2.90 (m_c, 4 H, 1′′-H_2, 2′′-H_2), 5.23−5.27 (m_c, 1 H, 1-H), 5.46 (m_c, 1 H, 2-H), 5.96 (s, 2 H, OCH_2O), 6.75 (s, 1 H, 4′′′-H), 7.00 (s, 1 H, 7′′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.4 (CH_3), 27.6 (C-2′), 28.1, 28.2 (C-4, C-6), 35.2 (C-1′), 43.6 (C-2′′), 48.6 (C-3′), 53.5 (C-1′′), 68.7 (C-1), 101.6 (OCH_2O), 110.0 (C-4′′′), 112.6 (C-7′′′), 113.9 (C-6′′′), 119.6 (C-2), 132.5 (C-5′′′), 144.1 (C-3), 147.2 (C-3a′′′, C-7a′′′), 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-{3-[2-(2-Bromo-4,5-dimethoxyphenyl)ethylamino]propyl}cyclohex-2-enyl Acetate (11c): According to General Procedure I, amine **9d**[5] (300 mg, 1.15 mmol, 3.4 equiv.) was alkylated with 3-(3-iodopropyl)cyclohex-2-enyl acetate[4] (104 mg, 337 μmol) in THF. Purification of the crude product by column chromatography (40 g SiO_2; EtOAc/MeOH, 15:1, + 1% Et_3N) afforded **11c** (134 mg, 304 μmol, 90%) as a pale-yellow oil; R_f = 0.23 (EtOAc/MeOH, 5:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3426 cm^{-1} (N−H), 2938 (C−H), 1726 (C=O), 1638 (C=C), 1510, 1246 (C−O), 1218 (Ar−O−C), 1166, 1030 (Ar−O−C), 910, 856, 800 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 204 nm (4.65), 287 (3.49). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (br. s, 1 H, NH), 1.54−1.85 (m, 6 H, 2′-H_2, 5-H_2, 6-H_2), 1.91−2.08 (m, 4 H, 1′-H_2, 4-H_2), 2.04 (s, 3 H, $COCH_3$), 2.63 (t, *J* = 7.2 Hz, 2 H, 3′-H_2), 2.85 (s, 4 H, 1′′-H_2, 2′′-H_2), 3.85 (s, 6 H, 2 × OCH_3), 5.20−5.30 (m_c, 1 H, 1-H), 5.45 (br. s, 1 H, 2-H), 6.75 (s, 1 H, 6′′′-H), 7.00 (s, 1 H, 3′′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.4 (CO*C*H_3), 27.7 (C-2′), 28.2, 28.3 (C-4, C-6), 35.3 (C-1′), 36.4 (C-2′′), 49.4, 49.7 (C-1′′, C-3′), 56.0 (OCH_3), 56.1 (OCH_3), 68.7 (C-1), 113.2 (C-6′′′), 114.1 (C-2′′′), 115.5 (C-3′′′), 119.6 (C-2), 131.2 (C-1′′′), 144.2 (C-3), 147.9 (C-5′′′), 148.2 (C-4′′′), 170.8 (CO). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 442/440 (100/94) [M + H^+], 380 (6) [M^+ − AcO], 362 (45) [M^+ − Br + 2 H], 279/277 (11) [$C_{10}H_{15}BrNO_2^+$ + NH_3], 262/260 (10) [$C_{10}H_{15}BrNO_2^+$], 200 (27). − $C_{21}H_{30}BrNO_4$ (440.4).

3-{4-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethylamino]butyl}cyclohex-2-enyl Acetate (11d): According to General Procedure I, amine **9b**[5] (1.90 g, 7.78 mmol, 2.5 equiv.) was alkylated with tosylate **10b**[6] (1.15 g, 3.14 mmol) in the presence of TBAI (1.73 g, 4.68 mmol, 1.5 equiv.). Purification of the crude product by column chromatography (110 g SiO_2; gradient column: 300 mL ethyl acetate; then EtOAc/MeOH, 5:1, + 1% Et_3N) afforded **11d** (1.02 g, 2.33 mmol, 74%) as a pale-yellow oil; R_f = 0.51 (EtOAc/MeOH, 5:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3326 cm^{-1} (N−H), 2933 (C−H), 1727 (C=O), 1666 (C=C), 1478, 1243 (C−O), 1116, 1039, 933 (C−O−C), 910, 860, 833 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.64), 236 (3.66), 294 (3.61). − ^1H NMR (500 MHz,

$CDCl_3$): δ = 1.38−1.52 (m, 4 H, 2′-H_2, 3′-H_2), 1.56−1.80 (m, 5 H, 5-H_2, 6-H_2, NH), 1.85−1.95 (m, 2 H, 4-H_2), 1.98 (t, *J* = 7.4 Hz, 2 H, 1′-H_2), 2.02 (s, 3 H, CH_3), 2.65 (t, *J* = 7.1 Hz, 2 H, 4′-H_2), 2.80−2.88 (m_c, 4 H, 1′′-H_2, 2′′-H_2), 5.21−5.25 (m_c, 1 H, 1-H), 5.43 (m_c, 1 H, 2-H), 5.93 (s, 2 H, OCH_2O), 6.73 (s, 1 H, 4′′′-H), 6.97 (s, 1 H, 7′′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.5 (CH_3), 25.0 (C-2′), 28.2, 28.3 (C-4, C-6), 29.5 (C-3′), 36.2 (C-2′′), 37.4 (C-1′), 49.5 (C-1′′, C-4′), 68.8 (C-1), 101.6 (OCH_2O), 110.2 (C-4′′′), 112.7 (C-7′′′), 114.4 (C-6′′′), 119.6 (C-2), 132.1 (C-5′′′), 144.4 (C-3), 146.8 (C-3a′′′), 147.3 (C-7a′′′), 170.8 (CO). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 440/438 (56/59) [M + H^+], 378 (6) [M^+ − AcO], 360 [M^+ − Br + 2 H], 263/261 (15) [$C_9H_{11}BrNO_2^+$ + NH_3], 246/244 (11) [$C_9H_{11}BrNO_2^+$], 183 (75) [$C_{11}H_{20}N^+$ + NH_3], 166 (51) [$C_{11}H_{20}N^+$]. − $C_{21}H_{28}BrNO_4$ (438.4): calcd. C 57.54, H 6.44; found C 57.60, H 6.36.

3-{3-[3-(6-Bromobenzo[1,3]dioxol-5-yl)propylamino]propyl}cyclohex-2-enyl Acetate (11e): According to General Procedure I, amine **9c**[5] (1.10 g, 4.26 mmol, 2.5 equiv.) was alkylated with tosylate **10a**[6] (600 mg, 1.70 mmol) in the presence of TBAI (943 mg, 2.55 mmol, 1.5 equiv.). Purification of the crude product by column chromatography (70 g SiO_2; gradient column: 150 mL of ethyl acetate; then EtOAc/MeOH, 5:1, + 1% Et_3N) afforded **11e** (566 mg, 1.29 mmol, 76%) as a pale-yellow oil; R_f = 0.49 (EtOAc/MeOH, 5:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3327 cm^{-1} (N−H), 2935 (C−H), 1726 (C=O), 1665 (C=C), 1478, 1243 (C−O), 1114, 1038, 933 (C−O−C), 911, 859, 831 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 201 nm (4.65), 236 (3.68), 294 (3.63). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.55−1.84 (m, 9 H, 2′-H_2, 2′′-H_2, 5-H_2, 6-H_2, NH), 1.93−2.07 (m, 4 H, 1′-H_2, 4-H_2), 2.04 (s, 3 H, CH_3), 2.57−2.72 (m, 6 H, 3′-H_2, 1′′-H_2, 3′′-H_2), 5.20−5.31 (m_c, 1 H, 1-H), 5.47 (br. s, 1 H, 2-H), 5.94 (s, 2 H, OCH_2O), 6.98 (s, 1 H, 4′′′-H), 6.71 (s, 1 H, 7′′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.5 (CH_3), 27.6 (C-2′), 28.2, 28.3 (C-4, C-6), 30.3 (C-3′′), 33.7 (C-2′′), 35.4 (C-1′), 49.1 (C-1′′), 49.5 (C-3′), 68.8 (C-1), 101.5 (OCH_2O), 109.8 (C-4′′′), 112.6 (C-7′′′), 114.2 (C-6′′′), 119.7 (C-2), 134.3 (C-5′′′), 144.2 (C-3), 146.5 (C-3a′′′), 147.3 (C-7a′′′), 170.8 (CO). − MS (70 eV, EI): *m/z* (%) = 440/438 (< 1) [M + H^+], 380/378 (17/23) [M^+ − AcO], 358 (70) [M^+ − Br], 298 (100) [M^+ − AcOH − Br], 272/270 (9/10) [$C_{11}H_{13}BrNO_2^+$], 215/213 (14) [$C_8H_6BrO_2^+$], 204 (37) [$C_{12}H_{14}NO_2^+$], 150 (39) [$C_{10}H_{16}N^+$], 121 (46) [$C_9H_{13}^+$], 44 (67) [CO_2^+]. − $C_{21}H_{28}BrNO_4$ (438.4): calcd. C 57.54, H 6.44; found C 57.05, H 6.30.

3-{3-[(2-Benzo[1,3]dioxol-5-yl)ethylamino]propyl}cyclohex-2-enyl Acetate (13): According to General Procedure I, 2-benzo[1,3]-dioxol-5-ylethylamine (540 mg, 3.23 mmol, 2.0 equiv.) was alkylated with 3-(3-iodopropyl)cyclohex-2-enyl acetate[4] (503 mg, 1.63 mmol). Purification of the crude product by column chromatography (100 g SiO_2; gradient column: 100 mL ethyl acetate; 300 mL of ethyl acetate/MeOH, 15:1, + 1% Et_3N; then EtOAc/MeOH, 5:1, + 1% Et_3N) afforded **13** (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 cm^{-1} (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 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 199 nm (4.68), 234 (3.60), 287 (3.57). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (br. s, 1 H, NH), 1.50−1.85 (m, 6 H, 2′-H_2, 5-H_2, 6-H_2), 1.90−2.05 (m, 4 H, 1′-H_2, 4-H_2), 2.04 (s, 3 H, CH_3), 2.59 (t, *J* = 7.2 Hz, 2 H, 3′-H_2), 2.65−2.86 (m_c, 4 H, 1′′-H_2, 2′′-H_2), 5.19−5.29 (m_c, 1 H, 1-H), 5.43 (br. s, 1 H, 2-H), 5.92 (s, 2 H, OCH_2O), 6.65 (dd, *J* = 7.8, 1.7 Hz, 1 H, 6′′′-H), 6.69 (d, *J* = 1.7 Hz, 1 H, 4′′′-H), 6.74 (d, *J* = 7.8 Hz, 1 H, 7′′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.4 (CH_3), 27.7 (C-2′), 28.16, 28.21 (C-4, C-6), 35.3 (C-1′), 36.0 (C-2′′), 49.4 (C-3′), 51.2 (C-1′′), 68.7 (C-1), 100.7 (OCH_2O), 108.1 (C-4′′′), 108.9 (C-7′′′), 119.6 (C-2), 121.4 (C-6′′′), 133.8 (C-5′′′), 144.2 (C-3), 145.8 (C-7a′′′), 147.6 (C-3a′′′), 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.

