Synthesis and SAR Studies of 3-Substituted 1′-Benzylspiro[[2]benzoxepine-1,4′-piperidines][‡]

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The preparation of the hitherto unknown spiro[[2]benzoxepine-1,4′-piperidine] ring system is described. The synthesis consists of a Wittig reaction of 2-bromobenzaldehyde (**4**) and (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**5**) to yield an α,β-unsaturated acetal. The double bond of **6** was subsequently hydrogenated. The resulting brominated acetal **7** was treated with *n*-butyllithium and then with 1-benzylpiperidin-4-one (**9**) to yield the hydroxy acetal **10**. Acid-catalyzed cyclization of **10** with *p*-toluenesulfonic acid or aqueous HCl resulted in the formation of the 1′-benzylspiro[[2]benzoxepine-1,4′-piperidines] **11** and **12**, respectively. The substituents in the 3-position of the spiro compounds **11** and **12** were further modified by reaction with trimethylsilyl cyanide or (cyanomethylene)triphenylphosphorane in order to introduce residues with one or two carbon atoms, respectively. The synthesized compounds were evaluated for σ_1- and σ_2-receptor affinity in vitro. The most potent σ_1-ligand was the methoxy derivative **11** (K_i = 2.56 nM), whereas the cyanomethyl derivative **20** turned out to be the most σ_1-selective compound (σ_1/σ_2 selectivity 768).

Introduction

σ-Receptors were originally defined as subtypes of the opioid receptors.[1] Later, they were classified as a separate receptor family consisting of σ_1- and σ_2-subtypes.[2] The amino acid sequence of the σ_1-receptor protein is structurally unrelated to any known mammalian protein.[3] The physiological role of σ-receptors and the mechanism of signal transduction are not yet completely understood,[4] although they seem to be involved in certain pathophysiological processes such as psychosis, depression, and uncontrolled cell proliferation. Therefore, selective σ-receptor ligands might be useful in the treatment of psychosis, depression, neurodegeneration, and cancer. Some compounds are already in clinical trials for treatment of psychosis (e.g., BMY14802)[5] and depression (e.g., E-5842).[6] The well-known antipsychotic haloperidol is a highly potent σ-receptor ligand (see Table 1). Among various classes of compounds with high σ-receptor affinity, some spiropiperidines are highly potent and selective σ-ligands.[7] In Parts 1[8] and 2[9] of this series we have already reported on the synthesis of novel spiro[[2]benzofuran-1,4′-piperidines] **1** (n = 1−2) and spiro[[2]benzopyran-1,4′-piperidines] **2** (n = 0−4) with various residues R in the 3-position of the spirocycle (Figure 1). Among these compounds, we have disclosed high-affinity and selective σ_1-receptor ligands. In particular, compounds with R = OCH_3 or CN and n = 1 possess σ_1 affinities in the range of 1−3 nM. In order to further extend the structure affinity studies, our intention was to synthesize homologous 2-benzoxepines **3**. Thereby, we focused on those compounds bearing residues that were expected to show high σ_1-receptor affinity and selectivity (e.g., R = OCH_3, CN; 1′-benzyl).

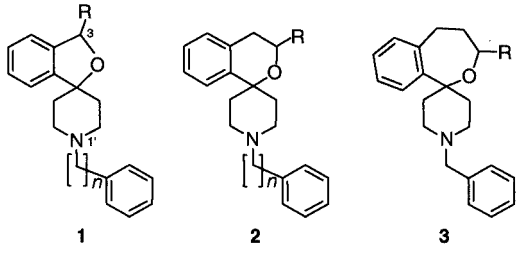

Figure 1. Homologous spirocyclic σ-receptor ligands

In this contribution, we describe the preparation and in vitro evaluation of a series of novel 3-substituted 1′-benzylspiro[[2]benzoxepine-1,4′-piperidines] **3**.

Results and Discussion

Chemistry

First, we assumed that a Wittig−Horner−Emmons reaction of 2-bromobenzaldehyde (**4**) with diethyl (2,2-dimethoxyethyl)phosphonate [$(CH_3O)_2CHCH_2P(O)(OEt)_2$]

[‡] Novel σ Receptor Ligands, 3. Part 2: Ref.[9] Part 1: Ref.[8]

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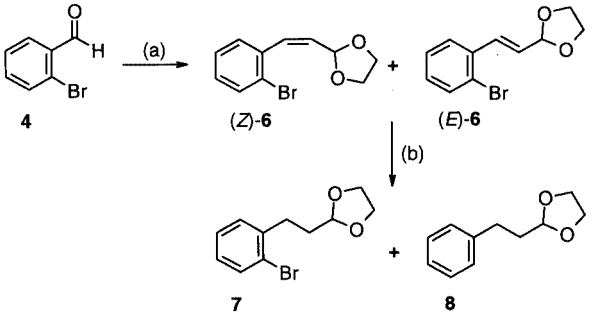
could be the initial step in the synthesis of the desired spiro-[[2]benzoxepine-1,4′-piperidines]. However, in spite of extensive variation of the base, solvent and temperature, this reaction did not succeed.

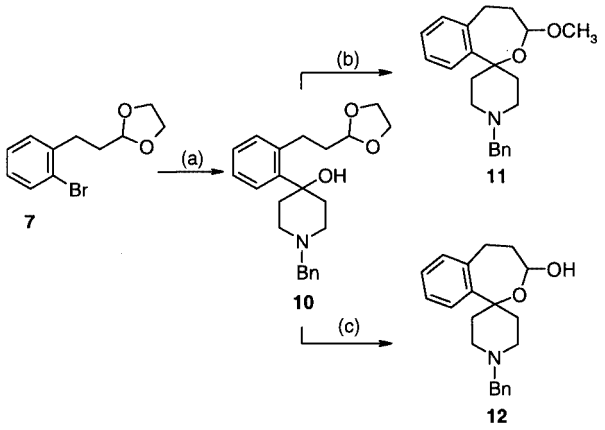
This prompted us to use the Wittig reagent (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**5**) instead of the phosphonate to obtain the 2-bromocinnamic aldehyde acetal **6** (Scheme 1). According to ref.[10] the phase-transfer Wittig reaction of the aldehyde **4** with the phosphonium salt **5** afforded the α,β-unsaturated ethylene acetal (*Z*/*E*)-**6** in 91% yield using a saturated aqueous solution of potassium carbonate as base. Tris[2-(2-methoxyethoxy)ethyl]amine in dichloromethane was added to the reaction mixture in order to activate the base by chelation of the potassium cation.[10] The ^{1}H NMR spectrum of the crude product revealed a (*Z*)-**6**/(*E*)-**6** ratio of 65:35, whereas according to the literature the (*Z*)/(*E*) ratio should be around 52:48.[10] Since both isomers have almost identical chromatographic properties the separation of (*Z*)-**6** and (*E*)-**6** turned out to be difficult. A pure sample of (*Z*)-**6** could be isolated by flash chromatography, but the complete separation of (*Z*)-**6** from (*E*)-**6** was not successful.