1-(2-Benzo[1,3]dioxol-5-ylethyl)-1-azaspiro[4.5]dec-6-ene (14): A mixture of amine **13** (20.3 mg, 58.8 μmol), [$Pd(PPh_3)_4$] (10.0 mg, 8.70 μmol, 15 mol%), and triethylamine (18.2 mg, 179 μmol, 3.0 equiv.) in CH_3CN was heated at 75 °C for 18 h. Work-up as described for **17a** and **17b**, followed by column chromatography (20 g SiO_2; EtOAc) gave **14** (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 cm^{-1} (Ar−H), 2936 (C−H), 1490, 1247, 1109, 1042, 931 (C−O−C), 863, 808 (arene), 742 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 199 nm (4.63), 231 (3.72), 287 (3.58). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45−1.90 (m, 8 H, 3-H_2, 4-H_2, 9-H_2, 10-H_2), 1.93 (m_c, 2 H, 8-H_2), 2.56−2.72 (m, 4 H, 1′-H_2, 2′-H_2), 2.82 (br. s, 1 H, 2-H), 2.99 (m, 1 H, 2-H), 5.46 (d, *J* = 10.1 Hz, 1 H, 6-H), 5.76 (dt, *J* = 10.1, 4.1 Hz, 1 H, 7-H), 5.91 (s, 2 H, OCH_2O), 6.65 (dd, *J* = 8.0, 1.6 Hz, 1 H, 6′′-H), 6.71 (d, *J* = 1.6 Hz, 1 H, 7′′-H), 6.72 (d, *J* = 8.0 Hz, 1 H, 4′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.1, 21.2 (C-3, C-9), 25.1 (C-8), 28.3 (C-4), 36.2 (C-2′), 38.3 (C-10), 50.6 (C-2), 51.8 (C-1′), 63.7 (C-5), 100.6 (OCH_2O), 108.0 (C-4′′), 109.1 (C-7′′), 121.3 (C-6′′), 128.9 (C-7), 133.2 (C-6), 134.7 (C-5′′), 145.5 (C-7a′′), 147.3 (C-3a′′). − 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 II. − Formation of the Nosylates 18b−e from the Corresponding Alcohols: To a 0.2 M solution of the alcohol in CH_2Cl_2 at 0 °C were added triethylamine (1.2 equiv.) and DMAP (0.1 equiv.), and then nosyl chloride (1.2 equiv.) was added portionwise. The mixture was subsequently allowed to warm to room temperature and stirred for 4 h. It was then diluted with CH_2Cl_2, washed with brine, dried with Na_2SO_4, and concentrated to dryness in vacuo. The residue was purified by recrystallization.

2-(6-Bromobenzo[1,3]dioxol-5-yl)ethyl 4-Nitrobenzenesulfonate (18b) via 2-(6-Bromobenzo[1,3]dioxol-5-yl)ethanol: To a stirred solution of 2-benzo[1,3]dioxol-5-ylethanol[20] (6.26 g, 37.7 mmol) in CH_2Cl_2 (60 mL), bromine (8.39 g, 52.5 mmol, 1.4 equiv.) was added dropwise. After 0.5 h, the excess bromine was destroyed with saturated Na_2SO_3 solution and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness in vacuo. The residue was recrystallized from PE/MTBE to afford the bromobenzoethanol (8.42 g, 34.4 mmol, 91%) as colorless crystals; R_f = 0.30 (PE/MTBE, 1:1). − IR (KBr): $\tilde{\nu}$ = 3222 cm^{-1} (OH), 1482, 1240, 1046 (C−O), 930 (C−O−C), 862, 832 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.55), 238 (3.64), 294 (3.61). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.57 (br. s, 1 H, OH), 2.93 (t, *J* = 6.7 Hz, 2 H, $ArCH_2$), 3.83 (t, *J* = 6.7 Hz, 2 H, OCH_2), 5.95 (s, 2 H, OCH_2O), 6.77 (s, 1 H, 4-H), 7.01 (s, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 39.1 ($ArCH_2$), 62.1 (OCH_2), 101.6 (OCH_2O), 110.7 (C-4), 112.7 (C-7), 114.6 (C-6), 130.7 (C-5), 147.0 (C-3a), 147.2 (C-7a). − MS (70 eV, EI): *m/z* (%) = 246/244 (35) [M^+], 215/213 (96/100) [M^+ − CH_3O], 164 (8), 135 (9) [$C_8H_7O_2^+$]. − $C_9H_9BrO_3$ (245.1): calcd. C 44.11, H 3.70; found C 44.05, H 3.52. − According to General Procedure II, the alcohol (4.54 g, 18.5 mmol) was treated with nosyl chloride (4.97 g, 22.4 mmol, 1.2 equiv.) in the presence of triethylamine (2.25 g, 22.2 mmol, 1.2 equiv.) and DMAP (226 mg, 1.85 mmol, 0.1 equiv.). Recrystallization of the

crude product from CH_2Cl_2/ethyl acetate afforded **18b** (7.07 g, 16.4 mmol, 89%) as yellow crystals; $R_f = 0.45$ (PE/MTBE, 1:1). − IR (KBr): $\tilde{\nu} = 1532\ cm^{-1}$ (NO_2), 1478, 1362 (NO_2), 1246, 1190 (SO_2), 1034, 970, 912 (C−O−C), 850, 832 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.60), 248 (4.08), 291 (3.88). − ^1H NMR (200 MHz, $CDCl_3$): δ = 3.01 (t, J = 6.5 Hz, 2 H, $ArCH_2$), 4.35 (t, J = 6.5 Hz, 2 H, OCH_2), 5.94 (s, 2 H, OCH_2O), 6.57 (s, 1 H, 4-H), 6.86 (s, 1 H, 7-H), 7.96 (d, J = 8.8 Hz, 2 H, Ar-2-H, Ar-6-H), 8.31 (d, J = 8.8 Hz, 2 H, Ar-3-H, Ar-5-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 35.5 ($ArCH_2$), 70.4 (OCH_2), 101.9 (OCH_2O), 110.9 (C-4), 112.8 (C-7), 114.5 (C-6), 124.2 (Ar-C-3, Ar-C-5), 127.9 (C-5), 129.0 (Ar-C-2, Ar-C-6), 141.5 (Ar-C-1), 147.3 (C-3a), 147.6 (C-7a), 150.4 (Ar-C-4). − MS (70 eV, EI): m/z (%) = 431/429 (8/7) [M^+], 356/354 (8/9), 229/227 (19/26) [M^+ − NsO], 228/226 (38) [M^+ − NsOH], 215/213 (54/56) [M^+ − $NsOCH_2$], 148 (20) [$C_9H_8O_2^+$], 44 (100) [$C_2H_4O^+$]. − $C_{15}H_{12}BrNO_7S$ (430.2): calcd. C 41.88, H 2.81; found C 41.63, H 2.84. − HRMS: calcd. 428.9518; found 428.9518.

2-(6-Iodobenzo[1,3]dioxol-5-yl)ethyl 4-Nitrobenzenesulfonate (18c) via 2-(6-Iodobenzo[1,3]dioxol-5-yl)ethanol:[9,10] To a stirred solution of 2-benzo[1,3]dioxol-5-ylethanol[20] (505 mg, 3.04 mmol) in CH_2Cl_2 (30 mL) was added CF_3COOAg (750 mg, 3.40 mmol, 1.1 equiv.) and iodine (940 mg, 3.70 mmol, 1.2 equiv.). After 2 h, the excess iodine was destroyed with saturated Na_2SO_3 solution and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness in vacuo. Purification by column chromatography (20 g SiO_2; PE/MTBE, 1:1) gave the iodobenzoethanol (861 mg, 2.95 mmol, 97%); $R_f = 0.29$ (PE/MTBE, 1:1); m.p. 69 °C (ref.[9]: 68−69.5 °C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.59 (br. s, 1 H, OH), 2.93 (t, J = 6.7 Hz, 2 H, $ArCH_2$), 3.81 (t, J = 6.7 Hz, 2 H, OCH_2), 5.95 (s, 2 H, OCH_2O), 6.79 (s, 1 H, 4-H), 7.24 (s, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 43.4 ($ArCH_2$), 62.4 (OCH_2), 88.0 (C-6), 101.5 (OCH_2O), 110.1 (C-4), 118.7 (C-7), 134.2 (C-5), 147.1, 147.2 (C-3a, C-7a). − According to General Procedure II, the alcohol (875 mg, 3.00 mmol) was treated with nosyl chloride (837 mg, 3.78 mmol, 1.3 equiv.) in the presence of triethylamine (378 mg, 3.73 mmol, 1.2 equiv.) and DMAP (40.0 mg, 330 µmol, 0.1 equiv.). Recrystallization of the crude product from CH_2Cl_2/ethyl acetate afforded **18c** (1.23 g, 2.58 mmol, 86%) as yellow crystals; $R_f = 0.40$ (PE/MTBE, 1:1); m.p. 127 °C (ref.[9]: 126.5−127 °C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 3.01 (t, J = 6.5 Hz, 2 H, $ArCH_2$), 4.33 (t, J = 6.5 Hz, 2 H, OCH_2), 5.94 (s, 2 H, OCH_2O), 6.59 (s, 1 H, 4-H), 7.09 (s, 1 H, 7-H), 7.96 (d, J = 8.8 Hz, 2 H, Ar-2-H, Ar-6-H), 8.31 (d, J = 8.8 Hz, 2 H, Ar-3-H, Ar-5-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 39.5 ($ArCH_2$), 70.7 (OCH_2), 88.0 (C-6), 101.8 (OCH_2O), 110.3 (C-4), 118.8 (C-7), 124.2 (Ar-C-3, Ar-C-5), 131.4 (C-5), 129.0 (Ar-C-2, Ar-C-6), 141.5 (Ar-C-1), 147.4 (C-3a), 148.8 (C-7a), 150.4 (Ar-C-4).