Scheme 1. Reagents and conditions: (a) tris(methoxyethoxyethyl)-amine, CH_2Cl_2, (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**5**), saturated aqueous solution of K_2CO_3 [(*Z*)-**6** + (*E*)-**6**: 91%]; (b) H_2, Raney nickel, CH_3OH (77%, **7**/**8** = 90:10)

In the next step, the double bond of the brominated acetal **6** should be hydrogenated to yield the (2-bromophenyl)-propionaldehyde acetal **7**. Attempts were made using the catalysts Pd/C, PtO_2, and Raney nickel at different hydrogen pressures. The reactions with Pd/C and PtO_2 were not successful: Either the α,β-unsaturated acetal **6** was completely decomposed or the debrominated derivative **8** was formed as the main product. Finally, the reaction succeeded with Raney nickel in methanol at a hydrogen pressure of 1 bar for 3 h to afford the (2-bromophenyl)propionaldehyde acetal **7**. However, even under these very mild reaction conditions, hydrogenolysis of the bromine atom was not completely suppressed and the product **7** contained about 10% of the debrominated by-product **8**. The flash chromatographic separation of **7** and **8** was not possible. However, the presence of **8** did not disturb the following reaction steps.

The aryllithium derivative, obtained by treatment of 2-bromophenyl acetal **7** with *n*-butyllithium at −78 °C in THF, was treated with 1-benzylpiperidin-4-one (**9**) to afford the hydroxy acetal **10** in 49% yield (Scheme 2). Cyclization of the hydroxy acetal **10** led to the racemic spirocyclic ring system: With *p*-toluenesulfonic acid in methanol the methyl acetal **11** was obtained in 65% yield, whereas the lactol **12** was formed with aqueous hydrochloric acid in THF in 72% yield.

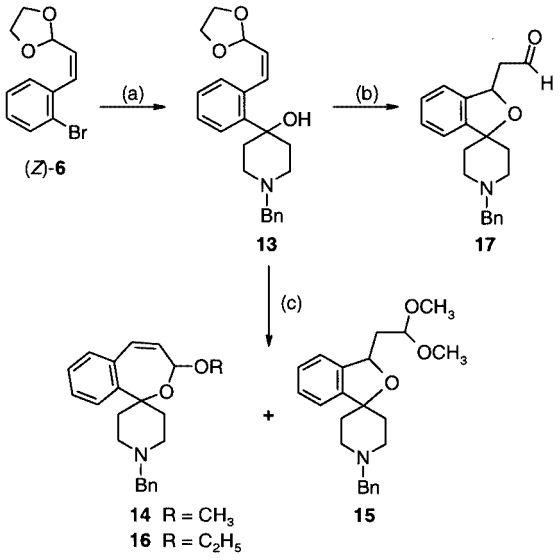


Scheme 2. Reagents and conditions: (a) 1. *n*-butyllithium, THF, −78 °C, 2. 1-benzylpiperidin-4-one (**9**), THF (49%); (b) *p*-toluenesulfonic acid, CH_3OH, room temp. (65%); (c) 2 M HCl, THF, room temp. (72%), Bn = benzyl

One aim of our structure-affinity relationship studies was to evaluate the influence of a double bond in position 4/5 of the spiro[[2]benzoxepine-1,4′-piperidine] system on σ-receptor affinity. For the synthesis of a 2-benzoxepine ring with an additional double bond, the brominated α,β-unsaturated acetal (*Z*)-**6** was treated with *n*-butyllithium and treated with 1-benzylpiperidin-4-one (**9**) (Scheme 3). The resulting alcohol **13** was subsequently cyclized according to the methods described above. Surprisingly, the reaction of **13** with *p*-toluenesulfonic acid in methanol for a period of 2 h led to a mixture of the spiro[[2]benzoxepine-1,4′-piperidine] **14** and the spiro[[2]benzofuran-1,4′-piperidine] **15**. In order to rationalize these findings, we varied the reaction time and found that after 20 min the desired 2-benzoxepine **14** could be isolated exclusively (66% yield), whereas longer reaction times favored the formation of the 2-benzofuran **15**. After 48 h, the 2-benzofuran **15** was isolated as the only product in 68% yield. Thus, kinetic control affords the 2-benzoxepine **14**, whereas thermodynamic control leads to the 2-benzofuran **15**.

Reaction of **13** with *p*-toluenesulfonic acid in ethanol for 15 min led to the ethoxy derivative **16**. The cyclization of **13** with dilute hydrochloric acid provided the spiro[[2]benzofuran-1,4′-piperidine]acetaldehyde **17**.

The unexpected formation of the spiro[[2]benzofuran-1,4′-piperidine] **15** can be explained in the following way: After protonation of the dioxolane **13** by *p*-toluenesulfonic acid the hydroxy group attacks the positively charged C-2 atom of the dioxolane ring to yield, after transacetalization with methanol, the methyl acetal **14**. A prolonged reaction time in the presence of acid and methanol leads to ring contraction of **14** affording the dimethyl acetal **15**.

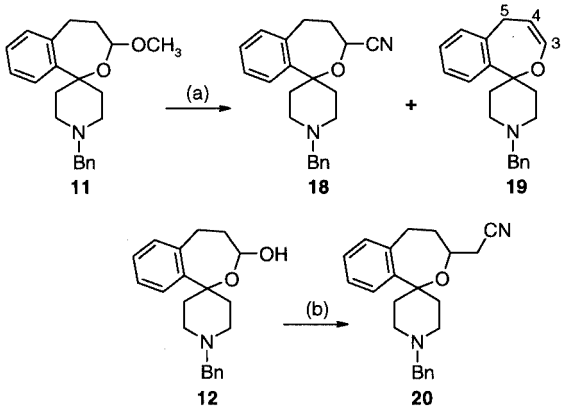


reaction time	14 : 15	yields
20 min	1 : 0	**14**: 66%
		16: 69%
2 h	1 : 2	—
48 h	0 : 1	**15**: 68%

Scheme 3. Reagents and conditions: (a) 1. *n*-butyllithium, THF, −78 °C, 2. 1-benzylpiperidin-4-one (**9**), THF (44%); (b) 2 M HCl, THF, room temp. (45%); (c) *p*-toluenesulfonic acid, CH_3OH or C_2H_5OH, room temp. (yields see table in the scheme)

One of the major goals of our structure-affinity relationship studies was to evaluate the effect of the side chain in the 3-position of the spirocyclic system **3** on σ-receptor affinity and selectivity. For this purpose the methyl acetal **11** and the lactol **12** were used as starting materials for the synthesis of modified spiro[[2]benzoxepine-1,4′-piperidines].