3-(6-Bromobenzo[1,3]dioxol-5-yl)propyl 4-Nitrobenzenesulfonate (18d) via 3-(6-Bromobenzo[1,3]dioxol-5-yl)propan-1-ol: To a solution of 3-benzo[1,3]dioxol-5-ylpropan-1-ol[11] (6.79 g, 37.7 mmol) in CH_2Cl_2 (60 mL), bromine (7.22 g, 45.2 mmol, 1.2 equiv.) was added dropwise and the resulting mixture was stirred for 1 h at room temperature. The excess bromine was then destroyed with Na_2SO_3 solution (2 × 100 mL). The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness. The residue was recrystallized from PE/MTBE to give the bromo compound (8.42 g, 32.5 mmol, 86%) as colorless crystals; $R_f = 0.31$ (PE/MTBE, 1:1). − IR (KBr): $\tilde{\nu} = 3277\ cm^{-1}$ (OH), 1485, 1040 (C−O), 933 (C−O-C), 864 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.55), 237 (3.64), 294 (3.62). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.51 (br. s, 1 H, OH), 1.84 (tt, J = 7.7, 6.4 Hz, 2 H, CH_2), 2.74 (t, J = 7.7 Hz, 2 H, $ArCH_2$), 3.68 (t, J = 6.4 Hz, 2 H, OCH_2), 5.94 (s, 2 H, OCH_2O), 6.73 (s, 1 H, 4-H), 6.98 (s, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 32.2, 32.8 ($ArCH_2$, CH_2), 61.9 (OCH_2), 101.5 (OCH_2O), 109.9 (C-4), 112.6 (C-7), 114.2 (C-6), 134.0 (C-5), 146.5 (C-3a), 147.2 (C-7a). − MS (70 eV, EI): m/z (%) = 260/258 (56/58) [M^+], 215/213 (98/100) [M^+ − C_2H_5O], 135 (97) [$C_8H_7O_2^+$]. − $C_{10}H_{11}BrO_3$ (258.0): calcd. C 46.36, H 4.28; found C 46.67, H 4.26. − According to General Procedure II, the alcohol (6.00 g, 23.2 mmol) was treated with nosyl chloride (6.46 g, 29.2 mmol, 1.3 equiv.) in the presence of triethylamine (3.03 g, 29.9 mmol, 1.3 equiv.) and DMAP (300 mg, 2.46 mmol, 0.1 equiv.). Recrystallization from CH_2Cl_2/ethyl acetate afforded **18d** (9.66 g, 21.7 mmol, 94%) as yellow crystals; $R_f = 0.45$ (PE/MTBE, 1:1); m.p. 115 °C. − IR (KBr): $\tilde{\nu} = 1533\ cm^{-1}$ (NO_2), 1477 (C−O−C), 1370 (NO_2), 1351 (SO_2), 1184 (SO_2), 1034, 955, 932 (C−O−C), 858, 834 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 201 nm (4.67), 247 (4.15), 292 (3.77). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.98 (tt, J = 7.4, 6.1 Hz, 2 H, CH_2), 2.69 (t, J = 7.4 Hz, 2 H, $ArCH_2$), 4.14 (t, J = 6.1 Hz, 2 H, OCH_2), 5.93 (s, 2 H, OCH_2O), 6.48 (s, 1 H, 4-H), 6.94 (s, 1 H, 7-H), 8.12 (d, J = 9.1 Hz, 2 H, Ar-2-H, Ar-6-H), 8.41 (d, J = 9.1 Hz, 2 H, Ar-3-H, Ar-5-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.7 ($ArCH_2$), 31.6 (CH_2), 70.5 (OCH_2), 101.7 (OCH_2O), 109.8 (C-4), 112.7 (C-7), 114.1 (C-6), 124.4 (Ar-C-3, Ar-C-5), 129.1 (Ar-C-2, Ar-C-6), 132.0 (C-5), 141.6 (Ar-C-1), 146.9 (C-3a), 147.2 (C-7a), 150.7 (Ar-C-4). − MS (70 eV, EI): m/z (%) = 445/443 (100/92) [M^+], 242/240 (32/33) [M^+ − NsOH], 215/213 (63/66) [$C_8H_6BrO_2^+$], 131 (35), 103 (19). − $C_{16}H_{14}BrNO_7S$ (444.3): calcd. C 43.26, H 3.18; found C 43.55, H 3.37. − HRMS: calcd. 442.9674; found 442.9674.

3-(6-Iodobenzo[1,3]dioxol-5-yl)propyl 4-Nitrobenzenesulfonate (18e) via 3-(6-Iodobenzo[1,3]dioxol-5-yl)propan-1-ol: To a solution of 3-benzo[1,3]dioxol-5-ylpropan-1-ol[11] (3.09 g, 17.2 mmol) in CH_2Cl_2 (40 mL) was added ICl (3.34 g, 20.6 mmol, 1.2 equiv.) and the resulting mixture was stirred for 3 h at room temperature. The excess ICl was then destroyed with Na_2SO_3 solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness. The residue was recrystallized from PE/MTBE to give the alcohol (3.08 g, 10.1 mmol, 59%) as colorless crystals; $R_f = 0.32$ (PE/MTBE, 1:1). − IR (KBr): $\tilde{\nu} = 3281\ cm^{-1}$ (OH), 1484, 1243, 1040 (C−O), 932 (C−O−C), 862 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 207 nm (4.54), 241 (3.83), 295 (3.62). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.69 (br. s, 1 H, OH), 1.82 (tt, J = 7.8, 6.3 Hz, 2 H, CH_2), 2.74 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 3.70 (t, J = 6.3 Hz, 2 H, OCH_2), 5.94 (s, 2 H, OCH_2O), 6.76 (s, 1 H, 4-H), 7.22 (s, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 33.2 ($ArCH_2$), 36.8 (CH_2), 61.9 (OCH_2), 87.6 (C-6), 101.4 (OCH_2O), 109.2 (C-4), 118.5 (C-7), 137.6 (C-5), 146.6, 148.4 (C-3a, C-7a). − MS (70 eV, EI): m/z (%) = 306 (29) [M^+], 261 (25) [M^+ − C_2H_5O], 135 (100) [$C_8H_7O_2^+$]. − $C_{10}H_{11}IO_3$ (306.1): calcd. C 39.24, H 3.62; found C 39.23, H 3.72. − According to General Procedure II, the alcohol (3.08 g, 10.1 mmol) was treated with nosyl chloride (2.68 g, 12.1 mmol, 1.2 equiv.) in the presence of triethylamine (1.32 g, 13.0 mmol, 1.3 equiv.) and DMAP (123 mg, 1.01 mmol, 0.1 equiv.). Recrystallization of the crude product from CH_2Cl_2/ethyl acetate/PE afforded **18e** (4.21 g, 8.57 mmol, 85%) as yellow crystals; R_f = 0.40 (PE/EtOAc, 3:1). − IR (KBr): $\tilde{\nu} = 1532\ cm^{-1}$ (NO_2), 1480, 1367 (NO_2), 1352 (SO_2), 1232, 1185 (SO_2), 1041, 940 (C−O−C), 860, 844 (arene). − UV (CH_3CN): λ_{max} (lg ε) = 204 nm (4.62), 246 (4.24), 292 (3.77). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.95 (tt, J = 7.6, 6.2 Hz, 2 H, CH_2), 2.68 (t, J = 7.6 Hz, 2 H, $ArCH_2$), 4.15 (t, J = 6.2 Hz, 2 H, OCH_2), 5.92 (s, 2 H, OCH_2O), 6.51 (s, 1 H, 4-

H), 7.17 (s, 1 H, 7-H), 8.13 (d, J = 8.8 Hz, 2 H, Ar-2-H, Ar-6-H), 8.41 (d, J = 8.8 Hz, 2 H, Ar-3-H, Ar-5-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 29.1 ($ArCH_2$), 36.1 (CH_2), 70.5 (OCH_2), 87.5 (C-6), 101.6 (OCH_2O), 109.2 (C-4), 118.7 (C-7), 124.5 (Ar-C-3, Ar-C-5), 129.2 (Ar-C-2, Ar-C-6), 135.6 (C-5), 141.7 (Ar-C-1), 147.0, 148.4 (C-3a, C-7a), 150.8 (Ar-C-4). − MS (70 eV, EI): *m/z* (%) = 491 (100) [M^+], 365 (10), 288 (29) [M^+ − NsOH], 261 (48) [$C_8H_6IO_2^+$], 162 (13) [$C_{10}H_{10}O_2^+$], 131 (37). − $C_{16}H_{14}INO_7S$ (491.3): calcd. C 39.12, H 2.87; found C 39.38, H 3.08. − HRMS: calcd. 490.9536; found 490.9536.

3-(3-Azidopropyl)cyclohex-2-enyl Acetate (15a): The tosylate **10a**[6] (8.51 g, 24.1 mmol) was dissolved in DMSO (50 mL) and sodium azide (3.55 g, 54.6 mmol, 2.3 equiv.) was added. After stirring for 27 h at room temperature, MTBE (200 mL) and water (200 mL) were added. The aqueous layer was extracted twice with MTBE. The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (210 g SiO_2; PE/MTBE, 5:1) to afford **15a** (5.10 g, 22.9 mmol, 95%) as a colorless oil; R_f = 0.64 (PE/MTBE, 1:1). − IR (neat): $\tilde{\nu}$ = 2940 cm^{-1} (C−H), 2100 (N_3), 1732 (C=O), 1666 (C=C), 1450, 1370, 1244 (C−O), 1020, 912. − UV (CH_3CN): no absorption. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60−1.84 (m, 6 H, 2′-H_2, 5-H_2, 6-H_2), 1.93 (dt, J = 17.5, 5.5 Hz, 1 H, 4-H), 2.01 (dt, J = 17.5, 5.5 Hz, 1 H, 4-H), 2.05 (s, 3 H, CH_3), 2.08 (t, J = 7.7 Hz, 2 H, 1′-H_2), 3.27 (t, J = 6.9 Hz, 2 H, 3′-H_2), 5.24−5.28 (m_c, 1 H, 1-H), 5.49 (m_c, 1 H, 2-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.4 (CH_3), 26.6 (C-2′), 28.2, 28.3 (C-4, C-6), 34.5 (C-1′), 51.0 (C-3′), 68.6 (C-1), 120.5 (C-2), 143.0 (C-3), 170.8 (CO). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 258 (10) [M + NH_4^+ + NH_3], 241 (6) [M + NH_4^+], 164 (100) [M^+ − AcO], 136 (16) [$C_7H_{10}N_3^+$]. − $C_{11}H_{17}N_3O_2$ (223.3): calcd. C 59.17, H 7.67; found C 59.29, H 7.91.

3-(4-Azidobutyl)cyclohex-2-enyl Acetate (15b): As described for **15a**, a solution of tosylate **10b**[6] (7.03 g, 19.2 mmol) in DMSO (40 mL) was treated with sodium azide (2.98 g, 45.8 mmol, 2.4 equiv.). The crude product was purified by column chromatography (210 g SiO_2; PE/MTBE, 5:1) to give **15b** (4.35 g, 18.4 mmol, 96%) as a colorless oil; R_f = 0.65 (PE/MTBE, 1:1). − IR (neat): $\tilde{\nu}$ = 2939 cm^{-1} (C−H), 2997 (N_3), 1730 (C=O), 1666 (C=C), 1455, 1371, 1243 (C−O), 1020, 911. − UV (CH_3CN): λ_{max} (lg ε) = 191 nm (4.10). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40−1.90 (m, 8 H, 2′-H_2, 3′-H_2, 4′-H_2, 5-H_2), 1.92−2.08 (m, 4 H, 1′-H_2, 4-H_2), 2.05 (s, 3 H, CH_3), 3.28 (t, J = 6.4 Hz, 2 H, 4′-H_2), 5.20−5.30 (m_c, 1 H, 1-H), 5.47 (br. s, 1 H, 2-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.4 (CH_3), 24.4 (C-2′), 28.2 (C-3′), 28.2, 28.4 (C-4, C-6), 37.0 (C-1′), 51.2 (C-4′), 68.7 (C-1), 120.0 (C-2), 143.8 (C-3), 170.8 (CO). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 255 (7) [M + NH_4^+], 212 (6), 195 (2), 178 [M^+ − Ac], 150 (100) [$C_8H_{12}N_3^+$]. − $C_{12}H_{19}N_3O_2$ (237.1): calcd. C 60.74, H 8.07; found C 60.85, H 7.95.

3-(5-Azidopentyl)cyclohex-2-enyl Acetate (15c): As described for **15a**, a solution of tosylate **10c** (2.00 g, 5.26 mmol) in DMSO (10 mL) was treated with sodium azide (854 mg, 13.1 mmol, 2.5 equiv.). The crude product was purified by column chromatography (70 g SiO_2, PE/MTBE, 5:1) to give **15c** (1.12 g, 4.94 mmol, 94%) as a colorless oil; R_f = 0.68 (MTBE). − IR (neat): $\tilde{\nu}$ = 2936 cm^{-1} (C−H), 2096 (N_3), 1730 (C=O), 1667 (C=C), 1454, 1371, 1242 (C−O), 1019, 911. − UV (CH_3CN): no absorption. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30−1.50 (m, 4 H, 2′-H_2, 3′-H_2), 1.50−1.90 (m, 6 H, 4′-H_2, 5-H_2, 6-H_2), 1.90−2.10 (m, 4 H, 1′-H_2, 4-H_2), 2.04 (s, 3 H, CH_3), 3.26 (d, J = 6.8 Hz, 2 H, 5′-H_2), 5.20−5.32 (m_c, 1 H, 1-H), 5.46 (br. s, 1 H, 2-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.1 (C-5), 21.4 (CH_3), 26.3, 26.8 (C-2′, C-3′), 28.2 (C-4′), 28.2, 28.6 (C-4, C-6), 37.3 (C-1′), 51.2 (C-5′), 68.7 (C-1), 119.6 (C-2), 144.2 (C-3), 170.7 (CO). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 269 (19) [M + NH_4^+], 209 (40) [M^+ − N_3], 164 (60) [$C_{11}H_{18}N^+$], 122 (4) [$C_9H_{14}^+$]. − $C_{13}H_{21}N_3O_2$ (251.3): calcd. C 62.13, H 8.42; found C 61.82, H 8.43.

1-Azaspiro[4.5]dec-6-ene (17a): To a solution of azide **15a** (2.00 g, 8.96 mmol) in ethyl acetate (120 mL) was added Lindlar's catalyst (700 mg, 5% Pd on $CaCO_3$). The mixture was stirred for 1 h under hydrogen, then filtered through Celite, and the solvent was evaporated. The crude primary amine **16a** was redissolved in acetonitrile (40 mL) and was cyclized in the presence of triethylamine (2.32 g, 23.0 mmol, 2.6 equiv.) and [$Pd(PPh_3)_4$] (350 mg, 303 μmol, 3.4 mol-%) at 70 °C for 18 h. The mixture was then diluted with MTBE and extracted twice with cold 1 M HCl. The combined aqueous layers were extracted with MTBE, then made basic with cold 10% aq. NaOH solution and extracted a further four times with MTBE. The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated. The secondary spirocyclic amine **17a** thus obtained was used directly in the next step without further purification. For analytical purposes, a small sample was purified by kugelrohr distillation (100−150 °C, 13 mbar). − IR (KBr): $\tilde{\nu}$ = 2800−3000 cm^{-1} (N−H), 2915 (C−H), 1650, 1402, 1022, 941, 868, 744 (=C−H) (hydrochloride). − UV (CH_3CN): no absorption. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.56−1.68 (m, 7 H, 3-H_2, 4-H_2, 9-H_2, NH), 1.70−1.89 (m, 2 H, 10-H_2), 1.91−2.03 (m, 2 H, 8-H_2), 2.94 (dt, J = 10.3, 6.6 Hz, 1 H, 2-H), 3.04 (dt, J = 10.3, 6.6 Hz, 1 H, 2-H), 5.54 (dt, J = 9.8, 1.7 Hz, 1 H, 6-H), 5.66 (dt, J = 9.8, 3.4 Hz, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.3 (C-3), 24.8 (C-9), 25.3 (C-8), 36.0 (C-4), 38.8 (C-10), 45.5 (C-2), 59.7 (C-5), 126.7 (C-7), 134.0 (C-6). − MS (70 eV, EI): *m/z* (%) = 137 (35) [M^+], 109 (97) [M^+ − C_2H_4], 91 (100). − $C_9H_{16}ClN$ (173.7) (hydrochloride): calcd. C 62.24, H 9.29; found C 61.70, H 9.34.

1-Azaspiro[5.5]undec-7-ene (17b): As described for **17a**, azide **15b** (1.06 g, 4.45 mmol) was reduced in ethyl acetate (70 mL) in the presence of Lindlar's catalyst (335 mg). The crude primary amine **16b** was redissolved in acetonitrile (20 mL) and was cyclized in the presence of [$Pd(PPh_3)_4$] (210 mg, 182 μmol, 4 mol%) and triethylamine (1.16 g, 11.5 mmol, 2.6 equiv.). The spirocyclic amine **17b** thus obtained was used directly in the next step. For analytical purposes, a small sample was purified by kugelrohr distillation (100−150 °C, 13 mbar) to give a colorless liquid. − IR (KBr): $\tilde{\nu}$ = 2800−3000 cm^{-1} (N−H), 2934 (C−H), 1583, 1443, 1091, 995, 866, 802, 741 (=C−H). − UV (CH_3CN): no absorption. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35−1.75 (m, 11 H, 3-H_2, 4-H_2, 5-H_2, 10-H_2, 11-H_2, NH), 1.92−2.04 (m, 2 H, 9-H_2), 2.80−2.90 (m, 2 H, 2-H_2), 5.68 (dt, J = 10.0, 3.3 Hz, 1 H, 8-H), 5.80 (dt, J = 10.0, 1.5 Hz, 1 H, 7 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 18.8 (C-4), 20.2 (C-10), 25.7 (C-3), 26.2 (C-9), 33.8 (C-5), 37.2 (C-11), 40.8 (C-2), 50.4 (C-6), 127.4 (C-8), 133.5 (C-7). − MS (70 eV, EI): *m/z* (%) = 151 (58) [M^+], 136 (15), 123 (100) [M^+ − C_2H_4], 109 (54) [M^+ − C_3H_6], (hydrochloride). − $C_{10}H_{18}ClN$ (187.7) (hydrochloride): calcd. C 63.99, H 9.67; found C 64.19, H 9.75. − HRMS: calcd. 151.1361; found 151.1360.

General Procedure III. − Alkylation of Secondary Spirocyclic Amines 17 with Nosylates 18b−e: To a stirred solution of the crude secondary amine **17** in acetonitrile (0.15 to 0.20 M), the nosylate **18b−e** (1.2 equiv.) and diisopropylethylamine (3.0 equiv.) were added at room temperature. Stirring was continued at 50 °C for 15−20 h. Thereafter, the mixture was diluted with MTBE and extracted with 5% aq. NaOH solution. The organic layer was dried

with Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography.

1-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethyl]-1-azaspiro[4.5]dec-6-ene (12a): According to General Procedure III, the crude amine **17a** (143 mg, 1.04 mmol) was treated with the nosylate **18b** (673 mg, 1.56 mmol, 1.5 equiv.) in the presence of diisopropylethylamine (450 mg, 3.50 mmol, 3.4 equiv.). Column chromatography (50 g SiO_2; gradient column: 200 mL EtOAc; then EtOAc/MeOH, 15:1, + 1% NEt_3) of the crude product afforded **12a** (231 mg, 631 μmol, 61% over 3 steps); R_f = 0.55 (EtOAc/MeOH, 15:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3012 cm^{-1} (Ar−H), 2930 (C−H), 1478, 1230, 1114, 1040, 936 (C−O−C), 860, 834 (arene), 736 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.60), 294 (3.65). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.42−2.00 (m, 10 H, 3-H_2, 4-H_2, 8-H_2, 9-H_2, 10-H_2), 2.53−2.63 (m, 2 H, 2′-H_2*), 2.77−2.87 (m, 2 H, 1′-H_2*), 2.85−3.08 (m, 2 H, 2-H_2*), 5.46 (d, *J* = 10.0 Hz, 1 H, 6-H), 5.75 (dt, *J* = 10.0, 3.7 Hz, 1 H, 7-H), 5.93 (s, 2 H, OCH_2O), 6.74 (s, 1 H, 4′′-H), 6.97 (s, 1 H, 7′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.1, 21.3 (C-3, C-9), 25.2 (C-8), 28.6 (C-4), 36.6 (C-2′), 38.3 (C-10), 49.8 (C-1′), 50.7 (C-2), 63.8 (C-5), 101.5 (OCH_2O), 110.3 (C-4′′), 112.5 (C-7′′), 114.4 (C-6′′), 128.9 (C-7), 133.1 (C-6, C-5′′), 146.6 (C-3a′′), 147.1 (C-7a′′). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 366/364 (98/100) [M + H^+], 286 (86) [M^+ − Br + 2 H]. − $C_{18}H_{22}BrNO_2$ (364.3): calcd. C 59.35, H 6.09; found C 59.15, H 6.27.