For the introduction of a one-carbon residue in the 3-position of the spiro[[2]benzoxepine-1,4′-piperidines] the methoxy derivative **11** was treated with trimethylsilyl cyanide in the presence of the Lewis acid boron trifluoride−diethyl ether complex ($BF_3{\cdot}Et_2O$) at −20 °C.[11] This reaction afforded the nitrile **18** in 47% yield and the by-product **19** in 6% yield (Scheme 4). In contrast to the synthesis of the corresponding spiro[[2]benzopyran-1,4′-piperidine]-3-carbonitrile[8] the Lewis acid catalyzed elimination of CH_3OH was not favored because the new double bond is not in conjugation with the benzene ring. The use of tetracyanoethylene[12] instead of $BF_3{\cdot}Et_2O$ led to a significant decrease of the yield of **18** (only 3.5%).



Scheme 4. Reagents and conditions: (a) trimethylsilyl cyanide, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C (**18**: 47%, **19**: 6%); (b) $Ph_3P{=}CHCN$, Cs_2CO_3, toluene, reflux (92%)

Starting from the lactol **12** the introduction of a two-carbon residue in the 3-position of the spirocycle was successful. Compound **12** was refluxed with (cyanomethylene)-triphenylphosphorane and Cs_2CO_3 in toluene to afford the ethanenitrile **20** in 92% yield. This tandem reaction includes a sequence of ring opening of the lactol to afford a hydroxyaldehyde, a Wittig reaction and an intramolecular Michael addition.

Receptor Binding Studies

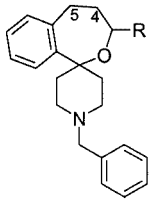
The σ-receptor affinities of the spiropiperidines **3** were determined in radioligand binding experiments. In the σ_1-assay homogenates of guinea pig brains were used as receptor material. The σ_1-selective compound [^{3}H]-(+)-pentazocine was employed as radioligand. A rat liver membrane preparation served as the source of σ_2-receptors in the σ_2-assay. Since a σ_2-selective radioligand is not available the non-selective radioligand [^{3}H]-ditolylguanidine was employed in the presence of non-radiolabeled (+)-pentazocine (100 nM) for the selective masking of σ_1-receptors.[8]

The σ-receptor affinities of the synthesized compounds are shown in Table 1. For comparison, the K_i values of the spiro[[2]benzofuran-1,4′-piperidine] **1a** (R = OCH_3, n = 1)[8] and the spiro[[2]benzopyran-1,4′-piperidine] **2a** (R = OCH_3, n = 1)[8] are also included. Additionally, the K_i values of the reference compounds haloperidol, ditolylguanidine (usually referred to as DTG), and BMY14802 are given.

All tested compounds showed σ_1-receptor affinities in the low nanomolar range. The methoxy derivative **11** with a K_i value of 2.56 nM reveals the highest σ_1-receptor affinity within the spirobenzoxepine series. However, its affinity is slightly lower than those of the 2-benzofuran **1a** and the 2-benzopyran **2a**. The 2-benzoxepine **14** with a double bond in position 4/5 displays a somewhat lower affinity (K_i = 4.05 nM) than the saturated analogue **11**. The polar lactol **12** has a fourfold lower affinity than the methoxy derivative **11**. Similar σ_1-receptor affinities were found for the homologous nitriles **18** (K_i = 3.54 nM) and **20** (K_i = 4.66 nM), although **20** possesses an additional methylene spacer between the ring system and the cyano group. The ethoxy derivative **16** has a fivefold lower σ_1-receptor affinity than the methoxy derivative **14**; it shows the lowest σ_1/σ_2 receptor selectivity within the 2-benzoxepine series. The 2-benzofuran derivative **15** (K_i = 28.8 nM) has a much lower σ_1-affinity than the 2-benzoxepines and the 2-benzofuran **1a**.

Generally, the σ_2-receptor affinities of all compounds are considerably lower than their σ_1-receptor affinities. The most σ_2-active compound in the 2-benzoxepine series is the methoxy derivative **11** with a K_i value of 475 nM, leading to a low σ_1/σ_2 receptor selectivity (185-fold). Due to the rela-

Table 1. σ-Receptor affinities of the synthesized spiro[2]benzoxepines



Compd.	R	C^4-C^5	$K_i \pm$ SEM [nM] ($n = 3$)		Selectivity
			σ_1	σ_2	σ_1/σ_2
1a[8]	OCH_3	[a]	1.14 ± 0.22	1280 ± 137	1130
2a[8]	OCH_3	[b]	1.29 ± 0.18	3500 ± 352	2710
11	OCH_3	CH_2-CH_2	2.56 ± 0.96	475 ± 138	185
14	OCH_3	CH=CH	4.05 ± 0.42	1040 ± 158	257
12	OH	CH_2-CH_2	11.4 ± 3.20[c]	1230 ± 25.0	107
18	CN	CH_2-CH_2	3.54 ± 0.67[c]	1510 ± 421	427
20	CH_2CN	CH_2-CH_2	4.66 ± 1.06[c]	3570 ± 667	768
16	OCH_2CH_3	CH=CH	20.4 ± 0.39	678 ± 142	33
15	$CH_2CH(OCH_3)_2$	[a]	28.8 ± 5.03	1200 ± 79.7	42
Haloperidol			2.20 ± 0.31	34.2 ± 2.3[c]	16
Ditolylguanidine (DTG)			164 ± 47.4[c]	63.9 ± 10.8	0.39
BMY14802			265 ± 32.0	390.7 ± 62.2	1.5

[a] Spiro[2]benzofuran. [b] Spiro[2]benzopyran. [c] $n = 4$.

tively low σ_2-affinity the highest σ_1/σ_2 selectivity was found for the cyanomethyl derivative **20** with a selectivity factor of 768.

Conclusion

A four-step synthesis of the spiro[[2]benzoxepine-1,4′-piperidines] **11** and **12** has been described. The spiro compounds **11** and **12** serve as starting materials for further modifications in the 3-position. The in vitro evaluation with radioligand binding assays allows the determination of relationships between substitution in the 3-position of the spirobenzoxepines and their σ_1- and σ_2-receptor affinity and selectivity. The ligands with a methoxy (**11**) and cyano (**18**) group displayed K_i values in the range of 2−4 nM. As a rule, the σ_1-receptor affinities and the σ_1/σ_2-receptor selectivities of the 2-benzoxepines are somewhat lower than those values of the corresponding 2-benzofurans and 2-benzopyrans.[8,9]

Experimental Section

General: Moisture-sensitive reactions were conducted under dry nitrogen. Tetrahydrofuran (THF), Et_2O, and toluene were distilled from sodium/benzophenone, CH_2Cl_2 from CaH_2, and CH_3CN from P_2O_5 prior to use. For thin layer chromatography (TLC) Merck silica gel 60 F_{254} plates were used. Flash chromatography (FC) was carried out with Merck silica gel 60, 0.040−0.063 mm, the terms in parentheses for FC include the following: diameter of the column [cm], eluent, fraction size [mL], R_f. Melting points were determined with an SMP 2 (Stuart Scientific) apparatus and are uncorrected. Elemental analyses were conducted with a VarioEL (Elementaranalysesysteme GmbH). The mass spectrometers used were models MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan). As specified, ionization methods were electron impact (EI) at 70 eV or chemical ionization (CI). IR spectra were obtained with a Perkin−Elmer 1605 FT-IR spectrophotometer and wavenumbers are given in cm^{-1}. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Varian Unity 300 NMR spectrometer operating at 27 °C. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. Coupling constants (J) are given with 0.5 Hz resolution. The assignments of ^1H and ^{13}C NMR signals were supported by 2D NMR techniques (correlation spectroscopy, COSY).