1-[2-(6-Iodobenzo[1,3]dioxol-5-yl)ethyl]-1-azaspiro[4.5]dec-6-ene (12b): According to General Procedure III, the crude amine **17a** (140 mg, 1.02 mmol) was treated with the nosylate **18c** (787 mg, 1.65 mmol, 1.6 equiv.) in the presence of diisopropylethylamine (450 mg, 3.50 mmol, 3.4 equiv.). Column chromatography (60 g SiO_2; gradient column: 200 mL EtOAc; then EtOAc/MeOH, 15:1, + 1% NEt_3) of the crude product afforded **12b** (219 mg, 532 μmol, 52% over 3 steps); R_f = 0.64 (EtOAc/MeOH, 5:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3012 cm^{-1} (Ar−H), 2930 (C−H), 1476, 1226, 1112, 1040, 934 (C−O−C), 860, 830 (arene), 736 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 206 nm (4.56), 240 (3.87), 296 (3.62). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.45−2.00 (m, 10 H, 3-H_2, 4-H_2, 8-H_2, 9-H_2, 10-H_2), 2.52−2.61 (m, 2 H, 2′-H_2*), 2.79−2.88 (m, 2 H, 1′-H_2*), 2.88−3.14 (m, 2 H, 1-H_2*), 5.48 (d, *J* = 10.2 Hz, 1 H, 6-H), 5.76 (dt, *J* = 10.2, 3.7 Hz, 1 H, 7-H), 5.93 (s, 2 H, OCH_2O), 6.77 (s, 1 H, 4′′-H), 7.21 (s, 1 H, 7′′-H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.1, 21.2 (C-3, C-9), 25.1 (C-8), 28.6 (C-4), 38.2 (C-10), 40.9 (C-2′), 50.0 (C-1′), 50.7 (C-2), 64.1 (C-5), 87.8 (C-6′′), 101.4 (OCH_2O), 109.6 (C-4′′), 118.4 (C-7′′), 129.2 (C-7), 132.8 (C-6), 136.6 (C-5′′), 146.7 (C-7a′′), 148.3 (C-3a′′). − MS (70 eV, EI): *m/z* (%) = 411 (< 1) [M^+], 254 (13), 150 (100) [$C_{10}H_{16}N^+$]. − $C_{18}H_{22}INO_2$ (411.3): calcd. C 52.57, H 5.39; found C 52.86, H 5.41.

1-[2-(6-Bromobenzo[1,3]dioxol-5-yl)ethyl]-1-azaspiro[5.5]undec-7-ene (12c): According to General Procedure III, the crude amine **17b** (540 mg, 3.57 mmol) was treated with the nosylate **18b** (2.29 g, 5.33 mmol, 1.5 equiv.) in the presence of diisopropylethylamine (1.62 g, 12.5 mmol, 3.5 equiv.). Column chromatography (100 g SiO_2; gradient column: 100 mL EtOAc; then EtOAc/MeOH, 5:1, + 1% NEt_3) of the crude product afforded **12c** (840 mg, 2.22 mmol, 62% over 3 steps); R_f = 0.65 (EtOAc/MeOH, 15:1, + 1% Et_3N); m.p. 71 °C. − IR (KBr): $\tilde{\nu}$ = 3012 cm^{-1} (Ar−H), 2948 (C−H), 1478, 1230, 1115, 1083, 1038, 928 (C−O−C), 857, 834 (arene), 733 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.57), 232 (3.74), 295 (3.63). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35−1.68 (m, 9 H, 3-H_2, 4-H_2, 5-H_2, 10-H_2, 11-H), 1.83−1.88 (m, 1 H, 11-H), 1.92 (m_c, 2 H, 9-H_2), 2.17−2.24 (m, 1 H, 1′-H), 2.48 (dt, *J* = 11.5, 3.0 Hz, 1 H, 2-H_{ax}), 2.60−2.67 (m, 1 H, 1′-H), 2.74−2.85 (m, 5 H, 2′-H_2, 1′-H, 2-H_{eq}), 5.33 (ddt, *J* = 10.1, 1.8, 1.8 Hz, 1 H, 7-H), 5.70 (ddt, *J* = 10.1, 3.9, 0.5 Hz, 1 H, 8-H), 5.94 (s, 2 H, OCH_2O), 6.71 (s, 1 H, 4′′-H), 6.98 (s, 1 H, 7′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.1 (C-4), 22.9 (C-10), 25.2 (C-9), 26.2 (C-3), 35.9 (C-2′), 36.3 (C-5), 46.5 (C-11), 51.8, 57.2 (C-1′, C-2), 101.4 (OCH_2O), 110.6 (C-4′′), 112.5 (C-7′′), 114.4 (C-6′′), 128.1 (C-8), 133.2 (C-5′′), 136.3 (C-7), 146.5 (C-3a′′), 147.0 (C-7a′′). − MS (70 eV, EI): *m/z* (%) = 380/378 (<1) [M + H^+], 215/213 (4) [$C_8H_6BrO_2^+$], 164 (100) [$C_{11}H_{18}N^+$]. − $C_{19}H_{24}BrNO_2$ (378.3): calcd. C 60.32, H 6.39; found C 60.42, H 6.24.

1-[3-(6-Bromobenzo[1,3]dioxol-5-yl)propyl]-1-azaspiro[4.5]dec-6-ene (12d): According to General Procedure III, the crude amine **17a** (395 mg, 2.88 mmol) was treated with the nosylate **18d** (1.68 g, 3.79 mmol, 1.3 equiv.) in the presence of diisopropylethylamine (1.30 g, 9.90 mmol, 3.4 equiv.). Column chromatography (70 g SiO_2; EtOAc/MeOH, 15:1, + 1% Et_3N) of the crude product yielded **12d** (574 mg, 1.52 mmol, 53% over 3 steps); R_f = 0.47 (EtOAc/MeOH, 15:1, + 1% Et_3N). − IR (neat): $\tilde{\nu}$ = 3014 cm^{-1} (Ar−H), 2931 (C−H), 1476, 1230, 1039, 936 (C−O−C), 839, 832 (arene), 735 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.55), 295 (3.59). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.41−1.45 (m, 1 H, 4-H), 1.50−1.60 (m, 2 H, 3-H_2), 1.69 (ddt, *J* = 7.8, 7.6, 7.2 Hz, 2 H, 2′-H_2), 1.70−1.85 (m, 5 H, 4-H, 9-H_2, 10-H_2), 1.91−1.96 (m, 2 H, 8-H_2), 2.43 (dt, *J* = 12.1, 7.2 Hz, 1 H, 1′-H), 2.48 (dt, *J* = 12.1, 7.6 Hz, 1 H, 1′-H), 2.59 (dt, *J* = 14.2, 7.8 Hz, 1 H, 3′-H), 2.64 (dt, *J* = 14.2, 7.8 Hz, 1 H, 3′-H), 2.71 (dt, *J* = 8.8, 5.7 Hz, 1 H, 2-H), 2.89 (dt, *J* = 8.8, 5.3 Hz, 1 H, 2-H), 5.45 (ddt, *J* = 10.3, 1.8, 1.8 Hz, 1 H, 6-H), 5.75 (ddt, *J* = 10.3, 3.2, 0.5 Hz, 1 H, 7-H), 5.92 (s, 2 H, OCH_2O), 6.70 (s, 1 H, 4′′-H), 6.95 (s, 1 H, 7′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.2, 21.3 (C-3, C-9), 25.2 (C-8), 28.4 (C-4), 30.0 (C-2′), 34.1 (C-3′), 38.5 (C-10), 48.8 (C-1′), 50.5 (C-2), 63.5 (C-5), 101.4 (OCH_2O), 109.8 (C-4′′), 112.6 (C-7′′), 114.2 (C-6′′), 128.7 (C-7), 133.7 (C-6), 135.0 (C-5′′), 146.3 (C-3a′′), 147.2 (C-7a′′). − MS (70 eV, EI): *m/z* (%) = 379/377 (2) [M^+], 351/349 [M^+ − C_2H_4], 254 (100), 150 (18) [$C_{10}H_{16}N^+$]. − $C_{19}H_{25}BrClNO_2$ (414.8) (hydrochloride): calcd. C 55.02, H 6.08; found C 55.31, H 6.35. − HRMS: calcd. 377.0990; found 377.0990.