(*Z*/*E*)-2-[2-(2-Bromophenyl)vinyl]-1,3-dioxolane (6): 2-Bromobenzaldehyde (**4**) (1.077 g, 5.83 mmol) and tris[2-(2-methoxyethoxy)ethyl-]amine (TDA-1, 1.884 g, 5.83 mmol) were dissolved in CH_2Cl_2 (70 mL) under nitrogen. Then, a saturated solution of K_2CO_3 (70 mL) and (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**5**; 2.50 g, 5.83 mmol) were added. This mixture was refluxed for 3 d and then the CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, silica gel was added and the solvent was removed under reduced pressure. The residue was purified by FC (5.5 cm, petroleum ether/EtOAc, 95:5, 50 mL) to afford two fractions: first (*Z*)-**6** was eluted ($R_f = 0.12$), then (*E*)-**6** ($R_f = 0.06$), which could not be completely separated from (*Z*)-**6**. Yields: (*Z*)-**6**: 0.50 g (34%), colorless oil, which solidified on standing, m.p. 54 °C, (*Z*+*E*)-**6**: 0.85 g (57%) colorless oil, overall yield: 1.35 g (91%). According to the ^1H NMR spectrum of the unpurified product the ratio (*Z*)-**6** to (*E*)-**6** was 65:35.

(*Z*)-6: IR (film): $\tilde{\nu}$ = 2956, 2884 (C−H), 1115 (C−O), 1031 (C−Br), 767, 744 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.87−3.96 (m, 2 H, OCH_2CH_2O), 4.04−4.10 (m, 2 H,OCH_2CH_2O), 5.37 (dd, J = 7.7, 0.8 Hz, 1 H, ArCH=CHCH), 5.80 (dd, J = 11.7, 7.7 Hz, 1 H, ArCH=CHCH), 6.88 (d, J = 11.7 Hz, 1 H, ArCH=CHCH), 7.17 (td, J = 8.1, 1.8 Hz, 1 H, 4′-H), 7.31 (td, J = 7.3, 1.5 Hz, 1 H, 5′-H), 7.48 (dd, J = 7.3, 1.8 Hz, 1 H, 6′-H), 7.59 (dd, J = 8.1, 1.5 Hz, 1 H, 3′-H) ppm. MS (EI): m/z = 254/256 [M^+], 182/184 [$BrC_6H_4CH=CH^+$], 175 [M^+ − Br], 73 [$OCH_2CH_2OCH^+$]. $C_{11}H_{11}BrO_2$ (255.11): calcd. C 51.8, H 4.35; found C 51.8, H 4.23.

In ref.[10] the spectroscopic data of **6** are not provided.

2-[2-(2-Bromophenyl)ethyl]-1,3-dioxolane (7): A mixture of **6** [(*Z*)/(*E*) = 1:1, 1.134 g, 4.4 mmol)] and Raney nickel (B, 113 W, Degussa−Hüls, 0.3 g) in CH_3OH (20 mL) was shaken for 3.3 h under H_2 (1.0 bar) in a Parr apparatus. Then, the mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was purified by FC (4 cm, petroleum ether/EtOAc, 96:4, 50 mL, R_f = 0.19). Colorless oil, yield 880 mg (77%). The product contained about 10% of dehalogenated compound **8** which could not be separated. IR (film): $\tilde{\nu}$ = 2954, 2880 (C−H), 1139 (C−O), 1025 (C−Br), 751 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.94−2.04 (m, 2 H, $ArCH_2CH_2CH$), 2.83−2.92 (m, 2 H, $ArCH_2CH_2CH$), 3.86−3.94 (m, 2 H, OCH_2CH_2O), 3.96−4.04 (m, 2 H, OCH_2CH_2O), 4.94 (t, *J* = 4.6 Hz, 1 H, $ArCH_2CH_2CH$), 7.02−7.09 (m, 1 H, 5′-H), 7.18−7.31 (m, 2 H, arom), 7.53 (dd, *J* = 7.6, 1.2 Hz, 1 H, 3′-H) ppm. $C_{11}H_{13}BrO_2$ (257.13) ppm. MS (CI, isobutane): *m*/*z* = 257/259 [M^+ + H], 177 [M^+ − Br], 73 [$OCH_2CH_2OCH^+$].

1-Benzyl-4-{2-[2-(1,3-dioxolan-2-yl)ethyl]phenyl}piperidin-4-ol (10): Under nitrogen a solution of *n*-butyllithium in hexane (1.6 M, 1.43 mL, 2.28 mmol) was slowly added to a cooled (−78 °C) solution of **7** (586 mg, 2.28 mmol) in THF (5 mL). The mixture was stirred at −78 °C for 10 min, then a solution of 1-benzylpiperidin-4-one (**9**) (345 mg, 1.82 mmol) in THF (3 mL) was slowly added and the mixture was stirred at −78 °C for 2.5 h and another 3 h at room temperature. Then, water was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by FC (3 cm, first petroleum ether/EtOAc, 95:5, then petroleum ether/EtOAc, 75:25, 20 mL, R_f = 0.05) to afford a colorless oil, yield 326 mg (49%). IR (film): $\tilde{\nu}$ = 3450 (O−H), 2927, 2873 (C−H), 1133, 1039 (C−O), 749, 701 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.90−2.07 [m, 4 H, $ArCH_2CH_2CH$ (2 H), $N(CH_2CH_2)_2$ (2 H)], 2.21 [td, *J* = 13.1, 4.3 Hz, 2 H, $N(CH_2CH_2)_2$], 2.56 [td, *J* = 11.9, 2.4 Hz, 2 H, $N(CH_2CH_2)_2$], 2.79 [br. d, *J* = 11.3 Hz, 2 H, $N(CH_2CH_2)_2$], 3.12−3.18 (m, 2 H, $ArCH_2CH_2CH$), 3.59 (s, 2 H, NCH_2Ph), 3.83−3.92 (m, 2 H, OCH_2CH_2O), 3.93−4.02 (m, 2 H, OCH_2CH_2O), 4.92 (t, *J* = 4.7 Hz, 1 H, $ArCH_2CH_2CH$), 7.14 (td, *J* = 7.0, 1.8 Hz, 1 H, arom), 7.20 (td, *J* = 7.3, 1.5 Hz, 1 H, arom), 7.23−7.41 (m, 7 H, arom) ppm. MS (EI): *m*/*z* = 367 [M^+], 276 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. HRMS for $C_{23}H_{29}NO_3$: calcd. 367.2147; found 367.2149.