1-[3-(6-Iodobenzo[1,3]dioxol-5-yl)propyl]-1-azaspiro[4.5]dec-6-ene (12e): According to General Procedure III, the crude amine **17a** (395 mg, 2.88 mmol) was treated with the nosylate **18e** (1.70 g, 3.46 mmol, 1.2 equiv.) in the presence of diisopropylethylamine (1.13 g, 8.76 mmol, 3.0 equiv.). Column chromatography (120 g SiO_2; gradient column: 300 mL EtOAc; then EtOAc/MeOH, 15:1, + 1% Et_3N) of the crude product afforded **12e** (962 mg, 2.26 mmol, 79% over 3 steps); R_f = 0.54 (EtOAc/MeOH, 15:1, + 1% Et_3N). − IR (neat over 3 steps): $\tilde{\nu}$ = 3013 cm^{-1} (Ar−H), 2930 (C−H), 1475, 1226, 1109, 1039, 935 (C−O−C), 858, 829 (arene), 736 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 206 nm (4.53), 240 (3.87), 296 (3.60). − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.46−1.51 (m, 1 H, 4-H), 1.60−1.64 (m, 3 H, 3-H_2, 4-H), 1.71 (tt, *J* = 7.9, 7.2 Hz, 2 H, 2′-H_2), 1.72−1.81 (m, 2 H, 10-H_2), 1.75−1.87 (m, 2 H, 9-H_2), 2.49 (dt, *J* = 12.0, 7.2 Hz, 1 H, 1′-H), 2.53 (dt, *J* = 12.0, 7.7 Hz, 1 H, 1′-H), 2.63 (dt, *J* = 14.2, 7.9 Hz, 1 H, 3′-H), 2.68 (dt, *J* = 14.2, 7.9 Hz, 1 H, 3′-H), 2.76 (dt, *J* = 8.5, 5.5 Hz, 1 H, 2-H), 2.94 (dt, *J* = 8.5, 5.5 Hz, 1 H, 2-H), 5.50 (ddt, *J* = 10.2, 1.8, 1.8 Hz, 1 H, 6-H), 5.79 (ddt, *J* = 10.2, 3.6, 0.5 Hz, 1 H, 7-H), 5.96 (s, 2 H, OCH_2O), 6.77 (s, 1 H, 4′′-H), 7.24 (s, 1 H, 7′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.2 (C-9), 21.3 (C-3), 25.2 (C-8), 28.4 (C-4), 30.3 (C-2′), 38.5 (C-10), 38.8 (C-3′), 48.7 (C-1′), 50.6 (C-2), 63.4 (C-5), 87.7 (C-6′′), 101.3 (OCH_2O), 109.1 (C-4′′), 118.4 (C-7′′), 128.6 (C-7), 133.6 (C-6), 138.5 (C-5′′), 146.4 (C-7a′′), 148.3 (C-3a′′). − MS (70 eV, EI): *m/z* (%) = 425 (17) [M^+], 397 (29) [M^+ −

C_2H_4], 298 (19) [$M^+ - I$], 270 (23) [$M^+ - I - C_2H_4$], 164 (11) [$C_{11}H_{18}N^+$], 150 (100) [$C_{10}H_{16}N^+$], 136 (46) [$C_9H_{14}N^+$]. − $C_{19}H_{24}INO_2$ (425.3): calcd. C 49.42, H 5.46; found C 49.72, H 5.78. − HRMS: calcd. 425.0852; found 425.0851.

1-(6-Bromobenzo[1,3]dioxol-5-ylmethyl)-1-azaspiro[5.5]undec-7-ene (12f): To a stirred solution of dibromide **18a**[7] (415 mg, 1.41 mmol, 1.6 equiv.) in acetonitrile (5 mL), the hydrochloride of amine **17b** (170 mg, 905 µmol), TBAI (502 mg, 1.36 mmol, 1.5 equiv.), and diisopropylethylamine (428 mg, 3.31 mmol, 3.7 equiv.) were added at 20 °C. Stirring was continued at 70 °C for 120 h. Thereafter, the mixture was diluted with MTBE, washed with 5% aq. NaOH solution, and the aqueous phase was extracted three times with MTBE. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (25 g SiO_2; PE/EtOAc, 15:1) to give **12f** (293 mg, 804 µmol, 89%); R_f = 0.60 (PE/EtOAc, 5:1); m.p. 68 °C. − IR (KBr): $\tilde{\nu}$ = 3015 cm^{-1} (Ar−H), 2926 (C−H), 1474, 1437, 1366, 1239, 1100, 1040, 934 (C−O−C), 885, 830 (arene), 736 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.62), 235 (3.81), 294 (3.64). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.40−1.73 (m, 10 H, 3-H_2, 4-H_2, 5-H_2, 10-H_2, 11-H_2), 1.92−2.00 (m, 2 H, 9-H_2), 2.41 (m_c, 2 H, 2-H_2), 3.32 (d, *J* = 15.5 Hz, 1 H, 1′-H), 3.64 (d, *J* = 15.5 Hz, 1 H, 1′-H), 5.39 (dddd, *J* = 10.2, 2.3, 1.5, 1.5 Hz, 1 H, 7-H), 5.71 (dddd, *J* = 10.2, 3.8, 2.9, 0.7 Hz, 1 H, 8-H), 5.92 (d, *J* = 1.5 Hz, 1 H, OCHO), 5.93 (d, *J* = 1.5 Hz, 1 H, OCHO), 6.92 (s, 1 H, 4′′-H), 7.23 (s, 1 H, 7′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.2 (C-4), 23.3 (C-10), 25.3 (C-9), 26.4 (C-3), 36.2 (C-5), 46.3 (C-11), 54.6, 56.7 (C-1′, C-2), 101.3 (OCH_2O), 109.5 (C-4′′), 112.1 (C-7′′), 113.5 (C-6′′), 128.5 (C-8), 134.0 (C-5′′), 136.6 (C-7), 146.4 (C-3a′′), 147.3 (C-7a′′). − MS (70 eV, EI): *m/z* (%) = 365/363 (18) [M^+], 284 (100) [$M^+ - Br$], 256 (66) [$C_{16}H_{18}NO_2^+$], 215/213 (71/66) [$C_8H_6BrO_2^+$], 150 (39) [$C_{10}H_{16}N^+$] (hydrochloride). − $C_{18}H_{23}BrClNO_2$ (400.7) (hydrochloride): calcd. C 53.95, H 5.78; found C 54.23, H 5.88. − HRMS calcd. 363.0834; found 363.0834.

1-(6-Bromobenzo[1,3]dioxol-5-ylmethyl)-1-azaspiro[4,5]dec-6-ene (12g): To a stirred solution of dibromide **18a**[7] (2.40 g, 8.16 mmol, 1.6 equiv.) in acetonitrile (28 mL), the hydrochloride of amine **17a** (880 mg, 5.1 mmol), TBAI (2.81 g, 7.61 mmol, 1.5 equiv.), and diisopropylethylamine (2.67 g, 20.6 mmol, 4.1 equiv.) were added at 20 °C. Stirring was continued at 70 °C for 120 h. Thereafter, the mixture was diluted with MTBE, washed twice with 5% aq. NaOH solution, and the aqueous phase was extracted three times with MTBE. The combined organic layers were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (190 g SiO_2; PE/EtOAc, 15:1) to give **12g** (1.26 g, 3.59 mmol, 71%); R_f = 0.21 (PE/EtOAc, 15:1); m.p. 68 °C. − IR (KBr): $\tilde{\nu}$ = 3014 cm^{-1} (Ar−H), 2929 (C−H), 1502, 1476, 1233, 1107, 1039, 935 (C−O−C), 831 (arene), 735 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 202 nm (4.61), 236 (3.89), 293 (3.65). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.56−1.65 (m, 3 H, 3-H, 4-H_2), 1.72−1.83 (m, 5 H, 3-H, 9-H_2, 10-H_2), 1.95−2.03 (m, 2 H, 8-H), 2.63−2.72 (m, 1 H, 2-H), 2.76−2.85 (m, 1 H, 2-H), 3.58 (s, 2 H, 1′-H), 5.56 (d, *J* = 10.2 Hz, 1 H, 6-H), 5.81 (m, 1 H, 7-H), 5.94 (s, 2 H, OCH_2O), 6.96 (s, 1 H, 4′′-H), 7.07 (s, 1 H, 7′′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 21.2, 21.5 (C-3, C-9), 25.2 (C-8), 29.3 (C-4), 38.3 (C-10), 50.5 (C-2), 52.7 (C-1′), 63.6 (C-5), 101.4 (OCH_2O), 110.0, 112.2 (C-4′′, C-7′′), 113.6 (C-6′′), 129.2 (C-7), 133.6 (C-5′′), 133.7 (C-6), 146.7 (C-3a′′), 147.3 (C-7a′′). − MS (70 eV, EI): *m/z* (%) = 351/349 (12) [M^+], 270 (19) [$M^+ - Br$], 242 (100) [$C_{15}H_{16}NO_2^+$], 215/213 (34) [$C_8H_6BrO_2^+$]. − $C_{17}H_{20}BrNO_2$ (350.3): calcd. C 58.30, H 5.76; found C 57.97, H 5.50. − HRMS calcd. 349.0677; found 349.0677.

3,4,5,6,7,8,9,10-Octahydro-15b*H*-[1,3]dioxolo[4,5-*j*]pyrido[2,1-*e*]-phenanthridine (19): To a solution of the tertiary amine **12f** (113 mg, 365 µmol) in a mixture of acetonitrile, dimethylformamide, and water (5:5:1) (5 mL) were added the palladium catalyst **20** (20.6 mg, 21.9 µmol, 6 mol-%) and tetra-*n*-butylammonium acetate (231 mg, 766 µmol, 2.1 equiv.), and the mixture was degassed by pump-and-freeze methodology. It was subsequently heated to 120 °C for 20 h, then diluted with MTBE, and extracted with dilute aq. NaOH solution. The organic layer was extracted three times with 1 M HCl. The combined aqueous extracts were basified with NaOH solution and extracted three times with MTBE. The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography (25 g SiO_2; EtOAc/MeOH, 20:1, + 1% Et_3N) to give **19** (77.6 mg, 274 µmol, 75%); R_f = 0.54 (EtOAc/MeOH, 5:1, + 1% Et_3N); m.p. 122 °C. − IR (KBr): $\tilde{\nu}$ = 3019 cm^{-1} (Ar-H), 2927 (C−H), 1489, 1242, 1141, 1034, 927 (C−O−C), 852, 838, 806 (arene), 704 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 200 nm (4.54), 293 (3.66). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.3−1.8 (m, 6 H, 5-H_2, 6-H_2, 7-H_2), 1.90−2.10 (m, 3 H, 3-H, 4-H_2), 2.45−2.80 (m, 3 H, 8-H_2, 3-H), 3.12 (m_c, 1 H, 15b−H), 3.49 (d, *J* = 16.2 Hz, 1 H, 10-H), 3.82 (d, *J* = 16.2 Hz, 1 H, 10-H), 5.66 (br. d, *J* = 10.0 Hz, 1 H, 1-H), 5.84 (d, *J* = 1.4 Hz, 1 H, 13-H), 5.88 (d, *J* = 1.4 Hz, 1 H, 13-H), 6.09 (dddd, *J* = 10.0, 5.6, 2.0, 2.0 Hz, 1 H, 2-H), 6.46 (s, 1 H, 15-H), 6.75 (s, 1 H, 11-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.4 (C-6), 23.3 (C-3), 26.9 (C-7), 33.0 (C-5), 42.6 (br., C-15b), 49.4 (C-8), 52.6 (C-10), 53.5 (C-4a), 100.5 (C-13), 105.9 (C-15), 107.3 (C-11), 125.0 (C-10a), 126.4 (C-1), 128.6 (C-2), 130.8 (C-15a), 145.2 (C-11a), 146.3 (C-14a). − MS (70 eV, EI): *m/z* (%) = 283 (39) [M^+], 282 (48) [$M^+ - H$], 228 (30) [$M^+ - C_4H_7$], 84 (96) [$C_5H_{10}N^+$], 69 (29), 56 (100) [$C_3H_6N^+$], 41 (53) [$C_3H_5^+$]. − $C_{18}H_{21}NO_2$ (283.4): calcd. C 76.30, H 7.47; found C 76.46, H 7.60. − HRMS: calcd. 283.1572; found 283.1572.