(±)-1′-Benzyl-3-methoxy-4,5-dihydro-3*H*-spiro[[2]benzoxepine-1,4′-piperidine] (11): A solution of **10** (457 mg, 1.24 mmol) and *p*-toluenesulfonic acid monohydrate (284 mg, 1.49 mmol) in CH_3OH (10 mL) was stirred for 24 h at room temperature. Then, an aqueous solution of NaOH (2 M, 5 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by FC (3 cm, petroleum ether/EtOAc, 3:1, 20 mL, R_f = 0.04) to afford a colorless oil, which solidified on standing (m.p. 75 °C), yield 272 mg (65%). IR (film): $\tilde{\nu}$ = 2945, 2821 (C−H), 1127, 1039, 1007 (C−O), 745, 698 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.72 [td, *J* = 13.7, 4.9 Hz, 1 H, $N(CH_2CH_2)_2$], 1.90−2.05 [m, 3 H, $N(CH_2CH_2)_2$ (1 H), $ArCH_2CH_2CH$ (2 H)], 2.13 [ddd, *J* = 13.7, 5.6, 2.7 Hz, 1 H, $N(CH_2CH_2)_2$], 2.44−2.75 [m, 5 H, $N(CH_2CH_2)_2$ (1 H), $ArCH_2CH_2CH$ (1 H), $N(CH_2CH_2)_2$ (3 H)], 2.85−2.93, [m, 1 H, $N(CH_2CH_2)_2$], 3.29−3.41 (m, 1 H, $ArCH_2CH_2CH$), 3.42 (s, 3 H, OCH_3), 3.57 (d, *J* = 13.1 Hz, 1 H, NCH_2Ph), 3.62 (d, *J* = 13.1 Hz, 1 H, NCH_2Ph), 4.48 (dd, *J* = 7.6, 5.2 Hz, 1 H, $ArCH_2CH_2CH$), 7.08 (dd, *J* = 7.3, 1.8 Hz, 1 H, 6-H), 7.15 (td, *J* = 7.0, 1.8 Hz, 1 H, 7-H), 7.21 (td, *J* = 8.2, 1.8 Hz, 1 H, 8-H), 7.24−7.40 (m, 6 H, arom) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.2 (1 C, $ArCH_2CH_2CH$), 32.8 [1 C, $N(CH_2CH_2)_2$], 34.2 (1 C, $ArCH_2CH_2CH$), 39.7 [1 C, $N(CH_2CH_2)_2$], 49.5 [1 C, $N(CH_2CH_2)_2$], 49.5 (1 C, $N(CH_2CH_2)_2$], 56.3 (1 C, OCH_3), 63.3 (1 C, NCH_2Ph), 78.1 (1 C, ArCO), 100.3 (1 C, $ArCH_2CH_2CH$), 125.4 (1 C, C-9), 126.9 (1 C, C-4′′), 127.0 (1 C, C-8), 127.3 (1 C, C-7), 128.2 (2 C, C-3′′ + C-5′′), 129.2 (2 C, C-2′′ + C-6′′), 130.4 (1 C, C-6), 138.2 (1 C, C-5a), 138.7 (1 C, C-1′′), 143.9 (1 C, C-9a) ppm. MS (EI): *m*/*z* = 337 [M^+], 322 [$M^+ - CH_3$], 246 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. $C_{22}H_{27}NO_2$ (337.46): calcd. C 78.3, H 8.06, N 4.15; found C 77.6, H 7.07, N 3.80. HRMS: calcd. 337.2042; found 337.2046.

(±)-1′-Benzyl-4,5-dihydro-3*H*-spiro[[2]benzoxepine-1,4′-piperidin]-3-ol (12): A solution of the hydroxy acetal **10** (100 mg, 0.27 mmol) in THF (2 mL) and HCl (2 M, 10 mL) was stirred at room temperature for 2 h. Then, an aqueous solution of NaOH (2 M, 12 mL) was added (pH = 10). This mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), then some silica gel was added and the solvents were evaporated under reduced pressure. The residue was purified by FC (1 cm, petroleum ether/EtOAc, 3:1, 5 mL, R_f = 0.01) to afford a colorless oil which solidified on standing (m.p. 121 °C), yield 63 mg (72%). IR (film): $\tilde{\nu}$ = 3392 (O−H), 2942, 2824 (C−H), 1068, 1034 (C−O), 747, 698 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.83 [td, *J* = 12.9, 5.0 Hz, 1 H, $N(CH_2CH_2)_2$], 1.88−2.06 [m, 3 H, $N(CH_2CH_2)_2$ (2 H), $ArCH_2CH_2CH$ (1 H)], 2.08−2.21 (m, 1 H, $ArCH_2CH_2CH$), 2.45 [td, *J* = 13.1, 4.3 Hz, 2 H, $N(CH_2CH_2)_2$ (1 H), $ArCH_2CH_2CH$ (1 H)], 2.60−2.94, [m, 4 H, $N(CH_2CH_2)_2$], 3.37 (td, *J* = 12.5, 6.7 Hz, 1 H, $ArCH_2CH_2CH$), 3.63 (s, 2 H, NCH_2Ph), 4.36 (br. s, 1 H, OH), 4.98 (dd, *J* = 8.5, 4.9 Hz, 1 H, $ArCH_2CH_2CH$), 7.07 (d, *J* = 6.7 Hz, 1 H, arom), 7.10−7.39 (m, 8 H, arom) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.7 (1 C, $ArCH_2CH_2CH$), 32.4 [1 C, $N(CH_2CH_2)_2$], 36.0 (1 C, $ArCH_2CH_2CH$), 39.0 [1 C, $N(CH_2CH_2)_2$], 49.0 [1 C, $N(CH_2CH_2)_2$], 49.1 [1 C, $N(CH_2CH_2)_2$], 62.8 (1 C, NCH_2Ph), 79.0 (1 C, ArCO), 92.3 (1 C, $ArCH_2CH_2CH$), 125.7 (1 C, arom. CH), 127.1 (1 C, arom. CH), 127.2 (1 C, arom. CH), 127.3 (1 C, arom. CH), 128.3 (2 C, arom. CH), 129.5 (2 C, arom. CH), 130.7 (1 C, arom. C-9), 137.3 (1 C, arom. C), 137.7 (1 C, arom. C), 144.0 (1 C, arom. C) ppm. MS (EI): *m*/*z* = 323 [M^+], 232 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. $C_{21}H_{25}NO_2$ (323.44): calcd. C 78.0, H 7.79, N 4.33; found C 77.3, H 8.28, N 4.19. HRMS: calcd. 323.1885; found 323.1885.