1-(1-Azaspiro[4.5]dec-6-en-1-yl)-2-(6-bromobenzo[1,3]dioxol-5-yl)ethanone (22a): At 0 °C, a solution of 6-bromobenzo[1,3]dioxol-5-ylacetyl chloride[16] (4.91 mmol, 1.1 equiv.) in diethyl ether (4 mL) was added dropwise to a solution of crude **17a** (642 mg, 4.68 mmol) and triethylamine (726 mg, 7.20 mmol, 1.5 equiv.) in CH_2Cl_2 (6 mL) and the mixture was stirred for 0.5 h at this temperature. It was subsequently diluted with MTBE and washed with water. The organic layer was dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (120 g SiO_2; PE/MTBE, 1:2) to give **22a** (794 mg, 2.10 mmol, 45% over 3 steps); R_f = 0.38 (PE/MTBE, 1:2); m.p. 128 °C. − IR (KBr): $\tilde{\nu}$ = 3013 cm^{-1} (Ar−H), 2925 (C−H), 1649 (C=O), 1483, 1407, 1229, 1172, 1118, 1031, 920 (C−O−C), 865, 831, 798 (arene), 736 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.60), 294 (3.59). − The NMR spectra showed double sets of signals (ratio 2:1): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.48−2.16 (m, 10 H, 3′-H_2, 4′-H_2, 8′-H_2, 9′-H_2, 10′-H_2); major isomer: 2.48 (dddd, *J* = 13.8, 12.6, 3.4, 1.4 Hz, 1 H, 3′-H), 3.54−3.59 (m, 1 H, 2′-H), 3.62 (s, 2 H, $ArCH_2$), 3.67 (ddd, *J* = 11.0, 7.6, 2.3 Hz, 1 H, 2′-H), 5.48 (dddd, *J* = 10.1, 2.8, 1.4, 1.4 Hz, 1 H, 6′-H), 5.73 (dddd, *J* = 10.1, 5.3, 2.1, 1.1 Hz, 1 H, 7′-H), 5.93 (d, *J* = 1.4 Hz, 1 H, OCHO), 5.94 (d, *J* = 1.4 Hz, 1 H, OCHO), 6.83 (s, 1 H, 4-H), 6.99 (s, 1 H, 7-H); minor isomer: 3.49−3.55 (m, 1 H, 2′-H), 3.75 (d, *J* = 16.5 Hz, 1 H, ArCH), 3.82 (d, *J* = 16.5 Hz, 1 H, ArCH), 3.83 (ddd, *J* = 10.5, 6.9, 2.1 Hz, 1 H, 2′-H), 5.58 (dddd, *J* = 10.1, 2.8, 1.4, 1.4 Hz, 1 H, 6′-H), 5.86 (dddd, *J* = 10.1, 3.2, 2.3, 1.8 Hz, 1 H, 7′-H), 5.95 (d, *J* = 1.4 Hz, 1 H, OCHO), 5.94 (d, *J* = 1.4 Hz, 1 H, OCHO), 6.80 (s, 1 H, 4-H), 7.00 (s, 1 H, 7-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.8, 21.4* (C-3′), 21.4, 22.9* (C-9′), 24.0*, 24.2 (C-8′), 30.0* , 33.2 (C-4′), 38.7*, 40.5 (C-10′), 41.3, 42.9* ($ArCH_2$), 48.2, 48.3

(C-2′), 63.0, 64.2* (C-5′), 101.6 (OCH_2O), 110.7, 111.0* (C-4), 112.4 (C-7), 115.0*, 115.1 (C-6), 126.5*, 129.0 (C-7′), 128.5*, 129.2 (C-5), 132.9, 133.3 (C-6′), 146.9, 147.3* (C-7a), 147.2 (C-3a), 167.5*, 169.1 (CO) (asterisks* denote signals of the major isomer). − MS [70 eV, CI (NH_3)]: *m/z* (%) = 397/395 (40/50) [M + NH_4^+], 380/378 (100/98) [M + H^+]. − $C_{18}H_{20}BrNO_3$ (378.3): calcd. C 57.15, H 5.33; found C 57.11, H 5.11.

1-(1-Azaspiro[5.5]undec-7-en-1-yl)-2-(6-bromobenzo[1,3]dioxol-5-yl)-ethanone (22b): At 0 °C, a solution of 6-bromobenzo[1,3]dioxol-5-ylacetyl chloride[16] (3.00 mmol, 1.0 equiv.) in diethyl ether (2 mL) was added dropwise to a solution of crude **17b** (437 mg, 2.89 mmol) and triethylamine (440 mg, 4.34 mmol, 1.5 equiv.) in diethyl ether (3 mL) and the mixture was stirred for 1 h at this temperature. It was subsequently diluted with MTBE and washed with water. The organic layer was dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (100 g SiO_2; PE/MTBE, 3:2) to give **22b** (567 mg, 1.45 mmol, 50% over 3 steps): R_f = 0.34 (PE/MTBE, 3:2). − IR (neat): $\tilde{\nu}$ = 3021 cm^{-1} (Ar−H), 2935 (C−H), 1645 (C=O), 1481, 1234, 1117, 1038, 927 (C−O−C), 863, 837 (arene), 731 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.59), 295 (3.63). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.50−2.27 (m, 12 H, 3′-H_2, 4′-H_2, 5′-H_2, 9′-H_2, 10′-H_2, 11′-H_2), 3.08−3.25 (m, 1 H, 2′-H), 3.70 (s, 2 H, $ArCH_2$), 3.70−3.84 (m, 1 H, 2′-H), 5.53 (ddd, *J* = 10.0, 4.4, 2.4 Hz, 1 H, 8′-H), 5.70 (dddd, *J* = 10.0, 2.8, 2.4, 2.4 Hz, 1 H, 7′-H), 5.94 (s, 2 H, OCH_2O), 6.77 (s, 1 H, 4-H), 6.99 (s, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 17.8 (C-4′), 19.8 (C-10′), 24.1, 24.1 (C-3′, C-9′), 35.2 (C-5′), 41.7 (C-11′), 43.1 (Ar−CH_2), 57.6 (C-6′), 101.6 (OCH_2O), 110.6 (C-4), 112.5 (C-7), 114.9 (C-6), 122.9 (br., C-8′), 129.0 (C-5), 137.4 (C-7′), 147.1 (C-3a), 147.3 (C-7a), 170.2 (CO). − MS (70 eV, EI): *m/z* (%) = 393/391 (9) [M^+], 312 (48) [M^+ − Br], 242/240 (26/27) [$C_9H_5BrO_3^+$], 215/213 (88/100) [$C_8H_6BrO_2^+$], 178 (21) [$C_{11}H_{16}NO^+$]. − $C_{19}H_{22}BrNO_3$ (392.3): calcd. C 58.17, H 5.65; found C 58.29, H 5.55.

1-(1-Azaspiro[4.5]dec-6-en-1-yl)-3-(6-bromobenzo[1,3]dioxol-5-yl)-propan-1-one (22c): At 0 °C, a solution of 3-(6-bromobenzo[1,3]-dioxol-5-yl)propionyl chloride[16] (4.16 mmol, 1.0 equiv.) in diethyl ether (4 mL) was added dropwise to a solution of crude **17a** (549 mg, 4.00 mmol) and triethylamine (620 mg, 6.13 mmol, 1.5 equiv.) in diethyl ether (5 mL) and the mixture was stirred for 0.5 h at this temperature. It was subsequently diluted with MTBE and washed with water. The organic layer was dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (100 g SiO_2; PE/MTBE, 1:2) to give **22c** (1.39 g, 3.54 mmol, 89% over 3 steps); R_f = 0.27 (PE/MTBE, 1:2); m.p. 111 °C. − IR (KBr): $\tilde{\nu}$ = 3021 cm^{-1} (Ar−H), 2943 (C−H), 1640 (C=O), 1473, 1223, 1110, 1035, 925 (C−O−C), 872, 842 (arene), 735 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.61), 236 (3.66), 294 (3.60). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42−2.30 (m, 9 H, 3′-H, 4′-H_2, 8′-H_2, 9′-H_2, 10′-H_2), 2.38−2.53 (m, 2 H, $COCH_2$), 2.62 (ddd, *J* = 7.6, 7.0, 3.5 Hz, 1 H, 3′-H), 2.99 (m_c, 2 H, $ArCH_2$), 3.32−3.54 (m, 1.5 H, 2′-H), 3.77 (m_c, 0.5 H, 2′-H), 5.27−5.50 (m, 1 H, 6′-H), 5.68−5.82 (m, 1 H, 7′-H), 5.94 (s, 2 H, OCH_2O), 6.77, 6.78 (s, 1 H, 4-H), 6.96, 6.97 (s, 1 H, 7-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.9, 20.4 (C-3′), 20.4, 22.8 (C-9′), 24.07, 24.09 (C-8′), 30.2, 33.4 (C-4′), 31.4, 32.3 ($ArCH_2$), 34.4, 36.0 ($COCH_2$), 38.7, 40.3 (C-10′), 48.0, 48.1 (C-2′), 62.6, 63.9 (C-5′), 101.4, 101.5 (OCH_2O), 110.3, 110.4 (C-4), 112.4, 112.5 (C-7), 114.1, 114.3 (C-6), 126.3, 128.5 (C-7′), 133.2, 133.4 (C-6′), 133.9, 134.0 (C-5), 146.6, 147.1 (C-3a), 146.7, 147.2 (C-7a), 169.5, 171.3 (CO). − MS (70 eV, EI): *m/z* (%) = 411/409 (19/17) [M + NH_4^+], 394/392 (100/95) [M + H^+], 314 (40) [M^+ − Br], 136 (49) [$C_9H_{14}N^+$]. − $C_{19}H_{22}BrNO_3$ (392.3): calcd. C 58.17, H 5.65; found C 58.46, H 5.71.