(*Z*)-1-Benzyl-4-{2-[2-(1,3-dioxolan-2-yl)vinyl]phenyl}piperidin-4-ol (13): Under nitrogen a solution of *n*-butyllithium in hexane (1.6 M, 0.76 mL, 1.21 mmol) was slowly added to a cooled (−78 °C) solution of (*Z*)-**6** (280 mg, 1.10 mmol) in THF (4 mL). The color of the mixture turned brown. Then, a solution of 1-benzylpiperidin-4-one (**9**) (166 mg, 0.88 mmol) in THF (2 mL) was slowly added. The color of the solution changed to yellow. The mixture was stirred at −78 °C for 7 h. Water was then added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by FC (2 cm, petroleum ether/EtOAc, 2:3, 10 mL, R_f = 0.08) to afford a colorless oil, yield 142 mg (44%). IR (film): $\tilde{\nu}$ = 3453 (O−H), 2884, 2815 (C−H), 1114, 1043 (C−O), 766, 700 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.90 [dd, *J* = 14.0, 2.6 Hz, 2 H, $N(CH_2CH_2)_2$], 2.14 [td, *J* = 13.1, 4.3 Hz, 2 H, $N(CH_2CH_2)_2$], 2.47 [td, *J* = 11.9, 2.4 Hz, 2 H, $N(CH_2CH_2)_2$], 2.73 [br. d, *J* = 11.3 Hz, 2 H, $N(CH_2CH_2)_2$], 3.54 (s, 2 H, NCH_2Ph), 3.75−3.81 (m, 2 H, OCH_2CH_2O), 3.94−4.00 (m, 2 H, OCH_2CH_2O), 5.23 (dd, *J* = 7.9, 0.6 Hz, 1 H, ArCH=CHCH), 5.63 (dd, *J* = 11.3, 7.9 Hz, 1 H, ArCH=CHCH), 7.19−7.35 (m, 8 H, arom), 7.40 (d, *J* = 7.3 Hz, 1 H, arom), 7.47 (d, *J* = 11.6 Hz, 1 H, ArCH=CHCH) ppm. $C_{23}H_{27}NO_3$ (365.47). MS (CI, NH_3): *m*/*z* = 366 [M^+ + H].

(±)-1′-Benzyl-3-methoxy-3*H*-spiro[[2]benzoxepine-1,4′-piperidine] (14) and (±)-2-{1′-Benzyl-3*H*-spiro[[2]benzofuran-1,4′-piperidin]-3-yl}acetaldehyde Dimethyl Acetal (15)

Procedure A: A solution of the (*Z*)-configured hydroxydioxolane (*Z*)-**13** (70 mg, 0.19 mmol) and *p*-toluenesulfonic acid monohydrate (54 mg, 0.28 mmol) in CH_3OH (10 mL) was stirred at room temperature for 2 h. Then, solid NaOH (30 mg) was added and the solvent was removed under reduced pressure. The crude product was purified by FC (2 cm, petroleum ether/EtOAc, first 2:1, then 1:1, 5 mL, R_f = 0.06) to afford a colorless oil, yield 28 mg. The resulting product contained **14** and **15** in a ratio of 1:2.

Procedure B: The product of Procedure A (28 mg, 0.08 mmol) was dissolved in CH_3OH (3 mL). Then, *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol) was added and the mixture was stirred at room temperature for 2 d. A solution of NaOH (2 M) was then added (pH = 10) and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue contained **15** as a colorless oil, yield 20 mg (68%).

Procedure C: A solution of the (*Z*)-configured hydroxydioxolane (*Z*)-**13** (35 mg, 0.096 mmol) and *p*-toluenesulfonic acid monohydrate (22 mg, 0.12 mmol) in CH_3OH (5 mL) was stirred at room temperature for 20 min. Then, an aqueous solution of NaOH (2 M) was added (pH = 10) and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by FC (2 cm, petroleum ether/EtOAc, 2:1, 5 mL, R_f = 0.06) to afford **14** as colorless oil, yield 21 mg (66%).

14: IR (film): $\tilde{\nu}$ = 2939, 2809 (C−H), 1650 (C=C), 1210, 1159, 1047 (C−O), 935, 752, 741, 699 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.75 [br. d, *J* = 13.7 Hz, 2 H, $N(CH_2CH_2)_2$], 1.91 [td, *J* = 12.5, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.14 [td, *J* = 12.8, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.45−2.59 [m, 2 H, $N(CH_2CH_2)_2$], 2.78−2.89 [m, 2 H, $N(CH_2CH_2)_2$], 3.58 (s, 3 H, OCH_3), 3.60 (s, 2 H, NCH_2Ph), 4.81 (dd, *J* = 12.5, 8.9 Hz, 1 H, ArCH=C*H*CH), 5.50 (d, *J* = 8.9 Hz, 1 H, ArCH=CHC*H*), 6.72 (d, *J* = 12.8 Hz, 1 H, ArC*H*=CHCH), 7.08−7.18 (m, 2 H, arom), 7.23−7.40 (m, 7 H, arom) ppm. MS (EI): *m*/*z* = 335 [M^+], 320 [M^+-CH_3], 244 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. HRMS for $C_{22}H_{25}NO_2$: calcd. 335.1885; found 335.1887.

15: IR (film): $\tilde{\nu}$ = 2940, 2809 (C−H), 1125, 1048 (C−O), 757, 743, 699 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.65−1.75 [m, 2 H, $N(CH_2CH_2)_2$], 1.86 [ddd, *J* = 13.7, 9.5, 3.4 Hz, 1 H, $ArCHCH_2CH(OCH_3)_2$], 1.92 [td, *J* = 13.4, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.10 [td, *J* = 13.1, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.17 [ddd, *J* = 14.0, 8.2, 3.4 Hz, 1 H, $ArCHCH_2CH(OCH_3)_2$], 2.47 [td, *J* = 11.8, 3.0 Hz, 1 H, $N(CH_2CH_2)_2$], 2.48 [td, *J* = 12.5, 2.7 Hz, 1 H, $N(CH_2CH_2)_2$], 2.77−2.88 [m, 2 H, $N(CH_2CH_2)_2$], 3.35 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.59 (s, 2 H, NCH_2Ph), 4.79 [dd, *J* = 7.9, 3.4 Hz, 1 H, $ArCHCH_2CH(OCH_3)_2$], 5.26 [dd, *J* = 9.5, 3.4 Hz, 1 H, $ArCHCH_2CH(OCH_3)_2$], 7.12−7.18 (m, 2 H, arom), 7.23−7.41 (m, 7 H, arom) ppm. MS (EI): *m*/*z* = 367 [M^+], 91 [CH_2Ph^+]. HRMS for $C_{23}H_{29}NO_3$: calcd. 367.2147; found 367.2145.

(±)-1′-Benzyl-3-ethoxy-3*H*-spiro[[2]benzoxepine-1,4′-piperidine] (16): A solution of the (*Z*)-configured hydroxydioxolane (*Z*)-**13** (80 mg, 0.22 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) in C_2H_5OH (6 mL) was stirred at room temperature for 15 min. Then, an aqueous solution of NaOH (2 M) was added (pH = 10) and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by FC (1 cm, petroleum ether/EtOAc, 5:2, 5 mL, R_f = 0.06) to afford a colorless oil, yield 53 mg (69%). IR (film): $\tilde{\nu}$ = 2939, 2810 (C−H), 1650 (C=C), 1179, 1047 (C−O), 996, 757, 699 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.75 [dd, *J* = 14.0, 2.5 Hz, 2 H, $N(CH_2CH_2)_2$], 1.91 [td, *J* = 12.8, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.13 [td, *J* = 12.8, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.45−2.58 [m, 2 H, $N(CH_2CH_2)_2$], 2.78−2.88, [m, 2 H, $N(CH_2CH_2)_2$], 3.60 (s, 2 H, NCH_2Ph), 3.73−3.85 (m, 2 H, OCH_2CH_3), 4.81 (dd, *J* = 12.8, 9.2 Hz, 1 H, ArCH=C*H*CH), 5.48 (d, *J* = 9.2 Hz, 1 H, ArCH=CHC*H*), 6.66 (d, *J* = 12.8 Hz, 1 H, ArC*H*=CHCH), 7.08−7.18 (m, 2 H, arom), 7.23−7.39 (m, 7 H, arom) ppm. MS (EI): *m*/*z* = 349 [M^+], 320 [$M^+ - CH_2CH_3$], 258 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. HRMS for $C_{23}H_{27}NO_2$: calcd. 349.2042; found 349.2041.

(±)-2-{1′-Benzyl-3*H*-spiro[[2]benzofuran-1,4′-piperidin]-3-yl}acetaldehyde (17): The hydroxydioxolane **13** (60 mg, 0.16 mmol) was dissolved in THF (2 mL) and HCl (2 M, 10 mL) and the mixture was stirred at room temperature for 15 h. Then, an aqueous solution of NaOH (2 M) was added (pH = 8) and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by FC (1 cm, petroleum ether/EtOAc, 1:1, 5 mL, R_f = 0.04) to afford a colorless oil, yield 24 mg (45%). IR (film): $\tilde{\nu}$ = 2917, 2812 (C−H), 1725 (C=O), 1109, 1048 (C−O), 741, 699 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.65−1.77 [m, 2 H, $N(CH_2CH_2)_2$], 1.95 [td, *J* = 12.8, 4.6 Hz, 1 H, $N(CH_2CH_2)_2$], 2.16 [td, *J* = 12.8, 4.3 Hz, 1 H, $N(CH_2CH_2)_2$], 2.47 [td, *J* = 11.9, 2.4 Hz, 2 H, $N(CH_2CH_2)_2$], 2.73−2.97 [m, 4 H, $N(CH_2CH_2)_2$ (2 H), $ArCHCH_2CHO$ (2 H)], 3.62 (s, 2 H, NCH_2Ph), 5.68 (dd, *J* = 6.7, 4.9 Hz, 1 H, ArC*H*CH_2CHO), 7.13−7.19 (m, 2 H, arom), 7.24−7.41 (m, 7 H, arom), 9.84 (t, *J* = 2.1 Hz, 1 H, $ArCHCH_2CHO$) ppm. MS (EI): *m*/*z* = 321 [M^+], 230 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+].

(±)-1′-Benzyl-4,5-dihydro-3*H*-spiro[[2]benzoxepine-1,4′-piperidine]-3-carbonitrile (18) and 1′-Benzyl-5*H*-spiro[[2]benzoxepine-1,4′-piperidine] (19)

Method A: Under nitrogen tetracyanoethylene (21 mg, 0.16 mmol) was dissolved in CH_3CN (2 mL). Then, a solution of the methyl acetal **11** (272 mg, 0.81 mmol) in CH_3CN (2 mL) was added. After 5 min, trimethylsilyl cyanide (0.5 mL) was added and the mixture was refluxed. Three further portions of trimethylsilyl cyanide (0.5 mL each) were added over a period of 24 h. On completion of the reaction, the solvent was carefully evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2. Silica gel was then added and the solvent was removed under reduced pressure. The residue was purified by FC (3 cm, petroleum ether/EtOAc, 3:1, 20 mL, R_f = 0.05). At first, a nonpolar compound was eluted, the structure of which could not be elucidated (R_f = 0.80), followed by the carbonitrile **18**. Colorless oil, yield 10 mg (3.5%).

Method B: Under nitrogen **11** (50 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (4 mL) and the solution was cooled to −25 °C with dry ice/acetone. Then, trimethylsilyl cyanide (0.3 mL, 2.2 mmol) and $BF_3{\cdot}Et_2O$ (70 μL, 0.54 mmol) were added successively and the mixture was stirred at −25 °C for 25 min. The mixture was then stirred at 0 °C for 1.5 h, CH_3OH and an aqueous solution of NaOH (2 M) were added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by FC (1 cm, petroleum ether/EtOAc, 4:1, 7 mL) to afford two colorless oils: at first, the elimination product **19** (R_f = 0.05), yield 3 mg (6%), and

afterwards the carbonitrile **18** (R_f = 0.04), yield 23 mg (47%) were eluted.

18: IR (film): $\tilde{\nu}$ = 2923, 2853 (C−H), 2212 (C≡N), 1086 (C−O), 741, 699 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.78 [td, *J* = 13.7, 4.9 Hz, 1 H, $N(CH_2CH_2)_2$], 1.85 [ddd, *J* = 13.4, 5.2, 2.4 Hz, 1 H, $N(CH_2CH_2)_2$], 1.98−2.14 [m, 2 H, $N(CH_2CH_2)_2$ (1 H), $ArCH_2CH_2CH$ (1 H)], 2.33−2.64, [m, 5 H, $ArCH_2CH_2CH$ (1 H), $N(CH_2CH_2)_2$ (1 H), $N(CH_2CH_2)_2$ (2 H), $ArCH_2CH_2CH$ (1 H)], 2.72 [br. d, *J* = 11.3 Hz, 1 H, $N(CH_2CH_2)_2$], 2.85 [br. d, *J* = 11.0 Hz, 1 H, $N(CH_2CH_2)_2$], 3.44 (td, *J* = 13.0, 6.8 Hz, 1 H, $ArCH_2CH_2CH$), 3.59 (s, 2 H, NCH_2Ph), 4.35 (dd, *J* = 11.3, 6.1 Hz, 1 H, $ArCH_2CH_2CH$), 7.09 (d, *J* = 7.0 Hz, 1 H, arom), 7.16−7.42 (m, 8 H, arom) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.1 (1 C, $ArCH_2CH_2CH$), 32.6 [1 C, $N(CH_2CH_2)_2$], 32.8 (1 C, $ArCH_2CH_2CH$), 39.0 [1 C, $N(CH_2CH_2)_2$], 48.9 [1 C, $N(CH_2CH_2)_2$], 49.2 [1 C, $N(CH_2CH_2)_2$], 59.1 (1 C, $ArCH_2CH_2CH$), 63.2 (1 C, NCH_2Ph), 83.2 (1 C, ArCO), 119.4 (1 C, CN), 126.5 (1 C, arom. CH), 127.0 (1 C, arom. CH), 127.8 (1 C, arom. CH), 128.0 (1 C, arom. CH), 128.2 (2 C, arom. CH), 129.2 (2 C, arom. CH), 131.1 (1 C, arom. CH), 135.9 (1 C, arom. C), 138.7 (1 C, arom. C), 142.4 (1 C, arom. C) ppm. MS (EI): *m*/*z* = 332 [M^+], 241 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. HRMS for $C_{22}H_{24}N_2O$: calcd. 332.1889; found 332.1890.