3,4,6,7-Tetrahydro-5*H*,15b*H*-cyclohexa[*a*][1,3]dioxolo[4,5-*h*]pyrrolo-[2,1-*b*][3]benzazepin-9(10*H*)-one (23): To a solution of tertiary amide **22a** (268 mg, 708 μmol) in acetonitrile, dimethylformamide, and water (5:5:1) (11 mL) were added the palladium catalyst **20** (34 mg, 36.2 μmol, 5 mol-%) and tetra-*n*-butylammonium acetate (560 mg, 1.86 mmol, 2.6 equiv.), and the mixture was degassed by pump and freeze methodology. It was subsequently heated to 140 °C for 30 h and, after cooling, was diluted with MTBE and extracted with water. The organic layer was dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography (27 g SiO_2; MTBE) to give **23** (116 mg, 390 μmol, 55%) as a mixture of two components (ratio 1:1.1). From a second column chromatography, 17 mg of the less polar component was isolated, which allowed an interpretation of the NMR signals; R_f = 0.28 (MTBE). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (ddd, *J* = 13.5, 10.1, 6.2 Hz, 1 H, 5-H), 1.68−1.82 (m, 3 H, 4-H, 6-H_2), 1.86−1.95 (m, 1 H, 4-H), 2.04 (dddd, *J* = 13.5, 3.4, 3.4, 0.7 Hz, 1 H, 5-H), 2.08−2.13 (m, 2 H, 3-H), 3.12 (d, *J* = 14.6 Hz, 1 H, 10-H), 3.30 (ddd, *J* = 12.9, 10.3, 3.7 Hz, 1 H, 7-H), 3.68 (ddd, *J* = 5.4, 2.7, 2.7 Hz, 1 H, 15b-H), 3.78 (ddd, *J* = 12.9, 9.9, 6.9 Hz, 1 H, 7-H), 4.45 (d, *J* = 14.6 Hz, 1 H, 10-H), 5.48 (dddd, *J* = 9.9, 3.9, 1.4, 1.1 Hz, 1 H, 1-H), 5.90 (d, *J* = 1.4 Hz, 1 H, 13-H), 5.91 (d, *J* = 1.4 Hz, 1 H, 13-H), 6.03 (ddddd, *J* = 9.9, 5.7, 2.5, 2.5, 0.9 Hz, 1 H, 2-H), 6.65 (s, 1 H, 15-H), 6.65 (s, 1 H, 11-H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.4 (C-6), 21.2 (C-3), 32.0 (C-5), 38.5 (C-4), 40.8 (C-10), 45.3 (C-7), 47.7 (C-15b), 64.2 (C-4a), 101.0 (C-13), 110.0 (C-15), 111.2 (C-11), 129.0 (C-2), 129.4 (C-1), 129.4 (C-10a), 129.5 (C-15a), 146.5 (C-11a), 146.7 (C-14a), 169.8 (C-9). Second component; R_f = 0.23 (MTBE). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (dddd, *J* = 17.2, 6.6, 4.4, 2.3 Hz, 1 H, 5-H), 1.54−1.86 (m, 3 H, 4-H, 6-H_2), 1.99 (dd, *J* = 17.2, 6.0 Hz, 1 H, 5-H), 2.23 (ddd, *J* = 11.5, 7.6, 1.2 Hz, 1 H, 4-H), 2.51−2.57 (m, 1 H, 3-H), 2.61 (ddddd, *J* = 18.6, 7.6, 4.6, 2.3, 2.3 Hz, 1 H, 3-H), 3.19 (dddd, *J* = 12.9, 10.1, 4.3, 0.7 Hz, 1 H, 7-H), 3.35 (ddd, *J* = 5.3, 2.7, 2.7 Hz, 1 H, 15b-H), 3.50 (d, *J* = 16.1 Hz, 1 H, 10-H), 4.22 (ddd, *J* = 12.9, 10.1, 6.7 Hz, 1 H, 7-H), 5.58 (dddd, *J* = 11.5, 5.7, 2.8, 1.6 Hz, 1 H, 1-H), 5.84−5.88 (m, 1 H, 2-H), 5.90 (d, *J* = 1.4 Hz, 1 H, 13-H), 5.91 (d, *J* = 1.4 Hz, 1 H, 13-H), 6.66 (s, 1 H, 11-H), 6.83 (s, 1 H, 15-H). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 18.6 (C-6), 30.0 (C-3), 30.9 (C-5), 35.7 (C-4), 41.3 (C-15b), 43.2 (C-10), 44.9 (C-7), 66.5 (C-4a), 100.9 (C-13), 107.0 (C-15), 109.5 (C-11), 125.2 (C-2), 127.0 (C-1), 127.5 (C-10a), 132.3 (C-15a), 146.0 (C-11a), 146.4 (C-14a), 166.8 (C-9). − IR (KBr): $\tilde{\nu}$ = 3032 cm^{-1} (Ar-H), 2891 (C−H), 1599 (C=O), 1503, 1482, 1262, 1034, 937 (C−O−C), 858 (arene), 727 (=C−H). − UV (CH_3CN): λ_{max} (lg ε) = 203 nm (4.61), 291 (3.63). − MS (70 eV, EI): *m/z* (%) = 297 (23) [M^+], 243 (100) [M^+ − C_4H_6], 214 (20) [$C_{12}H_8NO_3^+$]. − $C_{18}H_{19}NO_3$ (297.3): HRMS calcd. 297.1365; found 297.1365.

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[1] [1a]L. F. Tietze, T. Nöbel, M. Spescha, *Angew. Chem.* **1996**, *108*, 2385−2386; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2259−2261. − [1b]L. F. Tietze, T. Nöbel, M. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971−8977. − [1c]L. F. Tietze, R. Hannemann, W. Buhr, M. Lögers, P. Menningen, M. Lieb, D. Starck, T. Grote,

A. Döring, I. Schuberth, *Angew. Chem.* **1996**, *108*, 2840−2842; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2674−2677. − [1d]L. F. Tietze, T. Grote, *J. Org. Chem.* **1994**, *59*, 192−196. − [1e]L. F. Tietze, T. Grote, *Chem. Ber.* **1993**, *126*, 2733−2737. − [1f]L. F. Tietze, W. Buhr, *Angew. Chem.* **1995**, *107*, 1485−1487; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1366−1368. − [1g]L. F. Tietze, W. Buhr, J. Looft, T. Grote, *Chem. Eur. J.* **1998**, *4*, 1554−1560. − [1h]L. F. Tietze, R. Ferraccioli, *Synlett* **1998**, 145−146. − [1i]L. F. Tietze, H. Schirok, *Angew. Chem.* **1997**, *109*, 1159−1160; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1124−1125. − [1j]L. F. Tietze, H. Schirok, *J. Am. Chem. Soc.* **1999**, *121*, 10264−10269.

[2] [2a]S. Sinha, S. Jain, in: *Prog. Drug Res.* **1994**, *42*, 53−132. − [2b]D. C. Zhou, R. Zittoun, J. P. Marie, *Bull. Cancer* **1995**, *82*, 987−995.

[3] [3a]J. M. Whaun, N. D. Brown, *Ann. Trop. Med. Parasit.* **1990**, *84*, 229−237. − [3b]R. M. Ekong, G. C. Kirby, G. Patel, J. D. Phillipson, D. C. Warhurst, *Biochem. Pharmacol.* **1990**, *40*, 297−301.

[4] L. F. Tietze, H. Schirok, M. Wöhrmann, *Chem. Eur. J.* **2000**, *6*, 510−518.

[5] [5a]**9a**: P. W. Clark, S. F. Dyke, *J. Organomet. Chem.* **1985**, *281*, 389−396. − [5b]**9b**: K. Ito, H. Tamaka, M. Kayama, *Chem. Pharm. Bull.* **1977**, *25*, 1249−1255. − [5c]G. Rodríguez, M. M. Cid, C. Saá, L. Castedo, D. Domínguez, *J. Org. Chem.* **1996**, *61*, 2780−2782; **9c**: ref.[4]; **9d**: J. Fidalgo, L. Castedo, D. Domínguez, *Heterocycles* **1994**, *39*, 581−589.

[6] **10a**,**b**: S. A. Godleski, J. D. Meinhart, D. J. Miller, S. Van Wallendael, *Tetrahedron Lett.* **1981**, *22*, 2247−2250.

[7] W. F. Barthel, B. H. Alexander, *J. Org. Chem.* **1958**, *23*, 1012−1014.

[8] B. Weinstein, A. R. Craig, *J. Org. Chem.* **1976**, *41*, 875−878.

[9] M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1975**, *97*, 2507−2516.

[10] X. Lin, R. W. Kavash, P. S. Mariano, *J. Org. Chem.* **1996**, *61*, 7335−7347.

[11] G. W. Kabalka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, *54*, 5930−5933.

[12] Y. G. Gololobov, I. N. Zhmurova, L. F. Kasukhin, *Tetrahedron* **1981**, *37*, 437−472.

[13] H. Bayley, D. N. Standring, J. R. Knowles, *Tetrahedron Lett.* **1978**, 3633−3634.

[14] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141208. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1 EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

[15] [15a] W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989−1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844−1848. − [15b] M. Beller, H. Fischer, W. A. Herrmann, K. Öfele, C. Brossmer, *Angew. Chem.* **1995**, *107*, 1992−1993; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1848−1849. − [15c] W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Öfele, M. Beller, *Chem. Eur. J.* **1997**, *3*, 1357−1364. − [15d] M. Beller, T. H. Riermeier, C.-P. Reisinger, W. A. Herrmann, *Tetrahedron Lett.* **1997**, *38*, 2073−2074.

[16] Derived from the acid: M. Pailer, A. Schleppnik, *Monatsh. Chem.* **1958**, *89*, 175−185.

[17] Derived from the acid: R. D. Haworth, W. H. Perkin, T. Stevens, *J. Chem. Soc.* **1926**, 1764−1769.

[18] N. Mori, E. Nakamura, Y. Tsuzuki, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2189−2190.

[19] [19a] W. F. Gannon, H. O. House, *Org. Synth.* **1960**, *40*, 41−42. − [19b] J. B. Lambert, K. M. Taba, *J. Org. Chem.* **1980**, *45*, 452−455.

[20] [20a] J. C. Boehm, J. G. Gleason, I. Pendrak, H. M. Sarau, D. B. Schmidt, J. J. Foley, W. D. Kingsbury, *J. Med. Chem.* **1993**, *36*, 3333−3340. − [20b] E. R. de Oliveira, F. Dumas, J. d'Angelo, *Tetrahedron Lett.* **1997**, *38*, 3723−3726.

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