19: IR (film): $\tilde{\nu}$ = 3038, 2922, 2821 (C−H), 1660 (C=C), 1095 (C−O), 744, 700 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.09 [td, *J* = 12.5, 5.4 Hz, 2 H, $N(CH_2CH_2)_2$], 2.36−2.52 [m, 4 H, $N(CH_2CH_2)_2$], 2.80 [br. d, *J* = 12.2 Hz, 2 H, $N(CH_2CH_2)_2$], 3.56 (s, 2 H, NCH_2Ph), 3.59 (d, *J* = 5.2 Hz, 2 H, $ArCH_2CH{=}CH$), 4.77 (dt, *J* = 7.0, 5.2 Hz, 1 H, $ArCH_2CH{=}CH$), 6.27 (dt, *J* = 7.0, 1.5 Hz, 1 H, $ArCH_2CH{=}CH$), 7.04−7.08 (m, 1 H, 6-H), 7.12−7.21 (m, 2 H, arom), 7.24−7.38 (m, 6 H, arom) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.4 [2 C, $N(CH_2CH_2)_2$], 34.6 (1 C, $ArCH_2CH{=}CH$), 49.4 [2 C, $N(CH_2CH_2)_2$], 63.1 (1 C, NCH_2Ph), 78.9 (1 C, ArCO), 104.5 (1 C, $ArCH_2CH{=}CH$), 125.8 (1 C, arom. CH), 126.4 (1 C, arom. CH), 127.1 (1 C, arom. CH), 127.5 (1 C, arom. CH), 128.2 (2 C, arom. CH), 129.3 (2 C, arom. CH), 130.6 (1 C, C-6), 138.4 (1 C, arom. C), 139.0 (1 C, arom. C), 142.5 (1 C, arom. C), 142.8 (1 C, $ArCH_2CH{=}CH$) ppm. MS (EI): *m*/*z* = 305 [M^+].

(±)-2-{1′-Benzyl-4,5-dihydro-3*H*-spiro[[2]benzoxepine-1,4′-piperidin]-3-yl}ethanenitrile (20): A mixture of the lactol **12** (70 mg, 0.22 mmol), (cyanomethylene)triphenylphosphorane (130 mg, 0.43 mmol) and Cs_2CO_3 (30 mg) in toluene (10 mL) was refluxed for 19 h. Then, the solvent was removed under reduced pressure. The crude product was purified by FC (2 cm, petroleum ether/EtOAc, 5:2, 10 mL, R_f = 0.09) to afford a colorless oil, which solidified on standing (m.p. 97−105 °C), yield 70 mg (92%). IR (film): $\tilde{\nu}$ = 2940, 2816 (C−H), 2250 (C≡N), 1092, 1040 (C−O), 742, 699 (C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.77 [td, *J* = 12.8, 4.9 Hz, 1 H, $N(CH_2CH_2)_2$], 1.82−1.96 [m, 3 H, $N(CH_2CH_2)_2$ (1 H), $ArCH_2CH_2CH$ (2 H)], 2.06 [ddd, *J* = 13.7, 5.3, 2.5 Hz, 1 H, $N(CH_2CH_2)_2$], 2.45 [td, *J* = 12.2, 4.3 Hz, 1 H, $N(CH_2CH_2)_2$], 2.49−2.66 [m, 5 H, $N(CH_2CH_2)_2$ (2 H), $ArCH_2CH_2CH$ (1 H), CH_2CN (2 H)], 2.70 [br. d, *J* = 11.0 Hz, 1 H, $N(CH_2CH_2)_2$], 2.87 [br. d, *J* = 11.0 Hz, 1 H, $N(CH_2CH_2)_2$], 3.33−3.45 (m, 1 H, $ArCH_2CH_2CH$), 3.59 (s, 2 H, NCH_2Ph), 3.83−3.94 (m, 1 H, $ArCH_2CH_2CH$), 7.08 (dd, *J* = 7.0, 1.5 Hz, 1 H, arom), 7.14−7.41 (m, 8 H, arom) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.9 (1 C, CH_2CN), 30.7 (1 C, $ArCH_2CH_2CH$), 32.7 [1 C, $N(CH_2CH_2)_2$], 33.8 (1 C, $ArCH_2CH_2CH$), 39.2 [1 C, $N(CH_2CH_2)_2$], 49.3 [1 C, $N(CH_2CH_2)_2$], 49.6 [1 C, $N(CH_2CH_2)_2$], 63.2 (1 C, NCH_2Ph), 67.0 (1 C, $ArCH_2CH_2CH$), 80.7 (1 C, ArCO), 117.8 (1 C, CN), 126.0 (1 C, arom. CH), 126.8 (1 C, arom. CH), 127.1 (1 C, arom. CH), 127.4 (1 C, arom. CH), 128.1 (2 C, arom. CH), 129.1 (2 C, arom. CH), 130.5 (1 C, arom. C-9), 137.3 (1 C, arom. C), 138.7 (1 C, arom. C), 143.5 (1 C, arom. C) ppm. MS (EI): *m*/*z* = 346 [M^+], 255 [$M^+ - CH_2Ph$], 91 [CH_2Ph^+]. HRMS for $C_{23}H_{26}N_2O$: calcd. 346.2045; found 346.2040.

Pharmacology: The σ_1- and σ_2-receptor binding assays were conducted as previously reported.[8] The σ_1-binding assay was performed using a guinea pig brain membrane preparation as receptor material and [^3H]-(+)-pentazocine as radioligand. Nonspecific binding was determined with 10 μM haloperidol.[13] The σ_2-receptor affinity was determined using rat liver membrane preparations with the radioligand [^3H]-ditolylguanidine in the presence of 100 nM (+)-pentazocine to mask σ_1-binding sites. Nonspecific binding was determined with 10 μM ditolylguanidine.[14,15] K_i values were calculated according to Cheng and Prusoff[16] and represent data from at least three independent experiments, each performed in triplicate. The results are given as mean ± standard error of the mean (SEM).

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